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CELL & GENE THERAPY INSIGHTS

SPOTLIGHT ON:

Market access: evolving commercialization trends and strategies

GUEST EDITOR: Neil Palmer, President and Principal Consultant President and Principal Consultant at PDCI Market Access

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MARKET ACCESS: EVOLVING COMMERCIALIZATION TRENDS & STRATEGIES

SPOTLIGHT

FOREWORD

Under construction: roadmaps for HTA, pricing and reimbursement of cell and gene therapies

NEIL PALMER is Senior Strategic Adviser and President Emeritus of PDCI Market Access Inc., Canada's leading pricing and reimbursement consultancy that he co-founded in 1996. Prior to PDCI, Neil worked with the Patented Medicine Prices Review Board (PMPRB) where his responsibilities included policy development, overseeing the price review of patented medicines and conducting economic research. Prior to the PMPRB, he worked with the Health Division of Statistics Canada where he was responsible for economic and statistical analysis of health care costs and utilization. After completing his studies at the University of Western Ontario, Neil began his career in Montreal with the research group of the Kellogg Centre for Advanced Studies in Primary Care. He has presented extensively on pharmaceutical pricing and reimbursement issues and is a frequent speaker at conferences in North America and Europe.

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More than a dozen cell and gene therapies (CGT) are already on the market (e.g., LUXTURNA®, Kymriah®, Yescarta®, Zolgensma®) and there are several hundred cell and gene therapies in development [1]. McKinsey reports that "more than 750 trials of CGTs in almost 30,000 patients were underway as of June 2020", representing a growing proportion of the pharmaceutical industry's clinical and pre-clinical pipelines [2].

With the promise of significant and clinically meaningful advances in treatment, the early entrants are challenging national Health Technology Assessment (HTA), and pricing and reimbursement infrastructures around the world.

For traditional pharmaceuticals and biologics, the current HTA and market access roadmaps are generally clear, albeit often challenging. Analytical methods, standards and thresholds for assessing clinical and cost effectiveness are well established, limited primarily by gaps in clinical evidence than can sometimes be mitigated through risk sharing agreements with payers.

By comparison, the HTA and reimbursement roadmaps for CGT are still under construction, particularly in cases where there are unique or novel treatment modalities where there is no clear budget or funding mechanism within national or regional health care systems. Some CGTs are more akin to medical/surgical procedures than pharmacotherapy and require significant supporting medical care. And gene therapies for rare diseases may require cross-border travel to a specialized treatment centre (e.g., Strimvelis® in Milan) which raises logistics and reimbursement challenges [3].

This issue of *Cell and Gene Therapy Insights* addresses many of the important issues anticipated for HTA, pricing and reimbursement of cell and gene therapies.

Chaddah *et al.* report proceedings of their international workshop on the Challenges in the Adoption of Regenerative Medicine Therapies (CHART) [4]. The authors conclude that although current HTA methods are applicable to CGT, the dearth of long-term evidence greatly increases uncertainty that CGT are clinically and cost effective. The authors recommend improvement in clinical trial design, establishment of incentives for real world evidence, engagement of multiple stakeholders including policy makers, improvements to patient and data management, and finally, addressing payment challenges for technologies with high upfront costs but uncertain long term benefits.

Dabbous *et al.* provide an informative overview of European multinational collaborations in HTA and procurement of health technologies. Although more than 30 European countries are actively involved in such collaborations, only two have published reviews or activities with respect to gene therapies, a number that will surely grow [5]. However, despite multinational HTA and pricing collaborations, distinct national and sub-national treatment and funding pathways will likely persist given the unique characteristics of the respective healthcare systems.

Hague and Price question whether the value assessment criteria employed by HTA agencies to chimeric antigen receptor T-cell (CAR-T) therapies are fit-for-purpose given CAR-T's unique treatment characteristics and uncertainties in the evidence base. The authors recommend more systematic inclusion of evidence from patients and carers, a broader perspective of value to include productivity gains to address the limitations of cost-per-QALY value frameworks. They emphasize the important role of outcomes-based agreements to address uncertainty and the need for alignment on registries that will generate the evidence for the outcomes-based payment models [6]. Although, these concerns are not new to HTA agencies or payers as they face very similar challenges with highly specialized pharmaceutical technologies for rare diseases, the authors outline the specific concerns with respect to CAR-T.

The interview with Suzanne McGurn (President & CEO, CADTH) highlights the concerns of HTA agencies and payers that current and emerging CGT are novel and complex treatment technologies that need

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to be integrated into the healthcare system. Moreover, CGTs are highly heterogeneous in nature so the HTA review process needs to be adaptable to the technology and its place in the healthcare system. To that end, McGurn describes CADTH's separate review process for CGT including the screening process by which sponsors provide information on the complexity of the CGT and the treatment modality – information that allows CADTH to inform and engage with provincial ministries of health that will be reimbursing/funding the CGT within their respective healthcare systems. The process also allows early engagement between CADTH and sponsors [7].

In his interview, Professor Mondher Toumi addresses how HTA and market access for CGTs will evolve in Europe. And like McGurn, he highlights the heterogeneity of CGT technologies and the challenges of decentralized health care systems. Importantly, he warns that most CGT companies are not headed in the right direction when it comes to HTA, perhaps clinging to the misbelief that being highly specialized, traditional HTA would not apply to their technologies [8]. And while there may be updated HTA processes for HTA of CGT, as McGurn describes, current HTA methods will be adapted to address the unique characteristics of a CGT only if standard drug review process is not appropriate.

The interview with Parag Meswani (SVP, Commercial Strategy & Operations, Axovant Gene Therapies) highlights key learnings from his time with Spark and the commercialization of LUXTURNA® for a rare inherited ophthalmic condition and from his new role where the target is the much larger Parkinson's disease patient population. For rare diseases, the challenge is finding patients; for larger patient populations, it is identifying those patients who will benefit most from gene therapy and for whom the new technology offers greatest value compared to current treatments. In both cases, genetic testing programs will be important and clinical trial design needs to focus on safety and efficacy, but with HTA evidentiary requirements in mind. He discusses pricing, the importance of mapping pricing evidence requirements and stakeholder needs to support value communication. Finally, he stresses the need for flexibility in payment modalities across payers; to offer options for payers to assess price and to manage cash flow [9].

Janet Lambert (CEO Alliance for Regenerative Medicine) asserts that "payers, policymakers, and other stakeholders must implement the infrastructure necessary to ensure broad patient access and appropriate value-based reimbursement." [10].

However, the development and implementation of national CGT infrastructures is more likely to be evolutionary than revolutionary. And that evolution is already underway; led by individual firms and their innovative technologies that are blazing new trails for CGT products. There is no doubt that political awareness and informed policy makers are critical to a supportive environment; but it is the early CGT technologies and their pioneering sponsors, in collaboration with HTA authorities and payers, that will have the greatest influence (as borne out by the CHART workshop).

AFFILIATION

W. Neil Palmer
Senior Strategic Adviser and President Emeritus of PDCI Market Access Inc.

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CELL & GENE THERAPY INSIGHTS

MARKET ACCESS: EVOLVING COMMERCIALIZATION TRENDS & STRATEGIES

SPOTLIGHT

EXPERT INSIGHT

Challenges and proposed solutions to value assessment and reimbursement of CAR-T therapies in Europe

Clare L Hague & Martin J Price

Chimeric antigen receptor T-cell (CAR-T) therapy is a recently approved innovation that represents a novel approach to treating cancer. The aim of this paper is to describe some of the challenges to value assessment of CAR-Ts in Europe and put forward potential solutions to remedy these; maintaining the principles of respecting the need to accelerate broad patient access, address affordability concerns and reward innovation to maintain a sustainable life sciences industry. We explore whether the value assessment criteria employed by HTA agencies is appropriate for CAR-T therapies, considering the unique characteristics of treatment and uncertainties in the evidence base. Uncertainty is inevitable if the goal of timely patient access to innovation is to be pursued. We advocate for a more systematic inclusion of evidence from patients and carers in the HTA decision-making process, a broader perspective of value to be adopted by HTA agencies that take into account productivity gains from both patient and carers, and investment in data infrastructures to enable outcomes-based payment models. The limitations of cost-per-QALY value frameworks for CAR-T are highlighted as are their inability to capture productivity gains and solve for uncertainty. The important role that outcomes-based payment models play in enabling faster access through addressing uncertainties from an HTA perspective and payer perspective is emphasized. We conclude that multi-stakeholder collaboration across Europe is critical to ensure alignment on registries used to capture data for the regulatory mandated post-authorization study commitments and any additional data needed to support outcomes-based payment models for HTA agencies and payers.

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INTRODUCTION

Cancer remains a devastating public health challenge. Scientific research has focused on gaining an advanced understanding of disease, genomics and molecular characterization of tumors. This has led to the development of more targeted and innovative treatments that have altered the natural history of disease, particularly in hematology [1]. Such innovation includes advanced therapy medicinal products (ATMPs) which are medicines for human use based on genes, tissues or cells [2].

What is CAR-T therapy and what makes it different from other cancer therapies?

Autologous chimeric antigen receptor T-cell (CAR-T) therapy is a recently approved innovation that represents a novel approach to cancer treatment. It is typically administered as a one-time treatment where a patient's T-cells are removed from their blood and re-engineered to produce cells that are able to target and bind to cancer cells through recognition of chimeric antigen receptor (CAR) target antigens. CAR-T cells are then multiplied in the laboratory and reintroduced into the patient's body to target and kill cancer cells, and to prevent cancer cells from returning [3].

CAR-T therapies have been described as representing a "breakthrough for treating patients with cancer that have failed to respond to prior treatments" [4]. Whilst data on their long-term benefits are still evolving and hence uncertain, for many patients CAR-T therapy may offer a chance at a cure [5]. CAR-T therapies have however also captured headlines for their high price tags [6–8]. This has raised questions about their affordability and cost–effectiveness [9,10].

In 2018, the European Medicines Agency (EMA) recommended marketing authorizations for two CAR-T cell medicines in the European Union for blood cancer (specifically, for the treatment of acute lymphoblastic leukemia [ALL] and diffuse large B-cell lymphoma [DLBCL]) [11].

- Kymriah® (tisagenlecleucel) : indicated for the treatment of paediatric and young adult patients (up to 25 years of age) with B-cell ALL that is refractory or in second or later relapse, and in adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy;

- Yescarta® (axicabtagene ciloleucel): indicated for the treatment of adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy [11].

Another novel CAR-T, KTE-X19, is currently undergoing regulatory assessment by the EMA for mantle cell lymphoma [12] and there are over 280 Phase 1–3 trials actively recruiting patients diagnosed with multiple myeloma, acute myeloid leukemia, T-cell ALL and solid tumors amongst others (see www.clinicaltrials.gov).

The characteristics of CAR-T therapies that differentiate them from other cancer treatments are well described by Cook *et al.* [13].

In summary:

- They are ATMPs with a one-time treatment administration and a unique toxicity profile due to activation of the immune system after infusion of engineered T-cells that requires diligent monitoring [14]. The main safety concerns are cytokine release syndrome (CRS), which is a systemic response to the activation and proliferation of CAR-T cells causing high fever and flu-like symptoms, and neurologic toxicities. Both can be life-threatening, and in some cases even fatal [15];

- A manufacturing process that is complex [16] and where patients may have to wait between 3-4 weeks before their modified CAR-T cells are returned to them;

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- Stringent requirements for formal accreditation of hospitals are mandated to provide CAR-T therapies to patients.

The evidence base underpinning regulatory and HTA approval of CAR-T therapies of the first indications has been epitomized to date by the following characteristics:

- Open-label, single-arm (non-comparative) clinical studies with small sample sizes and short-term efficacy, safety and health-related quality of life (HRQoL) data but with a compelling treatment effect relative to (indirect comparisons of) alternative treatment options;
- Contextual comparative evidence generated for the standard(s) of care (SoC) that have been used to perform indirect comparisons of relative efficacy/safety;
- Post-authorization study commitments in form of safety studies (PASS) and efficacy studies (PAES).

These factors create some challenges for HTA decision-making because of the desire for HTA agencies and payers to understand:

- Relative efficacy from conventional randomized controlled trials (RCTs);
- Long-term efficacy, effectiveness, safety and HRQoL consequences of CAR-T therapies vs alternative treatment options;
- The likelihood of achieving a functional cure with therapy, which cannot always be defined *a priori*.

How do patients access CAR-T therapies outside of the clinical trial setting?

Following marketing authorization from the EMA, in many countries CAR-T innovators will be required to submit their evidence package to National HTA Agencies for a value assessment and either in tandem, or subsequently (depending on the country), a price for the CAR-T will be negotiated with national and/or regional/local payers. Health Technology Assessment is defined as "a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle, to inform decision-making that promotes an equitable, efficient, and high-quality health system" [17] (see **Supplementary material** for clarifying notes). However, it is important to note that the value assessment for HTA decision-making is typically the value determined at the time of launch based on the available evidence. In some cases, conditions and/or restrictions may be put in place that are contingent on the generation of additional evidence [18]. The challenge of determining when evidence is sufficiently 'robust' within a therapy's overall life cycle to undertake an HTA/cost-effectiveness assessment is summarized by what has been termed 'Buxton's law' (i.e. it is always too early until, unfortunately, it's suddenly too late) [19]. There are costs and unintended consequences associated with waiting for 'certainty' and it is important that these are better understood by all and particularly in relation to CAR-T therapies.

How is value determined by National HTA Agencies & is it appropriate for CAR-Ts?

It is important that the value assessment of CAR-T therapies is framed using a holistic definition of value, reflecting the perspective of all stakeholders, especially patients, where all relevant evidence and outcomes are considered. How value is characterized for CAR-T therapies however is not entirely straightforward.

The overall value will likely vary depending on the perspective taken, the stakeholders involved and the decision-making context [17]. Value for the same product can further

vary by indication, by sub-populations and by line of treatment. The dimensions of value referred to in Note 3 (Supplementary material) often include clinical effectiveness, safety, costs and economic implications, ethical, social, cultural and legal issues, organizational and environmental aspects, as well as wider implications for the patients, relatives, caregivers and the population. Additional value attributes for new treatments have also been suggested (see and include the value of 'hope', adherence-improving factors, the severity of illness, equity and scientific spillovers [20,21]. These are also applicable to CAR-T therapies.

Some HTA agencies focus exclusively on the clinical value of a new treatment relative to one or more alternative therapies (e.g. Germany). Others consider the cost of treatment more explicitly in their HTA assessment, relative to the costs and benefits of one or more alternative therapies (e.g. UK, Sweden). The economic case for reimbursing a given treatment will depend on many parameters specific to a country, jurisdiction or population such as health services used and their country-specific costs, available treatments, local clinical guidelines and societal impact and is not transferable between jurisdictions. In certain jurisdictions, the carers' health-related quality of life, the impact on social care and productivity gains are explicitly not permitted in HTA evaluations, recommending the inclusion of direct healthcare costs only.

Significant inter-country variation in the time to reimbursement of cancer medicines from EMA approval has been observed [22,23]. Such delays are particularly disconcerting for potentially curative treatments indicated for advanced stages of cancer, where the cost of delays is counted in lives cut short.

For the CAR-Ts in DLBCL, some countries have been very fast to issue a positive reimbursement recommendation (e.g. Germany, UK) whereas others (e.g. Sweden, Denmark, Netherlands, Norway) have taken longer to reach a decision. Uncertainty is inevitable for such a new technology at the time of regulatory and HTA appraisal if timely access to potentially curative treatment is pursued. Such uncertainty should be identified and managed through access solutions such as 'payment by results' e.g. outcomes-based payment agreements, rather than serving as a barrier to formulating timely HTA recommendations.

Despite the significant uncertainty in clinical evidence and cost-effectiveness, patient access to date has been largely reflective of the unmet need, payers' willingness to access CAR-T therapies and the high level of perceived innovation [24]. HTA agencies have employed the same evaluation criteria to appraise CAR-Ts as they do for other medicines. However, the methods by which 'value' is determined and the weight assigned to the various components of the evidence package can differ between countries [25,26].

Whilst all HTA agencies, when evaluating the CAR-T therapies for DLBCL, have expressed a strong preference from CAR-T innovators for RCTs as opposed to non-comparative single arm studies, longer duration of follow-up, mature overall survival, progression free survival and HRQoL data; others have focused more on the robustness of the economic case, the post-progression survival data, the assessment of prognostic markers and predictors of response. There is a need for greater consistency between HTA agencies overall but more explicitly on how CAR-T therapies are evaluated and how 'uncertainty' is perceived and handled in submissions.

The aim of this paper is to describe the unique challenges to value assessment of CAR-T therapies in Europe, and put forward potential solutions to remedy these – maintaining the principles of respecting the need to accelerate broad patient access, address affordability concerns and reward innovation to maintain a sustainable life sciences industry. We explore whether the value assessment criteria employed by HTA agencies is appropriate for CAR-T therapies considering the

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characteristics of treatment and underpinning evidence.

CHALLENGES FACING THE HTA OF CAR-T THERAPIES USING EXISTING VALUE FRAMEWORKS & BARRIERS TO ADOPTION

In this part of the paper, we will explore some of the unique challenges as they relate to the regulatory approved CAR-T therapies in hematology [27–29] focusing on Kymriah® (tisagenlecleucel) and Yescarta® (axicabtagene ciloleucel).

Clinical value assessment for HTA

For the DLBCL indications submitted to NICE, the clinical evidence on Kymriah® (tisagenlecleucel) came from a Phase 2, open-label single arm study (JULIET) and a small observational study [30]. Results from 111 patients from the JULIET study and 14 patients from the study by Schuster *et al.* (2017) were presented (see Table 1). The NICE appraisal committee concluded the tisagenlecleucel is clinically effective, but immature survival data and the lack of trial data directly comparing tisagenlecleucel with salvage chemotherapy means the size of this benefit is difficult to establish. Results from JULIET showed that all patients having tisagenlecleucel as a CAR T cell therapy had an adverse event after treatment. Most patients had severe adverse events (over grade 3). Cytokine release syndrome is a common toxicity of cellular immunotherapy and it affected similar proportions of patients in both Schuster and JULIET. The clinical experts explained that cytokine release syndrome is often mild and can be managed by tocilizumab treatment, close observation and supportive care. The committee also noted that more patients in Schuster had neurotoxicity than in JULIET. Neurotoxicity may also need intensive care treatment and monitoring [31].

For axicabtagene ciloleucel the clinical evidence came from ZUMA 1, an ongoing, Phase 1/2, multicentre, open-label, single-arm study. The company presented results from the study using a modified intention-to-treat analysis (only patients enrolled in the study who had axicabtagene ciloleucel infusion were included). All patients having axicabtagene ciloleucel had an adverse event after treatment. Events over grade 3 happened in 95% of patients. In the ZUMA 1 study, CRS affected 93% of patients. However, severe cases (affecting 13% of patients in ZUMA 1) need intensive care treatment and may lead to hemodynamic instability and other organ toxicity. The committee concluded that axicabtagene ciloleucel was clinically effective but agreed that the lack of comparative data made the assessment of comparative effectiveness (and any cost-effectiveness analyses) more challenging (see Table 2) [32].

Economic value assessment

Alongside the clinical assessment, some HTA agencies will also request a health economic evaluation. In some cases, the preferred

TABLE 1

Clinical effectiveness results for Kymriah® (tisagenlecleucel) [31].

Outcome	JULIET (December 2017 data-cut)	Schuster *et al.* (2017)
Overall response rate	51.6% (41–62%)	50% (23–77%)
Complete response rate	39.8% (not reported)	43% (18–71%)
Median overall survival (95% CI)	11.7 months (6.6 months – not reached)	22.2 months (not reached)
Median progression-free survival (95% CI)	Results are confidential	3.2 months (0.9 months – not estimable)

TABLE 2

Clinical effectiveness results for Yescarta® (axicabtagene ciloleucel [32].

Outcome	
Overall response rate	82%
Complete response rate	40%
Median overall survival (95% CI)	Not reached
Median progression-free survival (95% CI)	5.8 months (3.3 – not reached)

approach is to perform a budget impact analysis focusing primarily on the costs of treatment. In other cases, cost-utility analysis (CUA) is employed which is where the longer-term costs AND consequences of treatment are estimated through extrapolation/modelling techniques. Cost-utility analysis is the technique most commonly employed by HTA agencies to look at cost-effectiveness. CUA derives a ratio or relationship between costs and health outcomes, where value is defined as the outcomes achieved relative to costs spent for one treatment (Treatment A) vs other(s) (Treatments B, C, D, etc.) and framed in terms of an incremental cost effectiveness ratio (ICER) [33].

Whilst costs are relatively straightforward to measure and report in CUAs, health outcomes are expressed in Quality-Adjusted Life Years gained (QALYs) to describe the health benefit of any technology, regardless of the disease it is being developed for. The ICER for Treatment A is thus the difference in costs divided by the difference in outcomes (expressed as QALYs) between Treatment A and Treatment B, the alternative). Cost–effectiveness thresholds provide an indication of health systems' willingness (not ability) to pay, have been static in England for example (i.e. do not change over time, despite inflation) and vary across different countries. An ICER falling under a given threshold for Treatment A vs B is deemed 'cost-effective'; however, an ICER for Treatment A that sits above a given threshold would be deemed 'not cost-effective' and thus Treatment A would not likely be recommended for reimbursement. Very few countries state an explicit threshold and a higher willingness to pay has been granted for rare and ultra-rare diseases.

With respect to economic evaluations, there are further methodological differences between countries in relation to the perspective adopted, the inclusion or not of indirect costs and choice of discount rates.

The limitations of economic modelling for innovative medicines are well documented because of uncertainties in estimating relative efficacy from non-comparative trials, identifying the most appropriate model structure to reflect the pattern and duration of response to treatment and the choice of extrapolation assumptions when long-term outcomes may be incomplete to predict quality adjusted survival and the most plausible costs and consequences associated with different health states [29,34–37].

A rapid review of the published and grey literature of HTA submissions was undertaken where economic modelling was employed to support HTA submissions for tisagenlecleucel and axicabtagene ciloleucel. Although the USA has no formal health technology assessment (HTA) body in place, CAR-T therapies have been evaluated by organizations such as the Institute for Clinical and Economic Review (ICER). ICER recently reviewed CAR-T cell therapies in an evidence report released on March 23, 2018 [3].

One ICER submission [38], 3 NICE HTA submissions [31,32,39] and 3 SMC HTA submissions [40–42] were identified. Out of the seven identified HTA and ICER submissions, two focused on pediatric and young adult patients (up to 25 years) [39,40], four concentrated on adult patients [31,32,40,42] and one focused on both populations [38]. All the pediatric submissions focused on relapsed/refractory B-cell acute lymphoblastic leukemia (ALL), and the

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adult submissions reported on diffuse large B-cell lymphoma (DLBCL). The submissions consisted of one from a US third-party payer perspective [38], three from the England and Wales National Health Service (NHS) and Personal Social Services (PSS) perspective [31,32,39] and three from the Scottish NHS perspective [40–42]. Six of the seven reported cost-utility analyses [31,32,40–42] and one was a cost–effectiveness study [38]. All of the HTA submissions used partitioned survival models with some also using a decision tree to handle considerations around pre-treatment with CAR-T therapy.

ICER used a two-part decision-analytic model, consisting of a short-term decision tree and long-term semi-Markov partitioned survival model [38]. The decision tree calculated the costs and consequences from treatment initiation to assessment of response. Its purpose was to stratify the cohort by which treatment they ended up receiving, because the model started at treatment initiation, however pre-treatment costs were included and allocated at the start of the decision tree. Furthermore, the decision tree allowed for allocation of upfront costs by treatment and the stratification of the cohort by response status, which becomes important when considering outcomes-based pricing. The long-term survival and outcomes derived from the long-term, partitioned-survival model were dependent on the treatment received in the short-term decision tree model and were simulated using parametric survival modeling from the direct extrapolation of PFS and OS curves for 5 years after therapy completion. Thus, the companies concerned used a partitioned survival model from assessment of response to 5 years after treatment completion, followed by a Markov model from 5 years until death.

All seven submissions used a lifetime time horizon within their economic models and had three health states: pre-progression, post-progression, and death. Comments from an HTA-agency appointed Evidence Review Group (ERG) relating to one of the submissions, flagged that the model had a long-time horizon relative to the available data on the intervention (axicabtagene ciloleucel), and thus there would be uncertainty associated with the extrapolations used [41]. Regarding another submission, the ERG commented that: the long-time horizon was driven by the extrapolation and 'cure' assumptions within the company's model, which the ERG considered to be subject to significant uncertainties [32].

As noted above, the QALY methodology (grounded on survival and quality of life data) poses some particular challenges for reliable HTA assessments of CAR-T therapies because of the uncertainties associated with accurately estimating (a) the likely survival of patients; (b) the HRQoL of patients; (c) the costs of any subsequent treatments received or avoided; and d) the broader impact (externality) of the treatment on patients, carers, family members and ability to fulfil paid/unpaid work when these have yet to be observed.

It is recommended that productivity gains and losses due to health care interventions are explicitly measured and valued in HTA assessments however QALYs do not capture well the effect of health improvement on productivity in the workplace or outside of it [20]. Furthermore, the QALY has been criticized for not incorporating individual or community preferences about the weight given to health gain for example, about disease severity, equity of access, unmet need, etc. [43], or preferences for potentially curative therapies.

Framing reimbursement decisions based on limited evidence that relies on statistical extrapolation of QALYs and costs that are unknown, does not necessarily reduce the uncertainty but rather exacerbates it. It is for this reason that Clay *et al.* [44] suggest that although standard economic evaluation approaches based on CUA are theoretically applicable to these types of therapies, they may in reality be of little use to decision makers and patients due to substantial uncertainty around the results.

Patient & carer value assessment

Evidence from patients and their involvement in HTA decision-making is growing in importance across Europe [45–49]. There are two issues here; first, the systematic engagement of patients/patient advocates in HTA processes and second, the generation of patient-relevance evidence to inform HTA submissions. Lee *et al.* evaluated the role of patient-reported outcome (PRO) data and patient testimonial evidence (e.g. patient advocacy) in reimbursement decisions in 10 countries and found substantial inter-country variability (from formal patient submissions/consultations and committee involvement [e.g. Scotland, England, Canada] to limited/unclear patient involvement [e.g. France, Japan]) [50].

As far as evidence is concerned, a recent study of 664 CAR-T trials found that the utilization of PROs to assess the impact on HRQoL and disease related symptoms to be well under the industry average with only 6.17% (41/664) of studies including a PRO measure [51]. Admittedly, there are some limitations in the validated health status/HRQoL instruments available to assess CAR-T therapies which likely do not capture the patient experience in an optimal manner. Standard generic utility measures (e.g. EQ-5D) may not be sufficiently sensitive to measure important changes in HRQoL. Even disease-specific patient-reported outcome measures such as the EORTC QLQ C30 may be unable to capture the unique characteristics of treatment because these questionnaires were constructed prior to the development of CAR-T therapies. Despite these challenges, it is important to capture insights from patients who have received the CAR-T therapy and their carers for the benefit of future patients and to ensure that this evidence plays a prominent role in regulatory and health technology appraisals [51].

Budget impact

Affordability is a combination of ability and willingness to pay – both of which will likely vary by country, jurisdiction and payer. It also depends on who is the payer e.g. the health system, insurer or patient. Garrison *et al.* [21] describe the challenges that health system payers or insurers face when covering the costs (of a CAR-T therapy) because the benefits of CAR-T therapies (i.e. potential for future cost savings) may not be realized within the short time frame of the annual budget cycle. Due to the highly specialized nature of treatment, some healthcare providers have chosen to restrict the delivery of CAR-T treatment to a small number of hospitals which in turn, limits how many patients have the potential to receive a CAR-T treatment [52].

Barriers facing the acceptance & implementation of innovative payment models

The use of the term 'innovative' payment models that seek to spread the one-off treatment cost according to pre-determined milestones, provokes skepticism amongst the payer community. Such models are generally thought to add administrative burden and complexity, with payers often expressing a preference for simple discounts or rebates. To successfully implement outcomes-based payment models in a given country, it is important to have an infrastructure in place to capture high quality clinically meaningful real-world data using reliable sources that are trusted by both payers and innovators, where the administrative burden is minimized wherever possible.

Adoption/diffusion of CAR-T therapies once approved

A recent study carried out by PwC Strategy on behalf Gilead Sciences based on 18 interviews with CAR-T experts and representatives from large statutory health insurance companies found only a proportion of CAR-T eligible patients are receiving CAR-T therapy in Germany [53].

Cited reasons for this include:

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- Different levels of knowledge about these innovative therapies;
- Lack of clarity about the definition of the patient profile;
- Nationwide heterogeneous standards and processes;
- Missing mechanisms for the management of the financial risk of the treating CAR-T centers; and
- Insufficient possibilities for scaling as well as systematic exchange.

More work is needed at the country-level in working collaboratively with multiple stakeholders to ensure that the appropriate measures are put in place to encourage wider adoption of innovation.

SOLUTIONS TO ADDRESS THE ACCESS CHALLENGES OF CAR-T THERAPIES

The ways in which innovators have attempted to overcome some of the access challenges has been to offer one of more of the following: a patient access scheme (i.e. a price discount), establishment of a registry to capture real-world evidence and/or a commitment to generate further evidence within a defined time period. In this section, we will explore some of the potential solutions that have been proposed in the grey and published literature, supplemented by the authors' own suggestions.

Clinical value assessment

Clinical outcome assessments should adopt a holistic perspective and incorporate all available evidence from as many stakeholders as possible. Assessments made at a single point in time should move towards iterative processes of continual assessment, as more evidence becomes available on the longer-term safety and effectiveness of CAR-T therapies that emerge due to the maturity of data from clinical trials and post-authorization studies mandated by the regulatory agencies.

It is important, in order to maintain the integrity of the HTA processes, that assessments of the clinically meaningful benefits of CAR-T therapies and the quality of evidence are conducted independently to price negotiations with separate and distinct processes. There should be greater acceptance by HTA agencies of evidence generated by non-traditional methods including adaptive designs and non-comparative/single arm trials where randomization is problematic i.e.:

1. When clinical equipoise has waned – equipoise is particularly important for the ethical conduct of randomized trial and can affect feasibility and;
2. When studying treatments for late-stage disease in patients who have exhausted all effective treatment options and no 'standard' of care exists.

It is also imperative that the HTA agencies and Regulatory agencies come to an aligned position on the acceptance of surrogate/intermediate endpoints for the accelerated approval of innovative cancer therapies to avoid scenarios where one endpoint is accepted by EMA but then later challenged (or not accepted) by the HTA agencies [54,55]. Greater acceptance of clinical trial data from single arm studies supported with data from real-world/observational studies or indirect treatment comparisons and/or inclusion of meta analyses from existing trials should be encouraged, as these data generate valuable insights into the comparative safety and efficacy of CAR-T therapies.

Economic value assessment

Economic evaluations of CAR-T therapies need to focus strongly on the best available

evidence. While selective use of extrapolation techniques to examine likely overall longer-term benefits may be beneficial and appropriate in some instances, an over-reliance on long-term extrapolation of outcomes for CAR-T therapies should be avoided. A broad perspective is also warranted where inclusion of productivity gains and losses due to health care interventions are factored in. As far as the use of economic models for cost–effectiveness is concerned, improvements to existing modelling frameworks are needed to provide a more clinically meaningful representation of the disease and how it responds to CAR-T therapies. Suffice to say that alternative approaches to relying on the use of QALYs as well as the requirement to meet arbitrarily determined willingness to pay thresholds are warranted, given the considerable uncertainty around the input values and the limited value the resultant estimates offer in informing HTA decisions.

Patient & carer value assessment

Patients should have the opportunity to actively participate in all steps of the HTA process (including reassessments should they occur) e.g. priority setting, scoping, submitting evidence, commenting on draft reports and attendance at HTA appraisal meetings).

Hunter *et al.* [49] lists 4 key areas to implement recommended working methods for the inclusion of patient input into HTA processes in general (which are generalizable to CAR-T therapies):

1. Identifying and prioritizing which technologies to assess;
2. Scoping (developing a framework for an individual HTA);
3. Assessing and developing recommendations/guidelines;
4. Reviewing and disseminating HTA outcomes.

The authors consider that data on patients' experience of receiving CAR-T therapies in the clinical trial setting will be informative to decision-makers and future patients. For this reason, it should be mandated by both EMA and HTA agencies that these data should be more routinely captured in clinical trials. Finally, all types of evidence should be considered from patients e.g. qualitative interviews, videos, diaries, questionnaires, surveys, etc. [14].

Budget impact

Conversations around the likely budget impact of introducing a CAR-T therapy need to start earlier between innovators and payers. The budget impact of covering CAR-T therapies should extend beyond annual planning cycles in order to reap the potential for cost savings that these treatments offer, not only within the health system but also within society. The timely establishment of diagnosis-related groups (DRGs) has also been cited as an enabler to funding CAR-T therapies in Germany [3]. It is important that in those countries that use DRGs as the basis by which to reimburse hospitals that CAR-T therapies have been factored into these in a timely manner.

Solutions that overcome barriers facing the acceptance & implementation of innovative payment models

Alternative payment and financing strategies for cell and gene therapies may be needed to manage short-term affordability, while fairly rewarding value and providing the necessary incentives to maintain investment in future innovative therapies [28]. There are many different strategies that have been employed to manage expenditure for other types of high cost treatments. CAR-T therapies are not interchangeable – they are personalized therapies that are differentiated through distinct manufacturing processes and exhibit different

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safety and efficacy profiles and outcomes. For this reason, financial agreements and tenders that focus on cost alone at the expense of outcomes, are inappropriate for CAR-T therapies and unlikely to help payers achieve 'value-based' outcomes for their patients.

Investment in electronic health records (EHR) systems and providing incentives to providers to capture high quality data would be a significant enabler in being able to track patient outcomes for outcomes-based reimbursement schemes for CAR-T. Outcomes-based schemes are "commercial arrangements where a treatment's price is linked to the outcomes achieved for patients receiving the treatment in real-world clinical practice. Treatments that perform as expected and deliver pre-agreed outcomes are reimbursed at a pre-agreed price, while medicines that do not deliver on these outcomes are reimbursed at a lower price or not at all" (Cole *et al.*, 2019) [56]. If medicines exceed expectations, then a higher reimbursed price may be warranted. Table 3 list different outcome-based payment scheme categories suggested by Cole *et al.*

Coverage with evidence development schemes or outcomes-based agreements rely on the ability of the manufacturer to track the outcomes of patients in the real-world setting. CAR-T therapies lend themselves well to outcomes-based agreements, since it is easy to identify patients in the first instance from the regulatory mandated post-authorization studies and the longer-term effectiveness of treatment is the main driver of uncertainty and these types of agreements ameliorate this (uncertainty) in the most part.

Table 4 outlines some of the outcomes-based agreements (based on publicly available sources) that have been successfully employed in some countries for the two approved CAR-T therapies [57] to enable patient access whilst at the same time addressing data uncertainty and managing financial risk.

Multi-stakeholder collaboration across Europe is critical to ensure alignment on registries used to capture data for the above regulatory studies and any additional data needed to support outcomes-based payment models for HTA agencies and payers. This will help achieve operational efficiencies reduce the administrative burden at the hospital level. What we need to avoid is a fragmented array of CAR-T datasets that differ in terms of how they define, capture and report outcomes and how they assess data quality and completeness; the latter will serve only to introduce barriers that prevent timely analyses of data to inform real-time studies of the safety, effectiveness and cost–effectiveness of CAR-T therapies in Europe.

TABLE 3

Outcome-based payment scheme categories and definitions.

Scheme category	Definition
Cost sharing arrangements	Price reduction for initial treatment cycles until it is clear whether a patient is responding to the medicine
Payment-by-results	Innovators reimburse the payer in full in instances where the patient does not respond to the treatment
Risk sharing	Innovators reimburse a proportion of the cost of the medicine for non-responders
Outcomes guarantees/ pay-for-performance	Innovators provides rebates, refunds or price adjustments if the medicine fails to meet pre-agreed outcome targets at the individual patient level
Coverage with evidence development	Access to a drug is initially provided on the condition that further population-level evidence is gathered. Based on this further evidence the payer then makes a decision whether to continue funding the treatment or not
Conditional treatment continuation	Payment for the continued use of a given drug is based on intermediate endpoints at the individual patient level

Adapted from Cole *et al.* [56].

TABLE 4

Select examples of outcomes-based payment schemes for CAR-T therapies.

Country	Product	Description of outcomes-based scheme	Source document
Sweden	Yescarta®	A managed-entry agreement was negotiated at the national level which covers a refund of the cost by the manufacturer to the counties	[58]
Belgium	Kymriah®	Follow-up data on the response to treatment and the condition of the patient has been requested to be collected at 6 months, 12 months, 18 months and 20 months after the infusion of Kymriah®	[59]
Spain	Kymriah®	To address the uncertainty around the long-term efficacy and safety of Kymriah® in both indications, the following long-term and RWE generation projects are planned: A patient registry will be created; participation will be mandatory for all centers that provide Kymriah® (post-authorization study CCTL019B2401) A long-term follow-up study of patients who received Kymriah (study CCT-L019A2205B) has been requested	[60]
Italy	Kymriah®	There is a managed entry agreement that uses a conditional payment method (payment for outcomes), where payments are made in three instalments: at infusion and at 6 and 12-months' follow-up for responders only	[61]
France	Kymriah®	The Transparency Commission (TC) requested follow-up data from the JULIET trial, and data from the PAES studies and ATU, the establishment of a common register for medicinal products to collect short- and long-term efficacy and safety data, and identify predictors of treatment response (data should be collected from all eligible patients for Kymriah® in France, and not concern only patients actually treated) and the collection of clinical data of patients eligible for treatment under the post-ATU scheme	[62]
England	Kymriah®	Further data collection on long-term survival, post-progression survival, and immunoglobulin usage are required for funding Kymriah® through the Cancer Drugs Fund	[63]
Germany	Kymriah®	An outcomes-based payment model has been secured for Kymriah® where Novartis shares the risks of this arrangement by agreeing to partially reimburse these costs if the patient dies of their illness within a set period of time	[64]

Adoption/diffusion of CAR-T therapies once approved

Authors of the CAR-T Zell-therapien in Deutschland report (2020) [53] suggest the following measures could be implemented in order to improve adoption of CAR-T therapies in routine clinical practice:

1. Clarification and creation of an innovation-friendly climate;
2. Adaptation of the qualification and financing process;
3. Scalability through centralization and creation of uniform standards;
4. Further development and application of innovative remuneration models;
5. Promotion of the exchange of practice experience (with CAR-T therapies).

CONCLUSIONS

The aim of this paper was to describe some of the challenges to value assessment of CAR-Ts in Europe and put forward potential solutions to remedy these; maintaining the principles of respecting the need to accelerate broad patient access, address affordability concerns and reward innovation to maintain a sustainable life sciences industry. We explored whether the value assessment criteria employed by HTA agencies is appropriate for CAR-T therapies, considering the unique characteristics of treatment and uncertainties in the evidence base and conclude that change is needed in this respect.

Uncertainty is inevitable if the goal of timely patient access to innovation is to be pursued. We advocate for a more systematic inclusion of evidence from patients and carers in the HTA decision-making process, a broader perspective of value to be adopted by

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HTA agencies that take into account productivity gains from both patient and carers, and investment in data infrastructures to enable outcomes-based payment models.

We also maintain that an early and continuous dialogue between innovators, HTA agencies and payers is needed prior to, during and post-launch. The focus on eliciting scientific advice from regulators and HTA Agencies on the most appropriate evidence package for speedy HTA approval and adoption is insufficient by itself to ensure timely access to patient and widespread adoption.

We have highlighted the limitations of cost-per-QALY value frameworks for CAR-T in capturing productivity gains and handling uncertainty and flag the important role that outcomes-based payment models play in enabling faster access through addressing uncertainties from an HTA perspective and payer perspective. In conclusion, multi-stakeholder collaboration across Europe is critical to ensure alignment on registries used to capture data for the regulatory mandated post-authorization study commitments and any additional data needed to support outcomes-based payment models for HTA agencies and payers.

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AFFILIATIONS

Clare L Hague
Author for correspondence
Honorary Lecturer & Academic Supervisor, Department of Health Sciences and Medicine, University of Lucerne, Switzerland
and
Therapy Area Market Access Leader, Haematology (EMEA), Health Economics, Market Access & Reimbursement (HEMAR), EMEA Region, Janssen Pharmaceuticals (a Johnson & Johnson Company)
chague@its.jnj.com

Martin J Price
Vice President, Health Economics, Market Access & Reimbursement (HEMAR), EMEA Region, Janssen Pharmaceuticals (a Johnson & Johnson Company)

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CELL & GENE THERAPY INSIGHTS

MARKET ACCESS: EVOLVING COMMERCIALIZATION TRENDS & STRATEGIES

SPOTLIGHT

INTERVIEW

HTA evolution in Canada: considerations for cell and gene therapy

SUZANNE MCGURN joined CADTH in July 2020 as its President and Chief Executive Officer. She brings to the role a deep understanding of the complex issues surrounding the management of pharmaceuticals, medical devices, and clinical interventions in Canadian health systems. Prior to joining CADTH, Ms McGurn's distinguished career spanned clinical practice, patient support, and senior roles in government. Within the Ontario Ministry of Health, she served as the Assistant Deputy Minister of the Drugs and Devices Division and the Executive Officer of the Ontario Public Drug Programs. She also led the implementation of the pan-Canadian Pharmaceutical Alliance and served as its first chair. Ms McGurn holds both a Bachelor of Nursing Sciences and a Master of Public Administration from Queen's University.

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Q With both your new role leading a national health technology assessment agency (CADTH) and your former role heading Canada's largest government payer (Ontario Drug Programs Branch) in mind, can you compare the HTA challenges assessing the clinical and cost–effectiveness of cell and gene therapies with the drug plan

mandate to ensure timely access to innovative treatments, but within a limited budget?

SG: The first point of comparison I would make is to state that the importance of these decisions is considerable from both HTA and payer perspectives.

Similarities include the need to define what constitutes a timely decision on such important products, careful consideration of the evidence, and the need for diligence that accompanies all significant investments in health while being thoughtful regarding the significant repercussions for patients and their families. Another area of commonality relates to implementation.

Implementing a drug, even an innovative drug, into a community (e.g. a person consuming the drug at home) is in many ways quite straightforward. But once you start offering therapies including pharmaceuticals that require hospital settings (in-patient or out-patient), perhaps involving a more invasive procedure, and potential for more significant before or after care, it adds a lot of complexity. Implementation considerations are an important area where CADTH has started to support the jurisdictions/funders, and it is one where HTA organizations and jurisdictions are finding common ground, as they strive to identify potential concerns at as early a stage as possible.

Implementation concerns can cover a wide range of considerations, from the location where the treatment is offered, to the nature of the care needed including in some cases the other drugs that may be used in combination with the treatment. It's important for HTA bodies, such as CADTH, to be aware of these and include them as considerations in the HTA review process. This enhances the ability of the HTA work to inform both decisions, and if funded, greater likelihood of implementation success.

There are also ethical considerations and again, from both HTA and payer points of view, thinking about individuals and how they have access is important. For example, an approved complex therapy that might only be offered in a small handful of sites throughout Canada may raise important implementation sensitivities in terms of who can and cannot benefit from it.

I think one of the strengths that CADTH brings to these discussions is its reputation and strength as a convenor, a facilitator, that can bring the right people together to work through thorny issues. We certainly saw this in Canada with the introduction of CAR T cell therapy – CADTH played a really important role there in assisting funders (including myself in a former job) to understand what this new type of treatment could look like in Canada, and how we might be successful in using the best available evidence in a new way to inform our decisions.

Q What's your perspective in your current role at CADTH on outcomes-based risk-sharing agreements as a means of funding cell and gene therapies?

SM: I would firstly say that HTA assessment is based on the value of the evidence and of the opportunity cost based upon what we know at a given moment in time. CADTH has adopted a lifecycle approach to looking at these products, so when we

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consider longer-term funding models, we also have to be cognizant of the fact that what we know about the product may change over that period.

When it comes to risk-sharing and outcomes-based agreements, there are many cost management options that payers have to consider. In Canada, the pCPA (pan-Canadian Pharmaceutical Alliance) has certainly played an important role in helping to identify which options are feasible, and looking at how they could be managed, in order to support jurisdictions in making their decisions.

At the macro level, I think the challenge isn't the individual agreement, it's the complexity of the pipeline as a whole and the multiple different agreements that will be likely be involved or required. It's perhaps not an ideal analogy, but when I was first learning about outcomes-based agreements, or agreements that might be amortized over many years, one of the patient stakeholder group representatives I spoke with shared with me that in a former job, they adopted the same sort of model for building bridges and roads. Every year, municipalities make choices about which roads or bridges will get built and which ones won't. For payers in the healthcare system, those are even more difficult discussions and in the cell and gene therapy space, where there may be new treatments coming through for very small patient populations, just one or two additional individual patients may have a substantial impact on decision-making, even in a model where the funding risk is spread over years.

So there's no simple answers here. I can say with confidence that the payers in Canada are already well versed in a variety of options, and regarding outcomes-based agreements specifically, my experience to date is that there have been some very effective examples entered into, both in Canada and internationally. CADTH and other HTA organizations around the world will need to play a key role in helping payers with the evidence and analysis over time, helping identify further economic and other considerations that may be important to payers.

Q CADTH has established a separate review process for cell and gene therapies that requires sponsors/manufacturers to complete an implementation plan. Can you describe CADTH's objectives in seeking this information, how it will be used by CADTH, and the implications for CADTH recommendations for reimbursement?

SM: CADTH has established this process to gather the necessary information to ensure that cell and gene therapy products get screened in the right place to provide the best possible type of assessment, and for efficiency.

Sponsors are asked to provide information that helps CADTH understand the complexity of their therapies. This helps to determine whether a product is more suited to what is deemed a standard drug review process at the

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present time, or the new process for a cell and gene therapy. It is envisaged that there will be circumstances where the first couple of approved new types of therapies in a given modality might go through the new process, but once the technology becomes more familiar, then subsequent products will move into the more standardized drug review process.

A new therapy that is complex to administer and brings with it lots of concerns around implementation would be anticipated to go through our cell and gene therapy process.

The information that is gathered during this process allows us to engage and prepare the jurisdictions early on for issues that could arise from the health technology assessment. This proactive engagement is aimed at ensuring the review does meet the jurisdictions' needs in helping inform their decisions. It also provides the opportunity for industry to benefit from these early-stage conversations. When I started in my new role, the CADTH team shared with me that the evolution of this new process for cell and gene therapy followed an internal review. What they came to realize was that for cell and gene therapies, they wanted to leverage the strength of the two existing programs. The program for cell and gene therapy will offer stakeholders the benefits of a firm performance target and well-established processes for conducting the review and issuing recommendations – all things that are familiar to the industry and to patient groups, and that have timelines that people already understand. However, it also introduces the sort of ethical and implementation considerations that have always been an important strength of CADTH's medical device process.

Gathering information at the front-end allows for the best possible assessment of these important products as they're being brought to Canada, and to make sure that we're giving the provincial jurisdictions the specific information they need to inform their decisions around how to fund and integrate these new technologies.

For reference, below is our review process for cell and gene therapies:

- Descriptor: https://cadth.ca/cart
- Process: https://www.cadth.ca/sites/default/files/cdr/process/CADTH_Gene_Process.pdf

Q When should manufacturers of cell and gene therapies first approach and inform CADTH and government payers about new cell and gene therapies? What information should manufacturers be prepared to share and what advice can be provided by CADTH and government payers pre-assessment?

SM: This is another area where CADTH has done a tremendous amount of work. We would say that manufacturers should come and discuss their new therapies with us as early as possible. Even before a product is in the regulatory approval process, there are opportunities for engagement that may help – to have discussions that alleviate uncertainty for the developer and potentially help them refine their plans for generating evidence. This is key because we have learned that once a submission is prepared and the work has been done, it's much harder to address any uncertainty questions that may arise.

For example, the scientific advice program is something that many sponsors have considered in other technology areas and it may be of value to cell and gene therapy developers. From the

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"...manufacturers should come and discuss their new therapies with us as early as possible. Even before a product is in the regulatory approval process, there are opportunities for engagement that may help – to have discussions that alleviate uncertainty for the developer and potentially help them refine their plans for generating evidence."

Canadian HTA perspective, the early stages of drug development provide a real opportunity for valuable dialogue, hence the fact CADTH supports parallel scientific advice both with Health Canada and with NICE in the UK.

Typically, if you were proceeding to consider the scientific advice process, applications should be filed prior to the finalization of your pivotal trial protocol so that the feedback can be incorporated if necessary. Developers are required to submit a briefing book outlining the clinical development plan together with some questions for the HTA and regulatory agencies involved.

One notable part of the scientific advice program process that CADTH goes through is outreach to patients with the condition of interest. This helps us to understand from the patients' perspective what's important with regard to the drug and the drug development program.

I would say you cannot reach out to us at too early a stage. There is no harm in doing so: if it transpires you are too early, we will let you know and indicate when is the right time to return. And this 'the earlier the better' mantra is particularly valid when you have a product that carries a high degree of uncertainty, as many novel cell and gene therapies do.

It's important to note that our scientific advice program has been paused during the COVID-19 pandemic so that we could redirect our scientific resources towards assisting with the generation of COVID-related evidence. However, we are currently looking at resuming the scientific advice program in late September, early October.

Q You mentioned a collaboration with NICE there – can you go deeper on CADTH's international activities, and describe any initiatives that may lead towards harmonization of HTA methods and procedures for cell and gene therapies?

SM: While there is no formal international collaboration underway that is specific to cell and gene therapy at this time, it is obviously a top-of-mind conversation between all major HTA bodies at the moment. And CADTH does have a very significant

presence and works hard to enhance collaboration within the global HTA community. We're looking at sharing information, at defining and implementing best practices, and at enhancing our ability to build capacity for HTA. We are also following any regulatory harmonization that may be occurring between different jurisdictions.

Looking to the future, the sort of work we're doing with NICE in offering parallel scientific advice is something that could help facilitate discussions around efficient evidence generation, and potentially meeting the needs of more than one market at the same time. I also think that our collective experience with COVID-19 has encouraged and allowed individuals to talk with each other in new ways. So I remain optimistic that the strength of the relationships that have been built over the last few years with other HTA agencies does provide a real opportunity for greater international collaboration, regardless of whether it's specific to cell and gene therapy or pharmaceuticals in general. I think there are a lot of things that we can do better together.

Q CADTH has a structured process for patient groups to contribute a perspective to the assessment of all technologies – are there any special or unique considerations for patient input into assessments of cell and gene therapies, and do you have any advice for manufacturers who may offer financial assistance/support to patient groups?

SM: The first thing I would say is that in my last role, working on the pharmaceutical file, I truly enjoyed and valued the input of the patient community. And having arrived at CADTH, I see more of the same important recognition of, and gratefulness to, the patient community for the work they do in preparing patient input for submissions. They make a difference, and they are an important part of a good assessment.

For CADTH, the patient input received allows the organization to gain insight into the lived experience of people with a particular condition. And as I've said, it becomes a really important part of the discussion as the team works through their assessment.

For cell and gene therapy specifically, patient input is invited and if patient groups have questions about the process, or how they may be able to contribute the patient submissions themselves, we welcome them to contact the patient engagement team at CADTH.

With regard to financial assistance, we simply ask all groups who are submitting patient input to clearly declare their funding as part of the conflict of interest disclosure. This request has been in place for some time for all patient groups, not simply submissions that relate to cell and gene therapy. Of course, while we are looking for the disclosure of that information, we are also looking for the valuable content of what that patient group provides to us.

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Q As you embark on this new role, can you share any personal goals for your work at CADTH?

SM: Firstly, I'm certainly very excited to join the team here. I obviously learned about CADTH as a payer in a jurisdiction, and I really recognized the importance of health technology assessments and their value in helping you think through your options as a payer. I always described CADTH's input as one of the most significant pieces of advice that you would get as a drug plan manager. I also sat on the CADTH board as a jurisdictional representative, so I had the opportunity to see the agency at an organizational level. I was always very impressed with the thoughtfulness of the organization and its responsiveness.

In terms of my personal goal in coming to CADTH, I believe there are opportunities for the important evidence work that CADTH is so well known for to have greater impact and influence. Not just with funders, but on healthcare systems as a whole – on decision-makers within hospitals and other organizations, and on frontline clinicians.

I think this greater impact will come from us continuing to focus on how we can effectively communicate our evidence findings in a way that's consumable to the various audiences that are interested in, or rely upon, the work that CADTH does. Whenever there's discussion around the funding or non-funding of a drug, I want CADTH to be known as a trusted place that people will go to easily find information that helps them understand the evidence that has influenced a given funding decision, and the dialogue that may be going on around it in the public realm at that time. I'd like it to be a source of truth.

The current COVID-19 environment has really raised awareness of how important it is to have accurate information and evidence to inform healthcare decisions in as timely a way as possible, and to communicate clearly to people to help them understand why they should do or not do something. I want to be part to creating and effectively conveying evidence-based products that help people understand the available evidence and make informed choices about their own health, about the health system they work in, or as jurisdictions, about the choices they have to make as payers.

That latter piece of taking evidence to the next level, of building on the strength of CADTH, is key. I know for a fact that many jurisdictions rely on CADTH, for their drug programs and in other areas, I believe strongly that there's more that we can do to make HTA a more understandable process for people, to communicate the value and impact of the really important work that's done by the staff here so it can be utilized to the fullest. They are a bright, brilliant team, with so much to offer the health system.

AFFILIATION

Suzanne McGurn
President and Chief Executive Officer, Canadian Agency for Drugs and Technologies in Health

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CELL & GENE THERAPY INSIGHTS

MARKET ACCESS: EVOLVING COMMERCIALIZATION TRENDS & STRATEGIES

SPOTLIGHT

COMMENTARY

Joint collaborations and future perspectives for gene therapies

Monique Dabbous, Eve Hanna, Boris Borislav, Claude Dussart & Mondher Toumi

High cost innovative medicines increasingly seeking market access and reaching the market are further challenging national healthcare systems already dealing with finite, constrained budgets and resources. Since 2012, European countries have begun to establish joint collaborations to conduct information sharing, horizon scanning, joint assessments, joint negotiations, and joint procurements in healthcare. More than 30 European countries have partnered together in 13 joint collaborations, 11 targeting innovative medicines, 1 targeting biosimilars, and 1 targeting vaccines. The aim of these joint collaborations is to increase bargaining and purchasing power while ensuring patient access and maintaining sustainable healthcare systems. As of today, only 2 joint collaborations, BeNeLuxA and FINOSE, have published the outcomes of their joint activities - joint assessments of innovative gene therapies. While such joint collaborations are still young, an examination of their establishment and outcomes may be insightful as to their implications for market access of gene therapies, healthcare systems, and future perspectives.

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INTRODUCTION

In the European Union (EU), the central regulatory body, the European Medicines Agency (EMA), established in 1995, pools together participating member states' regulatory procedural efforts into one process resulting in a centralized marketing authorization granted by the European Commission valid in all EU

member states. This centralized route aims to improve the quality of market authorization and products entering the EU as well as to reduce costs, conserve resources and avoid delays, otherwise commonly incurred via individual member state regulatory appraisals and processes [1]. The single-entry point via the EMA into the EU market, however, does not automatically translate to direct and successful market access. The single European market has forced health technology developers to adopt international pricing strategies and to shift away from previously price-differentiated strategies due to issues such as parallel trade within the market, compounded by the effects of international referencing pricing [2,3]. At the same time, individual member states still subscribe to their individual, traditional health technology assessment (HTA) bodies and frameworks to appreciate and valuate health products in order to ensure market access and, ultimately, patient access. HTA bodies vary greatly depending on their frameworks and valuation criteria for pricing and reimbursement. However, before a medicine is made available to patients, decisions about pricing and reimbursement take place at the national and regional level in the context of the national health system of each country. These tailored market access strategies require large resources, both financial and capital, and may result in the delay of access in some countries.

Innovative therapies, such as gene therapies, require even further resources and unique consideration when compared to traditional pharmaceuticals. Gene therapies are characterized by their one-time treatment targeted at addressing disease causation. By targeting disease causation, gene therapy developers are able to make the claim that their health technologies are able to provide long-term, even lifelong benefits, if not cure patients. However, due to their inherent nature, prices associated with such treatments are extremely high and there remain uncertainties surrounding their benefits, which require a much longer timeline than traditional pharmaceuticals to be observed. Traditional frameworks applied by health authorities are struggling to quickly adapt procedures relating to the valuation, appraisal, pricing, and negotiation of such unique therapies.

In order for national healthcare authorities to increase their purchasing power while making efficient, effective, and strategic decisions related to pricing and reimbursement of such new, innovative products as gene therapies that are presenting with high price tags and limited evidence, joint collaborations have been established. This increasing European trend can be observed with joint, cross-country collaborations pooling resources together in order to conduct joint HTAs, joint negotiations, and joint procurement as well as to collectively engage in horizon scanning and the exchange of information for innovative medicines, including gene therapies. The first of these efforts was the Baltic Partnership Agreement [4] established in May of 2012 between Estonia, Latvia, and Lithuania for the joint procurement of vaccines and the most recent collaboration is the Norwegian-Danish Initiative established in September of 2018 between Norway and Denmark for the joint procurement of medicines [5]. Thirteen joint collaborations have been established within the last 8 years, with 11 dedicated to addressing the challenges of innovative therapies, including gene therapies.

Most interestingly, a cross-collaboration for HTA, FINOSE [6], has recently jointly assessed Zynteglo® [7], an orphan designated drug for the treatment of a genetic blood disorder known as beta thalassaemia. With an increasing number of these initiatives and innovative health technologies (especially gene therapies) in the pipeline, seeking market access, and reaching the market, an analysis and closer look at the accomplishments and shortcomings of such joint collaborations thus far may provide insight as to the future aims and future projects in assessing innovative health technologies, including gene therapies. As a recent, evolving area in healthcare, this manuscript details the inception and evolution of joint collaborations, their application to innovative health technologies, and provides

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insight into potential future perspectives for their role. Although some joint collaborations address specific pharmaceutical products, such as biosimilars and vaccines, the majority of joint collaborations have been established to address the challenges associated with innovative medicines [2], therefore, the scope of this manuscript is restricted to the consideration of joint collaborations targeting innovative health technologies.

JOINT COLLABORATIONS

What are joint collaborations?

Despite their recent inception, with the first joint collaboration established in 2012, these initiatives manifest in many forms. As of today, joint collaborations have no single, standardized definition nor term that is widely accepted. Joint collaborations may be bilateral or multilateral and may be dedicated to conducting a single activity or may be engaged in several activities facilitating market access for new health technologies, especially innovative medicines, including gene therapies. Common activities conducted by such initiatives include joint assessment, joint procurement, joint price negotiations, horizon scanning, and information sharing. These cross-collaboration projects ultimately seek more efficient ways to increase the purchasing power of participating members and to obtain sustainable prices, while facilitating secured market access in the face of an increasing number of innovative therapies seeking to enter the market [2]. Participating member countries recognize the importance in understanding and addressing the imbalances and challenges in the current healthcare processes and systems and believe that joint collaborations will allow them to address these as they aim to drive down the costs of highly expensive, innovative medicines, such as gene therapies, while increasing access to these products.

Joint assessment, as defined by the World Health Organization (WHO)'s International Health Partnership + Related Initiatives, is "a shared approach to assessing the strengths and weaknesses of a national strategy, which is accepted by multiple stakeholders, and can be used as the basis for technical and financial support [8]." The European Network for Health Technology Assessment (EUnetHTA) defines joint assessments as "HTAs jointly performed by 4 or more EUnetHTA partners in different European countries, EUnetHTA processes, guidelines, and the HTA Core Model are used for the production of assessments that are subject to extensive review procedures in order to ensure high quality. [Joint assessments] are centrally coordinated by the WP4 Co-leads and comprise a broad stakeholder involvement, including the use of a EUnetHTA submission file in addition to a scoping (e)meeting with industry [9]." It is interesting to note that joint collaborations engaged in joint assessments detailed in the following sections of this manuscript do not fall under EUnetHTA's definition of joint assessments as several collaborations consist of less than 4 participating member countries.

EUnetHTA, the EU-established European network for HTA bodies, was founded in the support of efficient HTAs across Europe [10]. EUnetHTA itself does conduct joint assessments – however, it primarily provides a platform where European HTA agencies can exchange information on developing HTAs and their methodologies. EUnetHTA, therefore, is an important step towards an all-encompassing joint HTA for the EU, but unlike the EMA for regulation and marketing authorization, EUnetHTA's decisions and outcomes are not decision-making processes themselves. It may be argued that there is redundancy with the co-existence of EUnetHTA and joint collaborations engaging in joint assessments. However, it is important to observe once again that while EUnetHTA's assessments should inform decision-making, they are not decision-making processes themselves [11]. Technically, and dependent on the joint collaboration body, participating members may not be obliged to adopt the outcomes. Joint assessment, essentially, may apply one assessment framework or the conducting of an agreed upon assessment on

behalf of participating member countries, previously established and approved, with its outcomes to be potentially adopted by and applicable to all member countries of the joint collaboration.

Other joint collaborations also engage in joint procurement. According to the European Commission Green Public Procurement Toolkit, joint procurement occurs when two or more procurement processes of the contracted parties, or participating countries of the joint collaboration, are combined into one process conducted on behalf of all participants with the distinct characteristic that only one tender is published on behalf of them all [12]. Although this definition was published within the GPP for environmental efforts, the definition is applicable to pharmaceuticals. In fact, in 2010 following the outbreak of the H1N1 pandemic influenza, the European Council appealed for an agreement adopting this definition and for the joint procurement of vaccines, which ultimately precipitated in the formation of the joint procurement of medical countermeasures with its provisions outlined in Article 5 of Decision 1082/2013/EU [13]. Ultimately, Directive 2014/24/EU addresses public procurement and clearly allows for joint procurement and for different member states to engage collectively in contracting [2].

Joint negotiations, horizon scanning, and information sharing are also important activities joint collaborations may engage in. Joint negotiations occur when two or more contracted parties negotiate together as one negotiating entity with the health technology supplier to secure better prices and access for therapies. One of the parties may negotiate on behalf of all involved in the joint collaboration, or a negotiating committee may be established representing the participating countries. In order to effectively conduct such joint negotiations, joint collaborations may also, in parallel, engage in horizon scanning and information sharing to better anticipate and prepare for important products and developments in their healthcare systems. This is in order to better position themselves in negotiation settings, and to create and maintain sustainable healthcare systems. Horizon scanning is key when anticipating the pipeline of innovative health technologies, such as gene therapies, which are costly yet provide tremendous benefits for patients in need. Conducting horizon scanning while information sharing (including but not limited to information regarding prior experience, methodologies, expertise, and skills) can facilitate more effective and efficient joint collaborations.

Countries' engagement in joint collaborations may vary from simple information sharing to horizon scanning ultimately leading to joint assessments and joint procurement, which require more commitment and participation. Espin *et al.* put forward a joint collaboration model detailing the levels of collaboration in procurement as ranging from informed buying to coordinated informed buying, group contracting, and central contracting and purchasing [2]. Espin *et al.* further elaborate on defining characteristics of joint collaborations, such as the type of ownership, financing mechanism, procurement activities, timeframe, range of products or services involved, and purchasing mechanism [2]. Joint collaborations, although young, can be found in a plethora of forms engaging in various degrees of activities.

As of today, there are currently 13 formal joint collaborations established in Europe with 39 European countries participating (Table 1) [8]. Of the 13 identified established joint collaborations, 11 are dedicated to innovative and expensive medicines, 1 is dedicated to vaccines, and 1 is dedicated to generics and biosimilars.

Why are countries engaging in joint collaborations?

Challenges, such as constrained and finite healthcare budgets, are further exacerbated by innovative health products targeting rare diseases with small populations presenting with limited evidence, with mounting concern

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TABLE 1

Joint collaborations.

Joint collaboration	Date established	Member countries	Scope	Activities	Major assessments
Baltic Partnership	May 2012	Estonia, Latvia and Lithuania	Vaccines	Joint procurement	Vaccines
BeNeLuxA-I	April 2015	Belgium, Netherlands, Luxembourg, Austria, Ireland and France (observer status)	Medicines, innovative and expensive therapies	Joint HTA/REA, joint price negotiations, horizon scanning, information sharing	Lumacaftor/ivacaftor (Orkambi®) for cystic fibrosis (failed) Nusinersen (Spinraza®) (positive) Obeticholeic acid (Ocaliva®) for of primary biliary cholangitis (negative)
Romanian+Bulgarian IFA	June 2015	Romania and Bulgaria	Medicines, innovative and expensive therapies	Joint HTA/REA, joint price negotiation, joint procurement	
Nordic Collaboration	June 2015	Denmark, Finland, Iceland, Norway and Sweden	Medicines, innovative and expensive therapies	Joint HTA/REA, information sharing	Gentamicin is mentioned as pilot
Nordic Pharmaceuticals Forum (NLF)	2015	Denmark, Iceland, Norway and Sweden	Medicines, innovative and expensive therapies	Joint procurement, horizon scanning	To focus on security of supply: ampicilline, benzylpenicilline, piperacillin/ tazobactam, calciumfolinate, methotrexate, ondansetrone, furosemide, meropenem, gentamicin, anagrelide, paracetamol (IV)
Sofia Declaration	February 2016	Romania, Bulgaria, Croatia, Estonia, Hungary, Latvia, Macedonia, Serbia, Slovakia and Slovenia	Medicines, innovative and expensive therapies	Information sharing	N/A
Visegrad+ Collaboration	March 2017	Poland, Slovakia, Hungary, Lithuania and Czech Republic (observer status)	Medicines, innovative and expensive therapies	Joint price negotiations, information sharing	Expected pilot project to start within HIV/hepatitis C therapeutic area
Southern European+	May 2017	Greece, Cyprus, Italy, Malta, Portugal and Spain	Medicines, innovative and expensive therapies	Joint price negotiation, joint procurement, horizon scanning, and information sharing	N/A
Valletta Declaration	May 2017	Italy, Cyprus, Greece, Malta, Portugal, Spain, Ireland, Romania, Croatia and Slovenia	Medicines, innovative and expensive therapies	Joint price negotiation, joint procurement, horizon scanning, and information sharing	Ocrelizumab (Ocrevus®) indicated for the treatment of multiple sclerosis. Nusinersen (Spinraza®)
Iberia Partnership	April 2017	Portugal and Spain	Generics and biosimilars	Joint HTA/REA, joint price negotiation, information sharing	Flu vaccine
France – Portugal Declaration of Intent	December 2017	France and Portugal	N/A	Joint price negotiation, information sharing	N/A
FINOSE initiative	March 2018	Sweden, Finland and Norway	Medicines, innovative and expensive therapies	Joint HTA/REA, information sharing	Pilot on 'simple' products to be completed Summer 2020, set to assess onasemnogene abeparvovec (Zolgensma®)
Norwegian–Danish Initiative	September 2018	Norway and Denmark	Medicines, innovative and expensive therapies	Joint price negotiations, joint procurement	Nusinersen (Spinraza®)

stemming from widespread anticipation of an increasing number of highly costly gene therapies reaching market. Current frameworks and regulations applied to the valuation, appraisal, pricing, and reimbursement of innovative therapies, including gene therapies, despite adapting dedicated pathways for such therapies, seem to continue to face challenges due to such health technology's inherent characteristics. In a recent publication by Qiu *et al.*, a review and international comparison of various regulatory policies of regenerative medicines (RMs), including gene therapies, has revealed that out of the EU and the 9 countries investigated (USA, Japan, South Korea, Australia, Canada, New Zealand, Singapore, China, and India) only the EU, USA, Japan, South Korea, and Australia had specific legislation already in place for the regulation and consideration of RMs [14]. While it is encouraging that the EU and these several countries have adopted specific pathways for the regulation of such therapies as gene therapies in accordance with their unique characteristics, the authors note that harmonization and international standardization of such regulations would alleviate administrative burdens on innovative health technology developers as well as health authorities, and would facilitate patient access more quickly [14]. Another review conducted by Qiu *et al.*, on advanced therapy medicinal products (ATMPs), which includes gene therapies, revealed that addressing uncertainties surrounding the value, pricing, and reimbursement of such therapies remains challenging for national healthcare authorities in Europe and for healthcare authorities in the USA [15]. Qiu *et al.*'s work further emphasizes discrepancies between HTAs and the weighting they assign to attributes assessed. However, it is interesting to note that the review reports that the EU countries considered and the USA all requested in one form or another further reviews upon the collection of additional data (due to lack of evidence at the time of assessment and uncertainties surrounding the proclaimed long-term benefits of such therapies) [15]. All the EU countries in the review and the US facilitated prompt market access by adapting pathways specific to gene therapies and ATMPs in general without impairing healthcare affordability [15].

Although discrepancies can be seen on the regulatory and HTA levels in relation to RMs or ATMPs, health authorities, innovative health technology developers, and patients all seek to facilitate their market access. However, this proves difficult and may lead to unsuccessful or delayed market access due to variations in institutions and their respective frameworks. If such efforts were pooled or standardized, it could not only alleviate the administrative burden on both developers and health authorities, but could also help improve health authorities positioning in negotiation and procuring such costly therapies ,and improve the quality of health technologies entering their markets.

Further challenges arise when considering smaller countries with small purchasing power and/or even smaller target patient populations, which may lead to a health technology developer pulling their product from such a market if the actual uptake is not as anticipated. This could certainly be the case with a gene therapy targeting a rare disease with a very small number of patients in certain countries. By pooling together several countries, a larger population, market size, and volume can be presented during negotiations with health technology developers [2]. Larger countries also benefit by pooling their resources and creating a larger market when conducting joint collaboration activities targeting innovative therapies and such small populations. Participating members in joint collaborations are able to exchange information, experience, and skills as well as potentially improve the quality of products seeking and entering market access.

Through such collaborations, these countries not only benefit by obtaining more sustainable prices through economies of scale, but are also able to enjoy reduced costs associate with transactions and can redirect resources previously associated with individual national processes. Participating countries

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enjoy the comfort of secured access to these therapies as do health technology developers, who may also benefit from one streamlined market access strategy and process for similar reasons, such as reduction in costs and invested resources. Joint collaborations further hope to increase transparency around pricing and strengthen information sharing – particularly information and knowledge on the efficacy, safety, and quality of the innovative technologies seeking market access.

The first joint collaboration established, the Baltic Partnership Agreement, was initiated as a response to the H1N1 Swine Flu pandemic. Latvia, Lithuania, and Estonia all have the same immunization schedule and effectively established a collaboration to procure vaccines multilaterally [4]. Although the first procurement project fell through when no tender was submitted, the establishment of the collaboration is significant in that vaccines procured through the Baltic Partnership Agreement can be lent and transferred between the participating member countries, ensuring optimization of market access and avoiding potential shortages of vaccines as was experienced during the H1N1 pandemic [2]. Such an establishment sought to secure access to a critical health technology while leveraging their position to create a larger market when engaging with health technology suppliers. Since 2012 and the Baltic Partnership Agreement, joint collaborations have continued to emerge to address challenges which may become crippling for the future of sustainable healthcare.

What does it take to establish & conduct joint collaborations?

Joint collaborations, ranging from simple information sharing entities to full bodies conducting joint assessments, negotiations, and procurement, all require dedicated cooperation in order to run efficiently. The complexity of establishing and executing such agreements and activities renders it necessary for solid and transparent foundations to be laid out. Such collaborations require clear roles and responsibilities to be outlined and trust to be built between participating countries. Governance and roles must be detailed with open communication to ensure transparency, accountability, and fairness. A critical component, especially in joint procurement activities, will be the financial management aspect. Tracking the financial responsibilities, including the funding and payments, will require detailed and intimate outlining and monitoring to ensure funds are available and purchases and payments are made in a timely manner. If agreements or deals are conducted via the joint collaboration, timelines must be clear and partnerships must be stable enough to maintain continuity through long contracting, and to ensure secured access to resources and, ultimately, the health technologies they seek to introduce to the market.

However, major obstacles remain when establishing joint collaborations. Governance remains an issue when deciding if one of the participating countries should govern, or a committee should be established representing all participants and ensuring everyone's responsibilities and accountability is upheld. As mentioned earlier, although these joint collaborations are unique in that they consider two or more countries in the processes, at the end of the conducted activities there are no obligations required for the participating countries to adopt the outcomes of the reports unless legally bound by a joint agreement: for example, for procurement where specific participating parties may be contractually obligated to execute specific financial responsibilities. Such contractual agreements and activities require well-defined and robust legal frameworks and some joint collaborations may even require extensive legislative implementation and adaptations to engage in these joint collaborations, which further requires time and legal investment. Furthermore, these joint collaborations have only just been established within the last 8 years with limited real-life experience and many, as detailed in the next section, are so burdened with the establishment of the actual joint

collaboration that they have yet to conduct pilot projects or any activities. Due to their recent inception, there is a lack of clarity regarding the degree to which they may influence the market, such as the risk in distorting the supply, purchase, as well as trade, and regarding the impact their activities may have on the healthcare system, even horizon scanning. Lastly, larger countries in the EU have increasingly voiced their interest in establishing or becoming participating members of joint collaborations, which although it may initially seem appealing for greater bargaining power, may result in these larger countries overshadowing smaller ones.

JOINT COLLABORATION BODIES

BeNeLuxA

In April 2015, BeNeLuxA was established between Belgium and Netherlands with the announcement to engage in joint price negotiations of orphan drugs [16]. Luxembourg and Austria later joined the joint collaboration in September 2015 and June 2016, respectively. In 2018, Ireland expressed its interest to also join the collaboration [17]. The collaboration together covers 42 million citizens and represents 8% of the EU's population. BeNeLuxA was one of the first, prominent European experiences in joint collaborations. Following the launch and difficult negotiations of the highly priced sofosbuvir (Sovaldi®) for the treatment of Hepatitis C, BeNeLuxA was established to combat such high prices and in the anticipation of the increasing arrival of highly costly gene therapies among other innovative therapies. It is dedicated to enhancing patient access to medicines with a focus on high-cost, orphan products. The BeNeLuxA initiative aims for sustainable access to, and appropriate use of, medicines in the participating countries. The joint collaboration strives to increase patients' access to high quality and affordable treatments [18]. The joint collaboration's activities consist of information sharing, optimization of patient access, focus on public policy issues development, harmonized evaluation methods and joint assessment, and increased bargaining power. The joint collaboration has also engaged in building an international horizon scanning initiative with BeNeLuxA partners and other interested countries as well. Information sharing has also been an ongoing activity with the joint collaboration holding meetings on patient registries in November of 2017 with Hungary and the UK. Interestingly, those discussions did not capture the interest of health technology suppliers who may seek to set up registries in the future.

Its pilot joint HTA and pricing negotiations with the industry began in 2017. BeNeLuxA assessed the combination of lumacaftor/ivacaftor (Orkambi®) for the treatment of cystic fibrosis. The combination was assessed by 2 out of the 4 member countries, with the leading countries being Belgium and Netherlands. The assessment ultimately ended with the absence of consensus on the product price, the product was not considered cost-effective, and the price was overestimated by 80% [19]. The second assessment and negotiation undergone by BeNeLuxA targeted the highly priced nusinersen (Spinraza®) for Spinal Muscular Atrophy (SMA) [20]. Nusinersen, assessed by the Netherlands and Belgium, received a positive reimbursement decision and the joint collaboration was able to reach an agreement on the pricing and reimbursement of the product successfully with only one negotiation process conducted instead of two separate ones. The Belgian Ministry of Health took the lead and weighed in on the process heavily to ensure its securement and demonstrate that joint procurement was feasible [19,21]. However, in 2018, BeNeLuxA did give another negative decision for the orphan drug obeticholeic acid (Ocaliva®) for the treatment of primary biliary cholangitis following a joint HTA assessment [22].

Most Recently, on May 19th, 2020, BeNeLuxA announced it will engage in a joint

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assessment for onasemnogene abeparvovec (Zolgensma®) [23]. The joint collaboration body is also in talks with other countries such as Italy, Romania, the Czech Republic, and Switzerland, with exploratory talks launched with France, and potential non-EU entities considered for partnership (European Commission, EUnetHTA, WHO, and the Organization for Economic Cooperation and Development [OECD]). To ensure the joint collaboration is effective in improving patient access to innovative treatment options, the process applied for the successful assessment and price negotiations should be implemented in future joint collaborations to ensure that the process can be replicated and yield valid outcomes [19].

Romanian-Bulgarian IFA

The Romanian-Bulgarian International Framework Agreement (IFA) was established on November 9th, 2016 to conduct joint HRA, joint price negotiations, and joint procurement between Romania and Bulgaria [24]. The agreement was ultimately established to ensure that patients in both Romania and Bulgaria have access to medicines, especially during instances where they have lacking pharmaceutical resources. The concept was initially presented at the Work Meeting of the Health Ministers from Central and Eastern European on the growing challenges in the field of medicine policy, on June 2nd and 3rd of 2016 in Sofia, after which other European countries besides Romania and Bulgaria, interested in joining signed a joint statement of intent. These other countries included were Croatia, Estonia, Latvia, Macedonia, Serbia, Slovenia, Hungary, with Poland as an observer. The Romanian-Bulgarian IFA has yet to conduct activities due to the changing political climate and the required ratification of two parliaments as an international treaty. Legislation in both Romania and Bulgaria will also need to be adapted for the pricing and reimbursement of medicines considered in their joint collaboration.

Nordic Collaboration

Denmark, Finland, Iceland, Norway, and Sweden are members of the Nordic Collaboration, which already addresses improvement and coordination of business and energy policy [25]. In June of 2015, it was determined that medicines and addressing their increasing costs would be added to the target of this joint collaboration and was addressed as the extended Nordic pharmaceutical cooperation for greater cost–effectiveness and safety [26]. It was formally adapted in November 2016. A closer cooperation has been started on pharmaceutical pricing policies and procurement [27]. Further development has led toward a provision of mandatory framework for exchange of information and experience on price and procurement of pharmaceuticals, as of March 2017. In 2017, the joint collaboration gained momentum, firstly with a pilot for joint purchasing of medicines (between Norway and Denmark), and then a Memorandum of Understanding (MoU) being signed by Finland, Norway, and Sweden in order to strengthen joint collaboration on HTA. Denmark, Norway, and Iceland announced a tender for spring 2018 with Sweden and Finland unlikely to participate. Gentamicin has been mentioned as a pilot for the joint collaboration's consideration. However, legal framework has yet to be established and final criteria to be identified.

Nordic Pharmaceuticals Forum (NLF)

Another Nordic joint collaboration, the Nordic Pharmaceuticals Forum (NLF), consisting of Denmark, Iceland, Norway, and Sweden, was established by Amgros, the Danish regional pharmaceutical procurement service in 2015 [28]. The NLF was founded to explore and develop joint tendering for pharmaceuticals and collaborations on horizon scanning. Its focus is targeted to four areas: horizon scanning, security of supply, new expensive pharmaceuticals, and manufacturers [29]. The objective

of its pilot project was to gain experience in completing joint tendering procedures and explore whether joint efforts can influence the pharmaceutical market, particularly in the acquisition of cheaper prices and more secure supply [30]. In September of 2018, an agreement of political intent on increased cooperation for joint tendering procedures and negotiations was signed between Norway and Denmark [29]. To date, the Joint Collaboration has conducted several important meetings and has been engaging in critical activities to firstly identify drivers and obstacles in their participating country members, legal options, and proposition of appropriate pharmaceuticals.

Sofia Declaration

The Sofia Declaration was founded with the following participating countries: Romania and Bulgaria as the leading countries and Croatia, Estonia, Hungary, Latvia, FYR Macedonia, Serbia, Slovakia, and Slovenia. The announcement of this cooperation came in May of 2015 and the declaration was finalized and signed by all country members in June of 2016 [2,31]. The ultimate goals of the Sofia Declaration are to increase their bargaining power as well as to engage in joint tendering of medicines. The joint collaboration is aiming to secure patient access to expensive, innovative medicines whilst maintaining a sustainable healthcare system [31]. As of today, the Sofia Declaration has not produced any joint tenders.

Visegrad+ Collaboration

Poland, Slovakia, Hungary, Lithuania and Czech Republic (observer status) began the Visegrad+ Collaboration in March of 2017 and the Memorandum of Understanding was signed in Warsaw within the context of high-priced medicines [32]. (Slovenia had considered joining – however, this country opted to join the Valletta Declaration instead, which is described later). The Visegrad+ Collaboration was established with the aim to develop procedures and guidelines for negotiations in order to secure fairer prices for high-priced medicines, including innovative and orphan drugs, and to engage in information sharing [32]. The joint collaboration founded a Coordination Committee, charged with the responsibility for outlining and detailing the specific procedures and guidelines for negotiations as well as to organize negotiations. In November of 2017, all the participating countries of this joint collaboration, with the exception of Lithuania, signed and committed to cooperating on long-term medicines subsidies as well as in the production and acquisition of vaccines in order to achieve more affordable prices and ensure supply security. Having no clear structure and a heterogeneous group of country members in terms of size and populations, this joint collaboration has yet to produce any outcomes or conduct activities. However, as of November 2019, interest and enthusiasm for joint price negotiations was reiterated by the "V4," also known as Poland, Slovakia, Hungary, and the Czech Republic [33].

Southern European+

In June of 2016, Greece, Bulgaria, Spain, Cyprus, Malta, Italy, and Portugal expressed the establishment of a Southern European+ joint collaboration targeting joint assessment with information sharing on clinical data and databases. The joint collaboration set out to establish a platform where the participating countries could further share expertise and experience in negotiations, pricing, and reimbursement in order to ultimately develop a transparent and effective collaboration. The Southern European+ joint collaboration aims to target innovative medicines as its main scope.

Valletta Declaration

The Valletta Declaration was signed on March 21st, 2017 in Valletta, with Italy,

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Cyprus, Greece, Malta, Portugal, Spain, Ireland, Romania, Croatia, and Slovenia as the signees, and Estonia as an observing member [34]. Together, these countries represent 32% of the EU's population with 160 million citizens all together [35]. The declaration defines and establishes a joint collaboration aimed to improve patients' access to innovative medicines, while maintaining a sustainable healthcare system. Its activities include joint price negotiation, joint procurement, horizon scanning, and information sharing. The joint collaboration's Technical Committee is charged with organizing and conducting meetings for further development of the collaboration's infrastructure, processes, and guidelines as well as for other discussions and activities relating to their objectives. The Valletta declaration has so far conducted two notable assessments, with Roche and Biogen, both for innovative products. The Valletta declaration group conducted its first confirmed pilot negotiations for ocrelizumab (Ocrevus®) for the treatment of Multiple Sclerosis. A second innovative health technology to be assessed by the Valetta Declaration joint collaboration was nusinersen (Spinraza®) for SMA.

As of 2019, the Technical Committee and Valletta Declaration Group has conducted 6 meetings dedicated to several topics, including the administrative establishment regarding objectives, scope, and cooperation in the joint collaboration [36]. Meetings also centered around the discussion and decisions of products for pilot assessments, the tracking, political analysis, and technical analysis of the declaration, the reinforcement of information sharing, exploration of new areas of activities, and the creation of a clear legal framework for the joint collaboration. Most interestingly and distinct to other joint collaborations is that the Valletta Declaration Group is particularly interested in and engaged in activities to influence political decisions. At their 5th meeting in Athens in July 2018, the joint collaboration explicitly stated that they would join forces to influence political decisions as the pharmaceutical industry does as well [36]. The following year, at their meeting in Zagreb (March 2019) the Valletta Declaration Group presented a drafted resolution seeking to promote increased transparency for pricing, research and development (R&D) costs, clinical trial data, and patent information. More specifically, the draft sought the requirement for results and costs from human clinical trials regardless of outcome or whether the results would support an application for marketing approval, and also the publication of annual reports on sales revenue, prices, units sold, marketing costs for individual products, and costs of each trial used in the support of marketing authorization applications. Additionally, details on financial support received during the development of the drug from public sources were included. The draft went further by calling on the WHO Director-General to put forth a model for a web-based tool to facilitate information sharing on medicines prices, revenues, units sold, patent landscapes, R&D costs, public sector investments and subsidies for R&D, marketing costs, and other related information [36]. A forum to develop alternative incentive frameworks to patent or regulate monopolies for new medicines and vaccines was also proposed by the draft, in order to incentivize innovation whilst promoting universal health coverage.

It is suspected that the number of country members may increase in the Valletta Declaration Group, although this may actually prove to be counterproductive due to a resulting increase in heterogeneity in the joint collaboration, which may render cooperation more complex and complicated to achieve. The group is also further interested in analyzing the therapeutic areas of growing expenditure, such as oral antidiabetics and oral anticoagulants, and reinforce the exchange of information in areas of common interest such as biosimilars [35]. Despite the Valletta Declaration Group engaging in several meetings and reiterating commitment and interest in conducting their activities, it has not yet confirmed the completion nor published the results of its two assessments of ocrelizumab and nusinersen.

France–Portugal Declaration of Intent

The France–Portugal Declaration of intent was signed in 2017. However, to date, there is no additional information accessible on the progress of this joint collaboration.

FINOSE

FINOSE, another Nordic joint collaboration, unites Finland, Norway, and Sweden. FINOSE represents the three national HTA agencies of each country, including the Finnish Medicines Agency (Fimea), the Norwegian Medicines Agency (NoMA), and Sweden's Dental and Pharmaceutical Benefits Agency (TLV) [6,37]. The project started in 2017 and culminated with the MoU signed in March 2018 officially establishing the joint collaboration [28,38]. FINOSE aims to conduct joint assessments of medicines, for both relative effectiveness and health economics. In addition, the joint collaboration aims to facilitate information sharing for knowledge gain about products, increase efficiency in production and assessment reports, discourage divergence in HTA methods and evidence requirements, and to reduce the complexity in industry submissions [39]. The FINOSE collaboration is not aiming for joint decision making, but rather focuses on joint assessments. Any health technology developer with a new but not yet authorized product may contact any of the three HTA bodies to inquire as to how to begin the joint assessment process [39]. The developer is required to sign a waive to enable information sharing between the three HTA bodies of the joint collaboration and they are required to submit simultaneously to all three HTA bodies comprised in the joint collaboration [39]. An additional and distinct characteristic of FINOSE to other joint collaborations is that it may use an available joint relative effectiveness assessment report from EUnetHTA as a ground for joint health economic analyses between Fimea, NoMA, and TLV [39]. The joint collaboration is specifically interested in joint assessments across European HTA agencies and how real-world evidence (RWE) can be integral to assessment decision-making processes [6,37]. FINOSE also appreciates efficiency and seeks to maintain a shorter assessment time than the individual national processes involved in the joint collaboration.

Initially, in June 2018, FINOSE stated it would assess simple drugs in their pilot joint assessments and would run these assessments until summer 2020 with the intent that if successful, the joint collaboration would become permanent. More interestingly and recently, FINOSE has assessed betibeglogene autotemcel (Zynteglo®) with Fimea and TLV as the authoring bodies and NoMA as the reviewer. The joint collaboration stated that with such a joint assessment for a therapy targeting such a small population, patient access to an innovative health technology could be secured [7]. The joint collaboration went further to highlight that it an assessment on the benefits and costs could aid in practical coordination for patients who may have previously needed to travel between countries to gain access to such a product [7]. FINOSE also recognized the importance of such an assessment and its potential role in future joint negotiations despite joint procurement not being a core activity of the collaboration, as its main focus is joint assessments. In addition, the joint collaboration introduced a new chapter on post-launch evidence generation through their assessment report by requiring a follow-up. It was also noticed in their assessment report that joint assessment submission could reduce administrative burdens for smaller companies with limited resources and organizations in each of the participating countries in the collaboration. Ultimately, FINOSE recognized the demonstration of Zynteglo®'s benefits in comparison to blood transfusions. However, there were no results on iron-related morbidity and survival due to limited follow-up time

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in clinical trials. FINOSE further noted the lack of health-related quality of life reported from the clinical trials, and noted that the number of patients treated with Zynteglo® is very small, given that there is substantial geographic, ethnic and genetic variation among β-thalassaemia patients [7]. In terms of Zynteglo®'s cost–effectiveness, FINOSE also recognized uncertainties in the number of patients eligible for treatment, whether the success rate is sustained, and whether the survival gains based on the assumption that complications associated with high iron levels are reduced. The model was found to be very sensitive to the disutility associated with chelation therapy affecting long-term utility gains [7]. The assessment report further and explicitly states that the generation of RWE can mitigate uncertainties identified by the joint collaboration. The report also mentions the importance of RWE in establish Managed Entry Agreements (MEAs), despite MEAs being out of scope of the joint collaboration's activities. As of today, this is the third assessment conducted by FINOSE.

Norwegian-Danish Initiative

This joint collaboration established between Norway and Denmark on September 18th, 2018 with the signing of its agreement is based on the previously existing Nordic Collaboration and remains welcoming to other countries wishing to participate [5]. Norway and Denmark's joint collaboration aims to enhance cooperation for joint procurement and joint negotiations to secure lower prices for innovative medicines while ensuring continuous, secured access in the context of potential shortages [5,40]. The joint collaboration was specifically interested in obtaining a lower, more affordable price for nusinersen (Sprinraza®) [40]. Currently, nusinersen is reimbursed in Denmark for patients with SMA types I and II as well as pre-symptomatic infants and it is reimbursed in Norway for patients under the age of 18 years old.

FUTURE PERSPECTIVES OF JOINT ASSESSMENTS

Despite being young, these joint collaborations are targeting the issue of ever-evolving health technologies, decreased purchasing power, finite budgets, and limited evidence and uncertainties surrounding the efficacy and cost–effectiveness of innovative health technologies, especially gene therapies. Out of the 11 joint collaborations identified targeting innovative medicines, only 2 have completed and published the results of their activities – BeNeLuxA and FINOSE – both in the area of joint assessments, which requires the integration of other joint collaboration activities (specifically, information sharing) (Table 2). BeNeLuxA was one of the first joint collaborations to be established and is only 5 years old, while FINOSE established in 2017 is only 2 years old. Both joint collaborations are relatively small with BeNeLuxA being a collaboration between 4 countries and FINOSE being a collaboration between 3 member countries. Both of these joint collaborations assessed innovative health technologies: BeNeLuxA assessed nusinersen and FINOSE assessed betibeglogene autotemcel, which are both innovative therapies targeting genetic disorders. BeNeLuxA granted a positive decision for nusinersen and was able to negotiate and procure the health technology, while FINOSE recognized the importance of betibeglogene autotemcel's benefits relative to its comparator and explicitly stated the need for additional follow-up and for RWE integration and implementation in this follow-up. BeNeLuxA did give the next orphan product it assessed, obeticholeic acid (Ocaliva®), a negative decision. The success of these 2 initiatives so far could lie in their small size, yet BeNeLuxA is already in talks with additional countries which may wish to join. Furthermore, their success could lie in the structures and open communication with emphasis on information sharing, as well as their close cultures and related understanding of one another.

TABLE 2

Joint collaboration assessments and outcomes.

Joint collaboration	Activity	Health technology	Outcome
BeNeLuxA	HTA and pricing negotiations	Combination of lumacaftor/ivacaftor (Orkambi®) for the treatment of cystic fibrosis	Absence of consensus on the product price, the product was not considered cost-effective, and the price was overestimated by 80%
	HTA and pricing negotiations	Nusinersen (Spinraza®) for the treatment of Spinal Muscular Atrophy	A positive reimbursement decision was given and an agreement on the pricing and reimbursement of the product was reached successfully, with one negotiation process conducted, instead of 2 separate ones
	HTA and pricing negotiations	Obeticholeic acid (Ocaliva®) for of primary biliary cholangitis	Negative decision
FINOSE	HTA	Betibeglogene autotemcel (Zynteglo®) for the treatment of transfusion-dependent β-thalassaemia	Recognition of demonstration of benefits, but also recognized the uncertainties especially surrounding the eligible patient population and the lack of health-related quality of life. The importance of real-world evidence in the mitigation of uncertainties and for the use in MEAs was highlighted in the report

With their publicized assessments, these two joint collaborations may quickly emerge as setting the standard for health technology developers seeking entry into their markets and for their health technologies' assessments. This may especially be the case with gene therapies, as BeNeLuxA will next be assessing onasemnogene abeparvovec (Zolgensma®), the most expensive advanced therapy on the market today. Overall, this may be positive for innovative health technology developers as they can secure a greater market and both developers and joint collaborations can ensure secured patient access. These processes may be more efficient with a one-point, one contact, one-time submission process, resulting in saved time and resources. However, these joint collaborations may have a negative impact on current products or the first to be assessed by such collaborations, as their structures and frameworks are still being established and will need to be tried, tested, and adapted. This may result in direct impact on pricing of current products, especially highly-priced gene therapies like onasemnogene abeparvovec (Zolgensma®) coming up for assessment next, and will depend on whether the joint collaborations clearly outline and establish appropriate legal frameworks to be able to negotiate the prices they seek.

The Valletta Declaration Group is also an interesting and potentially influential joint collaboration as it seeks not only to conduct joint collaborations and activities, but to also directly politically influence health technology developers' access to the market through requirements related to data submission, transparency, costs in R&D and trials, and costs of marketing amongst others. The Valletta Declaration Group's draft propositions, if enacted, could have a degree of direct influence on the pharmaceutical industry in terms of transparency, information sharing, price negotiations, and procurement and may therefore challenge traditional frameworks and processes in place, as well as shape the political environment and future of healthcare systems. Given their high R&D cost and the complexity of their pricing negotiations, gene therapies and their developers may in such a situation experience a particularly direct and large impact on how they present themselves during market access as well as their requirements for market access. However, this joint collaboration impact on the market access of innovative health technologies remains unclear as it is still being established and lacks legal framework. In comparison with BeNeLuxA and FINOSE, this joint collaboration also has a higher number of member

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countries, which may delay the maturation of this group due to lack of consensus and growing heterogeneity amongst its members. Yet, once again, if the Valletta Declaration Group is well-established and its proposition is adopted, it may have a high level of impact by creating a large market representing 32% of the EU's population (160 million citizens in total).

The remaining 8 joint collaborations identified, which represent the potential to harmonize processes in their regions, create larger markets, create additional budget, and guarantee supply of innovative products, are still in the establishment stages. As frameworks, and institutions for the regulation of and assessment of gene therapies, remain limited and are challenged, the number of joint collaborations established points towards the need for harmonization and standardization, which may facilitate optimal market access for all stakeholders involved in the process. The remaining 8 joint collaborations for innovative therapies vary in the range of participating member countries as well as in the activities they seek to conduct. However, the potential risks for all joint collaborations still apply: the lack of legal framework, clear administration, regulation, and accountability will threaten the success of all these joint collaborations. Ultimately, joint collaborations will experience their greatest challenge when faced with situations requiring legislative changes and implementations. For example, in joint collaborations, it must be highlighted that national regulations and legislation remains in place and precedes joint collaboration procedures, which should be supplementary and noncontradictory to national legislation and procedures [2,41].

In order for joint collaborations to succeed, there must be a solid, clear foundation beginning with a legal framework and agreements outlining roles and responsibilities for accountability and for their outcomes to be accepted at national levels without potential dispute. Joint collaborations must operate as single markets with a unique price and simultaneous access for all. Joining forces with like-minded and similar cultured countries may lead to further success, as seen with BeNeLuxA and FINOSE. Joint collaborations must select the appropriate products (with proven efficacy and robust evidence; targeting populations with high unmet needs) for their initial activities to test their models in preparation for evaluating complex, highly priced gene therapies with limited evidence. There remains the question of whether or not health technology developers will be interested in negotiating with a group of countries at the cross-border level as the ultimate goal of these joint collaborations is to lower prices to an affordable price. Small and large countries in joint collaborations may have different priorities and perceptions of the goals and aims of the collaboration and how to achieve them. Large countries inherently have higher bargaining power and may succeed in securing better discounts outside of joint negotiations, for example, whilst small countries may expect one unique price negotiation and one price for all countries. Expectations must be managed by setting clear goals and outlining methodologies and processes, as FINOSE did. There are many challenges yet to be overcome by joint collaborations. However, they will mature and if they are able to overcome and adapt to these obstacles, they may be successful in obtaining their goals. Both BeNeLuxA and FINOSE stand testament to their potential success.

DISCUSSION CONCLUSION

Joint collaborations have begun to be established with the aim to increase participating member countries' bargaining and purchasing power while ensuring patient access and maintaining sustainable healthcare systems in the anticipation of an increasing number of innovative therapies, especially highly priced gene therapies, seeking market access. Joint collaborations' activities may include information sharing, horizon scanning, joint assessments, joint negotiations, and joint procurement. EUnetHTA, also established as a

platform for joint assessment, is certainly a progressive step forward in terms of joint assessments, however, its definition that limits collaborations to those consisting of 4 or more country members discredits and does not consider initiatives established between 2 and 3 member countries. It is also dedicated solely to HTA activities and is not considered a decision-making process. EUnetHTA and its efforts have yet to gain increasing momentum.

Two joint collaborations, BeNeLuxA and FINOSE, have been successful in executing their joint assessments in the area of innovative therapies for genetic disorders. These joint collaborations are gathering countries of reasonably similar sizes and GDPs with close cultures, making the individual countries' will to efficiently and effectively work together more important than the overall political and governance matters. Large joint collaborations, such as Valletta, are gathering very heterogeneous countries with dissimilar populations along with dissimilar GDPs and health expenditures, making a joint procurement complex to achieve. Such joint collaborations may only work if the richest countries subsidize the price for the poorest EU countries through an internal compensation mechanism invisible to external third parties. This would assume a single EU price (with access to 580 million EU citizens) with a differential price per country and an internal subsidy mechanism. This may well be the way forward to establish EU equity in accessing gene therapies. If joint collaborations continue to mature and adapt, they may be able to influence the way innovative health technologies, especially the most highly priced treatments such as gene therapies, seek market access and may influence pricing and reimbursement. Joint collaboration activities require trust, communication, and a legal framework outlining roles and responsibilities in order to hold member countries accountable and ensure activities are being executed as intended. If joint collaborations are able to overcome their inherent obstacles, they will shape the future of innovative health technology and gene therapy market access in Europe, with the assumption that new regulations are put in place to allow a new governance within most member countries to delegate price negotiations to a joint body instead of national pricing committees.

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AFFILIATIONS

Monique Dabbous
Public Health Department, Research Unit EA 3279, Aix-Marseille University, 27 Boulevard Jean Moulin, 13385, Marseille, France

Eve Hanna
Creativ-Ceutical, 215 Rue du Faubourg Saint-Honoré, 75008 Paris, France

Boris Borislav
Prescriptia Ltd., Sofia, Hristo Botev Blvd. № 28, Bulgaria

Claude Dussart
Université Claude Bernard, Laboratoire Parcours Santé Systémique, EA 4129, Faculté de Médecine Laennec, 7-11 rue Guillaume Paradin, 69372 Lyon Cedex 08, France

Mondher Toumi
Author for correspondence
Public Health Department, Research Unit EA 3279, Aix-Marseille University, 27 Boulevard Jean Moulin, 13385, Marseille, France
mondher.toumi@univ-amu.fr

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CELL & GENE THERAPY INSIGHTS

MARKET ACCESS: EVOLVING COMMERCIALIZATION TRENDS & STRATEGIES

SPOTLIGHT

COMMENTARY

Challenges in the adoption of regenerative medicine therapies, meeting summary

Maya Chaddah, Allison Brown, Siofradh McMahon, James Kusena, Karen Bremner, Ann Perry & Murray Krahn

Currently, there is scant evidence of policies that adequately outline the process for therapies and technologies in the regenerative medicine (RM) field, known in the EU as Advanced Therapy Medicinal Products (ATMPs). Areas such as payment mechanisms, pricing and reimbursement schemes still remain largely elusive. Clear policies are pertinent due to ATMPs such as KYMRIAH™ and YESCARTA® that have been approved, but how they and future ATMPs will be sustainably paid for remains unclear for many healthcare systems globally. Also, their long-term effects are not yet known, and social, ethical and legal issues have not always been adequately considered.

The scarcity in defined reimbursement and adoption policies for ATMPs prompted the development of an international workshop on the 'Challenges in the Adoption of Regenerative Medicine Therapies (CHART)'. Co-hosted by Medicine by Design (a regenerative medicine initiative at the University of Toronto and funded by the Canada First Research Excellence Fund), CCRM, Toronto Health Economics and Technology Assessment (THETA) Collaborative, and the Centre for Biological Engineering at Loughborough University UK, CHART focused on the post-market approval challenges associated with economic evaluation, reimbursement and adoption of regenerative medicine products. The challenges were explored in the context of the Canadian and UK healthcare systems as provision of health in both countries is largely via publicly funded systems. The workshop was attended by 37 experts from institutions and companies from Canada, the UK, and the USA that included representatives of the Ontario government, National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Takeda Canada, Gilead Sciences Canada, Inc., Office of Health Economics (OHE), Centre for Health Economics (CHE), University of York, and Oxford Academic Health Science Network (OAHSN) amongst others.

Proceedings from the workshop demonstrated that challenges regarding ATMP adoption are not unique to the regenerative medicine field. (1) Current methods of evaluation are applicable to ATMPs, but the biggest challenge for these novel therapies is providing evidence that reduces the uncertainty of their long-term effects. (2) The generation of evidence of clinical effectiveness needs to be improved by ensuring clinical trial designs employ robust controls and increase their sample sizes while collecting data in the relevant setting. (3) Incentives for real-world evidence capture should be established to ensure that data are gathered and can be used to further evaluate the therapies for long-term clinical effectiveness and adverse effects. (4) The implementation of ATMPs will require concerted efforts from multiple stakeholders to ensure that the adoption pathway for ATMPs is efficient, effective and aligned with social values. (5) There needs to be greater interaction with policy makers, as political will is essential for research to progress into meaningful efforts. (6) There is a need to improve patient management and data management to aid in evidence generation and facilitate outcome-based payment mechanisms. (7) Payment mechanisms remain a challenge; the sustainability of current payment methods for expensive therapies will need to be evaluated, prior to the approval of more ATMPs. The next steps outlined from the workshop included: targeted policy maker engagement, relevant stakeholder engagement, addressing the evidence generation issues, and understanding future payment system mechanisms.

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PRESENTATION HIGHLIGHTS

Session 1: Evidence of Clinical Effectiveness

Speakers

- Pilar Pinilla Dominguez, Senior Scientific Advisor, National Institute for Health and Care Excellence (NICE; UK)
- Dr John Kuruvilla, Hematologist, Princess Margaret Cancer Centre, University Health Network (Canada)

Discussants

- Tania Bubela, Dean, Faculty of Health Sciences, Simon Fraser University (Canada)
- Alex Klarer, Biomedical Engineer, Hitachi Chemical Advanced Therapeutics Solutions, LLC (USA)

National Institute for Health and Care Excellence (NICE) experience on evaluation of cell and gene therapies

NICE was established as a legal entity in 1999 and for the past 20 years has been providing national guidance to improve the outcomes for those using the National Health Service (NHS) and other public health and social care services in the UK. In the context of regenerative medicine products, ATMPs are not new and assessing their clinical effectiveness is pivotal to informing payors and patients as to their clinical benefits.

The first NICE technology appraisal was in December 2000 for autologous cartilage transplantation for full thickness cartilage defects in knee joints. Since then there have been many product development failures, either due to clinical reasons or feasibility of commercialization. Many ATMPs have now been evaluated at NICE and seven have been recommended to date. For all new cases, the NICE framework addresses six key questions that together explore the clinical effectiveness of a therapy, and its added value, benefits and additional costs compared with established practice (Box 1).

These are exciting times, with the promise of major benefits stemming from novel ATMPs including CAR T and other gene therapies, as well as therapies targeting biomarkers, and combination therapies. CAR T therapy has grown out of decades of immunologic research, with the first CAR T clinical trial in 2006 for adult patients with ovarian or renal cancer, and the first pediatric patient, Emily

BOX 1

Key questions from NICE appraisals.

1. What is the evidence supporting the benefit and safety of ATMPs?
2. What is the structure of the data/evidence?
3. How do we ascertain the clinical benefits of ATMPs? Does their promise of cure/long-term effect make them different?
4. What is the strength of the evidence?
5. How can these technologies be evaluated when the sample size is very small?
6. How can both payors and regulators be satisfied by producing adequate data?

Whitehead, successfully treated for lymphoma in 2012. With the hope of treating cancer, CAR T has become a highly disruptive therapy that poses important challenges from a health technology assessment (HTA) perspective.

In HTA, the goal is to evaluate whether a technology is clinically- and cost-effective in order to inform whether it should be adopted in the health system. Timely patient access is also important for early HTA of emerging technologies. For single-arm trials, where a sample of individuals with a medical condition is given an experimental therapy and observed over time, NICE's technology appraisals of CAR T trials have uncovered some key issues relating to their clinical- and cost–effectiveness:

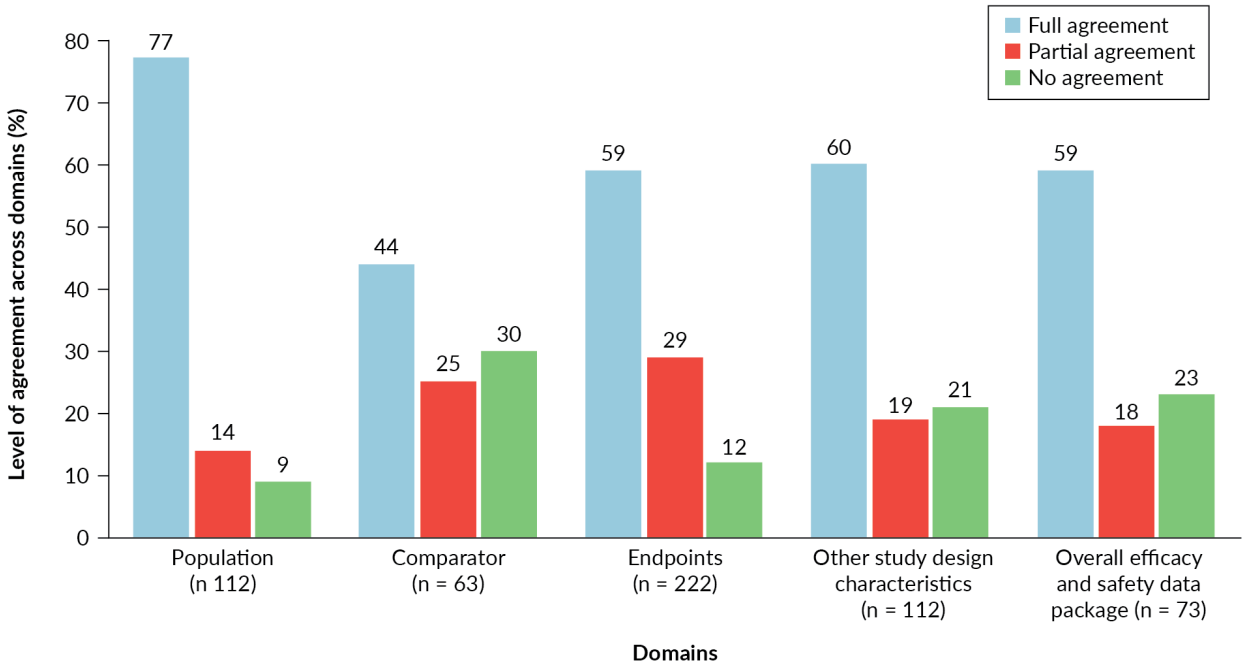
1. Inability to make a direct and robust comparison between trial and comparator groups;
2. Limited evidence where randomized controlled trials are not always possible, and sample sizes are small, limiting generalizability and external validity;
3. Short (or not yet reached) median follow-up involving a high degree of censoring;
4. Assumptions required about the curative effect and uncertain adverse effects of CAR T therapies;
5. Uncertainty around the number of patients who subsequently have a transplant (particularly relevant for acute lymphoblastic leukemia, ALL);
6. Uncertainty around the location in the treatment pathway with the most value;
7. Uncertainty around cost of long-term adverse effects and treatments that can extend the life of patients at end of life; and
8. No clear window into patient-relevant outcomes at the time of HTA evaluation; only data on surrogate or intermediate rather than final/clinical outcomes available.

In light of these limitations, the NICE committee agreed that while the trials are promising, the short-term follow-up and the many clinical uncertainties are still a major concern.

Many ATMPs have been developed by academic researchers or small and medium size enterprises (SMEs) where lack of funds means that HTA-relevant data may not always be generated from the outset. To help address this issue, NICE, through the Scientific advice programme, advises companies on their clinical and economic development program, HTA requirements and evidence needed to prepare for HTA evaluation. Companies most often have questions around single-arm trials, historical controls, matching adjusted indirect comparisons, trial design, patients as own controls, and questions related to extrapolation and follow-up. Many developers are more familiar with regulatory data requirements than HTA-related data requirements and are unaware that alignment between the two is an important consideration and

FIGURE 1

Alignment between Health Technology Assessment Bodies (HTABs) and regulators.



A retrospective analysis of 31 different procedures from 2010 to 2015 assessed the level of agreement between HTABs and regulators across five domains (population, comparator, endpoints, design, efficacy and safety data package). Blue indicates full agreement, red partial agreement and green no agreement. Across the five domains, the clearest misalignment is in the comparator domain [1].

impacts how HTA is conducted. As shown in Figure 1 [1], there has been an improvement in alignment between Health Technology Assessment Bodies (HTABs) and Regulators. The clearest misalignment between the two groups is in the comparator domain. This is a clear signal to companies that they need to think about HTA requirements earlier on.

Anti-CD19 CAR T cells for diffuse large B cell lymphoma (DLBCL) as a model

John Kuruvilla used the specific example of DLBCL to provide insight into the evidence development process for ATMPs, with the example of CAR T therapy. His group previously worked with Celgene and is working with Kite, a Gilead Company, as one of the Canadian sites, and will also be working with Novartis and Juno/Celgene/BMS.

In Canada, the expertise to transplant CAR T cells is concentrated in three to four centers that participated in the early-phase studies, but has since broadened to include approximately 15 centers across the country. Princess Margaret Cancer Centre at the University Health Network (UHN) is one of the largest bone marrow transplant practices in North America, with more than 600 transplants conducted every year. Due to this high volume of procedures, hematologists there are very familiar with the principles of CAR T in clinical practice (Figure 2).

All the first-in-human CAR T studies, done in academic centers, provided proof-of-concept for CAR T therapy but important lessons have emerged around feasibility, platform development, efficacy and safety. In terms of feasibility, the CAR Ts were manufactured in a single setting; an important question that arises is whether they can be scaled for multicenter trials and for a global setting. Lymphodepletion, cell dose, and product composition are also areas where current processes need to be improved. Lymphodepletion is particularly important because CAR T cells are a 'living drug' and without

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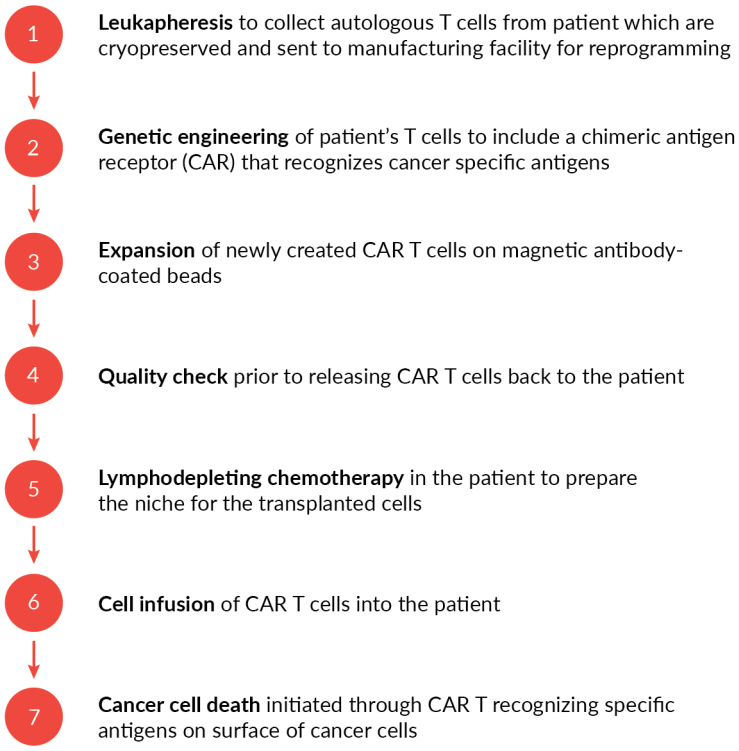
FIGURE 2

How CAR T therapy works in clinical practice.



The generation of CAR T cells from a patient's T cells is a lengthy process involving many steps (1–4). Chemotherapy to delete resident lymphocytes (5) is crucial for preparing the niche for the CAR T transplant. CAR T cells infused into the patient (6) are able to recognize specific antigens on the surface of cancer cells and initiate their destruction (7).

lymphodepletion, the transplanted cells do not expand. While there was a practical dose that led to the observed results in the early studies, the optimal dose has yet to be determined. In addition, the product composition varies by manufacturer, with only one company having looked at the ratio of $CD4^+$ to $CD8^+$ T cells. In the high-risk patient population that was studied, there were signs of efficacy but there are still unknowns about whether the responses are durable and the mechanisms of resistance or failure. One of the important lessons learned from these early studies was that two toxicities were identified: cytokine release syndrome (CRS), largely an interleukin (IL) 5-driven phenomenon leading to a cytokine storm, and capillary leak syndrome which requires intensive care.

To date, the trial with the longest follow-up is the ZUMA-1 study treating patients with refractory DLBCL with a CAR T therapy (axicabtagene ciloleucel) [2]. The Phase 1 portion of the study was a limited sample size and demonstrated that the cells could be manufactured and distributed to sites in the USA and Canada effectively. The expansion cohort of the Phase 2 trial included refractory DLBCL and two other subtypes of aggressive lymphoma. The trial was designed to assess the overall response rate, which was 82% (complete response rate 54%) with a 15 month progression-free survival (PFS) of 41%. The key toxicities generally occurred early but were manageable with a grade 3 or greater rate of cytokine release syndrome (CRS) and neurotoxicity rate of 13 and

28%, respectively. The late-event toxicities, including infectious toxicity, and sequelae of long-term B cell aplasia, suggest that CAR T cells are still present and active leading to prolonged B cell aplasia and hypogammaglobulinemia. Longer-term follow-up of the ZUMA-1 study with data follow-up at the 2-year mark was quite reassuring and there were no additional safety signals seen with later events [3].

For current Phase 2 trials, there is demonstrated proof-of-concept in terms of being able to do large, multicenter, global CAR T cell trials. But Kuruvilla cautioned that one cannot compare the roster of Phase 2 trials head to head as they may use different CRS grading systems, and the starting patient populations are not always identical. There are additional data coming from these trials that will inform whether chemotherapy can be given to patients while the CAR T cells are being manufactured.

One of the interesting questions that arises from current Phase 2 studies is whether CAR T cells need to be in the system forever or whether persistence may be a moving target in terms of the disease that is being treated. In many patients who are in remission, CAR T cells disappear but that doesn't mean impending relapse. There is a recovery of immunoglobulins and recovery of B cells in the peripheral blood so it may be sufficient for the CAR T construct to be in the system for as little as 6 months.

Going forward, many companies are opening randomized Phase 3 trials around the world. The Food and Drug Administration (FDA) has approved very similar designs in terms of the patient population and the standard, accepted surrogate end point of event-free or progression-free survival. Variations will be in cell dose, hospitalization or not, the subset of lymphoma and the Eastern Cooperative Oncology Group (ECOG) Performance Status, which scores a patient's level of function.

In summary, Kuruvilla stressed that compared to other therapies, CAR T is managed in the clinic as a 'one and done' treatment. That means that there isn't the same data collection that one sees in other studies where treatment is ongoing until progression. Although the CAR T therapy process is similar to other drug therapies, Kuruvilla noted that regulators and payors are pausing over the complexity of the products as well as the magnitude of the cost; the need for timely decision-making is huge.

Insight from discussants: session 1

Complicated therapies

We are victims of our own hype and this is accelerating ATMP products into the market at a rate that we would not otherwise see for other types of technologies.

"We need to innovate in this space; however, we need to be very careful about our incentives and keep our decisions informed by empirically-grounded evidence."

– Tania Bubela

Headroom analysis

It is important to consider whether there is a sufficient unmet need for candidate ATMPs to support a price consistent with an acceptable return on the investment.

"We see very limited target product profiles based on preclinical studies and surrogate analytical measures and they are not always tied to patient efficacy in the long term."

– Alex Klarer

Informing costs

We need to invest more in cell processing, manufacturing, and scale up, and economic models can help to inform developers in bringing down the costs.

Risk sharing

As a society we have not yet had a discussion about the extent to which we want public-sector dollars to pay for things that are currently

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in the research and development budgets of pharmaceutical and biotechnology companies. If developers are expecting these kinds of products to be coming through with conditional approvals, and if they are forced onto our public payor systems with a lower evidence threshold, then the developers should be expected to participate in risk sharing on the funding of these types of therapies.

Patient variability & product analysis

Many product profiles don't measure patient variability and there is limited incoming product analysis. For example, Juno Therapeutics, (now a Celgene company) is looking to reformulate its final product so that there is a one-to-one CD4/CD8 T cell ratio for the final product and to select for naïve markers in the starting product to reduce product variability.

Strong product profiles

Clinical stage companies heading to commercialization need to prepare for the Investigational New Drug (IND) phase or pre-IND by building a strong product quality profile that allows production of a consistent and efficacious product. With very accelerated clinical timelines and conditional approvals, there is little time to put more stringent measures in place and re-evaluate the product profile; that will affect long-term outcomes and drive long-term revenue from within whatever payor model companies are selling.

Highlights from open discussion: session 1

1. Lowering the bar for evidence generation is not the answer as we have a duty to patients to have some certainty around our recommendations. However, it is not yet clear how to complement sub-optimal evidence while understanding the manufacturers' difficulties in running the studies. Collecting clinical and patient-relevant outcomes will provide confidence to decision-makers that real-world evidence will be generated and can be looked at again.
2. Although randomized controlled trials (RCTs) are the gold standard, there are justifiable circumstances (e.g., treatments for rare diseases) in which the collection of gold standard evidence is very difficult. In such cases, it will be necessary to coordinate data internationally. This poses a problem in Canada because to date we are unable to easily share data among health authorities within and across provinces.
3. Canada needs a national registry and database to manage the follow-up of ATMPs. We lag behind other countries and are not well-funded provincially to manage these types of disparate data sets across national and international borders. The long-term follow-up is even more problematic with retrovirally-modified products which often require follow-up for 25 years.
4. Market access in Canada includes engagement with health systems. We need to promote to developers that they can have parallel engagement with both the HTAs (Canadian Agency for Drugs and Technologies in Health, CADTH, and Institut National d'Excellence en Santé et Services Sociaux, INESSS), and Health Canada.

Session 2: Health Economics

Speakers

- Ana Duarte, Research Fellow, Centre for Health Economics (CHE), University of York (UK)

Discussants

- Grace Hampson, Senior Principal Economist, The Office of Health Economics (OHE; UK)

- Pilar Pinilla Dominguez, Senior Scientific Advisor, National Institute for Health and Care Excellence (NICE; UK)
- William Wong, Assistant Professor, School of Pharmacy, University of Waterloo (Canada)

Challenges in economic evaluation of ATMPs

In 2014, the UK Department of Health set up the Regenerative Medicine Expert Group (RMEG) to develop an NHS regenerative medicine readiness strategy and assess the effect of regulation on the development of regenerative medicines in the U.K. In advancing this goal, the RMEG recommended that an exploratory study of the appraisal of regenerative medicine products be commissioned and published by NICE to highlight key issues in the evaluation of regenerative medicines and explore the suitability of current methods. Towards this goal, the University of York conducted an assessment of a hypothetical CAR T therapy. The mock technology appraisal was conducted by the Expert Panel, mimicking a NICE technology appraisal committee, which was informed by the University of York assessment and by the views of the expert panel members. The mock appraisal of a CAR T cell therapy explored two potential profiles of this technology: i) as a bridge to hematopoietic stem cell transplant (HSCT) or ii) with curative intent, using a hypothetical data set for acute lymphoblastic leukemia (ALL) in young adults and children. The benefits and costs of the two hypothetical target product profiles (TPPs) in Table 1 are taken from the report Exploring the Assessment and Appraisal of Regenerative Medicines and Cell Therapy Products [4]. The incremental quality-adjusted life year (QALY) benefit of either of the two explored hypothetical profiles far exceed that of conventional cancer treatments.

The general conclusions were that while the methodology of NICE and the decision framework were applicable to regenerative medicine and cell therapies, for technologies with high costs, limited evidence and benefits being accrued over long time-horizon, the exploration of uncertainty is key to inform decision-making. The York group devised a novel framework to assess this uncertainty that is not part of the standard NICE methods guidelines. Another concern was the extrapolation of benefits as a key driver of cost effectiveness and the risks of irrecoverable capital costs as therapies are rolled out. The appropriate discount rate to apply to costs and benefits was also an important point of discussion. The key recommendations for NICE were:

1. To continue to develop a framework to quantify and present consequences of uncertainty to decision-makers, building from the framework proposed by York;
2. To collaborate with other stakeholders to develop novel practical payment methods, such as leasing;
3. To consider the implications of this study when reviewing the criteria for the application of lower discount rates on costs and outcomes.

In the UK, NICE has conducted two appraisals on CAR T therapies (axicabtagene ciloleucel and tisagenlecleucel) that are now funded through the UK Cancer Drugs Fund (CDF) [5] via well-defined managed-access

TABLE 1

Hypothetical target product profiles (TPP) [4].

	Bridge to HSCT TPP	Curative intent TPP
Assumed individual patient level incremental quality adjusted life year (QALY) gain	7.46	10.07
Assumed price (acquisition cost of the therapy)	£356,100	£528,600

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BOX 2

The Cancer Drugs Fund (CDF) [5].

Established in 2011 and managed by NICE since 2016, the CDF is a tool for recommending cancer drugs with high clinical uncertainty that would not otherwise be recommended in NHS England. The new CDF framework is a managed-access scheme with clear entry and exit criteria that aims to:

1. Provide patients with faster access to promising cancer drugs;
2. Drive value for money for taxpayers in drugs expenditures; and
3. Offer pharmaceutical companies that price their products responsibly an accelerated NICE appraisal process and a new CDF managed-access scheme.

agreements (MAAs) (Box 2). For therapies to qualify for the CDF, all the plausible scenarios must be under the cost-effectiveness threshold. The manufacturer of axicabtagene ciloleucel agreed to an MAA, the details of which are confidential. In Canada, CADTH is the independent, not-for-profit organization responsible for providing Canada's healthcare decision-makers with objective evidence to make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in the healthcare system. Following the review of tisagenlecleucel and axicabtagene ciloleucel by CADTH, the Health Technology Expert Review Panel (HTERP) advisory board recommended the provision of both therapies in Canada, with conditions, including a substantial reduction in price.

The University of York, as the evidence review group for the NICE technology appraisals on CAR-T, identified key issues across all the CAR-T appraisals.

1. Target population and proposed positioning is critical in that the population defined by the marketing authorization is broader than the trial populations, and there are also concerns over finding the relevant comparator/standard of care in the treatment pathway.
2. Violation of the intention-to-treat (ITT) principle has implications on cost and health outcomes.
3. Extrapolation of overall survival is critical to cost–effectiveness, but assumptions need to be made around potential curative effect, longer-term excess mortality, and possible late relapse.
4. Resource and cost uncertainties arise because:

a. not all appraisals considered bridging versus lymphodepleting chemotherapy;

b. there were differences in administration and monitoring requirements (inpatient versus ambulatory); and

c. there were differences in incorporating relevant costs from managing adverse events (e.g., CRS and B-cell aplasia, intensive care, readmission).

5. Implementation issues for introducing CAR T therapy into the UK included:

a. lack of expertise and capacity to expand from other similar services like stem cell transplantation;

b. how to phase in implementation; and

c. the need for new training requirements.

Real-world evidence published post-appraisal identified other key issues.

6. The efficacy data for CAR T cells was reasonably consistent for fitter patients but less so for those with ECOG performance status greater than or equal to 2.
7. There were greater rates of drop off between the point of leukopheresis and

TABLE 2

Current approval status of CAR-T therapy [6].

	Tisagenlecleucel (Kymriah™)	Axicabtagene ciloleucel (Yescarta®)	Brexucabtagene autoleucel (Tecartus™)
Canada	Health Canada Sept 2018 CADTH Jan 2019 (pediatric ALL and DLBCL)	Health Canada Feb 2019 CADTH Aug 2019 (adult r/r LBCL)	
USA	FDA Oct 2017 (adult LBCL, DLBCL, primary mediastinal)	FDA May 2018 (adult DLBCL, high-grade CLL)	FDA July 2020 (adult r/r mantle cell lymphoma)
UK	EMA Aug 2018 NICE Dec 2018* (r/r ALL up to 25 years) NICE March 2019* (r/r adult DLBCL)	EMA Aug 2018 NICE Jan 2019* (adult DLBCL and primary mediastinal LBCL)	

* Recommended for use on the CDF only.

CAR T cell infusion than suggested by the trials.

8. The use of bridging chemotherapy in the population was considerable, whereas for some of the previous trials (e.g., ZUMA-1) bridging chemotherapy was not allowed.

9. Resource use associated with treatment of adverse events and rates of readmission were much higher than observed in trials.

These differences suggest that some of the costs of CAR T therapy may have been underestimated in the NICE appraisals, but the key driver for the estimate of cost-effectiveness was the choice of comparator data and the extrapolation of overall CAR T cell survival. And even though there is now more follow-up data, there are areas of uncertainty that remain; namely, the possibility of late relapse, and the duration of B cell aplasia and the need for treating it over time. The current approval status of CAR T therapies in Canada, the UK and USA is shown in Table 2 [6].

In summary, CAR T cells are highly innovative and have the potential to improve patient outcomes, but they are expensive and require infrastructure changes that might not be captured in the cost–effectiveness analysis. The group at York University, UK, still posits that the uncertainties and their consequences may not be fully considered in the NICE methods. The use of more innovative pricing arrangements, insofar as they are linked to a quantification of uncertainty and what that uncertainty

TABLE 3

BioCanRx modelling exercise [7].

CAR T wait time	ΔCost (CAR T vs chemo)	ΔQALY (CAR T vs chemo)	ICER (CAR T vs chemo)
No delay	$392,230	3.54	$110,799
1 month	$352,015	2.97	$118,524
2 months	$315,469	2.34	$134,816
3 months	$282,015	1.56	$180,779
4 months	$232,043	0.91	$254,992
5 months	$183,463	0.36	$509,619
6 months	$142,033	-.02	Dominated

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means in terms of opportunity costs elsewhere in the health system, still remains an important area of further investigation. Going forward, it is difficult to predict what shape the NHS England commercial deals will take after access within the CDF has expired.

Insight from discussants: session 2

Getting all the stakeholders in the room

In the UK, NICE looks at value through HTA, and NHS England is the main stakeholder in the commercial deliberations. We need to move away from having two sequential debates to instead having both stakeholders in the room.

Hypothetical wait time for CAR T therapy for DLBCL patients

A modelling exercise funded by BioCanRx, Canada's Immunotherapy Network, used the ZUMA-1 trial for the CAR T arm and the SCHOLAR-1 trial for the chemotherapy arm. (The SCHOLAR-1 trial was the first patient-level analysis of refractory DLBCL and pooled data from two Phase 3 clinical trials and two academic databases). This BioCanRx study showed that mortality increases with a wait times of longer than 3 months. At wait times of 9 months, the 1-year mortality rate for CAR T hits the standard chemotherapy arm. The impact of CAR T wait time on cost–effectiveness, QALY and incremental cost–effectiveness ratio (ICER) for CAR T versus chemotherapy in the BioCanRx Modelling Exercise is shown in Table 3 [7].

Highlights from open discussion: session 2 (see also Box 3)

1. Improving methodology: Little is new or different about trying to conduct a proper economic evaluation of an ATMP. However, there are specific issues that arise in trying to operationalize a conventional HTA; for example, immaturity of the data, extrapolation both with respect to survival and health-related quality of life effects, small sample sizes, single-arm and short-term trials, and surrogate outcomes. The current methods also require assumptions that the data are not always able to support so there is room for methodological improvement.

2. Randomized data: The lack of randomized data to populate these models creates a host of problems: estimating treatment effect correctly, estimating uncertainty associated with treatment effect, and correctly specifying lack of randomization with some parameter in the model. In addition, using non-randomized data means that one must potentially set differential start times for two cohorts.

3. Re-evaluating costs: In England, CAR Ts in the CDF will be re-evaluated after 5 years and that will provide an opportunity to look at data from the long-term clinical trials and the incidence of adverse events plus real word data collected through the CDF. It will also be important to assess program costs, population-level screening programs

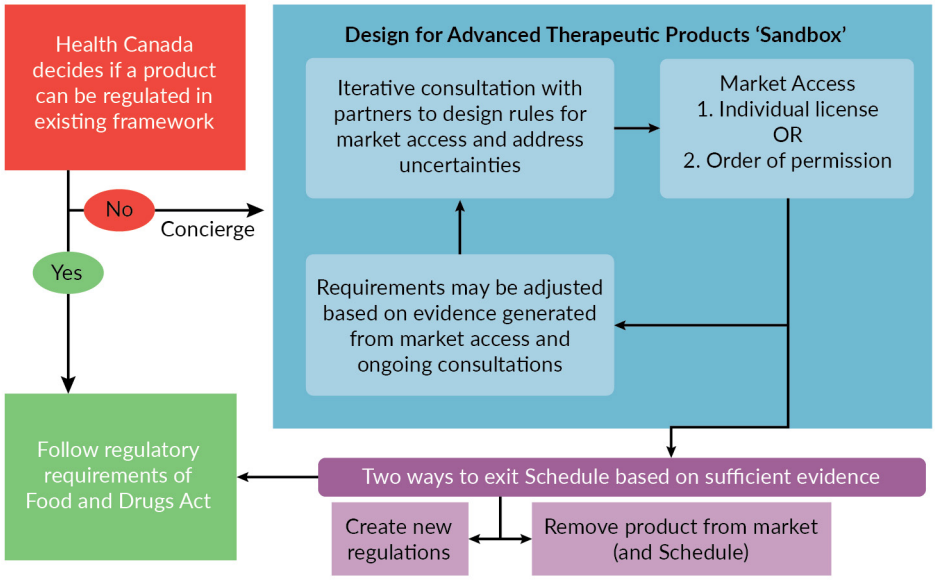
BOX 3

Questions for further consideration: session 2.

- Trial design: For single-arm trials, do we need more data for comparisons and new methods to make the comparisons or should we simply require RCTs?
- Impact on the ICER: Do we need new methods for dealing with the complexity of ATMPs or should we take a pragmatic approach based on the data we have?
- Uncertainty: How do we mitigate risk if we need to make the decision immediately? Are MAAs answering the question that we really need them to answer? Even if we wait to collect the data to mitigate risk, there are other uncertainties that play a big role.

FIGURE 3

Advanced therapeutics product pathway – proposed regulatory sandbox.



The regulatory sandbox is a new triage process for Health Canada to authorize unique advanced therapeutics. Health Canada provides a concierge service to help clients assess whether their products can be considered for the advanced therapeutics pathway and to design rules for market access via individual licences or orders permission [8].

and training costs, such as resetting a stem cell transplant unit to provide CAR T cell therapy treatments.

Session 3: Social Values in the Evaluation of Regenerative Medicine

Speakers

- Jennifer Gibson, Director, Joint Centre for Bioethics, University of Toronto (Canada)

Discussants

- Fiona Miller, Professor, Institute of Health Policy, Management and Evaluation, University of Toronto (Canada)
- Tania Bubela, Dean, Faculty of Health Sciences, Simon Fraser University (Canada)

Bioethics is considered the third pillar of HTA and often comes last in the discussions around evidence-based medicine and policy. Jennifer Gibson invited the audience to move away from this paradigm and to think upstream about the values that apply to emerging technologies.

In July 2019, as part of Bill C-97, Health Canada opened a consultation on clinical trial regulations and a newly proposed pathway for approval of "advanced therapeutic products". This new regulatory pathway, referred to as a 'regulatory sandbox', allows the regulator to work with the developer to appropriately regulate products that do not otherwise fit within existing definitions of medicines or devices (Figure 3) [8]. The regulatory sandbox provides a path to market for even the most complex and innovative therapeutic products and allows for controlled regulatory science experimentation, ensuring innovative products can be regulated appropriately and made available to patients who need them.

In the last few years, Canada, the UK and the USA have all approved to a greater or lesser extent CAR T cell therapies for particular populations (Table 2). The promise of these and other personalized medicines is driving

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the discourse around which technologies are explored at an individual level. However, as shown in Figure 4 [9], there can be tension between balancing the needs of individuals with the needs of the population across policies and practice. Health systems must also balance the principles of autonomy and non-malfeasance with solidarity, equity and distributive justice.

While the Canadian system has done a good job of implementing standards as they apply to drugs and devices, it is still exploring whether there is something unique about ATMPs that will require a different balance.

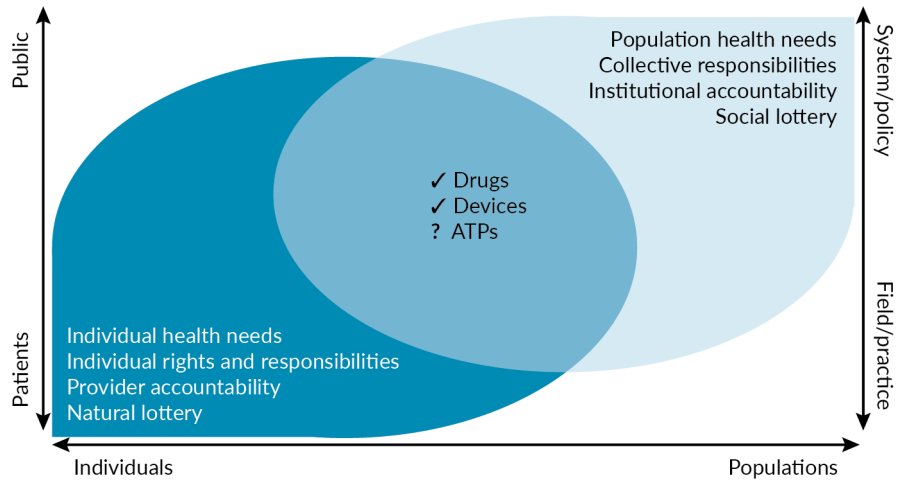
In collaborating with Cancer Care Ontario (CCO) to explore the ethics of CAR T therapy, Gibson was struck by the complex policy uncertainties around CAR T therapies, from classification, to regulatory, evidentiary, clinical, funding, and public values, and how the uncertainties could be approached in a publicly defensible way that would be evidence-informed, values-based and flexible enough to respond to an evolving context. She highlighted some of the key questions that capture the emerging uncertainties.

1. Should we be applying a research ethics paradigm or a clinical ethics paradigm?
2. Are the regulatory protocols fit for purpose to address policy and governance challenges?
3. What is the right balance between benefits for novel therapies versus the risk, and who ought to decide?
4. Who should have access to CAR T therapies given the risk and how and where should the therapy be delivered given that delivery within specialized centers will raise constraints on geographical access?
5. Are CAR Ts affordable? Who should pay for them, and what is the true cost of their implementation when factoring in the costs (e.g., travel) that patients will have to bear?
6. Which public values should inform the choices about ascribed risks and delivery of CAR T therapies?

In framing the complex policy uncertainties as different types of problems (technical,

FIGURE 4

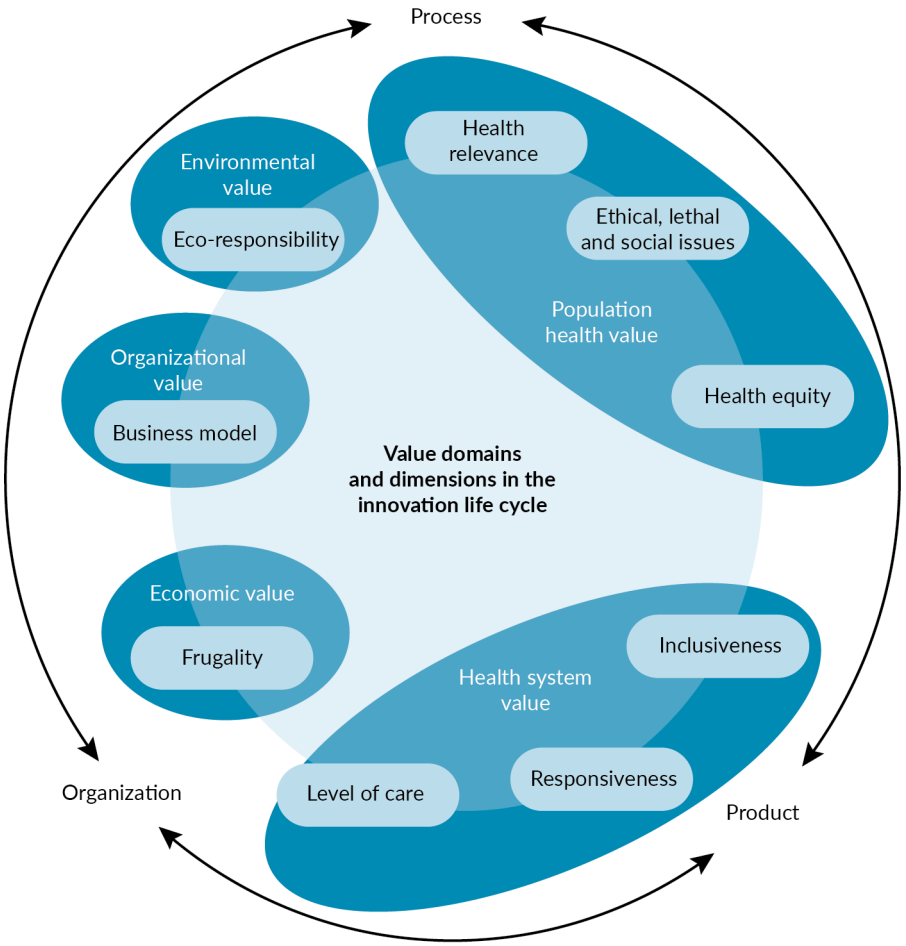
The promise of health systems.



Health policy works at the intersection between primary care and public health to find the right balance between the pursuit of individual health needs, population needs, and ethics (autonomy, non-malfeasance, beneficence, solidarity, equity and distributive justice). Health systems have already worked to reconcile these factors for drugs and devices, and now have to think about whether the same balance applies to advanced therapy products (ATPs) [9].

FIGURE 5

Responsible Innovation in Health (RIH) framework.



The RIH framework takes an integrative global perspective on health systems where evidence for process, products and organization that underperform across the five value domains (dark blue) and nine dimensions (light blue) help to address problematic gaps in the innovation life cycle of health systems [10].

process and social values), one can begin to flesh out some possible solutions. Technical solutions might include retrofitting current regulations, better use of data, developing better economic models based on that data, and refining HTA methods and tools. Process solutions could involve managing in a participatory way the institutions that are involved with decision-making (transparency), training, negotiation and post-market surveillance. Social values solutions could include public engagement, broad sampling of perspectives, contextual understanding and values.

Gibson emphasized that apart from the technical solutions that give the right answer or the process solutions that give a reasonable answer, it is critical in this rapidly evolving ecosystem of ATMPs to foster public trust. In Canada, recent polls have shown that public trust is highest for not-for-profit institutions such as healthcare providers and universities, and lowest for life and health insurance companies, politicians and the media.

Gibson also reviewed the principles of responsible innovation [10]. These came, in part, out of the Ethical, Legal and Social Implications (ELSI) program, founded as part of the Human Genome Project. Broadly speaking, responsible innovation means "taking care of the future through collective stewardship of science and innovation in the present" [9]. As it applies to health, the Responsible

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Innovation Framework (RIH) (Figure 5) [10] is "a collaborative endeavor where stakeholders are committed to clarify and meet a set of ethical, economic and social and environmental principles, values and requirements when they design, finance, produce, distribute, use and discard sociotechnical solutions to address the needs and challenges of health systems in a sustainable way" [11]. The value domains (population health, health system, economic, organizational, and environmental) of a responsible innovation in health framework are considered throughout the life cycle of health innovations. Gibson concluded that the particular values within each domain need to be further explored with the view to building population-relevant versus individual-relevant values into an iterative process. This discourse should engage patients, who need to be added to the regulatory sandbox as the primary stakeholders that inform complex policy uncertainties.

Insight from discussants: session 3

Questioning the high cost of CAR T therapies

There is a conflation of interest among researchers, industry, media and patients in getting good news stories out to the public. But in all the stories about CAR T, no one questions why they are high-cost despite the fact that CAR T was developed using National Institutes of Health (NIH) funding at the University of Pennsylvania, which is on the patents, and that there are requirements on rights of use for the USA federal government.

"A full suite of partners needs to be at the table for participatory governments to enhance trust in our institutions and decision-making bodies."

– Tania Bubela

Hype in the media

There is a definite bias in how stories are reported in the media, which is where a majority of people get their health information. For example, few stem cell products have been approved beyond bone marrow transplantation, a fact that gains little media traction, and rarely is it discussed that gene therapy is not curative where degeneration has already started. Similarly, because the results from stem cell clinical trials (e.g., cardiac stem cell trials) may not be reported, the public may not learn about the efficacy of regenerative therapies. These shortcomings lead to a hype-bubble of expectation that regenerative medicine will have a real clinical impact in a host of diseases for which we do not have treatment options and for which patients are desperate for any treatment, let alone a cure.

"We shouldn't just assume adoption. We should evaluate. We need to think much more creatively at the adoption stage about how we are going to deal with this innovation system because what happens here at adoption isn't just neutral, it has an effect."

– Fiona Miller

The hype-bubble has spawned thousands of clinics in the USA and Canada that are promising stem cell cures, using supposed treatments that are not benign. In sifting through the database of ongoing clinical trials to understand the landscape, it is important to note that clinicaltrials.gov, a database of privately and publicly funded clinical studies from around the world, is simply a registry and does not include any quality control. Regulators such as the FDA and Health Canada are now stepping in to try to shut down fraudulent clinics by clarifying the regulatory stance that cell therapies are in fact drugs; at the end of the day, the enterprise of science should be based on credible evidence of safety and efficacy for patients and identify issues that diminish the public's trust in regulatory and reimbursement agencies.

Strengthening our regulatory environment

We are functioning in a regulatory environment where people doing HTA and

reimbursement are dealing with decisions about what qualifies as adequate evidence to allow access to market, and where there is a stronger emphasis on market access than on public health. There has been some pushback to this, and in 2013 Health Canada raised the bar on transparency under Vanessa's Law to protect Canadians from unsafe drugs and devices. We need to be asking why statutory/regulatory review is emphasizing market access.

Innovation in finance

Finance for our innovation system is extraordinarily expensive and has a large number of players – from dominant enterprises that self-finance innovation and R&D, to start-ups and venture capital firms that want to get paid vast amounts of money. For this reason, we need to think more creatively at the adoption stage and innovate at the HTA reimbursement stage, particularly around transparency of R&D costs, transparency of where taxation is being paid, the acceptable return on investment for a company, and the price government will pay. It is not just about the ICER; it is a bigger upstream question.

Highlights from open discussion: session 3 (see also Box 4)

1. Engaging the public: We have to be careful to avoid falling into the deficit model of public understanding of science, which infers that if the public knew more about science, they would think more like scientists. In fact, people's judgments and values and heuristics about how they think through problems are generally defined from a suite of social characteristics that have little to do with how much more information they receive. We need to let unanticipated questions from the public rise to the surface and to be more innovative about where we engage in public discourse and go to the locations, like yoga studios and church basements, where people have conversations that matter.

2. Innovations in Canadian CAR T patent development: In Canada, we are using regulatory filings as a tailorable exclusivity period to provide developers with a fixed term, relative to their innovativeness, of exclusivity on the market after which time generics or biosimilars can have a rapid entry. We need to bring more innovation to our toolkit that applies to the intersection of intellectual property, data exclusivity and patent terms. For example, some suggest that an extended market exclusivity period could be granted commensurate to the degree to which companies agree to share their data in the public domain.

BOX 4

Questions and comments for further consideration: session 3.

- Some argue that HTA expresses social values related to our respect for science and for the wise use of healthcare resources. To what extent can we respect these values in this context by taking our HTA methods and our activities seriously? Transparency of rules and following them is one of the best ways to do that. But one of the problems with HTA is that it brings a distinct and arbitrary logic to the allocation system. It brings a value for money judgement that is absent from all other allocative decisions, which are based on a business model and return on investment. An HTA logic is not present in most of those allocative decisions and so we have an HTA system that is set up to be a front door for certain industries and products, but an enormous amount of the allocative decision-making is not going through that front door and is not subject to HTA reasoning. But social values reflected in HTA processes are important meaningful values that assess broad questions of social concern. They address questions of solidarity, equity and belief in science, which is something we want to foster and something that Canadians want to believe in.

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Session 4: Health Technology Assessment Overview

Speakers

- Heather Logan, Senior Advisor, Pharmaceutical Reviews, Canadian Agency for Drugs and Technologies in Health (CADTH; Canada)
- Pilar Pinilla Dominguez Senior Scientific Advisor, National Institute for Health and Care Excellence (NICE; UK)

Discussants

- Suzanne McGurn, Assistant Deputy Minister, Drugs and Devices, and Executive Officer, Ontario Public Drug Programs Government of Ontario (Canada)
- Rebecca Yu, Vice-President, Market Access & External Affairs, Takeda Canada (Canada)

HTA perspectives from the National Institute for Health and Care Excellence (NICE)

NICE's evaluations pertain to clinical and economic evidence for new technologies or existing technologies for new indications. The Department of Health and Social Care, UK, formally refers topics for NICE evaluation. By 2020, NICE will expand its scope to review all new drugs approved by drug licensing agencies in addition to most new uses of approved drugs. For updates, see [12].

Key elements that NICE values in its appraisals are clinical effectiveness, cost–effectiveness, end of life care, innovation, degree of need, equity and non-health objectives. The two key questions for NICE when doing health technology evaluations pertain to cost and benefit.

Benefit: How well does the technology work when compared with established practice in the health service?

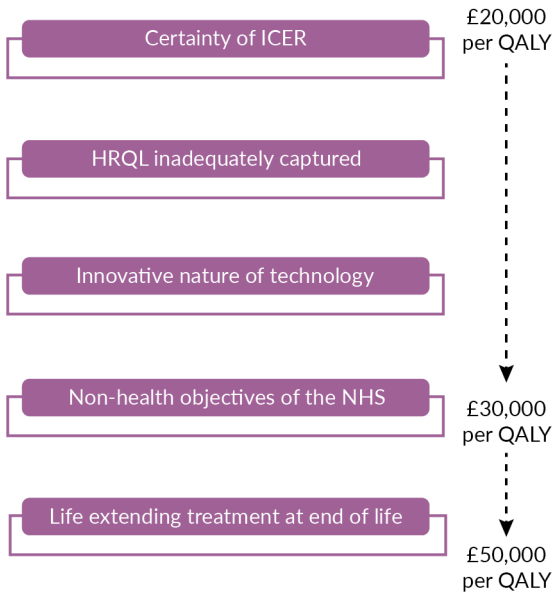
Cost: How much does this course of action cost compared with established practice in the health service?

One of the distinctions of the NICE appraisal process is that recommendations carry a funding mandate as acknowledged in the NHS constitution. This means that if NICE recommends a drug for routine use, it must be made available by NHS England within three months of NICE publishing final guidance. To use NHS resources cost-effectively, NICE's threshold is between £20,000 and £30,000 pounds per QALY gained. However, there is some room for flexibility in that NICE is also able to recommend treatments that extend the life of patients at end of life (EOL) up to a threshold of £50,000 per QALY, with QALYs given more weight for certain health benefits (Figure 6) [13].

Importantly, affordability is not one of the criteria that NICE values in its decision-making. This leads to the practical reality that

FIGURE 6

Flexible decision-making at NICE.



NICE's threshold for a good use of NHS resources starts at £20,000 per quality adjusted life year (QALY). Flexible decision-making based on the certainty of the ICER, adequate capture of the HRQL, innovative nature of the technology and non-health objectives of the NHS allows for increases in the recommendation to £30,000 per QALY. Committees are also able to increase the QALY to £50,000 to recommend treatments that extend life of the patients at end of life [13].

NICE might recommend treatments for a disease, such as hepatitis C, that are cost-effective but for which NHS England does not have the funds to cover within 3 months of the published NICE guidance. To address this issue, NICE and NHS England have introduced a budget impact test to balance cost and affordability by identifying technologies that might exceed £20M per year in any of the first 3 years. Such cases trigger an alarm for NICE to notify NHS England, giving it the opportunity to negotiate commercial arrangements with companies and apply for an extension to the implementation period of 3 months if needed.

What's new at NICE? As of April 2019, NICE started a cost-recovery tool for the technology appraisals process and is exploring new innovative payment methods that can help to offset the risks of drugs having substantial health benefits yet great uncertainty. NICE has also committed to timely guidance enabling patients to have access to treatments as soon as possible (Figure 7) [13], and has aligned its process so recommendations are available as close to marketing authorization granted by the regulators, such as the European Medicines Agency (EMA) centralized procedure (NICE Guide to the Process of Technology Appraisal) [12]. The major change is at the technical engagement step where there is now a consultation to tackle the uncertainties before the first NICE committee meeting. Following an initial evaluation, the two main ways to manage uncertainty are to collect more data to mitigate the clinical uncertainties and to do commercial negotiations that lower the risk of making a wrong decision.

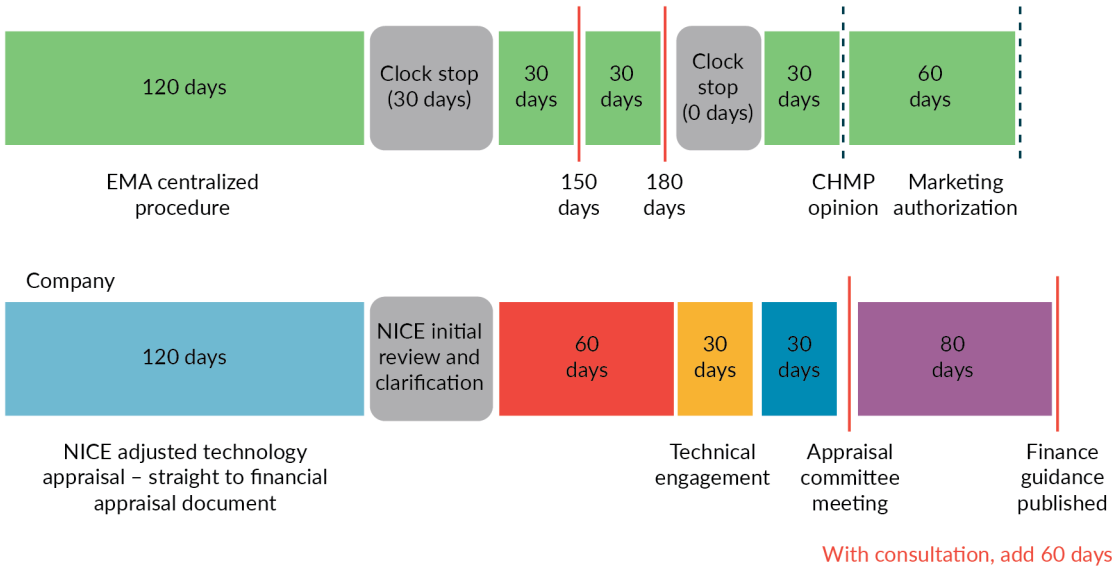
CAR T Evaluations at NICE. In the case of CAR T therapy evaluations, the committees could not recommend the technologies for routine commissioning to the NHS, with the following rationale.

1. All of the ICERs were above the threshold:

- Tisagenlecleucel-T for ALL (up to 25 years): >£30,000 per QALY
- Tisagenlecleucel-T for DLBCL: >£50,000 per QALY

FIGURE 7

New NICE timeline for technology appraisals.



NICE has aligned its technology appraisal process (bottom panel) with the regulators (e.g. EMA) (top panel) to expedite patient access to treatments and increase the capacity of NICE. Key time saving steps – having the consultation before the first committee meeting and having only one instead of two committee meetings – allow NICE to publish final guidance as soon as marketing authorization is out. CHMP; Committee for Medicinal Products for Human Use [13].

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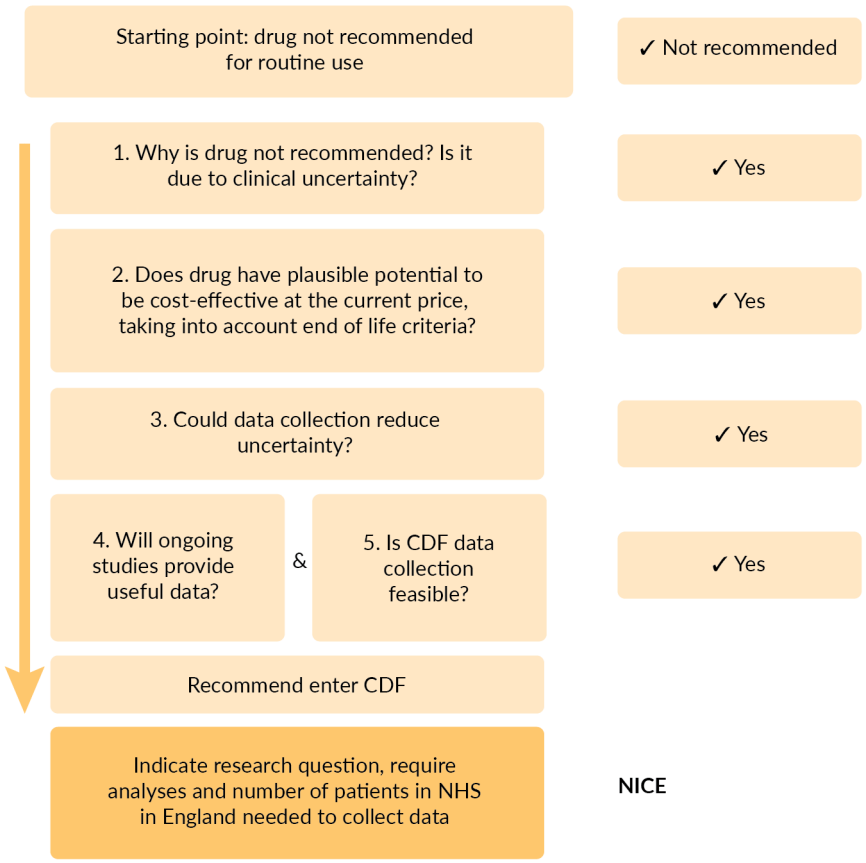
FIGURE 8

Committee rationale for recommending CAR T therapies to the Cancer Drugs Fund (CDF).



NICE inputs into the CDF since 2016 are understood as a tool for recommending technologies that wouldn't otherwise be recommended in the NHS because of their clinical uncertainty/high risk. The CDF serves as a gateway to evaluate if such technologies could be recommended for routine practice in the future. Following the steps shown, all three CAR-T therapies (Tisagenlecleucel for ALL, Tisagenlecleucel for DLBCL, and Axicabtagene ciloleucel for DLBCL were recommended within the CDF [13].

- Axicabtagene ciloleucel for DLBCL: >£50,000 per QALY

2. The committee rejected the non-reference case of applying a 1.5 percent discount rate because they did not consider that there was robust evidence to demonstrate a curative effect to sustain near full health over a long period of time.

3. The committee accepted the EOL criteria as they were met for the DLBCL examples in adults, but it did not accept them for the children ALL appraisal because they considered that the life expectancy with standard of care would be more than 24 months.

As noted in 'Session 2: Health Economics', technologies that would not otherwise be recommended in the NHS because of the high degrees of uncertainty and risk can be considered for time-limited funding by the CDF.

The committee's rationale for recommending all three CAR T therapies within the CDF is shown in Figure 8 [13], with the requirement for ongoing data collection and re-evaluation after five years. For the benefit of companies, NICE now has an Office for Market Access to facilitate conversations between stakeholders, and also offers scientific advice, including a parallel service with CADTH. Companies are encouraged to think about their uncertainties early and plan their regulatory and

HTA submissions in parallel, consider the key issues early for HTA and engage in order to obtain scientific advice on topics such as:

1. Clinical trial design and feasibility to conduct comparisons with established practice;
2. Relevant outcomes, their relationship with health-related quality of life and mortality, and frequency of data collection;
3. Proposed modelling approaches (based on clinical plausibility and data available to date) to deal with uncertainty at the time of submission;
4. Long-term evidence generation plans (often forgotten at early stages) to increase relevance of post-marketing authorization studies including clinical effectiveness and adverse effects data; and
5. Data collection in the relevant setting.

HTA perspectives from Canadian Agency for Drugs & Technologies in Health (CADTH)

CADTH programs and services include drug reimbursement recommendations, health technology management, scientific advice and knowledge mobilization, and liaison officers. CADTH receives funding from Canada's federal, provincial and territorial governments, with the exception of Quebec, where there is a parallel organization called INESSS. CADTH also receives industry funds through submissions. Heather Logan reviewed the differences between a drug and clinical intervention HTA, with a particular focus on lessons learned from the first CAR T evaluation. On the drug side, CADTH accepts submissions to review specific drugs on a drug-by-drug basis. For medical devices and clinical interventions, CADTH typically identifies the processes to review and jurisdictions to prioritize followed by the HTA.

In Canada, the first step for a new drug to access the market is to obtain a Health Canada approval (Figure 9) [14]. The manufacturer then starts the HTA review process by making a submission to CADTH and/or INESSS. At CADTH, drug submissions then track to one of two drug programs: the CDR (Common Drug Review) or pCODR (pan-Canadian Oncology Drug Review). On the drug side, CADTH looks at clinical and cost–effectiveness, patient values and implementation feasibility. Following that, the pan-Canadian Pharmaceutical Alliance (pCPA) negotiates on behalf of provinces that opt in to a negotiation. This work is designed to help provincial health ministries make decisions about drug and device funding, ensuring that the systems are sustainable.

With the intent of making the process as efficient as possible, CADTH is now conducting reviews in parallel with the Health Canada regulatory review. If the manufacturer is able to submit both the regulatory dossier and the HTA dossier at approximately the same time, the time to a CADTH recommendation after Health Canada approval can be shortened to mere days versus an average of six months previously.

Both the regulatory and HTA review processes in Canada are different for drugs and devices. Adding to the complexity, Canada is highly decentralized with every jurisdiction having the ability to make its own funding decisions. Within the HTA review for drugs, and particularly for pCODR, most cancer drugs, with the exception of biosimilars and line extensions, proceed through the HTA process. In contrast, medical devices and interventions can be implemented and funded in healthcare systems across Canada without going through the HTA review process. For devices, CADTH is asked to conduct a review on high-priority devices or technologies, often by provincial healthcare systems or other key players across the country.

The decision to evaluate a product as a pharmaceutical versus a clinical intervention/device depends on the mechanism for adoption within the province. For example, if the mechanism for adoption is being funded and placed on a formulary, then the pharmaceutical review process (pCODR or CDR) would apply. If the mechanism for adoption and funding is a complex implementation process, as for CAR T, the submission would

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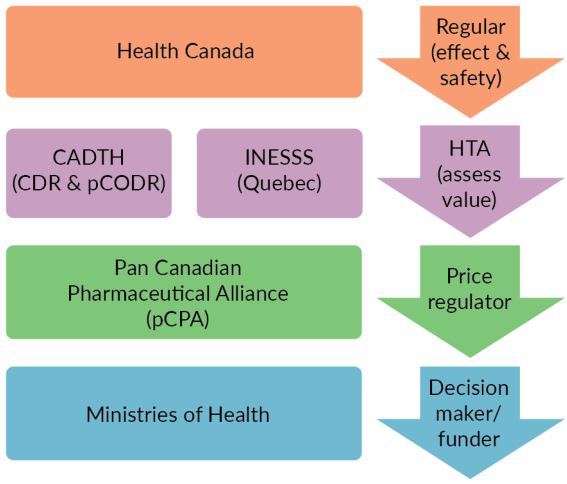
FIGURE 9

Overview of Drug Review in Canada.



Drug review in Canada starts with submission to Health Canada which looks at regulation, safety, marketing and manufacture of drugs. Drug value is then assessed in Ontario by CADTH, through the CDR or pCODR programs, or in Quebec through INESSS. Following this step, the pCPA negotiates price on behalf of the provinces that opt in to the negotiation. Finally, the Ministries of Health make decisions about drug and device funding, ensuring that the systems are sustainable. In Canada, following a submission to Health Canada, and with manufacturer consent, HTA and regulatory reviews can run simultaneously [14].

be a clinical intervention. The HTA Framework for Adoption, showing the ways in which the CADTH Health Technology Expert Review Panel (HTERP) deliberates on value for different HTA pathways is shown in Table 4 [14].

CAR T Evaluations at CADTH. For the first CAR T product reviewed, HTERP recommended the provision of tisagenlecleucel with the condition of a reduction in price, and an emphasis on implementation and ethics. These products are now available in a small number of centres and require careful decisions about patient access and equity. Specific recommendations from HTERP include:

1. The creation of interprovincial agreements to ensure equitable access to eligible patients in all jurisdictions, including consideration of financial and logistical support for required travel and short-term relocation;

2. The development of clear and transparent eligibility criteria that are acceptable to the needs of patients and clinicians, based on the approved indications; and

3. The collection of standardized outcome data in a pan-Canadian registry of patients, which uses a defined set of outcomes and definitions to generate real-world evidence for consideration in future reassessments of longer-term effectiveness, safety and cost–effectiveness (this speaks to some of the similarities of the NICE review).

From CADTH's first HTA review of CAR T therapy, it is clear that these are not only disruptive technologies, but also complex interventions involving multiple parts of the healthcare system. They are different from drugs, but they are not just devices or simple clinical interventions and they require a different order of magnitude of conversation around discussion and planning.

In closing, Logan noted that Canada has done well at managing this very disruptive therapy, and has moved from HTA to health technology management, reflecting the need as these new innovative, complex therapies with high value and high price tags come forward. But there is room for improvement. With a willingness to collaborate, learn and adapt, Canada can become better and faster at developing the networks that support the needed discussions, and do a better job of addressing the implementation issues by balancing the vigorousness of HTA with what decision-makers need.

TABLE 4

CADTH HTA framework for adoptions [14].

	Drugs	Clinical intervention
Relevance and unmet need	✓	✓
Benefits	✓	✓
Harms	✓	✓
Patient perspective	✓	✓
Economic impact	✓	✓
Implementation		✓
Legal		✓
Ethical		✓
Environmental impact		✓

Insight from discussants: session 4

Competing for finite resources

For evidence generation that underpins complex products, one of the hallmarks is increasing uncertainty, which is important for payors who must make choices about where to spend finite resources. Additionally, people don't always take into account the opportunity cost of what is not being funded. For example, we could have demand for a therapy to fill a critical unmet need with high uncertainty and at the same time have demand for a complex intervention with less uncertainty and a greater likelihood of success, but they are both competing for finite resources.

"HTA processes are the single greatest influencer of the funding decisions that we have. They provide a significant amount of information to inform our decisions and in some jurisdictions in Canada they become a gatekeeper of a 'yes' or a 'no', making a decision as to whether a jurisdiction will even consider to move on funding."

–Suzanne McGurn

Q and A from open discussion: session 4

(Q1) As more and more therapies come to market and as CADTH starts assessing non-T cell immunotherapies, will the classification of these drugs change?

(A1) At present, CADTH is still looking at CAR T therapies as clinical interventions because of the complexity of the cost. However, if supported by the jurisdictions, the need for a change in classification may arise and CADTH would need to consider that down the road.

(Q2) For disruptive technologies, are the de-implementation challenges greater because of the up-front investment in infrastructure?

(A2) NICE has had two technologies go through and exit the CDF and both have proved to be cost-effective and have been recommended for routine commissioning. During the CADTH review process, there were many attempts at the system level to piggyback and work with infrastructure that already existed. The platforms weren't built *de novo* so a system might change but an entire system would not need to be removed.

(Q3) How will taxpayers be given equal access to complex interventions?

(A3) In a country as large as Canada, the question of equity always comes up and there are therapies that will only ever be available in southern Ontario or Toronto. As a result of these logistical challenges, making some of these products available in Canada in a cost-effective way requires a different solution each time. That said, CADTH works very closely with the Canadian Association of Provincial Cancer Agencies (CAPCA) to look at patient access provisions across jurisdictions to ask if there is a way for a centralized review to prioritize which patients receive therapy and when they receive it, regardless of their geographical location. Different kinds of indications will require different processes. The ethics review at the HTA level raised these considerations as a fundamental part of implementing complex and hard-to-access therapies given the small number of potential administering locations.

"If you are a patient, these are transformative therapies. So how do we approach it so that patients get early access and are not denied early treatment, but at the same time, there is some assurance that the payors are getting what they think they are paying for?"

– Rebecca Yu

Session 5: Payment System Mechanisms

Speakers

- Ana Duarte, Research Fellow, Centre for Health Economics, University of York (UK)

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Discussants

- Rebecca Yu, Vice-President, Market Access & External Affairs Takeda Canada (Canada)
- Grace Hampson, Senior Principal Economist, The Office of Health Economics (OHE; UK)

HTA perspectives from the University of York, UK

In the past, the conventional reimbursement paradigm was 'to accept or not to accept'. Currently, technologies with higher up-front costs and uncertain health outcomes may require novel policy options so that decision-makers can appropriately take into account these features. In this session, Ana Duarte provided an overview of existing payment mechanisms to serve as discussion points for the ensuing dialogue.

In 2012, Walker and colleagues proposed a taxonomy of alternative payment arrangements named managed entry agreements (MEA). Walker's Framework for Coverage Decisions [15] distinguishes between two types of MEAs (Box 5). Walker concluded that it was important to go beyond considering the expected benefits of technology to also take into account the value of uncertainty around the estimate, how to incentivize further evidence generation, and the costs associated with the reversal of uncertain decisions and irrecoverable costs.

In 2016, Grimm updated the Walker taxonomy in 'Framework for Analysing Risk in Health Technology Assessments and Its Application to Managed Entry Agreements' [16]. Published by the NICE Decision Support Unit (DSU) the report developed a quantitative framework for MEAs a) with a reduction in price and b) with evidence generation. The rationales underpinning these MEAs are different. MEAs with a reduction in price reduce the payor's risk of funding a treatment that is not cost-effective, by ensuring that the treatment is more affordable (Box 6). MEAs with further evidence generation reduce uncertainty and with it the payor's risk (Box 7).

Duarte stressed that while the framework allows the assessment of which MEAs may be more appropriate without placing a higher evidence burden on the manufacturers, it relies on the appropriateness of the decision model to produce plausible probabilistic cost–effectiveness estimates and that uncertainty is duly captured by the probabilistic analysis. Additional financing schemes (Box 8) were proposed by Towse in 2014 specifically for the world of regenerative medicine [17].

Insight from discussants: session 5

Novel payment mechanisms

If we are going to invoke novel payment models, what is it about specific technologies that will prompt the change in standard operating procedures? We have a fundamentally sound process for evaluating 95% of health technologies. However, when we see something that meets an unmet need or produces an enormous effect size in a very small data set, we feel ethically bound to not withhold that from patients for the usual period of time for the HTA process. But novel payment mechanisms entail considerable administration and burden to management.

Challenges of the amortization approach

Neither payors nor manufacturers nor governments want to hold the risk and we don't

BOX 5

Managed entry agreements (MEAs) in Walker's framework for coverage decisions [15].

1. MEAs that consist of a reduction in the price of technology, outcomes-based or non-outcomes- based;
2. MEAs associated with further evidence generation, only in research or recommended with research.

BOX 6

Managed entry agreement (MEAs) with reduction in price [16].

Outcome based: patient level

- Money-back guarantee: manufacturer refunds money or stock to payor
- Conditional treatment continuation: payment only when target is achieved
- Price linked to outcome: reimbursement linked and/or weighted with different health outcomes

Non-outcome based: patient level

- Discount treatment initiation – lower price initially and then price reverts to list price
- Utilization cap – regardless of length of treatment, a cap ensures reduced budget impact of drug
- Fixed cost per patient – regardless of the number of treatments

Non-outcome based: population level

- Single discount – most commonly seen at NICE
- Expenditure cap – cap is regardless of the quantity that is provided
- Price volume agreement – discounted price when certain volume is reached for economies of scale

want to give it to patients. Financial markets are used to purchasing financial risk and being repaid through risk premiums, so this approach might be worth exploring. Other models include the mining industry, which issues bonds. But involving financial institutions with the risk of healthcare requires artificially attaching upside to the risk. If the inherent upside to drug production lies with the manufacturer, it would be better to push the risk towards the manufacturer as much as possible to avoid having to create an artificial upside. If the manufacturers are holding the risk, then they would need to be compensated for the risk. Another challenge is how to deal with multi-payor situations, as would happen if people were to change jobs and insurance providers part way through their treatments. Additionally, there are the legislative and accounting challenges that occur with party changes after elections.

BOX 7

Managed entry agreements (MEAs) with further evidence generation [16].

Recommended with research/only in research

- Reimbursement only – payor reimburses manufacturer for all patients but arrangements must be made as to who pays for research (payor, other entity, manufacturer?);
- Refund and reimbursement – payor initially pays for research but manufacturer provides refund if treatment or value was less than expected;
- Conditional flexible pricing agreement – price is revised at determined points as evidence is collected and further evidence is generated.

Operationalizing pay-for-performance schemes

Governments and HTA agencies want to pay for what performs, but the challenges include limited resources, infrastructure and staffing, and the need for up-front investment. In addition, the two-payor system in Canada – the private and public sector – adds a layer of complexity. Another issue is trust and whether industry is the right group to monitor outcomes. One option would be to give resources to an organization like THETA to develop a group that could collect outcomes. Another option might be to have manufacturers provide funds up-front for infrastructure investment (e.g., electronic data collection) as a cost-effective way to incentivize pay-for-performance.

Another huge challenge around operationalizing pay-for-performance schemes is around defining outcomes. Registries have few people treated and there is no way to know if the drug is continuing to work unless

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BOX 8

Financing schemes for regenerative medicines [18].

- **Amortization**: spreading out higher up-front costs over a period that reflects the time profile of the benefits
- **Pay-for-performance**: requires tracking the payment and the performance measure of success
- **Leasing**: dividing the cost over time to reflect the expected benefits, and if the measure of success is not being reached, then price is revisited and reduced over time; can combine amortization and pay-for-performance
- **Innovative financing from the financial markets**: payer sets up bonds that another entity buys, and payer provides return on investment (e.g., vaccines)

you have a comparator group that has not received treatment. The practical reality is that in the real world, discerning modest improvements in health requires a trial or some method of indirect comparison.

Highlights from open discussion: session 5 (see also Box 9)

1. How can we define data registries in a way that is relatively economical, and without a huge footprint in data entry? Electronic data collection in Canada is lacking. Currently, we can run parallel analyses across provinces, but we are not able to pool provincial data. We do, however, have provincial data that allows us to capture outcomes in a relatively cheap way, and we can look at survival, re-hospitalization and resource use in a way that doesn't cost a lot of money.
2. The challenge is to identify a core data set at the time that treatment is initiated. Ideally, this would include disease, stage, histology, line of therapy, pathology information, comorbidity information and untreated comparators, if available. Registries are often very expensive because they are data-hungry and require ongoing data collection. A lot of these analyses are done with the idea that the registry alone will be the full source of analysis, but a registry linked to administrative data is a way of making this national and economical.
3. HTA and payment schemes are separate but inter-related issues. In terms of the payment mechanism, setting up a data collection mechanism could be relevant before HTA. Perhaps the payors should be brought in at the scientific advice stage and decision-makers brought in as part of the journey of evidence generation. The challenge is that this would be time- and cost-prohibitive to get the perfect body of evidence and the right voices around the table.
4. How can we ensure that CAR T-like therapies are sustainable in the long term, especially if they are going to be used for solid tumors? This is a very complex question and it will be hard to put forth solutions until we know what's coming through the pipeline and how the original solutions that we have proposed and piloted actually play out. In the UK, these

BOX 9

Questions for further consideration: session 5.

1. Does payment for regenerative medicine/ATMPs require intervention at the national level?
2. How can we take our well-established HTA processes to inform our public sector R&D investments and to help those in academia where a lot of the initial research is done?
3. For immunotherapies (such as CAR T) and other gene therapies, is there a way to bring people together at a discrete point in time, rather than at every step of the process for every therapy, to have a discussion around access to data and desired outcomes?
4. Who should be at the negotiating table where the payment scheme is being discussed?
5. Should the public have to bear some of the risk for novel payments so that equity for the population is ensured?

existing therapies have been deemed to be cost-effective so we would expect there to be some cost offsets down the line.

5. Does the federated system in Canada present an additional challenge to novel payment methods? The interprovincial regulatory constraints in Canada mean that there are blockages in moving patient data and integrating data among provinces so that every piece of an analysis must be done in every province. In addition, payments are from the provinces, which do not have equal budget sizes, so not all provinces can implement all the different arrangements leading to equity of access interprovincially. It is not as simple as saying that there is a national body that can make decisions about the risk willing to be borne by the actual payor. The political will to address these challenges would have to occur at the inter-ministerial level.

Session 6: Adoption & Implementation

Speakers

- James Rose, Head of Clinical Innovation Adoption, Oxford Academic Health Science Network (OAHSN; UK)

Discussants

- Dr John Kuruvilla, Hematologist, Princess Margaret Cancer Centre, University Health Network (UHN; Canada)
- Linnea Doyle, Senior Director, Market Access & Government Relations, Gilead Sciences Canada
- Shahira Bhimani, Director, Health Solutions MaRS Partnerships (Canada)

Exploring adoption & implementation of ATMPs: a UK perspective

"Is the UK an attractive market for ATMPs?" This is the question posed by James Rose as he presented some real-world examples of how the UK is tackling the multi-faceted challenges in the field. He noted that meetings such as CHART are critical for bringing together the full gamut of stakeholders to drive the field forward.

The UK has invested heavily in the adoption of innovation across healthcare. With this mandate, the NHS funded 15 Academic Health Science Networks (AHSNs) in England. As one of the networks, the Oxford Academic Health Science Network (OAHSN) brings together 700 life science companies, six large acute hospital trusts, five universities and 3 million citizens. Their focus is to

TABLE 5

ATMPs licensed in the UK [18].

Name – manufacturer	Indication	Auth.	NICE TA
Strimvelis® – GSK	ADA-SCID	2015	Approved
Imlygic® – Amgen	Melanoma	2015	Approved
Holocar® – Chiesi	Severe limbal stem cell deficiency	2015	Approved
Zalmoxis® – Molmed	Stem cell transplantation (high-risk blood cancer)	2016	Approved
Spherox® – co.don	Cartilage defects in knee joint	2017	Approved
Alofisel® – Tigenix	Perianal fistulas in Crohn's disease	2018	Rejected
Yescarta® – Kite/ Gilead	B-cell lymphoma	2018	Approved
Kymriah® – Novartis	ALL, DLBCL	2018	Approved
Zynteglo® – Bluebird	Transfusion-dependent thalassaemia (TDT)	2019	Pending
Luxturna® – Bluebird	Inherited retinal disease	2019	Pending

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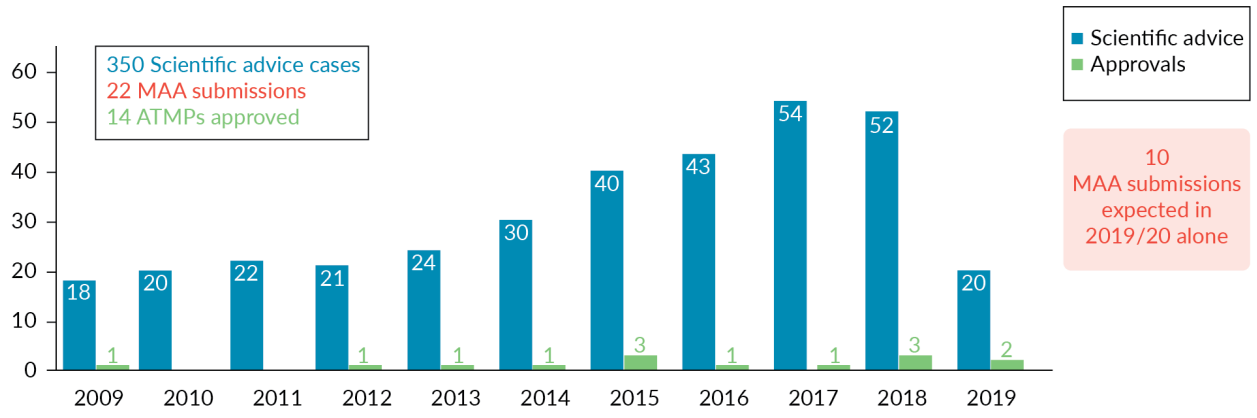
FIGURE 10

Expectations of steep rise in submissions and authorizations.



Since 2009 to 2019, there have been 350 new scientific advice cases and 14 ATMPs approved. Of the 22 Managed Access Agreement (MAA) submissions, 10 are expected in 2019/2020 [19].

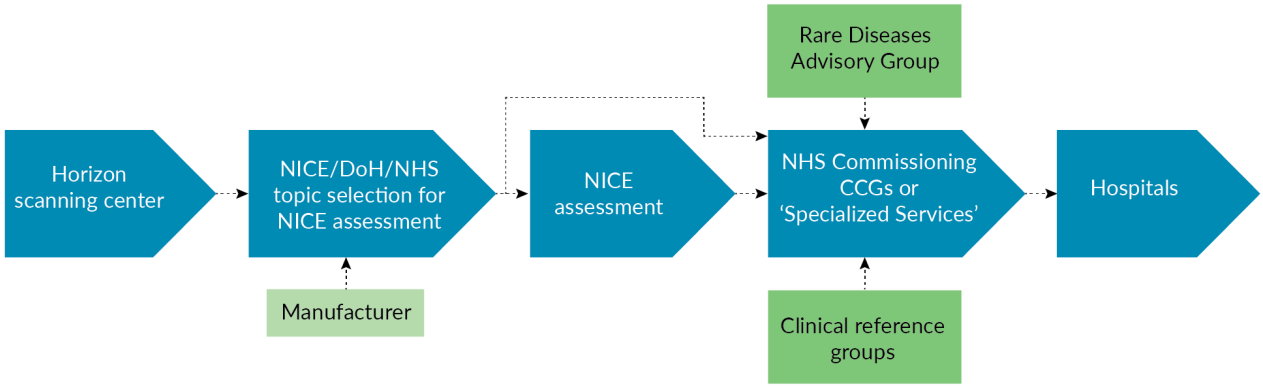
spread innovation 'at pace and scale', creating sustainable networks that improve health and generate economic growth.

The UK government has also invested specifically in the ATMP space, with £250M funneled to translation and adoption of ATMPs through Cell and Gene Therapy (CGT) Catapult, the CGT Manufacturing Centre, and Advanced Therapy Treatment Centres (ATTCs). Practically speaking, NHS England should be an attractive market for ATMPs: it is a single-payor market, with advantages in centralized commissioning, coordination, standardization, operators, risk management and data collection. But more experience with ATMPs is required to develop the needed processes and systems for adoption and implementation.

To date, 10 ATMPs have been licensed in the UK (Table 5) [18], seven with positive NICE technology assessments, one not recommended and two pending. With a spike of 350 new device submissions and 22 Managed Access Agreement (MAA) submissions (Figure 10) [19], 10 expected in 2019/20

FIGURE 11

Top-level road map to market access for licensed ATMPs in England.



The pathway to market access revolves around horizon scanning and feeds into NICE topic selection and assessment. The next steps involve a commercial negotiation, normally between NHS Specialized Commissioning and the manufacturer, with involvement from the Rare Diseases Advisory Group and Clinical Reference Groups [13].

alone, the EMA recognizes the need to be ready. The pathway to market access is relatively well-established in the UK (Figure 11) [13]. This process can be quite variable in terms of time, and sometimes NICE is criticized for how long it takes. But it can also happen quickly as it did in the example of CAR T, where there was a commercial arrangement 10 days after the first product was approved by the EMA. This demonstrates that speed is possible if there is political will.

Innovation adoption at its heart is a complex job. The pathway to adoption and implementation is much less established than market access, and there is considerable variation with hospital processes, governance structures and approval boards. Feedback from the 11 CAR T centers in the UK has flagged six institutional barriers to adoption (Box 10), with capacity and retraining dozens of staff for each new ATMP being the biggest issues.

The ATTCs are 'innovation hubs' set up across the UK to develop and deliver systems for cutting-edge cell and gene therapies. There are currently three ATTC hubs linking different geographical regions: Northern Alliance (Edinburgh and Newcastle), iMATCH (Manchester), and MW-ATCC (Midlands and Wales). In addition to these three centers, there are other centers that provide support and infrastructure for ATMPs such as the CGT Catapult, its Manufacturing Centre and the London Advanced Therapies Network. These networked hubs will increase the ability of NHS to deliver disruptive medicines by innovating around systems and processes (e.g., sample traceability and tracking) that can be rolled out to other centers. Some of the challenges the ATTCs are currently exploring include establishing clear pathways to gather industry feedback, defining a common framework to help companies navigate with harmonized procedures and practices, contract standardization, clinical scale-up requirements, patient engagement, patient monitoring, data collection and sharing.

The need to maintain a healthy public perception and manage expectations around availability and eligibility of ATMPs will also require understanding different perspectives of patients, clinicians, hospital managers and policy makers. Facilitating patient pull for these therapies will require more work around joint decision-making and patient education. Facilitating clinical champions will mean having more clarity around roles, responsibilities and governance. Buy-in from hospital managers will require them to understand the level of risk versus benefit for these therapies and how they align within the strategic priorities of their hospital trusts. Policy makers are willing to invest money in ATMPs, but there needs to be better alignment of policy and practice with patient need, up-scaling and the role of pharmacists, quality assurance, training, and creating a sustainable ATMP workforce to carry the therapies forward.

BOX 10

Institutional barriers to CAR T therapy [18].

1. **Capacity:** challenges around apheresis, stem cell freezing, staffing, ward intensive treatment unit (ITU) capacity
2. **Training:** standardized training and/or delivering more generic training
3. **Expression of interest accreditation:** thousands of person hours invested in accreditation and huge resource commitment to standards of practice, policies, pathways and guidelines
4. **Contracting:** variable rates and hospitals negotiating contracts separately and interpreting risk differently
5. **Governance:** multiple governance processes and more defined role of pharmacy in providing oversight of quality assurance required
6. **Patient management:** appropriate referral and patient review pathways and weekly meetings to review CAR T patients needed; ensuring that non-CAR T sites also have access to therapies

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In summary, Rose urged that we need to take this opportunity to learn from each other's innovation systems and how these complex problems are being tackled. We could manage the challenges of individual ATMPs, such as CAR T, but our systems are looking to adopt numerous ATMPs, underscoring the challenge of co-ordination and collaboration to ensure sustainable models for adoption.

Insight from discussants: session 6

Perspectives from clinicians

In Canada, accreditation is through a governing body called the Foundation for the Accreditation of Cellular Therapy (FACT). For clinicians looking to implement cellular therapy, the first question is the scope of cells involved (e.g., autologous or allogeneic stem cells, hematopoietic cells, cord blood, induced pluripotent stem cells, cardiac or musculoskeletal cells). As we start to navigate the delivery of such cells, building teams of content and modality experts will be key, but not without its challenges given the way that money and politics play into hospital decisions. Product cost is huge, but so too are the costs and resources for the machinery, freezers, apheresis, personnel, and beds needed to deliver the product.

For the short term, implementation of CAR T therapy can be grafted on to what is already in place for transplant work. But the data requirements, monitoring and follow-up clearly surpass the 'bricks and mortar' cash cost of the product. Lag time is also an issue because infrastructure takes time to build and is virtually non-existent apart from a few groups doing these therapies in research settings.

"Building teams of knowledgeable experts will be key for adoption and implementation of CAR T therapies."

– John Kuruvilla

From a patient perspective, equity of access is an issue in Canada, where the majority of expertise is in southern Ontario. Interprovincial funding relationships will need to be set up so that people outside Ontario can access the major treatment centers. Small centers will also face challenges in expertise around disease management versus modality expertise as it could be difficult to find people who can wear both hats. It is critical that people who have the expertise are involved earlier than at first-in-human studies. For early biotechnology start-ups, big centers are the place to go to look for people with the right expertise.

Perspectives from Canadian industry

CAR T therapy represents a new and unique space for pharmaceutical manufacturers. Because CAR T manufacturing uses an individual patient's T cells, comprehensive support systems are required to ensure that chain of custody and chain of identity for the patient's T cells are securely maintained both pre- and post-manufacturing of the cells. Unique systems, procedures, and processes are required from manufacturers to support product transport, delivery and administration and to ensure that quality requirements are met throughout with the least burden on institutional resources.

In Canada, manufacturers engage at three different levels to support adoption and implementation of CAR T therapies: the site level, the provincial health system level, and the national and interprovincial level. Opportunities and challenges at each level are shown in **Box 11**. Implementation at the site level builds on an existing network of FACT-accredited and transplant centers in hematological malignancies, with an established foundation for the multi-step pathway (quality, training, agreements) involving multiple stakeholders.

At the provincial and territorial level, Canada has 13 different health systems, each with a unique network of decision-makers (e.g., cancer agencies, provincial and regional health authorities, drug programs, Ministries of Health). Because CAR T therapy involves drug budgets and institutional

BOX 11

Engagement with Canadian manufacturers insight from the site level [20].

Site level opportunities

- Pre-existing FACT accredited stem cell transplant network
- Site level clinical/administrative champions
- High commitment to ensure readiness
- Extensive US experience (Kite/Gilead)

Site level challenges

- Number of people engaged in site readiness and training
- All sites unique (no 'one size fits all')
- Investment in readiness challenging in advance of confirmed provincial funding
- Time needed for contract reviews and finalization
- Site capacity
- Different standards of practice and work instructions for different manufacturers

Provincial level opportunities

- High awareness within ministries of health
- High engagement/interest for readiness
- Desire to set long-term system framework

Provincial level challenges

- Evolving pathways for decisions/multiple parties
- Budget alignment/ownership for CAR T therapies
- Inconsistencies in expectations/outlook may occur between sites and ministry of health
- Hospital capacity and capability – now and forward

National level opportunities

- Health Canada approach to address CAR T specific issues and to modernize framework for review of advanced technologies
- Novel HTA review process with high engagement
- Unique federal/provincial CAR T committee
- Pre-existing interprovincial frameworks
- Desire to set long-term system framework
- Willingness to regroup and debrief learnings through pan-Canadian process (CADTH, INESSS)

National level challenges

- Equity in access across provinces with and without sites
- Unique/evolving pan-Canadian negotiation pathway
- Longer-term policy development for cell and gene therapy

resources, a broader set of decision-makers are involved in the process. In light of this, Canada is seeing an evolution of provincial CAR T committees to support aligned decision-making.

At the national level, an important lesson has been the value of collaborative engagement, for example through the development of the initial CAR T Health Technology Assessment (HTA) review pathway with CADTH and INESSS. Industry engagement with Health Canada was also key. As CAR T pipelines evolve, industry will need to engage as early as possible to better understand the gaps and take that information back to R&D decision-makers to help build in the

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solutions as early as possible. Looking ahead to the multiplication of cell therapies in the hematological malignancy space and beyond, ongoing dialogue will be key to success.

Highlights from open discussion: session 6 (see also Box 12)

Lack of leadership in Canada

In Canada, one of the challenges is that there is a lack of ownership and leadership in this space. The Canadian Cancer Trials Group (CCTG) is interested in taking research forward: its mandate is to have real value for patients in Canada, but its expertise is around drugs. It has very little infrastructure around cells and is cancer-directed. The Canadian Bone Marrow Transplant group has just been rebranded as Cell Therapy Transplant Canada, and that group now sees the opportunity to take the lead on ATMPs and CAR Ts nationally. It has the people who run the labs, technicians who know how to handle cells, freezing, release criteria, etc., so it could provide leadership in this space.

Risk evaluation for contracts

The contracts coming to hospitals are of different qualities but the aspiration in the UK is that there might be a gold standard applied by NHS England to make sure contracts are up to scratch. It may mean bringing all the stakeholders around the table so that all partners are willing to sign the contracts. In Canada, there are some National Centres of Excellence (NCEs) and Centres of Excellence for Commercialization and Research (CECR), such as CellCAN, and CCRM, that could help with contracts. However, relying on them could be problematic as Canada has been defunding these types of network that bring actors together around knowledge mobilization and co-ordination activities.

Resources for adoption

In the UK, making business cases for additional staff is not trivial and there are many competing business cases being put forward. That will be a big challenge and the ATTCs are exploring what can be done. In Canada, therapies are becoming more and more complex and the busier things get, the more fatigue staff have and the more risk there could be to patients.

Developing expertise

In Canada, there aren't as many unique structures as in the UK or USA, and the same people are being called on to write responses to CADTH. In the UK, physicians typically engage through conferences and professional development as part of ongoing training, but there might not be training specific to ATMPs.

Pharmacist network connection

Some pharmacists in Canada recognize that they lack experience with ATMP products. Some argue that it would be better to minimally involve pharmacy since there are enough people already in the system who know how to deal with cells and release criteria etc. For example, at Princess Margaret Cancer Centre, UHN, pharmacy won't be involved because there is already quality infrastructure, auditing and management in place.

Harmonizing on-boarding processes

With multiple products and companies in this space, it appears that there are different on-boarding processes for every site to go through. This is not sustainable for every ATMP, so it will be important to find points of similarity (e.g., sampling, apheresis, logistics) to harmonize the process between products and reduce the burden of training and onboarding.

Selecting the workforce

Institutions in the UK are looking at apprenticeship programs to drive down the cost of ATMPs. For example, rather than having PhD students and career scientists making these products, it would be better to have apprentices brought up to that level. In the UK, the ATTC apprenticeship programs address

BOX 12

How to ease the pathway to implementation and adoption of ATMPs.

1. Find a solution for capacity. It is one of the single biggest challenges that will affect the sustainable adoption of future ATMPs.
2. Implement strategic proactive planning.
3. Start with the end in mind to understand how the policy-makers are engaged in the discussion and how the system could be structured.

the need for operators, managers and senior leaders, from bachelor's to masters-like technology qualifications. Done with success in the bioprocessing industry, this approach creates an incentive for partners to take on mentorship roles to help complement the workforce. Similarly, CCRM is recruiting for a broad spectrum of abilities in this space.

Speeding implementation & adoption

Having clinicians get involved with clinical trials might speed the implementation and adoption processes; the team would be more knowledgeable and pharmacists involved in the trial could help educate other pharmacists. It's also important to have policy makers, such as the provincial CAR T Committee in Canada, and decision-makers on hand because the clinical buyers of technology and innovation are different from the economic buyers.

Equity of access for children

Few places in Canada have the background expertise and facilities to do ATMPs and a much smaller number have experience in pediatric leukemias, so access for children will be an issue.

TRANSLATIONAL INSIGHTS

Globally, the ATMP space is bursting with opportunity. Canada, the USA and UK are well-positioned to be part of this ecosystem through their leadership in regenerative medicine clinical trials, centers of excellence hosting first-in-human pivotal studies, and early-phase clinical trial manufacturing capabilities. Around the world, hundreds of ATMP trials are being planned and within the next few years, numerous therapies could be approved and brought to market. The demand for such regenerative medicine products/ATMPs and the number of patients treated with them is therefore poised to increase significantly.

The adoption of new therapeutic products is predicated on the value assessment of clinical safety and efficacy as well as cost–effectiveness within a healthcare setting. While the challenges in the adoption of ATMPs are not unique to the regenerative medicine field, there are still many uncertainties, spanning from research and development to regulatory review and approval, manufacturing, reimbursement, ethics, and implementation. Adding to the complexity of the adoption process, ATMPs, such as CAR T therapy, are highly disruptive, enormously costly and onerous to bring to market, posing important challenges from an HTA perspective. Clear policies are urgently needed to inform how ATMPs will be sustainably paid for and to adequately consider the social, ethical and legal issues around their adoption.

The consensus from the CHART workshop point to seven touchpoints that need to be further explored to advance the adoption and implementation of complicated ATMPs, such as CAR T therapy.

1. Current methods of evaluation are applicable to ATMPs but the biggest challenge for these novel therapies is providing evidence that reduces the uncertainty of their long-term effects. Currently, there is a paucity of well-controlled clinical evidence driving the adoption of ATMPs, with examples of products having case studies of only 100

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participants who are non-randomized and non-controlled. This is not sufficient to evaluate outcomes over time.

2. The generation of evidence of clinical effectiveness needs to be improved by ensuring clinical trial designs employ robust controls and increase their sample sizes while collecting data in the relevant setting. It is critical to develop a research and policy agenda around improving the clinical evidence base as well as collecting real-world evidence – as distinct from real-world data such as patient submissions or economic evaluations – through vehicles such as registries and trials. Addressing five critical needs could improve the evidence base: (1) conduct controlled trials; (2) define evidence versus data; (3) develop methods to evaluate real-world evidence and outcomes over time; and (4) consider costs, patients and relevance to policy.

3. Incentives for real-world evidence capture should be established to ensure that data are gathered and can be used to further evaluate the therapies for long-term clinical effectiveness and adverse effects.

4. The implementation of ATMPs will require concerted efforts from multiple stakeholders to ensure that the adoption pathways are efficient and effective, and aligned with social values. The question is how best to ensure politicians will pay attention and invest in the infrastructure required to facilitate the adoption and implementation of ATMPs with the appropriate evidence base and HTA. A targeted approach could involve: (1) using documents such as this one to inform relevant scientific, policy, traditional HTA and economic groups; (2) creating unique business cases including outcomes and impact to mitigate risk; and (3) creating targeted messaging for financial asks.

5. There needs to be greater interaction with policy makers, as political will is essential for research to progress into meaningful efforts. For example, Canada has a long and complex list of policy makers, so it is important to be selective about who to engage and how to engage them to avoid diluting efforts. Practical strategies within Canada might include: (1) watching for shifts in provincial health because Ontario Health (including Cancer Care Ontario, Health Quality Ontario, eHealth Ontario, Trillium Gift of Life Network, Health Shared Services Ontario, HealthForceOntario Marketing and Recruitment Agency, and 14 Local Health Integration Networks) is evolving; (2) securing top-level buy-in at the Executive Director level for integrated implementation and adoption work in the ATMP field; (iii) continuing to have regular conversations with other provinces and jurisdictions as changes unfold within the provinces; (4) making a value case to policy makers and framing health outcomes and budget as well as broad societal perspectives and the return on investment.

6. There is a need to improve patient management and data management to aid in evidence generation and facilitate outcome-based payment mechanisms. To that end, we should identify allies in our ecosystem who might have the same problems or challenges. In the ATMP field, obvious partnerships to leverage would be from other high-value, high-risk fields such as oncology, rare diseases and pediatrics.

7. Payment mechanisms remain a challenge; in addition, the sustainability of current payment methods for expensive therapies will need to be evaluated, prior to the approval of more ATMPs. Creative payment mechanisms including amortization, pay-for-performance, leasing, bonds and risk fund hedging exist in other industries (e.g., accounting, natural resource extraction, aerospace) and could be further explored for ATMPs.

In summary, addressing the challenges in adoption and implementation of regenerative medicines/ATMPs requires a deeper

understanding of the landscape. Future working groups could prioritize evidence generation issues, stakeholder and targeted policy maker engagement, and payment system mechanisms. The creation of a stakeholder map would also be a valuable tool for identifying stakeholders who could help tackle the remaining challenges, create targeted information for policy makers, and drive the field forward.

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20. Linnea Doyle, Gilead Sciences, Inc.

AFFILIATIONS

Maya Chaddah
Science Communications

Allison Brown
Director, Strategy & Translation, Medicine by Design, University of Toronto

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Siofradh McMahon
Senior Manager, Clinical Translation & Regulatory Affairs, CCRM

James Kusena
Centre for Biological Engineering and Wolfson School of Mechanical, Electrical and Manufacturing Engineering, Loughborough University, UK

Karen Bremner
Research Associate, Toronto Health Economics and Technology Assessment (THETA) Collaborative, University Health Network (UHN)

Ann Perry
Associate Director, Administration, Medicine by Design, University of Toronto

Murray Krahn
Toronto Health Economics and Technology Assessment (THETA) Collaborative, University Health Network (UHN)

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CELL & GENE THERAPY INSIGHTS

MARKET ACCESS: EVOLVING COMMERCIALIZATION TRENDS & STRATEGIES

SPOTLIGHT

COMMENTARY

Innovative payments for innovative therapies: adopting value-based models in the regenerative medicines & advanced therapy sector

Janet Lambert

With this new wave of transformative therapies rushing towards us, payors, policymakers, and other stakeholders must implement the infrastructure necessary to ensure broad patient access and appropriate value-based reimbursement. As the leading international advocacy organization dedicated to realizing the promise of regenerative medicines and advanced therapies, the Alliance for Regenerative Medicine (ARM) is laser focused on the legislative, regulatory, and reimbursement initiatives that will incentivize this innovation and help patients access these therapies as quickly as possible post-approval. This article details key priority areas for advancing market access to cell and gene therapies, as well as recent successes and remaining challenges in the USA and Europe.

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In May of this year, despite the challenges presented by the COVID-19 pandemic, the Alliance for Regenerative Medicine (ARM) hosted its largest ever US Legislative Fly-In – one of the first large-scale virtual advocacy days attempted in the USA. More than 120 ARM members from 24 US states scheduled conference calls and Zoom meetings with Members of Congress and their staff. The participants urged lawmakers to remove legislative barriers to value-based payment models for regenerative medicines and advanced therapies.

Across the USA and Europe, payors and policymakers are already

preparing for a revolution in healthcare. Recently approved regenerative medicines and advanced therapies demonstrate profound, durable, and potentially curative benefits that are already helping thousands of patients worldwide, many of whom have no other viable treatment options. And hundreds of additional product candidates are contributing to a robust pipeline of potentially life-changing therapies.

With this new wave of transformative therapies rushing towards us, payors, policymakers, and other stakeholders must implement the infrastructure necessary to ensure broad patient access and appropriate value-based reimbursement. As the leading international advocacy organization dedicated to realizing the promise of regenerative medicines and advanced therapies, ARM is laser focused on the legislative, regulatory, and reimbursement initiatives that will incentivize this innovation and help patients access these therapies as quickly as possible post-approval.

PROMOTING A POSITIVE VALUE STORY

With durable or curative therapies near at hand for a range of severe diseases and disorders, it has become clear that payors need a different model for assessing the value of these innovative treatments. Existing models are intended to evaluate traditional pharmaceuticals, which are often administered over a long period – sometimes throughout a patient's lifetime – to alleviate the symptoms of a disease. These models fail to adequately capture the full value of regenerative medicines and advanced therapies, which can provide significant increases in quality of life and productivity for patients, their family caregivers – many of whom have historically sacrificed their careers to provide better care for their loved ones – as well as overburdened health care systems and society.

This past January, ARM published a study on the potential for regenerative medicines and advanced therapies to provide medium-to-long-term cost savings to society. Performed by the Marwood Institute, the study used a first-of-its-kind 'Transformational Therapy Value Model' (TVM) to demonstrate the benefits of durable therapies for three rare blood diseases: multiple myeloma, sickle cell disease, and hemophilia A.

These diseases are cumulatively projected to cost the US $163 billion per year by 2029; however, there are currently late-stage innovative product candidates in development to treat each of them, with likely approvals in the short-to-medium term. Looking at a 10-year time frame – the same as used by the Congressional Budget Office when evaluating policy decisions – the study found that a durable therapy for each of these indications could result in aggregate cost-savings of $33 billion by 2029. These savings could begin to be realized in as few as 5 years.

MITIGATING BARRIERS TO INNOVATIVE PAYMENT MODELS

While regenerative medicines and advanced therapies can provide substantial cost-savings over a patient's lifetime, the high upfront cost of these new treatments can present a significant obstacle for existing reimbursement systems. These systems are typically designed to pay for treatment over an extended period – potentially even throughout a patient's lifetime. While reimbursement systems still have a way to go to catch up with the immense value provided by regenerative medicines and advanced therapies, they have begun to make changes to accommodate these new treatments.

Advances in value-based reimbursement can help both public and private payors absorb the higher upfront costs of innovative therapies and realize the medium-to-long term cost-savings they can provide. One example of a new value-based payment model is tied to clinical outcomes. In this case, a payor does not have to pay for the full cost of a therapy if it fails to produce the intended health outcomes, which allows payors to

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share the perceived risk of a new therapy with the developer.

Spark Therapeutics offers outcomes-based arrangements for Luxturna®, their gene therapy to treat certain forms of inherited blindness. In January of this year, bluebird bio announced that they had reached an agreement with multiple statutory health insurances (sick funds) in Germany for outcomes-based reimbursement of their gene therapy Zynteglo® to treat transfusion-dependent β-thalassemia, a rare blood disorder that can causes severe and potentially fatal anemia. In the USA, the Centers for Medicare and Medicaid Services (CMS) recently proposed a draft rule that would allow state Medicaid programs to enter into outcomes-based arrangements without running afoul of Best Price and Average Manufacturer Price (AMP) requirements.

Another form of value-based financing that can help to alleviate the high cost of new therapies is the annuity – or payment over time. This model, which can be used as a stand-alone or in combination with outcomes-based arrangements, allows payors to make installment payments for a therapy over a predetermined period, amortizing the cost of the therapy to the value it provides. This type of payment option is offered by bluebird bio for Zynteglo®, as well as by AveXis, a Novartis company, for their gene therapy Zolgensma® for the treatment of spinal muscular atrophy, a rare neuromuscular disease which, in the most serious cases, leads to death or permanent ventilation by the age of 2.

Other forms of value-based payment models are beginning to receive traction as well. Cigna's Embarc Benefit Protection program, which allows payors to enroll for about $1 per employee per month, is intended to create a dedicated fund for innovative therapies, alleviating high out-of-pocket costs for patients and preventing shock claims for employers and plan sponsors. The 'Netflix Model', a subscription-style payment plan adopted last year by the Louisiana state Medicaid program to pay for expensive Hepatitis C drugs, has been suggested as a potential option to pay for regenerative medicines and advanced therapies as well. This model allows the state to pay a fixed price each year to the developer to treat all patients, eliminating uncertainty for both the payor and the developer in forward-looking budgets as well as lower per-patient cost. Other strategies – including risk-pooling and reinsurance – have been used for years to cushion payers against high-cost procedures like bone marrow and solid organ transplants.

Innovative therapies require innovative payment models. Existing reimbursement system were not designed for these new therapies or these new payment models and in many cases, they have structural barriers that prevent or inhibit the adoption of new financing options. Fortunately, given the growing number of regenerative medicine and advanced therapy products on the market, we have begun to see a shift in both public and private payors. ARM continues to advocate for broad-based adoption of value-based payment models and is working with stakeholders around the world to identify and mitigate barriers.

ADVANCING PATIENT ACCESS TO ATMPS IN EUROPE

Europe has been a leader in scientific innovation and regulatory advancement in the sector, overseeing some of the earliest approvals of advanced therapy medicinal products or ATMPs. Nevertheless, the region has also seen commercial failures: Glybera® was the first gene therapy to receive approval from the European Medicines Agency (EMA) in 2012. It was marketed to treat lipoprotein lipase deficiency (LPLD), an ultrarare inherited disorder that can cause severe pancreatitis, affecting only one in 1,000,000 people. The therapy, which was only ever administered to 31 patients, was withdrawn from the market two years post-approval due to lack of coverage by health insurers.

While Europe has made extensive strides since its first gene therapy approval, commercial challenges remain. Individual countries have their own respective healthcare systems, requiring developers to negotiate with

multiple, even dozens, of payors to ensure equal access across the region. Specialized 'centers of excellence' for the administration of innovative therapies can lower costs and help to improve patient outcomes – but navigating cross-border access when there are only a handful of administration sites throughout Europe can prove challenging for patients and payors alike. Furthermore, rigidity and lack of harmonization in Health Technology Assessments (HTAs) requirements, which are often ill-suited for the evaluation of durable or curative therapies, can pose a significant barrier to effective value demonstration.

In 2019, ARM released 'Getting Ready: Recommendations for Timely Access to Transformative Therapies in Europe'. This report, designed to create consensus on recommendations for improved patient access, provides a comprehensive review of the regulatory and market access framework across key European countries and identifies potential hurdles to the uptake of ATMPs in these areas.

In the report, ARM highlights four recommendations for improved patient access to ATMPs in Europe. These include (1) better adapting HTA frameworks to ATMPs; (2) wider application of conditional reimbursement schemes to offset uncertainty concerning the durability of innovative therapies at the time of approval; (3) the development of harmonized pan-European initiatives in areas such as Real World Evidence infrastructure, new early dialogue opportunities for developers and payors, and timely access to cross-border healthcare; and (4) a more comprehensive application of innovative financing arrangements like those detailed earlier in this article.

With the EMA expecting an uptick in the number of cell and gene therapy approvals in coming years – and multiple Marketing Authorization Application (MAA) decisions expected in the coming months, including those for BioMarin's gene therapy for Hemophilia A and Orchard Therapeutics' gene therapy for metachromatic leukodystrophy, ensuring timely patient access post-approval will be critical.

CMS & CELL-BASED IMMUNOTHERAPIES IN THE USA

The 2017 approval of two novel chimeric antigen receptor T cell (CAR-T) therapies – Novartis's Kymriah® and Kite/Gilead's Yescarta® – meant the Centers for Medicare and Medicaid Services (CMS) was faced with reimbursing these novel therapies in the Medicare program. The effectiveness of CAR-T is unprecedented among patients with blood cancers where multiple previous lines of treatment have failed. Many of these patients are experiencing complete remission or positive responses after a single administration of CAR-T.

While the New Technology Add-On Payment (NTAP) program provided an additional short-term payment for CAR-T providers, the lack of a dedicated diagnosis-related group (DRG) meant that, once the NTAP expired, hospitals that administered CAR-T therapies could lose an average of $50,000+ per Medicare patient, disincentivizing its use. In 2019, CMS extended the NTAP payment for CAR-Ts in response to commentary from ARM as well as other patient and industry groups – the first time the agency has ever done so. Stakeholders are continuing to urge CMS to implement a longer-term solution.

In May of this year, CMS released their FY21 Inpatient Prospective Payment System (IPPS) proposed rule, which included a provision establishing a new DRG for CAR-T therapies. Since the rule was published, a broad range of stakeholders – including ARM, the American Cancer Society Cancer Action Network, and the Association for Clinical Oncology, among others – have voiced their support for this hard-fought success, ensuring Medicare patients will continue to be able to receive this life-saving therapy.

With additional CAR-T therapies poised to come to market in the coming years for a wide variety of serious cancers – from multiple myeloma to solid tumors – there is no doubt that the creation of this DRG is a timely victory. Furthermore, CMS's decision signals its commitment to ensuring patient access to a wide variety of innovative therapies

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– from cell-based immunotherapies like tumor-infiltrating lymphocytes and natural killer-cell therapies, which help the immune system to better target and kill cancer cells, to gene therapies for rare disease.

MARKET ACCESS AMIDST COVID-19

Managing and reacting to the ongoing public health crisis caused by COVID-19 has become the priority for many policymakers, regulators, and public sector payors. Additionally, the pandemic has created new financial pressures that could impact payors' ability and willingness to reimburse high-cost therapies appropriately.

Nonetheless, huge unmet medical needs remain for hundreds of thousands of patients with rare diseases, cancer, cardiovascular diseases, and other severe diseases. For these patients, timely access to life-saving treatments is critical, and any disruption in care, due to COVID-19 or to cost, can have devastating consequences.

Regenerative medicines and advanced therapies can offer profound, durable, and potentially curative treatments that can not only mitigate unmet medical needs, but can also change how, where, and how frequently healthcare is administered to patients. Durable and curative treatments for serious diseases can reduce the amount of care many patients need amidst the unprecedented strain of COVID-19 on global healthcare systems. In addition, these therapies have the potential to offer tremendous value to the healthcare system through the realization of increased economic, productivity, and quality-of-life gains for patients, their caregivers, and society.

Payors must continue to shape and adopt systematic approaches to innovative payment models to ensure patient access to regenerative medicines and advanced therapies while minimizing the economic burden on patients and payors alike. As the voice of this groundbreaking sector, ARM is committed to continued collaboration with policymakers, payors, and other stakeholders to bring these life-changing therapies to patients in need.

AFFILIATION

Janet Lambert
CEO, Alliance for Regenerative Medicine

AUTHORSHIP & CONFLICT OF INTEREST

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CELL & GENE THERAPY INSIGHTS

MARKET ACCESS: EVOLVING COMMERCIALIZATION TRENDS & STRATEGIES

SPOTLIGHT

INTERVIEW

From rare monogenic diseases to Parkinson's: market access considerations for gene therapy across large and small indications

PARAG V MESWANI, PharmD, serves as Axovant Gene Therapies senior vice president of commercial strategy and operations. Dr Meswani has over 17 years of experience in the biopharma industry, having served in various commercial and medical affairs leadership roles at Novartis, Pharmacia, Biogen, and most recently, Spark Therapeutics. At Spark, he served as head of US marketing and diagnostics, leading the development and execution of the brand strategy for LUXTURNA™. Prior to Spark, Dr Meswani held several corporate and franchise leadership roles at Biogen, including serving in the office of the CEO, commercial operations, the multiple sclerosis franchise and the US hemophilia franchise. Dr Meswani earned his MBA from Columbia University and his PharmD and BS from the Ernest Mario School of Pharmacy at Rutgers University.

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Q What are you working on right now?

PM: I lead commercial strategy and business operations at Axovant Gene Therapies, a clinical-stage gene therapy company developing innovative gene therapies for neurodegenerative diseases.

On one end of the spectrum, we are focused on rare diseases for pediatric lysosomal storage disorders, specifically GM1 and GM2 gangliosidosis (also known as Tay-Sachs and Sandhoff disease), which we view as classical applications of AAV-gene therapies. In many ways, this is an area that is viewed as de-risked: these are monogenic diseases using adeno-associated virus (AAV)-based approaches that have been used in the past - for instance, for the approval of LUXTURNA™ and ZOLGENSMA®. These indications also benefit from a robust natural history dataset, where we are leveraging learnings both scientifically and from a regulatory/commercialization perspective towards the development of those programs.

On the other end of the spectrum, we have a gene therapy program for Parkinson's disease (PD). We are one of the few companies that is extending the reach of gene therapies beyond these rare monogenic conditions to more complex diseases like PD, following the science that has been accumulated over the course of the past several years. We're in an ongoing Phase 2 study right now and we intend to have some data available later in Q4 2020 that's going to inform our next steps and the likely start of a randomized, controlled clinical trial in 2021.

Q What were the key learnings you took from your experience with LUXTURNA™ at Spark Therapeutics that you are seeking to leverage now at Axovant to succeed in what is an increasingly challenging healthcare marketplace?

PM: If you think about orphan drugs and about cell and gene therapies, what you find at the intersection is that they require a specialist approach and mindset that cuts across local intervention.

In terms of finding patients, we know that with rare diseases it can take a decade before a proper genetic diagnosis is made. That's a massive issue, especially in the setting of gene therapies for rare diseases where it is so vital to raise awareness, accelerate diagnosis timelines, and ultimately deliver a therapeutic intervention. You are reliant on finding these patients and finding many of them as early as possible within their disease continuum. That is a challenge that needs to be managed and dealt with early in the drug development process, well before you think about commercialization.

"In terms of finding patients, we know that with rare diseases it can take a decade before a proper genetic diagnosis is made."

Secondly, there are now many gene therapies in development. As I look to the future, I predict that the role of patients and caregivers

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in patient-centric drug development, and the role of policy makers in drug development, will only increase. It behooves us to think about those considerations now. Patients deserve to have a voice in what endpoint you are measuring, what treatments to consider, and how this may impact their lives. At the same time, policy makers have a say in considering how you develop these drugs, how you measure response, and how you measure the durability of that response over time. And ultimately, how you think about paying for it, which is something we think about often in the context of PD. We're talking about millions of patients across the globe. Here in the USA alone, there are slightly over a million patients according to the Michael J. Fox Foundation for Parkinson's Research. It's key to have a mindset towards shaping your efforts around the needs of the patients, the needs of policy makers, in addition to traditional stakeholders like physicians and payers.

"The elephant in the room is what does the future look like with respect to the cost and payment model?"

The elephant in the room is what does the future look like with respect to the cost and payment model? As I mentioned, we're talking about the fast growth of the orphan disease market in general, and we've seen this trend for over a decade now. This growth is now compounded by growth in the cell and gene therapy market that is targeting these orphan diseases. We're going to see – I think we're already seeing to some extent – a meaningful increase in the overall prescription drug market and the landscape for advanced therapies. This is only going to be compounded as more and more gene therapies make it through development to commercialization.

This is a good thing from a scientific perspective, and it is a great thing for patients, but it is also a burden on the global healthcare system. Various countries are dealing with it differently. The USA is starting to put some frameworks around this both at a commercial payer level and much further behind, from a government insurance perspective. In many ways, I think the government insurance policy perspective in the USA is very similar to where things are in Europe and perhaps other places: they are playing catch-up and trying to figure out how they're going to contain costs in future.

This poses quite a challenge for gene therapies where there is a one-time delivery that may come at a substantial cost. When considering the high annualized cost of these drugs versus traditional prescription drugs, the need to advance alternative financing models is paramount. Right now, companies are performing pilots for therapies that are approved and on the market. However, it's going to be incumbent on companies that are moving through their drug development and registration process to be smart and proactive, and to think about unique pathways towards patient access. This could include a spectrum of financing options, from paying for it in the traditional way we do now as an upfront cost, to trying to spread the cost out over the course of several years. Another option is to get even more creative and put outcome-based models into place, so that providers or payers can get a rebate or refund if the drug does not work for certain a period of time, or if certain predefined metrics are not met.

This is all incredibly complex stuff and I don't think we're anywhere near figuring it out. Even so, I am optimistic because there are a lot of incredibly smart people and companies working on

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the problem, and there is great collaboration occurring right now across stakeholders that I don't think has happened before. We're seeing dialogue and cross-talk between payers and biopharma, between patient groups and payers, and between all three parties, to figure out what benefits can be derived for patients and how to ensure these innovations ultimately make it to them.

Going back in a roundabout way to the lessons I've learned, a big one is that we have to iterate. We have to iterate on these dimensions: how you find patients, how you manage stakeholder pressure, and how you leverage all those learnings in order to drive innovative ways to finance these gene therapies.

Q What specific challenges did you experience while working on LUXTURNA™?

PM: There were two key issues that arose as a byproduct of market development that we uncovered fairly early on in the process for LUXTURNA™.

Awareness of rare diseases is low, and awareness of inherited diseases of the eye is incredibly low. As a result, many rare disease patients with blindness caused by a genetic mutation were undiagnosed, as they weren't getting a genetic test and being genotyped to identify the gene causing their disease. One reason why a genetic diagnosis can take many years is that there is a perceived element of complexity around getting a genetic test done, and not enough knowledge of what to do when those results come in.

Because patients weren't being genetically tested, you could not find patients early on that would benefit from LUXTURNA™. LUXTURNA™ was a breakthrough; the clinical trial data was exceptional. The challenge was how to find the patients with very specific mutations in one very specific gene.

One of the solutions to mitigate this and try to increase the rate of patients you could identify was to figure out a way to accelerate the adoption of genetic testing in patients with any form of inherited retinal blindness. The specific gene associated with LUXTURNA™ is *RPE65*,

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but there are over 250 different genes that can contribute to an inherited form of blindness – the only way to know which gene mutation you have is to get a genetic test. So the company sponsored genetic testing programs in order to accelerate the adoption of genetic testing in any patient with an inherited retinal disease, and to ultimately facilitate ease of access to that test. The aim was to make it very simple and accessible so that a physician and patient can do it in a straightforward way, to empower physicians and patients to get that genetic diagnosis.

The benefit for the patient is they get a genetic diagnosis, and for the company, you can help identify patients who will benefit from LUXTURNA™ while supporting the community in a way that isn't purely self-serving. If we were just trying to find patients that would benefit from LUXTURNA™, it wouldn't have worked as well because the disease is so rare. With this approach, you're actually launching an initiative that can target the needs of a much broader subset of patients and empowering them with a genetic diagnosis that would not otherwise have occurred.

A lesson learned from that process is that it was a good program and it worked, but it can't be done in isolation. You have to look at multiple different levers to support patient identification. There is not a one-size-fits-all approach for gene therapies and rare diseases.

Genetic testing is one component of that, and patient advocation and patient education is another lever, meaning that you have to make sure the patients know where to find information. You have to make it accessible online or through social media, as this is how a lot of these groups communicate. You have to be part of that conversation with them.

The final lever is finding the right physician and provider targets. Getting in front of the right physicians, with the right analytics so that you can find advocates and champions in support of your patient identification efforts is key – and all of these things work hand-in-hand: you find the right physician who can do genetic testing, then you offer a genetic testing program. At the same time, you activate patients to want to seek more information about these types of resources and tools. From a patient identification perspective, these strategies were relevant and impactful for LUXTURNA™, and they're relevant and impactful for many other rare disease therapies in development today.

Q Turning to PD, how does targeting these larger indications with a gene therapy compare and contrast with targeting a rare monogenic disease – for example, when it comes to health technology assessment (HTA) considerations?

PM: PD is an interesting one. Most of the rare diseases that are being targeted by gene therapies do not have any therapies available. This is both a pro and a con in my view. Because there are no therapies, you are in a white space and you can build your own economic model, assuming there is a safe and effective gene therapy being developed. You can take that white

"You have to look at multiple different levers to support patient identification. There is not a one-size-fits-all approach for gene therapies and rare diseases."

"When you introduce a therapy where there was none before, you add cost to the system. You have to look at creative ways to justify what the price might be and what a demonstration of economic evidence of effect might be."

space and really make the case for gene therapy. That can be challenging – for LUXTURNA™, this was a disease that didn't have any approved therapies. So the question was: how do you put a price on blindness? How do you quantify the value of restoring vision, when there aren't any comparables out there, and no therapies? When you introduce a therapy where there was none before, you add cost to the system. You have to look at creative ways to justify what the price might be and what a demonstration of economic evidence of effect might be. The case we looked at was when somebody is injured at their job, what is their vision worth? If they go to work and sue their employer, what do juries award in that setting? We did some work there and found some analogues, and we found what juries tend to award victims of loss of vision at work – that gave us an analogue to look at price. It was a very non-traditional way of doing things.

With something as prevalent as PD, there's a different challenge. There are already very well-articulated direct and indirect costs of the disease. So you have to build the right assessment into your clinical trial process very early on to demonstrate response in the setting of standard of care, and prove that you actually remove cost from the system with a one-time gene therapy. You have to show that can have durable response out to 3–5 years or more. You also need to compare and contrast with standard care and the cost of those offerings based on what they deliver, in order to demonstrate the incremental benefit that gene therapy can provide above and beyond what's on the marketplace.

As you think of evidence generation, you have to understand and evaluate the commercial potential early on, and make sure you're mapping out some of the pricing evidence requirements in the context of standard of care. To contrast that again with the rare disease side, it's a little bit different. Where there is a gap, you can fill that gap with a drug that has proven to be safe and effective, and you need to decide how to price it in an appropriate way. That's one part of evidence generation.

You also need to consider value communication. This goes back to stakeholder mapping and understanding the needs of patients, payers, physicians, and advocacy groups. You can use that insight to pre-empt potential evidence gaps and get ahead of it, and to leverage the feedback from stakeholders to inform value communication.

All of these considerations ultimately inform your route to market and your decisions on the appropriate commercialization model, the appropriate regulatory pathways on that route, and how that informs price, access, launch sequencing, and so on.

Q What will be the key challenges in getting gene therapies into larger patient populations, potentially on a global basis, and what are the next steps towards addressing them?

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PM: When considering PD, in the US, there are about a million patients who have some form of the disease. The question will be: who are the patients who will benefit most?

The total addressable market is quite large, but that doesn't mean gene therapy is appropriate for all of these patients. It will require being smart about patient segmentation, and beginning to paint a very clear picture of what the correct area for gene therapy is: who will benefit and equally importantly, who may not benefit. Having that level of clarity in the drug development process will open doors and help provide a lot of understanding on who might benefit best from this type of approach, and on what continuum in their disease. Keeping it open and lacking that specificity will just create concerns and complexity. Our job will be to create clarity out of the clutter in these larger diseases, and fit ourselves into the treatment algorithm in a way that is understandable, data-driven, and rational. At the same time, we want to avoid overly minimizing the impact the therapy could have across the spectrum of different PD populations.

At Axovant, we're addressing this through the creative design of our clinical trials as well as through regulatory engagement. The feedback we have received from regulators has been very clear on patient populations, and that they want to see safety and efficacy first.

We will begin to open the aperture over time, so that we can think about expanded patient populations that can be evaluated within the context of our clinical development program, according to the lifecycle management of that initiative. We are looking at the holistic group of addressable patients that could benefit, but we're not just trying to jam all that into one. We are taking a sequential, phased, and methodical approach towards drug development that starts with one core of patients and will then expand out.

This is not something that's going to end in Phase 2 or Phase 3, which is similar to the situation with other biologics for larger indications, and other large-market indication drugs in general. We can take a page from their playbook and look at lifecycle management in a holistic way for large indications with gene therapy, which is something that you just can't do with rare or orphan disease therapies because the market is so small.

Q What's your current view the most likely pathways forward for gene therapy reimbursement models that suit all stakeholders?

PM: With gene therapies, you obviously need to ensure you're collecting payer input early on to optimize gene and cell therapy pricing and payment modalities. A trend we are likely to see is that you shouldn't allow yourself to be beholden to a single path. There are multiple different options, multiple modalities, that have been identified. There are likely to be others that will emerge as more gene therapies advance and get approved. If you want to take the traditional route and start with a one-time payment, plus performance-based milestones, that's fine. If you want to have outcome-based reimbursement model in some other way, which is how LUXTURNA™ tried to approach it using prespecified milestones and prespecified metrics, that's also fine. Ultimately, it's about having optionality by giving your payers different means to assess price and value for money, and being able to manage what are likely to be not-insignificant price points.

For PD, because of the large population, the trade-off is a price and volume one. With rare diseases, you are going after much smaller indications, so you will likely have to price these therapies for the vast majority of those patients. For larger indications, in order to have broad market access, you are going to have to come up with an equally responsible way to price it. If you do that, you have the opportunity to be utilized in a much larger segment of the PD population. This is the price/volume trade-off specific to larger market indications. This goes back to the point I made about weaving these considerations into your clinical trial process, thereby allowing you to be a bit more creative with payment modalities and pricing potential across different countries.

Q Can you sum up Axovant's chief goals and priorities over the next 12–24 months?

PM: For the company, our priorities are focused around our three clinical programs. For PD, our goal is to continue to advance the program in development and initiate a placebo controlled clinical trial where we aim to begin enrolling patients in 2021 within the USA and Europe. That will be an important milestone for the company and an important milestone for the PD space, and it will be one of the furthest along gene therapies for a large target indication that is out there. We are laser focused on executing our clinical plan for PD and believe we have a treatment that could tackle the greatest challenge for people living with PD – improving motor function and quality of life

On our rare diseases side, we have a GM1 gangliosidosis program, and a program on Tay-Sachs and Sandhoff disease (GM2). We have a very clear clinical development plan laid out that starts initially with an assessment of safety and secondarily efficacy, which is then supplemented by a program that is focused primarily on efficacy. Our goal is to advance that through drug development in an expedited manner, and to make the case to regulators for these diseases as quickly as we can based on the evidence and the data we are generating, and the massive need that exists for these children. These are devasting diseases. Many of these children will die by about 3 years of age and there are no approved disease modifying therapies on the market that can stabilize or perhaps even improve function. We feel a personal responsibility to move these through the clinic and hopefully, to registration in an expedited manner over the course of the next 12–24 months, with the goal of commercializing within the next few years.

AFFILIATION

Parag V Meswani, PharmD
Senior Vice President of Commercial Strategy and Operations, Axovant Gene Therapies

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CELL & GENE THERAPY INSIGHTS

MARKET ACCESS: EVOLVING COMMERCIALIZATION TRENDS & STRATEGIES

SPOTLIGHT

COMMENTARY

Bringing advanced therapies to the clinic: the Swedish National ATMP Consortium (CAMP/SWElife ATMP)

Stefan Scheding, Heather Main & Pontus Blomberg

Advanced therapy medicinal products (ATMPs) have the potential to transform medicine, with the promise to treat, manage and cure some of the most severe diseases. However, the development of ATMPs is complex and successful transition from preclinical research to the approved clinical product faces a number of hurdles regarding technical as well regulatory and societal challenges. The closely interacting national initiatives CAMP (Center for Advanced Medical Products) and SWElife-ATMP aim to establish Sweden as one of the international leaders in the ATMP field. Taking into account Sweden's systems and organizational challenges, these programs nationally coordinate efforts focusing on industry and SME growth, clinical practice, research and education, advanced production, and a flourishing innovation and business environment that in the long term has potential to become a major driving force for the development of a new sector in the Swedish life science industry.

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TRANSLATION INSIGHT

Background

Although it has been more than a decade since the publication and entry into force of the European Regulation 1394/2007/EC on advanced therapy medicinal products (ATMPs) (Box 1) [1], these novel forms of therapeutics have first started to enter broader clinical practice in the last few years.

A recent European Union (EU) survey showed that numbers of clinical trials using ATMPs were only slowly

BOX 1

Advanced therapy medicinal products (ATMPs).

Any of the following medicinal products for human use:

- A gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC.
- A somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC.
- A tissue engineered product defined by containing or consisting of engineered cells or tissues, having properties for, or is used in or administered to human beings with the intent to regenerating, repairing or replacing a human tissue.

Cells or tissues shall be considered 'engineered' if they have been subject to substantial manipulation* or are not intended to be used for the same essential function or functions in the recipient as in the donor ('non-homologous' use).

*Substantial manipulation is negatively defined by a list of manipulations that are particularly considered as non-substantial.

increasing during 2010–2015 while the focus was still in early development [2]. Furthermore, the work was mainly carried out by small and medium-sized enterprises (SMEs), academia, and hospitals [2]. One likely reason that contributed to this modest development of ATMPs was the lack of necessary multidisciplinary skills that were needed to overcome the complex regulatory barriers [3]. Accordingly, a survey of European academic and non-industrial facilities showed that facilities experienced in manufacturing cell therapy transplant products were the most successful in developing ATMPs whereas new centers lacking this background faced considerable difficulties to enter the field [4]. Furthermore, gene therapy development was delayed by lethal side effects and insertional mutagenesis events leading to intense efforts to develop safer vectors and therapy designs. So, at the end of the extended transitional period of Regulation 1394/2007 in 2012 only two products, ChondroCelect® (autologous *ex vivo* expanded cartilage cells) and Glybera® (gene therapy product containing the active substance alipogene tiparvovec), were centrally licensed in the EU (central market authorization, MA), but limited commercial success has led to the discontinuation of both products.

However, after these early years of slow development, the ATMP field has gained considerable momentum, in parallel with an increasing engagement of larger pharmaceutical companies. In 2018, the numbers of ATMPs with MA in the European Union (including those that were suspended and withdrawn, respectively) accounted to twelve [5,6], and also numbers of scientific recommendations on ATMP classification by the European Medicines Agency's Committee for Advanced Therapies (CAT) clearly show an increasing trend [7]. The recent rapid clinical development of chimeric antigen receptor (CAR)-T cell products, some of which have already entered routine clinical practice, is an excellent example of the dynamics in the field. However, one has to keep in mind that it has taken more than 30 years from the initial report of the concept of a chimeric antigen receptor to the approval of the first anti-CD19 CAR-T cell therapy [8].

The European Regulation 1394/2007/EC aims to apply, harmonize and extend the principles of existing legislation on medicines and to assure the position of the EU in scientific innovation. It furthermore clearly lays out marketing authorization as the default development path for ATMPs, which resulted in the difficulties that especially academia and hospitals faced to adapt to the novel and complex regulatory environment. Moreover, the situation was additionally complicated due to heterogeneous implementation of the regulation and preexisting profound differences in the organization of research and healthcare across and within EU member states (MS).

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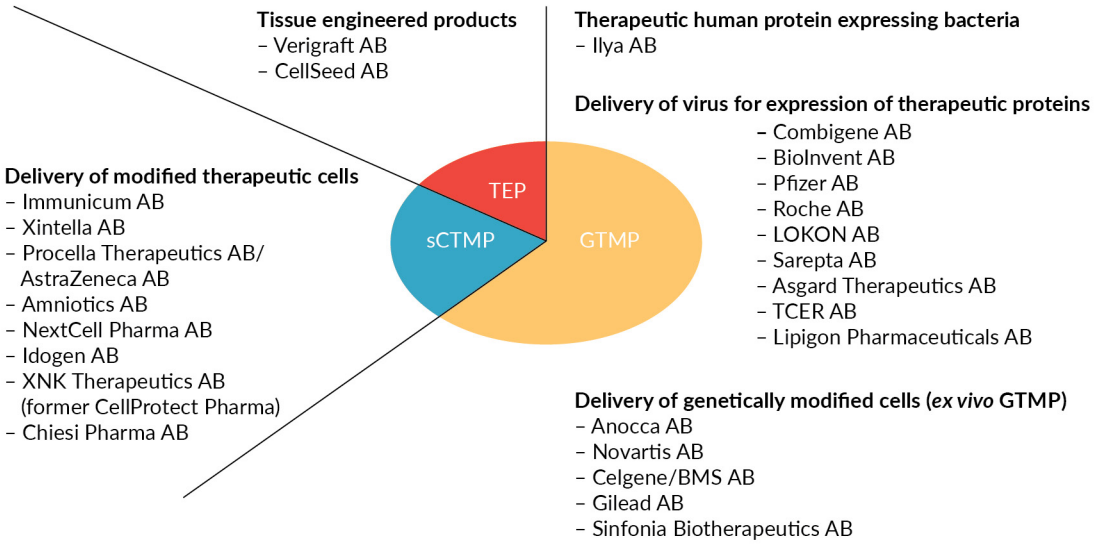
Sweden traditionally scores high on the European Innovation Scoreboard despite being one of the smaller European countries [9]. Here, it was realized that the development of the countries' full potential in this new and exciting field would critically depend on serious efforts to effectively coordinate and consolidate all stakeholders, i.e. industry, academia, healthcare, regulatory bodies/authorities and patients. It was furthermore realized that any public investment to facilitate Sweden to become one of the future leading countries in the field had to be coordinated on a national level. Applying this strategy would adequately address Sweden's systems and organizational challenges that had been identified as hurdles for development of ATMP research, production and commercialization. Based on these considerations, two closely interacting national initiatives (CAMP, Center for Advanced Medical Products, and SWElife-ATMP) were founded, both receiving substantial funding from the Swedish Innovation Agency, VINNOVA, which is a government agency under the Swedish Ministry of Enterprise and Innovation. These initiatives form a national center for ATMP development as presented below.

National initiatives to address system & organizational challenges for the development of ATMPs in Sweden

Beside regulatory considerations regarding clinical ATMP development which are common for all European MS, there are some aspects that are more country-specific, such as organization of the Swedish public healthcare system in relation to academic research institutes, universities and the commercial sector. For example, Sweden consists of 21 regions and it is the responsibility of the regions to organize health and medical care. Regional healthcare is conducted at all seven university hospitals in Sweden. However, some of the highly specialized medical care is centralized to one or two hospitals in order to achieve higher quality and more efficient use of resources. Any clinical development of ATMPs will therefore rely on the coordination of the different healthcare regions, which fortunately has already been established during 10 years' work in the national cell therapy group within the Swedish Association of Local Authorities and Regions' (SALAR) National

FIGURE 1

Swedish companies involved in ATMP development and production.



GTMP: Gene therapy medicinal products; sCTMP: Somatic cell therapy medicinal products; TEP: Tissue engineered products.
Source: ATMP Sweden [14].

BOX 2

CAMP partners.

Healthcare Regions and University Hospitals:

- Region Uppsala, Uppsala University Hospital*
- Region Stockholm, Karolinska University Hospital*
- Region Skåne, Skåne University Hospital*
- Region Örebro, Örebro University Hospital*
- Region Västerbotten, Umeå University Hospital*
- Region Östergötland, Linköping University Hospital*

Large Pharmaceutical/Life sciences companies:

- AstraZeneca AB*
- Pfizer AB*
- GE Healthcare Bio-Sciences AB (now: Cytiva Sweden AB)*
- Takara Bio Europe AB*
- Novartis Sweden AB

SMEs:

- Boobicell AB*
- Cellseed Sweden AB*
- Idogen AB*
- TATAA Biocenter AB*
- Xintela AB*
- Your Special Delivery Service Stockholm AB*
- Acousort AB
- Noricon AB
- Cellink AB
- Cobra Biopharma AB
- Nextcell Pharma
- Verigraft AB
- VivaBioCell S.p.A

Universities and Research Institutes:

- Umeå University (program coordinator)*
- University of Gothenburg*
- Karolinska Institutet, Stockholm*
- KTH Royal Institute of Technology*
- RISE Research Institutes of Sweden*

Others:

- Medicon Village AB*

*Indicates founding member.

Tissue Project [10]. Additionally, industrial production of a number of cell-based ATMPs will require the use of public tissue establishments for the procurement of patient and donor cells, e.g. autologous apheresis products for CAR-T cell production. Also, the public healthcare system serves as the resource for patient recruitment into academic and industry-sponsored clinical studies and will finally have to find solutions to finance effective but likely highly expensive future ATMP treatments and identify mechanisms to provide it to all Swedish citizens in need, once a treatment has entered routine clinical practice. In addition, university hospitals have to be prepared to process ATMPs and even to produce those ATMPs that already have or will enter standard clinical practice, but which are not developed commercially due to lack of (expected) profitability. One example for such a product are cultured autologous keratinocytes that have been used in many years for the treatment of severely burned patients in the two Swedish national burn centers. Cultured autologous keratinocytes were previously handled as other products intended for transplantation but have now to be produced as ATMPs by hospitals, i.e. non-commercial entities, with current regulations not being adapted to this special situation in which a standard-of-care product is not intended for, or even legally prohibited from commercial development. Lastly, ATMP research and development is traditionally concentrated in academia and SMEs (Figure 1), which ideally need to be interconnected with both the healthcare system and large pharmaceutical companies to enable effective ATMP development towards MA. Obviously, large pharmaceutical companies are also depending on the close cooperation with healthcare and academia, so that one of the obvious goals of the national ATMP initiatives is to provide the framework for a successful cooperation of these partners, ideally in close cooperation with the regulatory agencies.

CAMP & SWElife-ATMP structure, governance & participants

The application for the formation of CAMP as a national ATMP center was submitted to Vinnova by a total of 22 partners including all

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BOX 3

CAMP: overall goals.

- Build a strong public private partnership with government, universities, healthcare, patient organizations and industry to accelerate new breakthrough ATMP therapies to patients.
- Create strong research and development activities in Sweden to attract global interest and investments in the ATMP area.
- Provide a national infrastructure to pave the way for commercialization of ATMPs for the benefit of patients and the society.

The overall long-term objective is to develop general ATMP development principles and methods for an effective transfer from preclinical to clinical, GMP-compatible production.

Swedish Medical Regions, large pharmaceutical companies and SMEs as well as Swedish universities and the Swedish Research Institute, RISE (Box 2). The total budget of CAMP is 148 million SEK between 2018 and 2023. Vinnova will contribute 48 million SEK, which is a part of the 320 million SEK commitment of the Swedish government towards making Sweden a World leader in biologics. SWElife-ATMP was initiated by a mostly overlapping group of applicants aiming to complement the activities in CAMP. Since its inauguration in 2018, the number of partners and participants as well as activities and projects in both programs have increased considerably.

The organizational structure of CAMP was designed to realize the overall goals of the program (Box 3). All partners are represented in the General Assembly as the ultimate decision-making body, which elects the executive board as the supervisory body. The operational management is performed by the program office and the work is organized in work packages (WPs) and cross-cutting priorities (CCPs) (see below). New partners can join the consortium upon application and the program is open for proposals for new projects that fit the aims and objectives of the center. A new project can be initiated after submission and approval of a proposal, thus providing CAMP the opportunity to expand the program quantitively and qualitatively. Strong focus is put on that partners from the different groups participate in the projects. Results generated in the projects and technologies resulting from the project work are made available to the consortium. A strong international scientific advisory board (Box 4) was appointed to support the program, evaluate progress and give important input on the future development of the center.

SWElife-ATMP is a project within the strategic innovation program SWElife [11] and is tightly connected and coordinated with CAMP. Both programs use common decision-making bodies and share organizational and supporting infrastructures. The work in CAMP and SWElife-ATMP thus complement each other, with CAMP currently focusing on ATMP infrastructure and process development, whereas SWElife-ATMP projects focus on regulatory, ethical and financial aspects (see below). SWElife-ATMP is funded until the end of 2020. Activities will be continued in the recently-funded program

BOX 4

International advisory board members.

- Karin Hoogendoorn – Lonza, The Netherlands & Switzerland
- Mark Lowdell – Royal Free Hospital, London, United Kingdom
- Michael May – Center for Commercialization of Regenerative Medicine, Toronto, Canada
- Roke Oruezabal – Andalusian Initiative for Advanced Therapies, Spain
- Seppo Ylä-Herttuala – University of Eastern Finland, Finland

'Vision Driven Innovation Milieu' (for more details on this project, please see [12]).

Work packages & projects

The work in CAMP and SWElife-ATMP is organized in work packages, WPs. CAMP WPs address the topics process development, infrastructure for GMP manufacturing, quality control (QC), shelf-life and logistics. Currently, a total of seventeen projects are being performed ranging from work with pluripotent stem cells, stromal cells, immune cells and extracellular vesicles to the establishment of pre-GMP facilities and the design of QC and logistics strategies.

In addition to the WPs 'project management' and 'communication', SWElife-ATMP is responsible for the organization of the national conference 'ATMP Sweden', which has received increasing attention in the last years. The planned 2020 conference has been delayed due to the continuing Coronavirus situation but will hopefully be held in the Spring of 2021. Finally, five so-called System-Development Programs (SDPs) in SWElife-ATMP address questions regarding regulatory aspects for ATMPs, the ethical and legal framework of stem cell-based ATMPs in Sweden, business models and health economics for ATMPs, opportunities and challenges for Sweden to become internationally leading in the field of gene therapy as well as the foundation of Sweden's CAR-T Cell Competence Network (SWECARNET). Thereby, the work in SWElife-ATMP covers the topics that were initially outlined in the CAMP CCPs.

Progress and results of the center activities, such as a recently published draft report on health economy and business models for ATMPs, are regularly published on the common project homepage 'Sweden ATMP' [13]. The reader is therefore invited to visit this homepage, which also provides more in-depth and additional information about the center as well as general information about ATMPs.

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AFFILIATIONS

Stefan Scheding
Author for correspondence:
Division of Molecular Hematology and Lund Stem Cell Center, Lund University, Lund, Sweden
and
Department of Hematology, Skåne University Hospital, Lund, Sweden
stefan.scheding@med.lu.se

Heather Main
Department of Clinical Science, Intervention and Technology, Karolinska Institute, Stockholm, Sweden
and
Karolinska Cell Therapy Center, Karolinska University Hospital, Stockholm, Sweden

Pontus Blomberg
Karolinska Cell Therapy Center, Karolinska University Hospital, Stockholm, Sweden
and
Department of Laboratory Medicine, Karolinska Institute, Stockholm, Sweden

AUTHORSHIP & CONFLICT OF INTEREST

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CELL & GENE THERAPY INSIGHTS

MARKET ACCESS: EVOLVING COMMERCIALIZATION TRENDS & STRATEGIES

SPOTLIGHT

INTERVIEW

How should health technology assessment of ATMPs evolve in Europe?

MONDHER TOUMI is MD by training, has an MSc in Biostatistics, and in Biological Sciences (option pharmacology) and a PhD in Economic Sciences. He is Professor of Public Health at Aix-Marseille University. After working for 12 years as Research Manager in the department of pharmacology at the University of Marseille, he joined the Public Health Department in 1993. In 1995, he embraced a carrier in the pharmaceutical industry for 13 years. Dr Toumi was appointed Global Vice President at Lundbeck A/S. In 2008, he founded Creativ-Ceutical, an international consulting firm dedicated to support health industries and authorities in strategic decision-making. In February 2009 he was appointed Professor at Lyon I University in the Department of Decision Sciences and Health Policies. He launched the first European University Diploma of Market Access (EMAUD), an international course already followed by about more than 500 students. He is editor in Chief of the *Journal of Market Access and Health Policy* (JMAHP). In September 2014, he joined the research unit EA3279 of the public health department, at Aix-Marseille University (France), where he is a full Professor. Dr Toumi is also a visiting Professor at Beijing University (Third Hospital). He is a recognized expert in health economics and an authority on market access and risk management. He has more than 200 scientific publications and oral communications, and has contributed to several books. He authored the reference book on Market Access.

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Q What are your reflections on the current state of play regarding health technology assessment (HTA) methods of analysis and tools, especially in the advanced therapies area?

MT: It has become obvious that HTA current evidence analysis frameworks are poorly adapted to assess the specificities of regenerative medicines. Overall, the HTA bodies are very anxious to adjust their assessment framework for advanced therapy medicinal products (ATMPs) because the manufacturers of every other class of drugs are going to consider themselves differently and will request a specific process. Indeed, personalized medicines, drug–device combinations, and orphan drugs may all claim they are specific and deserve a specific framework. Therefore, manufacturers are going to push hard for changes as to how their specific product is assessed, whether it be a gene therapy, a cell therapy, etc. Adjustments to the process are justified for this specific therapeutic class, but you can say the same thing for other classes, such as orphan drugs – and in that particular case, it took a lot of time before the HTA bodies were ready to make any adjustments and some adjusted their practice but not their framework.

The European HTA agencies routinely say that there is too much uncertainty around ATMPs, but in practice, they do seem to be adopting them – especially Germany, the UK and France. However, the decisions of other countries are still pending, and if you look across the larger European countries and Canada, you see that most products have only been assessed in two or three of them. Of course, this does not apply to Kymriah® and Yescarta®, which have been assessed in all of these countries – Kymriah® has three indications and was recommended positively with no restrictions across the board, while Yescarta® has been recommended in all countries but one. But other ATMPs have received only very limited assessment to date.

Q How do you see these HTA models and tools evolving further over time, particularly as the ATMP field continues to grow and mature?

MT: The big issue for HTA is that one ATMP is not comparable to all ATMPs; it is a very heterogenous class. Some products have the potential to provide a dramatic benefit and some products have modest or little benefit. Additionally, the actual benefit may not be where you might expect it to be, and that is the real issue.

"The European HTA agencies routinely say that there is too much uncertainty around ATMPs, but in practice, they do seem to be adopting them."

If you consider a genetic disease where the patient is facing a significantly shortened lifespan or severe disability and there is no treatment, and your gene therapy is going to provide a dramatic improvement or prevent further deterioration, that is considered very important. However, if you take the same disease but we already have a therapy available that is working

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"...if products get rejected, investors may become less inclined to fund these programs. If we want the flow of new ATMPs to continue, payers have to show that they are open to them and to paying a fair price that is profitable for companies and fair to their budget. If none of these products are reimbursed .... companies will stop developing them."

pretty well, the situation will be different. For example, for some forms of mucopolysaccharidosis (MPS), there are effective enzyme replacement therapies (ERT) available. If you consider gene therapy in those specific indications, the comparative benefit would be in the convenience of use – you don't need to administer the gene therapy periodically, as you would the ERT (where delivery, often to children, is via IV or subcutaneous injection). The potential benefits of gene therapy are very different between these two scenarios, so the value arguments are not the same.

It is difficult for HTA bodies to simply create a new route to assess such diverse therapies. However, one very common aspect of ATMPs that does require a new, specific process is that we don't know what the long-term benefits are, because we don't have enough follow-up with patients. There could be future adverse events or issues with the durability of efficacy of these treatments. HTA bodies are not yet ready for this, though, as they are concerned about moving too quickly and making decisions that would be difficult to work back from.

The decision analysis framework needs to change and a certain degree of uncertainty needs to be accepted in order to allow companies to move forward. In most cases, long-term follow-up through the registry is already a regulatory requirement.

If we do not improve on the current situation, it could have a big impact on cell and gene therapy development – for instance, if products get rejected, investors may become less inclined to fund these programs. If we want the flow of new ATMPs to continue, payers have to show that they are open to them and to paying a fair price that is profitable for companies and fair to their budget. If none of these products are reimbursed, again, companies will stop developing them. There is a need to encourage companies and to encourage the development of scientific knowledge.

Q How do you predict the market access scenario will evolve in the rare disease space?

MT: The rare disease field has evolved a lot and for the most part, this evolution has been positive. In Germany, for example, there is a regulation that allocates – by law,

"...the field of orphan drugs is being reasonably rewarded. The problem for payers and for HTA is the sheer number of these products that are now coming through, each with the expectation of a high price-point."

and without assessment – additional benefit to any orphan designated product, whether it is a gene therapy or otherwise. And in the UK, therapies for ultra-rare conditions can go to a highly specialized therapy committee and benefit from the possibility of gaining a conditional reimbursement while they collect data to reduce any uncertainty. They also benefit from receiving the highest incremental cost–effectiveness ratio (ICER) threshold for recommendation. This is quite a unique opportunity.

If you look at nusinersen (Spinraza®), it has been shown to have a very high cost per quality-adjusted life year (QALY), according to the UK's National Institute for Health and Care Excellence (NICE). But despite this, it was endorsed for spinal muscular atrophy (SMA) type 1. And because patient groups were unhappy with that decision, NICE then decided to extend the recommendation to SMA type 2 patients, despite the data not being particularly impressive in that indication with regards to the ICER. This shows that the field of orphan drugs is being reasonably rewarded. The problem for payers and for HTA is the sheer number of these products that are now coming through, each with the expectation of a high price-point. Even if the individual numbers of patients are small per product, the budget impact of individual products may be affordable despite a high price-point. But when you multiply by the increasing number of products, it has a big impact on budget. Several orphan drugs have reached blockbuster status over the last ten years, and the spending on orphan drugs is growing much faster than for other pharmaceuticals, but this is causing regulators and payers to turn increasing scrutiny on these products.

Regulations have not increased, as such, but regulators used to be quite accommodating in terms of the data available, and would try to find a solution to accept and reimburse these products even if the data was not at the level of their usual requirements. Today, they are becoming increasingly stringent, requesting more robust data. A single arm study may no longer be accepted, unless there are very specific conditions demonstrating that it was necessary and not possible to do otherwise. The level of indulgence that orphan drugs have previously received is now reducing.

Q Moving to the uptake and integration of ATMPs into the various European healthcare systems, how should these therapies be made available, and who should be responsible for their administration to patients?

MT: At the moment, most of the products available are targeting severe conditions that are treated by highly specialized centers. These specialists are the ones

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diagnosing and treating patients, and in my view, they are the ones who should be administering these products.

But this model won't work in all cases: let's assume you have a gene therapy for diabetes. Most patients with diabetes are treated by their GP, not a specialist. The questions of whether a GP is going to prescribe this product, and what that process might look like, are both complicated. If you have a large patient population, you simply can't limit treatment to specialized centers. Another example is heart failure. If you have a cell therapy available, who will decide on the prescription? In my view, we can't rely on niche specialists in these cases; we need to open it up more widely – but the product may still need to be administered under specific medical supervision that can't be arranged at a doctor's office. Only experience will help decision-making in the future as there is still too much uncertainty and too many unknown features associated with this heterogeneous class of drugs.

Q We've discussed long-term follow-up as a standard for ATMP products reaching the market. But how will healthcare systems in Europe accommodate the extensive follow-up testing and monitoring that will be required? And who should be responsible for that?

MT: To date, it has always been the company that is responsible – they may receive a conditional approval for reimbursement and if that condition is long-term follow-up, it is the company that is going to pay for it and be rewarded if the evidence is conclusive. This is fair, because the onus is on the company to deliver the evidence that their product is reasonably priced and effective. When there is high uncertainty about the long-term results, it is their responsibility.

Some payers may agree to reimburse and then scrutinize the data collected through registries, as occurs in Sweden and The Netherlands, whilst others will accept a high listed price and request a high rebate until new evidence is available, as is the case in the UK and France. When new evidence is available, reducing uncertainty, then the rebate may be reduced – this is the case in the UK, but in France, this option remains theoretical and does not happen in practice.

Compared to other European countries, the UK and France have the highest net price of drugs, with discounts comfortably reaching 60%. But while UK pricing remain somewhat predictable, pricing in France has become unpredictable, lengthening the price negotiation period whilst patients are treated through a compassionate use program called post-ATU (Autorisations temporaires d'utilisation).

However, although there is agreement on who should pay for these therapeutics, there is a lot of discussion about who should perform the long-term follow-up. Should the pharma industry be doing it, the same way they do their development, or should an independent third-party be chosen? There are still question marks there and as yet, there is no clear consensus of opinion.

What we currently see is companies performing long-term registries for their products for 10 to 15 years. The manufacturers of Yescarta® are possibly the only ones doing a long-term clinical trial and not a routine clinical practice data collection.

Q How will countries with relatively decentralized healthcare systems, such as the UK, cope with an increasing number of ATMPs reaching the market?

MT: The UK is a highly decentralized system where GPs have much greater decision-making responsibility than their counterparts in Germany or France, where patients are regularly referred to office-based and hospital-based specialists. It would be a real challenge to find enough resources to treat patients in this way in the UK and unless new investments are made, I don't see how it will be possible.

Covid-19 has also shown us that in the case of a pandemic, without the infrastructure to isolate infected patients, there is a high risk of nosocomial infection for anyone going to hospital. This has led to a lot of patients abandoning their care. As a result, countries have decided to rethink and reinvest in their healthcare infrastructure. When doing so, it is important that they consider how ATMP therapies and the patients receiving them should be handled.

For a very long time, infectious disease has been considered a problem solely for developing countries. In developed countries, we have come to believe that we have such good health infrastructure that if a pandemic reaches our own country, we can easily control it and our risk is low. This caused countries to stop investing as much in infrastructure, because we considered ourselves to be well prepared. Obviously, we have now realized that this is not the case. Despite the dire current situation, this rethinking of infrastructure is actually a very positive thing.

Q What are your words of advice for developers to help them ensure their R&D plans for new ATMPs align to HTA requirements in Europe?

MT: An important step is to accurately identify your target population. Avoid aiming for the whole population – if some have less severe disease and others are much more severely affected, targeting mild severity patients will impact the value of your product. Understand which population you want to target, and why.

For the most part, developers should stop performing single arm trials because in the future, payers and HTA will accept or rely on these less and less. (Of course, this excludes very specific conditions where you have evidence that the product is going to work, and it would be unethical to give a placebo to patients – for example, if patients are going to die within 1 year and your product can help them to survive for three or four years, there is no need to have a comparator to show that three years is better than one). But the efficacy of the product needs to be outstanding. You also need to understand the confounders so that you can adjust for them when performing historical comparisons. Finally, you need to understand the heterogeneity of the population in order to compare apple with apple, and not apple with pear.

Right now, most companies are not moving in the right direction. In the future we may see products being stopped at HTA level because they don't fulfil the requirements for HTA assessment. For now, HTA are looking past this: they are complaining about it, but still

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recommending products. In the future they may not be so willing to do this. So I would also advise developers to anticipate changes in HTA assessment. It is the responsibility of the pharma industry to act and to work for adjustments in the way that HTA is being performed. There should be a lot of adjustment in how we value gene therapy and on the discount rates for gene therapy in the long-term that is used for health economics assessments. Finally, developers will have to work on market access conditions through specific market-entry agreements.

Possibly the most important issue will be to work on making these therapies eligible for amortization and depreciation, which is not the case today. If you buy a table for your office, you are going to amortize the table over 5 years. But if you buy a gene therapy that is a single administration with a 10, 15, or 20-year benefit, you have to put it on the budget within the year you acquire it. You cannot amortize this therapy and therefore, it has a very high impact on payer budget. When you delay a payment over 5 years, this time-delayed payment is just contributing to the payer cashflow, not contributing to the budget. The budget has to be entirely in the first year. There is a need for adjustment to the public accounting law in most countries to make this change feasible.

AFFILIATION

Mondher Toumi
Public Health Department, Research Unit EA 3279, Aix-Marseille University, 27 Boulevard Jean Moulin, 13385, Marseille, France
mondher.toumi@univ-amu.fr

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CELL & GENE THERAPY INSIGHTS

Vector Channel

VECTOR CHARACTERIZATION & VALIDATION EDITION

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VECTOR CHANNEL: Characterization & Validation

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COMMENTARY

INTERVIEW

CELL & GENE THERAPY INSIGHTS

VECTOR CHANNEL: CHARACTERIZATION & VALIDATION

COMMENTARY

The right analytical toolbox is key to moving your pipeline forward

Andrew Espejo

The advancements of vector analytics within the field of viral gene therapy have evolved past simple qPCR testing for viral genomes. These analytical techniques have become the backbone of any process optimization, and are critical in making the decision to move forward with any optimized manufacturing steps. With many AAV gene products entering early and late stage clinical trials, having the right process to ensure consistency, quality, and efficacy is critical now more than ever – and the right analytical techniques can guide you towards the right decisions. This article will describe the most advanced analytical tests available for in-process optimization, and will explore the best time to use them. As well as having the right techniques in place, exploring different avenues within other fields of science is another approach which can push analytical characterization in viral vector testing towards new frontiers.

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INTRODUCTION

The advancements of vector analytics within the field of viral gene therapy have expanded beyond simple qPCR testing for viral genome quantification. Applying well-established analytical assays to characterize vector quality is essential to improve vector consistency, which is necessary for comparing biological outcomes from studies using more than one production lot of rAAV. With many AAV

gene products entering early- and late-stage clinical trials, having the right process to ensure consistency, quality, and efficacy is critical now more than ever – and the right analytical techniques can guide you towards the right decisions. This article will describe the most advanced analytical tests available for in-process optimization and will explore the best time to use them. As well as having the right techniques in place, exploring different avenues within other fields of science is another approach that can push analytical characterization in viral vector testing towards new frontiers.

CHOOSING THE RIGHT TOOLS FOR THE JOB

The hottest ticket in biotechnology right now is the use of viral vectors for the delivery of therapeutics. If you were to walk just three blocks in Kendall Square, Cambridge, MA, it would be hard to spot a startup that isn't using these nifty little particles as their vehicles of transfer. One particular viral vector being used is the adeno-associated virus; AAV. AAV can come in several variations: you have the reliable AAV2 serotype that has been proven to be more than capable of treating a form of hereditary blindness [1], or the versatile AAV9 that is now treating spinal muscular atrophy (SMA) patients [2]. The list goes on; you have AAV5, 6, 7, 7m8, Anc80, 2tyf, DJ… these various serotypes brings along a wide range of unique biodistribution qualities, which helps explain why AAV is currently seen as a pillar of gene delivery [3]. Unfortunately, with so many variations, mutations, amino acid swapping and so on, those involved in AAV manufacture are having to come up with unique ways to grow and subsequently purify viral vector. These scientists, who are staring down 50-liter bioreactors, or pumping volumes upon volumes into ÄKTA™ chromatography systems, require the best analytics possible to ensure they get the right answers as to whether their optimization attempts are working or failing. Having the right analytical strategy in place is key to ensure the right decisions are being taken and that the answers being delivered are trustworthy.

Like any good carpenter or builder, analytical teams need access to the right toolbox to get the job done. Table 1 is what the right toolbox looks like – having these assays available will allow you to generate the answers you need to move your pipeline forward.

However, there is an important caveat: to get the answers you need, you need to know the right question to ask, i.e., the best test to use.

ANALYTICAL TOOLS FOR UPSTREAM DEVELOPMENT

Upstream engineers are the beginning; they are the first step in creating what will be the final therapeutic product. Equipped with their 50L reactors or their 0.5L shake flask, they are pushing the limits of their abilities in order to get the most out of the cells being used to produce what will be the pivotal gene delivery system. One of the best tools to use in this situation will be a tried and true genome quantification assay; droplet digital PCR (ddPCR). This is a method for detection of genome titer and is the reason why we are now moving away from standard qPCR. ddPCR has superior benefits to older methods: it provides an absolute value, is more accurate, and is less susceptible to common inhibitors to genome quantification output [4]. However, as an analytical scientist, using just one tool from the box is not enough! If the ddPCR titer is not what is expected, the next step will be to figure out what went wrong. To fully understand what is going into the cell and what is coming out, an analytical scientist will be required to implement two more assays; Western blot and total vector particles. These two assays will be able to help explain why a genome titer may be low.

Western blot will show the three AAV structural proteins, VP1, VP2, and VP3, as they are being expressed in the cell (doing a

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TABLE 1

Viral vector analytical toolbox.

Attribute	Assay	Method
Strength/dose	Vector genome titer	ddPCR, spectrophotometer, qPCR
	Infectious genome titer	TCID50
	Total vector particles	Dynamic light scattering (DLS), ELISA
	Activity (expression)	Cell based assay
	Potency (function)	Cell or *in vivo* assay
Identity	Genome DNA	NGS sequencing
	Capsid	Western blot, mass spectroscopy
Purity	Host cell DNA	ddPCR/qPCR
	Helper plasmid/helper virus	ddPCR
	Host cell protein	ELISA
	Residual production reagents (detergents, benzonase, BSA, column leachable	ELISA/HPLC/mass spectrometry
	Ratio full/empty particles	HPLC/ELISA/AUC/TEM
Safety	Sterility	EP 2.6.1, USP <71>
	Bacterial endotoxins	EP 2.6.14, USP <85>
	Mycoplasma	EP 2.6.7
	Adventitious viruses	EP 2.6.16
	Replication competent AAV	Cell based assay
	Particle size and vector aggregates	DLS

timepoint assay will be even better). It has been known for some time that each of the three VP proteins within the AAV have various functions inside the cell. According to Le *et al.*, VP1 drives the infectivity of the virus, VP2 is essential for particle formation, and VP3 drives the encapsulation of the genome [5]. Seeing the expression of these proteins will add to a full understanding of what the titer means. Along with the Western blot, utilizing anther virus quantification method is key to understand the output. Capsid ELISA methods have been utilized extensively in the determination of AAV particles [6]. These assays taken together will provide key information that can influence improvements to upstream process development.

ANALYTICAL TOOLS FOR DOWNSTREAM/FORMULATION DEVELOPMENT

Downstream purification specialists prioritize the avoidance of contaminates and removal of impurities; all whilst trying to maintain the highest quality and yield. They are also required to ensure the right formulation is in place to contain the viral vector and make it suitable for injection [7]. When optimization is required during these steps, the assays needed will have to be accurate, reliable, and of high throughput. Once again, the assay of greatest importance is viral quantification via ddPCR. However, although this assay will tell you how much virus you have, for downstream optimization, you need more information.

Along with ddPCR, assessments of purity, potency, and safety will all be required in order to understand if the optimized protocol is working [3,8]. With any optimized downstream procedure, the quantity of samples to be tested will be great and having the right assays in place to analyze them quickly is critical. Incorporating multiplex PCR assays to detect residuals such as host cell DNA/helper plasmids and viruses is one option, and this method will allow the analyst to look at AAV titer and subsequently calculate the amount of process residuals in place. Another assay to consider when testing a high number of samples is implementing HPLC detection of common in-process residuals

TABLE 2

Analytcal plan to assess key changes in process development.

Process step	Assay	Attribute
Upstream transfection/infection efficiency	ddPCR, Western blot	Vector genome titer and identity of VP proteins
Optimal harvest time		
Downstream purification	ddPCR multiplex assays (high throughput)	Vector genome titer, residual host cell DNA, helper plasmid/helper virus quantification
	HPLC (high throughput)	Process residuals (Benzonase®, detergents, column leachable)
	Potency	Vector changes due to purification changes
Formulation	ddPCR	Vector genome quantification
	DLS	Vector aggregation
	Potency	Strength
	DSF	Thermal identity

such as benzonase, detergents, and column leachable, as this method will allow for automation and a quick turnaround of results. It is also imperative to have a trustworthy potency assay in place to ensure that whatever is being done is not altering any capsid structure that will hinder the virus's ability to do its job.

Finally, formulation does not fall too far from the purification tree. The assays required here will first assess whether the right formulated concentration is in place in order to avoid the formation of aggregates in solution. Of course, the tried and true ddPCR should be implemented; but along with this assay, it is critical to implement a DLS (dynamic light scattering) assay that will give you particle understanding within the solution, as having the right formulation to avoid aggregation is critical. Moreover, improvements in purification strategies will result in the continual elimination of residual impurities, thus making vector formulation a constant endeavor.

CONCLUSION

The field of gene therapy is growing at an exponential rate, and with time it will become a prominent area of medicine. Having the right manufacturing process in place can make or break any biotechnology company working on utilizing viral vectors as a delivery tool. To have the right process in place, it is key to have the right analytical test in order to determine what is 'good' and what is 'bad'. Luckily, there is a plethora of tools available that can be used to answer these questions, but they must be used wisely to gain the required information without generating unnecessary data. Therefore, it is imperative for an analyst to have a plan in place to make the best use of his/her analytical toolbox. Table 2 provides a summary of the right approach to assess key changes in process development. By implementing the right assay at the right time, analysts can provide the key information needed to paint a useful picture of process development, allowing for process optimization and ultimately, for the progression of a product through the pipeline.

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AFFILIATION

Andrew Espejo
Lead Analytics Scientist, UCB Pharma

AUTHORSHIP & CONFLICT OF INTEREST

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CELL & GENE THERAPY INSIGHTS

VECTOR CHANNEL: CHARACTERIZATION & VALIDATION

INTERVIEW

Priorities for AAV vector analytics development

CHRISTINE LE BEC joined Sensorion Pharma in early 2020 as Head of CMC Gene Therapy. She is responsible for all CMC activities, including pre-clinical development, CMC transfer to CMOS, manufacturing and supplying of Phase 1 and 2 clinical trails. Before joining Sensorion Pharma, she worked for more than 20 years at Genethon in the field of Gene Therapy vectors (AAV, Lentivirus, Baculovirus) for rare diseases. She has a strong expertise in the development, qualification, validation of analytical methods for product characterization, release testing of gene therapy products and in stability studies. She has also a solid knowledge of International regulations and reviewing CMC documents for clinical trial applications.

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Q What are you working on right now?

CL: I just recently joined a French company, Sensorion Pharma. I'm the Head of CMC Gene Therapy, which is a role that covers all aspects of CMC, including technical development, manufacturing, and supply for Phase 1 and Phase 2 clinical trials.

Sensorion was founded in 2009 as a spinoff from INSERM and is focused on developing therapies and recently AAV vector-based gene therapies to treat, prevent, and restore in the field of hearing loss.

Q Last time we spoke, you commented on the pressing need for more specific analytical tools and methods that are better suited to the gene therapy field – have you seen any recent progress in this regard and if so, where?

CL: One fairly recent development of relevance here is that previously in AAV vector-driven gene therapy, if you had different entities working on the same field or disease, it used to be difficult to compare AAV vectors in terms of titers, yield, target doses, etc. because of the degree of difference in methods used from one manufacturer or facility to another. Results would very much depend on the individual vector manufacturer, the individual laboratory, the target sequence for the qPCR, etc. Today, though, regulatory agencies such as the FDA have really tightened up and have become more stringent in this regard. They have indicated following a workshop meeting by the end of 2018 that they now require very low variability in terms of methods used – not more than 15%, which means that if we have very low variability in the titer, we can now potentially make easier comparisons between clinical studies.

That relates to more rigid titer. In terms of specific analytical tools emerging for the AAV vector space, the focus is more on infectivity and potency. There is more work being carried out now on relative potency, and comparing one method, one vector to another over time.

We still need to focus more on what we need to do in the way of quality control (QC) for GMP AAV vector batches. Currently, almost half of your AAV vector batch will be used up in QC testing. If you look at titers, total production volume, and the cost of a single AAV batch, that's a huge amount. Some companies are developing QC tests that require less material, which is very good news.

There is also greater attention being paid to AAV vector characterization, where the current focus is largely on describing full vs. empty capsids. We now have a couple of methods available for assessing full and empty particles – for example, previously, we largely depended upon analytical ultracentrifugation (AUC) or CryoTEM which require to use a purified product whereas we now have the possibility to use high-performance liquid chromatographic (HPLC) analysis for in-process control. That may be chiefly for the final product, but it's also going to be very useful for progressing and accelerating development. It also helps us strike the right balance between the characterization and quality of the product, and the process development.

Q What is your assessment of current inline analytical tools available to the gene therapy space, and where would you like to see further innovation in this particular area?

CL: It's fairly poor at the moment. Most of the analytical tools for in-process controls we have currently are for impurity and yield – we only have a relative few for achieving major results within a short period of time. The manufacturing process can involve in 10 different steps across upstream and downstream and it may take 4 days to get from harvest to the final drug substance,

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but we don't currently have the inline analytics available to allow us to change a parameter in this timeframe. This is a clear barrier to accelerating gene therapy product and process development.

We can look at vector genome (vg) titers, at yield, and at recovery. In-process impurity is mainly based on qPCR for residual DNA testing and for full and empty particles. But if you want to identify and potentially change the base plasmid ratio – the base transfection reagents, for transfection systems, or the base cell clones – then this development will obviously take time.

Q What for you are the most pressing priorities in terms of advancing viral vector product and process development today?

CL: I think the overall priority is around safety and quality, of course. You need to know the product and the process. But having said that, we've been developing gene therapy in the industrial setting for more than 15 years now, and we now know better what the process and the product are – that is true for both AAV and lentiviral vectors.

The most pressing priority, then, is to go further in terms of yield and concentration. For example, a decade ago, it was very difficult to go beyond a concentration of 1E+12 vg/ml. Today, the target concentration might be 1E+13 vg/ml, or even 1E+14 vg/ml, if you are aiming for local delivery such as in the CNS. The priorities there are to find some base formulation buffer and adjuvant for your final product, and to avoid aggregation in terms of sticking on the filters, container, that sort of thing. When you are targeting a very high concentration, it can present some issues for the formulation buffer, and it's imperative to get a good, long-term stability of the product, avoiding aggregation of your product at the beginning.

Q There is a clear drive in gene therapy towards improving our understanding of what exactly is packed into the capsid – what specific aspects of this work are most important, from your point of view?

CL: The field is striving to understand not only what is outside the vector but what is inside, and how important all of this is for the process characterization. We do now have some tools that at least give us a better picture of what is inside the viral capsid, such as next-generation sequencing (NGS), qPCR, and digital PCR.

It is important to understand that we should not be afraid of the fact that there will be some DNA coming from the process, such as the host-cell DNA – it is possible to determine the quantity, the size, the sequence, and to evaluate whether is acceptable or unacceptable. But nonetheless, the main concern is obviously around safety. We don't yet know

> "...the main concern is obviously around safety. We don't yet know whether 'empty' capsids really are empty..."

"When you are targeting a very high concentration, it can present some issues for the formulation buffer, and it's imperative to get a good, long-term stability of the product..."

whether 'empty' capsids really are empty, or the significance (if any) of those vector capsids that are only partially full for patient safety and the efficacy of the product.

So we do need to well know what is it inside as well as outside of the particle. We need to know what the impurity is, what is coming from the process, and to try to reduce this impurity through our process development. This is a huge area of focus for the gene therapy community as a whole, and I believe we are now more open about it, and not so afraid to discuss and present some data around impurities and what they may mean for the final product and patient. Everybody has the same challenge.

Q Finally, can you summarize your own main goals and priorities in your role over the coming 12–24 months?

CL: Sensorion has a small molecule approach in the pipeline for the treatment and prevention of hearing loss, but we do also want to restore hearing loss through our new gene therapy programs. We have two different gene therapies in development currently: one is for Usher Syndrome Type 1, and the other is for Otoferlin deficiency. My main goal is to develop these two products and progress the AAV vector manufacturing as quickly as possible to allow us to dose our first patients in Phase 1 trials for these two candidates.

AFFILIATION

Christine Le Bec
Sensorian Pharma

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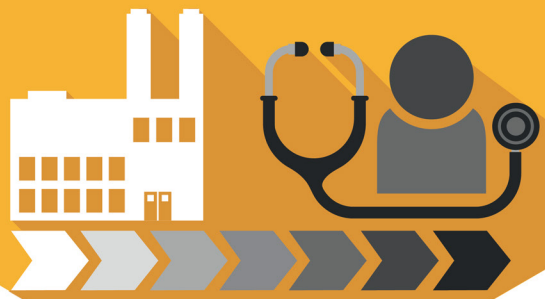
Supply Chain Channel



BIOPRESERVATION & COLD CHAIN MANAGEMENT

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INTERVIEW

How will COVID-19 impact the cord blood banking sector?

Wouter Van't Hof

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INTERVIEW

How will COVID-19 impact the cord blood banking sector?

WOUTER VAN'T HOF holds a PhD in Cell Biology from Utrecht University in the Netherlands, and has over 15 years of biotech experience in the USA in translational research and development of adult stem cell therapies, including bone marrow stromal cells (MSC) and HPC, cord blood. He is currently Cord Blood Bank Director of the Cleveland Cord Blood Center (CCBC). Under his direction, CCBC obtained FDA approval for the manufacture and distribution of HPC, Cord Blood under federal license, as one of only eight nationally licensed cord blood banks in the USA. As Cord Blood Bank Director he oversees Laboratory Operations, including CMC, Process Validation, Aseptic Processing, and GMP compliance. In addition, Wouter leads the Cell Therapy Incubator (CTI), a new CCBC initiative facilitating internal and external programs for broader development of cord blood cell-based therapies in regenerative medicine. From 2002 to 2013, he was a Director at Athersys, Inc., with responsibility for technology transfer, product and process development, preclinical safety, and was deeply involved in regulatory discussion for clinical study design and management of a GVHD prophylaxis trial. He was the scientific lead on the completed Phase 1 safety study in HSCT support for the MultiStem Product. During his academic career, Dr Van't Hof was an Assistant Professor of Cell Biology in Medicine, Department of Medicine, Division of Pulmonary and Critical Care Medicine, and Assistant Professor of Genetic Medicine, Institute of Genetic Medicine, Weill Medical College of Cornell University.

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Q What are you working on right now at your cord blood bank?

WVH: My main responsibility in my day job as Cord Blood Bank Director at the Cleveland Cord Blood Center is ensuring that the laboratory operations for cord blood processing, archiving and distribution are functioning properly, and remain in sync with the upstream cord blood collections and the downstream quality review for timely product release for hematopoietic cell transplant. As the only public cord blood bank in the State of Ohio, we procure cord blood at 5 collection sites: two in Cleveland, OH, two in Atlanta, GA, and one in San Francisco, CA. The other locations were chosen to increase collection of cord blood units from minority groups that remain underserved in the cord blood inventories. Since its start in 2008, CCBC has collected more than 70,000 cord blood units. On a daily basis these collected units are shipped to the processing facility in Cleveland, OH, for centralized processing, cryopreservation and frozen storage. CCBC currently has over 10,000 frozen clinical-grade units in inventory and listed in the NMDP and WMDA searchable databases. To date, we have shipped more than 670 cord blood units to transplant centers throughout the USA and in 17 countries world-wide. We are one of only 8 FDA licensed cord blood banks in the USA and remaining compliant and dealing with regulatory inspections requires ongoing attention. Here I am very fortunate that our small organization does an outstanding job in systematically and efficiently dealing with licensure and accreditation expectations. I am very proud of our CCBC staff, some of whom have been with CCBC from the very early days in 2008 and 2009, much longer than my own involvement. With the compliance programs on track and well monitored, the door opens for me to work on areas of organizational need and professional interest.

Q Can you describe those mentioned incremental cord blood needs and interests?

WVH: Another core aspect of our mission is to make cord blood that is not used for processing available for research and development. Our center has provided over 11,500 research-grade units to investigators in both academic and biotechnology organizations. We believe this is crucial, both for the future of our cord blood bank and for the industry. Along this line, CCBC, which is a non-profit entity, established two social enterprise subsidiaries in 2020, to focus on the next iteration of its mission. Enabling the use of donated cord blood, beyond HCT, into the bigger realm of regenerative medicine is a major objective of these new efforts. So, the other part of my day job is leading the Cell Therapy Incubator (CTI), one of the two new CCBC subsidiaries. The CTI is housed in a

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"Transmission of infectious agents from tissue or blood cell donors to recipients is a major regulatory concern, and COVID-19 would fall right under that. So if coronavirus would be detected in cord blood, we may be asked to include coronavirus testing for product release and reject at risk units. That could have a great impact on units produced since late 2019."

separate facility with GMP capability, built for execution of programs that increase utilization of collected cord blood, and/or support development of new cord blood based cell therapy products or technologies. Initial CTI projects are producing non-clinical grade isolated CD34 cells from cord blood. We see increased demand and opportunity for this as a consistent source material in the biotech environment, with a growing number of companies developing cord blood derived NK cells, Tregs and other specialty products. Ultimately, we want to support manufacture of clinical grade CD34 or cord blood derived cell products. For now, the nonclinical production arm boosts higher utility of collected cord blood, which is a cornerstone of the CCBC mission. In these beginning stages of the subsidiary, I am pursuing new collaborations and contracts. With new research funding opening up for COVID-19, we are receiving many requests for our clinical grade materials, so that is keeping us busy at the moment.

Q Can you outline the technical procedures in your cord blood cell banking and processing work, including those relating to biopreservation?

WVH: Our processes are based on US regulatory and international accreditation compliant procedures and technologies, standard in the industry, with certain specific iterations. We only collect cord blood via umbilical cord puncture in utero, rather than from the delivered placenta, using a single use FDA cleared collection bag set containing CPD anticoagulant. This approach minimizes contamination risk during collection. It also allows for collection at shorter time after delivery, with better chance of obtaining the required volume and cell numbers. If those requirements are met, collected cord blood is then processed. CCBC uses the AXP AutoXpress™ System from Thermogenesis. This is a semi-automated process using centrifugation to separate cord blood into three separate fractions, red blood cells, white blood cells, and a RBC/plasma fraction obtained by volume reduction of the white cell fraction. The white blood cell fraction, containing the desired hematopoietic stem and progenitor cells, becomes a minimally manipulated product, specified as HPC, Cord Blood. This

"...physical cord blood quarantining is a very important aspect of inventory protection and is now demonstrating its relevance in the context of the current COVID-19 pandemic."

final product is formulated in a 25 mL volume, supplemented with 10% DMSO and 1% dextran. The freezing bag itself is divided into a 5 and a 20 mL part, both sealed to allow future use separately, where desired. Importantly, before freezing, each HPC, Cord Blood unit is placed into a sealed overwrap bag to minimize any cross-contamination risk during storage. We must keep in mind that product sterility testing is not completed until 2 weeks after freezing, and that there is a 5–10% baseline for cord blood contaminations, mostly related to collections. This physical cord blood quarantining is a very important aspect of inventory protection and is now demonstrating its relevance in the context of the current COVID-19 pandemic.

As is standard in our field, cryopreservation must be initiated within 48 hours of the time of cord blood collection. The start is defined as the insertion of the canister with the processed unit into the automated, controlled-rate freezing element of the BioArchive® System from Thermogenesis. BioArchives® are big liquid nitrogen units or dewars that accommodate long-term storage of up to about 3,600 units in liquid nitrogen at -196°C, with continuous monitoring. Associated computer modules assign a specific address to each frozen unit inside the freezer inner storage structure, allowing for controlled retrieval. Each stored product is tested for purity, identity, sterility, and potency. Upon batch record review, units complying with donor eligibility and product requirements are released from administrative quarantine and made available for search by transplant centers. We ship the majority of our units through the National Marrow Donor Program logistics system. There is obviously much more underlying detail, but this is the gist of the technical aspects around our inventory and its use.

Q You mentioned COVID-19. Can you frame for us the potential threat it presents to the cord blood banking field?

WVH: As for anybody else, all of our staff are directly impacted by the federal, state and local stay at home directions. We have implemented a minimal staffing strategy to ensure sufficient staff presence on site to monitor and manage our liquid nitrogen storage systems, and to accommodate any cord blood unit requests for transplant. This has worked out well, and we have continued to ship out units efficiently, a few of those within 24 hours of receiving the request. This process requires final review by operations, medical and quality staff members, most working from home, but it is good to see we can handle this under the current societal constraints caused by the pandemic.

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With respect to our products, the general threat of COVID-19, as with any tissue, blood or cell contaminant, is in theory very serious and could endanger all ongoing collections, our future products, and their use. We don't think that's what is actually transpiring. At this time, (early May 2020) outside of the risk for staff in delivery wards, the reality looks like the cord blood industry might hopefully be spared from major harm. COVID-19 is widely understood to not migrate from the mother via the placenta to the cord blood, minimizing risk for the baby. This is a very different scenario from the Zika virus threat a few years back. Absence of COVID-19 in cord blood also means it remains safe to collect and process donated cord blood and it justifies continued cryopreservation of cord blood collected during the active pandemic. Our cord blood collection sites have mostly remained open and actively collecting. Processing at our center in Cleveland has also managed to continue under minimal staffing strategies, with appropriate and workable social distancing procedures. We have been encouraged by production rates remaining very similar as to prior to the pandemic. This may not be the case for all public cord blood banks.

A hidden threat could be that with emergence of more sensitive tests, this coronavirus might in the future actually be found in cord blood stored during the pandemic, with different associated risks. First, in each BioArchive® unit, all frozen units are submerged in a singular liquid nitrogen supply, not in the liquid nitrogen vapor phase. In theory, over the commonly long storage times of cord blood, virus could leak from contaminated frozen cord blood bags, compromising an entire inventory within a shared BioArchive® unit. This is a possible, but very unlikely risk scenario. It would require virus to survive long-term in liquid nitrogen and pass through the walls of two different types of bags. As mentioned earlier, all cord blood units are individually wrapped within protective overwrap bags, so the risk for spread of infectious organisms from contaminated bags and subsequently into 'clean' products is really very minimal. In terms of use of the products, coronavirus contaminated units obviously would not be acceptable for transplant, especially in immune-compromised recipients. Transmission of infectious agents from tissue or blood cell donors to recipients is a major regulatory concern, and COVID-19 would fall right under that. So if coronavirus would be detected in cord blood, we may be asked to include coronavirus testing for product release and reject at risk units. That could have a great impact on units produced since late 2019. On a side note, but related to this topic, current prophylaxis strategies for transplant include more potent combinations of antibiotic, antifungal and antiviral agents. This allows transplant physicians nowadays more aggressive risk-benefit considerations with 'risky' cord blood products, within reason, and especially for patients in immediate critical need. Such considerations are made, for example, for cord blood carrying CMV risk. There also appears to be different responses to COVID-19 between children and adults, and the risk-benefit balance may have different answers for different age groups. Again, these are theoretical considerations, I am not a transplant physician, and in no way should

"...protecting our bank from the COVID-19 impact will involve closely following new regulatory guidance and ... technology development..."

this be construed as a defensive or self-serving statement, advocating risky strategies to benefit use of potentially coronavirus-tainted cord blood. On the contrary. But things do change over time, and a current contamination risk, perceived or not, may become less of an acute problem – for example, with advancement of antiviral agents.

Q What's the current consensus of opinion in terms of whether COVID-19 is having, or will have, an impact, and what steps are you and others in the field taking now to respond?

WVH: If anything, believe it or not, the coronavirus pandemic might actually result in broader use of cord blood as a transplant strategy. Procurement of adult hematopoietic stem cell products, which are bone marrow or mobilized peripheral blood derived, is impacted more directly by coronavirus. The involved collection procedures for adult grafts include more virus exposure risk between donors and collectors. Adult HSCT products are mostly used 'freshly', within short times (hours to days) after collection and with less opportunity for testing prior to transplant. Donations for bone marrow and peripheral blood have gone down, in large extend due to travel restrictions not allowing donors to get to collection centers. However, cord blood, as a frozen and tested product, obtained prior to the COVID-19 pandemic, remains readily available for safe use without virus transmission risk. It is too early to tell how this will play out, as all transplants have largely been put on hold by the worldwide lockdowns and stay at home directions in March and April of 2020. Any new trends in cord blood transplant as a consequence of COVID-19 will unlikely become evident before transplant centers open back up again sometime in 2020. Meanwhile, protecting our bank from the COVID-19 impact will involve closely following new regulatory guidance and keeping an eye on technology development for coronavirus testing in people and products. Finally, the scrutiny from our past regulatory and accreditation reviews, and numerous inspections, has taught us how to implement appropriate documentation and control systems. This will ensure required safety and activity of our cord blood products, even for those manufactured during a global threat of an infectious virus. I must tell you that some of these inspections are no picnic, and again, kudos to our dedicated staff. But under current circumstances, it is encouraging to know that we are following due process, to the best of our knowledge and in line with industry standards. We are controlling what is within our area of control. This awareness provides a great morale boost under strain, be it caused by Zika, COVID-19 or any future challenge.

AFFILIATION

Wouter Van't Hof
Cord Blood Bank Director, Processing Facility Director, Cleveland Cord Blood Center, OH, USA
wvanthof@clevelandcordblood.org

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AUTHORSHIP & CONFLICT OF INTEREST

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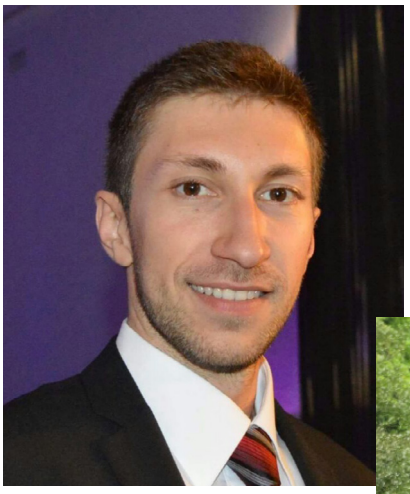

Fighting a global pandemic with an army of robots

EDITORIAL

Nikolaos Pantidos & Rennos Fragkoudis

INTRODUCTION

Over the past 20 years, the field of Synthetic Biology has emerged as a potential solution to tackle many of the modern world's problems [1]. It has grown to be regarded as one of the main fields that will drive the next industrial revolution [2,3]. In 2012, the UK Research Councils deemed that innovation should focus on the eight great technologies of Advanced Materials, Agri-Science, Big Data, Energy

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Storage, Regenerative Medicine, Robotics and Artificial Intelligence, Satellites and Synthetic Biology. From combating antibiotic resistance to personalized medicine and vaccines, Synthetic Biology is a promising field of research for the years to come. More recently, with the ongoing spread of SARS-CoV-2 causing the COVID-19 pandemic, Synthetic Biology has been at the forefront in the combined worldwide efforts to develop and test, at the necessary scale, tools for virus diagnostics (molecular and serological), therapeutics (novel and existing compounds), and vaccines.

ENGINEERING BIOLOGY

Synthetic biology is an interdisciplinary field that involves re-designing existing organisms for our benefit. It aims at the production of biological materials and systems that do not naturally exist in the ecosystem [4]. The field emerged from an amalgamation of Engineering and Biotechnology which differentiates it separate from conventional genetic engineering whereby both principles are combined to create a beneficial outcome. By taking the Design, Build, Test, Learn (DBTL) cycle approach from Engineering, and combining it with the powers of Biotechnology, Synthetic Biology has already started to make its mark in the 21st century.

For many years, scientists were limited by the technological advances of their tools to study biology. Even performing the smallest of changes in the genetic code of a living organism required a slow and painstaking manual process. The conventional methods used in the designing and building stages of Synthetic Biology have a laborious and repetitive nature, and often allow the introduction of errors when done on a large scale.

The solution to tackle the above problems is the creation of a lab that would be capable of performing the same tasks done by scientists, but taking the laborious, repetitive elements out of the equation.

In 2012, the Synthetic Biology Leadership Council published the Roadmap for Synthetic Biology which in turn resulted in a significant investment to promote the field of synthetic biology in the UK. To accelerate current academic and industrial research efforts in this field, a total of three DNA Foundries were established with funding from the BBSRC and the UK Research Councils Synthetic Biology for Growth Programme. These were the Edinburgh Genome Foundry (EGF), Liverpool Gene Mill and Earlham BIO Foundry. Later, London BioFoundry and SYNBIOCHEM were established [5]. This initiative also saw the creation of six Synthetic Biology Centres throughout the UK, namely, BrisSynBio based in the University of Bristol, SBRC at the University of Nottingham, OpenPlant which is based at the University of Cambridge and the John Innes Centre, UK Centre for Mammalian Synthetic Biology at the University of Edinburgh, SYNBIOCHEM at the University of Manchester and the Warwick Integrative Synthetic Biology Centre based in the University of Warwick.

ROBOTS TO THE RESCUE

EGF, based at the University of Edinburgh on the King's Buildings campus is a £5M specialist large automated robotic research facility that enables the large-scale assembly of DNA fragments using a highly-automated, integrated platform **(Figure 1)**. The platform, which is species agnostic, was designed to build genetic constructs for academic and industrial customers to produce cells with novel or improved functionalities. The end-products of EGF are destined to be used in a diverse portfolio of projects such as the programming of cells for personalized medicine, vaccine development, living biosensors, gene therapy, optical tools for basic biological research [6] and more recently the development of a next generation serology test against SARS-CoV-2, the causative agent of COVID-19.

EGF is uniquely positioned to perform large-scale, complex projects from

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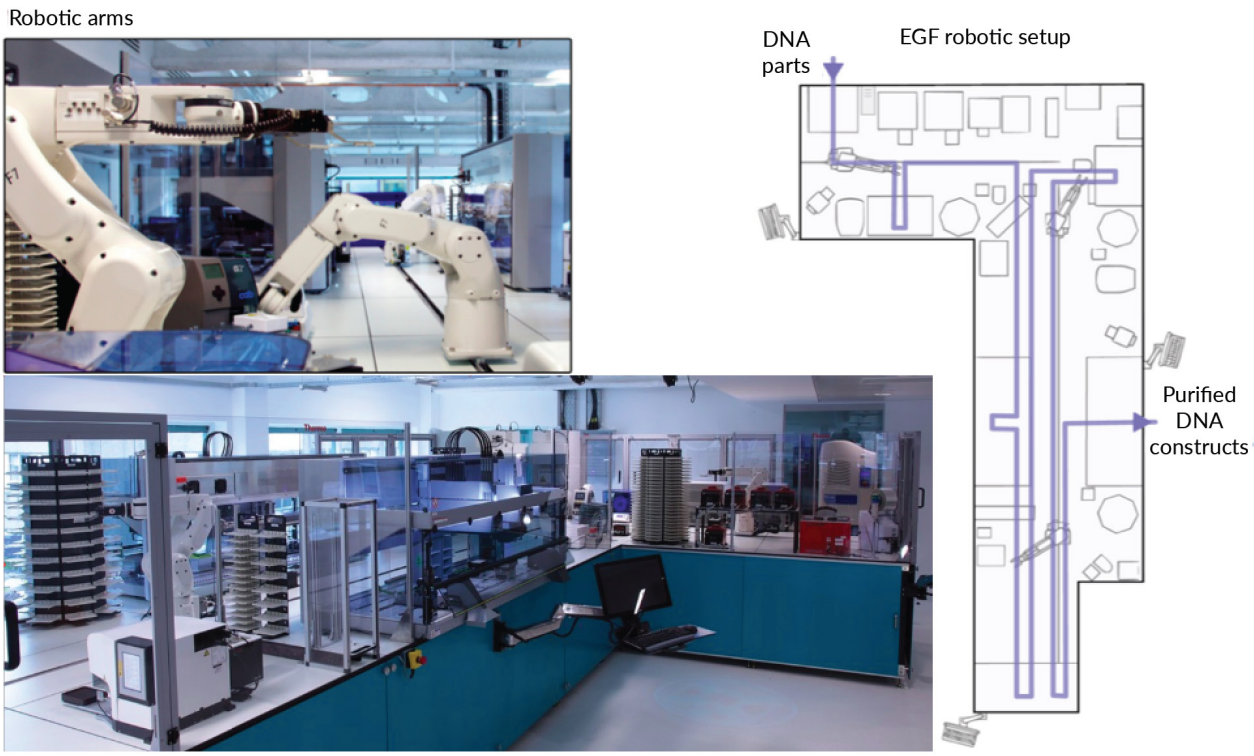
FIGURE 1

The highly-automated robotic laboratory setup of EGF.



All the necessary equipment is enclosed in the L-shaped platform for optimal performance.

conceptualization and design to building DNA constructs. The platform consists of automated versions of the conventional lab-based equipment found in most molecular biology labs but with an added bonus [7]; tasks can be performed under no supervision and at all hours of the day. The twist mentioned – and the heart of the platform – are three robotic arms that are used to integrate all the equipment in the platform, essentially acting as a robotic scientist capable of performing all the tasks a human scientist can do. Due to its nature, automation means that human error can also be avoided and limited to only the design steps of the whole process. Using this platform, scientists can now assemble DNA parts from the ground up and combine thousands of parts in almost unlimited combinations in order to gain a deeper insight into the world of genomes.

FOUNDRIES FIGHTING COVID-19

When it comes to combatting a global pandemic, biofoundries have the ability to significantly contribute in many different ways. EGF specifically, is equipped with the knowledge and facilities to provide help in numerous different ways. EGF can be used to enhance the capabilities of health structures for diagnostics and perform large-scale, high-throughput testing of patient samples with the use of laboratory automation (examples include nucleic acid extraction, qPCR, serology). EGF has developed and is continuously developing open source tools for the design and processing stages of all projects. These software tools are designed to assist in planning and translating project designs towards a high-throughput friendly way of research, as well as assisting in quality control of the products that are generated downstream

of each project. It is also possible to facilitate vaccine and therapeutics development at a large scale. Lastly, EGF can significantly help with basic research on pathogens by generating the tools that will allow researchers to gain useful insights into their inner workings and to understand the mechanisms of pathogenesis and disease (for example, to develop SARS-CoV-2 reverse genetics systems).

One of the problems that researchers and clinicians faced over the last few months in their efforts against COVID-19 was the shortage of reagents and materials. Biofoundries are capable of reducing the severity of these issues because of their ability to scale down molecular biology reactions, potentially cutting reagent cost by 20- to 100-fold [8]. Cutting edge technology is employed that allows the use of the smallest amounts of reagents needed to perform the work while improving time efficiency and decreasing waste generation (and subsequently significantly reducing costs). The advancements of acoustic dispensing technology enable us to transfer nanoliter size droplets, allowing effective miniaturization of reactions, thus saving on reagents and costs. At EGF, reactions that in a typical molecular biology laboratory occur in 20 or 50 µl (i.e. qPCR or restriction enzyme reactions) volumes are scaled down to a final volume of 1 µl, significantly reducing time and reagent usage. As the process does not utilize pipette tips, the probability of cross-contamination is also virtually eliminated.

EDINBURGH GENOME FOUNDRY'S RESPONSE

Currently, EGF is collaborating with a number of researchers from the University of Edinburgh lead by Professor Nick Gilbert, to develop – using structure-informed 3D computer modelling to identify immunogenic viral peptides – a next generation serology test that can be used to:

- Stratify individuals according to their SARS-CoV-2 exposure status;
- Analyze the longevity of the immune response to the virus and predict the re-infection rate;
- Assess vaccine efficacy.

EGF's work is focused on rapidly generating DNA constructs for the production of SARS-CoV-2 derived peptides. These constructs will then be used in a test detecting SARS-CoV-2 specific antibodies and provide a detailed "antibody fingerprint" for each patient. Using such assays, important epidemiological data can be acquired, used to model outbreaks and utilized to guide policy decisions.

Furthermore, EGF has been assisting Professor Alain Kohl's group (Centre for Virus Research, University of Glasgow), in the development of a virus replicon system for SARS-CoV-2. As this virus is an ACDP/BSL-3 pathogen, studying it is limited to institutions with high-containment facilities. Developing a replicon system has the potential to enable more researches to study the basic properties of the virus as well as screen a large number of compounds as possible therapeutics against it without the need for high-containment. This can significantly speed up research and lead to an effective intervention sooner.

Increasing throughput results in the generation of vast amounts of data, and the processing of such large datasets is often problematic and introduces a bottleneck to the process. Additionally, designing projects with large amounts of parts involved can be challenging and demanding. To solve these issues, software developed at EGF can also aid in the processing of large datasets that are produced at the start and end of experimental processes. For example, quality control software that helps in cross referencing large sets of assembled DNA constructs to the expected outcome in order to confirm the correct assembly. A task that would normally take several hours to perform can now be condensed to a few minutes. Another example is the ability to simulate DNA assemblies in large scale, rather than having to manually perform a simulation for each assembly separately.

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AFTER COVID-19

EGF is contributing to a wide range of projects including gene therapy, vaccine development, antibiotic resistance and diagnostics. EGF is heavily involved in the design, build, test steps of the process and works hand-in-hand with researchers to provide the best possible outcome. Another exciting aspect of the platform is the ability to modularize the equipment and perform a whole suite of projects independently. This gives EGF the all-important capability to simultaneously work and collaborate on a plethora of projects without affecting efficiency.

EGF is one of the few foundries set up around the world that is capable of performing Synthetic Biology projects at such scale and tackling a diverse range of problems. Five years after its launch, and being the most automated facility of its kind, it now stands firmly on the Synthetic Biology scene for its large scale and high-throughput research capabilities.

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AFFILIATIONS

Nikolaos Pantidos
Edinburgh Genome Foundry, Centre for Mammalian Synthetic Biology, The University of Edinburgh , Michael Swann Building , Max Born Crescent , Edinburgh, EH9 3BF, UK

Rennos Fragkoudis
Edinburgh Genome Foundry, Centre for Mammalian Synthetic Biology, The University of Edinburgh , Michael Swann Building , Max Born Crescent , Edinburgh, EH9 3BF, UK

AUTHORSHIP & CONFLICT OF INTEREST

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Innovation Insights

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COMMENTARY

Chemogenetics: drug-controlled gene therapies for neural circuit disorders

Scott M Sternson & David Bleakman

Many patients with nervous system disorders have considerable unmet clinical needs or suffer debilitating drug side effects. A major limitation of exiting treatment approaches is that traditional small molecule pharmacotherapy lacks sufficient specificity to effectively treat many neurological diseases. Chemogenetics is a new gene therapy technology that targets an engineered receptor to cell types involved in nervous system dysfunction, enabling highly selective drug-controlled neuromodulation. Here, we discuss chemogenetic platforms and considerations for their potential application as human nervous system therapies.

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INTRODUCTION

Nervous system disorders are among the most debilitating chronic diseases. Small molecule therapeutics that improve core symptoms of neurological and psychiatric disorders have benefited millions of people worldwide. Despite this progress, patients with nervous system disorders have large unmet needs. A minority of patients with neuropathic pain respond to available treatments, and amongst those responsive patients, pain is only relieved by approximately 50% [1]. For epilepsy, a

degree of seizure control can be achieved in approximately 60% of patients; however, a third of patients that are treated with antiepileptic drugs still have seizures. Moreover, efficacy can be accompanied with neurocognitive side effects, and a large percentage of patients are either refractory or intolerant to pharmacotherapy [2]. In addition, there are insufficient treatment options for most neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS).

Other therapeutic modalities are used to address the unmet needs of pharmacotherapy. Surgical nervous system resections are last-resort treatments. Although surgery can yield improvements in neuropathic pain or pharmacotherapy-resistant epilepsy, tissue resection or ablation may require multiple surgeries, can leave permanent deficits, and generally faces resistance from patients and physicians [3]. Moreover, many nervous system disorders are not candidates for surgical resection. Deep brain stimulation (DBS) is an alternative and mostly non-destructive surgical method that implants a stimulating electrode [4]. DBS modulates the activity of cells at the stimulation site but also axons-of-passage, potentially recruiting many different brain areas, thus limiting mechanistic understanding and reducing generalization of the approach [4,5].

Gene therapy is an additional therapeutic option being developed for neurological diseases [6]. Approved gene therapies for neurological disorders target large volumes of the nervous system and are designed to correct the function of a disease-causing underlying genetic mutation, as with Zolgensma® for pediatric patients with *SMN1* mutation leading to spinal muscular atrophy. Other gene therapies in development target endogenous enzymes or neuropeptides to specific brain areas, for example to increase dopamine production [7]. All three of the aforementioned approaches to neurologic treatment have strengths that must be balanced with considerable weaknesses (Table 1).

Here, we discuss the potential for a new therapeutic modality, called chemogenetics, which combines the respective advantages of pharmacotherapy, DBS, and gene therapy while minimizing drawbacks (Table 1 & Figure 1). Chemogenetics is a method by which a cell is modified to express an engineered receptor so that it can be selectively activated by its cognate drug [8,9]. The receptor can be targeted to a local region of the nervous system with greater specificity than DBS and with the temporal and scalable neuromodulation of traditional pharmacotherapy. We first briefly discuss the reasons behind the need for new therapeutic approaches to neurological diseases that are most relevant to chemogenetic technologies. Then, we describe some of the background to chemogenetics, before focusing on considerations for translation of chemogenetics into a human gene therapy.

DRUG DEVELOPMENT & TARGET SELECTION IN NERVOUS SYSTEM DISORDERS

The molecular biology revolution of the 1990s led to a better understanding of the gene products targeted by available pharmacological therapies for neurological and psychiatric disorders, most of which had activity at multiple receptors [10]. This transformed the approach to drug discovery and led to a hypothesis that generating highly selective molecules for single molecular targets could potentially achieve efficacy without unwanted side effects. Molecular target-based approaches resulted in small molecules modulators, peptides, or antibodies being directed to a plethora of drug targets, including subtypes of neurotransmitters, their reuptake transporters, ion channels, enzymes, and misfolded proteins. There have been a few notable successes in this single-target approach, such as monoclonal antibodies against CGRP for the prophylactic migraine treatment, 5HT2a partial agonist for psychosis in PD; α4b2 nicotinic acetylcholine receptor partial agonists for smoking cessation, and hypocretin (HCRT1/2) receptor antagonists to promote sleep. However, the target-based approach in

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TABLE 1

Treatment approaches for nervous system disorders.

	Advantages	Disadvantages
Pharmacotherapy	▶ Molecular targeting ▶ Dose-dependent dynamic range ▶ Reversible	▶ Systemic treatment of focal disorders ▶ CNS access of drugs ▶ Typically, indirect modulation of neuron electrical activity ▶ May only work in a specific patient population
Surgical resection	▶ Eliminate disease tissue	▶ Permanent tissue loss ▶ Post-operative side effects ▶ Patient and physician stigma ▶ Need for repeated surgeries
DBS	▶ Local targeting ▶ Scalable ▶ Reversible ▶ Real-time control	▶ Surgery with permanent implant ▶ Local targeting reduced by activation axons-of-passage ▶ gof or lof mechanism of neuromodulation is unclear ▶ Hardware-related complications
Gene therapy (traditional)	▶ Replacement of missing or dysfunctional gene product ▶ Can by locally or broadly targeted	▶ Static effect, no additional control over neuromodulation ▶ Irreversible ▶ Usually cannot non-invasively assess localization and expression
Chemogenetic gene therapy	▶ Cell-type-specific targeting ▶ Dose-dependent dynamic range ▶ Pharmacologically reversible ▶ Local targeting ▶ Mechanistically straightforward ▶ PET to non-invasively assess localization and expression	▶ Best suited for local brain disorders ▶ Non-natural elements in engineered proteins ▶ Three components (small molecule, receptor, AAV)

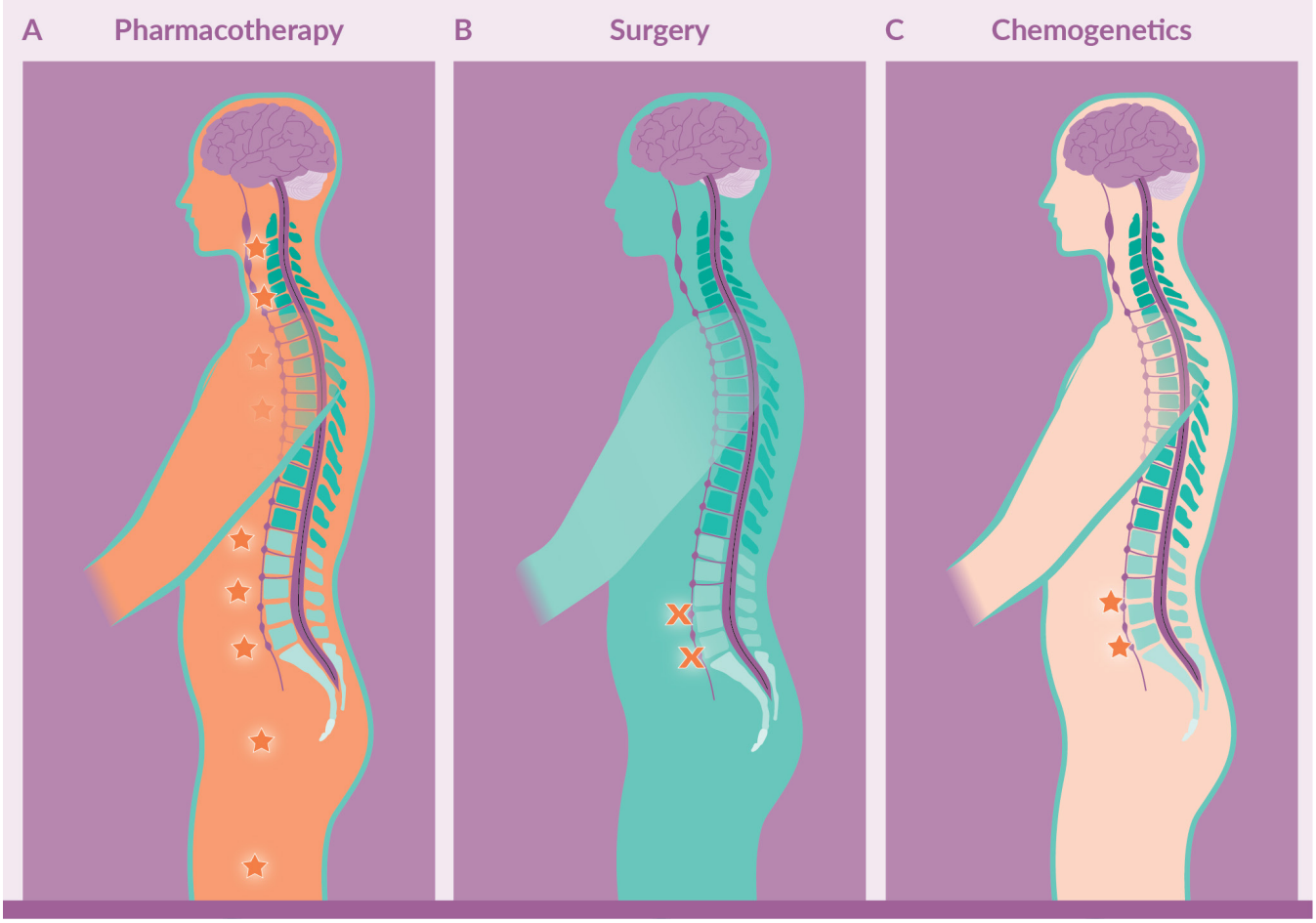
neuroscience drug development, comes with common failure-modes from attempting to drug the wrong targets or from insufficient target engagement. These problems can be due to: (1) an incorrect biological hypothesis, (2) limited nervous system exposure of the drug, or (3) a need to balance target engagement in the treatment-relevant cells while minimizing adverse effects of target engagement at cells that are unrelated to efficacy.

Choosing the wrong target is a pernicious error that can sometimes become apparent only after attempting to understand the failure of a large clinical trial, and, in some cases, even then the reasons for the failure may be unclear [11]. In addition, achieving sufficient exposure of a drug at the target is associated multiple tradeoffs often requiring structural changes that may reduce affinity or selectivity. However, it is the complexity of the nervous system that is one of the greatest challenges to overcome for developing new therapies.

The NIH Brain Initiative® (Brain Research through Advancing Innovative Neurotechnologies) and Europe's Human Brain Project are research initiatives aiming to understand the integrated functions of the brain. A key observation from this work has been that there are many functionally specialized networks in the brain that are important for normal brain function. For example, intermingled neuronal subtypes in sensory

FIGURE 1

Three treatment approaches to nervous system therapy, example of chronic neuropathic pain.



Systemic pharmacotherapy results in widespread distribution of the drug (orange), which modulates (red stars) the affected sensory ganglia as well as all other sensory ganglia, the brain, and other peripheral organs that also express the target for the drug. Surgery procedures permanently disrupt the sensory ganglia (red x's) to block sensory transmission. Chemogenetics achieves local, tunable, and reversible neuromodulation by targeting a chemogenetic receptor solely to the neuropathic pain-causing ganglia. Ultrapotent chemogenetic receptors use low doses (light yellow) of the chemogenetic drug.

ganglia are responsible for transmitting information about touch, pain, and itch [12]. Furthermore, the perceptual and emotional qualities of these distinct sensory modalities are established in separate brain regions by distinct downstream circuit connections of these cell types [13]. The different functional specializations of intermingled cell types and their connections points to an organizational framework that offers a solid mechanistic foundation for understanding brain function. In principle, any of the nodes (cells) or wires (axons) in these neural circuits can experience dysfunction that can lead to neurological disease. The development of maladaptive synaptic circuits resulting from neuroanatomical and/or neurochemical changes have implicated hyperactivity or hypoactivity of specific neuronal circuits in epilepsy [14,15], pain [16], AD [17], PD [18], schizophrenia [19] and addiction [20].

Each cellular circuit node in these networks expresses thousands of gene products that are potential targets for pharmacotherapy. However, brain-localized differential gene expression is restricted to fewer than 100 genes, distributed across neurons, glia, and other nervous system cell types [21,22]. Moreover, brain-wide analysis of gene expression distribution reveals few genes that are limited to a single brain region [22,23]. In addition, effective nervous system therapies often attempt to increase or

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decrease neuron activity, thus target selection is further limited to druggable, neuron-activity-modulating gene products. Thus, the major limitation of traditional pharmacotherapy is that most molecular drug targets are not localized to one circuit, or even to the brain. A systemically administered drug, distributed throughout the body and brain, will likely exhibit additional interactions that will interfere with efficacy and produce dose limiting side effects. Despite the successful generation of new chemical entities that are highly potent and very selective for their intended target, regional specificity is not achieved.

In light of these limitations, deep brain stimulation has been adopted to control neuronal circuit activity focally in the nervous system. DBS is FDA approved for medically refractory PD, essential tremor, dystonia, and obsessive-compulsive disorder [4]. However, the mechanism by which DBS works is unclear. For example, there remains mechanistic uncertainty about whether DBS activates or inhibits circuits. This makes it difficult to predict what sites would be effectively treated by DBS, and treatment design is largely empirical [4]. Moreover, DBS is not sufficiently region-specific as it stimulates neurons as well as long-range axons by modulating a local electric field. Because of these issues, clinical outcomes from DBS are difficult to predict and may also have tolerability issues.

Thus, despite the enormous investments in small molecule drug discovery for neuroscience, there have been few examples of novel targets showing efficacy in the past two decades. As such, it is necessary to adopt alternative strategies for nervous system diseases. Importantly, these novel strategies should limit the risk of testing an unvalidated target, increase the selectivity of neural circuit control, and address the fundamental issues of hyper- or hypo-excitability in nervous system disorders.

CHEMOGENETICS: BACKGROUND

Chemogenetics inverts traditional drug discovery. Typically, drugs are developed for an endogenous cellular receptor that modifies neuronal activity to ameliorate a disorder. Chemogenetics determines a clinically approved drug upfront based on its bioavailability, stability, pharmacokinetics, and tolerability. This drug is then used as the target around which the receptor is designed [24]. Although this can be difficult, protein engineering offers a diverse range of options. The underlying receptor platform is chosen by considering its functional consequences when expressed in a cell, potential for modularity to achieve different functional effects, and the simplicity with which it can be delivered by gene therapy.

Chemogenetics is widely used in biological research for altering the activity of defined cell populations [8,25]. In neuroscience, there is a ubiquitous experimental approach that aims to selectively activate or inhibit specific neuronal subtypes in the brains of model organisms. This permits gain-of-function (gof) or loss-of-function (lof) perturbations in neural circuits to examine the sufficiency or necessity, respectively, of a neural circuit node in a particular aspect of nervous system function [26]. For example, chemogenetic activation or silencing of Agouti regulated protein-expressing (AGRP) neurons in the hypothalamus dramatically increase or decrease food consumption [27], while perturbation of nearby cells influence aggression, sex, emotion, sociality, and thermoregulation [28]. This highlights the impressive selectivity of chemogenetics in the brain for cell type-specific evaluation of brain functions.

Chemogenetics generalizes chemical control of cellular pathways by engineering a limited set of tunable, modular, and selective receptor/ligand systems that can be installed in virtually any cell population. Optimal chemogenetic tools possess two core properties: 1) the engineered receptor actuator is normally non-perturbative to cells, i.e. it has low constitutive activity and low responsiveness to endogenous ligands; 2) the exogenously applied ligand is non-perturbative to cells that lack the actuator transgene.

There are two main platforms for modular chemogenetics in neurons: ligand gated ion channels (LGICs) and G-protein coupled receptors (GPCRs). GPCRs were used to develop the first chemogenetic system at Merck in 1991 [29]. Additional improvements led to the development of designer receptors exclusively activated by designer drugs (DREADDs). This was first achieved by directed evolution of an improved interaction of the Gαq-coupled muscarinic acetylcholine receptor 3 (hM3) with clozapine-*N*-oxide (CNO), which is an ostensibly inactive metabolite of the antipsychotic drug clozapine [24]. The same mutations also enhanced clozapine potency for this engineered receptor [24], which was named hM3Dq. Conversely, the potency of acetylcholine, the endogenous hM3 agonist, was reduced by >50,000-fold for hM3Dq. Heterologous expression of hM3Dq in cortical neuron cultures did not significantly affect membrane potential in the absence of CNO [24]. In the presence of CNO, neurons were rapidly depolarized due to Gαq→protein lipase C (PLC)-mediated closure of M-current (Kcnq) potassium conductances. A neuronal silencer DREADD was generated by applying the hM3Dq mutations at homologous residues in hM4, which is an endogenous Gαi-coupled receptor. Expression of hM4Di in neurons rendered cells sensitive to CNO-induced hyperpolarization due to activation of G-protein inwardly rectifying (GIRK) potassium conductances and resulted in reduction of neuron activity [24,30,31]. hM4Di-mediated neuronal silencing has also been found by inhibition of synaptic release [30,31], which may involve additional pathways that are modulated by G-protein signaling. Importantly, neuromodulation is dependent on the effectiveness of the G-protein signaling pathways coupling to a specific set of ion channels or synaptic proteins that must be present in the targeted cell type, which may be unknown in human neurons under disease conditions. The modularity of this chemogenetic design was extended using previously established structure-function analyses of GPCRs, which were applied to hM3D receptors to produce receptors that selectively signal through Gαs or β-arrestin [32,33]. Thus, the discovery of mutations that produce new pharmacological selectivity has been exploited in conjunction with GPCR structure-function information to produce a range of chemogenetic research tools for control of different cellular signal transduction pathways, many of which couple to ion channels (Figure 2).

The primary limitation of the DREADD/CNO system is that CNO has been found to be excluded from the brain, in part due to P-glycoprotein pump activity, and the in vivo activity of CNO in the brain is due to metabolic CNO conversion to clozapine [34]. The hypnotic drug perlapine, which is used in Japan, has been shown to be an DREADD agonist [35,36], although perlapine shows similar binding affinity for DREADDs as endogenous receptor, suggesting little selectivity [35]. One potential alternative is a set of DREADD mutations that has been applied to the kappa opioid receptor [37], but the agonist, Salvinorin B, is poorly water soluble and also a P-glycoprotein pump substrate [38]. Thus, DREADDs are an expanding research toolbox that enables selective pharmacological control over distinct signaling pathways and offer a new capability for sophisticated analysis of cellular and circuit functions. Additional work is needed, but progress is being made to identify selective, stable, and brain penetrant agonists aside from clozapine [39–41].

The second major chemogenetic system uses LGICs for direct pharmacological control over ion conductance. The functional properties of ion channels are primarily dictated by their ion selectivity. Inward flux of cations or outward flux of anions depolarizes cells, and correspondingly inward flux of anions or outward flux of cations leads to cellular hyperpolarization [42]. Several LGIC families have been developed as chemogenetic tools, including the large superfamily of Cys-loop receptors.

To utilize the functional diversity of the Cys-loop ion channel family, a set of chemogenetic technologies was created based

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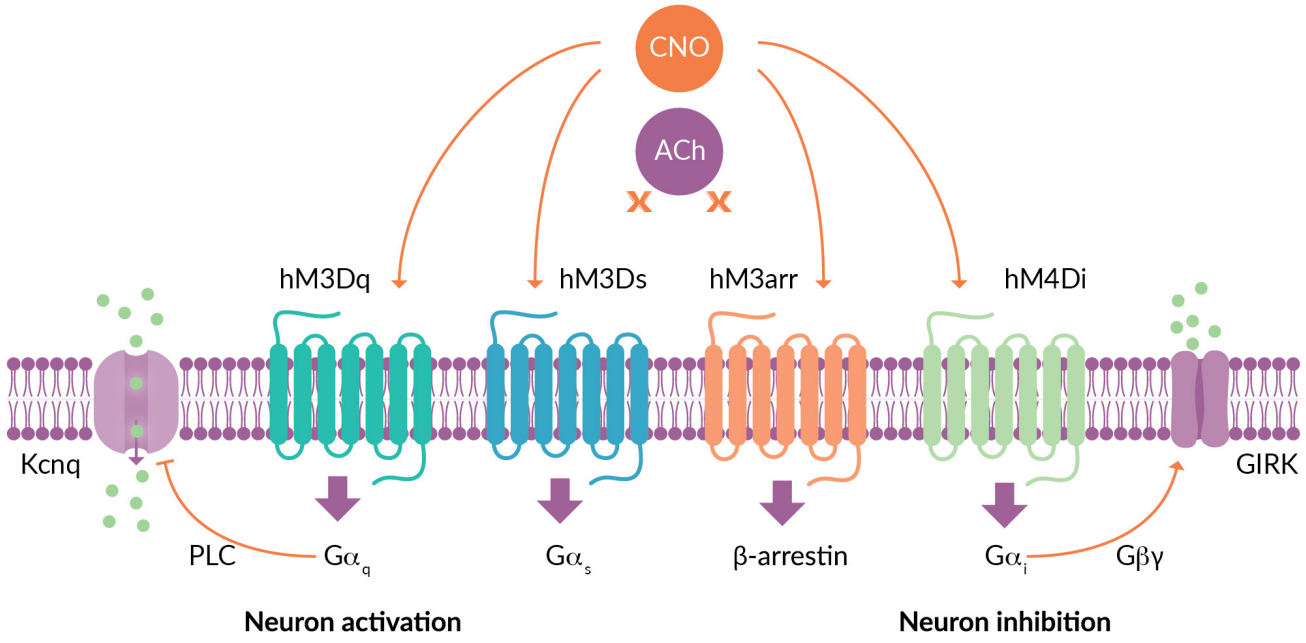
FIGURE 2

DREADD family of chemogenetic receptors.



Receptors based on modifications to the human muscarinic receptors are activated by CNO and have greatly attenuate responsiveness to ACh. hM3Dq activates neurons by inhibiting Kcnq potassium channels. hM4Di inhibits neurons by opening GIRK channels. Other DREADDs, based on modifications of hM3D, engage additional G-protein signaling pathways.

on chimeric LGICs derived from α7 nicotinic acetylcholine receptor (nAChR) and other Cys-loop family members. Importantly, the extracellular ligand binding domain (LBD) of α7 nAChR is transferrable to the transmembrane ion pore domains (IPDs) of other members of the Cys-loop LGIC family [43–45]. This property allows the pharmacology of the α7 nAChR to be maintained while accessing the ion conductance properties of other LGICs, such as the cation-selective serotonin receptor 3 (5HT3) or the anion-selective glycine receptor (GlyR).

To leverage these characteristics, mutagenesis of the α7 nAChR LBD conferred selective agonist activity to structurally distinct small molecules while reducing endogenous agonist potency of acetylcholine (ACh) [45]. The mutated LBDs were termed pharmacologically selective actuator modules (PSAM, pronounced as sam) [45]. PSAMs and their cognate agonists solve the LGIC pharmacology problem once; then they can be used to achieve a variety of functional effects on cells depending on what IPD they are spliced with to form chimeric LGICs.

PSAMs have been used to construct a variety of chimeric ion channels that directly control neuron electrical activity. PSAM-5HT3 provides prolonged depolarizing currents in the presence of the corresponding agonist [45] and results in sustained neuron activation. PSAM-GlyR has large chloride-selective conductance with a long steady state window current to maintain silencing as long as the agonist is present [45]. Cells expressing PSAM-GlyR channels have similar electrical properties as those that lack the channels, but in the presence of one of the cognate pharmacologically selective effector molecule (PSEM) agonists, neurons dramatically reduce input resistance, silencing the neurons by making it difficult to fire action potentials (Figure 3) [45].

Multiple PSAM LBDs have been developed using combinations of mutations that confer selectivity to different small molecules. For example, distinct PSAMs have been

produced for the clinically used drugs tropisetron (an anti-emetic) and varenicline (an anti-smoking drug), as well as chemical derivatives of those molecules [46]. These modular chimeric LGICs offer potent, bi-directional control over neurons activity.

CONSIDERATIONS FOR THERAPEUTIC CHEMOGENETICS

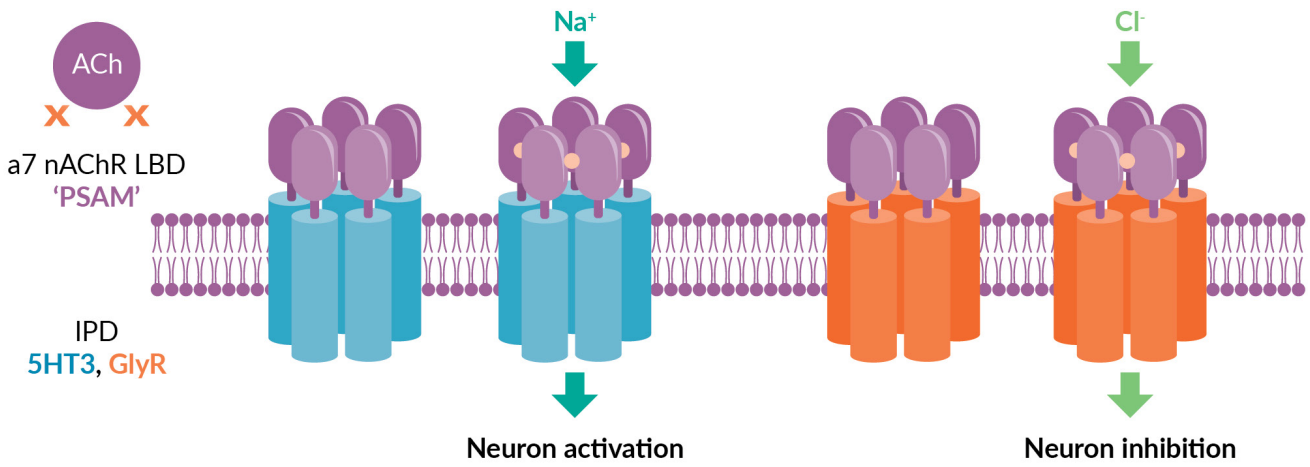
The broad utility of chemogenetics for research purposes, including in preclinical models of human neurological disorders, has generated interest in extending chemogenetics as a human gene therapy. Optimally, a chemogenetic system should have several characteristics for therapeutic use in the nervous system:

1. The introduced receptor should be activated by low agonist doses;
2. Human use will be facilitated by a chemogenetic agonist with an established human tolerability profile at a dose sufficient to modulate the chemogenetic receptor;
3. If the brain target is the central nervous system, then the drug must cross the blood–brain barrier;
4. The receptors should activate or inhibit neurons efficaciously, durably, and reversibly;
5. Chemogenetic modulation should be restricted to the therapeutically relevant region and cell types;
6. Involvement of a cell type or brain region in a nervous system disease should be well-validated, for example by prior surgical resection or nerve-block studies;
7. The site and level of expression of the chemogenetic receptor should be measurable noninvasively.

Chemogenetic receptors are locally delivered by viral injections, primarily using AAV vectors, which have been demonstrated to be suitable for human gene therapy applications [6,7]. The relatively short coding sequences of both DREADDs and PSAM channels allow efficient packaging into viral vectors. For therapeutic applications, a small

FIGURE 3

PSAM chimeric ion channels.



PSAMs developed from the ligand binding domain (LBD) of the α7 nAChR are spliced to either the IPD of 5HT3 or GlyR to produce chimeric channels for neuron activation or inhibition, respectively. The same PSAM and its cognate agonist (yellow circle) are used for both types of channel. Mutations in the LBD increase drug-potency and reduce ACh sensitivity. PSAM chimeric channels are homomeric pentamers.

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amount of an AAV that carries DNA encoding the chemogenetic construct is delivered by direct injection to the affected part of the nervous system [6,7]. An array of AAV serotypes must be screened and optimized for each tissue target in rodent and non-human primate models as well as human explant tissue if it is available [6]. Small promoters (<1 kb) are preferable for AAV gene therapies due to small genome packaging size of AAV. Within the brain, cell type-specific promoters for neurons (*Synapsin*) or glia (*Gfap*) are often used [47]. This is important to restrict expression to the cell type of interest in the nervous system.

Chemogenetic receptors are expressed on the cell surface where they are ideally inert. This can be achieved by using receptors with low constitutive activity and lacking response to endogenous agonists. It is preferable to find the lowest receptor expression level that is compatible with functional efficacy to minimize the potential for protein interactions that may be perturbative to the targeted cell [48]. Both DREADDs and PSAMs are well-suited for low expression levels because GPCRs utilize an amplification signal transduction cascade and PSAM-based ion channels have high single channel conductance.

One of the most important considerations for chemogenetic therapeutics is selection of the small molecule agonist. Human use is facilitated by a chemogenetic agonist that is an approved drug with suitable pharmacokinetics and that crosses the blood–brain barrier. In addition, the potency of the drug should be similar to or even better than at the endogenous target for which the drug is already approved. For DREADDs, the atypical antipsychotic drugs clozapine and olanzapine have been suggested as the best candidates because of their high affinity and potencies at DREADD receptors [49,50]. However, these molecules also have high affinity interactions with a large range of targets [10]. The use of clozapine is limited by potentially fatal side effects and contraindications that requires frequent monitoring [51]. Olanzapine also has many contraindications and produces iatrogenic weight gain [52]. It remains to be seen whether these antipsychotics are sufficiently tolerable to be used as components of long-term chemogenetic gene therapy.

PSAM chimeric LGICs that are potently activated by the FDA-approved anti-smoking drug, varenicline, were developed for human clinical use [46]. The potency of varenicline for the chemogenetic silencer channel is >100-fold more potent (~2 nM) than the anti-smoking target of varenicline, which is partial agonism at the α4β2 nAChR. Varenicline is particularly attractive for potential therapeutic applications because it shows limited metabolism, durable pharmacokinetics, and high oral and brain bioavailability. Because the engineered PSAM has such high potency for varenicline, lower systemic exposures of varenicline will likely be sufficient for activation of the engineered ion channels than what is currently used in the clinic for smoking cessation. This is a crucial consideration because it exceeds the basic design requirement of therapeutic chemogenetic systems. In addition, with PSAMs, chemogenetic inhibition or activation was sustained for at least 2–3 weeks of continual exposure to varenicline, indicating suitability for chronic use [46]. Robust responses to chemogenetic silencing of neurons using low doses of varenicline have also been demonstrated in rodent and nonhuman primate models [46].

An additional consideration for chemogenetic applications in the brain is the need for precise and quantitative methods to establish the expression level and distribution of the chemogenetic receptor in patients. Positron emission tomography is the well-suited to this because it uses micro-doses of a radiolabeled ligand for the target receptor, and it permits localization of the chemogenetic receptor to be accurately localized with MRI overlay of the underlying tissue. DREADD localization in the brain can be detected by radiolabeled clozapine and other ligands by PET [34,39,41,53] and the functional consequences of DREADD activation can be monitored

by functional MRI [54]. Likewise, expression of PSAM ion channels was visualized noninvasively using positron emission tomography with ^{18}F-ASEM [46], a ligand previously used in people [55]. For both chemogenetic platforms, PET has been used for noninvasive measurement of the expression and anatomic site of chemogenetic receptors.

APPLICATIONS OF CHEMOGENETICS IN NERVOUS SYSTEM THERAPEUTICS

The first therapeutic applications of chemogenetics are likely to meet at least 5 criteria:

1. A localized disease focal point at which neuromodulation will provide clinical benefit;
2. Disorders of hypo- or hyper-excitability that are well suited for the mechanism of action of chemogenetic receptors;
3. Significant unmet medical need;
4. Existing surgical procedures that are part of the standard of care that can be adopted for targeting the affected tissue with AAV; and
5. Requirement for tunable control over the activity in the affected tissue by adjusting the dose of the chemogenetic agonist.

Pain and epilepsy are two canonical hyperexcitability disorders of the nervous system, and chemogenetics is effective in rodent models of pain and epilepsy (Table 2). One of the major goals in pain research is to control nociceptive afferent excitability. Viral injections of the inhibitory DREADD, hM4Di, into sciatic nerve were used to target sensory neurons that carry pain signals, which showed CNO-dependent inhibition and increases in mechanical and thermal pain thresholds [56]. Using PSAM chimeric LGICs, pain responses can be modulated bidirectionally with opposite neuron activity perturbations in D1R and D2R neurons in the mouse striatum [57]. These studies showed that D2R neuron activation increases pain while D2R neuron inhibition increases pain sensitivity. Activation of a different population called POMC neurons in the mouse hindbrain also reduced thermal pain withdrawal responses, presumably due to endogenous β-endorphin release [58]. The magnitude of the analgesic effect was similar to morphine in the same assay [58]. Thus, there is considerable potential to use chemogenetics to suppress chronic pain conditions, by neuromodulation of specific localized sensory ganglia or by suppressing central representations of the negative emotional qualities of pain.

Chemogenetics also has promise as a focal epilepsy therapy. Epileptic foci can be mapped by electrophysiology and then targeted with stereotactic delivery of the chemogenetic AAV. Chemogenetic inhibition of motor cortex in rats has been shown to reduce seizure frequency in a focal epilepsy model [59]. Intracortical injections of the muscarinic receptor agonist, pilocarpine or the GABAA receptor antagonist, picrotoxin evoke acute seizures in rats. For rats expressing the DREADD hM4Di receptors in motor cortex delivered focally by AAV's, seizures could be reduced when CNO was administered to the animals following either pilocarpine or picrotoxin intracortical injections. Similarly, spontaneous seizures elicited in a tetanus toxin model of neocortical epilepsy were also suppressed by CNO in rats expressing hM4Di receptors [59]. These findings suggest that there was sufficient expression of the chemogenetic transgene to modulate circuit-based hyperexcitability and therefore highlights the potential for AAV-based chemogenetics in control of seizures.

PD, which is caused by cell death of dopamine neurons that innervate the basal ganglia, leads to severe motor impairment, in part due to excessive inhibition of the motor thalamus by the basal ganglia. Disruption of components of the basal ganglia using lesions, traditional pharmacology, and DBS improve the motor symptoms of PD [60–62]. Chemogenetics has been demonstrated to improve

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TABLE 2

Nervous system disorders potentially suitable for chemogenetic gene therapy.

Nervous system disorder	Circuit pathophysiology	Neuromodulatory focus	Conditions/unmet medical need
Neuropathic pain	Ectopic firing and hyperexcitability of ganglionic cell bodies	Peripheral neuronal ganglia e.g. trigeminal and dorsal root ganglia	Pharmacotherapy-resistant trigeminal neuralgia, lower back pain, osteoarthritic joint pain, intractable sciatic nerve pain
Epilepsy	Electrophysiologically mapped cortical hyperexcitability leading to focal seizure	Cortical tissue at site of epileptic foci Options for increasing the activity of inhibitory inter-neurons or decreasing the activity of excitatory neurons	Treatment-refractory epilepsy
Parkinson's disease	Loss of dopamine neurons leads to hyperactivity of the striatum. The internal segment of the globus pallidus (GPi) and subthalamic nucleus (STN) becomes over-activated, inhibits motor thalamus, and suppresses movement	Inhibition of hyperactivity of the GPi and/or STN	Parkinson's disease movement initiation
Obesity	Disruption of hypothalamic signaling in neurons that regulate appetite	Inhibition of appetite-promoting neurons or activation of appetite-suppressing neurons	Pharmacotherapy-resistant monogenetic obesity disorders, morbid obesity

motor symptoms in rodent PD models by inhibiting the Globus Pallidus, internal part (GPi) and Substantia Nigra reticulata (SNr) [63]. Chemogenetics using PSAM-GlyR and varenicline have been shown to strongly suppress SNr in mice and GPi in a monkey [46]. Thus, chemogenetics is a promising approach to 'release the brake' on motor functions in PD [18]. The advantage of this approach over DBS, which is currently used for treating PD symptoms, is that it eliminates the need for a permanent stimulating electrode implant, while maintaining scalable control over neuromodulation controlled by the dosage of the chemogenetic effector drug.

The application of chemogenetic neuromodulation to slow the causes of neurodegenerative diseases has only been lightly explored. One study investigated an amyotrophic lateral sclerosis (ALS) mouse model expressing mutated superoxide dismutase (SOD) to test a hypothesis that the level of activity in motor neurons was associated with cell death. Brief periods of chemogenetic activation with PSAM-5HT3 chimeric LGICs resulted in a sharp reduction in motor neuron loss and retention of motor neuron innervation of associated muscle fibers [64]. It is not known if a similar principle can be applied to other neurodegenerative diseases. However, a related phenomenon was found in a study from the same research group using chemogenetic neuromodulation in a schizophrenia mouse model with chromosome 16 deletions that mimic 22Q11 deletion syndrome [65]. Transient activation with PSAM-5HT3 of parvalbumin-expressing interneurons in the prefrontal cortex or ventral hippocampus was effective at improving cognitive function and restoring gamma oscillation activity in the prefrontal cortex of the mice [65]. Additional studies are needed to establish how often neuromodulation needs to be applied, with what intensity, and whether the neuromodulation procedures can be extended to the natural disease state.

Anxiety disorders can be debilitating in some patients, and a considerable number of individuals are resistant to anxiolytic pharmacotherapy or cannot abide the side effects of high doses of these drugs. A large number of brain regions have been identified with optogenetic or chemogenetic neuromodulation in rodent models to produce

anxiolytic or anxiogenic responses [66–68]. However, these brain regions, which include the prefrontal cortex, amygdala, and hippocampus, are also needed for other critical human functions. The unmet need in these patients makes consideration of chemogenetic approaches to therapy appealing. Localized, scalable control over the level of activity in anxiogenic or anxiolytic brain regions could be implemented with patient-controlled dosing to influence anxiety-specific responses without the considerable side effects associated with systemic treatment using traditional pharmacotherapy.

Obesity is typically a life-long struggle, especially when associated with genetic causes. Morbid obesity can be associated with defined monogenic mutations or of unknown cause and is associated with dysfunction in appetite-controlling neural circuits [69,70]. Most anti-appetite drugs have serious dose limiting side-effects that result in insufficient weight-lowering efficacy and major post-approval adverse health events leading to a series of high profile drug withdrawals [71–73]. In principle, an approach that selectively targets appetite-control circuits would circumvent many adverse outcomes that are due to drug-effects in other brain circuits and tissues. Regionally targeted chemogenetic neuromodulation therapies could circumvent the extensive side effects associated with past efforts at appetite control.

In general, chemogenetics will have the most unique advantage over current drugs, devices, and surgical approaches if it can be reliably coupled with selective promoter elements that can target specific neuronal subtypes within a targeted brain region. Short promoter elements that target excitatory and inhibitory neuronal subtypes have been demonstrated to be selective in rodents, nonhuman primates, and human explant tissues. Systematic approaches to identifying these short synthetic promoter elements are under development [74–76]. However, locally targeting specific neuronal subtypes has the potential to revolutionize nervous system treatments because it would allow perturbations at the level of molecularly defined circuits that are thought to be used by the brain to serve distinct functions.

CONCLUSIONS

Pharmacological treatment of nervous system diseases is often stymied by insufficiently selective receptor expression. Chemogenetics offers a generalizable therapeutic strategy by engineering a receptor-drug interaction and then using gene therapy to deliver the chemogenetic receptor to the affected tissue. This permits highly effective neuromodulation that combines a neural circuit-based understanding of brain function with familiar principles of pharmacotherapy. By solving the 'pharmacology problem' once, chemogenetic gene therapies can be applied to an extraordinarily diverse set of disease symptoms caused by localized dysfunction of hypo- or hyper-activity in neural circuits.

The potential therapeutic advantages of selective chemogenetic neuromodulation could be transformative for many nervous system disorders. Initial therapeutic applications of chemogenetics will likely target tissues by modifying surgical approaches that are already standard of care for tissue ablation or resection. In addition, the commercial framework of current gene replacement therapies with a very small number of patients receiving an exceptionally high-priced therapy would likely change with a chemogenetic treatment. The indications envisioned for chemogenetics are larger patient populations with debilitating but not life-ending diseases. This democratization of gene therapy would be facilitated by the small amounts of viral vectors required for focal targeting, which are 100–1000s of times less than what is required for most current gene therapies. The long-term clinical potential of chemogenetics can potentially fill a significant gap in treatment options to improve the lives of millions of people that are afflicted by debilitating neurological and neuropsychiatric diseases.

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AFFILIATIONS

Scott M Sternson
Janelia Research Campus, HHMI, 19700 Helix Dr. Ashburn, VA 20147, USA

David Bleakman
Redpin Therapeutics, 1329, Madison Avenue, Suite 125, New York, NY 10029, USA

AUTHORSHIP & CONFLICT OF INTEREST

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CELL & GENE THERAPY INSIGHTS

Innovation Insights

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INTERVIEW

Keys to remaining at the forefront of innovation in cell and gene therapy

MANUEL CARRONDO is the Founder and Vice President of the Institute for Experimental and Technological Biology (iBET). He is also a Professor of Chemical and Biochemical Engineering at the Faculty of Sciences and Technology, University Nova de Lisboa (1995–2018; jubilated). He has been a member or advisor on the boards of numerous professional bodies, including the Portuguese Academy of Engineering, the Max-Planck Institute for Dynamics of Complex Technical Systems and the IBMT – Fraunhofer Institute for Biomedical Engineering. He has a MSc and a PhD in environmental engineering from the Imperial College of Science and Technology.

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Q Tell us about iBET and your role there.

MC: I founded iBET over 30 years ago, and for the last 7 years I have been Vice President in charge of business development. As we have been growing, I have been focusing on business and corporate development on behalf of the board of directors. I'm working to expand the network of partnerships and collaborations iBET has throughout the world, and enlarging our footprint in terms of collaborations with both large pharma companies and small start-ups.

At iBET, we started working in gene therapy back in the 1990s when it was really nobody's field yet. This has given us extensive experience with viral vectors as the field developed. Since the early 2000s we have also been working with stem cells growing into cell therapy and we have experience in creating 3D cell models – initially for toxicology and preclinical use, but these are now becoming more relevant for immunology studies in cell and gene therapy. We are in a very fortunate position as we have been around for a long time and have had the opportunity to work with a lot of players in the cell and gene therapy space.

Q In your view, where is the current cutting edge right now in cell and gene therapy?

MC: Companies in this space are growing and so are the potential markets for cell therapy products, as the shift from autologous to allogeneic continues. A lot of the associated scaling-up of processes requires much improved technology. For example, improved tangential flow filtration, which is still relatively new in terms of application in this field. We are seeing additional chromatography steps now, too – it's the same thing that we saw in the late '80s and early '90s with antibodies: people had to use chromatography techniques that had been developed for much smaller products than antibodies, which subsequently drove the development of dedicated downstream processing tools for the protein therapeutics field. Today, we are in the process of transferring some of those competencies and technologies to cell and gene therapy applications. I do not think there are a lot of brand new approaches in cell and gene therapy right now. Instead, we are trying to adapt and improve all of these existing steps, not only to fit our current needs but in order to be able to operate under continuous manufacturing, and to finally integrate everything – the pumps, filters, chromatography, bioreactors, and so on. In a way, this is typical process development for engineers, continuous integrated processes, facilitating aseptic operation.

We are also having to do this for newer modalities. The mesenchymal stem cells of the past still work, but we're now seeing not just the CAR T cell therapies coming in, but also natural killer cells, tumor infiltrating lymphocytes, and more. These all require new tools. I wouldn't yet call them platforms as they are not at that stage, but they are very much in demand.

It's a phenomenal time where you're both developing new modalities and improving the tools at hand for the processes. For some of this development work, we are in collaboration with the tool providers and in some instances, we are creating or optimizing newer tools for the newcomers in the field. We've done this sort of work before with adenoviruses and then for adeno-associated virus (AAV). These aren't ground-breaking changes; instead, we are just continually improving operations and deciding which direction to go next.

"I think there will be a fight for balance between viral and non-viral vectors in the coming decade. But oncolytic viruses will survive for much longer!"

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"A lot of clinical trials are no longer done with just a CAR T cell therapy or just a gene therapy – they are done with the addition of antibodies, cytokines, or nanopeptide particles, and so on. It's like painting; the palette of colors is growing richer all the time, and the opportunities for personalized medicine are increasing in number and effectiveness."

Q How do you expect iBET's activities to evolve in step with current and future innovation trends in the cell and gene therapy field?

MC: I anticipate that eventually, viruses will slowly fall out of favor for use in CAR T-like applications. However, if you can lower the cost of the viruses for these current cell therapies to perhaps a tenth of what it is now, the advancement of non-viral options may become less attractive. And of course, as in any industry, once people are used to a given tool and a given system, change requires everybody to learn new tricks. Not just the scientists, not just the researchers, but also the people on the shop floor: the technicians and the analysts. You only want to replace things when the advantages are substantial. For this reason, one of the areas on which we have been betting is to work on producing viral vectors for CAR T applications more cheaply, better, and in much larger batches. I think there will be a fight for balance between viral and non-viral vectors in the coming decade. But oncolytic viruses will survive for much longer!

You have got to look also at cell therapy for solid tumors. As mentioned earlier, this is where natural killer cells (NK)s, tumor infiltrating lymphocytes, and more new cell types will come in, and we'll be looking at a whole new field. There may be some things that remain analogous, but the cells are different, so a lot of our approaches will need to be revisited. And as we have so many different potential cells, we expect to not only see new modalities but also combined modalities becoming more popular. This is something that's already happening to some extent.

A lot of clinical trials are no longer done with just a CAR T cell therapy or just a gene therapy – they are done with the addition of antibodies, cytokines, or nanopeptide particles, and so on. It's like painting; the palette of colors is growing richer all the time, and the opportunities for personalized medicine are increasing in number and effectiveness.

These areas will continue to grow for at least the next 10 years. And of course, in between, some of the applications will become more mature. There is still so much to explore – I don't think we'll be out of work in the next 10–20 years! It's a phenomenal field to be in and I sense that there are a lot more opportunities and options to be found and a lot more tools to be developed.

Q What are the main priorities both for yourself and for iBET as a whole over the next 12–24 months?

MC: One key area of focus for us at the moment is the immune aspects of AAV vectors. We need to understand better what the immune effects are from using these vectors in different organs. We have 3D cell models for some of these organs and we hope to partner with companies to combine their knowledge of immunological aspects with our 3D cell models, our viral production capacity, and our tools and analytics.

At the same time, by understanding this better we are also exploring the immune aspects of the viral gene therapies that are essentially targeting cancer. Immunology is a new area for us and frankly, we're not experts, but we believe we have skills and tools we can apply to this area. For example, artificial intelligence and machine learning can be applied to the large amounts of complex data being generated by our omics tools.

If you're a small team like us, you can only grow from your strengths. There's no way that you can pay for entry into a new area where you need 10 million just to reach entry level. So that's what we do: grow from knowledge, grow from strength. By being in that position, we get more partners to come on board. Our business model is to network and link to biopharmaceutical organizations in both Portugal and around the world, and in this way enlarge the footprint of Portuguese science.

We are expanding from systems biotechnology to big data and artificial intelligence, which is required to work with the data being produced by the immunology field. It's a slow process, but these areas are becoming more and more relevant. We hope to reinforce these critical skills now as we expect them to become even more important in the future. And hopefully, to enjoy ourselves along the way, as that's how you keep your motivation to work hard and develop new scientific knowledge!

AFFILIATIONS

Manuel Carrondo
Vice-President, Instituto de Biologia Experimental e Tecnológica (IBET)
and
Instituto de Tecnologia Química e Biológica (ITQB)

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Commercial Insights

CELL & GENE THERAPY INSIGHTS

COMMERCIAL INSIGHT: JUNE 2020

Commercial Insight: cell & gene therapy

Providing a critical overview of the sector's commercial development: M&As, licensing agreements & collaborations, financial results, IPOs and clinical/regulatory updates, with commentary from our Expert Contributors.

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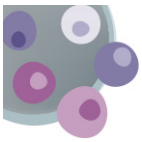

CELL THERAPY – Mark Curtis. Director, Manufacturing Partnerships, AVROBIO

Bayer-backed Century Therapeutics acquired a small Canadian start-up, Empirica, in June to gain access to Empirica's CAR-T expertise and add glioblastoma to its pipeline. This is the second foray for Bayer in Canada in recent times as it continues to make inroads into the cell and gene therapy industry. Empirica's team will remain in place under the umbrella of Century Therapeutics Canada. Biotechs continue to push the envelope in terms of deal sizes and Sana may have set a record recently with its $700M raise. It is no surprise that the syndicate included a large number of top-shelf VCs and private investors. The size of the deal is commensurate with the company's ambitious plans to develop multiple stem cell-based and gene therapy-based platforms simultaneously.

GENE THERAPY – Richard Philipson. Chief Medical Officer, Calliditas Therapeutics

The world of exosomes is in the news this month, with Sarepta entering into a deal with Codiak Biosciences to develop engineered exosomes for neuromuscular diseases. This follows hot on the heels of an announcement from Evox Therapeutics earlier this month of a research collaboration and license agreement with Eli Lilly, using the company's exosome platform to develop and deliver RNAi and antisense oligonucleotide treatments for neurological disorders. Elsewhere, development of treatments for hemophilia remains extremely active, with news of encouraging long-term data for Biomarin's AAV-based treatment for hemophilia A, as well news of the licensing of UniQure's experimental gene therapy for hemophilia B to CSL Behring for $450 million in cash.

Clinical Regulatory

COVID CONTINUES TO PLAGUE CLINICAL TRIALS

The far-reaching impact of Covid-19 continues to be felt within the cell and gene therapy industry – but there are also reasons to be optimistic, according to industry experts.

At a webinar hosted by the organizers of the annual World Orphan Drug Congress which featured Sander van Deventer (uniQure) and Thomas Bols (PTC Therapeutics), the consequences to clinical trials and the industry as a whole were discussed. The takeaway? While clinical trials are suffering, the biotechnology industry has escaped relatively unscathed financially, and the industry as a whole is used to high risk and a quickly changing landscape.

"We are, of course, not directly dependent on consumer demand. In this case, that's a good thing," van Deventer commented during the webinar. "Investors in biotech are used to working with loss-making companies. Also, managing delays and hurdles is business as usual. There is no single successful biotech company that I've been involved with that hasn't had major periods of delays and hurdles. We are used to managing timelines and budgets, and adapting rapidly to changing situations," he added.

On the other hand, the realities of a pandemic raise considerable operational challenges to clinical trials that can force delays. Slow enrollment, limited access to hospitals, missing data and the involvement of high-risk patients have all contributed to an average 6 month delay.

But despite this, the future is still bright. Thomas Bols commented, "The overall pharmaceutical sector shows positive growth, despite the pandemic. We have to count our blessings in these very difficult times. Yes, there are some negative elements, but I think the future looked bright before — and still looks reasonably bright."

ORCA BIO SURFACES WITH A KILLER PLAN TO CHANGE APPROACH TO BONE MARROW TRANSPLANTS

Bone marrow transplants can save lives – but due to their complicated nature and the significant associated risks, they're often seen as a last resort once other treatment options have failed. US biotech Orca Therapeutics is hoping to make them an option for more

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patients by making the treatment safer and more effective.

Orca has just completed a series D round of funding which has netted the company $192 million, and the company plans to progress their pipeline of allogeneic cell therapies and accompanying technology. Their approach is to take donor T cells and stem cells and sort and combine them in order to treat disease. "We don't genetically modify them. But if we now take these cells and build a proprietary mix of them with single-cell precision, we can define the function of what they're going to do," Orca CEO and co-founder Ivan Dimov said in a comment to Fierce Biotech. "We can elicit powerful curative effects and control toxicities in a precise way to enhance safety and efficacy in patients that essentially need a whole new blood and immune system."

As the process uses donor cells, it could eventually work for patients who do not have enough high-quality T cells; it's faster too, so could reach more patients before they succumb to their disease. The two existing programs are targeting terminal blood cancers, but could be aimed at patients earlier in their disease progression should the approach prove safe. The company hasn't yet announced their plans beyond this, but Dimov commented that the approach could be useful in treating autoimmune diseases.

Ones to Watch

There has been considerable interest in industry over the last several years in technology that can improve outcomes following bone marrow transplant, with a focus on improved HLA-matching and reduction of GVHD. Companies like ExCellThera, Nohla, and Gamida have developed cord blood expansion technologies to improve access to cord blood units in public banks. Orca Bio has taken an entirely different approach to the problem with a novel, high-throughput, single cell sorting platform that generates allogeneic bone marrow grafts with precise compositions of stem and immune cells. By sorting out different subsets of each cell type and recombining them in a manner tailored to each patient, Orca Bio hopes it will be able to use the technology to create safer and more efficacious transplants for patients. The company just raised $192M to make it happen. – Mark Curtis

HEMOPHILIA TREATMENT ACHIEVES OVER 90% DROP IN BLEEDING RATES

A single dose of Biomarin's investigational gene therapy for hemophilia A, valoctocogene roxaparvovec, achieved an over 90% drop in annual bleeding rates and the use of exogenous

clotting factor VIII in men with hemophilia A up to four years after treatment, new data shows.

The ongoing Phase 1/2 study comprised 7 men who received a higher dose (6e13 vg/kg) and 6 who received a lower dose (4e13 vg/kg) of the therapy. Annualized bleed rates dropped by 95% in the higher dose cohort, and 93% in the lower dose cohort. Mean exogenous factor VIII usage was also reduced by 96% in both groups – representing a drop from over 130 infusions per year to roughly 5. In the last year of the trial to date, 86% of men treated with the high dose and 67% who received the low dose had no bleeding events, and 83% of men in the low dose group experienced no spontaneous bleeding.

Both groups continued to produce endogenous clotting factor at the end of the fourth year, and mean activity levels of factor VIII remained in the therapeutic range for all participants.

The trial's chief investigator John Pasi, commented in a press release:

"With four years of data, this study represents the longest duration of clinical experience for any gene therapy in hemophilia A. It is exciting to observe that all study participants remain off factor VIII prophylaxis therapy, while also experiencing a greater than 90 percent reduction in bleeding episodes from a single administration of valoctocogene roxaparvovec. These data demonstrate the very real potential of a paradigm shift in the treatment of hemophilia A and that ongoing research into gene therapies could represent an entirely new way to approach meeting the high unmet need in patients."

Expert Pick

Biomarin's AAV-based treatment for hemophilia continues to produce excellent efficacy data from ongoing trials, with clinically meaningful increases in factor VIII levels at the two higher doses administered, accompanied by reductions in annualized bleed rates and marked reductions in exogenous factor VIII requirements. The safety profile looks to be reasonable too; the most common adverse events associated with treatment included transient infusion-associated reactions and transient, asymptomatic, mild to moderate increases in liver enzymes, with no long-lasting clinical sequelae. Importantly, no patients have developed inhibitors to factor VIII and there have been no thrombotic events. The views of FDA should be known very soon, with a PDUFA action date of August 21, 2020; the opinion of CHMP is expected by the end of the year or early 2021. – Richard Philipson

MEMORIAL SLOAN KETTERING TEAM TARGETS SENESCENCE WITH CAR TS

Cellular senescence is defined as an irreversible cell-cycle arrest mechanism that causes cells to stop proliferating, and it is believed to play a role in both normal ageing and

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also many age-related diseases including diabetes, atherosclerosis, osteoarthritis, liver fibrosis, and more. A new class of drugs known as senolytics has emerged in order to create therapies which can clear senescent cells.

Researchers at Memorial Sloan Kettering Cancer Center have set out to apply CAR T technology to the issue of senescence, and have detailed their findings in the recent *Nature* paper; "Senolytic CAR T cells reverse senescence-associated pathologies".

"Senescence is a double-edge sword. Cells in this state play an important role in wound healing and cancer deterrence. But if they linger for too long, they can cause chronic inflammation, which itself is a cause of many diseases,"

explained corresponding author Scott Lowe.

The first step was to find a CAR T target on senescent cells – by screening molecules on the surface of senescent cells and comparing these to other cell types, the team identified urokinase plasminogen activator receptor (uPAR), a molecule that is enriched on senescent cells and mostly absent on other cells. They then designed CAR T cells with the ability to recognize uPAR and tested them in mouse models of age-related disease. The results were promising: in two murine models of liver fibrosis, the CAR Ts successfully eliminated senescent cells and reduced liver scarring. They also improved survival in cancer models when administered alongside drugs given to induce senescence.

Next, the team plan to find out whether uPAR-direct CAR Ts can treat other senescence-related diseases, and hope to eventually translate their findings to the clinic.

Expert Pick

To date a large majority of CAR T companies have focused on the obvious market – oncology. Some companies have ventured off the beaten path to look at infectious disease and autoimmune disease. An area that remains uncharted is the use of CAR T cells for treating diseases related to cellular senescence. An accumulation of senescent cells in the body has been linked to chronic inflammation and myriad diseases. Researchers at the Memorial Sloan Kettering Institute were able to identify a surface antigen expressed on senescent cells that is rarely found on healthy cells, uPAR, and use this to generate CAR-T cells to target senescent cells *in vivo*. Studies conducted by the researchers showed that CAR-T cells targeting uPAR were able to reduce fibrosis in a mouse model of liver fibrosis. Similar studies showed the same T cells were effective at treating symptoms of nonalcoholic steatohepatitis (NASH), and the investigators will expand their research to atherosclerosis, diabetes, and osteoarthritis. – Mark Curtis

GERMAN PATIENTS SET TO BE FIRST IN EU TO RECEIVE ZOLGENSMA

Following the European Commission's decision to grant conditional marketing authorization for the spinal muscular atrophy (SMA) gene therapy Zolgensma from AveXis, it is likely that German patients are likely to gain first access, as negotiations with other European countries continue.

The conditional approval covers the treatment of babies and young children weighing up to 21 kilograms with a clinical diagnosis of SMA Type 1, the most severe form of the disease, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to three copies of the *SMN2* gene.

Since 2011, newly-introduced therapies in Germany have a year to have their benefits assessed before a price is set, under the Arzneimittelmarkt-Neuordnungsgesetz (AMNOG) cost effectiveness system (English: Pharmaceuticals Market Reorganization Act). Price negotiations begin after a final decision on the medical benefit of a new drug is made.

Mike Fraser, General Manager of Europe, the Middle East and Africa at AveXis, said:

"All gene therapies are required to go through the benefit assessment process (AMNOG) in Germany and this will be ongoing in the coming months, potentially making Germany one of the first countries to make gene therapy available as a treatment option for SMA patients."

T CELL TREATMENT FOR TYPE 1 DIABETES EDGES CLOSER TO REALITY

David Rawlings, Professor of Pediatrics and Immunology at the University of Washington School of Medicine, has spent almost a decade dreaming of developing a therapy for children with type 1 diabetes that uses their own immune system to target and treat their disease. But it might not remain a dream for much longer.

"What started as a dream is now within reach," Rawlings said in a press release. "My hope is that our research will lead to a new treatment that turns off the destructive immune response leading to development of type 1 diabetes in children."

The research, led by Rawlings, focuses on engineering $CD4^+$ T cells to express FOXP3. These edited regulatory-like T cells (edTregs) can enter the pancreas and suppress the overactive immune response, protecting the function of islet cells. In mouse models of graft-versus-host disease and multiple sclerosis, the edTregs prevented symptoms and improved survival – and the team believe the approach could have broad future clinical application in autoimmune disease.

"This data offers the first proof that engineering by way of turning on FOXP3 is sufficient to make a functional Treg-like cell product," commented Rawlings. "Not only is it a landmark research finding, but it's directly translatable to clinical use."

A SERENDIPITOUS DISCOVERY OFFERS HOPE FOR PARKINSON'S TREATMENT

Xiang-Dong Fu and his team at University of California San Diego School of Medicine have spent years studying the basic biology of RNA. Now, an accidental discovery has

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launched them on a new and unexpected path towards seeking a treatment for Parkinson's disease.

The team was working with the RNA-binding protein polypyrimidine tract-binding protein 1 (PTB), and experimenting with ways to silence the *PTB* gene. In a stable mouse cell line permanently lacking PTB that they had created, they noticed something exciting: within a few weeks there were very few fibroblasts left, and the dish was instead almost filled with neurons. This finding implied that inhibiting or deleting PTB transforms several types of murine cells into neurons.

Next, the team applied their discovery to a mouse model of Parkinson's disease; sure enough, a single treatment to inhibit PTB in mice converted native astrocytes into dopaminergic neurons. The mice's motor deficits were rescued and the disease phenotype was successfully reversed. The full results are described in the Nature study, "Reversing a model of Parkinson's disease with in situ converted nigral neurons."

The treatment has a long way to go before it potentially reaches human subjects, but the study provides a proof of concept, and the team now plan to further refine and test their approach.

"It's my dream to see this through to clinical trials, to test this approach as a treatment for Parkinson's disease, but also many other diseases where neurons are lost, such as Alzheimer's and Huntington's diseases and stroke," commented Xiang-Dong Fu in a press release. "And dreaming even bigger – what if we could target PTB to correct defects in other parts of the brain, to treat things like inherited brain defects? I intend to spend the rest of my career answering these questions."

Ones to Watch

As so often in science, a serendipitous discovery by a researcher at UCSD could eventually give rise to a disease-modifying treatment for Parkinson's disease. Experiments published recently in Nature have demonstrated efficient conversion of isolated mouse and human astrocytes to functional neurons by depleting the RNA-binding protein PTB. Furthermore, *in vivo* experiments in a mouse model of Parkinson's disease, using an antisense oligonucleotide to deplete PTB, demonstrated conversion of astrocytes to new dopaminergic neurons which reconstructed the nigrostriatal circuit, restored dopamine levels and rescued motor deficits. Of course it's a huge step to translate from the mouse to man, but the work done at UCSD has discovered fundamental biological factors that control neuronal cell differentiation. – Richard Philipson

EMPIRICA'S CAR T AGAINST GLIOBLASTOMA CATCHES CENTURY'S EYE

Century Therapeutics has bought Empirica Therapeutics, which will now be known as Century Therapeutics Canada. The acquisition was prompted by Empirica's work

towards creating a CAR T treatment for glioblastoma, the most aggressive form of cancer originating in the brain.

Empirica was created by scientists from McMaster Children's Hospital and the University of Toronto in order to use functional genomics and patient-based brain cancer models to develop therapies. The team recently published a paper describing anti-CD133 immunotherapies against glioblastoma, in which they found that CAR T cells show more promise than antibody or dual-antigen T cell engager approaches. This work caught Century's attention, and combining Empirica's brain tumor targets with Century's own processes for creating master cell banks could allow for the creation of a potential therapy quickly and at scale. However, it remains to be seen if this potential will translate into clinical studies, as studies so far have been *in vitro* and in mice.

DO GENE THERAPY CMC REVIEWS NEED AN OVERHAUL?

A "new playbook" is needed to ensure consistent chemistry, manufacturing, and controls (CMC) reviews for gene therapy products, according to an FDA official.

Peter Marks, director of the FDA's Center for Biologics Evaluation and Research, speaking at the virtual Drug Information Association annual meeting alongside panelists from within the industry, said "we do not have the preclinical pathways set up and the clinical set up and the regulatory paradigm is yet to be fleshed out. Now is the ripe time to get things right."

Logistical and technical challenges alongside a lack of standards and lack of a regulatory framework were described by panelists as significant roadblocks faced by developers of new gene therapy products. A lack of consistent reviews is hindering the field, Mark added, saying

"it has become apparent over the last couple of months that, while we have excellent reviewers, it does happen that people can have differences of opinion. I think we will have to come around and have a clear playbook so that everyone gets the same advice especially as we have grown. I know that someone out there will say, 'we had two different CMC reviewers and two differences pieces of advice.' I am not going to argue with that. That is an issue here. As we come to the post-COVID period we should to try to have more unity in what comes from our CMC reviews. I cannot say the problem is solved but the problem has been identified and is amenable to solutions."

One potential solution is for gene therapy reviews to move towards a device-like manufacturing approval process, Marks said – an idea he originally suggested earlier this year. "It is becoming increasingly clear that for cell and gene therapies, the manufacturing is more like a device paradigm with continued innovations," he explained. "With a traditional drug you come up with a chemical process to make a small molecule and you are probably using the process similarly across the lifecycle, but you are not constantly finding ways to do things that fundamentally change the yield or quality of a product. Here we have issues that manufacturing changes can potentially change the product for the better."

UNIQURE'S UNEXPECTED $450M HEMOPHILIA SALE SURPRISES ANALYSTS

Dutch gene therapy developer UniQure has had something of a beleaguered past – after pioneering the first approved gene therapy in Europe, Glybera, the company saw the

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treatment withdrawn and had stock drop to just $5 per share. Despite these setbacks, the company has made a comeback with the development of its experimental gene therapy for hemophilia B, known as EntranaDez.

In an unexpected move, UniQure has now licensed the treatment to CSL Behring for $450 million. The company may also get up to $1.6 billion more in conditional payments if the therapy progresses as hoped, and royalties on net sales. The deal will also see CSL reimburse UniQure's remaining development costs and cover regulatory submission expenses.

But why did UniQure choose to sell the therapy? According to CEO Matt Kapusta, the competitive nature of the hemophilia market was a key factor. "This decision was based specifically on analyzing the competitive dynamics associated with the hemophilia market," he commented during a conference call, adding: "Partnering this globally was the best way to get EntranaDez to as many patients globally as efficiently as possible and as fast as possible within this specific market."

CSL already sells hemophilia treatments globally and will now take on the challenge of making a success of EntranaDez. Meanwhile, UniQure plan to use the financial boost it receives from the sale to invest in other programs, such as its gene therapy for Huntington's disease, which has become the first such gene therapy to enter human testing.

Licensing agreements & collaborations

SAREPTA THERAPEUTICS TURNS TO EXOSOME TECHNOLOGY

Adeno-associated virus (AAV) vectors have played an important role in the development of gene therapies and continue to be the vector of choice for many developers – but they are not without challenges. For example, natural immunity to this type of virus can render treatment ineffective, which has led some within the gene therapy field to search for alternatives.

For US gene therapy specialist Sarepta Therapeutics, exosomes could be the answer. In a 2-year agreement, the company is teaming up with Codiak BioSciences to develop engineered exosomes for the delivery of gene therapy, gene editing or RNA-based treatments. Codiak's engEx Platform engineers drug molecules into exosomes which are derived from human cells, allowing them to bypass the immune response.

Under a deal which will see Codiak receive up to $72.5 million in upfront and near-term license fees along with research funding, Sarepta will have the option to progress candidates for up to 5 targets in the neuromuscular space. Codiak will be responsible

for research and clinical development until IND preparation, and then Sarepta will take over to progress clinical development and commercialization.

"As Sarepta expands its leadership position in precision genetic medicine, this alliance with Codiak furthers our goal to deliver the most advanced therapies to patients ... Codiak's exosomes are engineered for precise tissue targeting and offer a non-viral delivery approach with non-immunogenic potential, thus opening up avenues for more efficient delivery and potential re-dosing,"

said Sarepta CEO Doug Ingram in a statement.

However, Sarepta isn't putting all its eggs in the exosome basket: the company also recently formed a collaboration with Dyno Therapeutics, a company using machine learning technology to generate and test new AAV variants with synthetic capsids that work better than the current options available.

Finance

POSEIDA RAISES $110 MILLION TO WORK ON CELL AND GENE THERAPY CANDIDATES

Clinical-stage biopharmaceutical company Poseida Therapeutics has secured $110 after a Series D financing round. The financing was led by funds advised by Fidelity Management Research Company, with participation by Adage Capital Management and Schonfeld Strategic Advisors, as well as a number of current investors.

The company's portfolio includes allogeneic and autologous CAR-T candidates for blood and solid tumor oncology, as well gene therapy programs targeting orphan diseases.

"This financing supports the approach we are taking to leverage our broad proprietary gene engineering platform technologies, including the piggyBac DNA Modification System and Cas-CLOVER site-specific gene editing system, for the creation of numerous differentiated cell and gene therapy product candidates,"

commented Poseida CEO Eric Ostertag in a press release.

JW THERAPEUTICS RAISES $100 MILLION IN SERIES B FINANCING

JW Therapeutics, a CAR T-focused joint venture company established between Juno Therapeutics, and WuXi AppTec, raised $90 million in series A funding when it launched

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back in 2016. Now it has followed up with $100 million in series B, in a round co-led by CPE and Mirae Asset, and joined by CR-CP Life Science Fund and Oriza Holdings as well as existing investors including Loyal Valley Capital, Temasek, Sequoia Capital China and ARCH Venture Partners.

Combining Juno's CAR T platform with WuXi's R&D and manufacturing platform has resulted in the investigational therapy JW-CAR029, a CD19-directed CAR-T therapy against B-cell malignancies which is now in midstage testing.

SANA RAISES $700 MILLION IN INITIAL FUNDING

Seattle-based Sana Biotechnology has bagged a cool $700 million during an initial financing round, and shareholders include ARCH Venture Partners, Flagship Pioneering, Canada Pension Plan Investment Board, Baillie Gifford, F-Prime Capital, Alaska Permanent Fund, the Public Sector Pension Investment Board, Bezos Expeditions, GV, Omega Funds, Altitude Life Science Ventures, and "multiple unnamed institutional investors", according to a press release.

Sana has big plans for the money, with plans to advance platforms including gene delivery, immunology, stem cell biology, and gene modification and control. The proceeds will support IND-enabling and initial clinical studies for multiple therapeutic candidates, according to the company, and will be put towards building manufacturing capabilities and expanding Sana's technology portfolio.

"Sana is dedicated to modulating genes in cells as well as replacing damaged cells in the body," said President and CEO Steve Harr. "The commitment from this group of long-term investors enables us to concentrate on making discoveries that overcome the most important challenges to making gene and cell therapies that improve the lives of a broad swath of patients. I am proud of our progress to date in turning our technologies into potential therapies for serious diseases such as cancer, central nervous system diseases, heart disease and various genetic disorders."

POSEIDA SETS SIGHTS ON IPO AND $110 MILLION FUNDING ROUND

A year after pulling the plug on its IPO plans, Poseida is planning to go ahead, but with a new $110 million funding round ahead of its $115 million public offering.

The company's last IPO attempt was pulled in favor of a $42 million series C round, with over half of the money coming from Novartis. Poseida has a number of CAR T candidates, and the new earnings from the funding and IPO are to be put towards the company's lead candidate, an autologous CAR T for multiple myeloma dubbed P-BCMA-101.

"This financing supports the approach we are taking to leverage our broad proprietary gene engineering platform technologies, including the piggyBac DNA Modification System and Cas-CLOVER site-specific gene editing system, for the creation of numerous differentiated cell and gene therapy product candidates,"

said Poseida CEO Eric Ostertag in a statement.

Movers & shakers

BLADDER CANCER BIOTECH APPOINTS NEW LEADERS ON PATH TO COMMERCIALIZATION

Gene therapy startup FerGene is aiming to commercialize the first gene therapy for patients with non-muscle invasive bladder cancer (NMIBC) – and it has recently appointed a trio of experienced biotech leaders to help make those aspirations a reality.

The new appointments see Ambaw Bellete, Vijay Kasturi and Peter Olagunju join FerGene. "We're thrilled to welcome these phenomenal leaders to our new company," said David Meek, FerGene CEO, in a statement. "They bring the expertise and capabilities needed to build a best-in-class organization poised to truly change the treatment paradigm in bladder cancer and make a meaningful difference in the lives of patients."

Ambaw Bellete is now Chief Operating Officer at FerGene, and brings over 30 years of biotechnology and pharmaceutical experience at both large global companies and startups.

Vijay Kasturi, the new Vice President of Medical Affairs, is both a hematologist/oncologist and biotechnology executive. Following many years working as a practicing physician and professor, he went on to be responsible for developing global and regional strategies for new therapies in immunology, hematology and oncology for EMD Serono.

Last but certainly not least, FerGene has named Peter Olagunju as Senior Vice President of Technical Operations. Peter brings experience in leadership roles overseeing global technical operations, manufacturing, quality and supply chain for cell and gene therapy companies including bluebird bio.

ARTIVA BIOTHERAPEUTICS LAUNCHES WITH TEAM OF CELL THERAPY AND CANCER EXPERTS

San Diego-based startup Artiva Biotherapeutics has uncloaked with $78 million in series A financing, a next generation immuno-oncology platform, and a team of cell therapy and oncology veterans at the helm.

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Artiva's CEO, President and Director is Tom Pharrell. Tom is former President and CEO of Bellicum Pharmaceuticals, a company which he led through a through a successful IPO in 2014, raising a total of more than $300 million. During his time at Bellicum he also brought five cell therapies into clinical development.

Tom is joined by Jason Litten, Chief Medical Officer, who has over 11 years in the biotechnology industry. Tom has previously held positions as Vice President of Clinical Development at Juno Therapeutics, along with positions at Optera Therapeutics and Amgen.

Artiva plans to develop off-the-shelf universal natural killer (NK) cells for use alongside monoclonal antibody and CAR-NK cell therapies.

"We have seen tremendous breakthroughs in redirecting immune cells against cancer, but patient access to these therapies has been limited by safety, scale, manufacturing, logistics, and cost issues," said Farrell. "Our goal at Artiva is to do more, leveraging GC LabCell's foundational work on true off-the-shelf NK cells into a pipeline of product candidates that are accessible to any cancer patient who may benefit."

– Written by Roisin McGuigan,
Cell and Gene Therapy Insights

CELL & GENE THERAPY INSIGHTS

COMMENTARY

Two new capture options for improved purification of large mRNA

Pete Gagnon, Blaž Goričar, Špela Peršič, Urh Černigoj & Aleš Štrancar

One of the barriers to development of industrial purification platforms for large mRNA has been an inadequate selection of high-performing capture-purification tools. Hybridization-affinity uses a polythymidine (Oligo dT) ligand to base-pair with the polyadenine tail of mRNA. It can be used for capture but it cannot discriminate dsRNA (double-stranded) from ssRNA (single-stranded) and it supports only brief cleaning with 100 mM sodium hydroxide. Traditional anion exchangers elute only mRNA smaller than about 500 bases unless the columns are heated to 50–70°C. Hydrophobic interaction chromatography (HIC) and reverse phase chromatography (RPC) separate ssRNA from dsRNA and short transcripts, but their sensitivity to fouling by proteins and aggregates makes them better suited for polishing than for capture. Better capture options are needed to meet the needs of large clinical trials, scale-up, and manufacture of vaccines. Beyond that, a new spectrum of gene therapy treatments await. This article introduces two new capture options that both eliminate dsRNA, DNA, and proteins in a wash step, then provide high-resolution polishing of ssRNA in an elution gradient at ambient temperature. One represents a new class of anion exchangers. The other exploits hydrogen bonding. Both support prolonged exposure to 1 M sodium hydroxide. Easy transition to either HIC or RPC provides high-resolution orthogonal polishing.

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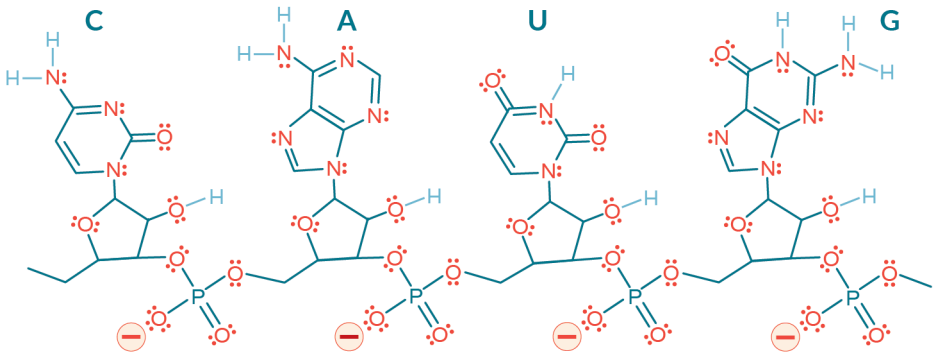
INTRODUCTION

One of the barriers to development of industrial purification for large mRNA has been an inadequate selection of high-performing capture-purification tools. Hybridization-affinity uses a polythymidine (Oligo dT)

FIGURE 1

Charges, hydrogen donors, and hydrogen acceptors on RNA.

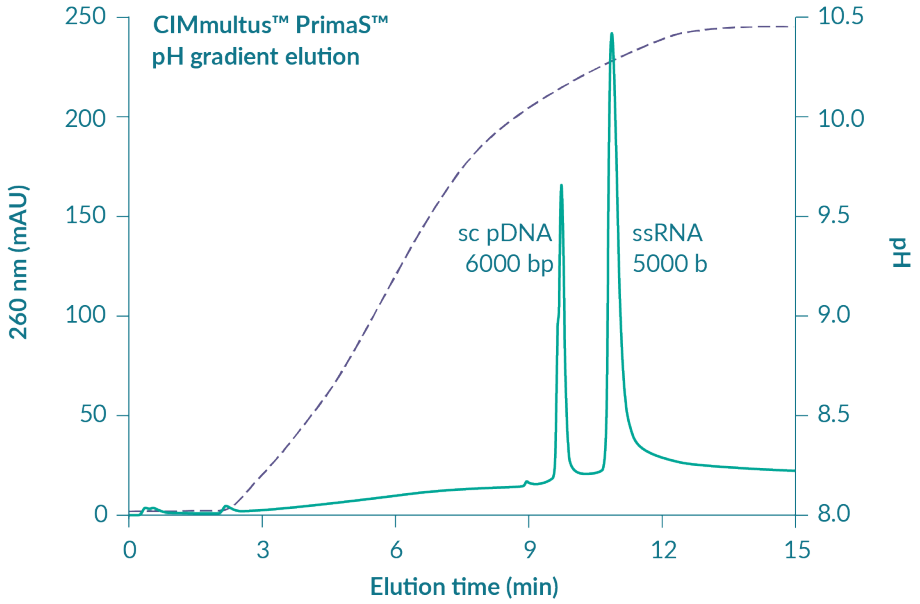


Negative charges are shown in red with a yellow halo. Each pair of red dots indicates a free lone pair of electrons that can act as a hydrogen acceptor. The term "lone pair" refers to a pair of valence electrons that are not shared with another atom in a covalent bond. Hydrogen donors are shown in blue.

ligand to base-pair with the polyadenine tail of mRNA. It can be used for capture but it cannot discriminate dsRNA (double-stranded) from ssRNA (single-stranded) and it supports only brief cleaning with 100 mM sodium hydroxide [1–3]. Ambient temperature operation of traditional anion exchangers elutes only mRNA species smaller than about 500 bases [3–5]. Elution of larger species requires elevation of operating temperature into the range of 50–70°C [6]. Hydrophobic interaction chromatography (HIC) and reverse phase chromatography (RPC) separate ssRNA from DNA, dsRNA, and short transcripts, but their sensitivity to fouling by proteins and aggregates makes

FIGURE 2

Separation of plasmid DNA and ssRNA in a pH gradient.



Buffer A: 50 mM Tris, pH 8.0. Buffer B: 125 mM glycine, pH 10.5. 50 CV linear gradient from A to B at 5 CV/min.

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them better suited for polishing than for capture [3,7–10].

Better capture options are needed to meet the needs of large clinical trials, scale-up, and manufacture of vaccines. Beyond that, a new spectrum of gene therapy treatments await. This article introduces two new capture options that both eliminate dsRNA, DNA, and proteins in a wash step, then provide high-resolution polishing of ssRNA in an elution gradient at ambient temperature. One represents a new class of anion exchangers. The other exploits hydrogen bonding. Both support prolonged exposure to 1 M sodium hydroxide. Easy transition to either HIC or RPC provides high-resolution orthogonal polishing.

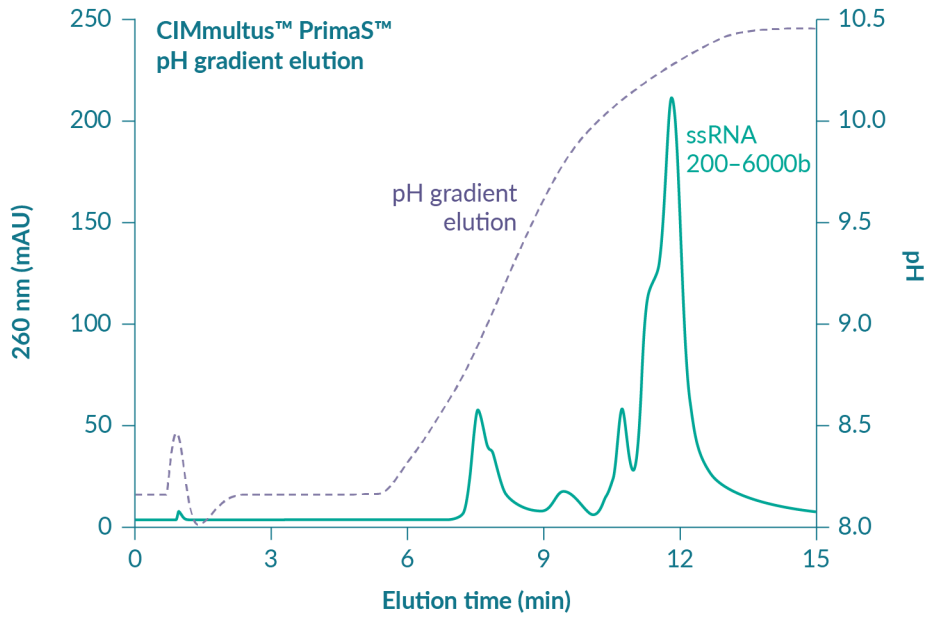
EXPERIMENTAL

CIMac™ (100 µL) or CIMmultus™ (1 mL) PrimaS™ and H-Bond™ monoliths with 2 µm channels were obtained from BIA Separations. Single-stranded and dsRNA ladders, DNA ladders, and species of single size were obtained from New England Biolabs. Analytical grade or American Chemical Society grade buffering agents and salts were obtained from Sigma-Aldrich. Buffers were prepared fresh with European Pharmacopeia grade water and filtered to 0.22 µm before use.

Purified samples of defined content were used to eliminate ambiguity of interpretation and facilitate comparison across laboratories. They were equilibrated before injection by dilution with a 10-fold volumetric excess of the column equilibration buffer. Many examples were performed with sample mixtures containing supercoiled DNA of 6000 base pairs and ssRNA of 5000 bases. Injection volumes ranged from 50 µL to 200 µL depending on the size of the column. Specific sample composition and buffer conditions are described in the Figure legends. Columns were operated at a flow rate of 5 column volumes per minute (300 CV/h). Results obtained from experiments with conditions and samples of broader scope are described in [3].

FIGURE 3

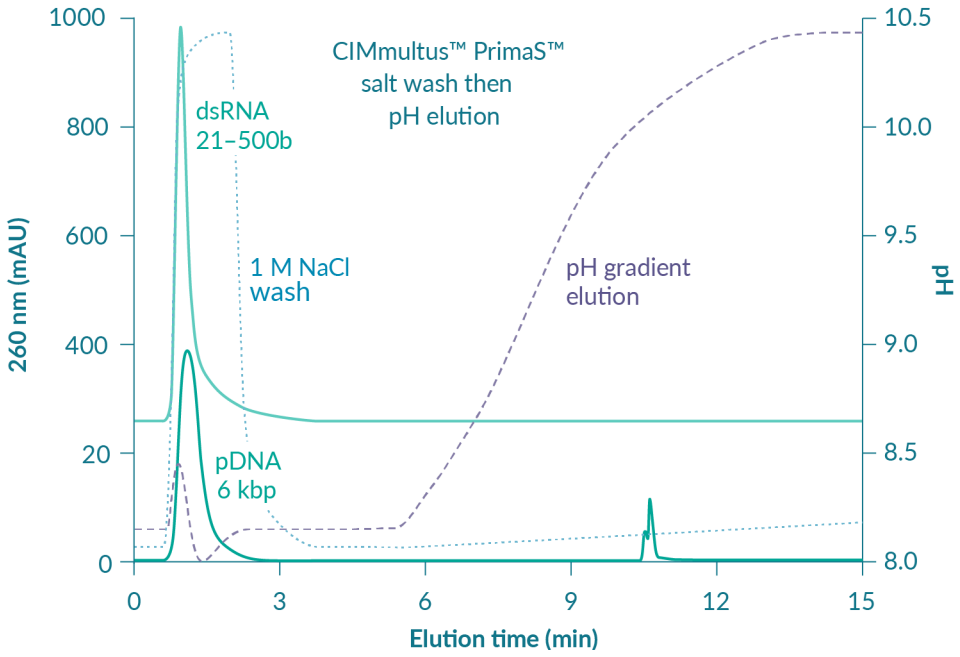
Elution of a ssRNA ladder in a pH gradient.



Same protocol as Figure 2.

FIGURE 4

Removal of DNA and dsRNA with a salt wash before pH elution.



Equilibration and elution as in Figure 2. First wash: 50 mM Tris, 1 M NaCl, 10 mM EDTA, pH 8.0. Second wash with equilibration buffer. Same elution as Figure 2. Overlay of two different chromatograms.

RNA CAPTURE BY ANION EXCHANGE CHROMATOGRAPHY, ELUTION BY PH GRADIENT

The necessity to heat traditional anion exchangers represents a burden at all stages of process development and manufacturing but it also provides a clue. The inability to elute large mRNA at ambient temperature derives from the elevated hydrogen bonding capacity of RNA [3]. The ratio of hydrogen donors and acceptors to negatively charged phosphatidic residues on the polymer backbone is more than 20:1 (Figure 1). The majority are not involved in base-pairing but they can bond with complementary features of anion exchange surfaces. An anion exchanger with reduced hydrogen bonding potential should be able to reduce the net contribution of hydrogen bonding and elute RNA at ambient temperature.

Figure 2 validates this hypothesis with ambient temperature elution of a sample mixture containing ssRNA with 5000 bases. An ascending pH gradient elutes ssRNA from CIMmultus™ PrimaS™ in a sharp peak, well separated from an earlier-eluting 6000 bp DNA plasmid. The rationale for increasing pH is that it reduces protonation and reduces the number of hydrogen bonding partners for RNA. This approach does not work with traditional anion exchangers, which tend to exhibit stronger binding with increasing pH [11,12]. Figure 3 shows pH elution of a single-stranded mRNA ladder that contains species ranging from 200 to 6000 bases. They elute in order of increasing size.

Contaminating double-stranded nucleic acids, including both DNA and dsRNA, are serious concerns from an immunological perspective [13]. Residual plasmid DNA is immunogenic [14,15] and may be present in range of degradation states at 1–2% of total RNA after transcription. Proportions of dsRNA are less well characterized but still important. Cells interpret dsRNA as a viral infection [16]. It can trigger a cytokine storm with sudden and serious health consequences. Figure 4 shows that dsRNA and DNA are both removed in a 1 M sodium chloride wash with 10 mM EDTA. Single-stranded RNA

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remains bound. After returning the column to equilibration conditions, DNA and dsRNA are essentially absent from the pH elution profile. The presence of salts during pH gradient elution causes ssRNA to elute at lower pH values (Figure 5).

The pH of the eluted ssRNA should be neutralized during or shortly after elution. Both methods are standard practice in the field of protein affinity chromatography where fraction collection vessels either contain a pH-titrating buffer so the product is neutralized upon collection, or the product is neutralized at the end of the run. Preliminary data indicate that brief exposure to alkaline elution conditions causes no modification of mRNA but prudence suggests avoiding prolonged exposure.

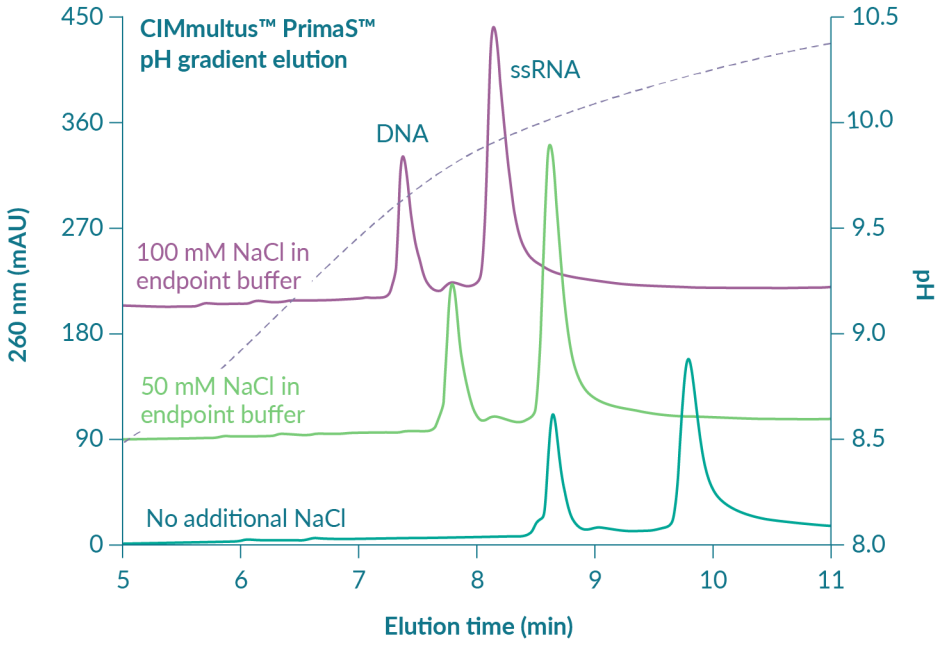
The column can be cleaned extensively with 1 M NaOH. Brief cleaning is recommended after every run since it will reveal the amount of material remaining on the column after elution. Columns loaded with large volumes of crude samples may require cleaning for 1 hour. Badly fouled columns can be restored to baseline performance by cleaning for 16–24 hours. Cleaning can be enhanced by co-formulating NaOH with 1–3 M NaCl and 10–20 mM EDTA.

RNA CAPTURE BY HYDROGEN BONDING, AFFINITY ELUTION BY DIPHOSPHATE DISPLACEMENT

Figure 6 illustrates elution of ssRNA at ambient temperature from CIMmultus™ H-Bond™ with a gradient to 100 mM pyrophosphate at neutral pH [3]. Hydrogen bonding has been exploited sporadically on conventional ion exchangers since 1960 [17–20]. The H-Bond™ ligand is more enriched with hydrogen donors and acceptors so that up to 80% or more of its binding energy comes from hydrogen bonding (Figure 7) [3]. DNA binds H-Bond™ more strongly than it binds strong anion exchangers at all pH values but binding becomes disproportionately stronger with decreasing pH. The trend becomes

FIGURE 5

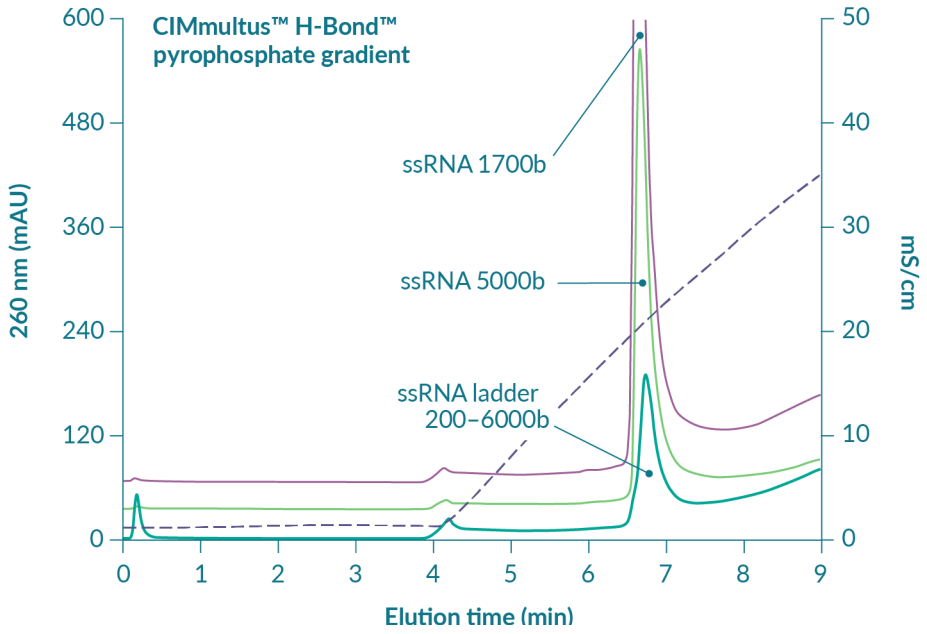
Earlier retention time and increased RNA recovery by the presence of salt during pH elution.



DNA: 6000 bp. RNA 5000 b. Protocol of Figure 2 except with the indicated concentrations of NaCl added to the gradient endpoint buffers. Overlay of 3 chromatograms.

FIGURE 6

Elution of ssRNA of different sizes in a pyrophosphate gradient.



Buffer A: 50 mM Hepes, pH 7.0. Buffer B: 50 mM Hepes, 100 mM potassium pyrophosphate. 50 CV linear gradient at 5 CV/min. Overlay of three different chromatograms.

steeper below pH 6. The differential compared to the strong anion exchanger is attributed to hydrogen bonding becoming more prevalent with increasing protonation [3].

Pyrophosphate is a diphosphate (P2O7) with up to 4 negative charges and up to 18 hydrogen donor/acceptors depending on pH (Figure 8). It represents the terminus of adenosine diphosphate (ADP) and it is a ubiquitous contaminant of phosphate buffers. All sizes of ssRNA elute at the same pyrophosphate concentration (Figure 6). Remarkably, dsRNA elutes in order of increasing size but even very-large species elute before ssRNA (Figure 9). DNA shows limited heterogeneity with respect to size, as seen in the trailing shoulder on the main peak in Figure 10, but no useful size separation overall. It elutes in advance and well separated from ssRNA.

Figure 7 suggests that reducing pH will increase RNA capacity but also predicts that elution of ssRNA will be shifted to a higher concentration of pyrophosphate [3]. It does not necessarily follow that separation between ssRNA and double-stranded contaminants will remain the same but that concern can be managed in a different way. As with anion exchange chromatography, DNA and dsRNA are eliminated at neutral pH by a wash step with 1 M NaCl and 10 mM EDTA [3]. At lower pH, increasing the salt concentration in the wash should compensate for stronger binding and leave the gradient to polish out trace-level contaminants from highly purified ssRNA.

Running the gradient at alkaline pH and/or in the presence of non-pyrophosphate salts elutes ssRNA at lower pyrophosphate concentrations. Combinations of other salts and alkaline pH can elute ssRNA without pyrophosphate but only pyrophosphate elution separates dsRNA from ssRNA. Optimization parameters and ranges are discussed in detail in [3]. H-Bond supports the same robust NaOH tolerance as PrimaS™.

Pyrophosphate anions must be removed from the final product because, *in vivo*, they form precipitates with calcium that can cause adverse health consequences. Pyrophosphate has the same charge as RNA, which suggests they should repel each other. However,

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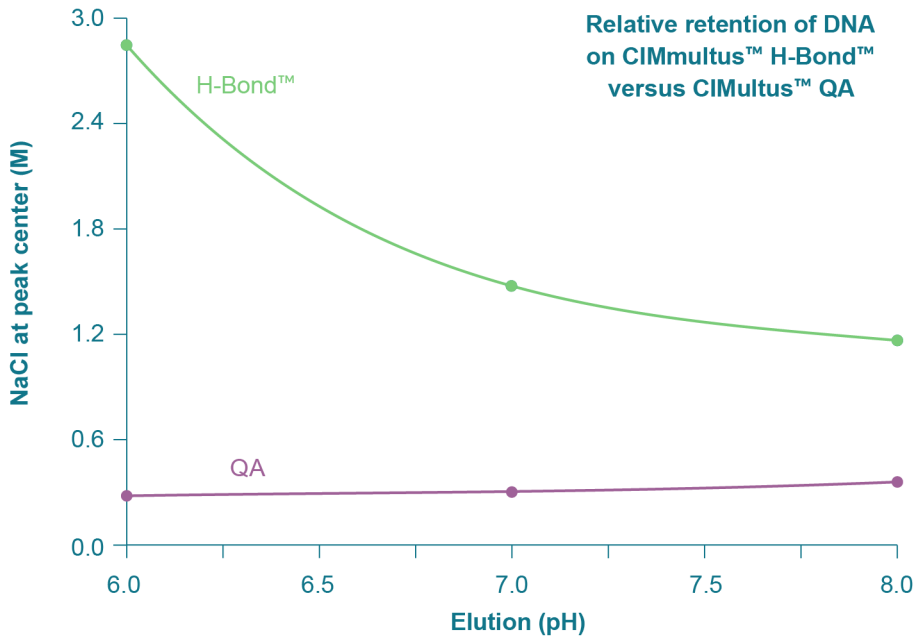
FIGURE 7

Elution of DNA from a hydrogen bonding column in a salt gradient at the indicated pH values.



Salmon sperm DNA from Sigma-Aldrich. Equilibration buffers: 50 mM MES, pH 6.0; Hepes, pH 7.0; or Tris, pH 8.0. Elution in a linear gradient, same buffers plus 4 M NaCl. Flow rate 10 CV/min.

their shared metal affinity creates potential for them to form stable coordination bonds via multivalent metal cations [3]. A chelating agent needs to be present at a significant concentration. Pyrophosphate removal can be performed during final formulation by diafiltration but doing it in the context of a polishing step achieves the goal earlier in the process and increases confidence that it will be absent from the final product. Sensitive pyrophosphate assays to validate clearance are available from global suppliers.

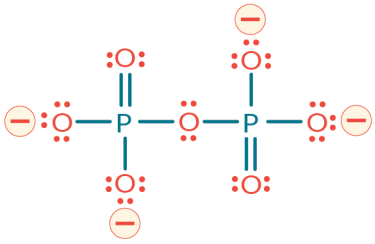
POLISHING AFTER CAPTURE

Coming out of a capture step with highly purified ssRNA, particularly lacking in double-stranded nucleic acids, contributes robustness to purification platforms using two chromatography steps. Removing the majority of DNA and dsRNA in advance allows the polishing step to accomplish what it is intended to do: polish. This is substantially preferable to the alternative of coming from capture with virtually the entire load of the most toxic contaminants at full strength, then relying on a single polishing step to fully remove them.

Otherwise, polishing may employ the same options used after capture by hybridization-affinity chromatography. HIC or RPC each provide independent orthogonal ability to separate ssRNA from dsRNA, DNA, and proteins, and each achieves a degree of size separation to remove short transcripts.

FIGURE 8

The distribution of charges and hydrogen acceptors on pyrophosphate, shown fully unprotonated.



Negative charges are shown in red with a yellow halo. Each pair of red dots indicates a free lone pair of electrons that can act as a hydrogen acceptor.

RPC gives better resolution than HIC but it requires the use of flammable solvents at elevated operating temperatures. RPC can be performed with either styrenedivinylbenzene (SDVB) or C-18 media but only SDVB is cleanable with 1 M NaOH [3,7–10].

HIC-polishing after either anion exchange or hydrogen bond chromatography enables exclusively ambient aqueous purification. In place of hazardous materials and conditions, HIC imposes a lesser logistical burden. Binding ssRNA to HIC media requires high concentrations of salts to drive retention. Those salts promote precipitation of RNA. If the RNA precipitates before it reaches the binding surfaces inside the column, those precipitates interfere with sample loading, they depress capacity, and they depress purification performance.

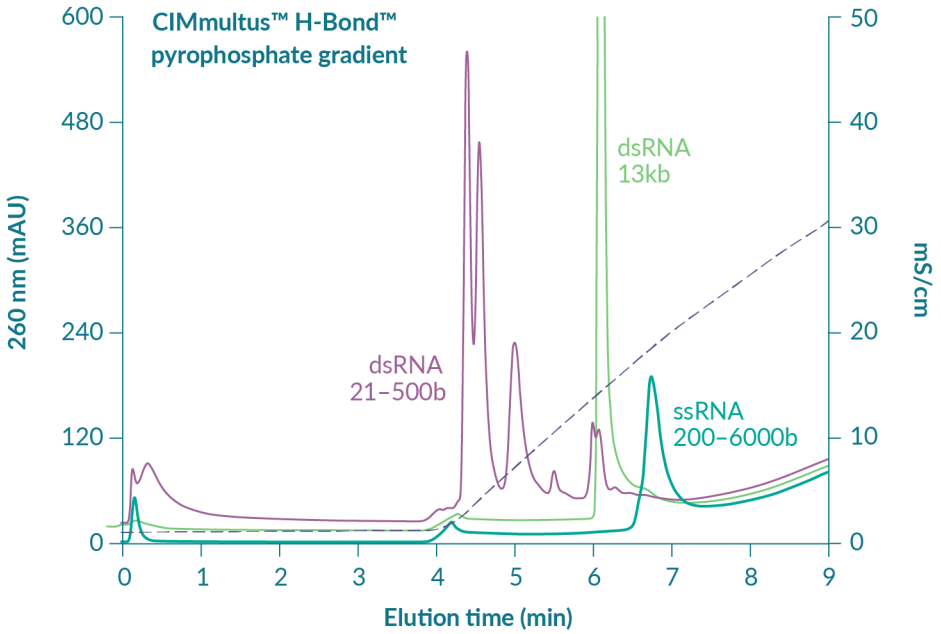
This challenge was resolved decades ago for preparative HIC purification of proteins. It requires sample loading by a technique known as in-line dilution. In-line dilution requires two input lines that meet at a mixer immediately before the column. This reduces the pre-column residence time of the ssRNA in high-salt to seconds, which prevents formation of large precipitates that would negatively affect chromatography. In addition, pre-column residence time of the sample in high salt remains uniform throughout the entire sample application phase, no matter how large the volume and how long it takes to load. Capacity and purification performance both benefit.

The first input line carries either low-salt buffer or sample, with an in-line 3-way valve to select one or the other. The second input line carries a high-salt diluent. Column equilibration is conducted with a mix of low-salt buffer with the high-salt diluent, for example 4 parts diluent to 1 part low-salt buffer. Sample application is done by switching the valve to deliver sample at the same mixing proportion. A wash step is performed by switching the valve back to low-salt buffer. Elution is performed by reproportioning the high and low salt buffers. HIC sample-loading by-in-line dilution is discussed in detail in [3].

All of these options support smooth workflow. The low salt concentration of ssRNA

FIGURE 9

Separation of dsRNA from ssRNA in a pyrophosphate gradient.



Overlay of 3 separate chromatograms, each run according the protocol of Figure 6.

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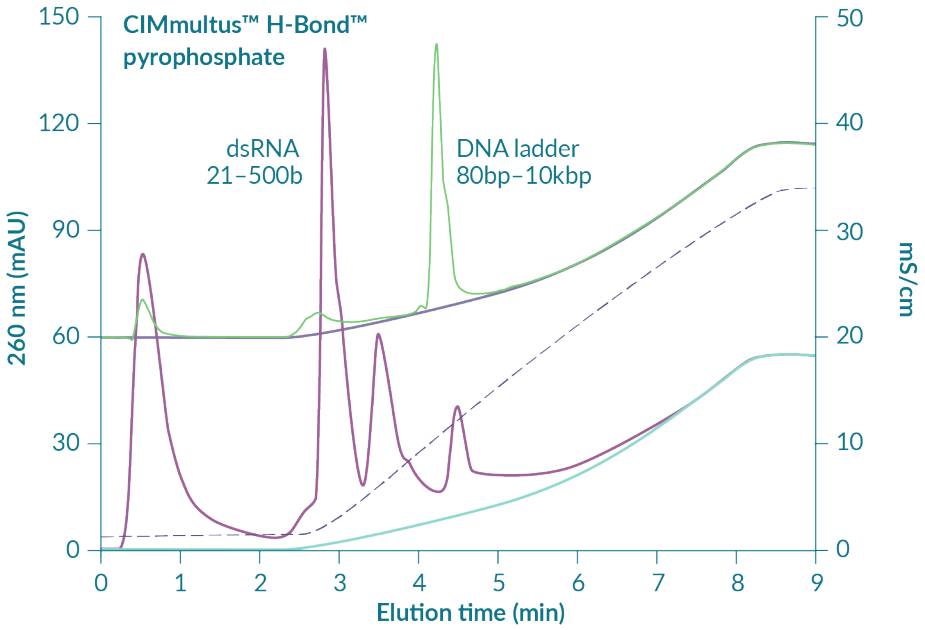
FIGURE 10

Elution behavior of DNA and dsRNA ladders in a pyrophosphate gradient.



Overlay of two chromatograms, same protocol as Figure 6.

after pH elution from PrimaS™ simplifies sample preparation going into the low-no salt method of RPC. After either anion exchange or hydrogen bonding chromatography, applying the sample to HIC simply requires adding salt. Inclusion of EDTA in the HIC binding salt helps displace residual pyrophosphates and it is also good insurance to eliminate residual metal ions carried over from any previous step.

CONCLUSIONS

Anion exchange and hydrogen bond chromatography can both be used to prepare research quality ssRNA in a single step. More importantly, they both provide an improved capture-foundation for two-step purification of clinical-quality single-stranded mRNA. Thanks to their ability to largely eliminate dsRNA and DNA with a salt wash, linear gradient elution can be converted to a step format with little or no compromise to purification of ssRNA. Both methods reduce the overall contaminant load going into polishing and they enhance robustness of the platform overall. Both methods support aggressive cleaning and sanitization with sodium hydroxide to enable multiple use, and both support a full range of scale-up options.

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AFFILIATIONS

Pete Gagnon
CSO, BIA Separations

Blaž Goričar
Project Manager, BIA Separations

Špela Peršič
Research Scientist in Process Analytics Development, BIA Separations

Urh Černigoj
Senior Scientist, BIA Separations

Aleš Štrancar
CEO, BIA Separations

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AUTHORSHIP & CONFLICT OF INTEREST

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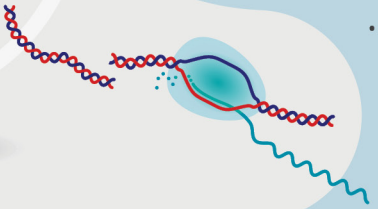

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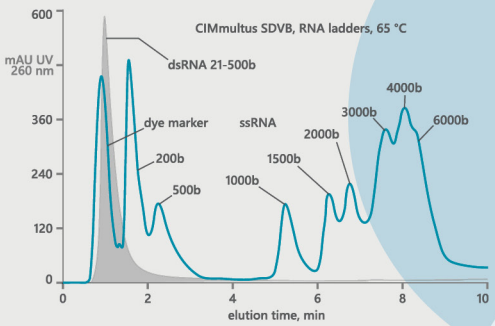

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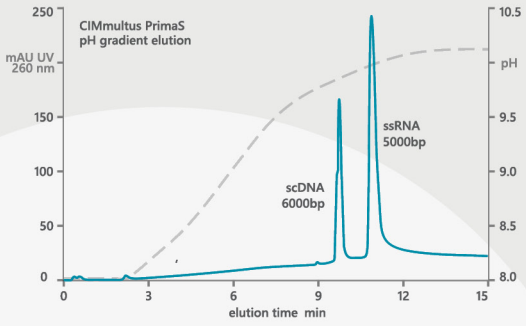

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