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CELL & GENE THERAPY INSIGHTS

SPOTLIGHT ON:

Immuno-oncology: manufacturing & commercial business models for the new decade

GUEST EDITOR: **Dr Usman Azam, President & CEO, Tmunity Therapeutics Inc**

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IMMUNO-ONCOLOGY: MANUFACTURING & COMMERCIAL BUSINESS MODELS FOR THE NEW DECADE

SPOTLIGHT

There has never been a more exciting time in the field of immuno-oncology, where the nexus of research, translational medicine, manufacturing, regulatory, clinical development and commercial is integrating...

FOREWORD

Usman Azam

As we emerge out of the global pandemic of COVID 19, I am humbled to be the guest editor to this Cellular Immuno-Oncology Spotlight. If the recent events have taught us one thing, it's that the need for novel biopharmaceuticals and therapeutics has never been greater. The tragedy of the pandemic not only impacted those who succumbed to the SARS-Coronavirus-2, but the wider impact to healthcare systems, and in particular

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the management of patients suffering with cancer.

In a recent editorial in the *New England Journal of Medicine* entitled 'The untold toll – the pandemic's effect of patients without COVID-19' by Lisa Rosenbaum [1], there is a poignant reminder of the challenges patients with cancer are facing during these difficult times. One of her colleagues describes the most vulnerable cancer patients during this pandemic. The first are the subgroup of patients with lymphoma for whom CAR-T therapy is potentially curative. More than half of these patients receive therapy in clinical trials, many of which have been paused amid society-wide shutdowns, compounded by concerns about the need for ICU care in a pandemic resource-constrained system. Secondly, concerns for patients requiring bone marrow transplants, given their high risk of infection and potential need for ICU care. Finally, patients with refractory tumors who are nearing the end of life, but for whom an experimental targeted therapy may hold promise.

It is with that background during these challenging times that I am delighted that colleagues who I have had the pleasure to know in the cell therapies sector for many years, are truly 'disruptive' innovators, are passionate about the work they and their teams undertake in the field of immuno-oncology, have come together to share their thoughts around the next generation of T cell engineered products, both from a scientific and future commercial stand point.

This spotlight will cover all the major T cell platforms (TILS, TCRs, CARs) as well as commercial thoughts on both the opportunities and challenges innovators face in making the next generation of T cell therapies a reality for patients. There has never been a more exciting time in the field of immuno-oncology, where the nexus of research, translational medicine, manufacturing, regulatory, clinical development and commercial is integrating these essential disciplines to make the next decade a reality for cell therapies in treating many forms of cancer.

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AFFILIATION

Usman Azam
President and CEO, Tmunity Therapeutics Inc

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IMMUNO-ONCOLOGY: MANUFACTURING & COMMERCIAL BUSINESS MODELS FOR THE NEW DECADE

SPOTLIGHT

EXPERT INSIGHT

Innovating CAR T cell therapy for today and tomorrow

David Chang, MD, PhD

A new era has emerged in the cancer treatment landscape as cell therapies demonstrate their potential to be game changing. Inherent limitations of autologous CAR T cell therapies exist, which can restrict their application. Therefore, further exploration into engineered allogeneic CAR T cell therapy is needed as early research in hematologic cancers has demonstrated the potential of this powerful immunotherapy.

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Immunotherapy has come a long way from the skeptical reaction that greeted it as recently as 2010. As we enter the 2020s, immunotherapy is taking its place as the fourth modality for treating cancer, along with surgery, radiation and chemotherapy. Decades of scientific research leading to the first chimeric antigen receptor (CAR) T cell therapies approved in 2017 point us toward unlocking the potential of cell therapy. Previous questions about the viability of CAR T cell therapy have now shifted to the feasibility of wider use.

While there are two FDA-approved autologous CAR T therapies, Kymriah® and Yescarta®, the excitement of CAR T therapy is dampened by the higher cost, manufacturing challenges and lack of accessibility. In currently approved CAR T therapy – autologous cell therapy – a patient's own immune cells are used to create the treatment. This requires an individual manufacturing run for each patient, which, in addition to complex logistics, can lead to a lengthy wait time and variable potency. Utility, and the long-term potential of CAR T cell therapy on an outpatient basis,

will remain limited unless we can develop treatments that can be delivered on demand, more reliably and at a lower production cost. Our challenge now is to grow and expand the reach of this type of immunotherapy to a broader patient base and to a wide range of cancers with therapies that can be mass produced [1].

This means developing allogeneic CAR T therapies that can be manufactured in advance instead of on a patient-by-patient basis. The potential benefits of this approach, including the elimination of certain manufacturing logistics required with autologous cell therapy and the ability to generate potential over 100 doses from a single manufacturing run [2], have become even more apparent during the COVID-19 pandemic. Scientific advancements and innovation have given us the tools we need – specifically the application of gene editing – that now allow us to potentially realize allogeneic cell therapy as a next innovation in cancer treatment.

The initial challenge of allogeneic CAR T therapies is fundamentally different from the challenges of autologous CAR T, in that we are looking to overcome millennia of evolution and self/non-self-recognition – the core of immunology [3]. There are two pieces to overcoming this challenge: One, we must ensure that cells can be safely administered from one individual into another. Emerging data suggests that editing out a T cell receptor can inhibit graft-versus-host (GvH) response to a meaningful degree [4,5]. Two, a window for donor cell expansion and persistence must be created in the patient to ensure that the allogeneic cells are not prematurely rejected by the patient's immune system. This is a more significant undertaking. At Allogene, we believe the key lies in our proprietary lymphodepletion regimen and protecting allogeneic CAR T cells from the effects of this lymphodepletion.

To address these challenges, we utilize the TALEN® gene editing technology, developed and owned by Cellectis, which allows us to delete two genes – *TRAC* (a subunit of T-cell receptor) and *CD52*. The latter enables the use of an anti-CD52 monoclonal antibody (mAb) to selectively deplete the patient's immune cells that mediate the rejection of allogeneic CAR T cells, without depleting the allogeneic CAR T cells. Enthusiasm for gene editing technology must be balanced by the risks of potentially introducing multiple translocations [6] which may cause off-target gene inactivation or even confer a survival advantage to tumor cells. Early data with TALEN® suggests a low risk of conferring a proliferative advantage with the use of two TALEN®s, but further investigation is needed to better understand this risk [5].

There are many reasons to be optimistic about this approach with an anti-CD52 mAb and the results from preclinical and early Phase 1 research of allogeneic CAR T therapies are encouraging. At the American Society of Hematology Annual Meeting in 2018, Allogene and Servier presented results from an updated analysis of pooled clinical data from two ongoing Phase 1 studies of UCART19, the first allogeneic CAR T cell (AlloCAR T™) therapy in clinical study, in pediatric (PALL) and adult (CALM) patients with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL). The analysis showed that 82% (14/17) of patients who received a lymphodepletion regimen consisting of fludarabine, cyclophosphamide and an anti-CD52 mAb (FCA) achieved a complete remission (CR) or complete remission with incomplete blood recovery (CRi). In the four patients who received fludarabine and cyclophosphamide (FC) only, there was minimal UCART19 expansion and no response. The most common adverse events were related to cytokine release syndrome (CRS) and GvH – which was reported as transient skin rash in two patients – and were generally manageable [7]. The UCART19 data demonstrate that the selective knockout of the *CD52* and *TRAC* genes, together with the use of anti-CD52 mAb, may be sufficient to minimize the risk of GvH response and premature rejection of allogeneic CAR T cells [7]. These data also

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suggest an anti-CD52 mAb is an important addition to the lymphodepletion regimen for allogeneic CAR T cell expansion. The study design prohibited the ability to follow patients to determine durability but established proof-of-concept.

We began Phase 1 studies in 2019 of ALLO-501 for the treatment of relapsed or refractory non-Hodgkin lymphoma (NHL) with an optimized lymphodepletion regimen utilizing ALLO-647, our proprietary version of an anti-CD52 mAb. ALLO-501 has the same anti-CD19 CAR construct as UCART19, manufactured with a process developed by Allogene. A year later at the 2020 American Society of Clinical Oncology virtual meeting, Allogene released positive initial data from its Phase 1 ALPHA study evaluating ALLO-501. Of the 19 adult patients with relapsed or refractory NHL who were evaluable for efficacy, seven achieved a CR and five achieved a partial response (PR) for an overall response rate (ORR) of 63% and CR rate of 37%. Nine of 12 (75%) patients remained in response as of the time of data cutoff for the data presentation. Higher response rates were observed in CAR T naïve patients (N = 16) with an ORR of 75% and CR Rate of 44% [8]. The reported short-term efficacy data are in line with what has been observed with autologous CAR T in patients with lymphoma (71% ORR; 57% CR) [9].

There are other validated targets in addition to CD19 that hold great potential for CAR T cell therapy. In relapsed or refractory multiple myeloma, the therapeutic response of autologous anti-BCMA CAR T cells diminishes after 12–18 months [10,11]. Previously, Allogene published data that shows that allogeneic anti-BCMA CAR T cells are therapeutically active against primary multiple myeloma cells from patients, in a clinically relevant model that includes the bone marrow microenvironment. The CAR T cells produced from healthy donors also appeared to have functional and phenotypic differences that may be advantageous. The next step is to evaluate these differences further and determine whether the therapeutic activity is sustained [12]. Allogene is conducting the Phase 1 UNIVERSAL trial of ALLO-715, an investigational anti-BCMA AlloCAR T™ candidate, in patients with relapsed or refractory multiple myeloma.

There has been an explosion of interest in allogeneic CAR T over the last several years as evidenced by the number of assets in preclinical and clinical development, including those from companies such as Precision BioSciences and CRISPR Therapeutics, which utilize different technologies to deliver CARs and disrupt relevant host genes.

If clinical research establishes safety and efficacy, there is enormous potential to improve and expand allogeneic CAR T cell therapies. Beyond hematologic cancers, solid tumors present a host of challenges not encountered in blood-related cancers [13]. The diversity of solid tumors and the tumor microenvironment, which can suppress the immune system, challenges our ability to effectively target therapies. Current efforts generally follow two tracks: translating existing CAR T therapies to solid tumors and developing stronger, more durable CAR T therapies for hematology. This is where allogeneic CAR T therapy shows enormous promise, especially when coupled with advances in cell engineering that enable precise targeting once correct targets are described.

We believe CD70 – which is expressed in both hematologic and solid tumors – may bridge the gap toward unlocking the potential of AlloCAR T™ therapy in solid tumors. Renal cell carcinoma (RCC) is a high T cell infiltrated tumor type, but despite demonstrated responsiveness to immuno-oncology agents, overall rates of complete response are very low with yet unknown durability [14–16]. CD70 is a well-established, selective target specifically expressed in RCC. Based on the biology of CD70, we believe we can potentially avoid some of the off-tumor effects that may be associated with a less established target while still maintaining high therapeutic activity. However, as CD70 is expressed on a subset of activated T cells [17], fratricide is

a concern. During the selection process, we screened for CARs that were less impacted by this issue. When we tested targeting CD70 with RCC cells *in vitro*, allogeneic CAR T cells targeting CD70 showed significant activity [18].

In addition to pinpointing additional targets, our work is aimed at improving T cell fitness and working on immune evasion, which is an alternative to immune-suppression and may have clinical advantages. Therefore, Allogene developed TurboCAR™ technology which allows cytokine signaling to be delivered selectively into in CAR T cells, and not host immune cells. TurboCARs™ can be tailored with different signaling domains to enhance T cell activation and persistence. The goal of TurboCAR™ technology is to minimize systemic toxicity, avoid stimulation of host immune cells which could reject the CAR T cells and deliver survival benefit selectively to CAR T cells and not the host. If successful, these TurboCARs™ could improve efficacy, potentially reducing CAR T cell dose requirements and overcome exhaustion.

Combining allogeneic CAR T cells with other therapies, such as in our collaboration with SpringWorks Therapeutics and their investigational gamma secretase inhibitor (GSI) nirogacestat, has the potential to deliver stronger, more targeted responses. We know that BCMA expression on myeloma cells can be quite variable. Gamma secretase inhibition prevents the cleavage and shedding of BCMA from the surface of myeloma cells. GSI changes the cell surface expression of more proteins than BCMA and so further investigation of off-target effects will be warranted. However initial trials have suggested an appropriate safety profile for this class of drugs. In preclinical models, nirogacestat has been shown to increase the cell surface density of BCMA and reduce levels of soluble BCMA, thereby enhancing the activity of BCMA-targeted therapies [19]. In addition, emerging clinical data suggest that a GSI may increase antitumor efficacy of BCMA-targeted autologous CAR T therapy in patients with relapsed and refractory multiple myeloma [20,21]. Allogene and SpringWorks plan to pioneer this approach in AlloCAR T™ therapy.

Finally, allogeneic CAR T cells that can be clonally produced and are not reliant on healthy donors have the advantage of true homogeneity, which must be our goal if we want to provide off-the-shelf therapies. Leveraging the scientific understanding of autologous cell therapies as well as emerging clinical data for donor-based allogeneic cell therapies, renewable-source, master cell banks – like induced pluripotent stem cells (iPSCs), which we are exploring in partnership with Notch Therapeutics – may also have the potential to improve outcomes and expand applicability to new therapeutic immunity-related areas.

At Allogene, our vision for shaping the next revolution in cancer treatment means preventing GvH and graft rejection, improving T cell fitness, expanding a target repertoire and eventually, exploring iPSCs as a renewable source for allogeneic cell therapy. We believe this differentiated combination will be the best path forward for creating the AlloCAR T™ of today and tomorrow.

TRANSLATIONAL INSIGHT

Ultimately, off-the-shelf CAR T therapies could be truly revolutionary in the treatment of many cancers. We have already demonstrated that allogeneic CAR T cells can be manufactured in a large-scale process. Because allogeneic CAR T cells are produced from healthy donors, they have the potential to be stronger and more efficacious than therapeutic cells produced from the patient's own cells. Numerous efforts are underway in both the private sector and academic laboratories to advance these treatments into clinical research. Sustained investment and scientific leadership will likely bring dramatic new treatments to patients in the years ahead.

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AFFILIATION

David Chang, MD, PhD
President, Chief Executive Officer and Co-Founder, Allogene Therapeutics

AUTHORSHIP & CONFLICT OF INTEREST

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EXPERT ROUNDTABLE

Evolving autologous and allogeneic cell therapy manufacturing models in the commercial setting

DEREK ADAMS
Chief Technical Officer & Manufacturing Officer, bluebird bio.

Derek Adams has served as Chief Technology and Manufacturing Officer at bluebird bio since March 2017. Prior to joining bluebird, Derek was the Senior Vice President of CMC at Evelo Biosciences where he established the initial process development function and supply chain for clinical studies, and drove strategy for product development.

GREG RUSSOTTI
Chief Technology Officer, Century Therapeutics

Greg Russotti is Chief Technology Officer at Century Therapeutics. Before joining Century in January 2020, Greg was Vice President of Cell Therapy Development and Operations at Celgene, where he guided CMC efforts for five different cell therapy products to IND and clinical stage development.

JOHN LUNGER
Chief Patient Supply Officer, Adaptimmune

John Lunger is Chief Patient Supply Officer at Adaptimmune. John leads the teams responsible for producing and delivering products to patients, accelerating supply execution, and optimizing the supply chain to be ready for commercialization.

EVONNE FEARNOT
Marketing Manager, Roche CustomBiotech

Evonne Fearnot is Marketing Manager at Roche CustomBiotech. Evonne has over 8 years of experience in cell and gene therapy, developing and marketing bioprocessing products and equipment, and is currently responsible for growing the cell and gene therapy brand as part of Roche CustomBiotech's commitment to advanced concepts for next generation commercial cell and gene therapy manufacturing.

EMILIE GAUTHY
Industrialization Manager, Celyad Oncology

Emilie Gauthy is Industrialization Manager at Celyad Oncology and a Bioengineer by training with a PhD in immunology. In her role at Celyad, Emilie oversees CMOs & CROs work and acts as the Raw and Starting Materials Site Matter Expert in the context of autologous and allogeneic CAR-T manufacturing.

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Q What is your organization's current manufacturing model, and how might it change as you get closer to commercialization?

GR: Century Therapeutics is focused on allogeneic therapies, and our model is to begin with induced pluripotent stem cell (iPSC) lines derived from peripheral blood mononuclear cells, or other sources.

These iPSCS can be modified using extensive genetic modifications. We can choose single-cell clones from these modified cell lines, and from there create master banks and whichever immune effector cells we require, such as T cells or NK cells. This allows us to make large amounts of cells per batch, thereby reducing the cost of goods, increasing the capacity per batch, and allowing us to make an off-the-shelf cell therapy that can be cryopreserved and shipped as needed.

EG: At Celyad Oncology we currently have a centralized model to manufacture allogenic and autologous CAR Ts. In fact, we have had our own manufacturing capability based in Belgium for more than 10 years, which has already supported us up to a Phase 3 trial where we were developing a cell therapy for cardio applications. I'm personally convinced that this brought a lot of knowledge to the organization and allowed us to quickly adapt in response to our clinical results.

Of course, the choice of the manufacturing model towards commercialization will largely depend on the type of therapy, and would be quite different for autologous or allogeneic therapies. A decentralized model could make sense for autologous, but probably less so for allogeneic therapies.

Nevertheless, multiplying manufacturing sites is key to moving towards commercialization, at least for increasing the production capacity. Having production on different continents can also ease scheduling and aid in delivering the product around the world.

The current pandemic shows how quickly we can be affected by what is happening on other continents. For example, apheresis supplies have been impacted by the COVID-19 pandemic, which demonstrates how regional measures on the US side have resulted in global repercussions. We have had great support from our own partners in securing supply and mitigating impact, but this situation demonstrates that having multiple collection sites for healthy donor apheresis in the context of allogeneic therapies, perhaps more locally for some markets, may be important in order to resist such crises in the future.

> "...apheresis supplies have been impacted by the COVID-19 pandemic, which demonstrates how regional measures on the US side have resulted in global repercussions."
>
> – **Emilie Gauthy**

DA: At bluebird bio we are focusing on autologous *ex vivo* cell therapies that are based off of lentiviral vector technology. Our manufacturing model is focused on centralized manufacturing in different regions. Therefore we are investing in a lot of contract partners to be able to manufacture these products in these different locations. We are also investing in internal vector

manufacturing, and we've been doing that for the last couple of years.

The biggest thing about going into commercialization, which is something we are on the threshold of, is that the regional and centralized manufacturing model requires a very robust control over the supply chain. The proverbial needle-to-needle time matters a lot. The manufacturing process, which as we all know is not hugely mature at these stages, is actually part of the patient experience. With the integration of the manufacturing model and the supply chain team, communication is really important to also integrate it with the commercial teams. This is fairly unique in the biotechnology field, and it's a really exciting part of what we're trying to do at Bluebird.

JL: Adaptimmune also has three autologous products in the clinic. We have a mix of internal and external manufacturing, both for vector and T-cell products.

Manufacturing is primarily internal for T-cells. We've learned that in the autologous space, as Derek mentioned, the vein-to-vein, which he referred to as needle-to-needle, time and turnaround time are important, as is flexibility. Having our own capability to manage all the aspects of needle-to-needle time has been valuable.

Additionally, as Emilie mentioned, the learnings you take at this early stage of the process internally are important. We're focused on an internal network, and this is the same for vector production. While we outsourced most of our vector supply initially, given the constraints in the market at the time. In addition, new vector production is a process that takes many months. As of now, though, we have been able to build our own in-house vector production.

As we move towards commercialization there is the obvious expansion of capacity, which we do intend to continue to do with internal resources. There's also the question of supply redundancy, in particular with autologous therapies. We are for all intents and purposes sole-sourced on one manufacturing site, and something that COVID can teach you is if you have something go through your facility, you can shut down trials and shut down commercial immediately. The idea of having redundancy in manufacturing for autologous cell production, which serves somewhat the same purpose as finished inventory in the allogeneic world, is something we're thinking about as we go towards commercialization.

> "The biggest thing about going into commercialization ... is that the regional and centralized manufacturing model requires a very robust control over the supply chain."
>
> - **Derek Adams**

This can be prohibitively expensive when you're in early phase trials, but it quickly becomes something to consider.

Q With regards to centralized versus distributed manufacturing models for cellular immunotherapies, what do you see as the chief barriers to commercial manufacturing success currently confronting each model?

DA: We all wrestle with this all the time. Cellular immunotherapies encompass a broad range of manufacturing technologies, modalities and distribution models. It's a broad term.

If we look at the area bluebird bio is focused on, the centralized manufacturing of autologous therapies, we have a really big supply chain challenge in moving either cryopreserved cells or fresh cells with tight time limits, in a one batch at a time or one patient at a time mode. In addition to being very complex, it is also very expensive to do.

Centralized manufacturing allows you to have a measure of control over your manufacturing process, and to have a centralized area for all of the traditional biotechnology and pharmaceutical quality systems and manufacturing approaches that you can use. But the shipping and logistics of moving cells around, and making sure you can line up the scheduling with the patient experience, is a unique challenge with centralized manufacturing of autologous cells.

To me, decentralized manufacturing starts to blur the line between being an actual biopharmaceutical manufacturer or a provider of a device or technique in support of a clinical practice. It starts to become a little bit confusing, at least to my very traditional biomanufacturing eyes. How does decentralizing the manufacturing and having many different manufacturing sites look in terms of control of the manufacturing process? Is it even a manufacturing process?

You may be able to reduce the complexity of the shipping of cells, and certainly be much more responsive to patient needs for scheduling. This is really important because all of this is surrounding the needs of the patient, and speed is crucial, therefore the decentralized model has a lot of compelling features. For any Star Trek fans, my vision is to ultimately have a Star Trek-style replicator in the lab so that you can just dial in the cells you want, they appear immediately, and you can give them to a patient right there on the bedside. That would be wonderful. But in the meantime, we have other limitations we have to work around that present some interesting challenges.

GR: I'd like to expand on the challenges Derek mentioned around the decentralized model, and particularly the question of whether it's manufacturing,

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device, or technique. In my opinion as long as it's a manufacturing process, I don't see how the decentralized model can work.

It's a big challenge to transfer these processes which are fairly complex, and also subject to patient-to-patient variability from starting material. That challenge is hard enough when you have a site in each region, but in cases where you have hundreds of sites I don't know how you can do that and have a robust process and the right quality controls in place. Even though the centralized model is a batch-by-batch, expensive proposition, you have some economies of scale. All of the ordering, quality control and quality assurance is done in one place. You lose all of that economy of scale in the decentralized model.

Some may say that decentralized manufacturing is cheaper, and Derek is right that it can be cheaper because of the lack of shipping need, but it's so much more expensive in other ways, and much more risky from a quality standpoint.

If you think about autologous CAR T as it is today, cells are isolated, activated, transduced, grown – there are so many steps there that make it a manufacturing process. It's not simple. Until it changes and becomes much simpler, it has to be done in a centralized model, otherwise you really risk both the quality of the product and the safety of patients.

JL: One element to highlight is cryopreservation. Most autologous companies have cryopreservation on the apheresis side for the starting material, as well as the final product. Doing that regionally or at the clinical site, depending on the complexity, takes away at least some of the time pressure – particularly for the manufacturing side.

It doesn't alleviate the vein-to-vein time which is still very important, particularly in where we are with solid tumors. Turnaround time remains important, but these are operational issues that over time we will solve. We will figure out how to make that happen within a two to three week window for solid tumors and achieve that vein-to-vein time.

At Adaptimmune we ship fresh apheresis centrally to our sites, and we have a cryopreservation CDMO in Europe for European sites. I can see us ultimately moving that towards the clinic. But the rest of the manufacturing process is too complex. The economies of scale are such that the cost to decentralize at this stage will be much, much greater than being centralized.

EF: I would add that one advantage of decentralized manufacture is due to the fact that there's a lot of market dynamics going on right now in the cell therapy space. You know with a centralized model that you have a higher cost of operation, a large flagship, and very specialized personnel that aren't able to adapt very easily. This makes them less flexible to addressing market changes.

It takes years to duplicate a large facility, so it becomes a multiyear project to expand. Decentralizing and having multiple sites with different specializations can allow you to identify an increase in market demand and add a contract, or a new area that's attractive, and add a different expertise. These advantages support a small degree of decentralization.

EG: From my perspective, the key would be the development of allogenic therapies. This would allow the field to get rid of many of the logistic constraints without putting additional pressure on the hospitals. Off-the-shelf allogeneic products utilizing

"Decentralizing and having multiple sites with different specializations can allow you to identify an increase in market demand..."

- Evonne Fearnot

cryopreservation would have a much closer manufacturing scenario to that of classical drugs and could be accessible to many more patients.

Q In your view, where on the centralized/decentralized spectrum is the 'sweet spot' for commercial scale production of patient specific advanced therapies?

JL: As discussed above, the move to decentralized cryopreservation with centralized manufacturing is, in my opinion, the next evolution.

Getting out of the centers of excellence and into the community is another element of the decentralized model. It can make sense to be in these centers of excellence, which are huge sites that have the capabilities to manage these kind of therapies. To Evonne's point, in order to get out into the community without having access to those centers, you're going to need some sort of support for them and potentially do the cryopreservation closer to the treatment center, or the apheresis for that matter. This is the mix we're beginning to see, at least for the near-term for commercial applications.

DA: Right now, centralized manufacturing is certainly the default for patient-specific therapies, essentially due to inertia. This is viewed as simply how we do things in manufacturing biotherapeutics at the moment, and we have a way of thinking and an organizational design already in place.

I think the point that Greg made is that the quality control and quality assurance aspects, i.e. having one place to assure we can make a quality product, are a huge need right now. Especially because we're finding that regulatory authorities are trying to figure this out just like the rest of us – how do you look at quality control, how do you look at process control, and how do you determine what is a good product? They're trying to catch up just as we are, and they're looking at it through the lens of somewhat more traditional manufacturing processes for drugs. They're applying many of the same guidances and many of the same principles. This makes it a little bit harder if you're thinking about decentralized manufacturing, even for patient-specific products.

The other challenge for patient-specific therapies in a more decentralized sense, or even in the centralized sense, is in how these therapies have been developed. They've been developed in collaboration with some very motivated and brilliant clinical physicians, at some great hospitals around the world. This includes the folks who believe that they have a big stake in what this product really means for their patients.

As you get towards commercialization, there's this interesting dynamic of how to communicate with the treating physicians, and what is a good product. When you're using centralized manufacturing to produce your product and delivering it very much like a traditional therapy, there's a barrier to overcome in how much information the

> "Getting out of the centers of excellence and into the community is another element of the decentralized model."
>
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"...there needs to be an incredible simplification of the manufacturing process. I know there are companies looking at building systems ... you press a button or two and have a product at the end. I think you need more than that."

- **Greg Russotti**

physicians actually want to know about the product. This is very different than if they simply had a bottle of bills in a pharmacy that they offered.

Right now are just scratching the surface of how we're all going to communicate on this, because it's really important that the treating physicians understand what's best for their patients. It's very patient specific, and the manufacturing process is part of all that. I'm fascinated about the interactions we're having.

GR: For decentralized manufacturing to have a place in the current autologous world, there's going to have to be two major changes. One is that there needs to be an incredible simplification of the manufacturing process. I know there are companies looking at building systems that in some ways would simplify that; you press a button or two and have a product at the end.

I think you need more than that, as the processes are still too complex. One approach is to try to find the right cells up front, and isolate them early, so you don't have to have as much *ex vivo* expansion. This would provide a more efficacious product with lower doses, thereby shortening and also simplifying the process. If that can be done, with a device that is foolproof so that that every time you run it you get the same product when using the same conditions, or at least some feedback control to give you similar conditions but the same product, it could work.

The bigger barrier is patient-to-patient variability. I don't think it's insurmountable, and as we understand more about what patient attributes lead to different process outcomes, and ultimately product attributes, we can control that and characterize the patient up front. Then we can put them in a general category so that they can go into Program A, B or C, and get the same product every time. But that's an absolutely huge proposition that's going to be very hard to meet.

Q How important will in-house facilities be for cell and gene therapy manufacturers moving forward? And what would you consider the most critical considerations for anyone considering establishing a new in-house facility today?

DA: The current environment we see with constrained capacity and very complicated manufacturing processes, and the speed with which we need to be able to both provide therapies and react to changes, is a very big driver to having internal manufacturing capacity if you don't have a really tight partnership with a contractor partner. It's a question of the needs of your business and how you can overcome that. Sometimes you're going to have to spend a lot of money either way: either you spend a lot of money on working with a contract partner to secure capacity, or you spend money up front to build out your own internal manufacturing. CMOs are building as fast as they can to try to keep up with demand, but right now the

capacity is simply lagging behind the demand we have.

One of our key considerations at bluebird as we commercialize our therapies and learn about supplying products at a commercial scale, is that when you're building internal manufacturing, especially for smaller and earlier phase biotechnology companies, you need to understand what are you building that facility for. Are you aiming for that facility to simply support clinical proof of concept? Or are you going to build it for commercial scale? Because that means something completely different, and I think that most traditional biotechnology companies wildly underestimate the commercial complexities, the amount of focus you need, and the amount of capital that you need to be able to do it at a commercial scale.

EG: I agree – as mentioned previously, I'm convinced that having direct control on at least part of your manufacturing gives you an advantage. It gives you flexibility in your scheduling, but also to quickly adapt to changes. It gives you knowledge, by facilitating your discussion between your R&D and production teams, supporting continuous improvement of your process. And it also gives you a real control of your product quality. Clearly this was Ceylad's choice to start with, and it was a real advantage for the fast transition to the clinic, and swift increasing of our production pipeline.

Besides the obvious considerations when you establish your own facility – such as where to put it in proximity to airports, or if there is a risk of Mother Nature in certain areas and so on – I would say that one of the key points is the ability to recruit the real experts in the field. In some areas these might be easy to find, but you might need to fight with competitors. Being able to pay for the cost of recruitment is also a factor to consider when establishing your own facility.

GR: Emilie nicely summed up the advantages of in-house manufacture for flexibility, control, the learnings you gain by seeing it yourself, and the co-efforts between development, manufacturing and research. It lets you solve problems quickly, make changes, and to have a vision of where you're going and to stick to it.

However, it's also important to have the flexibility to have a CDMO. You may need to flex sometimes and plan for more capacity, especially in the autologous space. It's good to have that option as well. And for a small company like Century that is starting out, it depends on your resources and where you want to allocate them. It is expensive to build in-house, and it takes time and certain expertise. If you don't have all of

those things, sometimes you may have to start with a CDMO until you do, and that's fine. If it is a strong relationship and you feel comfortable you can stick with it. But ultimately, for the reasons we discussed, having your own in-house manufacturing is something everyone should really strive towards.

EF: Roche CustomBiotech continues to see more and more companies moving towards in-house facilities. We've seen this being done to build up extensive QC capabilities to have greater control on quality, to have close-to-real-time data available to further understand their manufacturing process, and also to reduce product release timelines and cost.

JL: I see a bit of a misalignment between early stage biotechnology companies, cell therapy and the CDMO model. For early stage biotechnology companies in this space, every patient is a critical piece of data, and frankly a critical piece of evaluation for the company. The ability to flex and respond to patient needs is crucial. This can take a little bit more risk, and whether it's looking at the logistics side or changing the process, there's an incentive for the companies to learn everything they can.

Whereas for the CDMO, it's a margin on one particular manufacturing run, and you're one client amongst a huge order book. For most small companies at an early phase, every patient is the future of the company. I could see a CMDO becoming part of our network in the later stages, when things are a bit more established.

Regarding Derek's point about commercial scale and underestimating those needs, we've spent a couple of years implementing our own manufacturing. We've also made a real investment in IT systems, whether it's the chain of custody, chain of identity, electronic batch records, or electronic lab systems. This is something I would never have done in a prior life in an early stage biotech. Now, it's looking like a smart decision, because it takes years to do this. As an early stage company, if you do have access to the resources, then it makes sense to do these things much earlier than you would at any other biotechnology or pharmaceutical company.

> "CDMOs also play a big role in manufacturing key materials. A classic question is whether you should internalize or outsource manufacturing of vectors..."
>
> - **Emilie Gauthy**

Q How important are CMOs and CROs to manufacturing business models in the future, and do you expect to see the advanced therapies service sector continue to develop in step with the commercializing advanced therapy field?

EF: Even though we're seeing more manufacturers utilize in-house facilities or move towards in-house facilities, I think CMOs and CROs will continue to play a critical role in manufacturing cell and gene therapies in the future. Contract manufacturing capabilities need to continue to increase with

the market growth that we're anticipating, especially as more advanced therapies commercialize.

With market expansion and more commercial successes, my hope is that suppliers, including Roche CustomBiotech, will continue to innovate and provide advanced solutions that will be implemented at CMOs and CROs, and in-house facilities. This will allow for more standardization and advancement.

"Having standardized parts of the process helps everyone, including letting regulators understand us better."

- Derek Adams

EG: As mentioned earlier, at some point in moving towards commercialization you will need to multiply your manufacturing sites, both to increase your production capacity and to de-risk supply failures. When you go for commercialization, the demand for your product will not be completely predictable at the start. Seeing how companies will make use of CDMOs at that stage to deal with fluctuation will be interesting.

CDMOs also play a big role in manufacturing key materials. A classic question is whether you should internalize or outsource manufacturing of vectors, for instance. On the one hand, outsourcing might bring you new knowledge and expertise that would be costly to integrate. You need to create a strong partnership and collaborate with your CDMO to bring their production to the level of your commercial needs. Your partner will need to be ready to work on developing its infrastructure and intensifying its production.

On the other hand, this might become very binding, and you don't want to get stuck in a business position where you don't have alternatives and you rely on your CDMO's production availability. For this reason, keeping some internal production assets remains important.

DA: To build on what Evonne said about driving standardization, I think that's one of the biggest ways that partnerships with contractor manufacturers can help the industry.

A partner of ours at one of our CMOs said, "We want to get good at manufacturing everybody's secret grandma cookie recipe". That is where we are today, but part of what will help the industry and patients in the future is if we start to align on standards for processes that aren't necessary for being competitive. Many of us have been at conferences and heard the history of other biotechnology processes that have coalesced around some standards, such as monoclonal antibodies. Having standardized parts of the process helps everyone, including letting regulators understand us better. Contract manufacturers have a huge part to play in helping lay that groundwork and bringing early phase manufacturing and sponsors into a template that will help the whole industry move forward. We can't underestimate how much we need CDMOs to help us create standards.

GR: The future remains really bright for cell therapies – we've only begun to scratch the surface of how wonderful they can be.

Anybody that knows the autologous CAR T clinical data and commercialization stories of Kymriah® and Yescarta® knows that these therapies truly save lives. There may have been some challenges along the way, but they're just going to get better. As we understand the science more, I believe they can become curative, and will go on to affect many other types of cancer.

Solid tumors are a big challenge, but it's certainly a challenge worth undertaking. I believe we're going to get there, but I don't know

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how fast. For hematological malignancies, the effect of these therapies is going to become greater and greater, and the cost is going to become less as we learn and understand more. That means the demand is going to go up, and that's where CDMOs are going to come in, because I don't know if people can keep up internally. They'll want to, but having that capacity at your disposal will allow you to flex very quickly and meet the increasing demand.

Q How will the manufacturing model evolve with the ongoing emergence of allogeneic therapies, and their progress towards commercialization?

EG: The allogeneic manufacturing model will be quite different from the current design and infrastructure developed for autologous manufacturing. Allogeneic manufacturing will be much closer to classical manufacturing design, with continuous production and no planning based on patient apheresis schedules. Of course, de-risking of allogeneic therapies may still require multiplying manufacturing facilities, and CDMOs will likely play a big part in supporting the increasing demand.

However, new constraints are emerging, and could become real issues, as we aim to treat large indications with allogeneic therapies. The availability of the raw and starting materials comes to mind –the market for some key materials is already tense, so with the emergence of new allogeneic therapies, we may see a huge increase in demand that would put additional pressure on supplies. My fear is that this could become a critical problem if the costs start to rise, as materials are already a big part of the cost of the cell and gene therapies. This could ultimately jeopardize patient access to drugs if the cost becomes prohibitively high.

From a technology perspective, fill and finish technology will become a new constraint with allogeneic therapies. Finally, one point that we sometimes underestimate is the potential issues linked with the storage of a large amount of cryopreserved product. We need to consider who will manage them, and where. Will hospitals be able to provide these storage capacities?

GR: Scale up is a big challenge, as is the expandability of the cells. You want to make large enough batches to make this worthwhile – if it's only marginally better than autologous in terms of the number of doses you can make per batch, it's not going to be cost effective.

Then there is the cryopreservation challenge. Where are these products going to be stored? If they're going to be stored at the hospitals, do the hospitals have the infrastructure to store these, or can we build the infrastructure? If we do, how are we going to maintain and qualify it? Things are going to have to change somehow in order to accommodate that. The alternative is that you ship just in time, which is not quite as bad as an autologous because your product will always be ready, but it's a challenge in itself.

If we can get away from cryopreservation, even just to dry ice shipping, that would change things a lot. We could use minus 80

> "I predict that allogeneic therapies will eventually get there and will work. But it's a matter of time, and also a matter of cell quality."
>
> - **Greg Russotti**

freezers, or if you want to be more futuristic than that, perhaps freeze dried cells. That could be a huge game changer.

These challenges are not easy to overcome, but they can be overcome with time.

DA: For the autologous cell field, the allogeneic approach feels like both a threat and an opportunity. The amount of infrastructure the autologous world requires presents a lot of different challenges that allogeneic therapies don't necessarily have to tackle.

How long it will be before allogeneic takes over as the dominating technology is a question everybody has. What we know right now is that the autologous approaches are probably ahead, and most of the data seems to indicate they're doing amazing things for patients. For those of us who have to try to think about and predict the future, the allogeneic world does seem to fit much more with traditional models of making and distributing biopharmaceuticals. It has a lot of compelling features that make us think if we can only get there, we won't have to worry about the complexities of the autologous world. But right now, the autologous world is providing such great clinical benefits that there's still a need to invest in those as well.

GR: In addition to that, the autologous world is not just a little ahead, it's very far ahead. We know it works incredibly well, whereas the allogeneic space is completely unproven.

I predict that allogeneic therapies will eventually get there and will work. But it's a matter of time, and also a matter of cell quality. Not all allogeneic cells will be equal, and not all will work well. We know that not all autologous therapies are equal in the sense that some patients just can't produce cells that are good enough.

That's also why I think this field is still very promising, because as we move these hematological trials into earlier therapies, where patients and their cells are not as beaten up, they're likely going to work even better. For these reasons, there's going to be a place for both for a long time. Allogeneic therapies will work in certain cases for certain products, but autologous therapies are going to continue to work very well.

JL: In my mind there is a race – the operational development of autologous therapy as we get better at the execution of a complex supply chain, versus the developing science of allogeneic therapies.

Greg mentioned the point of earlier line therapies. When you're working on a therapy for a patient in second or third line of treatment who has failed everything, vein-to-vein time is critical. In an earlier line therapy, it may not be as important.

There is also the concept of 'off-the-shelf' autologous therapy: if you're a second line therapy you can collect the material initially, the patient can go on the first line therapy while you manufacture, then you have off-the-shelf autologous product available if that patient progresses.

This presents a business risk, but it has happened serendipitously in some of our trials. We've received a patient's material, made the cells, and then they're not ready for them. Later, they are ready for their cells and within a week they're being treated. This is a powerful mode of operation, although whether or not there's a business model that can support it is something to consider. Operationally, it was pretty exciting to have an investigator call us and ask for the patient's cells and be able to say yes, we have stability data, we have them in the freezer, and we'll send them to you tomorrow.

"as a biomanufacturer ... It's your absolute duty to monitor, measure, and mitigate risk, whenever possible."

- John Lunger

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Q Where do you see the sector's focus fall in terms of cost control moving forward, in both autologous and allogeneic setting?

JL: For material costs, we're getting there. With things like vectors, costs are coming down precipitously as yields get better, and as scale grows. I think vector will ultimately become a lower element event, not to mention that there are other gene transfer technologies which may do away with vector all together in the future.

Another component is the labor that's involved in manufacturing. Automation will help with this, as will different utilization of facilities. However, for larger markets in the autologous space we don't have an inventory to account for varying demand, so instead we have people. We consider it almost like a volunteer fireman position: you have to wait for the cells to come in, and you have to be there when they do. Once you have a higher volume of demand, that becomes a much higher utilization.

In these two areas as we get to more patient indications, costs will come down. Automation will come as we understand our processes better. So in this race between allogeneic and autologous therapies, if you look at the cost element, the gap will continue to close over time.

EF: As a supplier of critical raw materials, we can continue to create structures like master service agreements, or supply agreements, with CMOs or manufacturers to create tiered pricing structures that reduce costs of these materials for manufacturers. Commercialization will increase economies of scale for suppliers, and this will then reduce running costs.

GR: When you think about both allogeneic and autologous therapies and their raw materials we are considering cytokines, growth factors, some of the more expensive reagents, and disposables. Disposables might be tougher to drive down, just because the cost is the cost, but for reagents there could be opportunities to make those cheaper. Providers should be looking at ways to make materials affordable, because market demand is going to go up. This will be a big need in the allogeneic space in particular.

> "Continuing to keep these conversations open in order to enhance partnerships will allow the industry to grow together."
>
> - **Evonne Fearnot**

Q How are regulators influencing both manufacturing and commercial business model decision making? And how does the incorporation of risk-based approaches in much of the recent regulatory guidance play into these decisions?

EF: Both regulators and the addition of the risk-based approaches and newer guidances are driving centralized models, in my opinion. Regulators are interested

in quality and they inspect on quality. Additionally, regulatory compliance costs money to uphold quality and/or remediation. Again, this will influence companies towards choosing a centralized model.

Traditionally regulators will tell you their requirements, you will demonstrate you have met them, and you will be given approval. But with risk-based approaches, the manufacturer has to do lot more work up front to identify their procedures, their risks, and how they are going to control them, and then present that to the regulators. A centralized model makes it easier to create risk assessments and to create procedures to address those, as well as to create and retain records.

Q What are the key elements that every manufacturer needs to consider when approaching commercialization to in order manage risk and cost, and achieve sustainable commercial success?

EG: You should start thinking about what your commercial product manufacturing should look like, and what the easiest route towards commercialization would be, as early on in your product development as possible.

I strongly believe that building first on your in-house manufacturing is key to moving quickly through the initial stages and facilitating swifter implementation of process improvement. However, moving closer to commercialization, you need to ensure you bring the right partners and suppliers along with you.

Another key aspect is to secure raw materials with the right quality, and strong contracts that will ensure supply and avoid unpredictable costs. You need to identify the right alternatives to support fluctuation in your product demands, and address supply risk without impacting your product quality. This is not an easy task when dealing with cell-based products and very complex materials, so I would suggest starting with the most critical supplies using a risk-based approach. This will probably bring you to work with your suppliers to make sure they address your specific needs and support them to intensify their production. Finally, you should keep in mind that the ultimate goal is to secure the availability of your drugs to the patients who require them.

JL: The idea of an infrastructure for growth is important, particularly for personalized therapies, where a thousand patients equals a thousand batches. Invest early in things at scale –that's everything from training systems, electronic batch record systems, bar coding systems, to electronic environmental monitoring. Think of everything that you need for doing thousands of batches. Even in my history in small molecules we didn't do thousands of batches at a time, and we had huge systems. You have to be thinking about the infrastructure that you can scale, because it takes years to get that infrastructure in place.

GR: Invest early on in process characterization and assay characterization. The more you understand about the process and the product attributes, the better a job you can do at scaling up, scaling out, tech transfers, and more. It gives you more strength in the probability of success of these various things.

For assay characterization, make sure you have assays that are reliable early on. If you don't know what you're measuring, then nothing you do really matters.

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DA: To commercialize a therapy remember that you have to approach it with your eyes and your check book wide open. You have to have a lot of humility knowing you're going from amateur to professional status, and there's not a lot of wiggle room there.

There's a lot of speed in the early phases to get clinical data, and then the clinical data look amazing. But when you reach commercialization, there are more barriers that have to be surmounted. The clinical data may be awesome, but you need to be able to address the risks, and this is not something regulators have a sense of humor about.

EF: I would add that we should continue to focus on strong partnerships. I think that this goes beyond just CDMOs and therapeutic manufacturers and includes both regulators and suppliers. Continuing to keep these conversations open in order to enhance partnerships will allow the industry to grow together, and get to where it needs to be.

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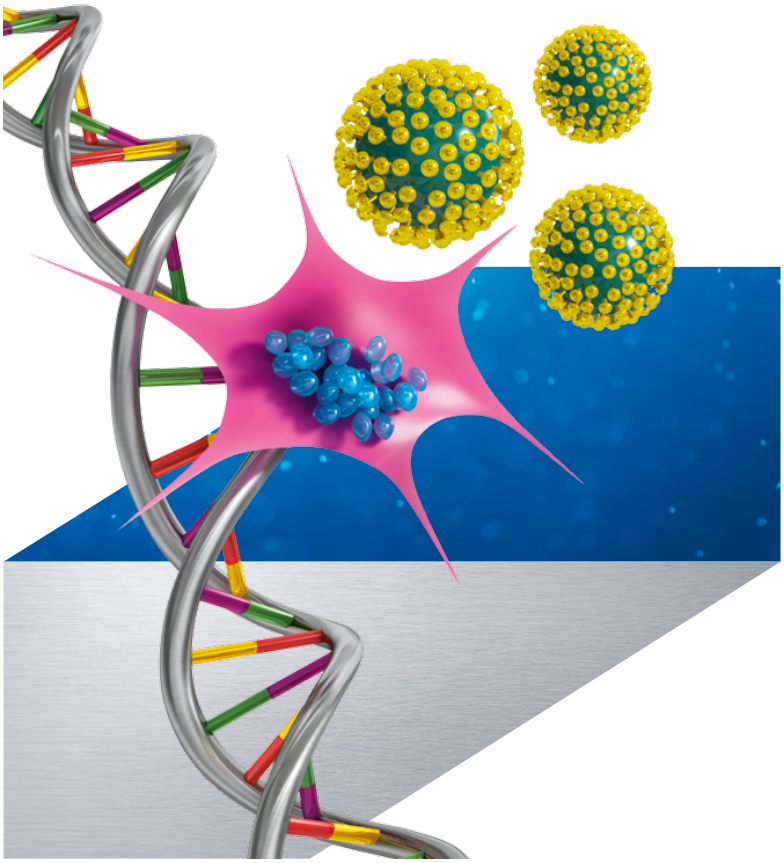

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*Armstrong SE, Mariano JA, Lundin DJ. The scope of mycoplasma contamination within the biopharmaceutical industry. *Biologicals*. 2010 Mar;38(2):211-3. https://www.ncbi.nlm.nih.gov/pubmed/20362237. Date accessed: Jan 11, 2017. **Data on file.

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Please contact your local CustomBiotech representative

United States
Phone +1 800 428 5433, ext. 14649 (toll-free)
Fax +1 317 521 4065
custombiotech.ussales@roche.com

Canada
Phone +1 450 686 7050
Fax +1 450 686 7012
custombiotech.can@roche.com

Roche Diagnostics Corporation
9115 Hague Road
Indianapolis, Indiana 46256

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SPOTLIGHT

EXPERT INSIGHT

Decentralized manufacturing: from stem cell transplants to the next generation of cellular immunotherapies

Matthew Li & Sadik Kassim

Cell and gene therapies are emerging as pillars of modern medicine. Yet, there remain significant challenges related to drug product manufacturing scale out, accessibility, and overall pricing of these potentially curative therapies. To date, drug developers have pursued more traditional models of centralized manufacturing to enable for the commercial scale out of approved cell and gene therapies. These traditional manufacturing models enable process and product control. The pursuit of a centralized manufacturing model for autologous personalized cell and gene therapies, however, could lead to significant complexity with respect to overall logistics and manufacturing costs. A more distributed model of manufacturing can potentially provide patients with faster access to drug product and lead to greater overall cost savings. A decentralized model, could however, also lead to significantly less process and product control for the drug developer. This brief article will examine the potential path that drug developers can pursue to enable decentralized manufacturing for commercial cell and gene therapies. Specifically, we discuss the existing stem cell transplant center infrastructure in the USA and how it may be leveraged to enable for a more decentralized model of manufacturing.

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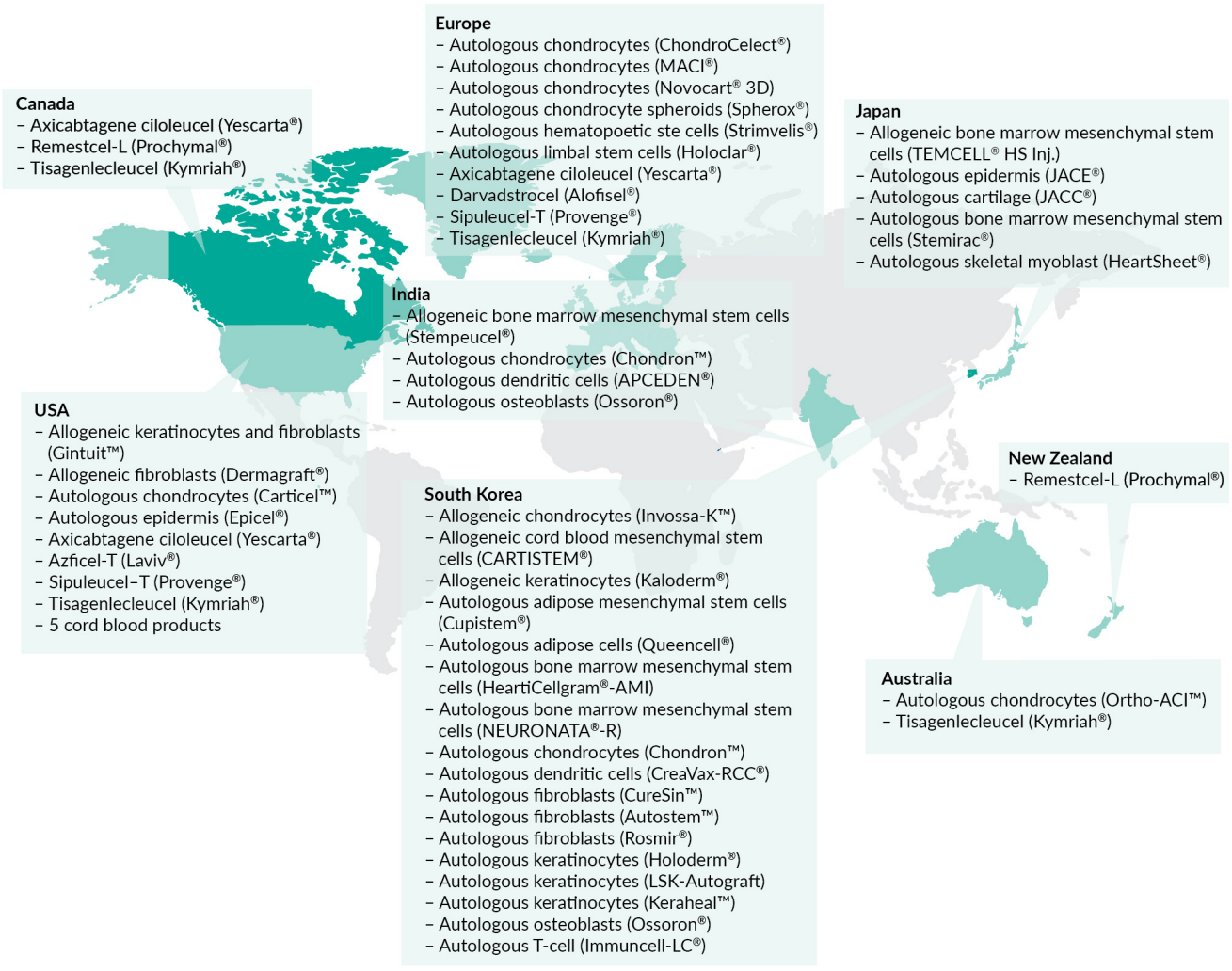
INTRODUCTION

Cell therapy drug development continues to expand into applications for a myriad of human disease. Figure 1 highlights the global, although highly concentrated, nature of approved cell therapy products. Note that this list also includes some tissue engineering products for which the primary products constituents are cells imbedded in a matrix. Interestingly, very few therapies have received intercontinental approval, and none have reached full global dissemination. Increased research efforts stemming from both academia and industry has driven a proportionate number of therapies into clinical trials. However, the conversion rate from late stage to regulatory approval is low compared to more mature pharmaceutical drug classes; specifically under 20% for cell and gene therapies compared to nearly 50% for more traditional drug products [1].

The clinical successes and commercial approval of Kymriah® and Yescarta® have led to a greater amount of drug development for potentially curative cell and gene therapies. Greater focus is now shifting towards critical problem solving and planning to ensure

FIGURE 1

Global approved cell therapy products.



Worldwide distribution of approved cell therapies demonstrates widespread, yet concentrated, adoption of cell-based therapies. Notably, intercontinental approval is severely limited and South America, Africa, and the majority of Asia lack any representation.

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improved manufacturability and increased patient access [2–5]. High cost of goods (COGs), cumbersome manufacturing processes, complicated logistics, and institutional overheads are innate to these first in class cell therapies [6]. Although an evolving fit for purpose ecosystem is now emerging for these advanced therapies, the tools and systems that surround their regulated clinical manufacturing are lackluster. From highly efficient unit operation tools that become entangled in a web of sterile welds, to elegant 'GMP in a box' solutions that prescribe solutions to ameliorate, and entrench users in technology for problems of the now with a limited runway to the future, through to enterprise IT solutions that tackle critical logistics problems for which actual root cause solutions may not be addressed. These problems are not new, nor surprising [7].

To enable sustainable manufacturing of these advanced therapies, the industry has focused significant efforts on the development of process instrumentation, analytical tools, and services. Significantly less effort has been placed in dissecting, understanding, and identifying the Achilles heel of various manufacturing modalities that will drive their success or failure. To date, nearly all successful cell therapies have originated from an academic institute and were subsequently licensed to commercial entities for late stage clinical development and commercialization [8,9]. To probe this model further, one can break down the current cell therapy process into major segments: donor, collection site, manufacturing site, and administration site, Figure 2. In a purely academic paradigm, all these components exist at roughly the same site which can enable streamlined operational logistics. Traditionally, the transition to a commercial entity results in the fragmentation of this workflow to provide greater control over the critical process development and eventual manufacturing of the drug product, Figure 2A. Other non-traditional models attempt to shift the clinical manufacturing back into distributed academic centers to leverage the simplified logistics and increased access to patients while still relying on commercial partners for late stage development expertise, Figure 2B. Towards a full academic ecosystem, increased capabilities of academic and clinical centers are now beginning to perform rudimentary in-house process development and minimize reliance on industry Figure 2C. It should be noted, however, there is still a clear knowledge gap in performing full DOE process development campaigns, quality by design (QBD), and commercial process control from academic entities. Perhaps it is of interest to somehow bridge this gap in order to ease the transition out of academia and into the commercial realm.

Interestingly, in the EU, the quickly evolving nature of these advanced therapies paired with the ability to provide rapid patient access is widely viewed as a challenge. To counteract this, the creation of a hospital exemption for ATMPs attempts to alleviate these issues and has the potential to pave the way for this pure academic model and enable clinical centers at large to develop and eventually market their own therapies [10,11]. However, the more likely *de facto* route will still require typical cGMP infrastructure and, as the name implies, this exemption stature is not applicable for any and all therapies. These models herein illustrate possible paradigms, however one can envision numerous paths beyond these three. In this article, we begin to address what it might take to enable non-traditional manufacturing modalities. First, however, we would like to clearly define what we mean by centralized and decentralized manufacturing.

Centralized manufacturing

The therapy provider is in control. From cold chain logistics, manufacturing, QA/QC, and release – the therapy provider establishes centralized geographic nodes to accomplish this. Additional costs associated with set-up, qualification & validation, and general overhead are absorbed as well. This model provides the most parental oversight with regards to the process and product and follows

FIGURE 2

Transition to commercial manufacturing.

Three manufacturing paradigms for cell and gene therapies originating from academic environments. **(A)** Traditional handoff from academic to commercial entities results in limited centralized commercial manufacturing sites; **(B)** hybrid model with handoff to commercial for process develop and industrialization purposes but further transfer back to academic sites for decentralization and increased patient access; and **(C)** academic to academic model where entities are enabled to develop and market without commercial partner intervention.

along the traditional biopharmaceutical model. In a similar vein to centralization are CMO/CDMO models [12]. However, these outsourced models provide less control due to non-parent company facilities and employees and a fee-for-service business model that puts

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various customers in direct competition for manufacturing slots.

Decentralized manufacturing

The therapy provider relinquishes some control for improved patient access and potential cost reductions. In the context of this article, decentralization is viewed from the enablement of a clinical/academic site to manufacture the cell therapy product (CTP). This ranges from driving every clinical site to perform such operations through to a centers of excellence model with a limited number of vetted sites at strategic geographic locations. There are clear and significant hurdles to enact such a model as we herein discuss. While still new and mainly relegated to ailments of high unmet need, the establishment of a regulated process by which clinical centers are empowered to develop, manufacture, treat, and even potentially market is exciting as in the case of emerging EU hospital exemptions.

Decentralized manufacturing of late stage clinical or marketed products has yet to become a reality. We herein make the case that perhaps implementation is closer than one may realize. For decades, practitioners have been safely and effectively implementing one of the earliest cell therapy processes at clinics across the world: hematopoietic stem cell transplantation.

DECENTRALIZED MANUFACTURING & HEMATOPOIETIC STEM CELL TRANSPLANTATION: CLOSER THAN WE THINK?

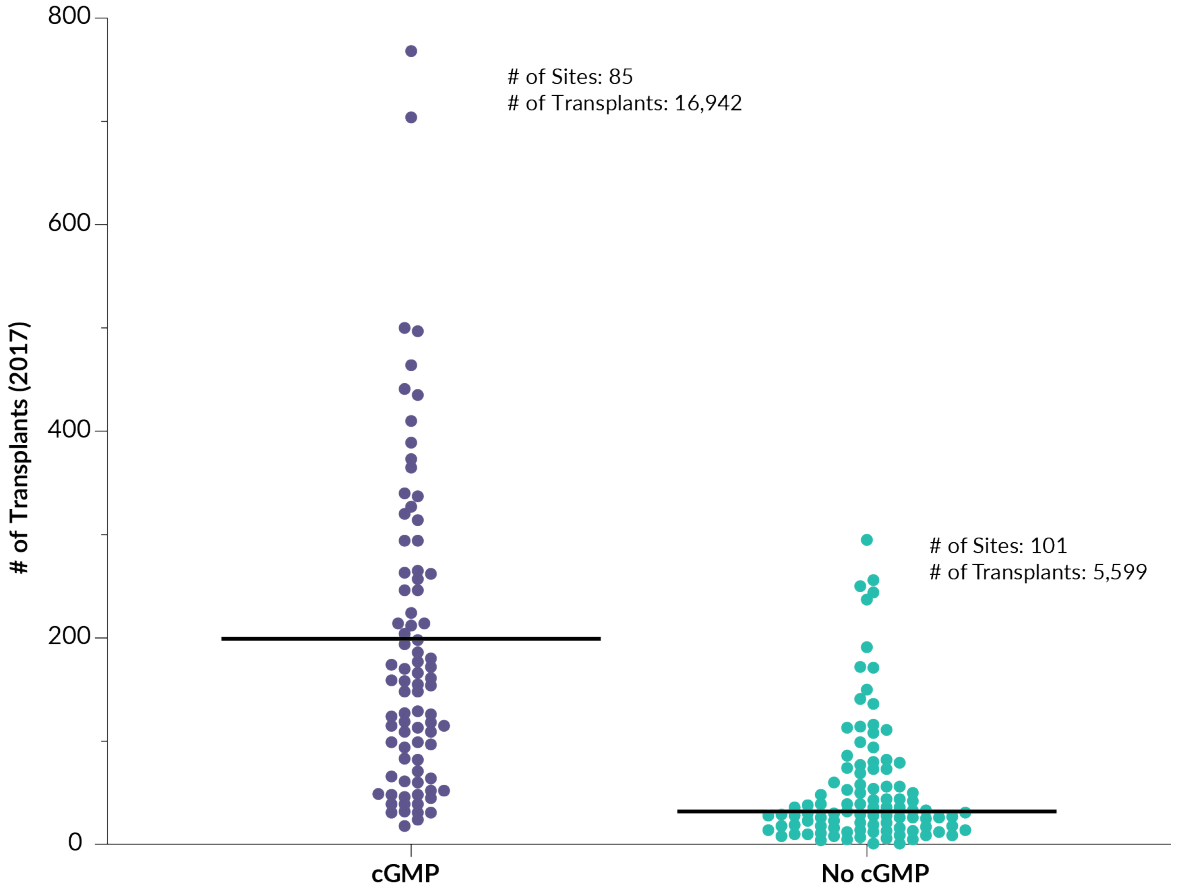
Hematopoietic stem cell transplantation (HSCT) is a cornerstone therapy for hematologic malignancies and can be considered one of the earliest proven cell therapies – predating modern immunotherapies by over half a century [13,14]. In principle, HSCT is elegant – reconstitute a primed patient marrow niche with healthy essential lymphoid and myeloid building blocks (HSCs). Autologous therapy enables the use of high dose induction regimes while allogeneic modalities provide curative potential from matched donor transplantation. While simple in concept, the patient journey is trying. Progression from induction therapy, to myeloablation, through to the graft transplantation itself results in a fragile patient. Risks of relapse, graft-versus-host disease (GvHD), graft failure, and/or opportunistic pathogens are prevalent [15,16]. While various experimental therapeutic regiments preceding and proceeding HSCT are still evolving, the process of cell retrieval, enrichment, and delivery back to the patient has more or less remain unchanged since its inception due to relative effectiveness and safety. To date, the subjectively largest advancement has been the delivery of specifically isolated $CD34^+$ cells and the development of automated companion technologies by companies such as Nexell/Baxter and Amcell/Miltenyi.

With decades of institutional knowledge, it should be of little surprise that many clinical centers with historically robust HSCT programs are at the cutting edge of providing next generation therapies. Data from the CIMBTR database shows that many high-volume transplant sites have enhanced cell processing capabilities that expand into early, phase appropriate (Ph1/2) cGMP capabilities for more advanced cell therapies, Figure 3. While all clinical transplant sites are FDA registered, it is not always apparent, from publicly available sources, whether affiliated cGMP resources for more advanced therapies are registered as well. cGMP compliance is sufficient for early phase trials, however the transition to commercial production necessitates full FDA compliance.

These sites are driving the growth of early proof of concept studies yet late stage through to commercial production and manufacturing has been largely untouched. Are there models for the field that can empower these institutions to provide improved patient access to a new era of lifesaving therapies?

FIGURE 3

Transplant sites with affiliated in network early phase cGMP facilities.



The number of transplants performed per site in 2017 (US) from 186 listed sites in the United States Health Resources & Services Administration database was segregated based on available public information on whether these centers were affiliated with an in-network entity with early, phase appropriate (Phase 1/2) cGMP capabilities for advanced cell therapies [17]. Clear separation is evident in which sites with a greater number of transplants per year have an increased access to cGMP capabilities. Note that centers with separately listed adults and pediatrics were combined. All NIH sites were also combined.

To take a step back, one needs to examine why a clinically oriented model of decentralized manufacturing makes sense; and within that context, how HSCT and emerging cell therapy cores have already laid foundational work.

Faster patient access

Novel cell therapies are presently relegated to last line status for safety and proof of concept evaluations. These new products are being slotted against the most stringent patient timelines where literal days can make the difference in saving a life. And against all odds, they are succeeding. A future exists in which these therapies evolve into frontline heavy hitters allowing for reduced time stressors – however, patients cannot afford to wait in the interim. Traditional centralized manufacturing of autologous therapies typically adds a minimum of 2 days for shipping to and from the clinic and manufacturing site. By retaining manufacturing at or near the treatment site – materials transport times can be drastically reduced and/or nearly removed. An additional consideration is the patient journey. Keeping patients closer to their preferred treatment center also reduces transit time to deliver therapies to patients while also reducing any added stress through potentially unnecessary travel to unfamiliar locations. This is far from blue sky territory.

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The acquisition, processing, delivery, and all tracking and record keeping between these steps is accomplished in the clinic already. On the extreme end, in minimally manipulated HSCT products, donor cells are transfused to the recipient within hours of harvest. There is clear infrastructural precedence with a proven historical track record.

Reduced critical starting materials mishandling

Shipment and delivery anxiety is commonplace today; the expectation that an order is to be delivered on time and in the desired condition is not always met. These concerns unfortunately still occur in the transportation of life saving treatments. For instance, the field of organ transplantation experiences delivery issues ranging from weather induced delays to materials forgotten on flights [18]. While typically less time critical than organ transplantation, cell therapy logistics are still vulnerable. To instill greater confidence in this critical materials movement step, shipping validation studies during development include metric assessments of temperature stability and drop tests [19]. While these measures are important to the eventual clinical execution, they can add significant time and costs to development. Simplifying or outright removing this potentially problematic materials movement step is one way to minimize concerns. This is again demonstrated at clinical centers of excellence that keep these critical materials proximal to the site of manufacturing. Even in the instances of minor mishaps, products can be recouped in a timelier manner. An added benefit to this is a reduction in overhead costs related to engaging shipping logistics coordinators.

Simplified manufacturing logistics

Cell stasis through cryopreservation is a pillar in biological and health sciences with the intent to keep an organism in its present state for a future date. In the context of autologous manufacturing, cryopreservation reduces the time stressors surrounding the processing and delivery of a fresh product. In cold chain logistics, the secondary intent is to minimize temperature fluctuations during transport wherein materials are held at stable cryogenic temperatures in controlled shipping vessels. These remedies are innately integrated into the traditional manufacturing models that require extended hold times and logistics. On the receiving end of cryopreservation is the thawing process which can be equally important [20]. While instruments are emerging that provide improved thawing consistency, they have not been widely adopted, hence these methods more less still remain an art. Both freezing and thawing processes can draw significant resources during the development phase with regards to evaluating temperature change profiles and instrument validation.

In addition to the logistics for freezing, thawing, and shipping are implications during manufacturing and drug product formulation. Cell viability loss to this process are typically expected beyond 10% but vary in severity depending on methods and formulations used [21–23]. Accordingly, overages in final product vessels and/or manufacturing schema are typically included to ensure that patient doses can be manufactured and delivered. The generation of enough, let alone excess cell product is not easily accomplished across all therapies and can become a pain point during the transition to clinical manufacturing. By potentially removing the need to cryopreserve the primary drug product, burden can be eliminated from equipment, materials, process development, and manufacturing.

It is clear that cryopreservation improves logistical control and is implemented quite early on in development [21]. However, there exist uncertainties around the biology of a fresh versus frozen product. Differences in *in vitro* phenotype and clinical activity have been reported, but not sufficiently so as to suggest that one method is significantly

superior to another [22,24–26]. At the moment, present day logistics continues defers to a frozen product inasmuch that a patient will confidently receive their treatment – whether or not a fresh product adds a significant therapeutic advantage over frozen is still be seen. Of note, secondary doses and retention samples may need to be cryopreserved due to their future use; hence qualification of these drug products, as compared to a fresh product, will be required for comparability. It should be noted that there is a benefit of cryopreservation from the patient journey perspective. Many times, the product is ready while the patient is not – thus a short term freezing, potentially at -80 °C, may help as a stopgap in timing differentials.

Single site failure risk alleviation

Centralization offers immense oversight and control. Consequently, disruption at central nodes is catastrophic to patients. Regulatory concerns at Lonza resulted in the voluntarily suspension of media production which impacted ongoing CAR-T trials in 2017 [27]. While not a drug product, this exemplified the impact of single source reliance in the cell and gene therapy space and increased awareness to supply chain concerns. More recently, Novartis built new manufacturing capacity in Switzerland to increase patient access in Europe [28]. While increased access aligns with the goals of decentralization, these new facilities indirectly alleviate single site failures as well. Unfortunately, this is not a viable path for most burgeoning companies as the setup and maintenance costs for commercial facilities can be staggering [28,29]. Timing is also critical as therapeutic success drives commercial demand – fundraising to build out production space is challenging without proof of product efficacy. The majority of early phase trial manufacturing is thus being performed at CDMOs with late stage clinical and commercial strategies being deferred till positive early stage readouts.

In a decentralized model, at the tradeoff of complete manufacturing oversight and process control, manufacturing risk becomes attenuated across the numerous network sites. Barring shared supply chain issues, these sites can operate autonomously from one another. This model may even enable the establishment of workstreams and protocols that allow these disparate sites to function as backups to one another. The clear challenge is the establishment and maintenance of such a robust network, and how to harmonize operational excellence. To date, an entity such as the Blood and Marrow Transplant Clinical Trials Network (BMTCTN) that has performed decentralized manufacturing for multicenter clinical trials may represent a paradigm to learn from.

Existing clinical infrastructure

Existing transplant centers and cGMP cell therapy cores have safely produced therapeutic material, saved lives, and will continue to do so for the foreseeable future. While typically viewed as less institutionally rigid than large commercial operations – these sites are still bound by strict guidelines and accreditations including: The Joint Commission, FACT, CMS & CLIA, and/or FDA Registration while under the purview of cGMP operations. The infrastructure and regulatory standards around producing these therapies does not significantly lessen with the scale of the operation. A major distinction regarding facilities coincides with the regulatory status period of the product, IND or BLA. The inflection point of a BLA requires sites to be FDA registered whereas anything preceding is just be cGMP compliant [9]. An additional nuance between early and late phase lies in the fact that instrumentation, materials, and consumables are not necessitated to be fully GMP compliant early on, testing and validation to ensure patient safety is sufficient. Qualifications such as ISO13485, ISO9001, 21CFR, etc. requirements are deferred till late stage. While the facilities themselves may be up to code, these details around the processes being performed may not be. It thus

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becomes important for developers to understand early on what runways exist from early through to late stage manufacturing with specific sites.

In addition to these operational standards of excellence, one cannot belittle the history of these sites. Physical space that is qualified and validated, personnel with institutional expert knowledge, existing quality management systems, and direct proximity and integration with an existing clinical care infrastructure are among the draws of leveraging such a system. However, these facilities are presently setup to accommodate the scales of academic and early clinical trials. The question of how to enable, further equip, and interface with these institutions still remains to be addressed. The EU is potentially setting the precedence of this through hospital exemptions which requires the purview of an exclusive medical practitioner, for specific custom-made products for an individual patient, all within the same EU member state. Although still in the development and implantation stage, it exemplifies intriguing solutions to improve patient access and enable centers at large.

Enabling clinical centers can accelerate & democratize patient access to cutting edge therapies

Patient access to new cutting-edge therapies is challenging [2]. This becomes exacerbated by constantly evolving science and toolkits which makes setting operational standards complicated. By enabling smaller, leaner, and more nimble manufacturing, entities can better adapt to the rapid changes and advancements that are innately occurring through R&D and manufacturing. Present day clinical practice bends to the whim of ever-evolving patient disease states and continued expansion of our knowledge towards informing prognostic and diagnostic decision making. To prescribe a rigid infrastructure on the creation and delivery of a therapy in these early days of personalized medicine inherently creates friction. Many clinical centers of excellence are already manufacturing a variety of cell therapies for clinical use which span a wide range of implementation needs including different raw materials and production scales. It is inherent in the workings of these institutes to be flexible and adaptable.

It is hard to dispute the potential benefits of decentralized manufacturing. However, significant implementation hurdles must be addressed in the near and long term for this to become a viable mode of operation rather than mere fiction. A key theme in this discussion is multi-disciplinary communication. By distributing responsibility at large, multiple key players must now closely align.

Support from operational clinical end use

Early and constant communication between the commercial entity and clinical manufacturer is critical. A simple preliminary question is whether clinical sites have the appetite to support late stage and/or commercial manufacturing. And beyond this desire, can this realistically be accomplished given physical, operational, regulatory, legal, and/or financial constraints? Can industry help to alleviate these hurdles or is there inherently insurmountable dissonance between these two parties at this time? This is by far the most critical stage to 'get right' and requires a significant amount of effort to not only figure how to merely achieve decentralized manufacturing, but how to get there together and sustainably.

Beyond establishing this collaborative infrastructure, thoughts on new tool design and manufacturing implementation models fall on deaf ears without input from clinical end users. The creation of next generation automated tools has the ability to accelerate the implementation of decentralization by improving operational consistency across sites. In this model, the therapy provider defines the general brackets for the critical quality attributes (CQAs) but must engage with tool developers and end users as a catalyst to drive

development and implementation. However, questions arise: do new tools enable more robust decentralization? Or do collective, decentralized entities enable more robust tools? At the core of this is a more fundamental question, how do implementers guarantee consistency across sites? This is a major question that continues to plague the field and is likely why decentralization is still more of a concept than a practice. Neither path is fundamentally wrong, however one might be more tumultuous than the other. The reality will only come into focus once we begin to venture down a path.

Toolkits

A catchall processing and analytical toolkit does not currently exist. It is not necessarily for a lack of tools, but rather it becomes an exercise for each institution to build out their portfolio á la carte, with understanding of how they might evolve with new science, what may need to get replaced, and/or what gaps exist. Processing instrumentation presently comes with a large variation in closed, open, manual, and automated operations. Presently, many manufacturing processes end up as an amalgamation of all the above. One major hurdle is interconnectivity – how can tools better talk to one another and facilitate improved automation, integration, and begin to remove layers of potential human error. As mentioned previously, this further facilitates decentralization at large through improved process harmonization. Efforts have been made through *de novo* systems ranging from the presently ubiquitous Miltenyi Prodigy® through to more nascent ventures like the Lonza Cocoon™, Adva Biotechnology Adva_X3®, and Ori Biotech. However, issues of reliability, future runways, and overall utility are present.

While processing tools advance, analytics in the manufacturing space is trailing. Currently cell counts, viability, flow cytometry, and PCR based readouts are commonplace. These methods, however, typically require significant manual handling that can lead to increased readout variability. The advent of tools that minimize error from manual steps, such as offerings from Chemometec and Accellix, are greatly welcomed. Secondary to these are bioprocessing inline process analytical technologies (PATs) that can measure parameters such as glucose, lactate, pH, and dissolved oxygen to allow for on the fly correction of culture conditions. While namely integrated with more standard stir tank reactor setups, the field is attempting to understand how to adapt these technologies with more cell therapy-centric architectures. In addition, powerful tools such as digital droplet PCR (ddPCR) and next generation sequencing (NGS) will enable a high level of analytical granularity, but at the moment are often expensive, time consuming, or require specific R&D efforts just to implement. Translating these tools and methods from the bench to a clinical manufacturing workflow and will become a pain point as an increasing number of personalized medicines and gene editing based therapies find their way into the clinic. Further knowledge and guidance on analytical validation and product controls towards commercial manufacturing is critical to fully empower these academic sites.

A challenge within this framework revolves regulatory filings. Typically, within an IND and future BLA context, a given manufacturing process is validated and filed with specific methods and bracketed with certain measurable parameters. For a product to be manufactured outside of these parameters – using different, but comparable methods and/or readouts – amendments must be made to filings indicating these changes and often with supporting data of comparability or superiority of the product. Arguably, changes such as process closure may not need to be supported with as comprehensive a dataset but amending documents may still need to be submitted. The bottom-line result is increased development costs with the potential for savings in the future.

To expect a heterogeneous set of clinical facilities to have the exact same pieces of

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equipment, methods, and infrastructure is a tall order. To accommodate for this, a regulatory filing party would likely have to bracket and validate multiple manufacturing processes with nuances ranging from different equipment through to various cell counting methods. Clearly this is an impractical and an unrealistic model. Understanding yet not addressing the inherent operational variance upfront only spells disaster down the road. A more strategic approach is the modest rollout of vetted sites with similar toolkits. By carefully selecting these starting entities, risks to patients and complications during tech transfer and adoption activities will be minimized. The early identification of these entities is beneficial such that development work can be tailored towards their tools and settings. A centralized forum of information sharing that leads to a common standard of tools and analytics would greatly streamline development and eventual implementation. While the National Cell Manufacturing Consortium exists, their voice is yet to truly make an impact. To such an end, perhaps the role of a commercial entity is to help catalyze these conversations and even begin to enable this development – from unifying sites with existing tools through to engaging tool developers to produce better systems with a clear line of site to a defined group of end users. In light of this need, perhaps a new type of company may arise that work as 'GMP brokers'; entities that aim to fill the gap between academia and large pharma through an interconnected network of manufacturing sites with affiliated supply chain and quality infrastructure.

Along the lines of information sharing lies in the actual operation of a network of sites. It will be of the utmost importance, from a life cycle management perspective, to allow for secured database, control charts, and IT sharing resources such that the joint learnings across all sites can be used to driver all players involved forwards. A robust framework is no small task and proper diligence in setting up a system will pay in dividends down in the future and critical and ongoing stability and success. To date, this is presently being solved for by entities such as Skyland Analytics. Their Skyland PIMS® system aims to provide a digital end-to-end solution for connecting process, product, and patient data management while furthering layering on analytics tools which will be critical for correlative, multi-site analyses.

Quality & regulatory gaps

Quality is critical to ensure patient safety. While working in a quality regulated environment can be cumbersome and confusing at times, the intent is to produce traceable, safe material that will bring benefit to the patients without any foreseeable risks. Both clinical centers of excellence and commercial entities are bound to operate under these stringent regulations. However, the range of implementation of procedures and systems can be quite varied including: facilities cleaning, gowning, instrument operation and maintenance, materials storage, and quality management systems (QMS) for example. To what extent variability can be tolerated requires much further scrutiny for any given product. For instance, it is likely that differences in gowning procedures are a nonissue, whereas harmonizing batch records and manufacturing operations across various QMS will be challenging. An added level of operational excellence exists through FDA registration. While all clinical HSCT must be registered, accompanying in network cGMP resources may not be, especially if located at a physically separate location. Phase appropriate cGMP guidelines are sufficient for early, Phase 1 and Phase 2 IND supporting clinical trials. However, approaching BLA territory necessitates FDA registration and governance (21 CFR Parts 200-299, 300-369, 600-680, 1270 and 1271) prior to commercial manufacturing. At present, it is likely that such institutions will have the expertise to execute on all these points in an efficient manner. In the best case, a commercial sponsor will likely be the guiding light towards execution. Stepping back, such an establishment may begin

to detract from the nimbleness and ingenuity imparted by early clinical trials. Will the inherent mentalities between academic and commercial create underlying dissonance in such a facility? Perhaps one model may be the guided establishment of commercial ready infrastructure while still operating under phase appropriate guidelines. Thus, early trials may still progress unburned by late stage regulatory while having a potential clear operating framework to streamline commercial intent.

In light of this, process validation through split donor runs and detection of process drift and shifts across sites becomes very challenging. Systems and procedures must be thought through and enacted prior to actually become widely disseminated. Depending on the cell therapy and manufacturing process at hand, split donor runs across numerous sites will not be possible due to highly limited starting material – new methodologies must be developed. From a materials perspective, it may be possible to create 'test' materials from highly characterized cell lines that serve as standardized controls; this clearly depends on what parameters are being examined of course and will very clearly deviate from potential intended biological function and readouts. From a logistics perspective, an associative property model, with strongly powered statistics, may be utilized. For instance, Site A and Site B may be vetted with one set of limited materials, then Site B and Site C with another. If Site C falls within some determined statistical range from assessing validation runs across A vs. B and B vs. C, then by an associative property, A could be compared to C and thus all 3 sites could potentially be considered within acceptable tolerances. Given the cell number limitations on starting material, implementation of split donor runs may change as the field progress. A fixed number of runs at each site, with disparate donors, that meet a predetermined set of criteria may eventually be sufficient.

Furthermore, the lack of FDA guidance with respect to the combination of new therapies, instrumentation, and manufacturing paradigms is challenging. While HSCT is time tested, it is regulated as a tissue/cell based product (HCT/P; 21 CFR 1271) and not a biologics drug product as precedented by commercial CAR-Ts (21 CFR 601/610) [30–33]. Transference of infrastructure will thus not be one to one and the gaps must be more clearly understood and addressed. For instance, allowance for specific manufacturing room classifications (i.e., ISO) for a given product in minimal or beyond minimal manipulation contexts. Will new automated and closed processing technology blur the lines further? And to that end, what compliance checkpoints will be enacted to ensure and pressure test safety in a future decentralized setting? It is likely that feasibility data will need to be generated in early phase trials and that regulators, therapy providers, and manufacturing institutes will be required to work hand in hand as the field evolves.

Additionally, testing for incoming raw materials is required for commercial products; this includes materials such as excipients, critical analytical reagents, control cell lines, etc. While sound in concept, many times reference controls simply do not exist in the realm of cell therapies – especially around potency assays in the math that may be attributed to dose calculations. It may likely fall on the sponsor to provide methods and tools, where existent, to support such methods. It is unlikely that clinical centers have the breadth and knowledge to cover the wide myriad of materials and methods for all current and potential pending cell therapies. An ideal scenario would be efforts made in standardization in the field at large – one can easily imagine sites being overwhelmed by an untenable scenario of continually growing needs on a sponsor to sponsor basis without the ability to leverage and streamline similar workstreams.

Product release

Underpinning these nuances is the release of the drug product – who is liable for the

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success or failure to treat a patient? Proper harmonization across sites minimizes unexpected variability and manufacturing deviations. To that end, does a future exist in which each site able to release products autonomously? Or will the commercial entity still require qualified personnel to have the final sign off? While autonomy makes for less work, the true reality is that to maintain levels of control, there is likely to be a centralized method of batch record review through to sign off that the commercial entity still controls. This does not necessarily arise due to a lack of trust, but more so due to the legality of treating patients. Unfortunately, this begins to complicate decentralization as it still necessitates centralized overhead which detracts from lean and streamlined operations. At present, the BLA owner is responsible for the final commercial product. Who is actually responsible for the activities that contribute to this needs to be determined within any given product, but the end liability falls on the parental entity. Control is at the heart of this matter. Process and product control must be demonstrated every day to ensure a quality product is consistently released. To coordinate activities to align quality regulations, process control testing and implementation, is nothing short of a herculean effort – however not impossible. Alignment and openness between therapy providers, clinical sites, and regulators will be critical to realizing decentralization in this current form.

Challenges from a CMC regulatory filing perspective revolve around potential processes that are can be difficult to validate (typically those arising from an academic setting). CMC packages revolve around the ability to demonstrate sponsor control over their product and are often laden with quantitative support from process and assay development through to full scale clinical engineering runs and beyond [34,35]. Ideally, lessons learned from manufacturing in industry can be passed along during these partnerships such that early clinical trials can be better imbued with a more commercially viable manufacturing processes and associated qualification assays. This early upfront investment will greatly accelerate access to patients by easing the transition to commercial manufacturing.

Costs

Decentralization improves patient access to life saving therapies. The other fundamental intent is to reduce overall manufacturing costs which can enable more financially accessible products. The theory behind cost reduction is, as mentioned previously, leveraging of internal clinical resources and services and simplification of shipment logistics. From a purely academic clinical operations viewpoint, this is logical. As a commercial entity, the reduction can additively come from removing dollars spent during both development and validation phases as well. However, logistical improvements do not necessarily equate to total cost savings:

Incentives

The ability for a commercial entity to enter a clinical space and require on demand access to facilities and resources for clinical phases through to commercial manufacturing in the face of a numerous other ongoing internal workflows is unlikely. The precedence of paying for dedicated space exists and is a guaranteed way to ensure consistent access [36]. While commercial entities may not have to fund entire buildings, the upfront cost of paying for space (buildouts or rentals), equipping them, and covering any dedicated FTE time begins to curtail any initial perceived savings.

True costs

Internal leveraging of shared resources is an attractive way to reduce costs as the entirety of certain charges become split across various avenues. Comparing a dollar for dollar value to standard internal centralized or CDMO models makes this appealing. However,

academic and clinical sites operate in such a manner that indirect overhead charges average roughly 60% with outliers on the high end nearing nearly 100% [37]. Thus, while direct costs may be comparable or at a discount to other modalities, the inclusion indirect costs significantly increases pricing.

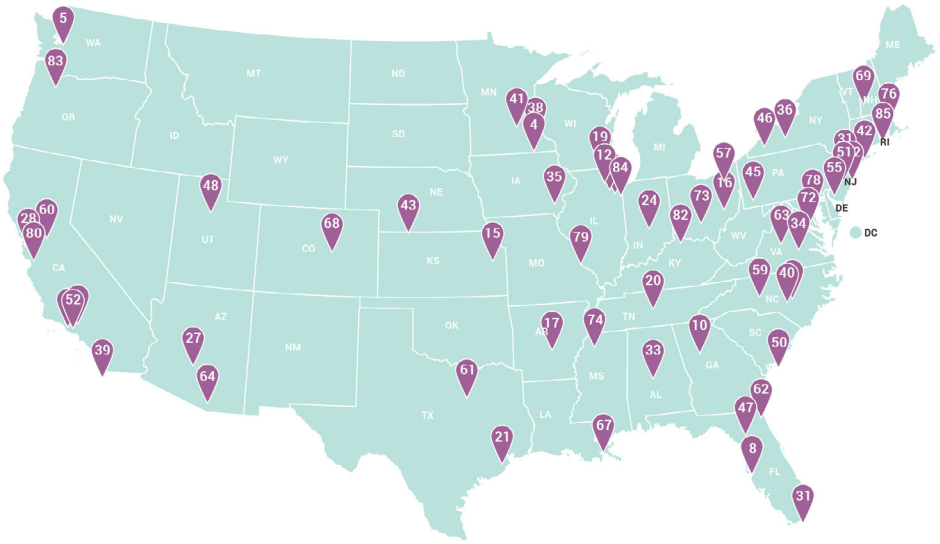
Increased scrutiny into the financial realities of implementing a decentralized model is direly needed. Until real numeric values are in hand, any conclusions are just speculation. Given that current CAR-T therapies are perceived as expensive, a critical public lens has been put into the pricing of cell therapies. Unjustified and further financially inaccessible drugs should be hedged off early.

Reach

Decentralization claims to drive increased access to patients, and in many geographic locations, this can be true. However, several factors play into this. In the USA, competing financial interest at clinical sites means that dollars are lost to one site if a patient is referred to another. Thus, unless a new particular therapy evolves into the standard of care or if a patient requires a specific therapy provided at only a limited number of sites, there is less incentive to direct patients to outside institutes. Compounding this is the heterogenous spread of clinical sites with associated cGMP capabilities. Building off the sites in Figure 1, Figure 4 shows the geographic distribution within the USA. It is instantly clear that the reach of these sites is insufficient to entirely cover the country and that areas on the East Coast and certain portions of California are disproportionately dense. To enable a broader access, more traditional HSCT will need be enabled. Additionally, the possibility of a decentralized private network of cGMP entities may be a potential model. While large C(D)MO presently exist, perhaps small offshoots abutting clinical centers are a viable path forward. From an enablement standpoint, models of cGMP leased space may be an enticing route to allow parent companies to maintain control without needing to internally setup costly manufacturing infrastructure.

FIGURE 4

Distribution of clinical transplant sites with in-network early, phase appropriate cGMP capabilities in the United States.



While covering the majority of the United States, it is clear that highly concentrated and completely desolate areas exist. It is apparent that theoretical widespread dissemination through clinical sites may not be readily possible with presently enabled sites.

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TRANSLATIONAL INSIGHT: SO WHAT?

Decentralization is often discussed yet little traction has been demonstrated. It is clear that there are significant hurdles without clear answers which make counting on success precarious. Looking beyond the often-myopic view of a singular company or therapy – what could a step in this direction mean for the field at large?

Immunotherapies

While this focus has been on leveraging the HSCT history, the clear behemoth in the field is immunotherapy – typically within the CAR-T domain. As previously noted, the only two commercial CAR-T therapies are struggling to bring back monetary value to their parent companies – even while new commercial centralized GMP facilities are being acquired or built. More so, these life-saving therapies are already beginning to look tired as the next wave of innovation is already emerging from clinical academic centers and smaller companies. The vast majority of cGMP enabled sites in Figure 3 are equipped to produce CAR-T therapies already. Expanding and bolstering decentralized manufacturing means better therapies will get to patients faster while democratizing the field away from multibillion-dollar entities controlling the commercial realm.

Personalized medicine

In addition to the field of immunotherapy arises personalized medicines in which therapies are specifically tailored to a singular patient. As we are further able to delve into the 'omics' era, patients can be more finely distinguished from one another and greater pathologic heterogeneity is becoming more appreciated. A reality exists wherein therapies can be tailored to the phenotype of a specific individual and move beyond a one size fits all approach. Including the immunotherapy realm, this may begin to enter the ecosphere of differentiated stem cells, regenerative medicine, and even gene therapy where the scale of these workstreams will more closely align with autologous therapies and have the potential to thus benefit from the establishment of such an infrastructure.

Changing business models

A shift to decentralization may also drive changes in the business model for therapy providers. With manufacturing accomplished elsewhere, companies may become more of an internal intellectual property generator and external reagents and consumables kit provider. Kitting has the ability to enable more consistent manufacturing by providing all needed components in a succinctly packaged manner to better fit into a clinical manufacturing workstream. This will allow companies to parse down to the essentials of science creation and critical materials provision.

Centralized manufacturing

A world in which both decentralized and centralized modalities exists. A hybrid model may be necessary where centers of excellence cover a finite geographic area and smaller company owned centralized site(s) are needed to address regions beyond the scope of these other clinical sites as indicated by the gaps in Figure 4. This model clearly detracts from faster patient access and reduced costs for these non-decentralized supported sites but may be a necessity in the interim until enough centers of excellence are established or tools have advanced to sufficiently disseminate a 'GMP in a box' solution that can be readily adopted at large.

Significant efforts in the 'off the shelf' allogeneic space also allude to changes in business models where centralized manufacturing, more akin to traditional pharma, makes the most sense. In these allogeneic therapies, the production of large, homogenous batches

removes the personalized medicine aspect and becomes business as usual in the lot production of biopharmaceuticals for patients. The concurrent existence of a decentralized model may even offload manufacturing burdens in the portfolio of these companies wherein personalized medicines may be manufactured in a decentralized model and bulk allogeneic products can be manufactured centrally.

We are clearly living in an exciting time where the possibility for developing curative cell and gene therapies seems limitless. The ability to decentralize manufacturing of these therapies will enable greater access to financially affordable therapies for patients. Rather than proceed with a traditional biopharmaceutical model of commercial scale out for these therapies, it may be of use to further evaluate the present landscape of alternative manufacturing models, such as HSCT, and to enable new paradigms that will lead to broader access and affordability for patients.

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AFFILIATIONS

Matthew Li
Senior Scientist
Vor Biopharma

Sadik Kassim
Chief Technology Officer
Vor Biopharma

AUTHORSHIP & CONFLICT OF INTEREST

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CELL & GENE THERAPY INSIGHTS

IMMUNO-ONCOLOGY: MANUFACTURING & COMMERCIAL BUSINESS MODELS FOR THE NEW DECADE

SPOTLIGHT

INNOVATOR INSIGHT

Simplifying GMP CART and CAR NK cell therapy manufacturing processes

Sarah Dluczek, Kate Fynes, Stephan Fricke, Ulrike Köhl, Martha Elia Luevano Salinas & Xiuyan Wang

There are currently around 550 active clinical trials utilizing CAR T cells. The industry is growing by as much as 37.5%, according to recent reports, and in terms of investment, almost $975 million has been spent. Two therapies are now approved, with more set to follow. Almost half of all clinical trials that were initiated in 2019 have a sponsor or involve collaborations, illustrating the importance of collaboration to this field: industry, academia and small biotechnology companies all have a role to play. But even as this dynamic field sees such promising growth and investment, questions remain over what the future of cell therapy manufacture will look like. There are emerging trends which provide clues – for example, the increasing use of allogeneic cell sources as off-the-shelf drugs are developed. This is being seen not only in CAR T cells but also in natural killer (NK) cells and even in macrophages. Switch receptors and control receptors are also areas seeing further development, and CARs are being developed that secrete a range of cytokines and enzymes, enabling them to migrate to different locations within tissues and tumors. Combination therapies may also prove to be key to the further success of the field. However, cell therapies differ greatly from small molecules and other drugs, and the way they are manufactured is complex and involves a variety of steps. Especially when using manual manufacturing systems, a lot of risk is introduced. This increases cost, as skilled staff and stringent manufacturing conditions are required. Concerns over manufacturing challenges associated with cell therapies, such as product shortages/delays that could threaten growth and directly impact the length of time to market, are growing within the industry. In this roundtable, six cell manufacture experts discuss the progress towards standardized and fully automated generation of gene modified CART and CAR NK cells – and address the remaining obstacles.

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Q What are some of the main differences and similarities in working with CAR T versus CAR NK cells?

SF: The biological and functional differences between NK cells and T cells ultimately have a significant influence on the production and manufacturing processes. Aside from this, the main differences between CAR NK and CAR T cells are in the selection process; T cells need a CD3 selection, and the NK cells first need a CD3 depletion and then a CD56 selection, in order to remove the NKT cells. The stimulation processes are also different in T and NK cells. T cells need beads for stimulation, while NK cells need cytokines like IL-2, IL-15, and IL-21.

We also have different time points for transduction processes. Where normally CAR T cells are transduced at the beginning of the process, NK cells are normally more efficiently transduced in later cultivation stages; day 8 is a very important point.

Next, there is influence of cryopreservation. When working with CAR NK cells, they normally have to be re-cultivated after they are cryopreserved, whereas when you work with apheresis material in CAR T cells, you can go immediately into the manufacturing process.

When you look at apheresis material and CAR NK cells, you have to keep in mind the role of impurities. That's a very important point when you work with feeder cells for instance, or if you have T cell impurities in your final product. Occurrences of side effects after transfusion into patients, such as graft-vs-host disease, may be higher than when you work with autologous CAR T cells. The role of pre-treatment and cultivation procedures will have a great impact on the fitness of the cells.

The cultivation times between CAR NK and CAR T cells are also different. Normally, CAR T cells are ready for use a little bit earlier than the CAR NK cells, and the in-process controls in the CAR T process are better developed than in the CAR NK process.

Q What are the key considerations and best practices in transitioning from open manual to closed automated bioprocessing in this particular therapeutic technology field?

> "When you look at apheresis material and CAR NK cells, you have to keep in mind the role of impurities."

KF: As a field we certainly need to see a shift in our approach to manufacturing. We need to move away from the manual open processing steps that we often associate with the early academic processes. These often include many open manual steps which can have quite long, complex protocols and expensive clean room requirements. Often many different pieces of equipment are required, along with skilled operators and extensive operator training requirements. A shift towards automated closed systems will reduce manual handling and contamination. Increased reproducibility in simplified tech transfer should be another goal – all of these changes are

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ultimately going to allow us to reduce cost of goods and improve patient access to cell and gene therapies.

In terms of best practices, you need to ensure that you know your product. You must fully understand the critical quality attributes, so that as you are making these changes, you are able to accurately predict and control how they are affecting both your cells and ultimately your product. You also want to make the changes as early as possible in the development process.

Engage with regulators early, and evaluate as many of the pieces of kit that are out there for automation as you are able. Ensure that your chosen process or your chosen equipment is fit for your specific purpose.

> "We need to move away from the manual open processing steps that we often associate with the early academic processes."

XW: This is something we're struggling with almost every day, especially in the academic setting, where we need to consider the upfront costs of a large instrument. There are so many challenges, starting from your supply chain. It's important to talk about whether it's the right decision to incorporate automation into your system.

Understanding the process is key – as is estimating the scalability of the process, and having staff members properly trained. For us, if we transition from an open process to a closed system, we need to first understand whether the supply chain could pose an issue. Not every reagent you use in an open process can be readily transferred into a closed system. For example, Dynabeads®, versus TransAct™ beads: you may have to choose one if you decide to use a different platform, and change of the manufacturing platform may require additional testing.

You must also have a plan for quality control – if you change from a manual process to automation, how easy will sampling be? At which point do you want to sample? Maybe your sampling plan will be a lot simpler if it's a closed automated system. The batch record is also a big part of the transition. If it's automated, there is in-line recording, so this may also make documentation easier. How easy you want it to be, and how much control you want to have during this transition period, are other important questions to consider.

UK: At Fraunhofer, we have a lot of experience with manual as well as semi-automated CART cell manufacturing. It is a lot of work, but on the other hand, if you have a very well-trained team, it also saves time and works very well.

I clearly see an advantage in using closed and automated systems like the CliniMACS Prodigy®, but for me it is not the end of the story. Right now, we are only talking about two types of disease treated with licensed CAR T cell products as well as a limited number of patients – either an automated or a manual process is possible here.

What is missing in the development of automated processes is AI-mediated digitalization for triggering the automation that we would need for hundreds of patients in parallel. This is of major importance if we want to address tumors, and not just leukemia and lymphoma.

We need to start with robotics and digitalization right now – and that is not just about the manufacturing process. The same question arises regarding complex quality control. These processes have to be automated and digitized so that everything, including documentation, is contained within an automated system. This is necessary to avoid mistakes.

Q What is the current technological state of the art in in-process controls (IPCs) and quality control (QC)?

MELS: Part of my job is listening to the requests and wishes of the field, and I think one of the main things I have been hearing in the last year concerns these IPC/QCs.

Taking a global perspective, the main issue is it is not harmonized. You can have different requirements when producing CAR T cells in Germany compared to the USA, or in China compared to South Korea. Now that we have multinational companies working in this area this is the beginning of a big challenge.

Regarding technology, I agree with Ulrike that we need to be looking into automated, autonomous robotics. There is a lot of potential to utilize block chain technology to transfer data and make it transparent. Artificial intelligence (AI) is already here, and we are seeing advances in big data analysis and digital platforms. However, in my experience even though some companies may already have the tools available, there is some skepticism and reluctance in the field to make everything connected and available – although I do believe this is where we are going.

We need to embrace it more, and address any concerns people may have about this technology. Especially for IPC/QC the potential is significant – I envision that at some point we could have automated sampling for which you don't even need a person to go into the GMP room. The sample could be taken automatically for you and transferred automatically into MACSQuant® Analyzer, for example. A robot could essentially perform the analysis and send you the results.

UK: It is understandable that people are cautious, because IPC/QC is not only focused on flow cytometric controls, but on a broad range of tests. We need an intelligent system – one that is flexible, modular and automated, that allows different manufacturers worldwide to use their own systems. Martha mentioned the MACSQuant® platform (Miltenyi Biotec) for the flow cytometric side, but there are other similar platforms here as from BD for example.

> "There are so many challenges, starting from your supply chain. It's important to talk about whether it's the right decision to incorporate automation into your system."

For a successful intelligent modular system, there must be interfaces between different devices. In the past, it has been difficult to set international standards for accreditation and validation in QC, and to have such a system work the needs of different manufacturing sites throughout different countries will have to be considered. In my opinion, this will not be easy.

XW: Another question I'd like to raise is the issue of scale out. For example, if we are trying to create allogeneic procedures and we are using a scale out approach, we're going to have many devices. What is the best approach to taking samples – do we sample from each device to show they are comparable, or do we choose one of them as the read out for all?

Further, how do we know instruments and other devices being used are compatible? We often see a lack of standardization in testing. To go a step further, are we

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happy with the surrogate readout of just the transduction efficiency of the CAR T expression or the CAR expression on NK cells as a release criteria?

We are also seeing people within the field report a two-day manufacturing process for CAR T cells – which does not allow enough time for the CAR to express on the surface. This highlights on obvious need for QC to be reconsidered.

> "We need to start with robotics and digitalization right now..."

UK: If you change to a two or three day manufacturing protocol, then you must also change the IPCC/QC procedures, because if you work with the normal lentiviral platform it's currently not possible from the regulatory side to give that product directly to a patient.

If you change the system you're using to a gene editing platform or use transposon sleeping beauty technology, then you can use that sharpened manufacturing protocol, because then it's clear when you have the CAR expression already in place. This is another kind of IPC/QC, in my opinion.

In terms of harmonization, the whole IPC/QC system needs to be modular. There is a variety of manufacturing protocols, both long and short, and differing transduction and even transfection systems, and so on. In a modular system, harmonization is possible because the minimum criteria can be the same for nearly everybody, and then you can add on the specific IPC/QC for your respective system.

Q What specific areas should be prioritized in the quest for standardization?

SF: When we look at the manufacturing process, we can start with leukapheresis, for instance. The time point of leukapheresis is very important, as is pre-treatment of patients. We do not have enough data concerning how the pre-treatment of patients influences the NK cell or T cell fitness, for example, and we should look more closely at when leukapheresis should be done.

Next, the selection processes could be standardized. What kind of cytokines and beads we should use, and so on. There are different protocols in the USA and in Europe – we also talked about harmonization, so is what we do in these different areas truly comparable?

Ulrike also mentioned transduction methods. We have the retroviral methods and lentiviral transduction methods, and the sleeping beauty, but what about CRISPR CAS technology, for instance? We do not talk about it, but it is probably more able to be used in a standardized way.

The expansion is very important and there are a lot of different protocols: cytokines, combinations, IL-2, IL-15 and IL-21, but nobody knows the exact time points. We also need to standardize formulation and cryopreservation. There are protocols with 5% dimethyl sulfoxide, or 10% or 7.5%. Nobody knows the "right" way to formulate the final product. When we look at the clinical side, there are a lot of chemotherapy protocols before infusion of our final product, which also have a great impact on the functionality.

The last point I would mention is that we have no standardized functional test assays to compare how effective our product is. Maybe we have the wrong functional tests. When we say the produced cells are functional, they may in fact be less functional if we use another test system – or possibly not functional at all.

There are a lot of points to be addressed where we could all work together to get the best results.

Q Turning to in-line analytical tools, what is the current state of the art, and where do you hope to see further innovation in this regard?

SD: In the field of analytical tools, there are standard tools such as automated cell counting, pH or dissolved oxygen. They directly measure one distinct parameter, but not all of these tools are firmly established and possible for use in in-line probes.

On the other hand, there are several powerful non-destructive in-line tools on the market, or under investigation, that use surrogate measurements. These include for example Raman, infra-red or fluorescent spectroscopy, and the procedure is the same for all of them. You collect data, and use it in a preliminary study together with manually measured data to create a multivariate model.

In this way, you can predict parameters that cannot be measured directly with the respective technology, for example glucose concentration. This means that with in-line probes, and a suitable multivariate model or algorithms within software, you can monitor interesting parameters without sampling.

In my view, in-line measurements would especially benefit critical process steps like thawing, or harvesting, or even cell collection. They would also be useful for the time consuming cultivation steps, and then you can utilize adaptive process strategies such as automated feeding.

Q How do starting materials affect the automation picture – and what are the strategies for measuring or minimizing this impact?

> "...in-line measurements would especially benefit critical process steps like thawing, or harvesting, or even cell collection."

KF: I think this question is affecting nearly everyone in the field at the moment. The problem is that we still aren't sure what qualities in the apheresis are going to make an effective high-quality product. We need to be retrospective and make sure we are compiling historical analysis; looking at which products in the clinic have a good clinical outcome, and performing tracing studies to see what the attributes of the apheresis were.

Validation is another really interesting aspect to consider. There are of course ethical considerations when using

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patient material for validation, and you often need large volumes of cells. If you need to use healthy donor tissue to validate your process, it's important to understand the differences between the patient samples and that healthy tissue. The problem you may encounter is that you are setting quite a high bar for your release criteria. We've heard from Novartis and other companies that a drug product is sometimes not meeting those release criteria, but then goes on to work well when it is infused into the patient. We have to make sure that the release criteria are realistic and take into account these differences between donor and patient material.

> "Taking a global perspective, the main issue is it is not harmonized."

Q What does the cell factory of the future look like, and where do you see the remaining obstacles to its realization?

SD: The cell factory of the future will definitely include automated and modular process plans, which are digitally controlled in some way. The modules should be flexible and connectible to adapt different processes, and AI-based robotics could be used to minimize manual steps. At points where manual steps are still included, virtual or augmented reality could be used as a guide.

As already discussed, an important point is also automated documentation. All process steps should be monitored, and this can be summarized in electronic batch records over the whole lifecycle of the product. This could facilitate and speed up the release in the end.

XW: What Ulrike just discussed is definitely my dream – and I suspect the dream of everyone in cell manufacture. My personal experience is that sometimes when we go towards automation, the instruments bring their own risks. I would like to see the handling/trouble-shooting of an instrument as simple as possible, and real time autonomic data generation/communication. It is a lot of pressure for people working on an expensive and important product. Therefore the simpler the design of the instrument, the better. Of course, we're talking about complicated procedures, but this would be my dream – making these complicated processes as simple as possible.

KF: Short term, I would like to see a better understanding of the properties of our cells and our drug products. This is likely to require better analytical testing, and perhaps a move towards functional systems that allow us to understand our CQAs better. Ultimately we'll be able to control these properties better and keep improving our systems once we understand them more.

Further into the future, it would be interesting to think about treating patients vein-to-vein at the bedside, but this is quite far away I suspect.

MELS: I want to work towards connectivity everywhere, by utilizing artificial intelligence, the cloud, and digital connectivity of all kinds. Ultimately the goal is to minimize the amount of risk as much as we possibly can when manufacturing these precious samples.

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AFFILIATION

Sarah Dluczek
Technical Leader, GMP Process Development, Fraunhofer Institute for Cell Therapy and Immunology

Kate Fynes
Investigator, Process Development – Cell and Gene Therapy Platform, GlaxoSmithKline

Stephan Fricke
Head of GMP Process Development, Fraunhofer Institute for Cell Therapy and Immunology

Ulrike Köhl
Director, Fraunhofer Institute for Cell Therapy and Immunology

Martha Elia Luevano Salinas
Global Product Manager, Group Leader, Immunology Engineered Cells

Xiuyan Wang
Associate Director, Michael G. Harris Cell Therapy & Cell Engineering Facility, Memorial Sloan Kettering Cancer Center

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Miltenyi Biotec B.V. & Co. KG | Friedrich-Ebert-Straße 68 | 51429 Bergisch Gladbach | Germany
Phone +49 2204 8306-0 | Fax +49 2204 85197 | macsde@miltenyi.com | **www.miltenyibiotec.com**

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SPOTLIGHT

EXPERT INSIGHT

Commercialization of TCR T-cell therapy: patient journey implications

Kimberly Freeman

T-cell receptors (TCRs) are the natural antigen recognition machinery of a T cell. Unlike the antibody recognition modality used in chimeric antigen receptors (CARs), TCRs recognize proteins that are expressed inside the cell, then broken down and presented on the cell surface in the context of the antigen presenting machinery called human leukocyte antigen (HLA). Because TCRs can access proteins expressed inside the cells of solid tumors, this allows access to a much broader range of potentially unique cancer targets. Adaptimmune engineers TCRs to specifically target intracellular proteins that are expressed in solid tumors. These TCRs are then put into a patient's own T cells and given back to the patient to fight their cancer. Using this autologous cell therapy approach, Adaptimmune has multiple TCRs in clinical trials targeting a wide range of solid tumors. The commercialization of TCR T-cell therapies will be unique for a variety of reasons. Although we can learn from the currently marketed cell and gene therapies, cell therapy for solid tumors has its own set of specific challenges. Early commercial planning and cross-functional collaboration will be important components of successfully bringing these therapies to market. Here, we review three areas that impact the patient journey for TCR T-cell therapy including factors in patient identification and time to treatment, qualified treatment centers, and reimbursement implications specific to the US market.

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THE PATIENT JOURNEY IN TCR T-CELL THERAPY

A successful commercialization strategy must focus on the entire patient and cell journey. This journey includes patient identification, apheresis, successful manufacture of transduced cells, T-cell infusion, subsequent side-effect management, and long-term follow-up. The entire process requires close collaboration between the manufacturer, medical center staff, logistics providers, payers and – of course – the patient.

The duration of this patient journey is critical to successfully treat patients with relapsed/refractory disease for whom time is often a critical factor. Patients identified for treatment are very heavily pretreated and many do not have weeks to wait for a cell therapy to be administered; therefore, ensuring the shortest possible time between eligibility for cell therapy to TCR T-cell administration is crucial. One key factor in the successful commercial uptake of autologous cell therapy is reducing the time between apheresis and T-cell infusion, commonly referred to as 'vein-to-vein' time. Several cell therapy manufacturers, including Adaptimmune, have made great strides in shortening the number of days in the vein-to-vein process.

Adaptimmune is a fully integrated cell therapy company with in-house manufacturing as well as vector production capabilities. This full integration has enabled rapid process improvements as well as the ability to streamline various steps to ensure a shorter manufacturing time. It also allows for critical planning of patient manufacturing slot availability, ensuring cell manufacturing when needed. Manufacturing success rates are also critical as providers, patients and payers are at risk for failed manufacturing processes. Being a highly personalized therapy, the complex, multistep process of generating autologous cell therapy increases the risk of production failure which can delay and, in some instances, even deny access to the therapy.

One unique aspect of TCR T-cell therapy includes testing for the relevant HLA and antigen expression to determine patient eligibility for therapy. It is important to factor the testing logistics and turnaround time into the patient journey in addition to the vein-to-vein time. Educating providers of the importance of early testing for both HLA and antigen will be crucial for the commercial success of these therapies. The preferred scenario would have automatic or reflex testing established at initial diagnosis of a patient's disease. The path to achieving this will require demonstration of the efficiency of the process, preferably across multiple tumor types as well continued educational initiatives for both treating and referring oncologists. Engagement with clinical pathways and other decision support tools such as the National Comprehensive Cancer Network (NCCN) Biomarker Compendium [1], which is designed to support decision-making around the use of biomarker testing in patients with cancer, will be important steps for comprehensive testing awareness.

ROLE OF CENTER OF EXCELLENCE (COE) NETWORK

The Center of Excellence (COE) model has been the ideal approach for initial cell and gene therapies. These models currently play an important role in the specialized delivery of care for cell therapy treatments. Expertise is required for successful delivery of these therapies, including cellular collection, cellular handling and processing and a multidisciplinary clinical team experienced in managing cellular therapy and its complications.

COE networks can be defined by payers, regulators and manufacturers. In the cell therapy space, payers have initially accepted de facto COEs created by manufacturers of cell therapy products and established in the process of clinical trial execution. The goals and standards of the payer requirements may be different versus those of the manufacturer. Efforts could be put forth earlier to ensure as much alignment as possible. There may be emphasis on different things e.g. value versus

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scientific expertise, which could impair patient access as they will need to seek overlap between the requirements of their payers as well as clinical and geographic needs. With increases in the numbers of patients treated, payers may appropriately exert pressure on manufacturers to include centers that fit their geographic or value-based needs, although all parties have an inherent interest in maintaining quality standards and outcomes.

Establishing the appropriate standards and capturing the right information in solid tumors may look different compared to hematologic malignancies. Organizations like the Foundation for Accreditation of Cellular Therapies (FACT) have led the development of quality standards and accreditation practices that are often required for COE inclusion but can be adapted to the needs and resources of individual centers. FACT-accredited organizations voluntarily seek and maintain this status through a rigorous process. Major third-party payers require FACT accreditation for reimbursement or COE designation for certain therapies or procedures. Although FACT standards address processes, documentation and oversight, they are not capturing all the quality elements or manufacturing steps for any given cell product [2]. The Center for International Blood and Marrow Transplant Research (CIBMTR) is collaborating with FACT and specialty societies including the American Society of Blood and Marrow Transplantation (ASBMT) to develop platforms for assessment, reporting, and risk adjustment that can encourage and reflect quality practices.

Limitations of number of COEs is not ideal for patients, yet understandable given the complexity of administering these early therapies. The pivotal trials performed to date by individual manufacturers of cell and gene therapies have typically utilized a small number of COEs (e.g., <50), expanding after commercialization. A larger number of centers and potential expansion to the community could benefit the sites of care and, most importantly, patient access. The ideal treatment setting would be as an outpatient through specialized centers with trained staff, moving from academic inpatient centers to community inpatient and ultimately outpatient use. The need for investment in infrastructure is critical for treatment delivery and follow-up care, particularly if a backlog or surge arises for TCR T-cell therapy if such therapies are successful in multiple solid tumors. Compared with existing inpatient centers of excellence, outpatient centers may need to expand and upskill many of their staff, invest in infrastructure to handle billing and coding as well as administration and capacity to treat.

A key question is whether the COE networks have capacity for the growing number of clinical trials as well as an increase in the number of commercially available products. The introduction of solid tumor products as well as additional products in hematologic malignancies will significantly increase the demand for cell and gene therapies. One example of possible capacity constraints is the limited number of apheresis chairs. Typically, a percentage are designated for clinical trial use and the others to commercial product utilization as well as all other therapeutic needs that require the use of the apheresis unit. If capacity constraints become an issue this would increase days in the patient journey and possibly delay the cell dose.

There is also the concern of patient travel and long-term follow-up requirements. Some treating physicians within the COEs would like patients to get back home and be seen by their local community oncologist. Would payers be willing to create unique reimbursement for long-term care and tracking of cell and gene therapy patients outside the COE particularly if there is a cost offset from paying the travel and other related costs of the patient being seen for follow-up in the COE. Allowing the patient to get back to their life is an important step in their journey and an advantage of a one-time therapy.

Some mechanism may be needed to finance this expansion in capacity and capabilities. From a payer perspective, narrow networks present a similar challenge at managing policies and setting coverage. A major treatment

paradigm shift may be needed to move from an inpatient, center of excellence treatment setting to a community outpatient setting. This shift would need further support by the medical community – for example, by changing clinical guidelines and patient pathways.

In the current model of specialized hospital centers, a challenge that may be heightened in the solid tumor setting is the issue of patient referral to a COE. Community oncologists will need to be educated on the importance of referring to the COE and coordinating care in the already complicated patient journey. Manufacturers will need to work with community oncology practices on educational initiatives around screening, travel and logistics to the COE, side-effect management as well as long-term follow-up requirements. Pilot programs and educational initiatives with large community networks will also be needed.

REIMBURSEMENT CHALLENGES

There will be important considerations in terms of pricing and reimbursement of TCR T-cell therapies in the treatment of solid tumors. Current reimbursement dynamics, particularly within the Medicare channel, have been a key factor in limiting commercial uptake of currently marketed chimeric antigen receptor (CAR) T-cell therapies. It is estimated that approximately 50% to 65% of addressable CAR-T patients are Medicare-eligible.

In May 2020, the Centers for Medicare and Medicaid Services (CMS) announced a proposed path forward for Medicare CAR-T reimbursement in its FY2021 inpatient prospective payment system (IPPS) proposal, which will go into effect on October 1st. Included in the proposed rule is a new Medicare Severity-Diagnosis Related Group (MS-DRG) for CAR-T-therapy [3]. Furthermore, CMS is proposing discontinuation of the new technology add-on payments for currently marketed CAR-T therapies. It is yet to be defined whether this new code is applicable to all T-cell therapy.

Improvements with CAR-T reimbursement, in theory could help TCR T-cell therapy across various solid tumor indications by providing more reasonable reimbursement and limiting financial losses for treatment centers. Some key questions payers will have in evaluating TCR T-cell therapy in solid tumors are around actuarial risk with varied incidence rates depending on tumor type. There is also the question of combination therapy, combining cell therapy with currently available treatments, particularly in the earlier line setting.

The Massachusetts Institute of Technology's New Drug Development Paradigms (NEWDIGS) consortium Financing and Reimbursement of Cures in the US (FoCUS) conducted a survey that was focused on assessing payer perspectives regarding current and future management of high-cost durable therapies with one-time administration. They reported that payer concerns included actuarial risk, therapeutic performance risk, and payment timing relative to benefit gained. They also found payers emphasized the impact of the total cost of treatment, both for an individual patient and the burden of multiple high cost therapies [4].

Payers are managing these treatments using many of the current management strategies they employ for other high-cost treatments. Alternative financing solutions could provide benefits to payers, providers and patients. Payers are interested in managing the financial risk and impact associated with these high-cost one-time therapies differently. Payers are open to multiple different approaches, although most favor short-term milestone-based contracts where therapy is paid for upfront and potential refunds are tied to failure to achieve performance metrics over the first two years following treatment. Other solutions include reducing upfront budget impact of the new therapy by smoothing payments over time, aligning the timing of the therapy costs with its benefits, and only paying for therapy that works by including performance-based requirements for initial or continued payment.

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Tracking patients for short and longer-term outcomes, which will be needed for FDA post-approval requirements, will be expensive and have unique challenges. Both require scalable, systematic ways of tracking and measuring outcomes, accounting for patient mobility between payers, but also settings of care. With solid tumors, the community specialist centers will need to be more closely involved. Moreover, the risks potentially taken on by outpatient providers would prove to be prohibitive for their participation without measures that would quickly pre-authorize treatment and ensure reimbursement.

TRANSLATIONAL INSIGHT

Autologous TCR T-cell therapy is expanding cell therapy treatment to the solid tumor setting. Ongoing collaboration across manufacturers and relevant stakeholders will be critical as we continue to make improvements along the patient journey and move toward commercialization. Shortening time between patient identification and treatment, advances in manufacturing, expansion of the qualified treatment center footprint, and continued payer engagement will help short-term accessibility of these therapies.

Allogeneic cell therapy offers the promise of overcoming some of the logistical and commercial challenges seen with autologous therapies. Many of the constraints associated with the complex manufacturing process of the current generation of autologous TCR T-cells could be resolved with allogeneic, off-the-shelf products. These next-generation products offer an efficient way to deliver a cell-based therapy to patients thus reducing the time gap between prescribing and administration. This would be particularly beneficial for patients with rapidly progressive disease. Additionally, allogeneic cells represent a universal product capable of treating multiple patients thus overcoming the scalability challenges and potentially reducing overall therapy costs associated with cell-based therapies. However, the safety and efficacy of allogeneic based therapies remains to be determined before this innovative approach can be incorporated into routine clinical practice.

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AFFILIATION

Kimberly Freeman
Adaptimmune Therapeutics

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CELL & GENE THERAPY INSIGHTS

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SPOTLIGHT

EXPERT INSIGHT

Current and future directions for tumor infiltrating lymphocyte therapy for the treatment of solid tumors

Maria Fardis, Kelly DiTrapani, Cécile Chartier & Friedrich Graf Finckenstein

Cancer is the second leading cause of death in the USA. Over 90% of cancers involve solid tumors while 10% are hematological malignancies. Adoptive cell transfer (ACT) utilizing chimeric antigen receptor (CAR) T cells has recently been approved as treatment for a subset of hematologic cancers, changing the prospects of a small fraction of cancer patients. Patients with solid tumors though have not received significant benefit from CAR T therapy and many remain without therapeutic options after progressing on standard of care, including immune checkpoint inhibitors. First tested more than 30 years ago and optimized over the decades, ACT with tumor-infiltrating lymphocytes (TIL) was shown to be remarkably efficient for the treatment of metastatic melanoma, and is now re-emerging as a promising therapeutic option for heavily pre-treated patients with melanoma and other solid tumors. TIL therapy is a one-time treatment that involves the adoptive transfer of autologous T cells isolated from the tumor tissue and expanded *ex vivo* to a patient who has been lymphodepleted to remove their immunosuppressive tumor microenvironment which is supportive of a tumor in a cancer patient. The authors have established a streamlined GMP process for the production of TIL and demonstrated efficacy of the product in several highly unmet medical need patient populations, as evidenced by durable responses as assessed by RECIST 1.1. Two pivotal clinical studies in melanoma and cervical cancer indications are ongoing to support bringing this product to the market.

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Immunotherapy represents a potentially life-saving option in the treatment of patients with cancer. Because of the enhanced understanding over the past three decades of the adaptive immune system, as well as of immunologic signaling and immunosuppressive pathways in cancer, immunotherapy has emerged as a major focus of cancer research and a novel treatment option. However, currently approved immunotherapy drugs work through mechanisms that are not tumor specific and can lead to immune related organ toxicity that can limit benefit for patients [1]. In addition, various mechanisms can drive both primary and acquired resistance to currently available immunotherapeutics in a meaningful proportion of patients [2]. Despite novel advances geared at taking off the brakes on immune responses to tumors, treatment options remain limited for patients who cannot tolerate, do not initially respond, or develop resistance to currently approved immune checkpoint inhibitors.

As part of normal immune response, TIL migrate to the tumor site after circulating in blood and through recognition of chemokines produced by the tumor, penetrate the tumor stroma and engage in tumor cell killing. Cancer prevails in cases where the tumor microenvironment overpowers the immune response [3–6].

ACT utilizing autologous TIL is building on this tumor specific physiological immune response mechanism and has demonstrated the potential for durable complete responses in immunogenic tumors such as melanoma, in studies conducted at the National Cancer Institute (NCI) and other institutions globally [7]. Responses are demonstrated even in heavily pretreated patients irrespective of prior therapy, including checkpoint inhibitors [8–11]. The encouraging results of TIL therapy in melanoma have led to further exploration of ACT with TIL as a treatment option for multiple additional cancer indications [12,13].

The principle behind TIL therapy is to amplify and rejuvenate the cancer patient's immune system thereby enabling it to eliminate tumor cells. To translate the approach in a commercially viable product, the authors initially focused on optimizing the manufacturing process. The original process from NCI required approximately 6 weeks-for completion. A new manufacturing process for TIL was developed lasting only 22 days and called Generation 2 (Gen 2). The authors' Gen 2 manufacturing process is robust with well over 90% success rate in >300 patients treated to date. This product is investigated in two pivotal programs for melanoma and cervical cancers, with intent to commercialize the Gen 2 manufacturing product in the USA subsequent to submission of a BLA to the FDA.

TIL MANUFACTURING PROCESS

TIL manufacturing starts with the surgical resection of a tumor. The resected tumor is shipped to the central manufacturing facility where it is fragmented and placed in media. Upon placement of tumor fragments in the presence of IL-2, the TIL egress from the tumor while expanding in media. After completion of expansion, approximately 10^9–10^{11} cells are produced and harvested. The TIL cells are washed, placed in media in the infusion bags and cryopreserved **(Figure 1)**.

TIL ADMINISTRATION TO PATIENT

Subsequent to TIL product manufacturing, the TIL which may recognize multiple patient-specific antigens expressed by the tumor, are now available in great numbers and with restored functionality. In preparation for the therapeutic TIL infusion, the patient receives non-myeloablative lymphodepletion (NMA-LD) with cyclophosphamide (60 mg/kg, IV x 2 doses) and fludarabine (25 mg/m^2 x 5 doses) to eliminate potentially suppressive immune cells which support the tumor and to maximize engraftment and potency of TIL therapy through homeostatic proliferation [14]. The patient is

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then infused with their expanded therapeutic TIL (lifileucel [LN-144] or LN-145) and subsequently receives up to 6 doses of IL-2 (600,000 IU/kg) to promote activation, proliferation, and anti-tumor cytolytic activity of TIL (Figure 1).

The IL-2 is administered to allow for TIL to survive and expand *in vivo*. IL-2 administration is limited to up to 6 doses given over approximately three days, which compared to therapeutic IL-2 is significantly sub-therapeutic by dose and duration of administration which is limited to approximately 3 days.

Iovance's 22-day Gen 2 expansion protocol demonstrated significant improvement over classical methods of generating TIL which involve multiple ex-vivo incubation steps to yield a noncryopreserved, infusion product. The Gen 2 TIL manufacturing process abbreviates the *ex vivo* culture duration to 22 days, is suitable for centralized manufacturing and yields a cryopreserved TIL infusion product that brings convenience in scheduling, logistics, and delivery to clinical sites at commercial scale [15]. The release criteria have been well defined and observed for each patient. The Iovance TIL therapy administration process has been implemented globally in multiple institutions offering broad access for melanoma and cervical patient populations in multiple geographic locations.

MECHANISM OF ACTION

Mechanistically, the reinfused TIL circulate in the blood until they detect the tumor in the vicinity due to chemokines produced by the tumor. The TIL then depart the capillaries and migrate to the site of tumor (Figure 2). Upon arrival at the tumor, the TIL recognize tumor antigen peptides presented by MHC molecules on the surface of the tumor cells via their T cell receptors. Upon tumor antigen recognition, the TIL get activated and secrete perforin, a pore-forming protein. The newly formed pores allow for the delivery of granzyme, a pro-apoptotic protease which is also released by the activated TIL and causes lysis of the targeted cancer cell. The infused TIL

FIGURE 1

Proprietary TIL therapy process.

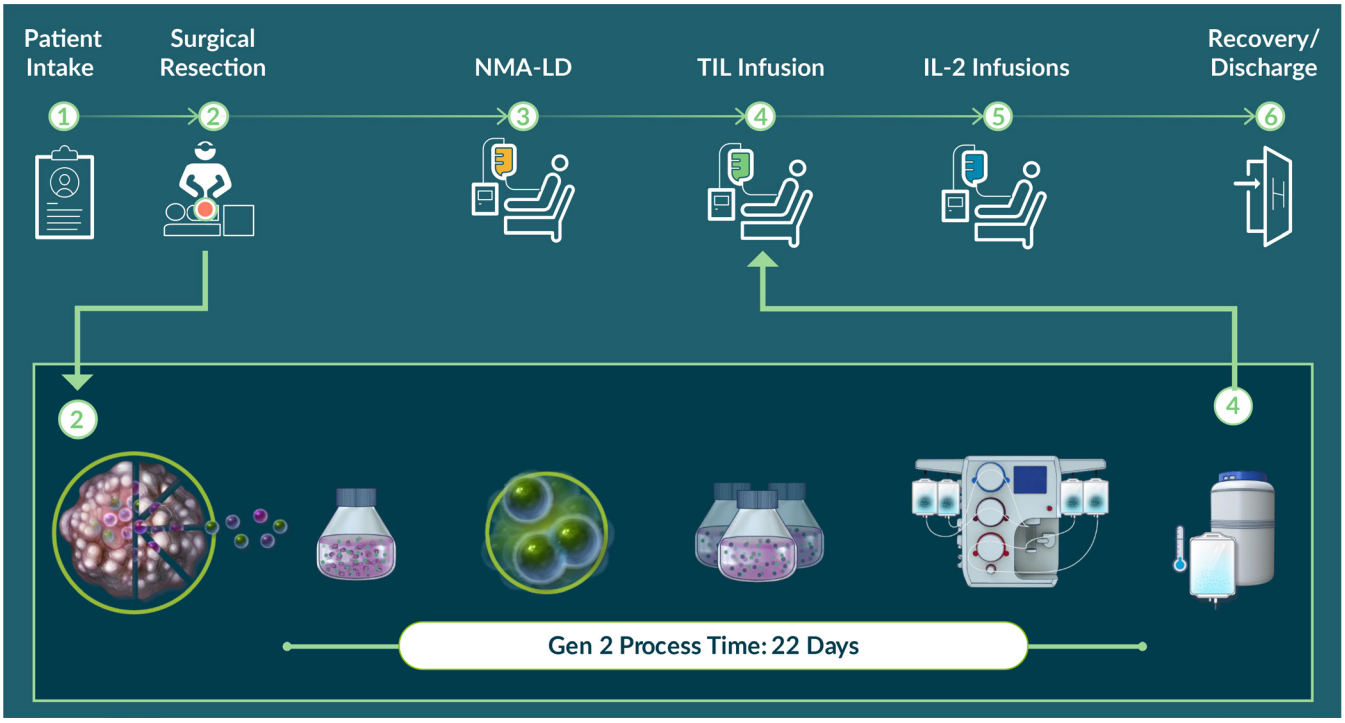
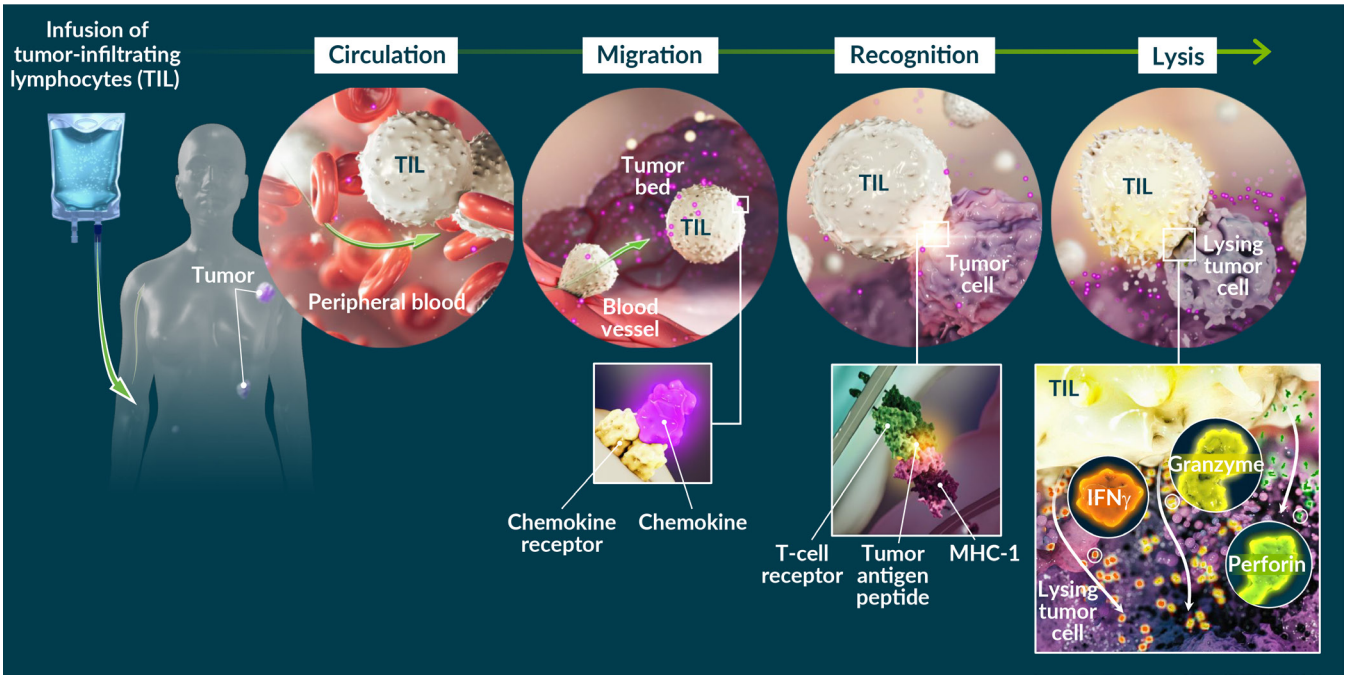


FIGURE 2

TIL mechanism of action.



thus mediate regression of tumors by direct cell kill but may also induce cytokine-mediated tumor cell killing [16,17].

TIL have clear advantage in treatment of solid tumors due to multiple differentiating factors:

1. Tumor recognition: TIL therapy is autologous, targeted, and enriched for tumor-specific T cells because the TIL were isolated from the site of tumor, where they have previously experienced the tumor-specific antigens [18];

2. Personalized: in solid tumors a single common target neoantigen has not been identified to date. In absence of such a target, TIL therapy relies on the recognition of patient specific tumor peptide antigens by the correct T cells;

3. Polyclonal: the mutational load is high in solid tumors when compared to hematologic malignancies. The polyclonality of TIL that can recognize an array of different tumor antigens best addresses this high mutational diversity. This is a significant strength of TIL as a therapeutic option, and possibly is why TIL is able to generate clinical response in diseases with high mutational load such as melanoma [19];

4. Neoantigen-specific: the spectrum of neoantigens that need targeting to drive an antitumor response is unknown and highly specific to each patient. Per design, the TIL process ensures the inclusion of neoantigen-specific T cell clones without prior knowledge of the number or identity of those neoantigens;

5. Clinical efficacy: ultimately, clinical data from clinical trials in melanoma and cervical cancer clearly indicate the effectiveness of the polyclonal T cell.

CLINICAL TRIALS

A total of four company sponsored studies in locally advanced, recurrent or metastatic cancers including melanoma, cervical cancer, head and neck, and non-small cell lung cancer are currently being conducted (Table 1).

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TABLE 1

Current clinical pipeline and select collaboration studies.

	Regimen	Trial	Indication	N	Partner	Phase 1	Phase 2	Pivotal
Company sponsored studies	Lifleucel	C-144-01	Melanoma	178	–			
	LN-145	C-145-04	Cervical cancer	138	–			
	LN-145/ LN-145-S1	C-145-03	Head and neck cancer	55	–			
	Lifleucel + pembrolizumab	IOV-COM-202	Melanoma		–			
	LN-145-S1		Melanoma					
	LN-145 + pembrolizumab		Head and neck	~75				
	LN-145 + pembrolizumab		Non-small-cell lung					
	LN-145		Non-small-cell lung					
Select investigator sponsored proof-of-concept studies	MDA TIL	NCT03610490	Ovarian, colorectal, pancreatic	~54	MD Anderson Cancer Network			
	LN-145	NCT03449108	Ovarian, sarcoma	~54	MD Anderson Cancer Network			

C-144-01 METASTATIC MELANOMA

Melanoma represents 5.5% of all new cancer cases with over 96,000 new cases and 7,000 deaths in the USA. Rates for new melanoma cases are still rising [20]. Major advances in the treatment of advanced melanoma have been made with the integration of immune checkpoint inhibitors and targeted therapies into clinical practice. However, treatment options for patients with advanced melanoma who have progressed on or after these therapies are limited, with chemotherapy expected to offer objective response rates (ORR) between 4% and 10% [21,22].

C-144-01 (NCT02360579) is a multi-cohort, Phase 2 clinical trial evaluating the safety and efficacy of lifileucel in patients that have been diagnosed with unresectable or metastatic Stage IIIc or IV melanoma. Patients must have received at least one prior treatment with systemic therapy including an immune checkpoint inhibitor, and if BRAF mutation positive, a BRAF inhibitor or BRAF inhibitor in combination with MEK inhibitor. Initial data from 66 patients in Cohort 2 showed a 36.4% objective response rate (ORR) by investigator and median duration of response (DOR) not reached at 18.7 months of median study follow up in the full cohort (Table 2). Adverse events (AEs) were generally consistent with the underlying advanced disease and the known profiles of the lymphodepletion chemotherapy and IL-2 regimens (Table 3) [9].

In a sub-group analysis of 42 patients who were primary refractory to Anti-PD-1 (defined as best overall response of progressive disease to the earliest anti-PD-1 treatment), the ORR was 40.5%, comparable to the overall cohort. AEs in the primary refractory subgroup are consistent with prior reports on the full Cohort 2 analysis set [10].

TABLE 2

C-144-01 cohort 2 efficacy outcomes.

Response	Patients, N = 66 n (%)
Objective response rate	24 (36.4)
– Complete response	2 (3.0)
– Partial response	22 (33.3)
Stable disease	29 (43.9)
Progressive disease	9 (13.6)
Non-evaluable†	4 (6.1)
Disease control rate	53 (80.3)
Median duration of response	**Not reached**
Min, max	2.2, 26.9+

†NE due to not reaching first assessment.

TABLE 3

C-144-01 Cohort 2 treatment-emergent adverse events occurring in ≥20% of patients.

Preferred term, n (%)	Cohort 2 (N=66)		
	Any grade	Grade 3/4	Grade 5
Number of patients reporting at least one treatment-emergent adverse event	**66 (100)**	**64 (97)**	**2 (3)†**
Thrombocytopenia	59 (89.4)	54 (81.8)	0
Chills	53 (80.3)	4 (6.1)	0
Anemia	45 (68.2)	37 (56.1)	0
Pyrexia	39 (59.1)	11 (16.7)	0
Neutropenia	37 (56.1)	26 (39.4)	0
Febrile neutropenia	36 (54.5)	36 (54.5)	0
Hypophosphatemia	30 (45.5)	23 (34.8)	0
Leukopenia	28 (42.4)	23 (34.8)	0
Fatigue	26 (39.4)	1 (1.5)	0
Hypotension	24 (36.4)	7 (10.6)	0
Lymphopenia	23 (34.8)	21 (31.8)	0
Tachycardia	23 (34.8)	1 (1.5)	0

†One death was due to intra-abdominal hemorrhage considered possibly related to TIL and one was due to acute respiratory failure assessed as not related to TIL per investigator assessment.
Patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term.
Treatment-emergent adverse events refer to all AEs starting on or after the first dose date of TIL up to 30 days.

Treatment options are particularly limited for these patients given that 40–65% of all metastatic melanoma patients are primary refractory to initial immune checkpoint inhibitor therapy [23].

An important consideration is the relative safety associated with TIL therapy. This one-time autologous treatment involves a product individually derived for each patient, it is not selected for the recognition of shared antigens that would be expressed in normal tissues, and is specific to the tumor neoantigens, reducing the risk for autoimmune toxicity. In addition, the TIL mechanism of action does not rely on engineered receptors but maintains some physiologic control and avoids hyperactivation that may be responsible for complications from CAR-T cell therapy such as cytokine release syndrome or neurotoxicity. TIL therefore offers a differentiated safety profile compared to CAR-T products or immune checkpoint inhibitors and confirms the differentiation discussed above.

C-144-01 is the first study to demonstrate the scalability and reproducibility of a centrally manufactured frozen TIL product. Cohort 4 of the study (N=75) is the pivotal cohort in support of registration of lifileucel in post- anti-PD-1 melanoma patients. Enrollment in Cohort 4 completed in Jan 2020, in approximately 8 months, well in advance of the expected enrollment target possibly indicating the unmet need in this patient population.

TABLE 4

C-145-04 efficacy outcomes.

Response	Patients, N = 27 n(%)
Objective response rate	12 (44.4)
Complete response	3 (11.1)
Partial response	9 (33.3)
Stable disease	11 (40.7)
Progressive disease	4 (14.8)
Non-evaluable	0
Disease control rate	23 (85.2)
Median duration of response	**Not reached**
Min, max (range)	2.6+, 9.2+

C-145-04 metastatic or persistent cervical carcinoma

Cervical cancer is a leading cause of cancer-related death in women with over 12,000 new

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TABLE 5

C-145-04 treatment emergent adverse events.

Preferred term, n (%)	Cohort 2 (N=27)		
	Any grade	Grade 3/4	Grade 5
Number of patients reporting at least one treatment-emergent AE†	**27 (100)**	**26 (96.3)**	**0**
Chills	21 (77.8)	0	0
Anemia	15 (55.6)	15 (55.6)	0
Diarrhea	14 (51.9)	2 (7.4)	0
Pyrexia	14 (51.9)	1 (3.7)	0
Thrombocytopenia	14 (51.9)	12 (44.4)	0
Neutropenia	11 (40.7)	8 (29.6)	0
Vomiting	11 (40.7)	1 (3.7)	0
Hypotension	10 (37.0)	4 (14.8)	0
Dyspnea	9 (33.3)	1 (3.7)	0
Febrile neutropenia	9 (33.3)	8 (29.6)	0
Hypoxia	9 (33.3)	3 (11.1)	0
Leukopenia	9 (33.3)	6 (22.2)	0
Hypomagnesemia	8 (29.6)	0	0
Sinus tachycardia	8 (29.6)	0	0

†Treatment-emergent adverse events refer to all AEs starting on or after the first dose date of TIL up to 30 days. Patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term. Safety terms which describe the same medical condition were combined.

cases and 4,000 deaths in the USA alone [24]. Most patients are young and survival rates are poor. Objective response rates (ORR) for second-line therapies in the metastatic setting, are between 4 and 14% for chemotherapy and recently approved immunotherapy, pembrolizumab [25].

C-145-04 (NCT03108495) is a multi-cohort, Phase 2 clinical trial, enrolling patients with recurrent, metastatic or persistent cervical carcinoma which have exhausted the therapeutic options with surgery and/or (chemo) radiation, as well as palliative chemotherapy administered in the metastatic setting. The clinical trial is designed to determine if this investigational TIL therapy (LN-145) is safe and effective for the treatment of recurrent, metastatic or persistent cervical carcinoma. Initial data from N=27 patients demonstrated an ORR of 44.4% with a median DOR of not reached at a median study follow up of 7.4 months (Table 4). Adverse events in the cervical study were consistent with what was noted in the melanoma program (Table 5) [13].

Ongoing & future research

We are at early stages of understanding capability of TIL therapy and exploration. Understanding of the indications in which TIL therapy can be effective is at early stages and ongoing. Furthermore, genetic modifications, selection of tumor-exposed TIL as well as various operational efficiencies, such as further shortening the TIL manufacturing process and use of core biopsies are all opportunities that are being pursued by Iovance.

Work continues on optimizing TIL manufacturing and potency. Iovance has recently demonstrated the ability to utilize the Gen 2 manufacturing method reliably to expand TIL from core biopsies in multiple tumor types, yielding comparable final therapeutic products [26]. The company continues to seek further improvements by creating new generations of TIL, including exploration of abrogating PD-1 within the TIL product to reduce PD-L1-dependent TIL inactivation, and via intrinsic silencing of PD-1 in our TIL products.

TRANSLATION INSIGHT & OPPORTUNITIES

Relapsed, refractory and metastatic cancers represent high unmet medical need. Despite recent advances in immunotherapies in addressing multiple solid tumor indications, very few options are available to treat patients who progress on immune checkpoint inhibitors or never respond to such treatments.

TIL generated using Iovance's 22-day Gen 2 expansion process have demonstrated anti-tumor efficacy including durable responses in heavily pretreated metastatic melanoma and cervical carcinoma patients irrespective of prior therapy. This work is the first demonstration of the ability to produce therapeutic TIL in a rapid, centralized fashion with capability to serve multiple global treatment centers. Iovance intends to submit for regulatory approval, based on these data demonstrated in metastatic melanoma and cervical carcinoma, Development of newer generation of polyclonal TIL will continue in order to develop more potent and novel products with differentiated properties.

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AFFILIATIONS

Maria Fardis
Iovance Biotherapeutics

Kelly DiTrapani
Iovance Biotherapeutics

Cécile Chartier
Iovance Biotherapeutics

Friedrich Graf Finckenstein
Iovance Biotherapeutics

AUTHORSHIP & CONFLICT OF INTEREST

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CELL & GENE THERAPY INSIGHTS

IMMUNO-ONCOLOGY: MANUFACTURING & COMMERCIAL BUSINESS MODELS FOR THE NEW DECADE

SPOTLIGHT

EXPERT INSIGHT

Immuno-oncology cell therapies: commercial considerations and strategies for the new decade

Glen Firestone

The first two CAR-T therapies demonstrated impressive efficacy data, and following their FDA approval in 2017, there has been tremendous excitement in the scientific and investment community for immuno-oncology cell therapies. In the last few years, there has been unprecedented growth in the number of biotech startups and cell therapy clinical trials, supported by an infusion of cash from private (venture capital) and public (capital markets) entities, as well as acquisitions and strategic partnerships with pharmaceutical companies. It is anticipated that the introduction of these novel cell therapies will dramatically improve patients' lives and fundamentally transform the healthcare landscape in this new decade. This commercially oriented article focuses on innovative immuno-oncology cell therapies and explores key opportunities and challenges facing biotech companies, commercial plans to drive success, and strategies to disrupt the market.

Cell & Gene Therapy Insights 2020; 6(6), 789–798

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INTRODUCTION

In this new decade, innovations in information technology plus cell and gene therapies could fundamentally alter the healthcare landscape and disrupt the market. The application of big data (including real world data), artificial intelligence and machine learning will radically change the way in which new therapies are developed, diseases are diagnosed, patients are treated, healthcare

is delivered, outcomes are assessed, and value is measured. The introduction of cell and gene therapies has the potential to cure cancers, autoimmune diseases, infectious diseases, and genetic disorders. These new therapies will upend the way diseases are viewed and treated. The goal for these therapies will be to target the root cause of disease rather than just providing incremental benefit or symptomatic relief. Biotech, pharmaceutical, and academic organizations are leveraging their collective understanding of human biology and the genome while also applying new genetic engineering tools to develop innovative cell and gene therapies. The introduction of these therapies can dramatically improve patients' lives and fundamentally transform the healthcare space. The launch of these novel therapies will render this new decade as an inflection point in the evolution of medicine. The focus of this article will be on immuno-oncology cell therapies.

Market dynamics

The immuno-oncology cell therapy landscape experienced rapid growth following the approval of the first two CAR-T cell therapies, Novartis' Kymriah® for acute lymphoblastic leukemia (ALL) and Gilead/Kite's Yescarta® for diffuse large B-cell lymphoma (DLBCL) in 2017. Immuno-oncology cell therapy is a form of treatment that uses the cells of our immune system to treat or eliminate cancer. Through 2019, there has been tremendous expansion in the number of clinical trials for cell therapies, the majority of which are focused on immuno-oncology. Figure 1 [1] shows the rapid growth in cell therapy clinical trials over the past decade (mainly driven by immuno-oncology cell therapies). Many of these trials involve gene-modified cell therapies and for the first-time patients have been treated with a CRISPR-edited cellular immuno-oncology therapy (e.g. trial with CRISPR-edited NYESO TCR for myeloma and sarcoma by Penn Medicine/Tmunity/PICI). The immuno-oncology cell therapy market is expected to continue to expand during this new decade as new therapies are pursued for both liquid and solid tumors. By 2025, the FDA predicts that it will be approving 10 to 20 cell and gene therapy products a year based on an assessment of the current pipeline and the clinical success rates of these products [2].

Financing

In 2019, global financing of immuno-oncology cell therapy companies continued to be strong, with over $5 billion worth of new cash being infused into cell therapy biotech startups. Moreover, venture capital financing increased by 32%, public offerings remained a key funding source, and corporate partnerships provided upfront payments. Merger and acquisition activity in 2019 also reflected growing interest in cell and gene therapies [3]. Many large pharmaceutical and biotech companies have already invested in these biotech startups. Companies such as Novartis, GSK, BMS/Celgene, Johnson & Johnson, Pfizer, Gilead/Kite, Amgen, Takada/Shire and others now have investments in immuno-oncology cell therapy companies.

OPPORTUNITIES & CHALLENGES

In 2019, Gilead's Yescarta® generated $456 million in sales and Novartis's Kymriah® generated $278 million [4]. Some new market research reports are projecting that the CAR-T cell therapy market alone could surpass $8 billion in sales by 2026 [5]. As with any major paradigm shift in healthcare, the advent of targeted cell therapies brings a new set of commercial and manufacturing opportunities and challenges. Some of the key opportunities and challenges are captured in Table 1.

Opportunities

Immuno-oncology cell therapies (e.g. CAR-T, TCR, NK cells, TILs, etc.) are

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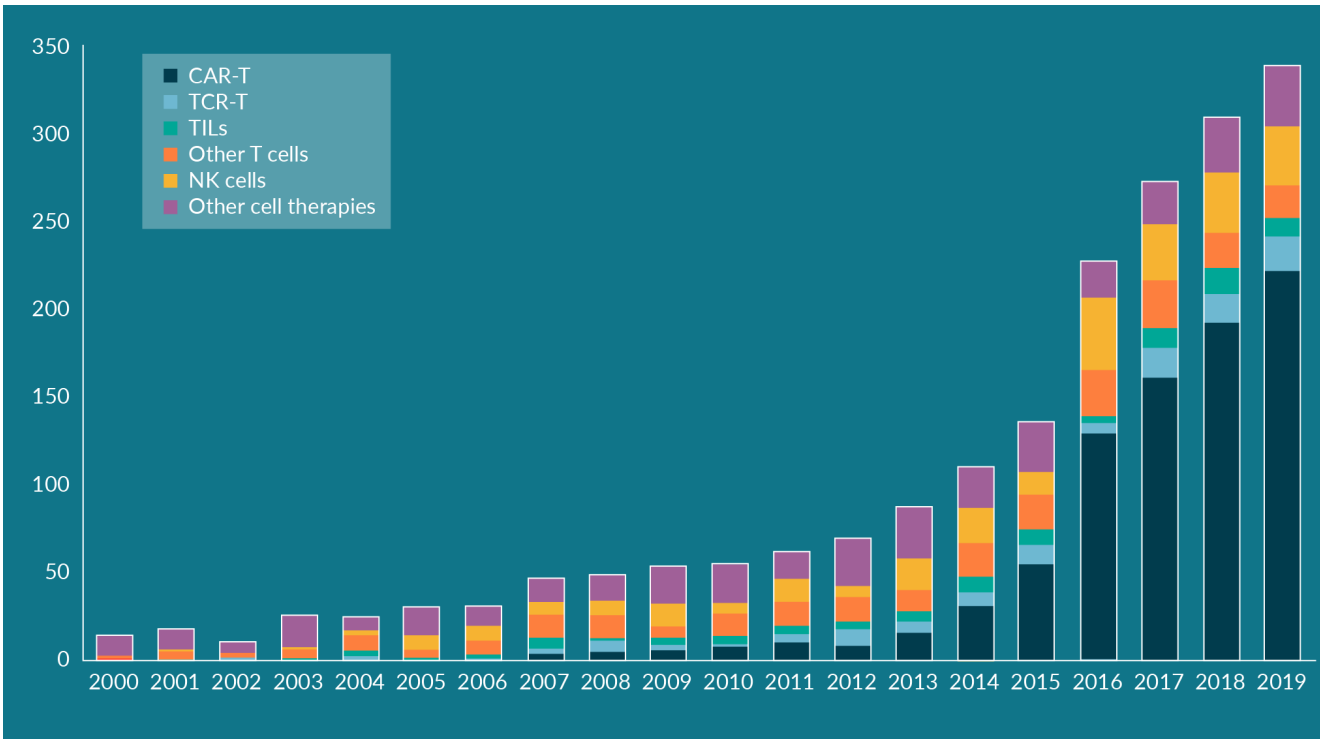
FIGURE 1

Rapid growth in clinical trials for cell therapies over time [1].



Trials evaluating more than one cell therapy type were counted per therapy type, excludes dendritic cell therapies.

opening new opportunities and autologous CAR-T therapies have demonstrated efficacy in hematologic cancer tumors with high overall response rate as well as complete response rates. In addition, new cell therapies are now being developed to tackle solid tumors. By combining the enhanced understanding of cell biology with gene editing tools (e.g. CRISPR CAS9, Base Editing, ZINC Finger, Talen, etc.) researchers are developing engineered constructs to create novel cell therapies, which can target and kill cancer cells while also distinguishing and preserving healthy cells. These therapies are restoring hope for metastatic cancer patients that have few treatment options, significant relapse/refractory risk, and low 5-year survival rates. Five-year survival rates are much lower for metastatic patients and in the single digits for some cancers (e.g. pancreatic, liver, and lung cancer) [6]. Cell therapies have the potential to provide a curative solution and play a role beyond their initial response by persisting over time, providing ongoing surveillance, and preventing future occurrences (e.g. micro metastasis in a portion of patients). Many of the initial patients treated with Kymriah® and Yescarta® have experiencing sustained long-term benefit from treatment. These therapies have the potential advantage of being 'one time' therapies that persist over time with limited need for redosing. Today, patients with advanced cancers often undergo a combination of multiple rounds of chemotherapy, checkpoint inhibitors, radiation, and surgery, which can have a lasting impact on a patient's quality of life. In the future, cell therapies may move up in the treatment paradigm and help decrease exposure to chemotherapy and radiation.

Challenges

Early experience with the first two CAR-T therapies highlighted a unique set of

challenges in manufacturing and commercializing autologous cell therapies. The approved CAR-T therapies used in hematological tumors can trigger severe cytokine release syndrome (CRS) and neurotoxicity in some patients. Because of safety concerns, these therapies are often administered in the inpatient setting and patients need to remain near the academic center during the four weeks following infusion. Some of the emerging CAR-T therapies appear to have low rates of CRS and may be considered for outpatient use. Autologous therapies are manufactured as a single lot using the cancer patient's own cells, modifying the cells, and returning them back to the patient, whereas allogeneic cell therapies are manufactured in large batches using a donor's cells. Due to the complexity of manufacturing autologous cell therapies, these products have high cost of goods (COGS) and there are also manufacturing failures. In addition, the vein-to-vein time for these therapies from patient apheresis to infusion can be three to four weeks [7], which may be too long for some patients with progressive cancer in the metastatic setting. The supply chain logistics for these therapies are complex requiring antigen screening, apheresis centers, cold chain transportation, manufacturing, quality controls, scheduling and unique product tracking (chain of custody/identify). Cell therapies are currently being administered in academic medical centers due to the complexity of these therapies, the systems/logistical needs, institutional training requirements, and the coordinated stakeholder effort. The limited number of academic medical centers can result in restricted access for patients that are unable to travel. Pricing and reimbursement systems are not prepared to address the unique dynamics associated with potentially one-time curative therapies where pricing is very high and outcomes are not certain, when historically medicines are dosed at regular intervals and payments are spread over many years. Finally, the first cell therapies demonstrated impressive efficacy in liquid (hematological) tumors, however achieving similar efficacy in solid tumors will be challenging due to the complexities of the solid tumor microenvironment.

COMMERCIAL PLANNING

The focus on commercial planning is increasing as more cell therapies progress through clinical trials toward approval. These plans will need to account for the opportunities and challenges discussed earlier.

Determining supply chain strategies

Some companies are shifting their focus to internal vector and cell therapy manufacturing. The capacity for viral vector and cell manufacturing has been constrained and developing in-house manufacturing capabilities can be viewed as a strategic priority. Investing in technical operations, analytics, quality processes, and manufacturing capability can become a competitive advantage and companies

TABLE 1

Opportunities and challenges to the commercial adoption of immuno-oncology cell therapies.

Opportunities	Challenges
▶ Efficacy in hematological tumors	▶ Efficacy in solid tumors
▶ Potential curative nature	▶ Safety (cytokine release syndrome, neurotoxicity)
▶ Restored hope for patients	▶ Manufacturing/supply chain logistics
▶ One-time treatment	Commercial model complexity
▶ Earlier use in the treatment paradigm	▶ Pricing and reimbursement
▶ Gene editing and engineered products	

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are beginning to invest in these internal capabilities earlier in their development cycles. Biotech and pharma companies will be faced with strategic choices:

- Internal manufacturing capability vs. CMO (contract manufacturing organization): Investing in capability building can develop internal expertise, optimize processes, control manufacturing capacity, and save money in the long run. However, utilizing CMOs can help provide flexibility in capacity planning, reduce commitments to evolving technology platforms, and reduce up front investments;

- Centralized vs decentralized manufacturing: Centralized manufacturing can help to standardize processes and achieve greater scale. Decentralized manufacturing and regional hubs may be required to support global markets and overcome transportation delays while also establishing dual sourcing in the event of quality issues and natural disasters.

Given the complexity of manufacturing immuno-oncology cell therapies, it will be vital for companies to anticipate and plan for challenges in global scale up and avoid manufacturing delays that have been problematic for other launches.

Managing commercial model complexity

The patient journey for cell therapies is complex. To deliver cell therapies to cancer patients requires a coordinated effort ('white glove service') across multiple hospital stakeholders. Some of the stakeholders include oncologists, hematologists, transplant physicians, transplant coordinators, ICU physicians, nurses, apheresis technicians, lab technicians, pharmacists, schedulers, and reimbursement/insurance coordinators. To commercialize and help hospitals prepare for cell therapies requires a customized approach supported by company medical personnel focused on scientific and therapeutic questions, and Key Account Managers (KAM) to help coordinate across hospital stakeholders, nurse educators to support training, and logistic coordinators to help manage the flow of customized autologous cell therapy (from apheresis to manufacturing, frozen shipments, scheduling, and infusion). Several other platforms are needed to support cell therapies and contribute to the full stack of services:

- Companion diagnostic tests need to be approved and commercially available to help ensure patients express the right antigens and will benefit from the cell therapy;

- Patient Hub services are important to help patients navigate the reimbursement process and confirm coverage;

- Training programs to help healthcare professional understand the unique requirements of administering cell therapies and managing patients;

- Chain of custody/identity systems are required to ensure cells from the patient are tracked through the various logistical and manufacturing steps and returned to the right patient.

As multiple new cell therapies gain approval over the next few years, hospital systems are at risk of becoming inundated with managing multiple training programs, protocols, and systems. There would be value in having manufacturers and third-party suppliers come together and align on standardized systems and processes to reduce complexity for hospitals.

Finally, improving product safety and shifting to allogeneic off-the-shelf therapies, would significantly reduce the need for some of these white glove services and simplify logistics. These changes would enable expansion beyond academic medical centers into top tier community hospitals and increase access for patients.

Addressing pricing & reimbursement dynamics

Payers are not prepared to address the unique dynamics of one-time potentially curative cell and gene therapies with high prices (e.g. list prices of $475,000 for cell therapies to $2,000,000 for gene therapies). To address the unique pricing dynamics for these therapies, companies will need to develop innovative pricing and reimbursement models. Some of the alternative financing solutions being explored include:

- Payments spread over three to five years rather than a one-time full upfront payment;
- Outcomes based contracting models with payment/reimbursement tied to the performance of the therapy during the initial years (e.g. upfront payment and refunds issued if the therapy does not achieve anticipated performance metrics, or payments over time contingent on reaching performance metrics).

Companies also need to anticipate reimbursement challenges and generate health economic data, in addition to clinical data, to justify the value of their novel therapies to payers. In additional, it will be important for companies to ensure the availability of companion diagnostic testing to identify patients that express relevant antigens and who will benefit from a given therapy. Health economic data combined with companion diagnostic data will be required to support favorable market access and reimbursement.

Another challenge is that the cost of administering these cell therapies is not fully covered under existing hospital Diagnosis Related Group (DRG) payments and therefore hospitals may be concerned about losing money. In addition, if there are CRS or Neurotoxicity issues, that require additional support (e.g. ICU time), the costs associated with these services, above the product costs, are not always factored into reimbursement models. Improving the safety profile of future cell therapies would reduce ICU time and other hospital related costs while also enabling these therapies to be administered in the outpatient setting.

COMMERCIAL STRATEGIES TO DISRUPT THE MARKET

There are several strategic moves that will help to accelerate the adoptive cell therapy market in this new decade: demonstrating success in solid tumors, gaining efficiencies through allogeneic therapies, and driving outcomes by treating earlier (refer to Figure 2).

Expand into solid tumors

Biotech companies have initially focused on cell therapies that target liquid tumors as these cancers are considered easier to solve than solid tumors which have complex tumor microenvironments. However, solid tumors contribute to approximately 90% of all cancer cases, and therefore targeting solid tumors provides a much greater opportunity to help patients. To overcome the challenges of the solid tumor microenvironment, companies are developing novel constructs that address the need for cell trafficking, targeting, signaling, persistence, microenvironment/immunosuppression, and control. Companies such as Autolus, Iovance, Bluebird, Fate, Celyad, Tmunity, TCR^2 and others are taking diverse approaches to overcome these challenges. Forming partnerships with academia and other companies will also be critical to gaining access to top scientists, innovative platforms, new therapies, and combination products to help confront the solid tumor microenvironment.

Treating patients with solid tumors will require greater coordination across hospital staff as oncology experts in solid tumors will often have less experience with immuno-oncology cell therapies than the experts working with liquid tumors. To bridge this divide and share best practices, it may be beneficial to connect

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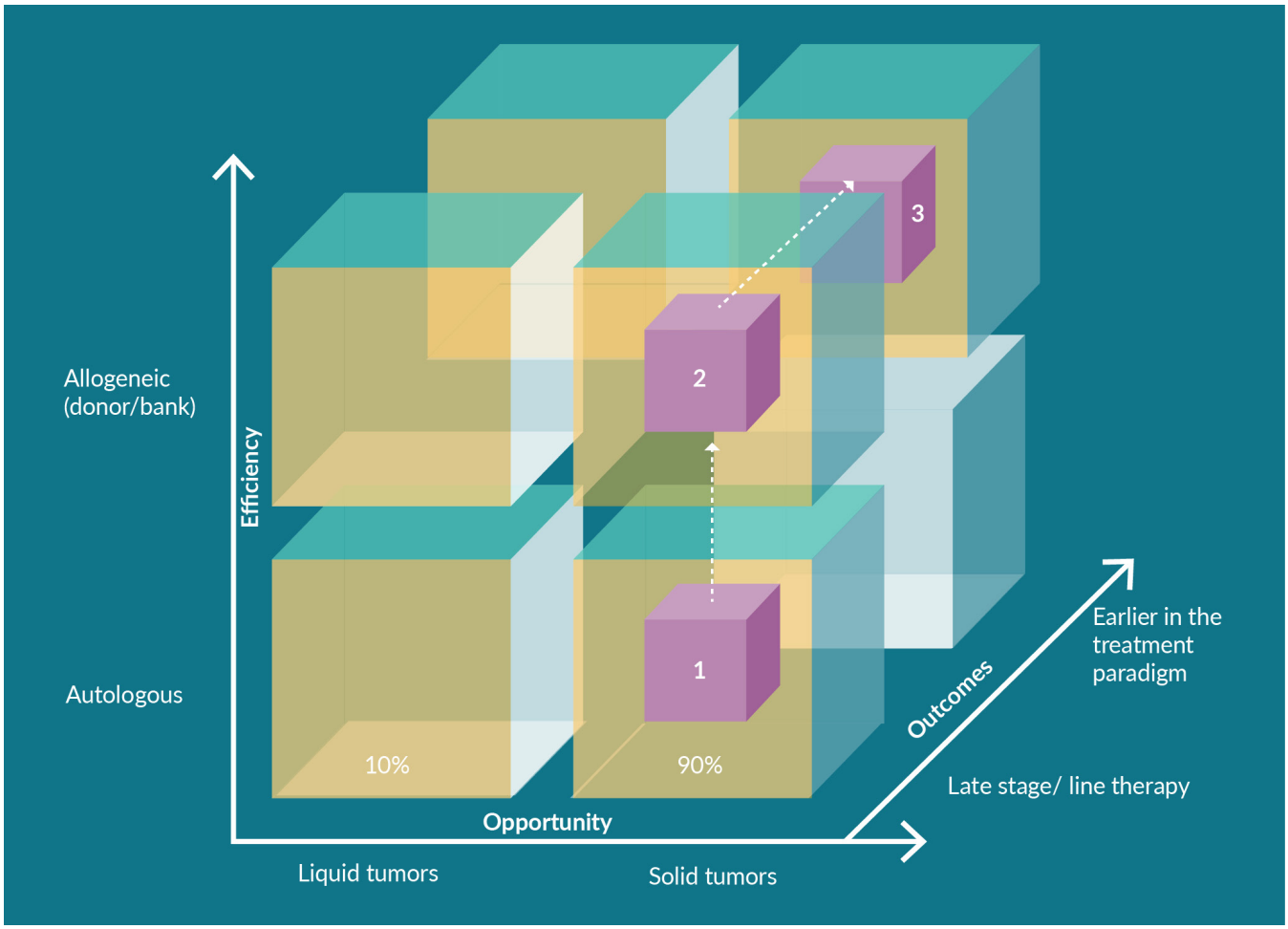
FIGURE 2

Strategies to disrupt the market.



Hematologists, who have stem cell transplant experience and early CAR-T therapy experience, with Oncologist treating patients with solid tumors.

Gain efficiencies

Cell therapies are expensive to manufacture and time consuming to produce due to the autologous nature of the initial cell therapies. To address these challenges companies will need to pursue manufacturing productivity improvement to reduce cost of goods by enhancing efficiency, automating manual processes, improving yields, and optimizing quality. Due to the autologous manufacturing process and high contribution of labor costs, economies of scale may be limited for the current generation of cell therapies. However, efficient use of established capacity will be a critical factor in reducing cost of goods [8]. It will also be important to reduce the current three to four weeks vein-to-vein cycle time for cell therapy manufacturing and logistics, particularly for metastatic cancer patients (initial candidates for cell therapy) who will be in urgent need of care. A significant portion of metastatic cancer patients may not be candidates for autologous cell therapy as they are unable to wait for manufacturing due progression of their cancer or due the poor quality of their own T cells (starting material for autologous manufacturing) following multiple rounds of chemotherapy.

Moving to an allogeneic platform has the following advantages: off-the-shelf availability, expanded patient eligibility (for therapy),

standardized starting material, manufacturing ease, and lower cost of goods. However, moving to an allogenic program introduces new challenges that will need to be solved such as managing risk of graft-vs-host disease, maintaining efficacy/persistency, identifying donors, and incorporating gene editing. To reduce the degrees of complexity and risk, most allogeneic therapies are being developed as next generation therapies using proven therapeutic targets for hematological cancers, before moving to solid tumor targets. The growing interest in allogeneic programs can be seen when evaluating the percentage of preclinical assets that are allogeneic vs. autologous relative to a similar comparison for the clinical assets in development as shown in Figure 3.

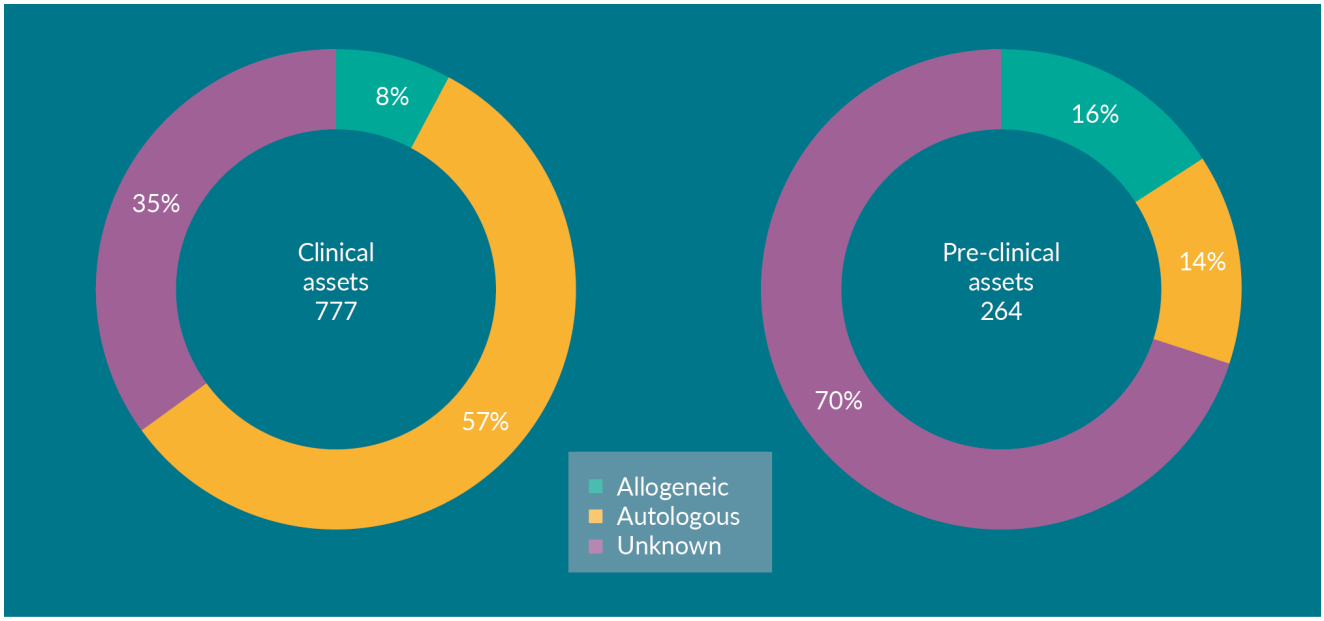
The initial focus for allogeneic therapies has been on donor-derived cells from companies such as Allogene, Precision, Cellectis, CRISPR, Sangamo/Kite, Atara, Poseida and others. Allogene shared encouraging allogeneic data and created excitement at the 2020 American Society of Clinical Oncology (ASCO) meeting [9]. There is also growing interest in the next generation of allogeneic therapies known as induced pluripotent stem cells (iPSC) which have the potential benefit of engineering multiple/complex edits into cells, screening for quality, and then developing a master stem cell bank to produce a renewable supply to treat large numbers of patients. If successful, allogeneic iPSC therapies have the potential to provide a consistent product, at a lower cost, and at manufacturing scale (more closely aligned with traditional biopharmaceutical manufacturing models). Companies such as Fate, Editas, Century, Allogene, and others are now pursuing iPSC-derived cell therapies. Producing efficacious, functional, and persistent iPSC cells will be challenging, but if successful, the benefit and impact during this decade will be significant.

Move earlier in the treatment paradigm

Initially, cell therapies will be used in the metastatic setting and in later lines of therapy due to the therapy costs, pricing/reimbursement challenges, logistical complexity, and safety concerns. However, the greater opportunity to help patients and increase commercial value will be in earlier lines of therapy or earlier stages of cancer where the tumor microenvironment is less complex, patient have better

FIGURE 3

Cell sources for CAR-T and TCR Therapies (April 2020) [10].



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health status (and higher quality T cells), vein-to-vein time is less critical, and patients can avoid chemotherapy/radiation side effects. To justify earlier use, companies will need to:

- Generate clinical data in earlier lines of therapy or earlier stages of cancer
- Build outcomes and health economic data to justify value
- Improve safety (e.g. CRS and neurotoxicity) and enable outpatient use
- Utilize predictive modelling, imaging, and omics to identify patient that will benefit from earlier use
- Reduce product costs

TRANSLATING INSIGHTS TO CREATE A NEW MODEL IN IMMUNO-ONCOLOGY

In this new decade, the introduction of immuno-oncology cell therapies has the potential to cure cancers, including solid tumors. The dramatic efficacy seen with the first two approved CAR-T therapies in hematologic cancers has helped fuel investor enthusiasm in funding new therapies and there has been a dramatic increase in the number of clinical trials globally for cell therapies, particularly in the oncology space. There are significant opportunities for these new therapies to help patients given the compelling initial efficacy data in cancer patients, the prospect of a one-time durable treatment, and the potential for a curative platform. To help accelerate the adoption of immuno-oncology cell therapies, companies will need to optimize manufacturing/supply chain strategies, manage commercial model complexities, and address pricing/reimbursement dynamics. To disrupt the oncology market with immuno-oncology therapies, it will be important to expand into solid tumors, gain efficiencies in manufacturing, and move earlier in the treatment paradigm. The introduction of these novel immuno-oncology cell therapies has the potential to dramatically improve patients' lives, radically transform the healthcare space, and mark this decade as an inflection point in the evolution of medicine.

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AFFILIATION

Glen Firestone
CEO & Founder, Firestone Advisors LLC
glenfirestone@gmail.com

AUTHORSHIP & CONFLICT OF INTEREST

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CELL & GENE THERAPY INSIGHTS

IMMUNO-ONCOLOGY: MANUFACTURING & COMMERCIAL BUSINESS MODELS FOR THE NEW DECADE

SPOTLIGHT

INTERVIEW

Understanding the drivers of success and failure in CAR T cell therapy

DR JAN JOSEPH (JOS) MELENHORST obtained his PhD at the LUMC (Department of Hematology) on the pathogenesis of Aplastic Anemia. In 1998 he moved to Bethesda, Maryland, where he did his research - first as a postdoc, later as a staff scientist - in the laboratory of Dr. John Barrett at the National Institutes of Health, on the immunobiology of marrow failure syndromes, leukemic disorders, and allogeneic stem cell transplantation. In 2012 he was recruited by Dr. Bruce Levine and Dr. Carl June to the University of Pennsylvania, first as Deputy Director of their clinical manufacturing (cGMP) facility. After a year he was promoted to Director of Product Development & Correlative Sciences. In this role, he was at the cusp of the first ever CAR T cell therapy approved by FDA: Kymriah. Dr. Melenhorst is interested in understanding and improving the anti-tumor efficacy and safety of adoptively transferred chimeric antigen receptor-modified T cells through correlative, mechanistic, and functional genomics approaches.

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Q What are you working on right now?

JJM: We are currently working on a number of projects that are all aimed at enhancing CAR T potency against certain leukemias. We discovered that in

"We now have evidence that the tumor plays a big part in the anti-tumor response as well; in providing sub-optimal stimulation for CAR T cells and in potentially synching a critical cytokine that drives T cell expansion."

chronic lymphocytic leukemia (CLL), the efficacy of CAR T cell therapies is largely determined by T cell intrinsic qualities. We now have evidence that the tumor plays a big part in the anti-tumor response as well; in providing sub-optimal stimulation for CAR T cells and in potentially synching a critical cytokine that drives T cell expansion.

In addition to that, we have extended our observations on pre-manufacturing T cells to other CAR T cell treated leukemias, and found that across the board, the memory functions of the pre-manufacturing cells are key components in the success of the CAR T therapies.

Finally, we are interrogating certain pathways in T cells that are in similar pathways as TET2 – in other words, we're looking at epigenetic regulators and how they affect the anti-tumor efficacy of CAR-engineered T cells.

Q What for you are the most vital lessons that the CAR T field has learned to date?

JJM: What we have witnessed over the last decade is that CAR-engineered T-cells using a patient's own immune cells can be incredibly efficacious – proof of concept has been delivered. However, the widely divergent response rate across the various malignancies is still poorly understood. Further to my previous comments, what we're seeing now is that the biology of T cells is an important contributor if not the driving factor in the efficacy of CAR T-cells. The implication here is that we should start our manufacturing process with the cells we have identified in such studies for cell manufacturing.

Secondly, what we have learned from our own studies and others is that there are soluble mediators such as cytokines, cytokine receptors, and others, that inflict toxicity and adverse events such as cytokine release syndrome (CRS). We are beginning to understand where these soluble mediators come from and also which pathways they are part of. We are in the process of finding out how we can intersect those pathways to make these therapies safer and more predictable.

The third lesson is that it is the quality more than the quantity of T cells that is really key in driving success. A higher dose doesn't necessarily translate to better efficacy; the type of cells that are infused is more important. This also means we can change the manufacturing process and potentially shorten the duration of culture. We published work on this two years ago in *Cancer Immunology*, and others have done similar studies that confirm this observation.

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Q In the cellular immuno-oncology space, are there any particular emerging modalities that stand out for you in terms of the impact you expect them to make?

JJM: From our immunology studies we have learned a great deal about the contributors to, and the determinants of, both success and failure. We have also learned that by combining CAR T therapies with other drugs such as small molecules, we can enhance the potency and extend the group of patients we can treat – I think that's the next iteration in CAR T cell immunotherapy.

Studies by Saar Gill and David Porter here at the University of Pennsylvania, and also Cameron Turtle and his team in Seattle, show that you can safely combine CD19 specific CAR T-cells with the small molecule ibrutinib, which inhibits CLL. Depending on how the trial is designed, if the patients are pre-treated with the drug to reduce tumor burden, this can potentially augment T-cell function. I think this is a good example of the synergy between small molecules and CAR T cells, and we've seen similar synergies between checkpoint inhibition and CAR T cells from various groups, including our own with Dr Stephen Schuster.

I would add that the ways that we engineer these cells and the way we culture them is more focused nowadays on preserving memory function. The cytokines and media that we and others use are different from what was done before in terms of preserving these qualities.

Q Are there any particularly pressing translational CMC issues you see within the cellular immunotherapy area that you feel should be prioritized by the community?

JJM: We are faced with a number of issues, one of them being the supply chain itself. In the United States and Europe, many groups are still using serum in their media for culturing cells whilst China has started manufacturing processes in serum-free media. In my view, if we want globalized therapies for various indications, we need to have a manufacturing process that uses serum-free culture media, and potentially also reduce the media volumes used and shorten the process altogether. We also need to work on securing the pipeline – the current coronavirus epidemic has really exposed some of the weak links in the supply chain; that needs to change.

> "...by combining CAR T therapies with other drugs such as small molecules, we can enhance the potency and extend the group of patients we can treat"

Then there is the streamlining of the manufacturing process itself. There is work being done at various institutions to automate the process and potentially generate a process that's "in a box". This can more easily be rolled out – right now, manufacturing is very centralized, but in my opinion, we should aim to decentralize it.

We have learned the lesson from a number of hematologic malignancies that immune cells in these patients, for various reasons including tumor-mediated suppression during the course of the disease and potentially toxic prior therapies (as shown by David Barrett and others at the Children's Hospital of Philadelphia), have a great impact on the performance of CAR T-cells. Some patients will not have the right cells to effect a clinical response. In cases like these, we should resort to using universal donor CAR T cells. This is not just informed by the poor performance of the patient's cells, but also from an economic standpoint in that the manufacturing of these cells is a lot cheaper and the cells are more readily available.

Q Moving forward, where do you see the greatest breakthroughs coming in the cellular immunotherapy CMC realm?

JJM: We have just published a paper in which we describe using CRISPR/ Cas9 to edit patient's immune cells to make them less susceptible to negative regulation by the tumor and/or tumor microenvironment, by knocking out a checkpoint regulator called PD1. I think that's one of the breakthroughs in cell manufacturing. There is persistence of the cells that are engineered with this tumor antigen-specific T cell receptor, and a similar process is feasible using CAR T cells.

In terms of enhancing the efficacy and streamlining of the process, as I mentioned earlier, the key is in knowing which cell population is needed as a starting point for manufacturing, and also understanding how to best preserve the required qualities by modifying the culture conditions and the media used.

Q Where do you see your own work going next?

JJM: My lab is a translational science laboratory and has a major focus on understanding what drives success and failure, and on the key components of the toxicity of the therapies we administer to patients. The ultimate goal is to deliver safe, potent anti-cancer T-cells with consistent critical quality attributes. I think we are closer than one might think, but all starts with carefully designed correlative studies, followed by the disentanglement of the mechanistic underpinnings in human T cells.

Another line of research we started last year is to understand the biology of the engineering process. When we engineer our T cells with a lentiviral vector that inserts the CAR into the genome, we have learned that the insertion itself may cause a disruption of gene function. By doing so, it can affect the T cells by either enhancing their potency or reducing it. We are now interrogating these integration sites in hundreds of patients using advanced technologies via *in vitro* and *in vivo* evaluation

"The ultimate goal is to deliver safe, potent anti-cancer T-cells with consistent critical quality attributes."

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pipelines. Ultimately, I hope to identify novel genes and manipulate their expression in order to further boost anti-tumor efficacy.

AFFILIATION

Dr Jan Joseph (Jos) Melenhorst
Professor of Pathology & Laboratory Medicine and Director, Parker Institute for Cancer Immunotherapy Biomarker Program, University of Pennsylvania, PA, USA

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CELL & GENE THERAPY INSIGHTS

IMMUNO-ONCOLOGY: MANUFACTURING & COMMERCIAL BUSINESS MODELS FOR THE NEW DECADE

SPOTLIGHT

INTERVIEW

Looking to the future of stem cell-derived immunotherapy

PETER ZANDSTRA graduated with a Bachelor of Engineering degree from McGill University in the Department of Chemical Engineering, obtained his Ph.D. degree from the University of British Columbia in the Department of Chemical Engineering and Biotechnology and continued his research training as a Post-Doctoral Fellow in the field of Bioengineering at MIT. In 1999, Dr Zandstra began his faculty appointment at the University of Toronto's Institute of Biomaterial and in 2016 was appointed University Professor, the university's highest academic rank. In July 2017, Zandstra joined the University of British Columbia as the Founding Director the School of Biomedical Engineering and as the Director of the Michael Smith Laboratories. In these roles, he aims to build programs with deeper interactions between the Faculties of Applied Science, Science and Medicine, especially as related to innovative research and training programs.

Peter is the Canada Research Chair in Stem Cell Bioengineering and is a recipient of a number of awards and fellowships including the Premiers Research Excellence Award (2002), the E.W.R. Steacie Memorial Fellowship (2006), the John Simon Guggenheim Memorial Foundation Fellowship (2007), and the University of Toronto's McLean Award (2009). Dr. Zandstra is a fellow of the American Institute for Medical and Biological Engineering and the American Association for the Advancement of Science. Peter's research focuses on understanding how complex communication networks between stem cells and their progeny influence self-renewal and differentiation, and how this information can be applied to the design of novel culture technologies capable of controlling cell fate.

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"I'm really excited about the ability to use hPSC to generate a renewable source of well-defined, modular-designed and cost-effective immunotherapies for cancer, as well as for other indications."

Q What are you working on right now?

PZ: A lot of things, but there are two main projects in the lab. One is looking at generating functional T cells from pluripotent stem cells. The second is generating gastrulation-stage or early mesoderm patterned organoids from human pluripotent stem cells (hPSC). The idea there is that if we can understand how symmetry-breaking events occur during hPSC differentiation, we might be able to guide early functional tissue development better than we are currently able.

Q What do you see as the most promising technology area(s) when you look across the cellular immuno-oncology therapeutic field today?

PZ: It is clear there are a number of great benefits to the early immunotherapies in terms of the efficacy they have shown, but there are also some significant challenges.

These challenges include heterogeneity in terms of responses between patients, cost of manufacturing, and the challenges we face with primary cells to really take advantage of the enhanced functionality that we are after with engineered cell therapies. I think one of the platforms that overcomes these issues is pluripotent stem cell-based immunotherapy - I'm really excited about the ability to use hPSC to generate a renewable source of well-defined, modular-designed and cost-effective immunotherapies for cancer, as well as for other indications.

Q Can you go deeper on the challenges encountered by stem cell-based immunotherapy researchers?

PZ: There are a few different challenges that people are facing and working on at the cutting edge. One is developing clinically relevant protocols for generating cells under conditions which allow efficient maturation. There's some work being done to try to mimic and engineer and replicate the properties of the thymus to guide T cell development *in vitro* and *in vivo.*

Another challenge is that we still need to understand the relationship between the functional targeting moieties which are added to cells, such as CARs, and how they influence and impact

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the signals necessary for T cell development. There is some very innovative and interesting work going on around this question – both with respect to the design of CARs, and the design of stimulators for the differentiation and subsequent maturation and expansion that is needed for a therapeutically relevant cell product.

Another key consideration is the importance of trying to connect *in vitro* phenotype to *in vivo* models, and the relevance or correlation of these data to human patient studies.

There are a number of different steps that have to happen there. Given that many of the cancer models for immunotherapies are done under conditions where there's some form of modulation or compromise of the immune system, our ability to really predict in an effective way what responses will look like in a patient remains a significant and very interesting challenge. Opportunities for better disease modelling abound.

Disease modelling is in fact another area where stem cell technologies are having an impact. Examples include different ways of creating genetic disease models using induced pluripotent stem cells, as well as various cancer or other tissue/organ models using organoids. We are hopeful that one day these organoid models will have the potential to replicate complex interactions between the immune system and the specific disease that is being treated. In addition to the technical challenges I mentioned earlier, I think new computational or statistical approaches to increase our understanding of the relationship between cell therapy product quality attributes, the design of the cells, *in vitro* phenotypic assays, and eventual efficacy in patients, is a really exciting area of research.

Q What is the current state of the art in cell reprograming tools/approaches? And what direction could or should further innovation in this area take?

PZ: In terms of reprogramming, the field is moving quickly towards better ways to create GMP-ready material. That GMP-ready material needs to be robustly characterized and ideally, suitable for use in multiple patients. Collectively, we would like to shorten the time needed for bringing PSC derived cell therapy products to clinical trials.

> "...opportunities and learnings now extend from reprograming to pluripotency, to programing cells into specific lineages and having those cells be designed for specific clinical indications."

We had a publication earlier this year, which was led by Nika Shakiba(UBC) , that showed that cell competition is an important aspect in determining reprogramed cell output properties. Nika's paper taught us a lot about how we may be able to design cells to be able to select individual clones after they are reprogramed, and how we might be able to engineer cell behavior for desirable *in vivo* properties.

Another aspect that's important to recognize is that opportunities and learnings now extend from reprograming to pluripotency,

to programing cells into specific lineages and having those cells be designed for specific clinical indications.

Q Looking to the future, where next for your work in stem cell-derived immunotherapy?

PZ: One of the fundamental questions we're looking at is learning more about is the relationship between the different trajectories and lineages that have immune cell competence, and defined phenotypes and markers that can be used to characterize and optimize the production of these therapeutically relevant cells. New strategies and modelling approaches based on temporal measurements of single cell sequencing or more direct lineage tracing technologies will be very exciting and helpful for the field.

New strategies and modelling approaches based on temporal measurements of single cell sequencing or more direct lineage tracing technologies will be very exciting and helpful for the field."

I also think that we can go much farther in terms of designing cells with specific control or maturation modules in them to influence cellular options during differentiation. As we go from a pluripotent cell to, for example, a mature effector T cells, there are many places where the cell has to make decisions along the way. If we can reinforce those decisions using designed-based circuitry to change when they go myeloid vs lymphoid, or when they go to mesoderm vs blood, or even NK vs. T, I think we can make some very interesting improvements to the platform.

AFFILIATION

Peter Zandstra
Founding Director - School of Biomedical Engineering; and
Director, Michael Smith Laboratories
University of British Columbia

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CELL & GENE THERAPY INSIGHTS

July 2020

Clinical Trends

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Clinical Trends

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July 2020
Volume 6, Issue 6

COMMENTARY

INTERVIEW

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Clinical Trends

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COMMENTARY

Clinical trials in the era of Covid-19: successes, failures & ongoing challenges

In our July issue, Sven Kili focuses his regular analysis of current clinical trends on the far-reaching and in some cases devastating impact of the Covid-19 pandemic. From new investment trends and delayed trials to changes to approval processes, the shockwaves of the pandemic have been felt in almost every corner of the cell and gene therapy field.

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Since the emergence of Covid-19, the world has been plunged into various forms of isolation for the last 5 months. In response, the biopharma machine has swung into action, focusing thousands of researchers and clinicians on finding a cure for the pandemic – and now seems like a good time to take stock and see what progress is being made, what price has been paid, and where we may be heading next in these unprecedented times.

INVESTMENT IMPACT

We have all had to find new ways of working during the pandemic, and this has caused us to revaluate how we do business. This includes the venture capital (VC) world, where investment has become much more virtual. Both biopharma and tech VCs have embraced the 'invest at a distance' approach and deal-making has continued apace by virtual means [1]. In fact, the number of deals done in May was the highest in over 2 years, even if the actual investment volume was not as high as what we saw in March of 2020, as the virus really started to take effect in Europe and the USA [2,3]. It is too early to call this a true 'trend', but data starting to emerge from sources such as Pitchbook indicate Quarter 2 of 2020 was the largest VC capital

funding quarter in history for US biopharma companies [4]. The increased deal flow seems to encompass more diagnostics and smaller company investments. Despite the slight changes in focus, this is truly amazing – and encouraging.

This trend has also flowed through into initial public offerings (IPOs), where we are seeing a number of companies seeking well- and over-subscribed IPOs [5]. To date, approximately 23 companies have IPO'd with an average 80% return. This includes therapeutic developers as well as specialized suppliers. Given this positive investment sentiment, public companies are now also making use of the window to raise additional capital to finance what may be tough times ahead, but also to finance acceleration of Covid-19 related development plans [6]. By the end of May, in excess of $3 billion had been raised via new offerings and debt.

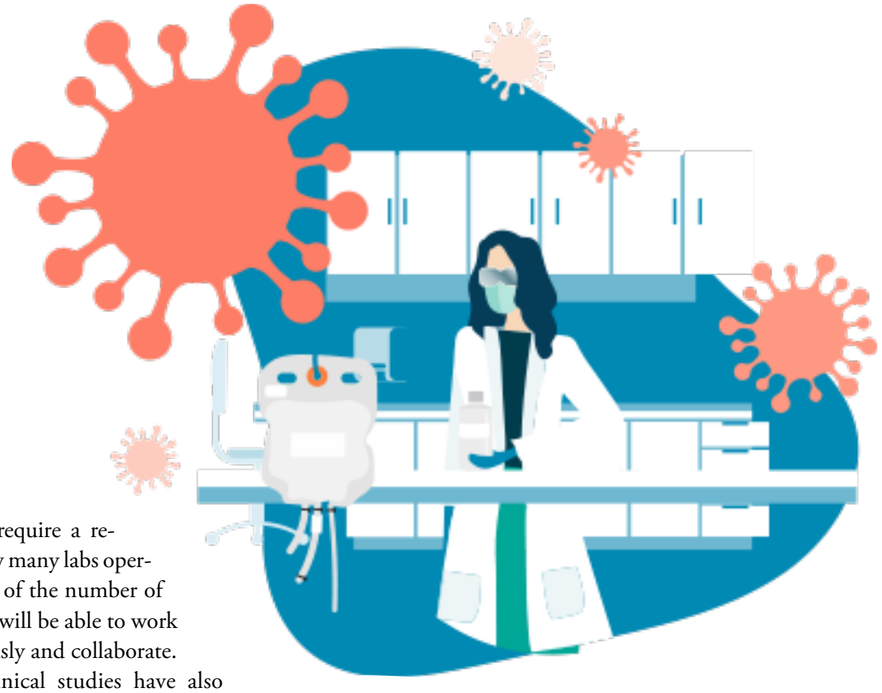
Biopharma is one of the few sectors that can really make a difference in the reach and effect of Covid-19 and this has not been lost on investors who are looking to be part of the solution, which when it comes will be extremely valuable. Just as with the rising tide, this positive investment sentiment has carried over to all levels of investment, even in areas that are not specifically working on Covid-19. So whilst this virus has caused havoc for the world's populations and economies, it seems to be having a rather positive effect on many cell and gene therapy companies. The one area of uncertainty is how long this positive situation will last. We have seen a number of new high-profile funds being raised and just starting the investment cycle, but delays to development and potentially meaningful progress will bring stagnation in the face of financial burn. How will investors respond to this? Will they keep more money in their funds to weather the storm, or will they seek to cull some investments and focus on supporting only a small number with greater long-term value propositions?

This early investment picture is in stark contrast to the wider deal-making world where investment and M&A has ceased or decreased dramatically [7] as larger companies scramble to stabilize their programs and staff.

COVID-RELATED TRIALS & TRIBULATIONS

Thousands of labs worldwide were forced to shut as part of the pandemic response with the result that many experiments have now been lost or severely delayed. Re-starting will take considerable time, effort and money [8]. To make matters worse, many labs are still waiting to restock various reagents which have expired and are no longer available until more are made, and awaiting fresh stocks of PPE. Additionally, when returning, many labs will be required to practice social distancing,

> "...for therapies being developed that are not focused on Covid-19, what lessons can be learned? Some of the recent examples have highlighted the critical need for regulators to be independent of the ruling government, so that they can make their assessment unencumbered by political conflicts and directives."



which will require a rethink of how many labs operate in terms of the number of people who will be able to work simultaneously and collaborate.

Many clinical studies have also been halted or substantially scaled-back to meet the demands of the Covid-19 response [9–12]. Various estimates abound, but GlobalData reports that at least 322 biopharma companies' trials have suffered [13]. The majority are mid-stage trials, but early and pivotal trials are also affected. The challenge is how these will restart: with the profusion of Covid-19 trials starting up, the clinical research infrastructure and staffing is unlikely to be able to cope. Most hospitals are still focused on treating Covid-19 patients to the exclusion of other sick patients requiring treatment, and experimental therapies do not feature strongly [14–17]. And in the UK alone, more than 2 million operations have been cancelled.

A small number of clinical studies, mostly for ultra-rare life threatening conditions, have managed to continue due to the unwillingness of dedicated units to be stopped in their crusade to do the very best for their patients. But even these centers have had to slow down to cope with new ways of working and the currently evolving access issues surrounding PPE, supplies and drugs.

On the other side of the coin, the number of trials and development programs targeted towards Covid-19 and its complications continues to climb: as of 1 July, 1,570 trials are registered globally for all modalities, and in excess of 70 for various cell-based therapies [18].

Stat News reports that since January 2020, 1,200 clinical trials have been developed to test various preventions and treatments for Covid-19 [11]. Unfortunately, the lack of centralized or even regional coordination of these studies has resulted in a large number of trials that will replicate data, not recruit sufficient patients, not generate clinically significant data, or not even manage to complete recruitment. In fact, many clinical studies are designed in such a way that they will not generate sufficient data with 39% enrolling fewer than 100 patients. 38% had not even begun enrolling by the start of July. This is a global problem and again indicates the lack of pandemic preparedness both locally and globally. With many of these trials being conducted in a single country or facility, the fragility of our international collaborative clinical site network is again exposed in favor

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of a growing nationalist approach. This may result in potentially differing outcomes and results in different countries, further contributing to the widening divide caused by this viral pandemic. The lesson we should learn here is that we need to find better ways of working together across borders to coordinate clinical studies for this and future pandemics [19]. This will help ensure that trials are well powered and designed, patients are available, outcomes are comparable, and results are usable by the various players. This coordination should be non-partisan and likely would fit well within the remit of the global regulatory bodies already set up for many of these activities. I believe there is a mechanism whereby commercial advantage and confidentiality can be retained in such a process.

A CHANGING CLINICAL LANDSCAPE

Of course, the global lockdown is not good news for patients awaiting potentially life-saving or life-changing experimental therapies. But in some ways, it may be even worse news for the companies and investigational therapies affected by the shut-down. As companies sit idle waiting for studies to re-start, they are still burning cash to keep the lights on, keep staff engaged from home, and have drug product stored. (They may even be getting ready to manufacture more product to replace expired materials). According to the experts, there is a good chance many companies will not be able to recover from this stoppage, negatively impacting both patients and the science.

This may be the best time for companies to take a step back and explore contingency planning and start-up plans in detail, both in isolation and in partnership with suppliers, providers, CDMOs, and other collaborators.

We still have no real idea when many clinical trials will be able to recommence, as regular clinical service must take precedence and the backlog must be cleared. When development does finally restart, there is a good chance that the clinical development landscape will look very different. Until a global vaccine is discovered and administered, some form of social distancing will continue to be required. Staff and at-risk patients (such as those with cancer and eligible for CGT trials) will need to be protected somehow, global and regional supply chains will need to reopen, suppliers and contractors will need to resume operations (supplies allowing) and hospitals will need to have the space and supplies to run the studies. With all of this there remain many big unknowns: how will Covid-19 affect clinical trial insurance premiums and risk? Will global supply routes return to a pre-Covid-19 state, or will nationalistic protectionism be the order of the day, as we have recently seen with PPE and certain therapies? What will happen to patients whose clinical programs disappear out from under them due to sponsor company collapse? Will the regulatory framework change to meet the challenge? How will companies prioritize non-Covid-19 therapies in the light of ongoing Covid-19 therapy development? How exactly will governments react to 'deglobalization' in terms of greater local support for therapies, especially those that may provide a strategic advantage in the future?

This 'deglobalization' seems to be affecting approved therapies for the moment, as seen by the recent US administration's deal to purchase all available stock of Remdesevir from Gilead, which was closely followed by the EU seeking to secure access for itself as a knee-jerk reaction [20]. This nationalism and 'me first' attitude is truly the worst in humanity beginning to show through the veneer of international cooperation. Global advanced therapy organizations need to push back against this selfish and disgusting activity and set a better example to politicians who are beginning to show their true colors. It is our duty to humanity to ensure that these therapies reach the patients most deserving – wherever in the world they are located.

EXPLORING NEW REGULATORY APPROACHES

The Covid-19 era has also brought additional changes from the regulators. In the early days of the US lockdown, the world stood witness to the effects of politics driving health regulation in the ultra-fast Emergency use Authorisation (EUA) of hydroxychloroquine and chloroquine by the FDA. This seemed to be based on much less data than would usually be required, but was accompanied by glowing presidential approval in speeches and on Twitter. Embarrassingly, on the 15th June the FDA was forced to backtrack in the light of clinical study data and withdraw the approval. It seems the new clinical study data showed that not only did hydroxychloroquine not provide any benefit, it may even cause more damage in certain at-risk patient groups [21–24].

The original approval decision shocked a lot of people, as the FDA has typically been one of the most detail-oriented and slowest moving agencies, making this blip in the approval radar even more concerning. It is very positive to see that the FDA is once again focusing on scientific rigor, and that they are engaging proactively with academia and industry to review programs and provide guidance in a variety of ways. This includes the Coronavirus Treatment Acceleration Programme (CTAP) as well as pre-IND and other consultation programs such as INTERACT. Promisingly, we are seeing shorter review and response times in line with the urgency of the pandemic.

The EMA has in turn also committed to accelerated scientific advice and review timelines for therapies linked to Covid-19, while stressing the need to retain quality and patient safety via the EMA pandemic Task Force (COVID-ETF) [25].

This approach is being replicated in various forms by most regulatory agencies globally as countries seek to support their researchers in finding a viable treatment or cure for the virus. Companies and development consortia will need to be extra vigilant in this space, as it is conceivable that the regulatory powers of a country may be used for nationalistic reasons, i.e., as a means to ensure a promising therapy is developed and made available primarily or solely in one country or territory. We have already seen the US purchasing the majority (or all, depending on the source) of the global Remdesivir stocks. In our global CGT environment, we must make sure that these life-saving therapies are not 'weaponized' by nationalistic elements in governments and are instead made available to the neediest patients globally on an equitable basis. This will not be an easy task, but then neither is developing life-saving therapies.

Going forward, and for therapies being developed that are not focused on Covid-19, what lessons can be learned? Some of the

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recent examples have highlighted the critical need for regulators to be independent of the ruling government, so that they can make their assessment unencumbered by political conflicts and directives. The focus must continue to be on safety and efficacy, which takes time – but we have seen review timelines shorten substantially in the pandemic. If this is something we would like to see continue, perhaps it is worth considering if we would be prepared to pay a little more for a faster review. Scientific advice has always been available, but shortening the timelines and decreasing the price is unlikely to be sustainable; encouraging a dialogue about what is possible on a more permanent basis may be the best way forward.

Despite the high death rate globally and the continued suffering of many people who have 'recovered' from Covid-19, there have been many positive developments and therapies to aid the fight against this pandemic. As we continue to move forward, it is imperative that we take the time to consider what went well and seek ways to maintain those improvements – before it is too late.

SVEN KILI is Principal at Sven Kili Consulting Ltd, where he provides specialist strategic consulting services to innovative cell and gene therapy companies. His clients include small and medium sized companies from formation through to clinical development and commercialization. He was previously the Head of Development for the Cell and Gene Therapy division of GSK Rare Diseases where he led teams developing and commercializing *ex vivo* Gene Therapies for a variety of rare genetic disorders including Strimvelis®, the first *ex vivo* gene therapy to be approved for children with ADA-SCID; Wiskott-Aldrich syndrome (WAS); metachromatic leukodystrophy (MLD) and beta-thalassemia. Prior to this, he was Senior Director, Cell Therapy and Regenerative Medicine for Sanofi (Genzyme) Biosurgery where he led the clinical development, approval and commercialization activities of the first combined ATMP approval in the EU for MACI®. He and his team also prepared and submitted Advanced Therapy regulatory filings for Australia and the USA, including health technology assessments and he was responsible for late stage developments for Carticel® and Epicel® in the USA. Before joining Genzyme, Sven led the cell therapy activities and oversaw all UK & Irish regulatory functions and was the QPPV for pharmacovigilance for the Geistlich Pharma. Sven trained as an orthopedic surgeon in the UK and South Africa and since leaving full-time clinical practise has developed expertise cell and gene therapy in clinical development, regulatory compliance, value creation, risk management and product safety, product launches and post-marketing activities. He is on the board of CCRM in Canada; Xintela – a Swedish Stem Cell company, the SAB for LGC Corporation and is the chair of the CGTAC as part of the UK BIA and a Board member of the Standards Co-ordinating Body for Regenerative Medicine. Most recently, Sven was appointed as Chair of the UCL course 'Masters in Manufacture and Commercialisation of Stem Cell and Gene Therapies' steering committee. Additionally, he still maintains his clinical skills in the UK NHS and serves as an ATLS Instructor in his spare time.

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AFFILIATION

Sven Kili
Principal, Sven Kili Consulting Ltd, UK
sven.biosurgery@gmail.com

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CELL & GENE THERAPY INSIGHTS

Clinical Trends

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INTERVIEW

Innovation in clinical translation of advanced therapies

MOHAMED ABOU-EL-ENEIN is a professor of regenerative medicine and head of clinical development platform at BIH center for regenerative therapies, Charité – Universitätsmedizin Berlin, Germany. He is a physician by training, received a master's degree in pharmaceutical sciences and biotechnologies from Strasbourg University, a clinical research certificate from Harvard Medical School, a doctoral degree in the economics of manufacturing cellular therapies from Charité and a master of public health from London School of Hygiene and Tropical Medicine. He is also trained as a qualified person (QP) for production and quality control of advanced therapies. Dr Abou-El-Enein is one of the recipients of the inaugural Lawrence Goldstein Policy Fellowship, was awarded the Max-Rubner Prize for innovation and the prestigious Eisenhower Fellowship, acted as the regional secretary of the International Society for Cellular Therapy (until June 2020) and is an active member of many international expert networks and committees. He has more than 10 years of experience as a clinical developer where he is responsible for the early-stage clinical development of several cell-based therapies. His research focuses on devising methods and tools to optimize the manufacturing, clinical translation and evidence synthesis for cell and gene therapies as well as improving the current regulatory frameworks governing the development of these novel products. Dr Abou-El-Enein is a strong advocate for equitable access to safe and effective medical innovations, protecting global health and public safety. He is committed to addressing the global rise of clinics marketing unproven stem cell interventions, as well as emerging health technologies beyond stem cell.

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Q What are you working on right now?

MA: My primary function is leading the translational/clinical development services at our research center. We are a translational academic center developing cell and gene therapies (referred to in Europe as Advanced Therapy Medicinal Products [ATMPs]), so I design mainly early-phase clinical trials in various disease areas. We have a particular interest in regulatory T cells (Tregs) since they possess immunosuppressive properties that are essential for the maintenance of immune homeostasis. We were one of the early centers to investigate the safety and feasibility of multiple doses of autologous Tregs (part of the ONE Study) as a potential therapeutic modality in solid organ transplantation to enable us to taper down the immunosuppression and their toxicities while maintaining graft acceptance [1]. The infusion of Tregs into live donor kidney transplant recipients was safe and feasible, and we are currently publishing the results of this Phase 1/2a trial. We are now planning subsequent clinical trials using Tregs in different patient populations. We are also moving toward the use of Chimeric Antigen Receptor (CAR)-Treg since merging the benefits of CAR technology with Tregs offers a promising, more potent therapeutic option for tolerance induction [2]. We also investigate other products, such as virus (EBV/CMV/BKV)-specific T cells, cardiac-derived stromal cells, placenta-derived stromal cells (collaboration with Pluristem Ltd), tissue-engineered heart valves and vessels, as well as TCR-transgenic and CAR-T-cells in different disease entities from rare to common diseases.

Being also a junior professor of regenerative medicine at Charité Medical University, I have research and teaching responsibilities. My research revolves around the scientific, regulatory, and ethical challenges in the development and clinical translation of cell and gene therapies and related technologies [3]. I am leading a small research team to investigate issues such as the strength of scientific evidence and develop tools to optimize manufacturing, clinical translation and regulatory science for these novel products. We aim to improve the clinical/translational methodologies that developers (including us) use to generate evidence on the safety and efficacy of cell and gene therapies, de-risk the process and provide guidance as to 'best practices' in this field [4]. For instance, we recently published what we consider a landmark study to evaluate the sufficiency of the evidence in regulatory submissions of advanced therapies for marketing authorization and to benchmark them against more established biological products such as monoclonal antibodies [5].

Given that 5 out of 15 currently approved ATMPs (as of July 2020) were withdrawn after gaining marketing authorization, analysis such as ours is essential to understand the reasons. Our results have debunked several myths about advanced therapies. Firstly, contrary to popular belief, regulators are very supportive and even somewhat flexible with the evaluation of submitted dossiers. Secondly, product

"I am leading a small research team to investigate issues such as the strength of scientific evidence and develop tools to optimize manufacturing, clinical translation and regulatory science for these novel products."

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manufacturing challenges are not unique to ATMPs but are seen in other biological products. Thirdly and most importantly, the clinical development of ATMPs is indeed challenging where most of the trials are underpowered and lack suitable comparators, mainly due to targeting patients suffering from rare, severe, or advanced diseases. However, we observed that the majority of regulatory objections to clinical development programs of some ATMPs were due to lack of adherence to Good Clinical Practices (GCP) and protocol compliance, among others, than can be reasonably avoided. We hope that this work will join other efforts in improving the development, uptake, and sustainability of advanced therapies.

> "Given that 5 out of 15 currently approved ATMPs ... were withdrawn after gaining marketing authorization, analysis such as ours is essential..."

We are also very much concerned with the ethical aspects of the unproven use of stem cells. We have previously published a comprehensive analysis of all adverse events from patients receiving unproven treatments [6], and we are in the process of further exploring that particular topic.

Q Can you go a little deeper on Charité Berlin's past and current activities in the clinical development of ATMPs, and how it became one of Europe's largest medical centers specializing in the field?

MA: The Charité is one of Europe's largest university hospitals (about 15,000 employees and around 1,000,000 patients/year). Regenerative medicine, immunology, neurosciences, cardiovascular medicine, and oncology are the five main clinical research areas of the Charité. One of the advantages that Charité provides is access to strong clinical expertise that we have in-house, which very much complements our scientific discovery and research work. I think that when you have these two aspects available and integrated in one place, it provides you with an excellent environment for translation. Charité's involvement in cell and gene therapy has been ongoing for a long time. The center that I am part of started in 2006 as the Berlin-Brandenburg Centre for Regenerative Therapies (BCRT), co-founded and led by Professor Hans-Dieter Volk. Recently it became integrated into the BIH (Berlin Institute of Health) – another long-standing initiative initially designed to strengthen the translational capabilities of Germany as a whole, and Berlin in particular.

Now named the BIH Centre for Regenerative Therapies, our primary focus is on diseases of the immune system (where I started as a student), musculoskeletal and cardiovascular systems, as well as areas of research that straddles different medical disciplines, such as tissue homeostasis and cachexia. This translational structure ensures the success of the therapeutic development program, including the manufacturing and clinical testing of medicinal products owing to our in-house Good Manufacturing Practice (GMP) facility, established and led by Professor Petra Reinke. Based on our experiences, we founded a new 'spin-off' structure called the Berlin Center for Advanced Therapies (BeCAT), which is fully dedicated to fostering the

development of advanced therapies. BECAT focuses on four research topics: (i) endogenous regeneration and immune regulation; (ii) combined advanced therapies (with medical devices); (iii) gene-editing technologies, and (iv) cancer immunotherapy. The center has the following integrated platforms: (v) manufacturing and product characterization; (vi) biomarkers; (vii) clinical development and health technology assessment. The new BECAT infrastructure, including building-up of an additional nine state-of-the-art GMP units, received in 2017 a €30 million granted following a highly competitive process of the German Council of Science and Humanities.

Over the past decade, the BCRT/Charité has become very well positioned in Europe in terms of cell and gene therapy translation, particularly via participation in European networks including the coordination of several consortia and/or work packages. One of the earliest is the ONE Study that I referred to earlier, a large consortium consisting of seven investigator-led trials done internationally at eight hospitals in France, Germany, Italy, the UK, and the USA to investigate the safety and feasibility of different Tregs and monocyte-derived (dendritic cell, Mreg) cell products in kidney transplant patients [7]. Both the ONE study and BIO-DrIM (another consortium focused on the implementation of biomarker-driven strategies for personalizing immunosuppression) received funding from the FP7 program of the European Commission. Currently, we are coordinating four Horizon 2020-funded consortia (PACE, HIPGEN, ReSHAPE, and RESTORE), all focusing on advanced therapy development.

We have also worked intensively to establish many vital external collaborations, either with research institutions or regulatory bodies. For example, my department, in particular, has a close connection with the Paul-Ehrlich-Institut, the German federal institute for vaccines and biomedicines, and the European Medicines Agency (EMA), as demonstrated by our frequent co-publications with colleagues there. We believe that this kind of bilateral dialogue between scientists and regulators is the most efficient way to move the field forward.

Q How has the COVID-19 pandemic impacted clinical development activities at BCRT/Charité, and how have you adapted?

MA: As you can imagine, the COVID-19 situation has brought disruption to everything we have been doing. In a short space of time, we needed to rethink the whole paradigm of clinical research activities. Charité actually developed one of the first diagnostic tests for COVID-19, as the result of the research work led by Professor Christian Dorsten, who is directing the Institute of Virology. Charité is also coordinating an initiative to tackle the current pandemic crisis by establishing a network, which pools all relevant expertise and supports COVID-19-related research across Germany. The initiative received €150 million from the Federal Ministry of Education and Research (BMBF). Charité has also postponed all planned medical procedures/operations to free up hospital beds and personnel capacities for patients in need of treatment for COVID-19. These recent developments and shifts in focus have, understandably, impacted ongoing clinical research activities in other disease areas. As we started to return partially to our daily routine, the university has regularly been releasing clear

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"Charité actually developed one of the first diagnostic tests for COVID-19, as the result of the research work led by Professor Christian Dorsten, who is directing the Institute of Virology. Charité is also coordinating an initiative to tackle the current pandemic crisis by establishing a network, which pools all relevant expertise and supports COVID-19-related research across Germany."

instructions for working in the laboratories and offices to ensure proper hygiene and protection of personnel. This also applies to the workflow in clinical trials.

Given my training as a physician and experience in translational immunology, it became natural, as part of adapting to the current situation, to get involved in COVID-19 related research. Currently, my team is working with researchers from Charité and other clinical centers in Germany in studying and understanding the T and B cell immune responses to the SARS-CoV-2 (the virus causing COVID-19). These efforts will support vaccine development and increase our apprehension of the immunopathogenesis of the disease. In terms of cell therapy development, we are collaborating with industry partners for the clinical testing of cell therapy product candidates as treatments for patients with severe SARS-CoV-2 pneumonia. We are also monitoring closely how regulatory authorities are responding to the pandemic and how this is influencing the regulatory landscape of drug development.

Q Are there any further learnings or changes that might impact ATMP developers' long-term from the COVID-19 pandemic experience?

MA: It's too early to draw any definite conclusions, but my feeling is that in the years to come, we will have to rethink the current therapeutic development strategies, particularly in case of public emergencies and urgent unmet medical needs. With COVID-19, we found ourselves in a very challenging scenario where we, the scientific community, didn't have any readily available and reliable solution. I think this will significantly change the way we do things moving forward, how we approach the drug development process, and how the regulatory processes can be further streamlined while striking a balance between accelerated development and generating sufficient clinical evidence.

Again, this is something that I personally have a great interest in. Striking this balance is not trivial – it's challenging, given the pressure on regulators from both the public and policymakers to push forward clinical trials and approve drugs. But at the same time, we have the responsibility to safeguard patients from potentially dangerous, poorly investigated therapeutic approaches. There is a lot of good science going on, but there is a lot of questionable science

"I think [Covid-19] will significantly change the way we do things moving forward, how we approach the drug development process, and how the regulatory processes can be further streamlined while striking a balance between accelerated development and generating sufficient clinical evidence."

as well, and we have to be able to distinguish between them. This should not solely be the responsibility of the regulators, but of the entire scientific community. Whether it be scientists reviewing articles for publication or external evaluators for funding applications, I think we all have to be very vigilant.

In terms of how this may impact the ATMP field, we already see more development of cell therapies for indications and complications resulting from pathogens, viral infections, etc. So I do foresee changes occurring both on the developer side – with the focus shifting to certain diseases or pathogens as being more relevant to target in the post-COVID-19 era – as well as on the regulatory side in terms of the regulatory structure, and systems for fast responses that needless to say should ensure the safety of patient populations. This expected paradigm shift will clearly influence the investment landscape for ATMP as well.

Q Where do you see evolution in the ATMP space in terms of innovation in clinical trial design?

MA: As mentioned before, the clinical development of ATMPs is plagued by myriad of challenges. One main issue is that the mechanism of action for most cell and gene therapies is not entirely understood, or might take a very long time to study, which makes it very difficult to set up reliable clinical endpoints through which you can adequately measure therapeutic effectiveness and improvement in patients. Consequently, there has tended to be a greater reliance on surrogate endpoints (such as biomarkers to measure molecular, histologic, radiographic, or physiologic characteristics) to try to measure clinical benefits. Unfortunately, relying solely on surrogate markers might misguide the actual effect and added value of the therapeutic modality. Even when using a surrogate endpoint in a clinical trial, those markers should be validated, and developers should prove that these endpoints can accurately predict or correlate with clinical benefit in the studied indication. A recent study has already reported that most of the pivotal trials supporting accelerated assessment and conditional marketing authorization routes submitted to the EMA (for all medicinal products, not just ATMPs) used nonvalidated surrogate endpoints [8]. Even though the authorization of these products remains conditional until developers fulfill several imposed postmarketing measures, I believe the situation warrants further attention. The EMA as well as the US Food and Drug Administration (FDA) have released guidance for the use of surrogate endpoints, but it remains a tricky area for the ATMP field.

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The question is, how can the situation be improved? I think before we talk about 'innovative' clinical trial designs, we should go back to basics and ensure that what we do is done correctly. We introduced in 2017 a 12-step guideline for reducing risks typically associated with translating biomedical technologies [4]. I think those steps have stood the test of time and remain as relevant as ever. In a nutshell, biomedical developers should take into consideration several vital aspects when approaching their clinical development program. They should consider the careful choice and design of the *in vivo* models and employ *in vitro* tissue like microsystems (e.g., organs-on-a-chip) to fill in gaps in preclinical knowledge, whenever possible. Early clinical studies should integrate smart study designs – and by smart, I mean well thought out, able to provide primary support for effectiveness, and aligned with clinical endpoints relevant to patients, providers, and payers [9]. If available, the use of validated biomarkers should be considered to allow a clinical trial to identify and differentiate between drug responders and nonresponders. One point, which despite being a standard practice in clinical research is usually overlooked, is defining clinical benefit by comparing baseline values with treatment-produced values for outcomes. Pivotal trials investigating rare diseases or life-threatening conditions with very low incidence/prevalence that can't enroll controls should consider the use of a control arm drawn from historical data, whenever possible. A comprehensive benefit–risk assessment strategy tailored to each product should be devised whilst satisfying regulatory expectations for product authorization. Finally, it is important to have a mindset when approaching early/small trials, that their design and analysis must enable a reasonable measure of clinical effect to be statistically asserted. As mentioned earlier, several problems we see with ATMP clinical evidence are avoidable [5] as some developers may tend to circumvent the need for comprehensive trial designs in a bid to decrease the financial burden and the time needed to perform trials.

There is no doubt that we want ATMPs to reach the market/patients as soon as possible, and we should take advantage of tools such as accelerated assessments and conditional approvals, etc. But in fact, it might not be in the developer's long-term interests to rush to marketing authorization with weak evidence. Particularly if post-marketing requirements imposed by regulators are too extensive, smaller companies may not be financially capable of surviving – this may in turn result in potentially valuable therapies being removed from the market. At the same time, we need to continue to improve the current post-marketing study methodology for ATMPs and support ongoing real-world data collection, which will better inform the long-term safety and efficacy of these products [10].

Q Lastly, what are your chief priorities and goals for your work over the coming 12–24 months?

MA: After more than a decade in Charité, it is time to explore new avenues. I will be assuming a new role which will be publically announced very soon. Nevertheless, my priorities did not change. One of my main priorities, as we are approaching the clinic ourselves with several CAR based therapies, is to join efforts in paving the way for faster and more efficient uptake of CAR T cells into clinical routine. It is becoming increasingly evident

that CAR T cell therapies are here to stay, and their product portfolio is expanding rapidly. Besides regulatory hurdles to be overcome, there also exist several other barriers to the availability of such cellular products [11]. That may be: (1) optimizing their manufacturing workflow; (2) improving the CAR structure to enhance the engineered T cells expansion and anti-tumor effects while reducing potential toxicities; (3) understanding the clinical factors around pre-existing and adaptive immune responses affecting product safety, efficacy and persistence; (4) standardizing the clinical trial design and reporting of these products, to some extent, in order to allow for an adequate interpretation of clinical result and valid pooling of data [12]; (5) devising workable models for a decentralized production to streamline logistics, and the list goes on.

As such, my research is very focused on these issues, including the development of new therapeutic concepts adopting CAR technology and genome editing [13,14].

We will also continue looking at how clinical evidence is being generated around the cell and gene therapy field. We are currently developing tools that can hopefully help developers ensure they have a better dossier at the time of regulatory submission. We are, in parallel, focusing on implementing machine learning tools and automated extraction of data to help us streamline what we are doing and to try to make better use of publicly available evidence. Finally, we will continue our work on the policy and ethical aspects surrounding cell and gene therapies.

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AFFILIATION

Mohamed Abou-El-Enein, MD, PhD, MSPH
Charité – Universitätsmedizin Berlin, Germany

AUTHORSHIP & CONFLICT OF INTEREST

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Commercial Insights

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COMMERCIAL INSIGHT: MAY 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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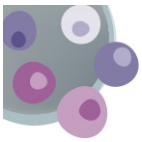

CELL THERAPY – Mark Curtis. Director, Manufacturing Partnerships, AVROBIO

J&J/Legend Biotech posted some impressive data this past month at ASCO from a Phase 1b study investigating an anti-BCMA CAR-T therapy in patients with relapsed or refractory multiple myeloma. Patients in the study were heavily pre-treated, some receiving several prior treatment modalities with little or no response. In the long-term follow-up portion of the study 86% of patients had a complete response at nearly 12 months, showing the therapy has durability in a subset of patients with otherwise poor prognosis. On the financing front, Legend Biotech announced plans to take the company public in the United States, listing on the Nasdaq to raise $100M. Legend will use the proceeds to continue funding development of its BCMA program. SQZ Biotech raised $65M to continue development of its cancer vaccine for HPV-positive cancers and expand its technology into the infectious disease space.

GENE THERAPY – Richard Philipson. Chief Medical Officer, Trizell Ltd, UK

This year's American Society of Gene & Cell Therapy (ASGCT) Annual Meeting was held virtually, but COVID19 did not impact the quality of the meeting, with a program of innovative science and the largest ever collection of abstracts. Both Pfizer and released important data at the meeting, with Pfizer presenting promising efficacy outcomes for its treatment for Duchenne muscular dystrophy alongside some potential safety concerns, and AveXis describing positive outcomes in animal models of Friedrich's ataxia that pave the way to human studies. In an important month for AveXis, the company also announced approval in Europe for its spinal muscular atrophy type 1 treatment Zolgensma, giving it approval in all three major territories. Elsewhere, Avrobio's *ex vivo* therapy for Fabry disease appears to have durable effects, with benefits persisting for 22 months of follow-up in the first patient treated.

Clinical Regulatory

PFIZER'S LATEST DMD GENE THERAPY DATA A MIXED BAG

Pfizer's Duchenne muscular dystrophy (DMD) gene therapy, PF-06939926, has shown promise in restoring muscle function in children according to results presented at the virtual meeting of the American Society of Gene & Cell Therapy, but safety continues to be an issue – and could prove an even bigger problem due to the current pandemic.

PF-06939926 increased the level of dystrophin in patient's muscles and improved their functional motor abilities using the North Star Ambulatory Assessment (NSAA), a 17 point rating scale used to monitor disease progression and treatment in children with DMD. A year after treatment, six patients – three administered a low dose and three who received a high dose – improved by a mean of 3.5 points on the scale. The high dose patients had dystrophin levels at 51.6% of normal levels, and the low dose group 24%.

However, the improvements come with caveats: when Pfizer previously reported on the treatment it was disclosed that two patients had to be hospitalized, with one requiring treatment for dehydration caused by vomiting, and the other requiring dialysis and immunosuppressants for acute kidney injury and complement activation. The most recent data adds a third patient experiencing side effects, who required a platelet transfusion and an immunosuppressant drug to treat complement-related complications.

Pfizer believe the side effects are caused by the AAV9 vector used in the delivery of the therapy, and the side effects have been deemed serious but manageable. But how significantly will these issues affect Pfizer's success, especially in the current climate?

One market analyst predicts that the issue could give Sarepta Therapeutics DMD gene therapy, SRP-9001, an advantage, as it utilizes an AAVrh74 vector.

"This aligns with our view based on the totality of historical data that SRPT's AAVrh74 vector may have intrinsic safety advantages over AAV9 based approaches, which will give SRPT an advantage both in clinical trials and in the commercial setting, even if PFE's AEs are ultimately monitorable/manageable,"

wrote BC Capital Markets analyst Brian Abrahams.

Another analyst, Alethia Young of Cantor Fitzgerald, noted

"[Even] if risk can be reduced with high dose steroids or Soliris pretreatment, this may not be viable in the real world. In light of COVID-19, we wonder the comfort level around even a small potential risk of complement activation

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and having to possibly be hospitalized for no matter how short".

Another DMD gene therapy offering from Solid Bio, SGT-001, was halted by the FDA in December last year after a patient experienced an adverse event involving complement activation, thrombocytopenia, a decrease in red blood cell count, acute kidney injury and cardio-pulmonary insufficiency.

Pfizer plans to move forward with Phase 3 of the study in the second half of 2020.

Ones to Watch

Treatment with Pfizer's AAV9-based gene therapy – PF-06939926 – in boys aged 6–12 years with Duchenne muscular dystrophy (DMD), appears to result in improvements in both the concentration and distribution of mini-dystrophin in muscle biopsies, as well as in the North Star functional assessment of ambulation. However, these apparent benefits come at the price of side effects suggestive of complement activation akin to atypical hemolytic uremic syndrome, which required treatment with the complement C5 inhibitor eculizumab. Pfizer chose the AAV9 delivery vector, which carries a shortened version of the human dystrophin gene (mini-dystrophin), because of its potential to target muscle tissue. However, this could put it at a disadvantage to Sarepta's microdystrophin-expressing AAVrh74 vector, which has not been associated with side effects related to complement activation. The company is nevertheless forging ahead this year with a randomized, double-blind, placebo-controlled Phase 3 study in 99 boys aged 4–7 years with DMD. – Richard Philipson

EARLY TRIAL OF ALLOGENE'S CAR T SEES 63% RESPONSE RATE IN LYMPHOMA

Allogene has reported a 63% response rate in an early trial of its off-the-shelf CAR T in lymphoma, after an earlier report of a 78% response rate in nine patients in an early clinical trial.

The latest data encompasses 19 patients out of 22 treated with the CD19-directed CAR T, ALLO-501, plus the antibody ALLO-647. Seven had a complete response, and five a partial response, with nine avoiding relapse during the follow-up period of just under 4 months.

For patients who received higher doses of ALLO-647, the complete response rate was 50%. Re-dosing also saw success in one patient who progressed 2 months after being treated: they received a second dose of ALLO-501 plus a higher dose of ALLO-647 and responded, remaining well at the time of publication. In terms of adverse events,

ALLO-501 was designed to reduce the risk of graft-versus-host disease, and no incidences occurred during the trial. Cytokine release syndrome was seen in 32% of patients, but was described as "mild to moderate" and resolved within 7 days. Three patients in the trial had previously been treated with personalized CAR Ts, which failed – and they didn't response to ALLO-501 either. Allogene CEO, David Chang, commented that this is something the company will look at more closely for clues as to which patients are most likely to respond to the treatment.

Allogene has now begun a further trial of an improved version of ALLO-501 that is designed to eliminate interactions with the antibody Rituxan, which can act as a "kill switch" for CAR T cells and is used to treat various cancers including non-Hodgkin lymphoma. If successful, the company plans to progress the improved therapy to Phase 2 trials.

GENE THERAPY RESULTS IN STRONGER, LEANER MICE

A recent report in *Science Advances* details a gene therapy that could hold promise for obesity-associated osteoarthritis (OA). Weight loss and exercise are considered potential interventions for patients with obesity and joint inflammation, but achieving long-term weight loss and strength gain can prove difficult, especially for frail or elderly populations.

Follistatin (FST) has been used in the treatment of several degenerative diseases – and the research team hypothesized that a gene therapy approach to deliver FST could increase muscle mass and reduce obesity-associated metabolic inflammation. The treated mice not only nearly doubled their strength without any extra exercise, they also shed weight and were found to have fewer metabolic issues and healthier joints, even when fed a high-fat diet.

"We've identified here a way to use gene therapy to build muscle quickly," commented senior investigator Farshid Guilak, professor of orthopedic surgery and director of research at Shriners Hospitals for Children, St Louis. "It had a profound effect in the mice and kept their weight in check, suggesting a similar approach may be effective against arthritis, particularly in cases of morbid obesity."

One area for caution is in the potential building of heart muscle – treated mice in the study were found to have healthier hearts than their untreated counterparts, but thickening of the walls of the heart could become dangerous over time, and further study is needed. However, the researchers are hopeful that the therapy could potentially be used to treat several conditions that involve muscle wasting.

"WORLD'S MOST EXPENSIVE DRUG" SCORES CONDITIONAL EU APPROVAL

Novartis, which bagged Zolgensma® with its $8.7 billion takeover of AveXis in 2018, has won conditional EU approval of the drug and is in pricing talks with various countries with the aim of a quick launch.

Zolgensma® is used in the treatment of spinal muscular atrophy (SMA) and is shown to be especially effective in improving survival and motor function in babies with SMA whose symptoms have yet to develop. 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

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5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene.

Given that the drug has been heralded as "the world's most expensive" with a cost of $2.1 million per dose in the USA, pricing has been an important talking point. Novartis is in talks over a "Day One" access program aimed at speeding access to treatment by dealing with payment issues up front.

"Even under the current pandemic conditions, the urgent need to treat SMA has resulted in access pathways in France and Germany for Zolgensma®, a potentially life-saving medicine delivered in a single dose. Additionally, we have met with more than 100 stakeholder organizations across Europe to discuss our 'Day One' access programme to enable rapid access with customisable options designed to work within local pricing and reimbursement frameworks"

commented Dave Lennon, president of AveXis.

Expert Pick

News of the approval of AveXis's Zolgensma® for the treatment of spinal muscular atrophy (SMA) type 1 in Europe completes an important turnaround for the product, which just under a year ago was under a cloud after the company informed FDA of possible data fabrication issues. However, following inspection of an AveXis facility, FDA considered that no enforcement action was necessary and concluded that Zolgensma® was safe and effective for its intended use. Following FDA approval, Japanese regulators have also given the nod to Zolgensma®, and a "yes" in Europe gives AveXis a full house of approvals in the big three territories. – Richard Philipson

CANADIAN STARTUP EMPIRICA HOPES TO BRING CAR T FOR GLIOBLASTOMA TO THE CLINIC BY 2022

Glioblastoma is the most aggressive form of cancer originating in the brain. Despite the advances the cancer field has made in surgical techniques and therapies, patients face an extremely stark prognosis: most will die within 12–18 months of their diagnosis.

Now, a team is looking to apply a novel cell therapy to the problem. The brain child of researchers at McMaster University and the University of Toronto, Empirica Therapeutics has launched to bring a promising CAR T treatment to the clinic.

In a paper titled 'The Rational Development of CD133-Targeting Immunotherapies for Glioblastoma', published in *Cell Stem Cell*, the researchers detail their findings. First, they

tested three treatments *in vitro* and in mice: a human IgG antibody, a bispecific T-cell engager antibody (BiTE), and eCAR-133, a CD133-specific CAR-T. eCAR-133 outperformed the other approaches in a preclinical model of human glioblastoma, and didn't induce acute systemic toxicity in mice.

The aim for Empirica now is to progress the potential therapy towards clinical trials in recurrent glioblastoma patients, something it hopes to achieve by 2022. And it is not the only company setting sights on a CAR T for glioblastoma – as interest in treating solid cancers with CAR T therapies grows, other groups are also exploring potential CAR T treatments for glioblastoma, including one based on a toxin found in scorpion venom.

Ones to Watch

Glioblastoma is a notoriously difficult indication to target in the clinic. Standard-of-care remains poor and patients are in dire need of novel treatment modalities capable of targeting glioblastoma cells in a targeted fashion. Early-stage, Canada-based biotech, Empirica, is developing a CD133-targeted CAR-T therapy that has shown promise in pre-clinical studies when compared to traditional antibody therapies, and bi-specific antibodies, which are able to simultaneously bind a cancer cell and a T cell in the tumor microenvironment. Empirica plans on bringing its novel CAR technology into the clinic, targeting its first study in 2022. – Mark Curtis

J&J CAR T THERAPY SHRINKS TUMORS AND ACHIEVES PROGRESSION-FREE SURVIVAL AT 9 MONTHS

Johnson & Johnson (J&J) has announced updated results from the Phase Ib/II CARTITUDE-1 study of its BCMA-directed CAR T, JNJ-4528, against relapsed or refractory multiple myeloma.

The therapy has seen 86% of patients achieve progression-free survival at nine months, and all 29 study patients had their tumors reduce in size. The study population is made up of patients whose cancer had returned after multiple other treatments, or who had never responded to treatment at all. Tumors began to shrink at a median of one month after treatment. Most (93%) of patients experienced cytokine release syndrome (CRS), and although most cases were mild, it did cause the death of one patient. Two other study participants also died; one from cancer progression and another from a non-treatment related leukemia.

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Mark Wildgust, vice president of global medical affairs, oncology, at Johnson & Johnson's Janssen R&D unit commented:

"These patients have essentially run out of treatment options. The median survival of this kind of patient is 6 to 10 months based on the literature. The fact that 86% of the patients are essentially progression-free at nine months is really good news for them. That starts to point toward durability. We still need to follow patients much longer, but we think that's very encouraging for these patients."

Jansenn's partner, Legend Biotech, has seen progression-free survival in patients in the LEGEND-2 study for 20 months, and Jannsen also hopes to achieve this – especially as the two therapies only differ due to manufacturing process differences between China and the USA.

PASSAGE BIO RECEIVES RARE DISEASE DESIGNATION FOR PBGM01

Passage Bio's PBGM01 gene therapy for infantile GM1 gangliosidosis (GM1) has already been granted Orphan Drug designation by the FDA, and has now also been granted Rare Pediatric Disease (RPD) designation.

The infantile form of GM1 gangliosidosis is the most severe and usually presents by the age of 6 months, with symptoms including developmental regression, skeletal abnormalities, seizures and profound intellectual disability. Most affected infants do not survive past childhood, and no disease-modifying therapies are currently available.

RPD designation is granted by the FDA for serious diseases mainly affecting those under 18 years old, that affect under 2000,000 people in the USA – and drug developers who qualify may receive a priority review voucher. PBGM01 is an AAV-based gene therapy that delivers a functional *GLB1* gene encoding β-gal to the brain and peripheral tissues in order to reduce the accumulation of GM1 gangliosides and potentially reverse neuronal toxicity. Preclinical studies have been promising, and a Phase 1/2 trial is planned for the fourth quarter of this year.

"This is the second regulatory designation we have received from the FDA for our lead program in GM1 and reflects the high unmet need in this patient population," commented Bruce Goldsmith, president and CEO of Passage Bio. "As a company we are committed to developing therapies that transform the lives of patients suffering from serious life-threatening CNS disorders. We believe that PBGM01 has the potential to restore developmental progression, enabling patients to achieve additional milestones and improve quality of life. We look forward to advancing PBGM01 into clinical testing later this year."

BMS REPORTS PROMISING OUTCOMES WITH IDE-CEL – BUT HITS FDA REVIEW STUMBLING BLOCK

Johnson & Johnson isn't the only player with a BCMA-directed CAR T against multiple myeloma currently in trials – Bristol Myers Squib's (BMS) offering, decabtagene vicleucel (ide-cel) is also showing promise in the clinic.

Developed in partnership with bluebird bio, ide-cel was tested at three dose levels in 128 patients with relapsed or refractory multiple myeloma, who had tried a median of six other treatments. The treatment shrunk tumors in 73% of participants and cleared tumors in 33%, with 78% of patients surviving for a year post treatment. Relapse was held off for a median of 8.8 months and extended

life by a median of 19.4 months. In patients whose cancer was cleared by the treatment, relapse was held off for 20.2 months.

The majority (84%) of patients experienced cytokine release syndrome (CRS), with mostly mild cases – although CRS did cause the death of one patient, and seven more (6%) required aggressive treatment.

"Now that BCMA as a target is getting validated, we continue to look at the identification of patients who are going to have better outcomes. Translational research is going to become very, very important," commented BMS CSO, Samit Hirawat. "We think we are making true advances in providing a safe medicine for these patients, but we have some ways to go in terms of learning and improving the overall safety profile," Hirawat added.

However, there is one additional obstacle to overcome: when BMS and bluebird bio filed for FDA review in March, the FDA refused to review the submission for ide-cel, citing concerns with the manufacturing process. The companies now aim to refile by July.

AVROBIO RELEASES PROMISING UPDATES ON ITS FABRY DISEASE THERAPY

A 22-month update on the Phase 2 trial of Avrobio's AVR-RD-01 gene therapy for the treatment of Fabry disease has seen the company release more positive results. The *ex vivo* lentiviral therapy delivers a working copy of *GLA*, the gene mutated in Fabry disease, in order to prevent the build up of the fatty substance globotriaosylceramide (Gb3) by replacing the enzyme alpha-galactosidase A.

In previous data from the first patient enrolled in the study released last year, it was reported that there was an 87% reduction in plasma lyso-Gb3 after 1 year. Now, at 22 months, the patient continues to have elevated alpha-galactosidase A, which has remained around the same levels after falling from an initial peak. Plasma lyso-Gb3 and total Gb3 levels remained lowered. For an additional three patients with a shorter follow up, enzyme activity was also increased and plasma lyso-Gb3 was lowered. At the cut off, the fourth patient, who had lower plasma lyso-Gb3 level at baseline than other subjects, had a plasma lyso-Gb3 lowered by 43%. For the first patient who had the highest baseline levels, the decline was 88%.

However, the long-term effects of the treatment remain to be seen – and some questions remain about the veracity of the link between plasma Gb3 and clinical endpoints such as renal function.

PHASE 3 TRIAL OF OMIDUBICEL IN BLOOD CANCER MEETS PRIMARY ENDPOINT

Omidubicel, formerly known as NiCord, has been shown to cut time to neutrophil engraftment in a Phase 3 trial. The cell therapy offering from Gamida Cell is being trialled in people with acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, myelodysplastic syndrome and lymphoma.

Patients with hematologic cancers are treated with hematopoietic stem cell transplantation to restore bone marrow function – but in cases where donor-matched cells cannot be sourced, patients receive alternatives including umbilical cord blood, which contains fewer stem and progenitor cells and can result in a longer time to engraftment.

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Gamida believes that omidubicel can improve on cord blood engraftment time – and the new data backs this up. In 125 patients randomized to receive either omidubicel or umbilical cord blood, neutrophil engraftment took 12 days in the cohort receiving omidubicel in contrast to 22 days in the cord blood cohort. A longer engraftment time can result in higher infection risk and longer hospital stays – and Gamida have previously said shortening the time by just one week would "make a difference in the value proposition" of omidubicel.

The rest of the data from the trial is still to be released, but Gamida has reported that the therapy was generally well tolerated, and associated with a higher rate of transplant success. The company now plans to begin a rolling submission to the FDA later this year.

LATEST DATA ON FRIEDREICH'S ATAXIA THERAPY SUPPORTS FIRST-IN-HUMAN STUDIES

AVXS-401, AveXis' experimental therapy for the treatment of Friedreich's ataxia (FA), is suitable for first-in-human studies, according to the latest data.

AVXS-401 utilizes an adeno-associated vector to deliver a functional copy of the gene *FXN* in order to restore the production of the protein frataxin in tissues most affected by FA, such as the heart and central nervous system (CNS).

The key takeaways from the new results are that the treatment proved safe and well-tolerated by healthy mice, and demonstrated improvement in phenotype in FXN-deficient mice as well as a 300% increase in median survival. Moving to primate studies, the treatment was again found to be safe and well tolerated with no observed pathology related to frataxin expression. At 6 months post treatment, AVXS-401 showed continuing mRNA transcription in the CNS and heart. The data, presented at the virtual American Society of Gene & Cell Therapy (ASGCT) Annual Meeting, concludes that "Together these pre-clinical data show that AVXS-401 is suitable for first-in-human studies."

FATE THERAPEUTICS ANNOUNCE IND CLEARANCE FOR FT538

The first CRISPR-edited, induced pluripotent stem cell (iPSC) derived cell therapy under development has had its investigational new drug application cleared by the FDA. Developed by Fate Therapeutics, FT538 is an off-the-shelf natural killer (NK) cell cancer immunotherapy.

FT538 is derived from a clonal master iPSC line engineered with three functional components designed to boost the innate immune response:

- Expression of a novel high-affinity hnCD16 Fc receptor, which improves antibody-dependent cellular cytotoxicity;
- Expression of the IL-15RF cytokine complex, which promotes NK cell survival and persistence;
- Elimination of CD38 expression, which enhances innate effector molecule function and prevents anti-CD38 antibody-mediated NK cell death.

Fate now plans to begin a first-in-human clinical investigation of the treatment in acute myeloid leukemia (AML), both as a monotherapy (regimen A) and in combination with the CD38-directed monoclonal antibody therapy daratumumab (regimen B). The trial will

involve three different once-weekly dose levels of FT538, and Fate may also initiate a third regimen involving lotuzumab, an FDA-approved anti-SLAMF7 monoclonal antibody.

Expert Pick

Induced pluripotent stem cell (iPSC) technology has come a long way and Fate Therapeutics has been at the center of activity in the space with a platform for generation of different cell types for therapeutic applications. The company recently announced an advancement in the field – the first IND of a CRISPR-edited cell therapy derived from iPSCs. Fate used gene editing technology to make a series of modifications to an iPSC master cell bank, which was then differentiated to produce an enhanced natural killer (NK) cell therapy. The drug product (FT538) will initially be tested in AML and multiple myeloma. – Mark Curtis

BMS ANTI-CD19 CAR T EXPERIENCES REGULATORY SETBACK

Coming shortly after its BCMA-directed CAR T was rejected for review by the FDA due to manufacturing concerns, Bristol Myers Squibb (BMS) has hit another CAR T-related snag – the FDA has delayed a decision on its anti-CD19 CAR T liso-cel.

Back in February, the FDA granted priority review for a filing for approval of liso-cel which would have led to an approval decision being made by August – but this has now been pushed back to November. BMS has attributed the delay to a request for additional information from the FDA, which when submitted, led the agency to require more time to review the application.

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Licensing agreements & collaborations

NOVASEP AND LYSOGENE TEAM UP ON GANGLIOSIDOSIS GENE THERAPY

Novasep and Lysogene have signed an agreement to develop and manufacture a gene therapy candidate for the treatment of GM1 gangliosidosis.

Lysogene, a Phase 3 gene therapy platform company, and Novasep, a supplier of services and technology in life sciences, plan to work on LYS-GM101, an AAV-based gene therapy candidate. This collaboration continues a partnership that began with work on Lysogene's lead gene therapy product for mucopolysaccharidosis Type IIIA, LYS-SAF302, which is currently in clinical Phase 2/3.

Mark Plavsic, Lysogene's Chief Technical Officer, commented:

"Following the successful relationship developed during the past 4 years, I am very pleased to continue working with Novasep, which is emerging as a true leader in gene therapy development and manufacturing. By extending our collaboration, we secure the clinical production of our experimental treatment for GM1 gangliosidosis and take an option for a smooth and effective technical transfer to a future commercial process."

BLUEBIRD BIO AND BRISTOL MYERS SQUIBB REWORK CAR T DEAL

Bristol Myers Squibb (BMS) and bluebird bio have reworked their deal concerning the anti-BCMA CAR T inde-cel, and the new agreement sees BMS handing over $200 million in order to remove its financial obligation to pay bluebird bio for ex-US milestones and royalties on both inde-cel and its follow up, bb2121.

BMS inherited the collaboration when it took over Celgene, and under the original terms of the deal Celgene and bluebird were set to evenly split US profits and costs for inde-cel, with bluebird set to receive royalty payments on ex-US sales.

Joanne Smith-Farrell, bluebird bio Chief Business Officer and leader of the company's oncology unit, commented:

"With bluebird exiting the passive participation as supplier outside the USA, we and BMS are taking steps to ensure an efficient and robust supply chain for this program. This, together with the monetization of our ex-US royalties and milestones will allow bluebird to

continue to participate in co-developing and co-commercializing ide-cel within the US and to refocus resources on our internal programs and pipeline."

As mentioned earlier, inde-cel has now experienced a setback in its FDA review timeline, but expectations for the treatment remain high based on its clinical outcomes.

PASSAGE BIO EXPANDS UPENN DEAL

Passage Bio launched in February 2019 with a research, collaboration and license agreement with the University of Pennsylvania (UPenn) that gave the company five gene therapy programs, and the option to license seven more. Now the deal is expanding, with Passage Bio offering $5 million more per year in exchange for the chance to license five more programs from Penn's gene therapy program and extend the deadline for implementing those programs from 2022 to 2025.

The agreement also expands Passage Bio's exclusive rights to new technologies such as capsids, formulation improvements and improvements to gene therapy safety, that come from the lab of gene therapy pioneer Jim Wilson, who also co-founded Passage.

"We have an expanded opportunity to incorporate advances that are happening at Penn—research advances that will help us [beyond] the initial programs we had options to," Passage CEO Bruce Goldsmith commented. "We want to be able to partner with Jim and his group on leading those advances and incorporating them into programs as appropriate … and on an ongoing basis," he added.

Finance

KRIYA THERAPEUTICS RAISES $80.5 MILLION TO TARGET GENE THERAPY FOR COMPLEX DISEASE

Traditionally, many potential gene therapies have targeted monogenic disease – but Kriya Therapeutics is moving in a different direction, and taking aim at more common and complex diseases such as diabetes.

After a series A round of fundraising which involved Dexcel Pharma, Foresite Capital, Bluebird Ventures, Narya Capital, Amplo, Paul Manning, Transhuman Capital, and more, the company plan to put the $80.5 million raised

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towards both programs it has licensed and to the discovery of its own gene therapies.

Kriya currently has three programs licensed from Universitat Autònoma de Barcelona and the NIH, all focused on adeno-associated virus (AAV) based gene therapy for metabolic disease, and all with applications in diabetes.

The aim, explained Kriya CEO Shankar Ramaswamy in an interview, is to take well-characterized complex diseases with proteins of known therapeutic relevance and build delivery technology that can deliver the right protein to the right tissue, while applying lessons already learned in the gene therapy field to overcome manufacture and design challenges. The company also plans to pick up treatments from academic teams who may lack the ability to translate their work into therapies.

"We view ourselves as a partner of choice for academic groups that may not have the necessary translational infrastructure that a select few universities have," commented Ramaswamy. "That will be a solution to a big bottleneck in the field. We feel fortunate to have the right team in place to do that," he added.

SQZ BIOTECH PLANS TO PUT THE SQUEEZE ON CANCER AND INFECTIOUS DISEASE WITH NEW FUNDING

SQZ Biotechnologies Company has announced $65 million in series D funding drawn from Temasek, GV, Illumina Ventures, Invus, Polaris Partners, NanoDimension and JDRF T1D Fund. SQZ hope to use the funds to progress its lead asset – a cancer vaccine for HPV-positive tumors – through phase I trials, to further develop its pipeline, and to expand into infectious disease.

SQZ's cell therapy platform involves utilizing microfluidic technology to squeeze cells in order to disrupt their membranes and allow materials to pass through, and is being applied in multiple therapeutic areas. Roche partnered with SQZ in 2015, and expanded the deal three years later. The partnership covers SQZ's cancer programs using antigen-presenting cells (APCs), including the lead program targeting HPV-positive solid tumors, known as SQZ-PBMC-HPV. The Phase 1 trial of SQZ-PBMC-HPV is focused on turning patient cells into treatments within just 24 hours, and SQZ hopes to develop a point-of-care system to allow the treatments to be created at the point of care, rather than sending cells to a manufacturing site.

SQZ is also working on its own cancer pipeline and on expanding its APC technology to treat infectious diseases.

"Our progress in oncology and recent expansion into the infectious disease space exemplifies the broad potential of the SQZ platforms. Coupled with our rapid central manufacturing and investment in developing a new point-of-care system, we believe SQZ's differentiated approach to treating disease could provide meaningful benefit to many patients,"

commented SQZ CEO Armon Sharei.

LEGEND BIOTECH PREPARES TO MAKE A SPLASH ON THE US MARKET

China-based Legend Biotech has raised $423.8 million in its initial public offering, and has listed stock on the Nasdaq under the ticker "LEGN", in a bid to fund a pipeline led by the anti-BCMA therapy JNJ-4528.

Johnson & Johnson paid $350 million upfront for a global license to JNJ-4528 in 2017. With a filing for approval looking likely, and other CAR T therapies in the pipeline, parent company Genscript Biotech have decided that the timing is right to spin out its cell therapy unit.

Genscript and J&J have high hopes that Legend can hold its own in a CAR T space currently dominated by US companies – and Legend could also see JNJ-4528 competing against other drugs that target BCMA, including GlaxoSmithKline's antibody-drug conjugate and Amgen's bispecific T cell engager.

But JNJ-4528 isn't the only arrow in Legend's quiver, with further autologous CAR Ts against CD19xCD22 and CD33xCLL-1 in the works, along with an allogeneic cell therapy for hematological cancer currently in the clinic.

Movers & shakers

RARE DISEASE SPECIALIST JOSEPH MCINTOSH JOINS ARUVANT AS CMO

Joseph McIntosh, MD, has left his position as Vice President and Head of Clinical Development at PTC Therapeutics to become Chief Medical Officer at Aruvant Sciences.

Aruvant launched in 2018 and has a focus on gene therapy for blood diseases. McIntosh's initial focus will be overseeing clinical development of ARU-1801, a one-time gene therapy for sick cell disease and beta thalassemia designed to increase functioning red blood cells.

With 16 years working in drug development and over a decade in rare disease, McIntosh has previously held positions at Eisai and Pfizer, before joining PTC where he was responsible for a portfolio of assets of chemical and gene therapies covering hematology, oncology and rare genetic disease. He also worked on the approval of Translarna, PTC's Duchenne muscular dystrophy offering.

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"I am thrilled for this exciting opportunity to work on ARU-1801 and to join such a talented team at Aruvant. We have the important goal of providing patients with sickle cell disease a potential cure with a lower conditioning chemotherapy burden," commented McIntosh.

"Dr McIntosh's extensive experience in rare disease and gene therapy will be invaluable as we advance the clinical development of our potentially curative gene therapy ARU-1801," commented Will Chou, Aruvant CEO. "Given the durable efficacy we have seen in the first sickle cell disease patients treated with ARU-1801, we are excited to accelerate this program forward under Dr. McIntosh's leadership," he added.

JAKOB DUPONT LEAVES GOSSAMER FOR ATARA AMID PANDEMIC DELAYS

Gossamer Bio Chief Medical Officer, Jake Dupont, was reported to be leaving the company to "pursue oncology opportunities closer to his family", and has now been named as a senior vice president and leader of global R&D at Atara Biotherapeutics.

The move comes amid a delay in the release of trial data from Gossamer's study of a PDGFR inhibitor for treating pulmonary arterial hypertension caused by the current COVID-19 pandemic. Dupont will remain as a consultant during a transitional period for Gossamer's DC11b agonist GB1275, which is currently being trialled alongside Keytruda or chemotherapy in patients with solid tumors. His new role will see him take charge of a pipeline focused on allogeneic T-cell therapies for Epstein–Barr virus (EBV), multiple sclerosis, solid tumors and blood cancers.

Dupont was a faculty member and laboratory researcher at Memorial Sloan Kettering Cancer Center (MSK) before he made the move to industry by taking a role as Global Medical Director of Avastin for Genentech/Roche. At Gossamer Bio, he oversaw global development, regulatory and quality activities in the areas of immunology, inflammation and oncology. Previously he has also served as Global Head of Breast and Gynecologic Cancer Development for Genentech and was involved in the global development of Herceptin, Perjeta, Kadcyla and more. Dupont also held the position of Chief Medical Officer and Senior Vice President with OncoMed Pharmaceuticals, where he oversaw eight successful investigational new drug applications and 26 clinical trial initiations.

"I have a long-standing interest and belief in the breakthrough technology that Atara is developing. Having spent most of my career in the oncology and cell therapy space, I believe that Atara has a strong pipeline, exciting technologies and a uniquely advanced manufacturing platform. I am confident in the Company's ability to be a leader in allogeneic T-cell immunotherapies. Atara has the most advanced Phase 3 allogeneic T-cell therapy candidate, followed by a strong pipeline across a number of vastly underserved diseases, and I am honored to join the team in our mission to serve patients," commented Dupont.

– Written by Roisin McGuigan,
Cell and Gene Therapy Insights

CELL & GENE THERAPY INSIGHTS

PRELIMINARY COMMUNICATION

A proposed protocol of derived mesenchymal stem cells for the treatment of COVID-19 patients

Alma Reyes-Calavera & Vasiliki E Kalodimou

Recent reports have shown that mesenchymal stem cells (MSC) could be used for transplantation in various diseases. Mesenchymal stem cells exhibit remarkable plasticity and harbor potential for use in therapeutic applications while mesenchymal stem cell research could lead to many therapies becoming available to treat or repair injured or diseased tissues in a range of diseases, such as COVID-19-related pneumonia.

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INTRODUCTION

On February 11, 2020, the WHO Director-General, Dr Tedros Adhanom Ghebreyesus, announced that the disease caused by the new coronavirus (CoV) was "COVID-19," which is the acronym of "coronavirus disease 2019". This new virus seems to be very contagious and has quickly spread globally. In a meeting on January 30, 2020, per the International Health Regulations (IHR, 2005), the outbreak was declared by the WHO a Public Health Emergency of International Concern (PHEIC) as it had spread to 18 countries with four countries reporting human-to-human transmission. It has been postulated that one of the underlying pathophysiologic mechanisms of disease worsening and progression of patients with COVID-19 is massive release of inflammatory mediators, including cytokines

(e.g. cytokine storm). The following article is a short preliminary communication based upon our experience of implementing a pilot trial treating COVID-19 infected pneumonia with MSC.

MESENCHYMAL STEM CELLS A DIFFERENT APPROACH FOR COVID-19

MSC are plastic adherent when maintained in standard culture conditions [1] and must express CD105, CD73, and CD90 over >95% and lack expression, less than <2%, of CD34, CD45, CD14, CD11b, CD79a, CD19 or HLA-DR surface molecules [2,3]. MSC play a positive role in two main ways: immunomodulatory effects, and differentiation abilities. Immunomodulatory effects are attained through the following possible mechanisms related to the release of TGF alpha: HGF, NO, IDO, ICAM-1, VCAM-1, and others. It may also inhibit proliferation of T cells in reaction to alloantigens and mitogens. In summary, MSC can secrete many types of cytokine by paracrine secretion or make direct interactions with immune cells, leading to immunomodulation.

THE PROPOSED PROTOCOL

A pilot trial of intravenous MSC transplantation was performed on two patients with COVID-19 infected pneumonia [4]. Researchers enrolled two patients who were confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) assay of HCoV-19 RNA. Included criteria were (1) patients age 18–95 years, and (2) those who had no improvement under the standard treatments.

The MSC screened for blood borne infectious agents such as HIV, hepatitis B, C, EBV, CMV and syphilis. Release criteria will ensure safety trough sterility testing for aerobic and fungal microorganism. Cell viability will ensure >80% of MSC are viable using flow cytometry.

Treatment of clinical grade MSC for COVID-19 once inclusion criteria for recipient is met will be given as follows:

- 0.5 x 10^6 cells per kg of recipient's body weight. Doses will be given at day 1, 3, 5 and 7 with a duration of 40 minutes, with a speed of 40 uggts/min. MSC are suspended in a blood transfer bag with 100 ml D5 LR;
- Vital signs are monitored every 15 minutes during infusion then hourly thereafter for 4x.

Primary efficacy data included cytokine and C-reactive protein (CRP) levels in plasma, as well as oxygen saturation. Secondary efficacy outcomes included the total lymphocyte count and subpopulations, the chest CT, the respiratory rate, and clinical symptoms (especially fever and shortness of breath). In addition, the therapeutic measures (i.e. antiviral medicine and respiratory support) and outcomes were also examined.

Data on the 2 patients shows detailed follow-up over 14 days post-transplantation. The patients had significantly improved pulmonary function and were well enough for discharge by day 10. Lab test on these patients also showed that peripheral lymphocytes increased with a shift towards the regulatory phenotype for both $CD4^+$ T cells and dendritic cells; and inflammatory cytokines significantly decreased (except for IL-10 which increased). There was no report of adverse reactions.

There are more than 14 studies currently listed in ClinicalTrials.gov using MSC for COVID-19 that are either recruiting subjects, have not yet started, or are withdrawn.

Proposed TMC protocol for treatment of patients with COVID-19 with MSC

Mesenchymal stem cells

1. Source is umbilical cord blood (UCB):
   a. Identified by the following positive surface markers: CD105, CD73 and CD

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90; negative for CD34, CD45, CD14, CD11b, CD79a, CD19 and HLA-DR;

b. Not-HLA-matched due to low/no MHC antigens making it immune-privileged;

c. Screened for infectious agents (HIV, hepatitis B, C, EBV, CMV, syphilis);

d. Release criteria will ensure safety thru sterility testing for aerobic anaerobic and fungal microorganism and cell viability test will ensure >80% of MSC are viable using flow cytometry.

2. Treatment will be administered as four separate intravenous doses of clinical grade MSCs, 5×10^5 cells per kilogram of body weight. Doses will be given at day 1, 3, 5, and 7, with a duration of about 40 minutes with a speed of ~40 drops per minute.

Inclusion criteria/indication for MSC therapy (combination of clinical and laboratory criteria):

1. Confirmed COVID-19 via PCR;

2. Clinical picture consistent with COVID-19:

a. CT imaging consistent with viral pneumonia;

b. Severe pneumonia consisting of:

i. Increased breathing rate >30 breaths per minute and/or cyanosis of lips;

ii. O_2 saturations <93%;

iii. PaO2/FiO2 <300.

3. Age 18 years and above;

4. Clinical diagnosis of cytokine storm/ cytokine response syndrome Grade 2 or higher (ASTCT, CTCAE, or Lee criteria);

5. Laboratory diagnosis suggestive of cytokine storm:

a. Elevated CRP;

b. Elevated ESR;

c. Elevated serum ferritin;

d. Other labs included in cytokine release syndrome scoring (i.e. H score):

i. CBC – any bicytopenia or tricytopenia;

ii. Triglycerides elevated;

iii. AST elevated;

iv. Fibrinogen.

6. No known history of cancer.

Exclusion criteria:

1. Patients with severe allergies or allergies to stem cell preparations and their components;

2. Patients with serious basic diseases that affect survival, including: blood diseases, cachexia, active bleeding, severe malnutrition, etc.;

3. Continuous use of immunosuppressive agents or organ transplants in the past 6 months;

4. *In vitro* life support (ECMO, ECCO2R, RRT);

5. Expected deaths within 48 hours, uncontrolled infections;

6. Patients with malignant blood-borne diseases such as HIV or syphilis;

7. Patient with pregnancy, are planning to become pregnant or breastfeeding;

8. Patients with poor compliance and unable to complete the full study.

Adverse events of MSC are the following and will be thoroughly discussed when securing consent. Infusion of MSC is relatively safe but the following adverse events may occur:

1. Fever during or 15 minutes after infusion. Oral or IV paracetamol will be administered if fever occurs or if temperature is >37.7 c at a dose of 500 mg per tablet x 1 dose or paracetamol 300 mg Iv x 1 dose to alleviate symptom;

2. Allergic reaction. A dose of diphenhydramine 50 mg IV will be given if allergic reaction occurs during MSC infusion;
3. Possible infection if sterility measure not ensured.

Monitoring:

A. Clinical signs and symptoms;
B. Laboratory parameters to be monitored (for safety and efficacy):
   1. Blood chemistry:
      a. CBC;
      b. Procalcitonin;
      c. ALT/AST;
      d. Bilirubins;
      e. D-dimer;
      f. ESR, CRP;
      g. Serum ferritin;
      h. Il6, Il 10 and interferon gamma level pre infusion of MSC on day 1, 3, 5 and 7;
      i. Bilirubin and ALT/AST as indicated by the attending physician.
   2. Chest imaging (chest x-ray or HRCT).

Informed consent and ethics approval:

1. Secure informed consent;
2. Application and approval from the ESCCT (Ethics Subcommittee on Cellular Therapy).

Cost (only for MSC processing. Does not include laboratory monitoring, etc.)

P 300,000 (approximately) [TMC P80,000 + ; Globetek P 212,000 +]

Process flow:

1. AP and medical team decides and discusses with patient/family option of MSC therapy. Can include consult with IPMM at this time;
2. ICF signed by patient.
3. Application for approval to ESCCT;
4. Infusion of MSC:
   a. Dose: $5x10^5$/kg cells suspended in 100 ml NSS;
   b. Given on day 1, 3, 5, and 7;
   c. Infusion given over 40 minutes. Given by NIC, with close monitoring.
5. Monitoring of clinical status and laboratory tests.

Outcome measures:

1. Primary outcome measures:
   a. Improvement in respiratory no more than 3 weeks;
   b. Pneumonia severity at 12 weeks;
   c. Oxygenation status at 12 weeks (P/F ratio);
   d. Resolution of cytokine storm 48 hours to 2 weeks;
2. Secondary outcome measures:
   a. Side effects in treatment group;
   b. Improved 28-day survival vs control (patients not treated with MSC);
   c. Organ failure assessment;
   d. CRP level;
   e. ESR level;
   f. Measurements of laboratory parameters such as Il 6. Il 10, interferon gamma CRP, ESR, Ferritin and LDH;
   g. Procalcitonin level;
   h. Lymphocyte count.

The mesenchymal stem cell therapy has not shown any adverse side effects on the patients, supporting our hypothesis for the

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importance of MSC use in these trials for COVID-19. However, the development of a new therapeutic approach for the treatment of the virus has many practical implications such as the cost and the availability of MSC.

The use of MSC as a potential therapy for the treatment of COVID-19 is still some way away, but there are some promising clinical trial reports to support consideration of MSC application for this new pandemic.

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AFFILIATIONS

Alma Reyes-Calavera
Program Head, Hematologic Oncology, Cancer Center, & Program Head, Bone Marrow Transplant Center, The Medical City
and
Section Head, Hematology, UERMMMCI & Assistant Professor College of Medicine, UERMMCI
and
Consultant Staff QMMC, VRPMC and The Philippine Heart Center

Vasiliki E Kalodimou
Flow Cytometry – Research & Regenerative Medicine Department, IASO Maternity & Research Hospital, Athens, Greece
and
CBB Director & Processing Facility Director at MedStem Services, Athens Greece
kalodimou@yahoo.gr

AUTHORSHIP & CONFLICT OF INTEREST

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