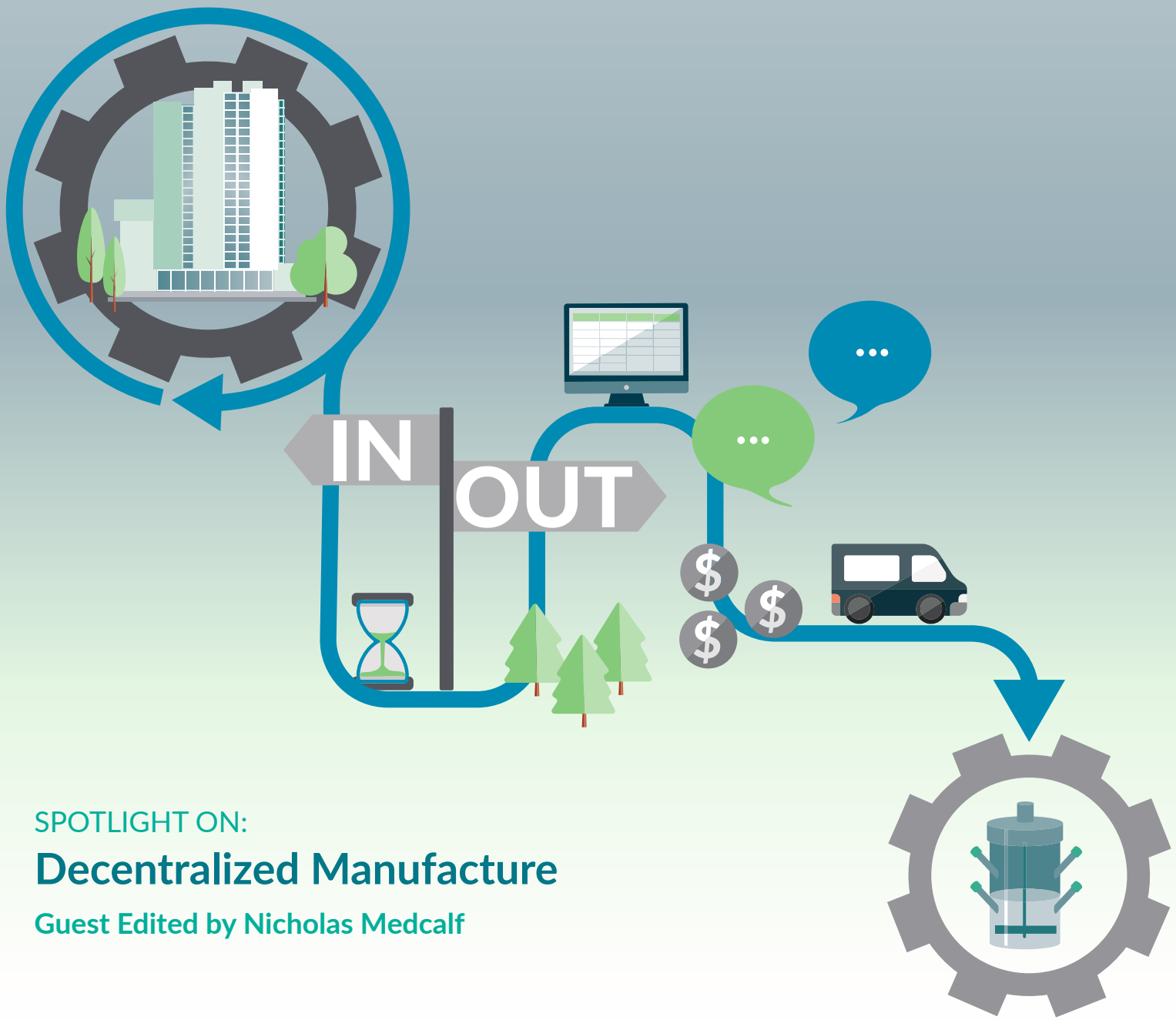
Volume 5, Issue 10

CELL & GENE THERAPY INSIGHTS



SPOTLIGHT ON:

Decentralized Manufacture

Guest Edited by Nicholas Medcalf

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CELL & GENE THERAPY INSIGHTS

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Decentralized Manufacture

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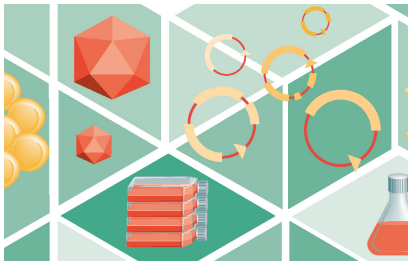

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CELL & GENE THERAPY INSIGHTS

DECENTRALIZED MANUFACTURE

SPOTLIGHT

TRANSLATION INSIGHT

Decentralized manufacture of cell therapies: the challenge of operational modeling

Nicholas Medcalf

Cell therapies may often benefit from a decentralized manufacturing approach. In order to choose from amongst the possible options and to coordinate the activity of the various agents in the chain of value the industry needs reliable decision-making tools. Three tools are offered here that will help with evaluation of this route. Tools for enterprise modeling, inclusive cost analysis and timing of research investment are introduced, showing the potential for applying systems engineering to decentralized manufacturing. The case is made for initiatives to encourage communities of practice and data-sharing for operational models and unit operations.

Cell & Gene Therapy Insights 2019; 5(10), 1133–1149

DOI: 10.18609/cgti.2019.121

INTRODUCTION: A CHANGE IN SUPPLY MODE

Products that contain living cells may benefit from decentralization of manufacture. The purpose of this Special Edition of Cell and Gene Therapy Insights is to acquaint the reader with the potential of this approach, the challenges in its adoption and, in particular, a procedure based on modeling tools that can be used to make informed decisions about its adoption [1]. Two of the tools will be more familiar to systems engineers than to biochemical engineers. The third is derived from options analysis.

The terms 're-distributed manufacturing', 'extended enterprise' and 'decentralized manufacture' occur in the business research literature in descriptions of manufacturing that does not rely on a single, central facility. These formats differ in detail. This article applies to all of them.

Manufacture of medicine evolved in stages. Early medicines were made on a small scale for local application. When economies of scaling-up were recognized manufacture was centralized where possible. With the advent of personalized medicines there is a move to decentralize once again, at least for some products. Hence the use of the term 're-distributed manufacturing' in ventures such as the 'Re-distributed manufacturing in Healthcare Network' [2] that evaluated the potential of this approach.

Business model research began to thrive as a discipline during the 1990s at about the same time that regenerative medicine was developed as a topic of industrial significance [3]. Commercialization has generally been based on centralized facilities with internal support services, the aim being to spread the fixed costs of production over many units and to keep oversight of the work in one location. As cell therapies become more personalized these principles become less relevant. Batch sizes are becoming smaller where there are haplobanking strategies [4], patient-specific autologous products [5] or simply because they are low-volume goods.

In the UK there have been initiatives to explore this topic. The Advanced Therapies Taskforce made a series of proposals amongst which was the establishment of a national network of cell and gene treatment centers. These will provide improved cooperation between hospitals, manufacturers, logistics companies and patients to provide more access to advanced therapies in a scalable way [6]. These 'Advanced Therapy Treatment Centers' (ATTCs) form part of the UK government investment in the Industrial Strategy Challenge Fund [7].

THE POTENTIAL BENEFITS OF DECENTRALIZED MANUFACTURE

There are several motives for decentralization of manufacture for some therapies. When manufacturing close to the point of use the cost and risk of long-distance, low-temperature transport can be reduced or avoided. When scaling-out to commercial volumes, rather than scaling-up, the management of the factory floor can become extremely difficult if all the separate lines are within one facility. This can be made more manageable by dividing up the total production between multiple sites. When manufacture and the points of patient contact are close together it becomes easier to coordinate the harvest of product with treatment schedules. At present it can be challenging to obtain venture funding for novel capital equipment and, by decentralizing manufacture, the investment in facilities may be made incrementally. By doing this in line with market growth, setting up one small facility after another to satisfy growing demand, it is possible to avoid the risks of sinking high initial investment in a single facility right from the product launch. At the technical level it is possible to shorten the development phase of the product,

DOI: 10.18609/cgti.2019.121

leading to earlier launch, by applying a manufacturing unit that has dynamic similarity to the research unit and is of similar scale. This has the added benefit of greatly reducing the technical risk associated with scaling up.

Table 1 shows broad categories of products and their potential for manufacturing decentralization.

OPERATIONAL CHOICES

Such benefits come with their own costs and risks. There are few existing examples of decentralized manufacture of medicinal products and the ones that do exist, such as oncolytics and radiopharmaceuticals, may not share the characteristics of advanced therapies. The choice whether to decentralize manufacturing or not will therefore be driven by the balance between the

TABLE 1.

Categories of products.

Characteristics of product	Potential benefit for decentralization of manufacture	Examples
Allogeneic injectable cell therapy from anchorage-dependent culture	For low intensity of manufacture (high activity per cell): centralized manufacture is manageable For high intensity of manufacture (low activity per cell and large cell numbers needed): decentralization permits easier operation where multiple fixed-bed reactors are needed. Use of microcarriers will encourage centralization.	Mesenchymal stem cells for treatment of graft versus host disease or erosion of cartilage
Allogeneic injectable cell therapy from suspension culture	Little incentive to decentralize. Product amenable to batch production at large scale.	Haematopoietic stem cell transplantation
Autologous injectable cell therapy from anchorage-dependent culture	Decentralization may permit avoidance of any unnecessary cryopreservation steps by coordinating production with delivery. Decentralization will avoid the need to manage line segregation for very large numbers of parallel cultures.	Adipose tissue-derived mesenchymal stem cells
Autologous injectable cell therapy from suspension culture	Decentralization offers agile production (quicker turnaround) to minimize delay in treatment (especially for life-threatening disorders).	CAR-T treatments
2-dimensional layered or printed cell bandages	This can be centralized (if allogeneic) with 'postponed manufacture' in a decentralized form if desired in which the cell stocks can be applied to specific delivery devices at locations close to clinic. If autologous treatment is needed then culture, harvest and assembly of dosage form is best conducted by decentralized route.	Retinal epithelial call implantation Urothelial tissue constructs Cardiovascular grafts
3-dimensional bioprinted constructs	Can be centralized or decentralized depending on opportunity for cryopreservation for transit.	Bioprinted orthoses Organoids Liver support devices

appetite for change and the risk that comes with being a first adopter. In this Special Edition there are viewpoints on the aspects that must be considered.

Assurance of process comparability is key. The design of processes to be intrinsically 'manufacturable' is examined by Prof Kino-Oka [8].

Management methods for procurement, stock control, materials movement, product release and administration can vary significantly from one hospital to another. Dr Ann Black deals with this aspect in her article [9].

Adoption policy for new products at a particular hospital may be influenced by different factors. Prof Andrew Webster addresses this [10].

The goods must be consistently of the required quality, safety and efficacy. Dr Ian Rees considers this aspect in more detail in an interview with *Cell and Gene Therapy Insights* [11].

A PROPOSED METHOD

In order to design a decentralized manufacturing business the features above must be placed in an operational context. A well-characterized manufacturing platform is needed to allow the design to succeed. The boundaries of the manufacturing activity need careful thought. For example, if autologous products are considered the collection of the starting material from the patient is influenced by the skill of clinical and materials movement staff. Downstream the journey of the Drug Product from the conclusion of packaging to clinical administration may involve supply chain operators, pharmacy staff and hospital staff. The product journey is a series of events that are experienced by the cell only as environmental changes. Each change may affect quality, safety and efficacy. Design for manufacture must take each of these into account. The system must be integrated from procurement of starting material to administration of product. This can be designed using a systems engineering approach.

There is unlikely to be a single operational solution to such diverse products [12,13]. It is necessary to compare alternatives to make a decision early in the product life cycle in order to avoid expensive and time-consuming comparability studies later [14].

Manufacturing research that is started early in development need not begin from first principles every time. The situation is similar to the development of 'unit operations' in chemical engineering. When manufacturers realized that new ways of working were needed to manage the impact of scaling up they discovered that it was time-consuming and expensive to start from a blank sheet every time. Engineers needed framework design principles upon which to base new processes. To allow findings from each design to be transferred from one situation to another the engineers created the unit operations approach. Unit operations are the groups of interrelated process features that are conserved whenever a generic step appears in a process. The amplitude, dimensions or balance of mass or energy of the step may vary but the key features are the same. Using unit operations a skilled engineer can assemble an outline process design quickly and tailor it to create a basic design. Simulations can then be run *in silico* to find the desired ranges for the controls. Verification and

DOI: 10.18609/cgti.2019.121

validation experiments can then be run to confirm the results. In the same way it is possible to build generic models of activities that are likely to be found together in a cell or gene therapy manufacturing process ('partial models') and build a library so that they can be re-used. Chemical engineering unit operations are confined to the technical features of a particular step. In a systems engineering model of a manufacturing operation the 'partial model' of the step is concerned with the surrounding human and resource activity as well.

Table 2 shows the unit operations that, in the author's view, can be associated with the steps typically encountered in the preparation of

TABLE 2.

Unit operations.

Process step	Class of unit operation	Proposed type of unit operation (from combined classes)
Preparation of the cell inoculum (from tissue, aspirate or drawn from the cell bank)	(Potentially, depending on primary isolate or withdrawal from cell bank): Mechanical processing (e.g. tissue disruption) Mass transfer Heat transfer (temperature control, cooling during handling, thawing) Fluid flow (mixing, effusion) Mechanical processes (separation, centrifugation or elution)	From tissue or aspirate: 'Isolate' (M, T, t, S) From cell bank: 'Manage phase change' (M, T, t, S)
Cell expansion	Mass transfer (chemical gradients) Heat transfer Fluid flow (mixing, fluid shear)	'Manage growth' (M, T, t, S): addition and removal of components, feedback
Cell harvest	Mass transfer (chemical gradients) Heat transfer (temperature gradients, hold steps) Fluid flow (fluid transfer, fluid shear) Mechanical processes (separation, centrifugation or elution)	'Isolate' (M, T, t, S)
Formulation of cells	Mass transfer (chemical gradients, management of osmotic pressure and pH) Heat transfer (temperature gradients, hold steps) Fluid flow (mixing)	'Stabilize' (M, T, t, S): addition and removal of components, no feedback for small batches
Filling of dosage forms	Heat transfer (temperature management during transfer) Fluid flow (fluid transfer)	'Transfer' (T, t, S)
Packaging o dosage forms	Heat transfer (temperature management)	'Hold' (T, t)
Cryogenic preservation of the dosage forms	Mass transfer (chemical gradients, management of osmotic pressure and pH) Heat transfer (temperature gradients)	'Manage phase change' (M, T, t, S)
Dispatch	Heat transfer (temperature management) Fluid flow (in the case of unfrozen product: fluid shear)	'Transfer' (T, t, S)

The "Proposed type of unit operation" is intended to allow a simpler identification of the potential critical control points in the process by concentrating the attention of the researcher and the process engineer on the fundamental environmental influences. M = mass, T = temperature, t = time, S = fluid shear

a cell therapy. For convenience the conceptual products are an allogeneic parenteral dosage form and a similar autologous product. For the sake of simplicity, genetic modification has been omitted.

In a large-scale plant the equipment for unit operations can be seen in concrete form as equipment skids. For cell therapies the situation is very different. The emphasis on maintenance of asepsis and avoidance of line mix-ups quickly becomes the dominant challenge as the number of parallel batches increases. Solutions for groups of unit operations at small-to-medium scale have been created as formally 'closed' systems. Equipment such as the Cocoon™ from Octane and the CliniMACS Prodigy® from Miltenyi Biotec have big advantages in terms of operability [15]. Re-configurable steps (isolation, expansion, purification and cryopreservation) can be achieved at small scale using platforms such as the G-Rex® system from WilsonWolf and the Xuri W25 and VIA Freeze/VIA Thaw systems from GE Healthcare/Asymptote Ltd. The control that can be achieved within the steps that are managed by these devices must be supported by satisfactory controls up- and downstream of the device. It is the definition of the unit operations, the ability to re-configure them in a practical model to include the steps necessary to service them and the ability to re-use the results that is important. A toolkit is needed that permits the assembly of a practical library of partial models down to a detailed activity level and to link them to provide a model of the whole operation.

Once the whole-operation models are available the manufacturer must be able to compare them in terms of cost to work out the impact on the cost of goods supplied (CoGS). Working out the costs of production for decentralized manufacturing is more challenging than for centralized manufacture. Progress has been made in this area [16]. It is important to include the impact of supporting or overhead activities in terms of their contribution to the indirect costs of manufacture. A further toolkit is needed at this point to make the comparison and this is described in the next section.

The innovator will now be armed with a cost comparison of the preferred operational models and can make a provisional choice between them. This comparison refers to the steady-state running of the business and in order to reach that point there must be a timely investment in manufacturing research.

Regulators including the FDA recognize the advantages of multi-center manufacture in some of the guidance but manufacturers may struggle to meet the degree of reproducibility needed between sites [17,18]. A major challenge is attaining comparability between sites and between teams. Choosing a decentralized manufacturing system influences the amount of manufacturing research that is undertaken and when it is started [19]. This implies much unwelcome additional work early in the research and development cycle but there is a silver lining.

A key difference between scaling up (centralized) and scaling out (decentralized) lies in the time needed to reach commercial operation. When scaling out the scale of each manufactured batch is generally the same as, or close to, that of the bench research batches. This means that the usual development

DOI: 10.18609/cgti.2019.121

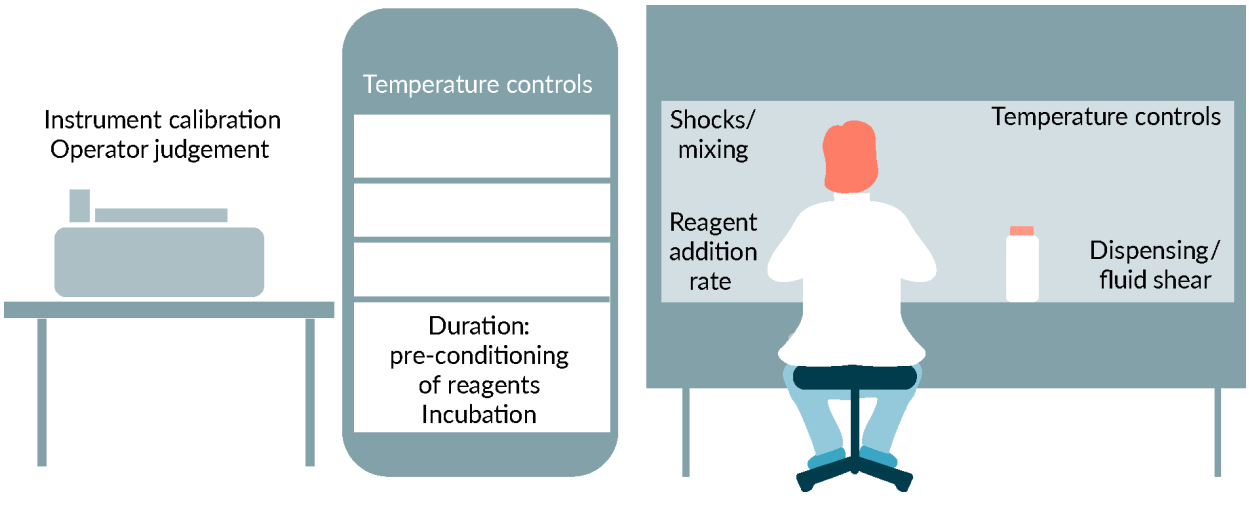
activity (increase scale by a factor of ten, make engineering batches, test and scale up by ten again and so on) is largely absent and so is the delay and risk that will be incurred. This is a big advantage as commercial launch can be brought forward. In order to realize this advantage it is important to choose technology platforms that are practical to use for research and that also can be applied for manufacture [20]. There must be adequate scope in the early manufacturing research to form a good comparability protocol for post-launch manufacture.

An example of the type of issues that need to be addressed in this early work can be drawn from autologous products where the variability of the starting material introduces a very large envelope of properties and the process must accommodate this. Added to this there is the variation as a result of local differences in practice in the harvesting step for the starting material. Several layers of control are possible. The first level might be pre-qualification criteria for the patient to ensure that the cell isolates lie within the calibrated range of behaviors for the process. At the second level the harvest technique can be normalized by introducing devices to assist clinical practice such as mechanical tools that constrain features of the harvest technique that cause unacceptable variation. An example might be a mechanized trochar and aspirator for bone marrow harvest or a simple damper and spring device on a syringe to ensure that the shear forces on manipulation are defined and volume is not excessive. The third level might be evolved during manufacturing a series of batches in the form of an adaptive control system based on data mining in the patient samples used to date. The sources of process variation are shown in Figure 1.

While full manufacturing automation is sometimes recommended to control variation in the main part of the process (cell expansion, purification, washing, collection) this can be expensive to acquire and to operate. A more nuanced approach might be to invest selectively in controlling only the features that really matter. Mechanization

FIGURE 1

Sources of process variation.



can help because it retains the decision-making element of human operation and constrains the amplitude of the features of concern (duration, temperature, volume etc.) at a fraction of the cost of full automation. In order to gain this insight the development team will need to make use of analysis of the human factors, the instrument and equipment variation, the responses from the cells and their effects in combination. It will be a combination of metrology and systems engineering research. Cells act in response to autocrine and paracrine signaling as well as to the primary external environment. They can reinforce any trend away from or towards the desired control state in a manner disproportionate to any change in control settings. The identification of the sensitivity to such changes is best carried out using a mixture of statistically-designed experiments and simulation. Suitable tools that bring deterministic modeling within the reach of non-specialists are in development [21] or are potential extensions of existing products [22].

In each of these three stages: system architecture, comparison of costs of options and decision about how much manufacturing research to conduct and when to do it, there is ultimately a cost-based decision.

TOOLS TO AID THE CHOICES

To bring together the key stakeholders and to direct the necessary research a set of tools is needed. To meet the practical challenge described above three toolkits are proposed below. Toolkits 1 and 2 are based on established practice in systems engineering. Toolkit 3 is drawn from the 'real options' method of research project investment. They are described in the order that they are to be applied following the method above.

Toolkit 1: Enterprise modeling

Activity-based modeling of whole or parts of enterprises has been available over many years [23,24,25]. Conventional practice is to concentrate on optimizing operations first and the costs will then be reduced as a result [26].

This technique is often referred to as 'business process re-engineering' (BPR) and is something of an adventure for those taking part. It differs radically from the incremental approach familiar from 'kaizen' improvement projects. This is seen in the five key principles [26].

1. Adopt a 'clean slate' approach
2. Adopt a cross-functional outlook
3. Set stretching targets and have confidence to achieve them
4. Use information technology to enable change
5. Make all the required changes in behavior and in processes that are needed to enable the re-engineering i.e. allow for any ways of working in the customer environment

In a good model a balance must be struck between the top-down vision and the bottom-up detailed analysis. To keep track of the findings, to express them clearly to the stakeholders and to manage a clear vision of the re-engineered process

DOI: 10.18609/cgti.2019.121

throughout successive versions requires tools that act as a database with a graphical front end. The results, in diagrammatic form, can be scrutinized by the potential users for bottlenecks, false assumptions, missing steps and unnecessary duplication. The results must be validated, preferably in a contained field trial, before roll-out. This must involve all stakeholders if the innovation is to succeed.

There are strategies to minimize the risk. The main one is to 'wargame' the proposed system design using representatives from each function that is involved. There should be no step without its own resources and there must be no loose ends or duplication. The engagement of a specialist in BPR is useful. However, the specialist must survey the proposed and existing system design by observation and by interview with staff from each aspect (operational, managerial and financial) to avoid any important omissions.

The evolution of computational modeling tools for this step has been analyzed elsewhere [27]. No single piece of software will be an all-encompassing solution. Most projects can be managed using a dual approach. Project management software addresses the cycle of project execution ("how to get there"). BPR software addresses steady-state operation after project completion ("how we operate when we get there"). For the models to be re-usable it is helpful to work to a tried-and-tested international standard. A good choice is 'Structured Activity and Design Technique' (SADT). SADT™ was created in the 1970s in the US Air Force and was later standardized to ensure operability between units [28]. Digital tools to enable rapid construction and rearrangement of models to this standard were developed by Knowledge-Based Systems, Inc.

Quality Assurance professionals will recognize this approach because it shares features with Quality Management Systems such as ISO9000 series and Good Manufacturing Practice. The principles are shown in Figure 2 and allow examination of the whole enterprise down to the smallest activities if necessary. Outputs as HTML files may be used to construct a re-usable library of partial models. The models of the overall system can be used by operators and for the next step of cost analysis in Toolkit 2.

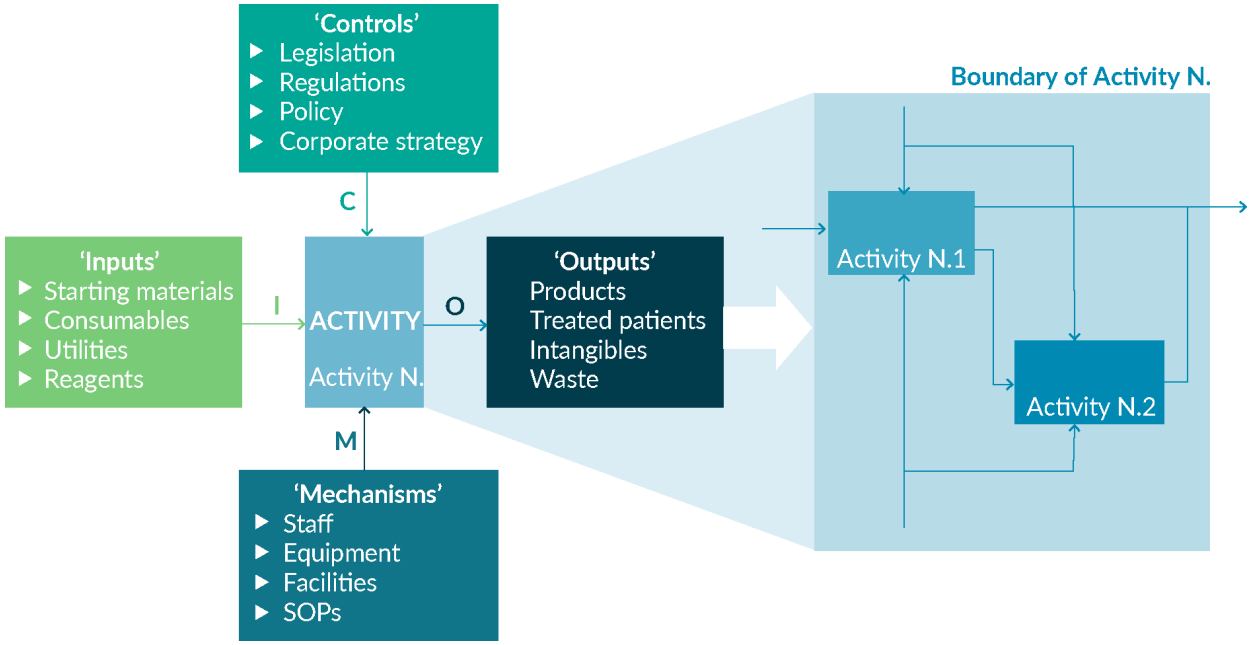
Toolkit 2: Inclusive cost analysis

Comparison of the costs of alternative methods of manufacture is well-established [29]. Cell and gene therapy manufacture involves a higher contribution of fixed costs than is the case for more conventional goods. The accurate inclusion of such costs is important for accurate projection of revenue stream [30].

This makes the inspection of whole operational costs difficult to perform using simple spreadsheet analysis (although it is possible [16]). In order to move from approximation to insight a powerful technique is to apply Activity-Based Cost (ABC) analysis to include the human activities. This is best carried out as cost roll-ups based upon the enterprise model from Toolkit 1. A typical analysis would cost each activity and then combine the costs, calculated as a multiple of the instances of use of

FIGURE 2

The architecture of SADT (Each activity is 'decomposed' to its constituent sub-activities until the necessary level of detail is achieved.).



each one, with the consumption of associated resources (person-hours, materials etc.) and their costs, generating a level of additional detail to R&D profit and loss models that could not otherwise be achieved.

Some service providers, such as BioPharm Services (BioSolve®) maintain current registers of data that can be applied to such roll-ups, for example labor rates, maintenance costs and utility rates. At this point the benefits of each option will be more apparent and the question of how much early research is needed and when to conduct it comes to the fore with Toolkit 3.

Toolkit 3: Decision-making tools for investment in process control

Toolkits 1 and 2 concentrate on the structure and cost of the enterprise once it is chosen and established. The final step is to determine when and how to make the investment in the manufacturing research that will make it happen.

Methods for applying process knowledge to prepare integrated systems have recently become available. Examples include the offering from Synthace and Torque's Slipstream technology which has recently been put forward to enable closed manufacture of deep-primed T-cells [31].

By combining the analysis from toolkits 1 and 2, above, it is possible to identify the dominant cost contributors to the manufacture. In the light of this information it may be possible to make interventions in the process design to constrain variability to an acceptable level. Some of the possible interventions will be strategic and others will be operational. Table 3 shows the origin of these interventions.

DOI: 10.18609/cgti.2019.121

TABLE 3.

Possible interventions and the level at which they may be resolved

Source of variation (with reference to Table 2	Intervention	Example
Isolate	Control of reagent contact time, cross-sectional interface and excision method (for explants only) and temperature	Control of tissue isolate dimensions and method of removal (explants) by use of mechanical trephine with self-cooling and power drain control. Tissue disruption and enzyme contact using enzyme bath with self-timer.
Manage phase change	Control of thermal gradient, interfacial heat transfer area and duration of thermal change	Solid-state freeze/thaw device which constrains dimensions and imposes release timer from contact plates e.g. Asymptote VIA Thaw CB1000.
Manage growth	Management of differences in concentration gradients, energy dissipation rate and duration of steps	Single-use fixed-bed bioreactors e.g. iCELLis®, DASGIP or Constellation. For T-flasks or roller bottles: mechanized inspection and timing with/without Near Infra-Red or phase contrast imaging (multiplexed).
Stabilize	Control of osmotic gradients, thermal shock and fluid shear	Mechanical dispenser triggered by the operator but dictating the dispensing rate, rate of addition and temperature of components (e.g. by in-line trace heating) and contact time.
Transfer	Management of oxygenation, temperature, duration of exposure and fluid shear (nozzles and tubing)	Mechanical aids to fluid transfer with in-line static mixers. Recirculation loop for process interruption. In-line gas-transfer membrane to ensure saturation. If less than full oxygenation is needed: gas inflow control.
Hold	Management of oxygen transfer (unstirred holding vessels) change in nutrient/waste ratio, duration	Small volume vessels: Holding cabinet for use in biological safety cabinet with headspace gas composition control. Medium volume vessels: Sparged tubular holding vessels with annular baffles and local oscillatory flow.

Knowing what to invest in is one part of the solution. The other part is when to invest and to what extent. The question can be addressed using an approach based on technology options investment and this has been described elsewhere [14]. Without repeating the full method description here it is enough to observe that the approach involves drafting and comparing a set of decision trees to represent the costs of carrying out the manufacturing research studies at each relevant time point. The probability-based expected current value of each decision tree is then calculated and compared with the alternatives. The maximization of the expected current value of the project forms the basis of the decision about which study to perform and when.

PUTTING IT ALL TOGETHER

The three toolkits described in this paper could be applied in the following manner. Beginning with the provisional product specification and the business case for its adoption the innovator is able to make a broad projection of how many cells in how many cycles will be needed during each year of production. A straightforward way to do this is in the form of a profit-and-loss (P&L) projection with very broad estimates (or targets) for the costs of manufacture and distribution and for significant overheads such as the cost of quality. At this point a provisional decision must be made about the operability of the process at the scale needed for peak sales because it is at this point that any issues with materials movement and line segregation will be at their most obvious. For example: a high-volume process in which large numbers of anchorage dependent cells are needed and for which all the work to date has been conducted in static culture systems will carry a risk when moving to suspension culture for scale up. It will not be known whether the product of a suspension system will be comparable to the one used for proof of concept. The innovator may decide to scale out instead and, in the interests of keeping the number of production units manageable, may opt to set up a regional operation first, duplicating the facility elsewhere as demand grows.

The conjectural model can then be examined in detail using Toolkit 1 to find the contribution of the indirect costs of production and delivery to the whole operation. This is done by decomposing the activities to the degree of detail needed and then carrying out a cost roll-up as in Toolkit 2. Different options can be compared in these terms and the dominant cost features can be scrutinized further for improved confidence.

While carrying out these steps it will become apparent that there are additional steps, delays or holding points that must be introduced in order to realize the operational model. The impact of these on the quality of the product can be examined in manufacturing research studies. The priority order in which these can be carried out can be determined by applying Toolkit 3.

DISCUSSION

The degree of decentralization may be considered as a spectrum with a single-center factory at one end of the range and intra-operative or in-clinic manufacture at the other. The parameters that determine the character of the business and its operation have been considered elsewhere [32]. Four forms of business can serve to illustrate the range of options. Towards the centralized end of the spectrum are national centers. These can form a multi-center manufacturing business with a foothold in separate market regions. Good examples are Fujifilm Diosynth (USA, UK and Japan) and Lonza (USA and Switzerland). At a higher level of distribution come regional manufacturing hubs. These provide rapid support to clinics from a center serving several hospitals. The series of hubs each associated with these hubs benefit from the proximity of manufacture to the point of use and they coordinate manufacture with the clinics while being

DOI: 10.18609/cgti.2019.121

supplied with materials from the hubs. The national hubs benefit from the purchasing power and business function of a large operation. A variant of this is to operate the spokes as franchises [33]. At the other end of the spectrum in-clinic manufacture offers the third and fourth kinds of model. In the product-based version the goods are manufactured from an operation that is set up in the hospital by the organization that holds the manufacturing license. In the service-based model the goods are made by trained employees of the hospital using equipment supplied by the innovating company. The latter is a form of support to the practice of medicine.

Cost contributions across this spectrum are split between the hub and the spokes and are made up of several broad components as shown in Table 4. The hub provides the materials upon which the final processing depends and the spokes manufacture the Drug Product from these materials using local resources. For autologous therapies the hub provides the consumables kit and this is transferred to the spokes. For allogeneic therapies the hub provides inocula of the working cell bank as well. In both cases there will be a division of quality control and quality assurance activity between hub and spoke and the materials movement will attract its own costs.

The availability and cost of low-temperature or fresh-preserved transport of goods used to be a dominant contributor to costs and, with more widely available services, it appears to be so no longer [34]. Instead the cost of quality management is likely to be a major determinant of the optimum degree of distribution in the network.

TABLE 4.
Origin of costs in the choice to decentralize.

Hub		Transport (Hub to Spoke)	Spoke		Transport (Spoke to Customer)
Overheads/Indirects	Labor: Quality assurance, Purchasing, materials Movement, Product Release, Production Scheduling Capital: Amortization of equipment	Cost per mile (Drug Product or intermediate)	Overheads/Indirects	Labor: Quality assurance, Purchasing, materials Movement, Product Release, Production Scheduling Capital: Amortization of equipment	Cost per mile (Drug Product)
Variable/Directs	Drug substance ▲ Labor: Manufacture, QC ▲ Consumables: Raw materials, Cleaning, Primary packaging		Variable/Directs	Drug substance ▲ Labor: Manufacture, QC ▲ Consumables: Raw materials, Cleaning, Primary packaging	
	Drug product/ Intermediate ▲ Labor: Manufacture, QC ▲ Consumables: Raw materials, Cleaning, Primary packaging, Secondary packaging			Drug product/ Intermediate ▲ Labor: Manufacture, QC ▲ Consumables: Raw materials, Cleaning, Primary packaging, Secondary packaging	

Assurance of quality at multiple sites will rely on a process understanding that is deep enough to ensure satisfactory reproducibility of product irrespective of site and production team. This requirement can be addressed through a combination of metrology and standardization. Relevant initiatives now include the VAMAS initiative at NPL, the NMS research supporting the '8 great technologies' [35] from LGC, including research into sources of biological variability for ensuring comparability, and the NIST program to build confidence in cell characterization.

A key to rapid progress will be the ability to share experience and data between organizations for mutual benefit without compromising commercially-sensitive information. This level of trust is not easy to achieve but the benefits could be significant. As noted above the ATTCs, under the coordinating guidance of the UK's Cell & Gene Therapy Catapult, aim to explore improvements to practice within the wider clinical network. The ADDoPT program provides a demonstrator of how research data may be shared to mutual advantage [36].

The accumulation of generic knowledge within the practitioner community offers the opportunity to build libraries of operational models using enterprise modeling techniques that can be adapted for early evaluation by innovators who are at the point of deciding on their own business format.

SUMMARY

Decentralized manufacture offers an attractive route for the commercial realization of some categories of cell therapy. Assessment of the suitability of this approach is best done *in silico* in order to avoid costly mistakes. A systematic approach to decision-making is essential. An approach to this challenge has been suggested here. The additional work that is needed at the outset can be offset by the rewards of faster access to market and reduction or removal of commercial risks.

The value chain will cross several inter-organizational boundaries and business models that encourage cooperative management are essential.

FUTURE VIEW

If a library of operational models can be established then there will be an opportunity to characterize points in the manufacture where production, packaging, materials movement, storage and transit must be managed more effectively in order to provide greater confidence [37]. Models of these points could be used to align the practice of the different operators in the chain. As the steps that are described by the partial models become well established it will become possible to create user requirement specifications that describe the characteristics of equipment to realize such steps. Such specifications would enable competitive equipment suppliers to develop new technology platforms to simplify decentralized manufacture.

In the ATTCs as well as practitioner groups we are beginning to see the formation of communities of practice that may provide such specifications.

Decentralized manufacture is one of several operating models that

DOI: 10.18609/cgti.2019.121

will enable advanced therapies to reach more patients more quickly. The early inclusion of metrology studies and systems engineers in the innovation process will enable that to happen. Knowledge-sharing mechanisms will ensure that the whole sector reaps the benefit.

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DOI: 10.18609/cgti.2019.121

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgments: *The opinions and insights shared in this article are the product of three main intervals in the author's career. His work at Smith & Nephew plc, and specifically the work on Project CARA with Prof Frank Barry's research team at NUI Galway, was the origin of the work on operability at scale. An EPSRC grant number EP/K037099/1 allowed the author to study the economics of the topic and the implications for automation at Loughborough University. Work as Head of Advanced Therapies and as Challenge Director for the Industrial Strategy Challenge Fund at Innovate UK, a part of UK Research and Innovation, is the basis for the more recent observations on the direction of relevant technology.*

Disclosure and potential conflicts of interest: *Dr Medcalf has worked with Cell and Gene Therapy Catapult, and the Advanced Therapy Treatment Centre Network as part of his employment at Innovate UK.*

Funding declaration: *The authors received no financial support for the research, authorship and/or publication of this article.*

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited; externally peer reviewed.*

Submitted for peer review: *Jul 16 2019;* ***Revised manuscript received:*** *Sep 9 2019;* ***Publication date:*** *Oct 23 2019.*

CELL & GENE THERAPY INSIGHTS

DECENTRALIZED MANUFACTURE

SPOTLIGHT

EXPERT INSIGHT

Decentralized manufacturing and institutional readiness: adoption as a distributed process

Andrew Webster

The model of decentralized manufacture is said to offer a new approach for more effective translation of cell and gene therapies to the clinic (and indeed in other sectors). Much of this depends on ensuring that key processes such as scalability and traceability are well-understood and properly managed as products move through to the clinic. The adoption of these therapies will require the creation of a novel trans-organizational innovation space. The latter can be better understood through deploying the social science model of institutional readiness to focus attention on the specific capacities that are needed to create not merely working but workable therapies, those that make sense in the clinical environment. This article outlines the model of institutional readiness, comparing it with the linear and primarily technically-based model of 'technology readiness levels', showing how it can help anticipate the specific capacities needed to build a new (decentralized) innovation space.

Cell & Gene Therapy Insights 2019; 5(10), 1061–1067

DOI: 10.18609/cgti.2019.113

DECENTRALIZED MANUFACTURE & INSTITUTIONAL READINESS

The concept of decentralized manufacture is seen to be of considerable value as a model for the effective production and use of especially personalized (typically autologous) therapies for just-in-time delivery to the clinic. Various authors have discussed the promise and challenge such a model brings, recognizing that as a manufacturing platform it poses a string of safety, quality assurance, regulatory, delivery and liability issues for all concerned [1–3]. Much of this literature has been focused on the manufacturing structures and processes that would be needed to make such a system work. This includes integrated platforms in regard to guaranteeing the quality of a complex and mobile product and, equally importantly, the standardization of associated information and clinical data. The scale-out approach on which this is based fits well with developments seen more widely in information systems [4]. At the same time, we need to understand what we call a hospital's *institutional readiness* for the arrival and use of these novel therapeutic (perhaps curative) products.

The concept of institutional readiness was developed through a three-year ESRC-funded project exploring the social, regulatory and organizational dynamics related to the emergence of regenerative medicine [5], addressing in particular the challenges associated with the adoption of biomedical innovation in clinical settings. This work now contributes towards one of the recently funded Advanced Therapy Treatment Centres (ATTC), the Northern Alliance ATTC (NAATTC) led by Newcastle Hospitals and the Scottish National Blood Transfusion Service [6]. Crucially, it moves away from the often-heard comment about 'barriers' to innovation' [7], that is, users' apparent conservatism in response to supply-side innovation. Rather, readiness looks at the specific contexts within which innovation is engaged with and made sense of by users, and how, in doing so, is often *adapted* in order to be *adopted*.

This work has been taken forward in new research (also funded by the ESRC) focused on the emergent fields of gene-therapy/editing, induced pluripotent stem cells, and 3D bioprinting [8]. These are described as 'biomodifying technologies', representing disruptive technologies that herald radical shifts in the nature of the science base whereby certain developments (such as CRISPR) actively modify and transform biological meanings of the body and disease and so the forms that both drug development and clinical intervention can now take [9,10].

By analogy, institutional readiness refers to the modifications needed in creating new capacity for the receipt of what are organizationally disruptive innovations – here cell and gene therapies. But this is never a one-way process – the responsibility of the 'end-user' alone – but an iterative, backwards and forwards process between hospitals and the network of actors involved, from the lab through the manufacturing center(s). In brief, institutional readiness identifies a range of skills, resources, capacities and the organizational processes through which these are enabled. The model is of value to both centralized and decentralized systems

DOI: 10.18609/cgti.2019.113

INSTITUTIONAL READINESS COMPARED WITH TECHNOLOGY READINESS LEVELS

The model of institutional readiness acts not only to draw attention to the social processes that shape adoption it also acts as a sociological check on the notion of 'technology readiness levels' (TRL), commonly used to assess the relative maturity of an emergent product, and used for example, by the UK's Cell and Gene Therapy Catapult when assessing prospective therapies companies bring to its scale-up facility in Stevenage. While TRLs assumes a sequence of levels that must be achieved before 'mission proven' arrives (a legacy of their origin in NASA spaceflight systems), IR focuses on orthogonal *capacities* needed to embrace and adopt innovation, here regenerative medicine products. This means a 'mature' and ostensibly *working* technology as defined solely in TRL terms may itself not be 'ready' for use in certain conditions. Readiness in TRL terms relates to signing-off risks (as manageable/known) but in doing so does not refer to the environment in which the technology is to be used, whereas IR is about a move towards a broader understanding of (e)valuation, which encompasses perceived risks, benefits, and most importantly the *workability* of the new (clinical) product in a given context [11]. There is an increasing recognition among firms of the need to engage early on with clinical sites where they hope their product will be used – for example, Autolus, one of the partners in the NAATTC, has a 'SWAT' team that engages with clinicians and procurement managers considerably in advance of their product offer to ensure its workability. This is a step in the right direction though it is important to note that the Autolus model still assumes a single (i.e., in effect centralized rather than decentralized) manufacturing and delivery process. As the ATTC partnership develops it is possible that a more co-produced, decentralized approach will be made possible, in part because deploying the IR model requires new forms of coordination and transparency across partners. Table 1 summarizes the principal components of the IR model and how these are operationalized.

How does this model apply in regard to decentralized manufacture? Perhaps the best way of exploring this is through focusing on two related issues that might be said to be of most importance in decentralized systems of manufacture in the cell and gene therapy/gene-editing field – scalability and traceability.

In regard to the first, those seeking to scale-up their product face two challenges that tend to work against each other. On the one hand there is a need to avoid too strong a lock-in to a manufacturing process that might prejudice future flexibility needed in ongoing product development. On the other hand there is the need to ensure robust and stable products at scale to ensure consistency in treatment (and so envisaged adoption by the clinic). In regard to the second, the traceability of supply is seen as a major requirement that seeks to map out and so manage a complex geography and quality arena – hence an important market niche for companies like Vineti (which uses a cloud-based software platform) and TrakCel to provide this sort of service (especially for autologous, patient-specific therapies). This is in effect an adjunct to scalability inasmuch as it

TABLE 1

The principal components of the institutional readiness model.

IR capacities	Operationally defined
Demand for new technology	Institution has key actors engaging with and identifying new technologies that meet field/organisational needs
Strategic focus	Institution has identified potential new technologies and determined their relation to existing ones
Relative need and benefit of new technology	Institution has key actors assessing capacity to take-on and develop new technologies within current and future contexts
(E)valuation processes in place	Assessments of the (diverse) values of new technologies are undertaken and shared
IR enacted through specific enablers	Key individuals/groups are formally tasked to enable adoption (in which technology will be used/ produced, assessed) especially in regards to meeting standards and regulatory requirements
Receptivity	Novel institutional structures are created, in anticipation of expected challenges/affordances presented by new technology. These structures reflect the need to retrain staff, the construction of new innovation spaces and new technology platforms, etc.
Adoptive capacity	Novel technology aligns with institutional priorities and organisational capacities. Initial problems and unanticipated challenges/ affordances are identified and seen to be manageable
Sustainability	Novel technology is routinely produced/used/assessed within institution. Current institutional arrangements and resources are sufficient for routine and ongoing production, assessment and deployment

aims to ensure that the product is of the right quality when it is released for delivery to the patient.

In a decentralized manufacturing system, these two aspects are more complex to manage than in a single-source manufacturer/user relationship (though that too has its challenges of course). A decentralized approach based upon a complex manufacturing chain opens up greater risk of variability and how much of this can be tolerated, and where and why in the development process. Social science work [12] has shown that data platforms (which will underpin decentralized manufacture) are subject to gradual change over time and are not in that sense fixed and stable: they too involve an iterative adaptation. Of central importance then are the ways in which this process is managed, communicated and agreed across the informational/therapeutic product/clinical pathway especially where there may be different proprietary algorithms at work to evaluate quality, safety, traceability and so on: these need to be commensurable, even interchangeable enough on some basic standards. Transparency about this matter will be vital to help build confidence in the system. This, in turn, raises questions about liability and where it sits within and across the chain [13], based not on a centralized scale-up process but a more flexible division of labor across partners deploying a scale-out approach. The scaling/traceability demands are therefore both more apparent yet more complex. TRL analysis says little about how these problems can be addressed and managed.

In contrast, the IR model can be used not simply to assess readiness *within* a specific organization, here the hospital (as it is being used in the NAATTC), but also in what can

DOI: 10.18609/cgti.2019.113

be seen as the *trans*-organizational context and challenges of decentralized manufacture. Two of its components (as in Table 1) – receptivity and adoptive capacity – directly address the scalability/traceability nexus. Those partners in a distributed site chain will need to be receptive towards the creation of new shared systems, especially technology platforms that are based on common infrastructural standards and quality and IP protocols that enable (in effect give affordance to) product quality and agreed ownership, and through which *new* firms might enter into what is in effect a scaled-out manufacturing regime and slot into the supply chain. In order to do this, multiple actors will need to be prepared to *adapt* their local practices to *adopt* the chain manufacturing model and liaise with hospitals, not least to meet their JACIE requirements (Joint Accreditation Committee ISCT-Europe & EBMT [JACIE] accreditation according to agreed cellular therapy standards). Without this, receiving hospitals will find that they are confronted by diverse products that carry discrete requirements – for example in regard to cryopreservation – which are impossible to handle in any number, and so make adoption more unlikely. To this extent, a decentralized system has to be seen as a distinct innovation space that disrupts conventional supplier/user relations, and defines adoption as a distributed process. Intermediary innovation agencies in the UK, such as the C&GT Catapult, could play an increasingly important role here alongside NHS England as commissioners for ATMPs, in helping to create this space. A key question however, yet to be answered, is whether there will need to be different types of innovation spaces/systems for different regenerative medicine products – such as CAR T cells compared with iPS-derived cell therapies and gene-edited products. In part this might reflect different regulatory considerations in different areas: regulation of CAR T autologous therapies will depend on whether such therapies are classified as product or process and in addition whether this is defined as a product, drug or device; in regard to iPS-based therapies, whereas a rather different regulatory provision may be needed in the future that encompasses iPS cells (and it is worth noting that the latter fall outside of current HTA oversight in the UK). Such considerations would affect how decentralized supply chains have to attend to discrete regulatory requirements and so manage different traceability and quality-assurance demands.

WIDER NEEDS

There will be complementary developments that will be needed here, to help build a socially and clinically robust system, especially the development of patient registries and the generation and collection of standardized data which will help to inform licensing and end-user assessment of new therapies and to meet patient need. This would go beyond the responsibility of those immediately involved in a decentralized manufacturing chain since data (including retrospective) from clinical studies and trials elsewhere are equally important. Integrated registers fit for purpose in the ATMP field are few and far between [15]. Decentralized manufacturing is then about the need to explore the new types of social relationships

and practices it will require (for example to contribute to and support these forms of data) and the innovation affordances these allow, as well as addressing the need for new forms of accountability, responsibility and collaboration [15]. This is as much a 'learning-by trying' model [16] as it is about developing specific skills or metrics relating to, say, standardized data assemblages.

TRANSLATION INSIGHT

There are many very valuable technical papers that describe the processes needed to ensure scale up/scale out and quality assurance in regard to cell therapies occur in a robust fashion. However, these papers rarely explore the actual organizational, and here in regard to decentralized manufacture, trans-organizational challenges that affect how therapies are *co-produced* across different actors, and so not merely 'working', but made 'workable'. This requires close inspection of the institutional readiness of the different players in this innovation space and in particular how the IR model can complement TRL approaches used by firms and innovation agencies and sponsors by prioritizing those socio-technical tasks that are geared towards adoption. Finally, the IR model has been developed within the context of the UK and is being deployed within NHS settings. The model, as summarized in Table 1 above, is not however specific to one form of innovation/health-care system. The same challenges are found in diverse contexts: what would differ would be the role of regional/national agencies in facilitating IR (as the ATTC does).

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Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The authors declare that they have no conflicts of interest.*

Funding declaration: *The research on which this article is based was supported by grant from the Economic and Social Research Council: refs ES/L002779/1] and ES/P002943/1.*

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited; externally peer reviewed.*

Submitted for peer review: *Jun 24 2019*; ***Revised manuscript received:*** *Aug 12 2019*; ***Publication date:*** *Sep 13 2019.*

CELL & GENE THERAPY INSIGHTS

DECENTRALIZED MANUFACTURE

SPOTLIGHT

INTERVIEW

Building flexibility into GMP CAR T cell therapy manufacture

CHRISTIN TISCHNER currently works at Miltenyi Biotec as a Clinical Supply Chain Manager. This interview was conducted when Christin was working in her previous role as Tech Transfer Project Manager for CAR-T Cell Manufacturing at Cellex. She is a Molecular Biologist by training and obtained a PhD in Genetics from the University of Cologne.

Cell & Gene Therapy Insights 2019; 5(10), 1385–1390

DOI: 10.18609/cgti.2019.144

Q What are your current responsibilities and activities at Cellex?

CT: I'm leading the project of design and set up our new GMP facility. We are operating a smaller Cell Factory in Cologne already, but due to the increasing demand we needed to increase our manufacturing capacities. My main responsibilities relate to facility design and process implementation.

Q It's an interesting period to be designing and establishing a new cell and gene therapy manufacturing capability. 'Flexibility' seems to be the watchword,

given the rapid development of both enabling and therapeutic technologies in the space – how are you seeking to build this key element in to your facility?

CT: There are different perspectives from which to look at it. First of all, it is good to have a flexible plan or a modular design that you can adjust and expand easily. Right now that is very important because both our own internal CAR T cell therapy program and also the projects we are running together with sponsors as a contract manufacturing organization are in the early stages.

When we think about future commercialization we obviously will need to increase our capacities. We took that into consideration from the very beginning. The modular design enables a ramp up when it's needed.

The other aspect, which makes flexibility a requirement for us as a CMO, is that we have to adjust our processes in accordance to sponsors technologies and requirements we need to implement.

We have taken a modular rather than an open space approach, because for us as a CMO, it's not really realistic to follow this 'ballroom' concept: when you have to orchestrate several customers, confidentiality becomes an issue. Therefore, it is essential for us to offer dedicated units. Especially, since we are not working completely paperless just yet, separation also helps to ensure chain of identity.

Q Can you tell us more about the process you are following in transitioning Cellex's proprietary CAR T cell platform into the GMP setting? What are/were some of the key issues and considerations, and how have you sought to address them?

CT: The company originally started as an apheresis collection center for hematopoietic stem cells with profound experience in cell therapy, so it was always in our mind that if we were to start with the CART cell approach, we would really want to prioritize bringing it into a GMP manufacturing setting.

From the beginning, it was our goal to conduct most manufacturing steps in Class D cleanrooms and avoid the need to work in higher cleanroom classes as much as possible, for cost reasons apart from anything else. So consequently, we really wanted to work in a closed, automated system.

That meant we made the fundamental decision to use the Prodigy platform early on and then, during the R&D process, we used MiniMACS separation columns and also the CliniMACS – so not automated, but with

DOI: 10.18609/cgti.2019.144

the same principle of cell sorting. That made it easier for us to go step-by-step as we progressed in our research and started scaling-up the process.

We stayed basically with the same core technique and that's why the transition for us was pretty straightforward. And although we're only at the tech transfer stage from R&D to GMP manufacturing for our first clinical trials, which should start at the end of 2019, we haven't observed any difficulties as yet.

Q What learnings and experience have you been able to leverage from other branches of the Cellex business – the HSC collection division, for example?

CT: I'm quite new in the cell and gene therapy field, but I think there has been a great deal of focus on the manufacturing process – which technologies and devices to use, where you can cut costs, etc. – and now people are starting to look in earnest at what is upstream and downstream of the process.

So upstream, of course, is the collection of the starting material and since we have extensive experience with apheresis, we know how different the starting material can be. You have that issue with healthy donors, but even more so with patients. However, we have great staff working in our collection site who are expert with the settings of the apheresis machines and who can really fine tune the collection process to obtain high quality starting material.

This is something to consider: some clinical sites conduct apheresis protocols very frequently, but many others don't. This means the staff are not always particularly experienced. In addition, clinics might perform apheresis collection for various CAR-T cell trials for different pharmaceutical companies and therefore the collection procedure might differ. So we decided to offer a kind of service whereby we train the staff at other collection sites with which we work, as well as our own staff, because we have this really good hands-on experience in-house. We realized the importance of this quite early on – that it was key to focus on this element in parallel with our manufacturing improvement.

"We have taken a modular rather than an open space approach, because for us as a CMO, it's not really realistic to follow this 'ballroom' concept..."

Of course, it's not just about the starting material collection and the bioprocessing – the delivery of the finished product to the clinical point of care and administration to the patient are also crucial. I think it is equally important to train clinical staff in these aspects.

"Another strong point of focus from the start for us was the supply chain, particularly relating to scheduling and transport of leukapheresis and the final drug product."

Another strong point of focus from the start for us was the supply chain, particularly relating to scheduling and transport of leukapheresis and the final drug product. For normal stem cell donation, you have to make sure the apheresis product arrives at the clinical point of care within the 72 hours shelf life. To facilitate a smooth and on time transport, Cellex always had a scheduling and logistic team in house. To avoid any transportation related problems and to guarantee chain of identity we use on-board couriers. Talking about CAR-Ts as a personalized therapy with even shorter shelf life, these precautions become even more important.

Q How and where specifically will utilizing the Prodigy system impact the ongoing manufacturing model and strategy that Cellex pursues? What's the direct impact on the design of your new facility, for example?

CT: As I mentioned previously, it definitely influences the cleanroom design – the completely closed and automated system will ensure we can have all of our manufacturing space only in Class D.

The open steps required for the medium preparation are performed in isolators, which are Class A devices positioned in Class C suites. All the other process steps like cell separation, transduction, cultivation, formulation – it's all Class D, which makes it much easier to work with. In addition, the environmental monitoring is less intensive and running expenses and maintenance costs are reduced. These aspects really influenced our choice of set-up. For us, it was very clear from the beginning that we wanted to try to put the Prodigy in the Class D cleanroom, and the local authorities approved it, which was great!

Q How important is a holistic approach to the entire manufacturing and supply chain in this particular technology space? How do you seek to apply this philosophy to Cellex's work in the cellular immuno-oncology field?

DOI: 10.18609/cgti.2019.144

CT: For advanced therapies like the CAR-Ts a holistic approach which unites all stakeholders including collection center, courier, manufacturing site, trial manager and sponsor is essential particularly when you think about scaling up for commercialization. Software solutions have been designed to efficiently schedule apheresis and manufacturing slots and the shipment from the clinical to the manufacturing site and vice versa and simultaneously control COC/COI. Those platforms allow traceability throughout the product life cycle and notification about deviation when they occur. However, implementation can still be affected by the IT infrastructure at the different sites.

I could envision that the application of those software solutions might be challenging especially for hospitals involved in several CAR-T trails when all sponsors use different approaches.

However, in preparation for higher patient numbers reduction of paper based work is crucial, not only to reduce the work load but also to support traceability.

Q What is the endgame for Cellex in terms of commercial scale CAR T cell immunotherapy manufacturing? What will that look like, ultimately?

CT: We believe it is most realistic, at least for the moment, to have centralized CAR T cell manufacturing. Our GMP facility in Cologne is centrally located within Europe enabling us to supply clinical sites without difficulties. However, since manufacturing capacity must be further increased to meet commercial need this could be divided to several sites spread out around Europe to reduce transportation time.

We feel it is probably too difficult to do bedside manufacturing. From our experience, Prodigy is easy to work with – the set-up is pretty straight forward – but it's still a sophisticated machine, and we want to have well-trained and experienced staff in our cleanrooms not least for troubleshooting. I am not sure whether or not individual clinical sites have high enough patient numbers to reach that routine or cover the costs related with setting up a GMP unit for ATMP manufacturing.

In the end, I think shortening the process is an interesting and important goal to work for. Reducing the transportation time and therefore even avoid the need for cryopreservation could be a step in the right direction.

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The author declares that they have no conflicts of interest.*

Funding declaration: *The author received no financial support for the research, authorship and/or publication of this article.*

ARTICLE & COPYRIGHT INFORMATION

Article source: Invited.

Publication date: Oct 23 2019.

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 DOI: 10.18609/cgti.2019.144

CELL & GENE THERAPY INSIGHTS

DECENTRALIZED MANUFACTURE

SPOTLIGHT

EXPERT INSIGHT

Implementation of advanced therapy medicinal products: a UK pharmacist's perspective

Anne Black

Advanced therapy medicinal products (ATMP) have introduced a new area of specialism to the clinical pharmacy workforce. The author will explore the role of the pharmacist in the UK in the delivery of cell-based medicines, emphasizing governance and clinical requirements, and recognizing that operationalizing ATMPs requires a collaborative multidisciplinary approach to ensure that the medicines are optimized for patients. This involves ensuring that whilst appropriate pharmacovigilance and pharmaceutical procedures are in place, handling is undertaken by a workforce that is trained and competent in the handling of cellular products.

Cell & Gene Therapy Insights 2019; 5(10), 1237–1246

DOI: 10.18609/cgti.2019.130

Advanced Therapy Medicinal Products include gene therapies, somatic cellular products and tissue engineered products. They have been defined as medicines in Europe since 2007 [1] and are centrally regulated by the European Medicines Agency in a process that aligns closely with EMA and FDA processes for other biological medicines. Pharmacists, as healthcare professionals concerned with optimizing medicines use for patient benefit, are key stakeholders in the adoption and implementation of ATMPs into routine clinical practice.

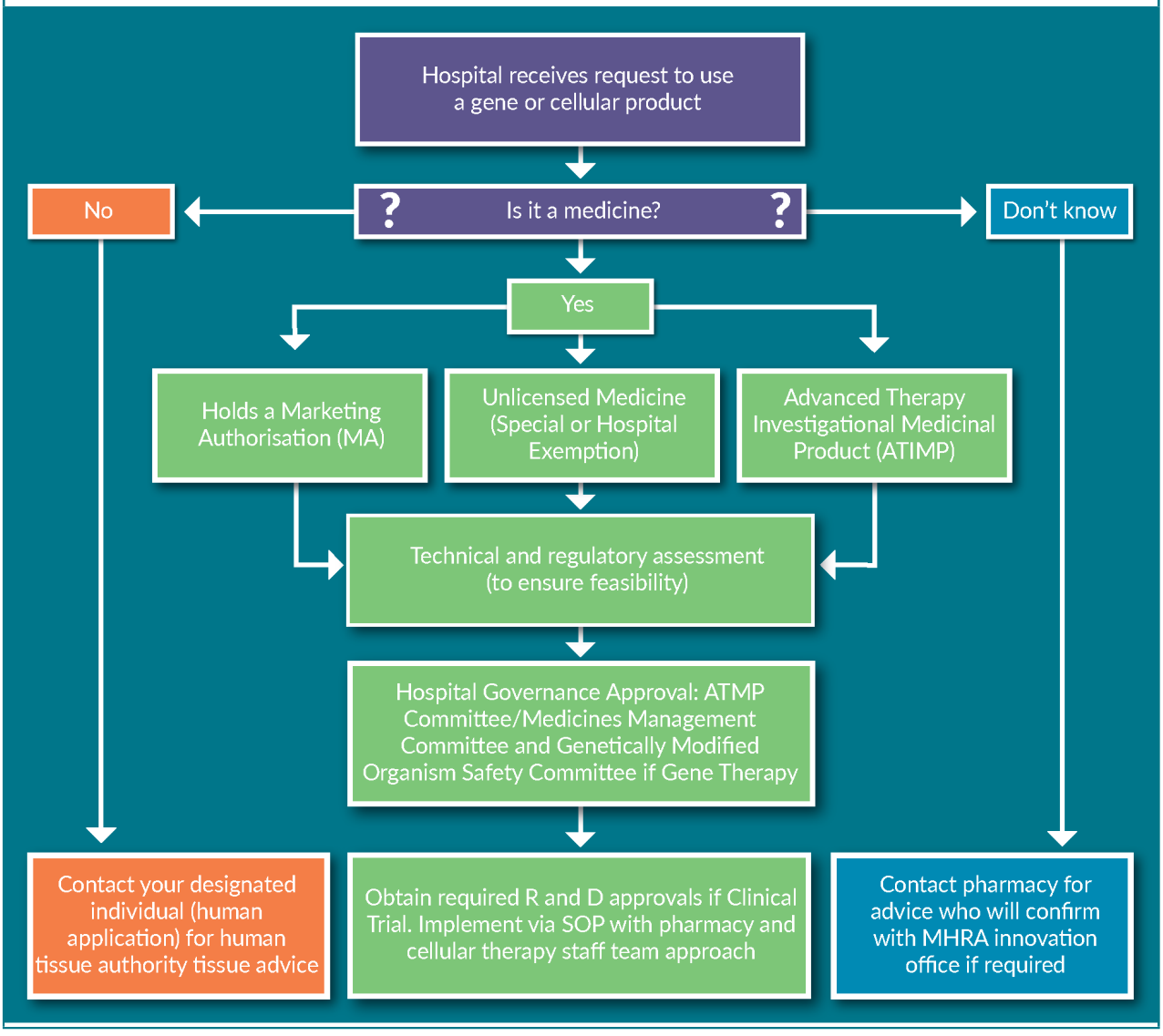
ATMPs, however, pose challenges for Pharmacy professionals. Whilst '*in vivo*' gene therapies, where genetic modification of cells occurs inside the body, provide little disruption to routine pharmacy practice, the same cannot be said for other ATMPs. The potential impact on pharmacy of cell and tissue based products, including innovative '*ex vivo*' gene therapies which genetically modify cells outside of the body during the manufacturing process prior to expansion and subsequent return to the patient, being designated as medicines, was not well recognized in the UK in 2007. It was 10 years later that the first advice for pharmacy leaders was

published [2] and simply advocated that appropriate medicines governance for ATMPs should be defined and implemented within healthcare organizations (Figure 1). This prolonged interval can be explained by the fact that evolution of ATMPs has been much more closely aligned with processes in place for stem cell transplantation than with those in place for development and handling of small molecule medicines or, indeed, biologicals such as monoclonal antibodies. Additionally, the time lag prior to investigational ATMPs being routinely introduced in hospitals acting as clinical trial sites or, indeed, ATMPs holding marketing authorizations, also contributed to this. However, with the definition of ATMPs as medicines came responsibility. Chief Pharmacists are routinely appointed by their hospital board to be the named individual responsible for the safe and secure handling of all medicines within their organization and are required to be responsible for the quality of medicines used within their healthcare establishment [3].

All medicine management in the UK is based upon the four guiding principles of medicines optimization

FIGURE 1

Advice to Chief Pharmacists on organisational governance requirements [2].



DOI: 10.18609/cgti.2019.130

which was defined by the Royal Pharmaceutical Society [4]. These principles are applicable across many healthcare systems however as they recognize that optimal patient benefit from medicines management requires collaboration, with the patient or carer, between healthcare professionals and recognize that support for medicines use may be needed at different points in the patient pathway. They are also in line with the International Pharmaceutical Federation objectives for Hospital Pharmacists [4], which promote integrating pharmacy services through communication and collaboration.

The principles align and resonate with the requirements for ATMPs. Regardless of the setting, be it as a licensed medicine holding a marketing authorization, as an investigational medicinal product in a clinical trial or as an unlicensed medicine for an individual patient with a special clinical need, a collaborative approach is required to ensure that any advanced therapy medicine is safely introduced into use. In particular, pharmacists recognize that handling and manipulation of cellular medicines is a specialist competency which is currently outside of the pharmacy workforce's curriculum, however ensuring that processes and procedures are in place to enable this to occur and to enable good clinical practice or compliance with the SMPC and/or pharmacovigilance responsibilities to be discharged requires a multidisciplinary collaboration including pharmacists as key stakeholders to ensure that the use of the medicine is compliant and that safety is optimized.

Medicines governance is required at various levels encompassing both national and local requirements.

As part of their overall responsibilities for medicine governance, Pharmacists have been advised to oversee the local governance arrangements and to ensure that ATMPs used are of appropriate quality for their intended use [5].

As ATMPs are innovative products often associated with challenges and service disruption, including an intense media interest, all requests to use ATMPs require scrutiny from the appropriate organizational multidisciplinary committee. This is in addition to approval via routine Research and Development routes where the ATMP is for use in a clinical trial. A suggested process flow for the governance process is given in Figure 1.

One large teaching hospital in the North of England has decided that, as ATMPs are often associated with a novel administration technique, the governance should be overseen and approved via the New Interventional Procedures Committee [6] which comprises a range of clinical specialism and includes the Chair of the Medicines Management Committee. Other hospitals have set up bespoke committees to evaluate ATMPs in response to the advice given.

Additional governance processes for ATMP medicines holding marketing authorizations are also managed centrally through the National Institute for Clinical Excellence Health Technology Appraisal process and the National Health Service (NHS) for England's Commissioning Process (and corresponding processes in the Devolved Nations). For the recently marketed Chimeric Antigen Receptor T cell (CAR-T) products these processes have run concurrently in England in order to expedite market access for NHS patients. Confirmation of the suitability and readiness of sites to deliver treatment with these medicines, which can have significantly

disruptive service requirements (e.g., guaranteed access to Intensive Care, treatment schedules determined by short in-use product shelf-lives), was assessed and assured following audits of prospective sites by the Joint Accreditation Committee of ISCT (Europe) and EBMT, and by audits undertaken by the MA holders. Clinical eligibility of potential patients is also currently assessed centrally by a multidisciplinary approval panel process. Pharmacists in the UK are encouraged to play a role in each of these stages which encompass clinical, operational and local medicines management. The principles of outlined for the role of the pharmacist will apply in any country adopting ATMP therapies.

MEDICINES MANAGEMENT ROLE

As ATMPs may be (very) high cost medicines, local pharmacy medicines management is also required to ensure compliance with relevant requirements at an individual patient level which will support financial reporting and ensure that agreed payments are received by the healthcare establishment.

On occasion, it may not be possible for the patient to receive the medicine for a variety of clinical reasons. Practical processes for refunds and cancellations are also conducted by medicines management teams.

Where the ATMP is autologous, i.e., derived from starting material procured from the patient but has failed to meet the criteria for final release as a licensed medicine, there are circumstances in which treatment may still be administered. Contrary to the rules for traditional medicines [7], EU Good Manufacturing Practice for ATMPs [8] allows in some circumstances for concessionary release of products which may not comply with their release specification as defined by the marketing authorization or the specification submitted for regulatory approval as part of the Clinical Trial Application. If the clinician wishes to administer the product which is not to specification this can, in some circumstances, be released for use on a compassionate basis, particularly as some ATMPs may be a providing a patient's last chance of survival. However, there are liability issues that require consideration in this circumstance. Where the product is not in full compliance with its Marketing Authorization, some administration liability therefore rests with the prescriber and the healthcare organization rather than with the manufacturer. Local ATMP/unlicensed medicine policies should ensure that the quality of the ATMP is assessed as suitable by, for example, a QA Pharmacist with relevant (ATMP-specific) expertise, as this is the expectation for unlicensed medicine use [9]. An understanding of the deviation that has occurred (reason for non-compliance with the full product specification detailed in the MA) may be required in order to assess this. The NHS holds a variety of MHRA manufacturing licenses for traditional pharmaceuticals and has a wealth of expertise in the application of Good Manufacturing Practice, meeting the requirements of pharmaceutical quality systems, and managing the consequences of deviation from them. The workforce includes Qualified Persons, as defined in Directive 2001/83/EC [10] and QA Specialists who can assist with ATMP assessment in collaboration with stem cell laboratory colleagues.

DOI: 10.18609/cgti.2019.130

OPERATIONAL ROLE

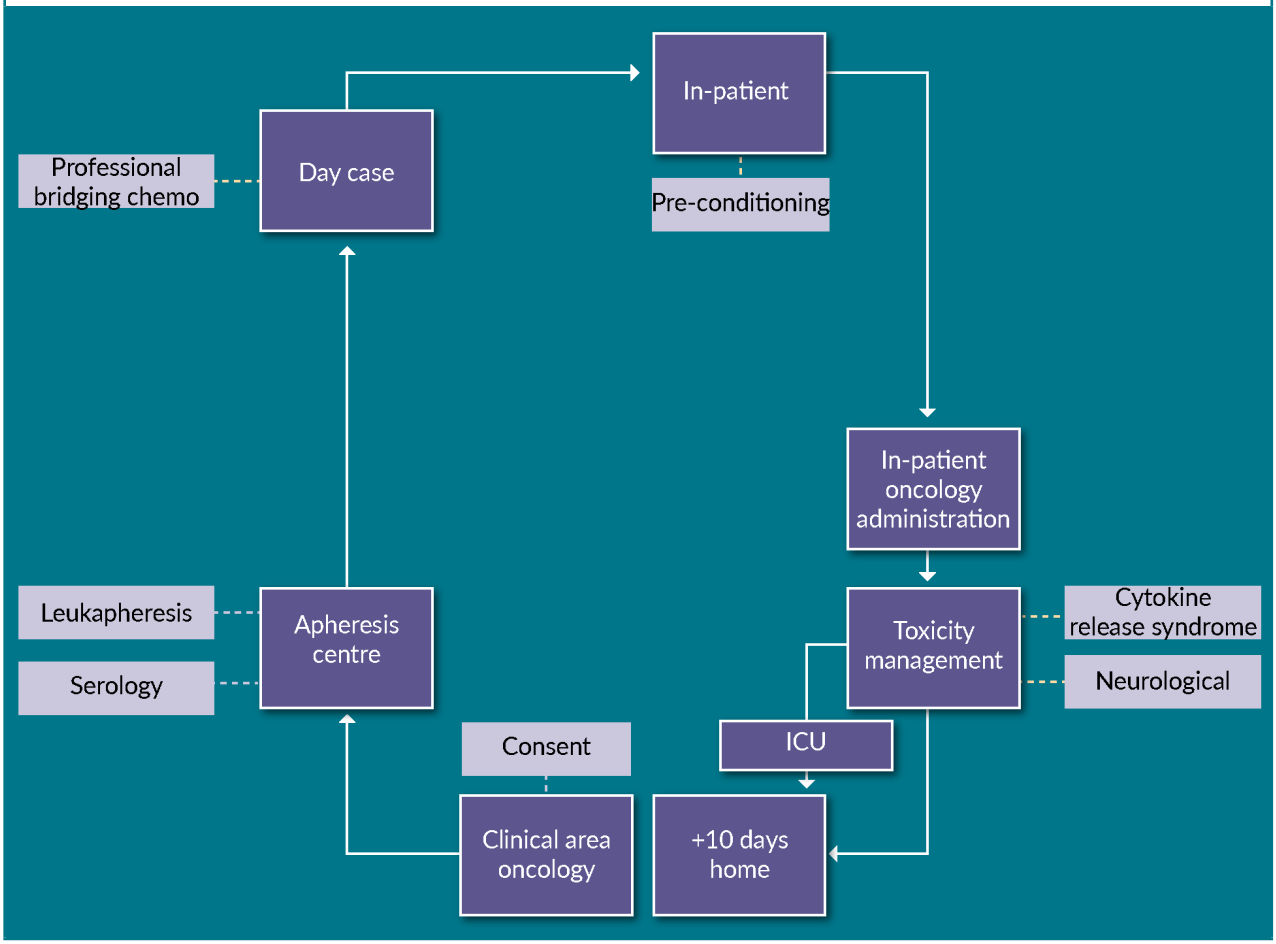
The operational role and responsibilities of the pharmacist can be best explained by using the example of marketed Chimeric Antigen Receptor T Cell (CAR-T) therapies. The following sequence of figures demonstrates the complexities of delivering autologous cellular medicines and considers where a pharmacist's input may be beneficial.

The journey of the patient shown in Figure 2 begins with a patient who fulfills the eligibility criteria for CAR-T consenting to the treatment. The patient then visits the apheresis center and after a period of weeks during which some bridging chemotherapy may be required to stabilize their disease, continues with the administration of a lymphodepleting regimen followed by the CAR-T therapy. Toxicities may ensue which require careful clinical management and the availability of an intensive care bed. The corresponding product journey is shown in Figure 3.

The starting material is procured in the apheresis center and is processed if required in the stem cell laboratory. It is subsequently packaged and shipped to the manufacturer where the regulatory controls shift from (in the UK) the Human Tissue Authority to the local medicines authority (MHRA in the UK). The medicinal product is cryopreserved and shipped to the stem cell laboratory where it is verified that it is of suitable quality and then stored under vapor phase nitrogen until required. It is then thawed in the

FIGURE 2

Marketed CAR-T patient journey.



clinical area and administered. The medicinal product requires specialist handling and each commissioned center has established the optimal process to allow this to occur.

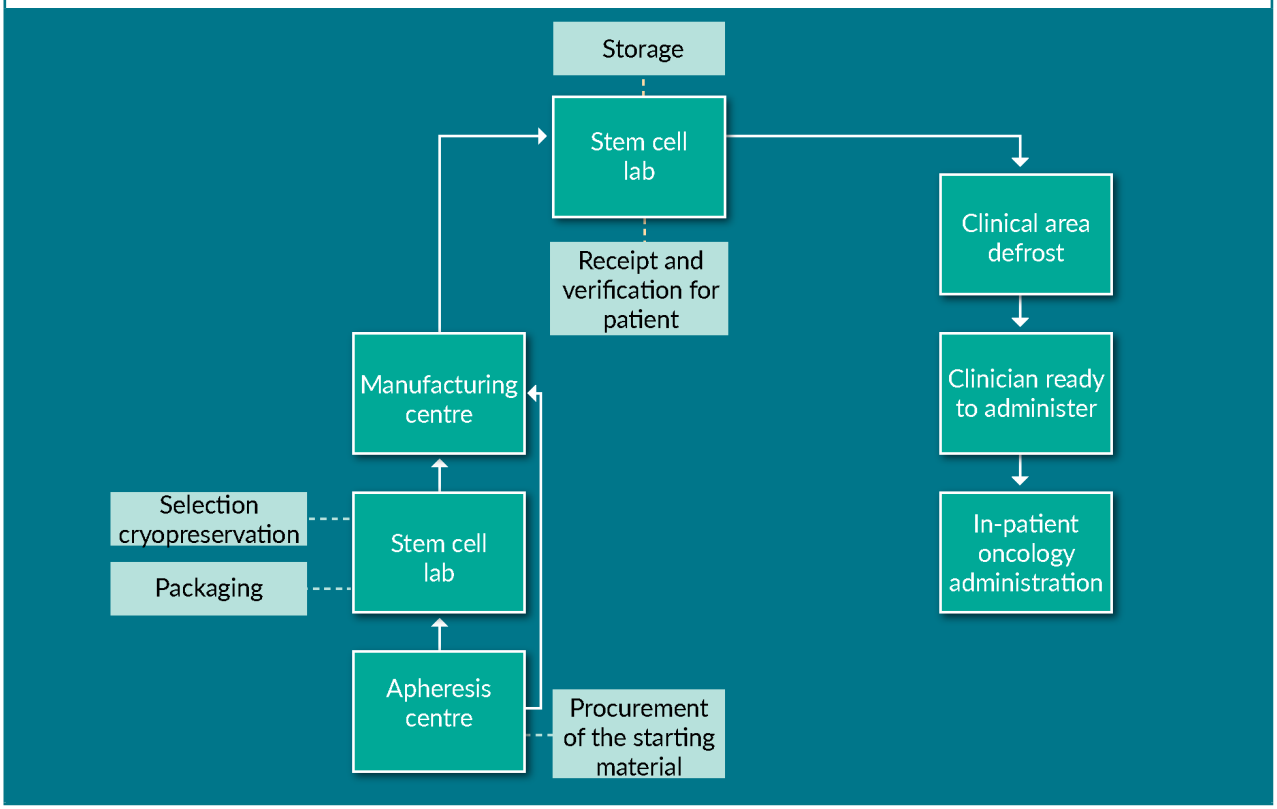
The final Figure 4 amalgamates Figures 2 & 3, giving a clear picture of the complexity of the processes involved in the provision of CAR-T therapy. The sections colored in yellow show areas that require pharmacist involvement. In order to ensure consistency and minimize variation in service provision the Pan- UK Pharmacy Working Group for ATMPs in conjunction with the NHS Specialised Pharmacy Service has produced checklists for each stage identified above requiring pharmacy input, which detail key points to ensure are covered by local systems. This allows pharmacy to consistently discharge their oversight of medicines responsibility whilst ensuring that the products are handled by staff with the appropriate skills and competencies. This document, Pharmacy Institutional Readiness for Marketed CAR-T therapies, is available on the NHS SPS website [11] has proved useful in the centers who are now providing the treatment. The principles outlined can be applied to other ATMPs.

CLINICAL ROLE

Whilst not losing sight of the importance of the governance and operational roles, in the UK it is the clinical role of the pharmacist which has become the primary focus for the pharmacy profession with Lord Carter's report into Acute Trusts Operational Productivity [12] advising that 80% of the pharmacy resources should be devoted

FIGURE 3

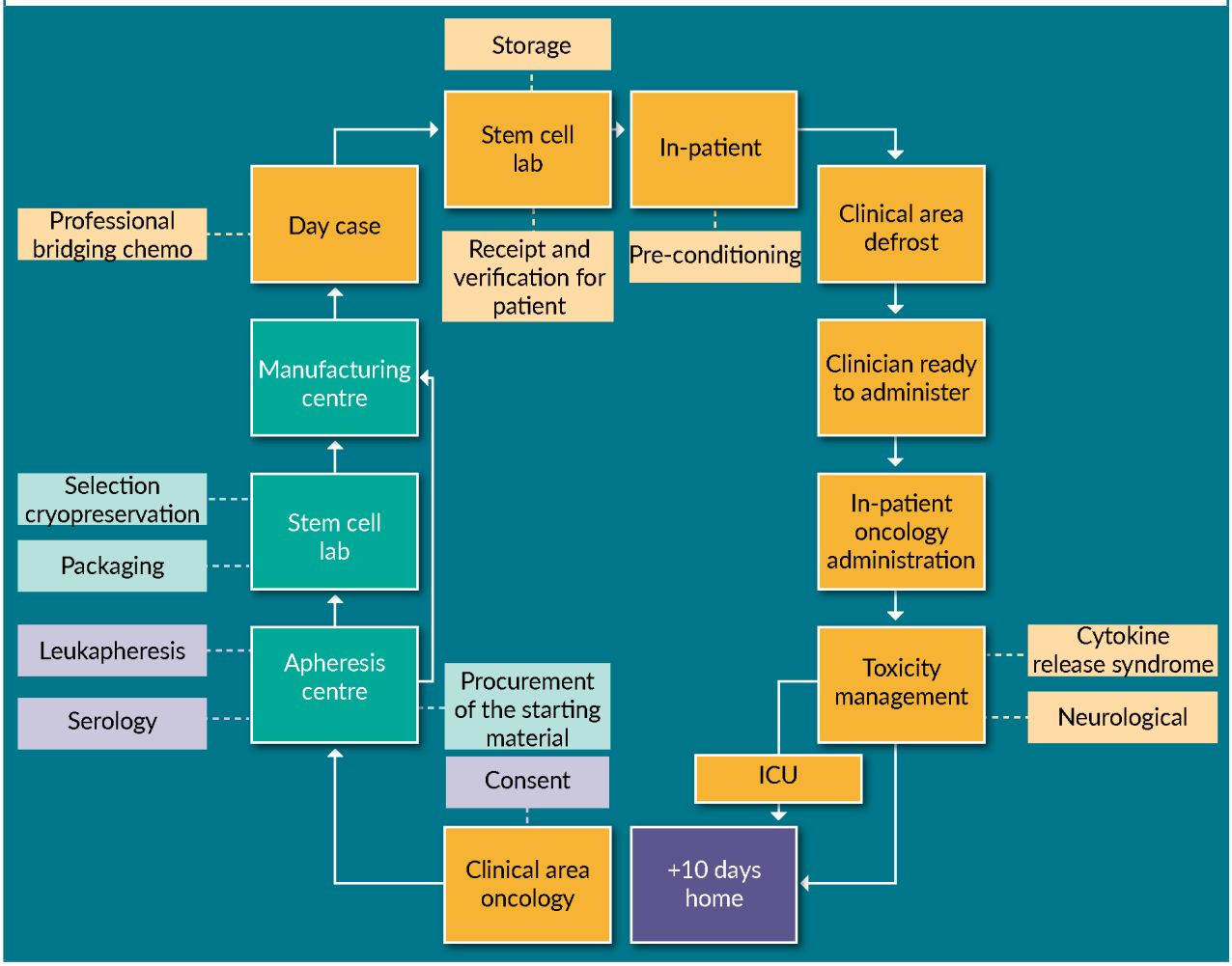
Marketed CAR-T product journey.



DOI: 10.18609/cgti.2019.130

FIGURE 4

Pharmacy involvement in marketed CAR-T journey.



to patient facing activities. The role of the clinical pharmacist in ATMP provision has become more defined and formalized since the advent of marketed CAR-T therapies. It centers around patient verification, linking with referral centers where required, and toxicity management. The Pan UK Pharmacy Working Group for ATMPs has established a clinical pharmacy subgroup which is defining this role and producing a standardized toxicity management tool based on clinical experience so far. The group also aims to use horizon scanning data to enable proactive collaboration and to facilitate the implementation of new ATMPs as they become available.

That said, at the time of writing most ATMP exposure remains in clinical trials. There are only 6 licensed ATMPS available for use in the NHS in England whereas there are 85 in clinical trials in the UK [13]. Most pharmacy departments have teams distinct from routine clinical pharmacy teams, whose role is to support implementation of Good Clinical Practice (GCP) in clinical trials. In reality, the accountability requirements of GCP are very similar to the careful tracking and tracing required for routine use of (licensed) ATMPs and many procedures for routine practice can be informed by those in place for clinical trials. The Pan UK Pharmacy

Working Group for ATMPs has also established a subgroup for clinical trials which aims to ensure that pharmacy trials teams are equipped to ask the appropriate questions at the various key stages from first contact to establishing trial feasibility through site initiation and into recruitment. At the time of writing, advice is also being prepared, around the governance and preparation requirements to initiate clinical trials involving gene therapy medicines. All outputs will be published on the NHS SPS website [14].

Experience so far has thrown up some obstacles which need to be overcome. For example the JACIE requirement for products to be overwrapped [15] prior to storage in nitrogen has proved difficult since the packaging of a licensed medicine is part of the marketing authorization and altering it arguably renders the

FIGURE 5

The three Innovate UK -funded advanced therapy treatment centres and the London Advanced Therapy Network.

DOI: 10.18609/cgti.2019.130

product unlicensed. Another example of the conflict at the regulatory interface involves the requirement for labeling. Labeling of medicinal products simply requiring a unique patient identifier [16] conflicting with the Human Tissue Authority requirements for the apheresis product [17] which requires labeling with a specifically constructed donor identification number. In practice however, all problems can be resolved and overcome by collaborative working.

Figure 5 shows the three Innovate UK -funded advanced therapy treatment centres and the London Advanced Therapy Network. The centers aim to foster collaboration between stakeholders in the ATMP pipeline, to identify and eliminate problems and to ensure that UK patients benefit from these innovative medicines. The Pan UK Pharmacy Working Group for ATMPs operates across these four networks and beyond to produce both proactive and reactive advice and to ensure that pharmacists are aware of the potential of this exciting group of medicines.

Pharmacy professionals have a wide reach. Rather like the ATMP pipeline, pharmacists cover many clinical specialisms in secondary care. Additionally, our primary care pharmacists support patients in the community and our GP pharmacists work at the interface. We are all excited by what ATMPs have already delivered and even more so by the promise of what they will deliver in future, and look forward to ensuring that our workforce is suitably informed to meet the ATMP challenges as we embrace these medicines which have the potential to be life changing for so many of our patients.

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Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *The author would like to thank members of the Pan-UK Pharmacy Working Group for ATMPs, including those from Wave 1 CAR-T commissioned sites, NHS Specialised Pharmacy Services colleagues and Northern Alliance Therapy Treatment Centre colleagues who have contributed to the evolution of the role of Pharmacy, and have therefore supported the contents of this article.*

Disclosure and potential conflicts of interest: *The author declares that they have no conflicts of interest.*

Funding declaration: *The author received no financial support for the research, authorship and/or publication of this article.*

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited; externally peer reviewed.*

Submitted for peer review: *Jun 29 2019; Revised manuscript received: Sep 24 2019; Publication date: Oct 18 2019.*

CELL & GENE THERAPY INSIGHTS

DECENTRALIZED MANUFACTURE

SPOTLIGHT

EXPERT INSIGHT

Regulatory considerations for decentralized manufacture of ATMPs

Alison Wilson & Alexis Cockroft

Decentralized manufacture (DCM) has the potential to facilitate uptake of advanced therapy medicinal products (ATMPs) within the EU. The new GMP guideline for ATMPs contains welcome new flexibility in regard to DCM and also in relation to use of automated equipment. However regulatory challenges extend beyond GMP issues, including questions of comparability of product manufactured at multiple hospital sites and mechanisms for introduction of new sites within the current variations framework. The need for additional guidance from regulators is discussed.

Cell & Gene Therapy Insights 2019; 5(10), 1213–1224

DOI: 10.18609/cgti.2019.127

Standards for the manufacture of medicinal products in the EU are established by Good Manufacturing Practice (GMP) directives [1–3] and elucidated in detailed GMP guidelines [4]. The basic requirement is that the manufacture of medicines and active substances for clinical trial and commercial marketing must be undertaken in a facility holding an appropriate Manufacturing and Import Authorisation (MIA) or Manufacturing and Import Authorisation for Investigational Medicinal Products (MIA/IMP). All manufacturing steps must be performed subject to the oversight of the Qualified Person (QP), who must, when releasing the batch of product under Annex 16 of the GMP guidelines for marketed products and Annex 13 for investigational medicinal products (IMP), certify that each batch has been produced in accordance with GMP. Certain simple activities required for preparation of the medicinal product immediately prior to administration may be conducted at the hospital

pharmacy or treatment area. These steps are termed 'reconstitution' and may include dissolving or dilution for infusion and rehydration of lyophilized medicines. These steps are considered to be outside of the scope of GMP and responsibility lies with the clinical site, including the necessity for appropriate management control and risk-based assessment for handling, preparation and administration [5]. Thus a MIA or MIA(IMP) is not required for reconstitution of marketed medicines or IMPs.

The idea of undertaking downstream preparation of medicines at the hospital/bedside has been adopted with enthusiasm by some advanced therapy medicinal product (ATMP) developers, largely because the manufacture of ATMPs has brought with it many technical and clinical challenges. In particular there are difficulties around production of viable cellular products with short shelf lives and considerable sensitivity to their environment. Developers have frequently attempted to develop ATMPs, in particular cell-based products, which require extensive 'preparation' at the clinic as a means of mitigating the difficulty of shipping living cells from the manufacturing site. Approaches ranging from simple thawing of a vial of cells to resuspension, cell count and dose adjustment, and even combining with a matrix or scaffold material are sometimes suggested as a means of managing the cell therapy delivery process. The difficulty with this approach is that under conventional pharmaceutical GMP, many of these processes are considered to be manufacturing steps and must therefore be performed in an authorized GMP environment and subject to QP oversight. An important consequence of the specific GMP guideline for ATMPs [6] is that it explicitly permits the preparation ("reconstitution of product after batch release") of ATMPs provided post-release processes are not substantial manipulation: such activities are manufacturing steps *per se* and must therefore be done under GMP.

Recognizing the need for additional flexibility in manufacture of ATMPs, via the risk-based approach which underpins the GMP approach for ATMPs, the ATMP GMP guideline also permits the manufacture of an ATMP "close to the patient": the decentralized manufacture (DCM) of ATMPs. The specific GMP requirements for DCM are set out in section 11.3.3 *Batch release process in cases of decentralized manufacturing*. The GMP guideline also addresses the concept of using automated equipment (Section 17 *Automated production of ATMPs*), which is an important concept for DCM in reducing the potential variability of manufacture. This additional flexibility is clearly aligned with the idea of facilitating new manufacturing paradigms such as DCM.

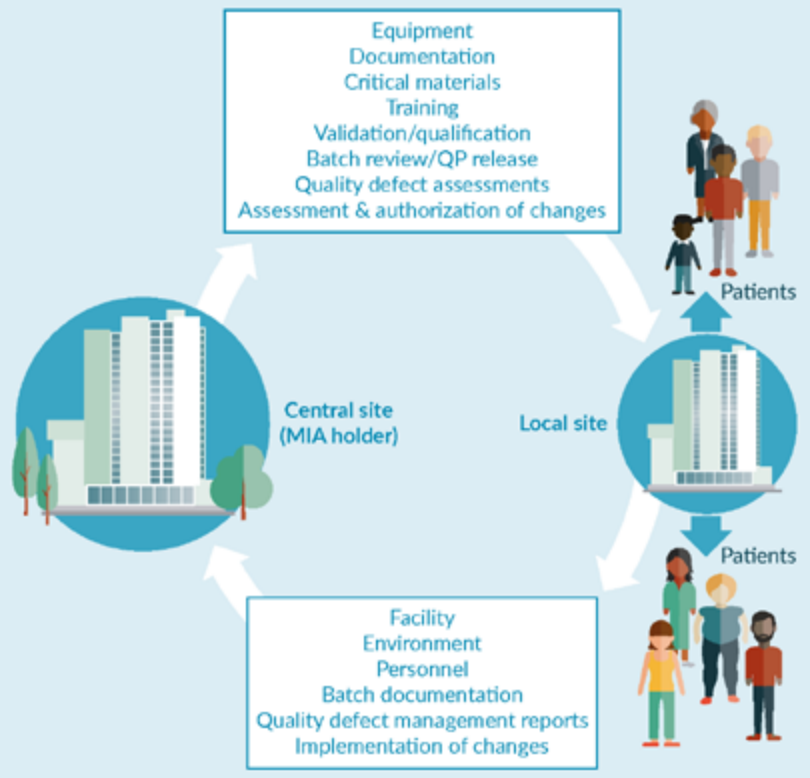
The concept of DCM includes the production of ATMPs via point-of-care devices which allow validatable, enclosed manufacture supported by appropriate instrumentation (Figure 1) [7].

The challenges and opportunities for DCM of cell-based therapies have been discussed in some detail in several papers arising from the EPSRC Redistributed Manufacture project (Redistributed Manufacturing in Healthcare Network (RiHN) project [8–10]; however, these focused on the 'mechanics' of DCM,

DOI: 10.18609/cgti.2019.127

FIGURE 1

Decentralized Manufacturing Model (EU/EEA-based sites).



The central site (MIA holder) provides key aspects for control of manufacture, including automated equipment, documentation and training requirements. Batch release and QP certification is controlled by the central site. The local sites are responsible for compliance with GMP, completion of batch documentation for release, and ensuring labeling and traceability of the ATMP. Local sites also implement changes as instructed by the central site, and communicate potential quality defects to the central site for assessment.

such as logistics, cost structures, economic value, organizational quality systems, process engineering and scalability.

There are consequences in the regulatory sphere beyond those relating to GMP. One of the key tenets of the pharmaceutical legislation is achievement of consistency: between batches of IMP; between batches on which safety and efficacy have been demonstrated and commercial product; and between batches of marketed product throughout the product lifecycle. Patient safety is dependent upon production of safe and effective medicinal products, which can only be assured via consistent product manufactured by reproducible processes. For conventional medicinal products which are mass-produced at scale in one or a few sites, this is a routine situation. For the special case of ATMPs, and in particular autologous ATMPs, the inherent biological variability of cells and variation between individuals is a major confounding issue [11]. If we then include the possibility that each batch (product for one patient) could be made in one of ten, or 20, or 50 different production locations, the challenges for achieving the necessary consistency are increased proportionately.

REGULATORY CONSIDERATIONS

Whilst there is now formal guidance and recognition of DCM at the GMP level, it is not yet apparent how Competent Authorities will view this approach in terms of clinical trials and marketing authorization. The fundamental question is whether local sites will be viewed as manufacturing sites in their own right even if they do not hold a MIA or MIA(IMP). It is assumed here that this will be the case since they will be responsible for the quality of ATMPs produced in their facility. The following Tables 1 & 2 highlights some of the differences in approach that will are potentially challenging for regulatory approval of ATMPs via Clinical Trial Authorisation application (CTA) or Marketing Authorisation Application (MAA). GMP issues *per se* are not included here, although there is inevitable overlap in some aspects.

COMPARABILITY

A key part of the MAA assessment process for biological medicines is an evaluation of the comparability of final drug product (and therefore impact of manufacturing process) used in pivotal safety and clinical studies to that proposed for marketing [12]. Comparability assessment is recognized as a particular challenge for ATMPs [13] because of the extraordinary complexity and biological responsiveness of the cell and the limitations of predicting potential impacts to the product and of the analytical techniques, especially at the (average) population level. The extent to which regulators may expect evidence of comparability of production between individual sites as part of a CTA, MAA or subsequent variation is as yet unknown. One optimistic viewpoint is that with consistent manufacture facilitated by tight control and confirmation of the performance of automated manufacturing equipment and assurance of the quality of materials used for manufacture, it should be possible to infer that resulting products will be comparable (within the acceptable variability of biological starting materials). Therefore quality, safety and efficacy would be assured through comprehensive qualification and validation activities prior to the 'local sites roll-out phase'. Developers seeking to leverage the opportunities offered by a DCM approach should consider early engagement to explore this issue with Competent Authorities.

CLINICAL TRIAL AMENDMENTS/ MODIFICATIONS

A substantial amendment to a clinical trial requires prior authorization from the national Competent Authority in which the trial is conducted, with a nominal timescale for assessment of 35 days under the current Clinical Trials Directive [14]; a substantial modification under the forthcoming Clinical Trials Regulation [15] allows up to 88 days for an ATMP. It is also not clear in the clinical trial scenario whether introduction of an additional site would require notification in all involved MS or just the one in which the patients would be treated. As manufacturing site details are part of the Part I application under the Clinical Trials Regulation the former situation may be more likely.

DOI: 10.18609/cgti.2019.127

POST-AUTHORIZATION LIFECYCLE MANAGEMENT OF VARIATIONS

The current system of variations to Marketing Authorisation will be challenged by DCM. At present, significant changes such as the introduction of a new manufacturing site require review by the European Medicines Agency (EMA) for authorized ATMPs. Addition of a new manufacturing site is a Type II variation under the EU Variations regulation [16], having a nominal 60-day assessment timescale plus 15 days for EMA/European Commission (EC) to notify the applicant of its decision. This does not take into account the submission 'windows', submission validation period or the clock stops and a Type II variation can take months to approve.

Use of the Post-approval Change Management Protocol procedure for the introduction of new sites may be an option to simplify some aspects of the variation process but may not be consistent with the current legislative framework. However, scientific advice could be requested in the pre- or post-authorization phase to discuss potential strategies for the addition of decentralized sites.

There are numerous practical and strategic challenges posed by DCM in this regard. The identification of the need for a process, material or software change will need to be a two-way process (Figure 2): local sites must have a clear mechanism for notifying the central site if they identify changes that may be necessary. The central site must then assess the need for a variation, and upon approval ensure that implementation of the change is correctly co-ordinated across all local sites. As DCM will probably be dependent upon automated cell processing devices, there will be a third partner in this relationship, the device manufacturer. Coordination regarding software updates that impact manufacturing processes will be critical to allow the MA holder to maintain compliance.

In both the clinical trial and marketing phase, such approval

TABLE 1

Differences between centralized drug product manufacturing versus decentralized manufacturing: some guidance available†.

Centralized manufacture of pharmaceuticals (traditional manufacturing model)	Decentralized ATMP manufacture†
All manufacturing sites named on application form	Central site only?
Manufacturer's authorization (MIA/ MIA[IMP]) for each site or listing all sites within the same EU/EEA Member State (MS)	Concept of a central site responsible for oversight of decentralized sites
QP certification /batch release at each site	QP for central site, optional at local sites. If no local site QP, trained and qualified individual(s) transmit(s) data and any deviations from each site to central QP. Release communicated remotely
GMP/environmental controls at each site – confirmed for QP release	Equipment maintenance/calibration/ – machine indication of successful process run. Assured by local sites in accordance with central site procedures (e.g., SOPs)

†Guidance in the ATMP GMP guideline but not covered in Competent Authority submission requirements for CTA/MAA.

TABLE 2

Differences between centralized drug product manufacturing versus decentralized manufacturing: guidance absent or insufficient.

Centralized manufacture of pharmaceuticals (Traditional manufacturing model)	Decentralized ATMP manufacture
Manufacturer's authorization (MIA/MIA[IMP]) for each site or listing all sites within the same EU/EEA Member State (MS)	Strategy to have MIA(IMP) for central site only
Specifications and in-process controls (IPC) defined by batch data from manufacturing site	Specifications and IPC imported from central site
Materials control against incoming material requirements: certificate of analysis checks, testing and release	Release by central site/shipped to local site? Alternatively, materials control directed by central site and purchased/controlled by local site Version controlled updates
Equipment controls (software) – responsibility of manufacturing site to assure suitability and performance of software and oversee version updates	Equipment controls (software) – responsibility of manufacturing site to assure suitability and performance of software and oversee version updates. Central site pre-assessment and direction?
Stability data/shelf life on product at each site	Stability data (in effect, in-use shelf-life) generated centrally or required to be done at each site?
Comparability data to be considered when changing manufacturing process/materials or adding new manufacturing sites	Prior development of a comparability and qualification protocol to confirm consistency of product manufacture between sites
Changes to registered detail via amendments (CTA)/variations (MAA): approval of revisions confirmed via manufacturing site procedures	Changes to registered detail via amendments (CTA)/variations (MAA): approval of revisions communicated by central site. Logistics and timing of implementation?
Labeling activities for finished product conducted by each manufacturing site or outsourced, in accordance with approved label.	Labeling activities for finished product conducted by each site. Approved label content communicated by central site

requirements may become extremely burdensome for the applicant when multiple new sites may be needed in relatively short timescales. Of note, authorized manufacturers of approved medicinal products are listed in Annex II of the MA documentation: this is updated by the European Commission (EC) and may potentially result in additional delays to finalizing any variations to add manufacturing sites. The development of a workable plan for lifecycle management will necessitate robust strategy development by regulatory affairs experts to ensure that the consequences of dossier content are fully understood and that post-approval changes can be managed within the DCM. This is as yet a moving target in the absence of any guidance on changes to authorizations involving DCM.

In neither situation (CTA/MAA) do the current application forms and requirements guidance allow for the possibility of decentralized manufacture as foreseen in the ATMP GMP guideline: evidence of GMP authorization is required for all manufacture-related variations, modifications and amendments.

APPLICATION OF TISSUES & CELLS LEGISLATION

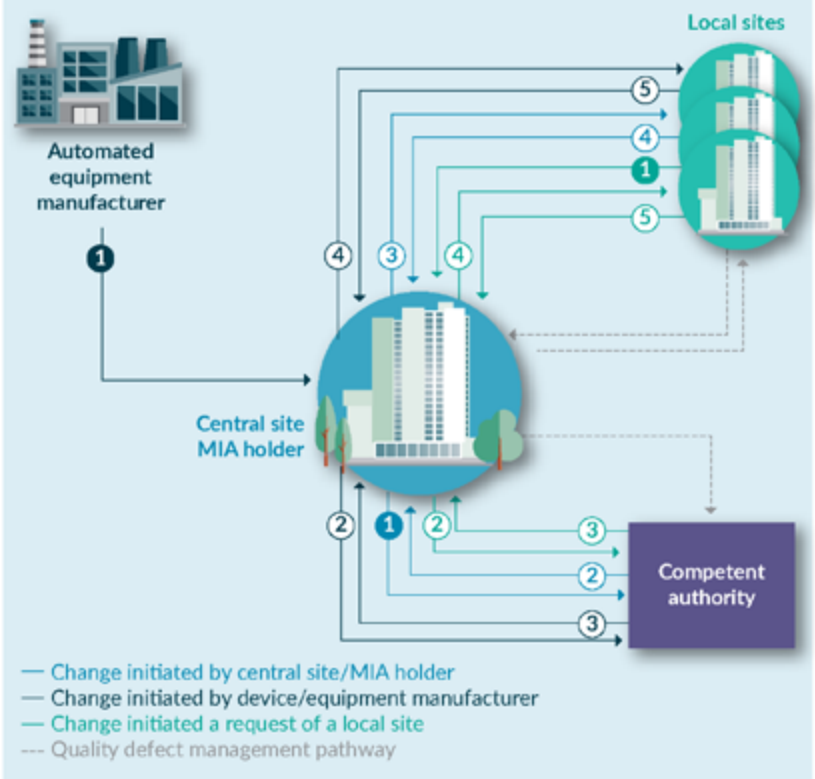
The idea of near-patient manufacturing raises questions around the

DOI: 10.18609/cgti.2019.127

"same surgical procedure" exemptions of EU Directive 2004/23/EC [17], which set quality and safety standards for human tissues and cells in therapeutic applications. Although sometimes thought of as a "get out of jail free" card in the context of autologous cells isolated in theatre, this public health legislation is without prejudice to the scope of the ATMP Regulation [18]. In other words, cells isolated and returned within the same surgical procedure will still fall within the scope of the ATMP regulation if the cells are "engineered" (Box 1). The Committee on Advanced Therapies clarification of this situation [19] was reinforced by the ATMP GMP guideline section 17.1: "*If the output of an automated production system (hereafter referred to as "automated equipment") meets the definition of ATMP, the requirements of*

FIGURE 2

Regulatory communications between parties in decentralized manufacture of ATMPs.



Changes initiated by the automated equipment manufacturer (e.g., to software or design) or requested by a local site will go to the central site (MIA holder) for assessment to determine whether the proposed change meets the criteria for a variation (marketed products) or an amendment/modification (clinical trial product). Changes proposed within the central site will need to be similarly assessed. If the threshold is reached a submission will be made to the appropriate Competent Authority. Following approval, the change will need to be communicated to the local sites, with coordination on implementation timing, consideration for re-training or amendment of procedures, etc. Finally implementation of the change will need to be confirmed to the central site. Management of quality defects is reported to the central site for assessment for investigation, identification of corrective actions and possible submission to the Competent Authorities. This pathway assumes the MIA holder and clinical trial sponsor/MA holder are the same entity: if these are different, additional communications structures will be required.

the Regulation (EU) No 1394/2007 apply."

NEW APPROACHES

A novel approach to development of cell-based therapies across multiple sites is being considered by the US Food and Drug Administration (FDA) [20], in which physicians/clinics can agree on common manufacturing specifications for a cellular product, manufacture and perform the same clinical trial at their respective sites. Each site may then submit pooled safety and efficacy data, along with their own manufacturing data, to apply for an individual Biologics License Application (BLA) for manufacture of the cellular product at their facility. This approach may help to support cell-based therapy development amongst hospital facilities or smaller companies by providing the opportunity to pool the costly clinical data necessary for a BLA, and in particular benefit the development of less complicated cellular products which may be more amenable to a 'decentralized' approach. Although not a direct parallel with the DCM under consideration, some similar regulatory issues around alignment of manufacturing process between sites, and product consistency and comparability, will doubtless arise in the assessment of such applications.

DCM is likely to become a facilitator for the uptake of other advanced manufacturing technologies such as 3D printing: the concept of a personalized shaped implant or tissue replacement, which may be seeded with cells during manufacture or immediately prior to implantation. There is little information from regulators on this approach, although in providing guidance on 3D printing ('additive manufacture') for medical devices, US FDA notes that interactions with multiple regulators may be required when these are combined with cells or tissues [21]. EMA's Innovation Task Force identified novel manufacturing and 3D printing as a new science and technology trend [22] but the significant additional regulatory challenges presented by this technology [23] have yet to be addressed.

One example of an approval for a clinical trial utilizing decentralized manufacturing comes from Rena Clinical Ltd. A recent presentation [24] described successful design and implementation of the framework to allow local manufacture of an IMP intended for treatment of an ultra-rare kidney disease. Starting from a patient's blood sample, the enzyme-based IMP had to be prepared and infused within a target of 4 hours; the IMP shelf-life was stated to be 30 minutes from completion of IMP production for each patient. This CTA was approved by the UK Medicines and Healthcare Regulatory Agency with a single centralized MIA(IMP) holder; manufacture at each site to be performed using a CE-marked machine and disposable product-contact equipment and solutions. Quality Management System and GMP-like controls were established for each clinical site. Interestingly this product was not an ATMP; the Competent Authority perhaps approved the application under an ATMP-only GMP provision due to the rarity of the disease and the fact that preparation under conventional pharmaceutical GMP would have been logistically impossible. However, this was within the same

DOI: 10.18609/cgti.2019.127

BOX 1

Regulation (EC) No 1394/2007 Article 2.1 (b) "Tissue engineered product" means a product that:

- contains or consists of engineered cells or tissues

2.1 (c) Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:

- the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,
- ***the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.***

Directive 2001/83/EC Annex Part IV 2.2.(a): "Somatic cell therapy medicinal product" means a biological medicinal product which has the following characteristics: (a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, ***or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor.***

EU Member State and therefore under the same Competent Authority (MHRA): it would be interesting to see whether other national CA took the same view and approved the CTA on this basis.

TRANSLATION INSIGHT

Fulfilment of the therapeutic potential of ATMPs will require several different manufacturing models: one size does not fit all [25], and DCM can provide a radical new approach to the uptake of autologous cell-based therapies. A key element of this uptake will be the concept of institutional readiness [26,27]; specifically in the context of DCM the full engagement of staff (operators, QC staff and management) in providing a rigorous approach to localized manufacture of ATMPs. This requirement is integral to the aims of the Advanced Therapy Treatment Units (ATTU) in the UK, which are intended to increase the adoption of regenerative medicine products. Such specialist treatment centers at regional, national and supra-national level are critical to the uptake of ATMPs [28]. The ATTU and similar centers in other countries may provide a stepping stone platform to uptake of ATMPs in 'ordinary' hospitals in which DCM may be the most attractive option for ATMP supply.

Acceptance by, and engagement with, the regulatory authorities will be key to the success of DCM, however a common approach across the EU will be needed. It will be essential to develop harmonization of expectations for accepting applications using DCM; specific regulatory guidance may well be required. There is a risk that clinical development will fail if a CTA is accepted in some Member States and rejected in others, especially for rare diseases with patients scattered across several countries, or that an approved ATMP cannot be fully commercialized because of difficulties in manufacturing reach. There is potential for immense additional complexity in lifecycle management for approved ATMPs; and since the application of the DCM concept to ATMPs is very new it will probably be some time before such guidance becomes a priority for within EMA or the Commission.

Standardization is frequently discussed as a mechanism for facilitating development of ATMPs. Although development of standards for cell-based therapies themselves will be challenging in the extreme, and may not be technically feasible or commercially desirable in the near or mid-term, exploration of opportunities in standardization of manufacturing processes should be beneficial [29]. This should also include state-of the-art (ideally in-line or at-line) analytical methods to remove the need for remote/off-site testing. The promise of DCM is only likely to be realized if regulators can be assured that the basic requirements for quality and consistency can be met at individual sites; any tools that can assist in this goal are to be welcomed.

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The authors declare that they have no conflicts of interest.*

Funding declaration: *The authors received no financial support for the research, authorship and/or publication of this article.*

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited; externally peer reviewed.*

Submitted for peer review: *Jul 26 2019; Revised manuscript received: Sep 20 2019; Publication date: Oct 2 2019*

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DOI: 10.18609/cgti.2019.127

CELL & GENE THERAPY INSIGHTS

DECENTRALIZED MANUFACTURE

SPOTLIGHT

ORIGINAL RESEARCH

Regenerative medicine as a disruptive technology: implications for manufacturing & clinical adoption

Geoffrey Banda, Joyce Tait & James Mittra

Although regenerative medicine has been described as a disruptive innovation, there has been little critical enquiry into the nature and location of the disruption. This paper, based on ten cases in the UK, analyses the nature of disruption for allogeneic and autologous therapies in terms of manufacturing, distribution and adoption in clinical settings. We discuss the challenges of dealing with inherent variability in living systems and how this necessitates co-evolution of technologies and innovations. We propose that understanding of the distinction between disruptive and incremental innovation, and of the nature, extent and location of the disruption across sectoral value chains, can help to guide company innovation strategies and government innovation support policies for regenerative medicine, as already proposed for industrial biotechnology.

Cell & Gene Therapy Insights 2019; 5(10), 1287–1303

DOI: 10.18609/cgti.2019.135

INTRODUCTION

Regenerative medicine (RM), which promises to cure disease and respond to currently unmet medical needs [1], is frequently described as a 'disruptive innovation' [2,3]. However, there has been little critical enquiry into the nature and location of the disruption, resulting in missed opportunities to shape the innovation ecosystem to make it more supportive of RM therapies. We have defined disruptive and incremental innovation as follows [4,5].

Disruptive innovation involves discontinuities in innovation pathways, requires new areas of research

and development (R&D), creation of new modes of production and/or new markets. It can lead to sectoral transformations and the displacement of incumbent companies, or the creation of entirely new sectors, all with significant societal and economic benefits. There is often no pre-existing business model on which to build a strategy for disruptive innovation and there may also be a need to create a new value chain, or a new role for the emerging technology in an existing value chain.

Incremental innovation fits well with the current business model of a firm. It generates competitive advantage and contributes to the economy through more efficient use of resources, or elimination of wasteful or environmentally damaging practices, but will not lead to sectoral transformations.

This paper builds on the authors' previous research [1,6,7]; providing new empirical data and analysis to inform our thinking on disruptive innovation and how the concept can be operationalized to deliver a more supportive policy environment [5]. The key to this approach is to attend to the extent of disruption of incumbent company business models, the location of that disruption within specific value chains, and the impact of regulatory and policy choices on the location and extent of disruption. Our case study of RM encompasses both allogeneic and autologous therapies:

Allogeneic therapies are developed by collecting cells from a donor, manipulating them to form a master-cell bank, then using them as starting material to produce multiple therapies administered to large numbers of patients, generating attendant economies of scale.

Autologous therapies are based on collection of cells from a patient, manipulation in the manufacturing environment and re-introduction into the same patient within a clinical setting.

In line with the above definitions, both allogeneic and autologous RM therapies are disruptive of the business models of incumbent small molecule pharmaceutical and bio-pharmaceutical companies [1], in that they require radically different approaches to R & D, manufacturing, distribution and marketing. Autologous therapies, while equally disruptive of pharmaceutical business models, could be regarded as a relatively incremental development for companies involved with organ transplants or for blood transfusion services (BTSs), albeit with some disruptive elements, given the nature of the properties of the material being handled.

The approach adopted in this paper contributes to understanding where and to what extent autologous and allogeneic therapies display disruptive or incremental innovation characteristics, based on original case study interviews with organizations involved in RM development in the UK. It builds on our previous research to show how a disruptive/incremental lens can add insights that are valuable in devising policies to support the development of innovative technologies.

BACKGROUND

Although there have been significant advances in scientific knowledge and understanding of RM, commercialization and large-scale production of autologous and allogeneic therapies have remained

DOI: 10.18609/cgti.2019.135

challenging. For allogeneic therapies, being developed in large scale, centralized manufacturing facilities [8], disruptive challenges include: the time and effort needed for donor material collection, processing and storage in a bio-bank under current Good Manufacturing Practice (cGMP), followed by further processing to produce therapies for patients; cryopreservation of living material, safe distribution of fragile living materials, ensuring traceability of cells following treatment; and dealing with immunogenicity issues in recipient patients. Many of these factors also apply to autologous therapies being developed in localized manufacturing facilities, with additional challenges related to the personalized nature of the therapy, ruling out economies of scale. The Department of Business, Innovation and Skills (BIS) in 2011 [9] suggested that manufacturing viable living cells for RM requires the development of "new technologies, tools and techniques" and, although considerable progress has been made, for example in manufacturing process development, RM therapy value chains are still a long way from delivering a reliable, profitable route to market [10,11].

Lipsitz *et al.* argued that the new RM-related technologies span manufacturing, distribution systems, shelf life enhancement and automation (especially closed manufacturing systems) [12]. This has led to further calls for advances in manufacturing and bio-processing, because of the non-scalability of existing technologies [9] and the need for skills development in the RM niche-focused areas. Abbasalizadeh *et al.* present a deeper analysis of the scientific, technological, and commercialization challenges of allogeneic therapies, suggesting that although autologous therapies are safer and often the preferred choice, they do not provide a simple off-the shelf product for clinical use [8]. They also argue that production of autologous therapies is time consuming, skilled labor-intensive and, from an operational perspective, the mechanics of isolating cells and delivering the therapy are problematic for elderly and critically ill patients unable to tolerate biopsies. Lipsitz *et al.* demonstrate that lack of highly skilled labor is caused by current manufacturing process requirements and the costs incurred in training operators, including routine validation of aseptic techniques for operators [12]. Additional issues include the need to independently verify batch record protocols, active working time delays due to suiting up procedures with laboratory garments, and the need for additional staff to facilitate gowning. The calls for 'closed manufacturing systems' are based on the need to reduce some of these 'necessary redundancies' of current clean room operation procedures for cGMP requirements. Other challenges include lack of value chain integration, technology delivery gaps, and arguably inappropriate or disproportionate governance of innovative technologies [4,6]. Given the disruptive nature of RM, new firm-to-firm linkages are needed to create new value chains and, during early development phases, brokerage is important to create links with stakeholders [6]. These disruptive challenges are not experienced by manufacturers of small molecules and other biologicals and they are important for understanding the unique hurdles RM manufacturers face in assuring cellular product

safety, quality and efficacy, as well as traceability and attendant ethical considerations.

Centralized & locally distributed manufacturing approaches

Harrison *et al.* argue that throughout history there has been a steady shift from localized, decentralized production systems to centralized production systems, underpinned by the need to achieve economies of scale and scope [13]. Centralization was possible where manufacturers were dealing with standardized bulk products, which could be easily characterized and analyzed and were accompanied by increasingly automated processing and quality assurance systems. Lipsitz *et al.* argue that, for RM therapies, scalable production methods will determine the cost of goods sold, leading to the policy focus on allogeneic therapies because of their *potential* economies of scale and investment palatability making them slightly less disruptive of incumbent pharmaceutical business models than autologous therapies [12]. However, allogeneic RM therapies are inherently disruptive of this centralizing trend because of the greater variability of biological inputs, creating technical difficulties in standardizing manufacturing and quality assurance and creating a need for close collaboration between therapy producers and clinicians (see 'RM manufacturing processes', 'The links between manufacturing systems and distribution models' and 'Clinical adoption of autologous therapies' sections). For these reasons, Harrison *et al.* foresee autologous therapies being manufactured in locally distributed, 'near-hospital' facilities [13]. This argument informs our focus on the nature and location of disruption in the development of RM therapies as it impacts on manufacturing, distribution and adoption in clinical settings.

Given the challenges of producing autologous cell therapies, decentralized or locally distributed manufacture is the only feasible approach for autologous and gene-based cell therapies. In response to BIS [9] and Abbasalizadeh *et al.* [8], Harrison *et al.* [13] argue that, as a result of recent advances in technologies that facilitate "reproducible, repeatable and reliable manufacture of highly specialist products at a small scale" and real-time monitoring Quality Management Systems (QMSs), it is increasingly possible to move towards such locally distributed manufacturing models. They also claim that this small scale, locally distributed technology approach makes it possible to handle "inherently unstable personalized cell and gene therapies".

Locally distributed manufacture of autologous cells will be an order of magnitude more disruptive of the existing pharmaceutical and biopharmaceutical business models than current manufacturing approaches to allogeneic therapies, hence the lack of interest in these therapies by these incumbent sectors. For allogeneic therapies, rather than adaptation of the existing big pharma business model there is a need to develop new business models and value chains, involving new start-up companies or existing companies moving into health care from other sectors of the economy (e.g., investment in manufacturing processes by Lonza and GE Healthcare).

DOI: 10.18609/cgti.2019.135

The option for pharmaceutical companies to purchase locally distributed manufacturers of autologous cell therapies with a view to centralizing production does not exist, given the countervailing factors described above. Where such purchases have been attempted, cell therapy manufacturers have been frustrated by the lack of understanding of the acquiring firms about how RM works and how the feasible business models are different from the small or bio-molecule contexts investors are accustomed to. This is a common experience where incumbent large companies attempt to take on disruptive technologies. Given these constraints on investment the Advanced Therapies Manufacturing Action Plan [14] called for systemic investment in the sector to engender a more competitive fiscal environment.

Clinical adoption of allogeneic & autologous therapies

Manufacturing challenges are not the only factor limiting the development and hence the adoption of RM therapies. We previously noted a lack of co-operation between manufacturers and clinicians affecting the adoption of RM therapies [6], a view supported by Gardner *et al.* who observed that RM products will need to "work hard to create an adoption space" in current healthcare settings [15].

Also, prevailing regulatory systems for RM therapies, along with other governance mechanisms such as the establishment of shared standards, have not been sufficiently adapted to meet the needs of centralized or locally distributed manufacturing systems and personalized delivery to patients. RM therapies are also disruptive on current regulatory frameworks because of the introduction of methods beyond minimal manipulation and raw materials that are outside current supply chains for transfusion and transplantation. These questions are not dealt with here but have been addressed elsewhere [1]. Faulkner has also identified the challenges of "opposing forces for gatekeeping and innovation" by regulators of manufacturing and clinical practices [16]. We have also argued that accelerating clinical adoption is dependent on the creation of innovation ecosystems that promote rapid integration of RM and allied business models as well as creating an environment where new business models are given a chance to thrive [6,17]. We have previously argued that the public-private interaction by innovation broker institutions such as the Cell and Gene Therapy Catapult are critical in the early phases of building supportive innovation ecosystems as they bridge value chain gaps, and de-risk early development stages [6]. This earlier work contributes to the frame described here to support analysis of the disruptive nature of RM therapies and the impact on: collaboration among clinicians, the clinical prescription system and hospital administrative systems; the viability of manufacturing processes; challenges related to ordering, storing and re-thawing therapies; and finally clinical adoption. We are aware that pricing and cost effectiveness are linked to manufacturing and clinical adoption, however we do not focus on them in this paper.

METHODOLOGY

We used the case study approach advocated by Yin for carrying out an empirical enquiry of issues that are embedded in real-life contexts [18]. In line with the argument by Stake we considered the complexity of the cases to understand the circumstances, contexts and other dynamics of the interactions of the organizations and actors we investigated [19]. We chose the case study approach because we were interested in the 'how and why questions' and the broader situational context within which these technologies are being developed.

Using a purposive sampling method, we approached 20 RM companies/organizations involved in RM-related activities in the UK and gained access to 10 of them. We conducted 18 semi-structured interviews (ten completed in 2014/15, with follow-up interviews in 2015/16). Semi-structured interviews allowed us the flexibility to follow themes and interesting leads that arose during the interview itself. After seeking informed consent, the interviews lasted between 1 and 2 hours and were audio-recorded and transcribed verbatim. Using manual thematic coding, we identified a number of salient themes, some of which are the focus of discussion in this paper. We used the STRATIS methodology to understand the business models, innovation ecosystems and value chains in the sector [20].

This paper also draws on our research on Proportionate and Adaptive Governance of Innovative Technologies [4], which has refined our thinking on the important features of, and differences between, disruptive and incremental innovations.

MANUFACTURING & CLINICAL ADOPTION OF RM THERAPIES: INTERVIEWEE PERSPECTIVES

Our analysis showed that allogeneic therapies are disruptive of many aspects of the business models of incumbent pharmaceutical firms, given the challenges involved in large scale manufacturing of cellular products, the storage and distribution of living materials, and delivery to very different markets. Large companies developing bio-pharmaceuticals will have overcome some, but not all of these disruptive challenges. Pharmaceutical companies' adherence to current business models, despite these disruptive features of allogeneic therapies, have led them to persevere in developing large scale, centralized manufacturing facilities, designed to deliver a commoditized product internationally to large numbers of patients, in order to make RM therapies an attractive investment proposition. This has become the dominant expected future business model for RM therapies, in the process side-lining the development of autologous therapies, which are much less capable of achieving compatibility with the current business models of pharmaceutical companies.

The following sub-sections use our interview data to reflect on issues related to the disruptive nature of cell-based therapies.

Raw material sourcing

The challenge of inherent variability in living systems

A factor acknowledged in the literature, and confirmed by respondents

DOI: 10.18609/cgti.2019.135

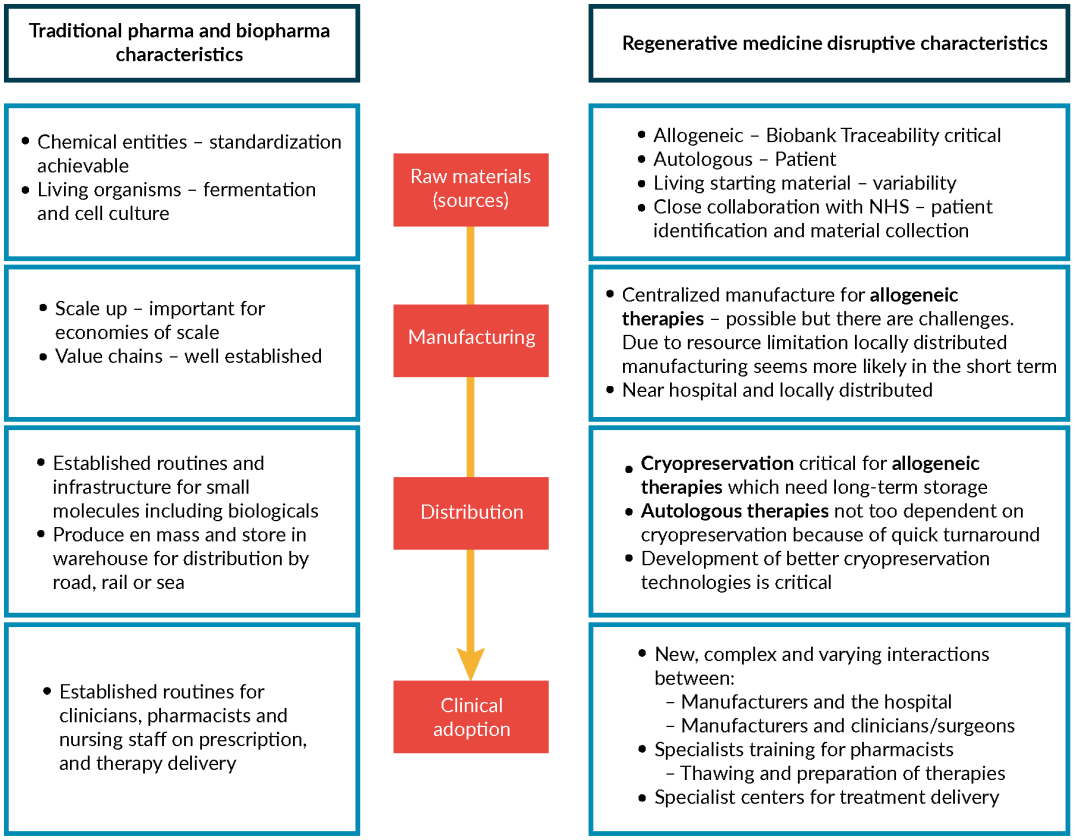
in all ten of our cases, is the complexity of working with raw materials composed of living systems which, unlike small molecules (**Figure 1**, left hand side), are difficult to standardize (**Figure 1**, right hand side). Specifically, the disruptive nature of RM first, emanates from these perspectives: RM raw materials cannot be subjected to traditional sterilization techniques and therefore need aseptic processing methods; second, because the therapy is integrated into the body unlike drugs which are metabolized and expelled, pharmacokinetics and pharmacodynamics are challenging; and third there is a need for defining, effecting and monitoring quality spanning the manufacturing and clinical phases. A respondent from a contract manufacturing organization reported that the private sector tends to play to its strengths by focusing on the "manufacturing piece because that's closer to what a standard pharmaceutical company would do", which covers raw material sourcing and processing. This implies that incumbent pharmaceutical companies, faced with a disruptive new technology, lock into what they already know and create an element of path dependency to make a disruptive transition more feasible. A disruptive element of the transition to RM for a conventional pharmaceutical company includes: incompatibility with chemical entities that can be easily standardized and produced in bulk and, because of chemical stability, intermediate and finished products can be stored for long periods with no need to identify the donor. Supporting these observations, he added:

"Here you have a product which has been derived from a human being, so it has all that … inherent biological variability, or even [a cell] derived from me on two different occasions, it can behave in a different kind of way. The cell obviously is a living system in its own right … it's a living system in vitro and then it's also a living system when you put it into the patient. So, like all living systems it has a nasty habit of doing its own thing." – Managing Director, RM firm in research and development and contract manufacturing.

Other respondents acknowledged that they still do not fully understand the cell's mechanism of action, having observed that cellular therapeutics work best when different types of cells are used in combination. So significant interactions between the different types of cell or tissue seem to be important for a functioning therapy. This is in contrast to small molecules and other biologicals where the biochemical pathways and pharmacokinetics end point are well known. Thus, for allogeneic therapies, innovators need to solve the challenge of standardizing and automating development processes for therapies with inherent variability, and to convince regulators of the robustness of their approach, especially for therapies that become integrated into the body. Furthermore, a product manufactured in the USA under FDA conditions cannot be assumed to be identical to a product manufactured in Europe under European cGMP conditions, according to respondents in our study. This creates manufacturing and regulatory

FIGURE 1

The contexts where regenerative medicine is disruptive of incumbent manufacturing, distribution and clinical adoption systems.



compliance challenges for firms operating across geographical regions with different regulatory systems, for example Europe, Asia and the USA. This has implications for validation and quality assurance processes across different manufacturing facilities for the same firm, making centralized manufacturing more problematic, and forcing firms into locally decentralized or locally distributed manufacturing, illustrating the disruptive impact. Given that large scale manufacturing by the same firm across different countries needs to comply with different national regulatory requirements, it is difficult to move employees in regulatory interfacing jobs across different countries, and it also multiplies the complement of regulatory personnel in the company compared to centralized manufacturing. This phenomenon affects both autologous and allogeneic therapies and impacts the whole process from donor selection to therapy delivery. Autologous therapies have an additional staffing burden where the manufacturing system is locally distributed.

The need for close collaboration between RM firms & the clinic

Another feature of the disruptive nature of RM development for

DOI: 10.18609/cgti.2019.135

conventional drug production is the intricate collaboration required between manufacturers and, for example, the National Health Service (NHS) in the UK, for sourcing cells or tissue, and manufacturing (**Figure 1** last box on the right). For a tissue regeneration case the respondent noted **(Figure 3)**:

"...There is need in the UK to collaborate with the NHS for cadaver identification, followed by organ harvesting leading to transport of the organ to a specialist de-cellularization facility and adequate storage of frozen samples." Respondent from a Tissue Regeneration Firm.

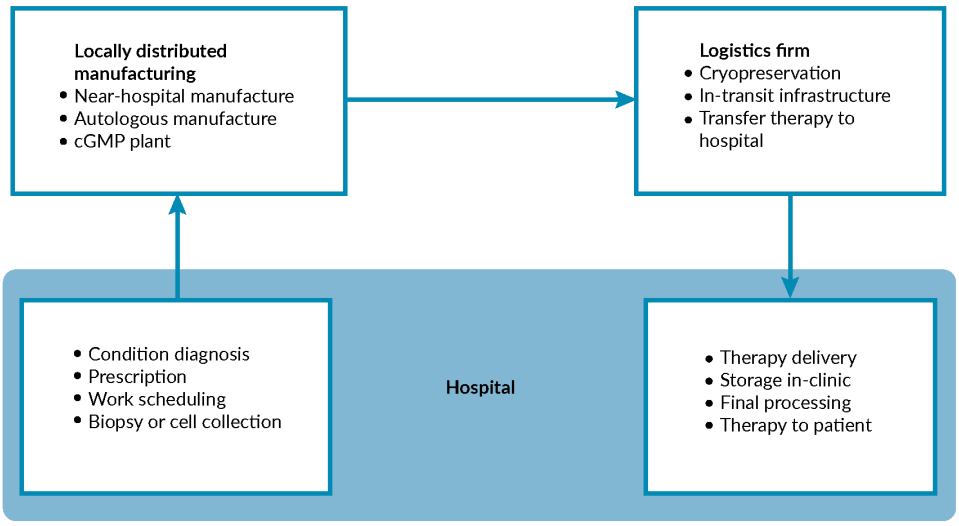
The NHS is critical for sourcing organs and, for some therapies, there is a need for the NHS to link up with manufacturers to collect cells from the patient for seeding a bio-matrix pre-surgery. This entails aligning work scheduling for manufacturing with patients' clinical visits. Such complex manufacturer-clinic interactions are an additional disruptive element beyond what is necessary for conventional drug or biopharmaceutical treatments. It requires RM firms to invest in specific RM technology delivery skills and training for pharmacists, specialist nursing staff, surgeons and technical/administrative supporting functions, including engineering and procurement. This also has important staffing and cost management implications for local NHS trusts, which are managed differently across the UK, affecting the ease of adoption into clinical practice.

RM manufacturing processes

Both allogeneic and autologous therapies are, or would be, disruptive of incumbent firms' small

FIGURE 2

The technical processes involved in clinical adoption of an autologous therapy such as CAR-T Cell.



molecule or biopharmaceutical companies on manufacturing processes, including the quality assurance techniques related to dealing with living cells which are inherently variable and difficult to standardize. However, allogeneic therapies can be scaled up (implying an incremental aspect), whereas autologous therapies cannot, although they can be scaled-out. The attraction of scale up, critical for building economies of scale for allogeneic therapies, is its similarity with manufacturing stages of conventional pharma business models, something investors in the sector are familiar with. A respondent from a firm specializing in allogeneic therapies reflected the scale up aspect as a key factor for their firm.

> "... our [allogeneic] technology approach really gives us the ability to generate lots and lots of doses... And it makes an allogeneic approach, perhaps, more achievable. Our cells are non-immunogenic, so they don't suffer the rejection problems that might be seen typically with an allogeneic approach." – Senior Executive for Cell Therapy Manufacturing Firm A.

For blood and tissue services, RM innovation is more incremental, as key processes such as raw material sourcing, manipulation and storage, and traceability requirements are already routine in the sector. However, there is lack of cross-sectoral knowledge about different therapy areas. Respondents in our study acknowledged that skills tend to be niche-focused and scarce in the industry, especially in development and translational activities. This has implications for business continuity and the need for emerging firms to retain staff, especially given the close linkages between the firms and the NHS.

The need for co-evolution of technologies & innovations

For some allogeneic therapies involving for example gene therapy or immunotherapy, our study revealed the need for close interactions between therapy developers, technology suppliers and the clinic. The link between the technology supplier and the clinic is also required for locally distributed manufacturing systems or in/near-hospital manufacturing systems as part of the collaboration between the therapy developer and the NHS.

A key challenge raised for therapy developers was the need either to re-purpose existing technology or to design new technologies for manufacturing and quality assurance of therapies, as highlighted here:

> "...when people are making ... protein therapeutics, which is the other large-scale culture technology, they don't want to keep the cells. They're deliberately breaking the cells up and trying to recover the protein out of them. We're doing exactly the opposite, we're trying not to damage the cells and get rid of everything else. So there is no technology out there at the moment that has been developed specifically for large scale cell recovery." – Senior Executive RM Collaborative Project

DOI: 10.18609/cgti.2019.135

This firm was attempting to recover intact cells from culture, and there was no technology on the market at the time capable of that function. They reached out to their collaborators and their suppliers to design equipment capable of harvesting intact cells and considerable progress is now being made in this area, relevant to both autologous and allogeneic therapies [21]. This also happened for two other cases, where the in-house developers worked with their suppliers to design equipment for their manufacturing needs.

Respondents from organizations developing allogeneic therapies also acknowledged the need for closer interaction with the clinical setting for cell harvesting and therapy delivery and, by implication, the design and operability of technologies and operations used by the clinicians. An additional collaboration that emerged is the triad of therapy developers, contract manufacturers and technology developers, especially during therapy development optimization stages. The triad is important as technology optimization costs are borne by the therapy developer, which in most cases is resource constrained. Over time the triad is likely to morph into a dyad (therapy developer-contract manufacturer) especially in cases where a market authorized therapy is contract manufactured for the lead firm in another geographical location, in which case the contract manufacturer works closely with the clinical setting.

Challenge of specialized skills

A 2011 study by BIS highlighted the challenge bioprocessing units faced in recruiting and retaining skilled staff for manufacturing, quality management, validation and batch release [9]. Our study confirmed these earlier findings, and our respondents reported that because of the niche focus of the technologies, training a person takes time and money, so it is important that those skills are retained.

The links between manufacturing systems & distribution models

Table 1 summarizes the expected manufacturing processes and likely distribution challenges faced by the ten cases we studied. At the time of the study none of the organizations had a market authorized product, and six therapy developers were at various stages of clinical testing.

Our study suggests that organizations are likely to favor centralized manufacturing for two reasons; skills shortages and infrastructure requirements for resource constrained SMEs that have to deal with infrastructural, technological, organizational, governance, value chain and regulatory hurdles when they are at a cash burn phase of development. Unless there are significant injections of cash, the locally distributed manufacturing approach may take time especially given the cost of setting up cGMP plants to manufacture clinical grade cell therapies. With dependence on central manufacturing come the challenges of cryopreservation and efficient distribution systems. Furthermore, this imposes an investment challenge for the clinic in terms of acquiring the cryopreservation infrastructure, and thawing therapies correctly just before use. These administrative and

DOI: 10.18609/cgti.2019.135

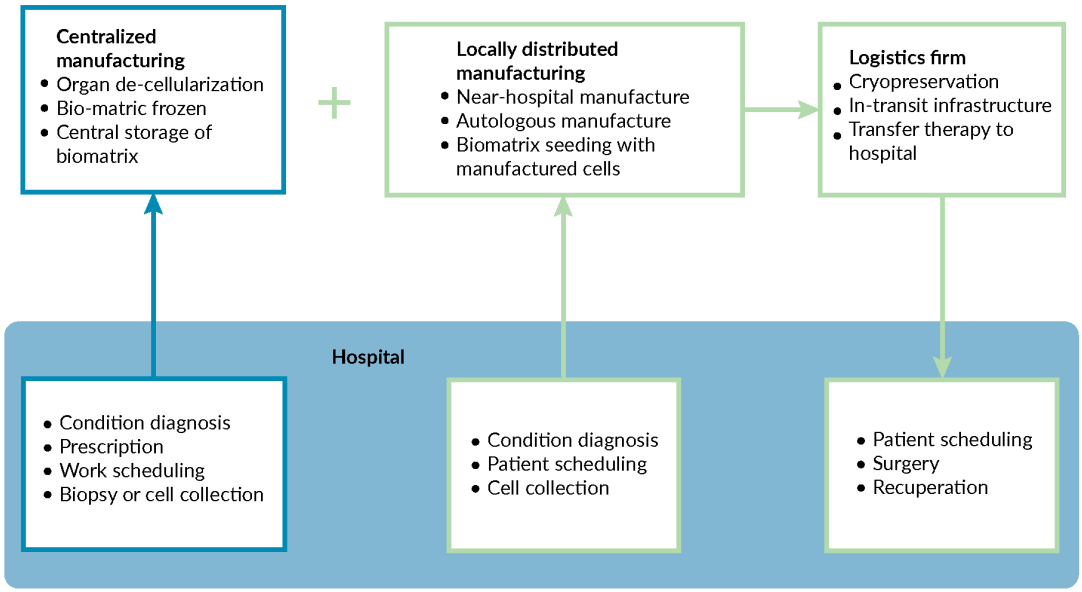
TABLE 1

An analysis of the likely manufacturing process and anticipated distribution challenges for the ten cases investigated.

Case study	Therapy produced		Manufacturing process	Distribution challenges
Contract manufacturer	Allogeneic – the main business model	Autologous – secondary business model	Centralized	Cryopreservation technology is important for extending shelf-life and therapy viability. For the clinic cost and management of cryopreservation equipment, and therapy handling
Blood and tissue; contract manufacture	Allogeneic – the main business model	Autologous – secondary business model		
Cell therapies	Allogeneic			
Cell therapies	Allogeneic			
Tissue regeneration	Biomatrix from cadaveric organ donations	Autologous	Locally distributed	Efficiently working with the NHS for identifying organ donors and acquiring viable tissue/organs on time
Immunotherapy – cancer		Autologous	Given that the companies are small and do not have resources to set up locally distributed manufacturing sites in the early days there will be specialist manufacturing centers where the company is sited	Requires efficient systems for cell collection and therapy delivery, whilst assuring therapy viability
Immunotherapy – cancer		Autologous		
Accelerated healing	Allogeneic		Centralized most likely	Requires efficient systems for cell collection and therapy delivery, whilst assuring therapy viability
Transfusion fluids	Allogeneic		Centralized or locally distributed if process automated	Similar to blood transfusion services

FIGURE 3

The technical processes involved in tissue regeneration combining donated cadaveric organ and autologous cells delivered through surgery.



technological challenges are key impacts of innovative technologies especially on resource constrained SMEs with no prior interaction with the health system.

Clinical adoption of autologous therapies

In this section we present two examples: autologous immunotherapy (Figure 2) and autologous tissue engineering based on a donated cadaveric processed biomatrix, where therapy delivery involves surgery (Figure 3). We focus on the technical issues of therapy delivery, and not on re-imbursement, which others have already covered in some depth. Compared to incumbent biopharmaceutical and traditional pharma models of therapy delivery, there will need to be close linkages between the hospital, manufacturers, and logistics firms. Condition diagnosis will not be different from current practice but an autologous therapy departs from conventional treatments in the prescription, requirement for work scheduling, and timing the collection of cells or biopsy with the work schedule in the cell manufacturing facility. The cell manufacturing plant also needs to align its production and delivery times with the time the patient has been booked to be at the hospital. Behind all these activities are numerous administrative tasks for the manufacturer, logistics firm and the hospital that are disruptive of the business model of a biotech or pharmaceutical firm. For blood transfusion services, already dealing with living materials, these logistic and administrative issues are closer to being incremental, although the challenges of clinical grade manufacturing of cells in bulk for therapy also include elements of disruption, albeit with a narrower gulf in skills

than for mainstream biotech and pharma companies.

Our second example, Figure 3, highlights the complex processes that need to be aligned when dealing with an organ transplant using autologous cells seeded on a donated organ. There would be a need to work closely with the NHS to identify organ donors and upon their death collect the organ while it is still viable. The organ would be processed to remove the cells of the donor and placed in cold storage. De-cellularization can be done in a centralized facility, as the organic matrix that will be obtained can be donated to any patient. For this part of the process the logistics and economies of scale suggest that a centralized manufacturing approach would be feasible. However, the autologous part of the process, collecting cells from the patient and growing them in a locally distributed manufacturing facility, presents the same challenges as discussed in 'The links between manufacturing systems and distribution models' section. In this case, the situation becomes more complicated because the seeded biomatrix is surgically inserted into the patient; increasing the number of actors that need to collaborate and align their processes in order to deliver tissue regeneration therapy.

Another interviewee reported that there is a need for co-evolution of processes, techniques and technologies between the clinical setting and the RM manufacturer, especially in the area of tissue regeneration as follows [Figure 3]:

> "When a patient has been identified from the clinical setting, there is cell-harvesting leading to cell culture/multiplication in a cGMP certified plant; re-cellularization of the matrix and surgery and recuperation of patient; all these activities need to co-evolve to allow adoption of an innovation."
> – Founder of a Tissue Regeneration Firm

Particularly in the allogeneic cases we studied, shelf life was identified as a key component, and this is closely linked to cryopreservation technology which, as respondents reported, needs to be improved to ensure cell or tissue viability after storage for long periods. These aspects are important for effective handling of the pharmacy procedures in the hospitals.

DISCUSSION & CONCLUSIONS

We propose that understanding of the distinction between disruptive and incremental innovation, and of the nature, extent and location of the disruption across sectoral value chains, can help to guide company innovation strategies and government innovation support policies for RM, as already proposed for industrial biotechnology [17]. The RM-related disruption for pharmaceutical industry business models comes on top of an earlier phase of disruption caused by biopharmaceuticals (large protein molecules and monoclonal antibodies) that had already begun to re-shape the sector [22–24] and so to some extent paved the way for RM. However, RM imposes additional disruption on pharmaceutical and biopharmaceutical business

DOI: 10.18609/cgti.2019.135

models to the extent that it has taken a decade of intensive intellectual and commercial investment to reach a stage where the small number of products that have been approved often under-perform and are withdrawn, and success is described narrowly in terms of the number of products in clinical trials [25]. Current analyses of the RM sector are still leading to calls for delivery systems designed for pills and biologics to be changed to accommodate cells [20].

Such difficulties and delays are more pronounced the more disruptive the technology is for the relevant sector. For RM therapies, faced with the individual disruptive elements described above, new value chains involving large companies that are new to the sector (e.g., Lonza, and GE Healthcare) and small innovative start-up companies are slowly beginning to emerge. Our analysis of the impacts of disruptive innovation includes the observation that innovation will proceed most rapidly and effectively if it is developed by the sector for which it is least disruptive and that, for life science innovation, government regulatory and policy decisions can make a transformative difference to the rapidity of uptake of a technology and the location of the innovation within an array of possible industry sectors [2].

The early regulatory choice to regulate stem cell therapies through the pharmaceutical regulatory system was one important factor driving the innovation trajectory for this technology towards the large scale, centralized manufacture of allogeneic therapies by incumbent pharmaceutical companies. These companies had an interest in the technology and the commercial capability to support its development but the extent of disruption of their business models has been one factor slowing and in some cases stalling development of therapies. The converse of the focus on pharmaceutical companies has been the relative lack of private sector investment in the development of locally distributed manufacture of autologous therapies [1].

It is interesting to speculate on what the nature of current business models and value chains for RM therapies might have been, given a decision to regulate RM therapies as medical devices rather than drugs, or to focus more strongly on standards and less on regulation as the basis for ensuring safety, quality and efficacy [2]. Many of the disruption-related challenges would have been removed or diminished, but the necessary private sector investment may still have been lacking. Under these circumstances, the public sector and philanthropic organizations often step in to fill the gap in translational funding [18], but without commercially viable business models this is not a long-term stable solution.

With the publication of the White Paper on Regulation for the Fourth Industrial Revolution [26] the UK government is embarking on a new approach to the governance of innovative technologies. This could provide a route to adaptation of the innovation ecosystem for RM therapies that would enable the more rapid emergence of a broader array of innovative business models delivering a greater variety of therapies to meet complex patient needs [2].

The data/transcripts used in this study were archived with the ESRC under the following reference: Archive. 10.5255/UKDA-SN-852913

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *We acknowledge the funding from ESRC Grant Ref: ES/L002779/1.*

Disclosure and potential conflicts of interest: *The authors declare that they have no conflicts of interest.*

Funding declaration: *The authors used a grant from the Economic and Social Research Council for this study.*

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited; externally peer reviewed.*

Submitted for peer review: *Jul 18 2019;* ***Revised manuscript received:*** *Oct 2 2019;* ***Publication date:*** *Oct 21 2019.*

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CELL & GENE THERAPY INSIGHTS

DECENTRALIZED MANUFACTURE

SPOTLIGHT

EXPERT INSIGHT

Cell manufacturability

Masahiro Kino-oka, Manabu Mizutani & Nicholas Medcalf

The manufacturers of cell therapy and regenerative medicine products must design manufacturing operations to deliver the required level of stability. Process consistency, maintenance of the aseptic environment (to prevent contamination), assurance of line separation (to prevent cross-contamination and operational confusion), containment (for avoidance of cross-contamination), and their routine management must be taken into account. In this article, we propose the concept of 'cell manufacturability' for process development in order to assist the design of cell manufacturing processes.

Cell & Gene Therapy Insights 2019; 5(10), 1347–1359

DOI: 10.18609/cgti.2019.140

INTRODUCTION

Regenerative medicine and cell therapy require manufactured cell transplants that rely for their development upon interdisciplinary activities. The disciplines needed come from the medicinal and biological fields and from engineering. Commercialization of cell-based therapies needs capable, scalable, manufacturing technologies [1,2]. It is necessary to ensure that these therapies meet regulatory requirements and are economically viable when manufactured at industrial scale. Innovative cell processing techniques have been developed for this purpose [3]. The processing system must lead to stable cell manufacture with the required level of safety, security and cost-saving [4]. There have been many instances where manufacturers have assembled multidisciplinary teams in order to create custom manufacturing solutions that maintain process stability. However, much remains to be done. We believe that it is important always to return to first principles. Careful scrutiny of the fundamental steps is necessary to establish the criteria of effective process design. Furthermore, early attention to process design, in order

to ensure a reproducible product, will reduce the amount of work that must be conducted late in development when it is important to reach market quickly. Without this work it may be impossible to avoid a situation in which any re-designed process differs in important ways from the process upon which the proof of concept studies were based. This article describes the features of cell processing that warrant examination and why, and proposes the concept of 'cell manufacturability' as the basis of stable, cost-effective process design. The descriptions in this article relate mainly to anchorage-dependent cells. The principles are applicable to suspension cell culture as well. In the interests of clarity we do not concentrate on the steps of transfection and rely on the reader's insight to convey the principles that can be applied even to that step.

FEATURES OF CELL PROCESSING

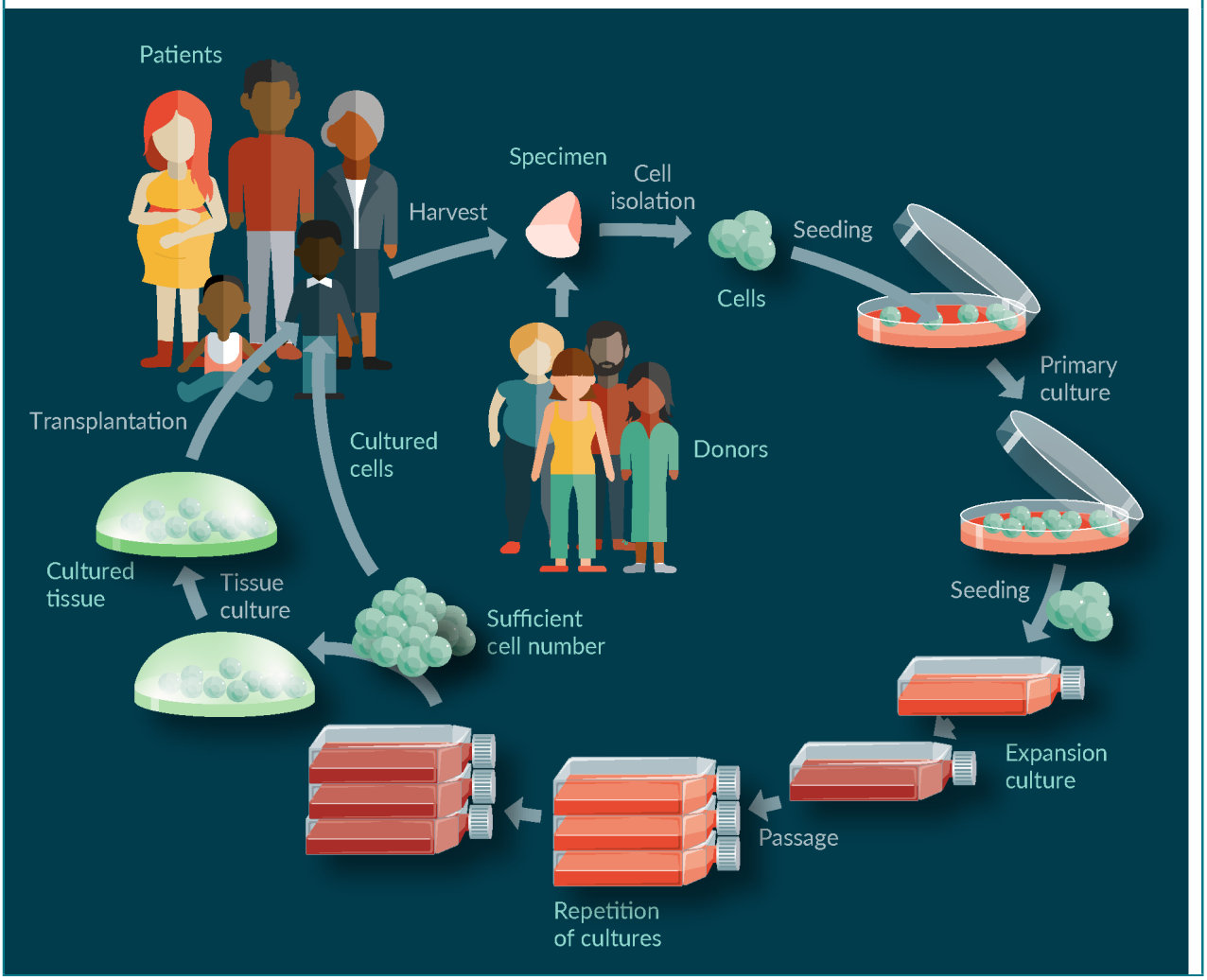
Cell manufacture consists of a series of steps. In the representative case of anchorage-dependent cell processing aiming at autologous transplantation of engineered tissue, as shown in Figure 1, the minimum practical biopsy is harvested from each patient ('cell procurement') and the biopsy is installed in the cell processing facility (CPF). The starting cell populations are prepared as raw materials ('cell isolation process'), and the isolated cells provide the seed stock in the culture vessel to start the primary culture for acclimatization to the *in vitro* environment ('primary culture process'). This initial cell acclimatization may involve one or two small-scale passages during which the cells undergo limited expansion Large-scale cell expansion is then performed through a series of subcultures in a batch-wise manner using a medium oriented to more intense cell growth ('cell expansion process'). At this point the cells will be used either for an autologous treatment, in which case they are used for product manufacture, or they will be used to establish a Master Cell Bank and Working Cell Bank from which successive campaigns of manufacture can be conducted. Following attainment of sufficient cell number, the suspended cells are transferred into the vials to be used for administration to the respective patients ('packaging process') or, as appropriate, to tissue cultures for the reconstruction process to form biologically functional tissue replacements as final products. The products for therapeutic use are cells and tissues originating from the patient. In the case of allograft transplantation, the raw materials used are the selected donor's cells, which are stored as cell banks. Each process consists of a series of operations that affect the quality of the cells and that require careful management of the integrity of the aseptic environment.

The primary culture process and the cell expansion process demand a high level of skill from the process designers [5]. The cells and the environment in which they are maintained are fragile and intrinsically unstable, and cell quality may easily fluctuate during operations in a manner that depends largely on the skill of the operators. Therefore it is preferable that the process is designed in such a way as to possess intrinsic 'operational stability', in other words the process design is based upon a quantitative knowledge of the level of expected variation in operator and machine action and allows for this

DOI: 10.18609/cgti.2019.140

FIGURE 1

Processes of cell manufacturing for cell therapy and regenerative medicine.



to deliver a product of the expected quality nevertheless. This means that the process is designed to be 'manufacturable'. In practice such a manufacturable process is based upon a detailed understanding of which process features give rise to significant variation in product properties. Studies are designed to examine the impact of the natural variation in operator behavior and skill, in instrument response and in equipment performance. Such studies benefit from the insights of experienced metrologists able to quantify the variation and to predict the impact of these tolerances in combination with other sources of variation. Specialists in the study of human factors may be needed. By combining this information the process engineer is equipped to design a process that either allows for these sources of variation or that designs them out, for example by imposing constraints in the form of automated controls that dispense with human operators at critical points.

Additionally, there will be sources of variation that arise from the intrinsic nature of the cells. In culture most therapeutic cell types are adherent and depend on the growth surface for their ability to reach commercial numbers. Amongst

static cultures cell adhesion on the surface of the vessel is usual and, starting from a poorly-mixed cell population, the result can be spatial heterogeneity. As the adherent cells become confluent due to cell division contact inhibition occurs leading to local patches of quiescence. The behavior reinforces itself leading to a spatially heterogeneous proliferation. In addition, recent discoveries suggest that mechanotransduction where the local cell colony is especially compact causes methylation which in turn affects the cell potency [6,7].

For autologous therapies the cell explant varies from batch to batch due to variation in anatomical harvest location and the patient's (or donor's) condition. Heterogeneity in the cell population changes as proliferation in serial batch expansion culture proceeds. This arises due to cellular hypopotency, including terminal differentiation attributed to cellular senescence and de-differentiation, causing poorly-organized tissues.

The combination of these features (operational stability, spatial heterogeneity and population heterogeneity), inherent to cell and tissue processing, poses a challenge to satisfactory process design. Robust and reliable strategies are desirable to assist operators so that they can identify the cellular states in the course of culture even under restricted conditions of sampling and sensing.

Asepsis must be maintained and the starting material and the final product comprise materials that cannot be sterilized without loss of potency. This feature means that operations must be conducted in a carefully-maintained aseptic environment throughout. Furthermore, after the aseptic process design has been completed it will be subject to validation and re-evaluation following any significant process changes, or annually as a minimum, to ensure that the basis of assurance of asepsis has not been compromised.

The final products must meet the needs of individual patients in terms of batch size and cell function. This requires manufacturing that is both scalable and flexible for small-scale and multipurpose production. Therefore, parallel production (for multiple products and multiple patients) must be achieved by designing shared space in the CPF to allow for line segregation of aseptic operations as well as for excellent management of spatiotemporal features such as any time-lag between operations and maintaining independent flows of operators and materials with frequent change-over and start-up.

Asepsis, scalability and flexibility are therefore the important for assurance of process quality in de-centralized systems. The fundamental feature for manufacturability is confidence that the operations can be trusted to deliver process consistency in terms of maintenance of aseptic environment (without extrinsic contamination), assurance of processing independence (to prevent cross-contamination and operational confusion), containment against contaminants and robust management during the frequent change-over and start-up activity in shared CPFs. Thoughtful management of manual operations is essential if error due to fatigue and repetitive stress is to be avoided.

When should such studies be conducted? Just as in the production of pharmaceuticals, cell

DOI: 10.18609/cgti.2019.140

processing is divided into the 'upstream process' (for cell expansion) and the 'downstream process' (of separation and purification, dispensing, freezing, and packaging). There is a limited range of separation and purification techniques downstream, therefore careful process design is needed to bring the capability of the downstream steps within the range necessary to remove undesirable cellular by-products and to reduce the formation of undesired cells upstream to a practical minimum. The influence of events before the cultivation of the seed cell stock and following the completion of packaging is much larger than is usual in the manufacture of non-living therapeutics. While consistency throughout the processes from cell procurement to administration to patients is essential, it is also necessary to consider what might be called the 'out-stream processing' such as cell transportation from the cell bank (or hospital) into the CPF or from the CPF to the hospital, as well as in-hospital processes for pre-treatment steps such as cell thawing and washing. The logistics of supply for the starting materials and for the product must be considered in detail to ensure that timing of delivery, any hold steps for product clearance through customs or freight loading and the suitability of carrier systems for each group of operators are suitable. The features of the whole process must be considered from explant harvest to application. This in turn means that the operational design for the business must be worked out early because the prudent choice of certain manufacturing steps will influence the engineer's ability to make the process manufacturable.

CELL MANUFACTURABILITY

'Design for manufacturability' (DFM) is the sum of the studies described above. It is the general engineering art of designing products in such a way that they are easy to manufacture [8]. This concept exists in almost all engineering disciplines, but the implementation differs widely depending on the manufacturing technology. DFM for cells includes not only conventional concepts but also novel considerations that arise from the inherent features of cell manufacturing. When manufacturing therapeutic cells there are many features in the cell products that are not as well defined as they are for synthetic or biologic drugs. Therefore, it is necessary to consider modifications specific to cell manufacturing: the construction of specific concepts is required. This point arises from the nature of cell-cell interaction and a brief description will help. When comparing the manufacture of a cell therapy to that of a conventional medicine two characteristics can be seen to give rise to the dramatic differences between the ways in which the products behave during manufacture. These are the relative size and complexity of the smallest unit of the therapy (a single molecule compared with a cell) and cell–cell communication. The behavior of a population of cells is complex, in the formal mathematical sense, in a way that a sample of a small-molecule drug is not. A sample of active pharmaceutical ingredient can be analyzed to specification and almost every significant fact about it can be known and related to the reaction steps that led up to it. By contrast, emerging patterns of

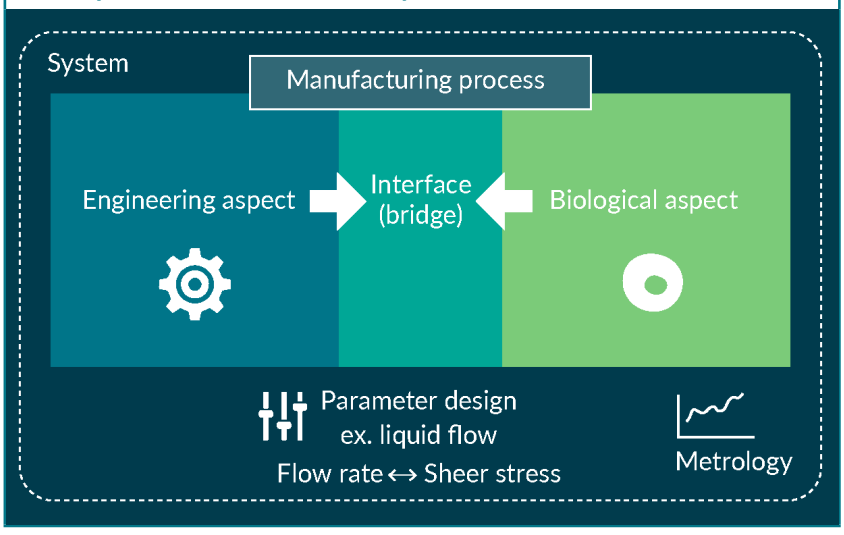
behavior in a cell sample can lead to transient states to the mixture that are not evident in the final batch. When the product is finally analyzed only a fraction of its properties are known. Characterization by, for example, flow cytometry of the final product may show a mixture. The pathway to that final mixture may not be traceable using analytical means but may only be understandable using agent-based modelling and applying knowledge of the changes in state of the cells and the known environmental triggers to those changes. The concept of agent-based modelling combined with studies of the process features that lead to undesirable outcomes may be the foundation of the engineering approach to intrinsically manufacturable cell products.

The novel concept of 'cell manufacturability', as shown in Figure 2, is proposed to describe the discipline of cell production, defined as "the attainment of the desired capability of a cell manufacturing process by bridging the gap between its biological and engineering aspects" [9]. To deliver quality by design (QbD) for the cell manufacturing processes, the allowable range of each important parameter and the tolerance of important equipment for that step must be identified. For example, one of the motion parameters experienced by the cell during medium exchange arises from the flow rate of the medium. However, the relationship between the engineering aspect and the biological aspect of this step arises from transduction of shear stress by surface channels or by cytoskeletal deformation. In a case where there is a known relationship between the engineering and biological aspects, it is relatively easy to design the required limits to the range of motion. Where the relationship between engineering parameters and biological parameters are not understood (or have not so far been examined) the establishment of capable manufacturing operations is difficult. This is the point at which metrological studies are essential to perform the QbD.

Metrology is the engineering science needed to provide system optimization for efficient, stable processes by understanding the requirement gap and reducing output fluctuation. For example, the examination of the behavior of a flow cytometer and the instrumental tolerances that can be expected can be combined with a practical study of the degree of variation that arises from human operators during sample preparation and analysis. This result can be compared with the variation in outcome of the process step from which the sample is removed. If the sources of variation in that step, due to the limits to control of features such as temperature

FIGURE 2

Concept of cell manufacturability.



DOI: 10.18609/cgti.2019.140

control, holding time of the sample etc. then a calculation may be made of the cumulative variation to be expected in the observed output and the tolerances that can be allowed before control over product quality is lost.

DFM may be perceived as unwelcome additional work at a time when cost containment may be essential but it is needed to ensure consistent product quality and to secure delivery of safe, effective products to the customer. By considering the impact of transportation and preparation events outside the factory the innovator delivers cost saving through process simplification based upon the governing principles of cell behavior. Persistent efforts towards systematization in the metrological approach in manufacturing process design will lead to sustained high performance of the therapy. As shown in Figure 3, the system of cell manufacturing consists of the process(es) and its/their input, output and environment. The quality of cell product as the output of the system is sensitive to fluctuations derived from several factors:

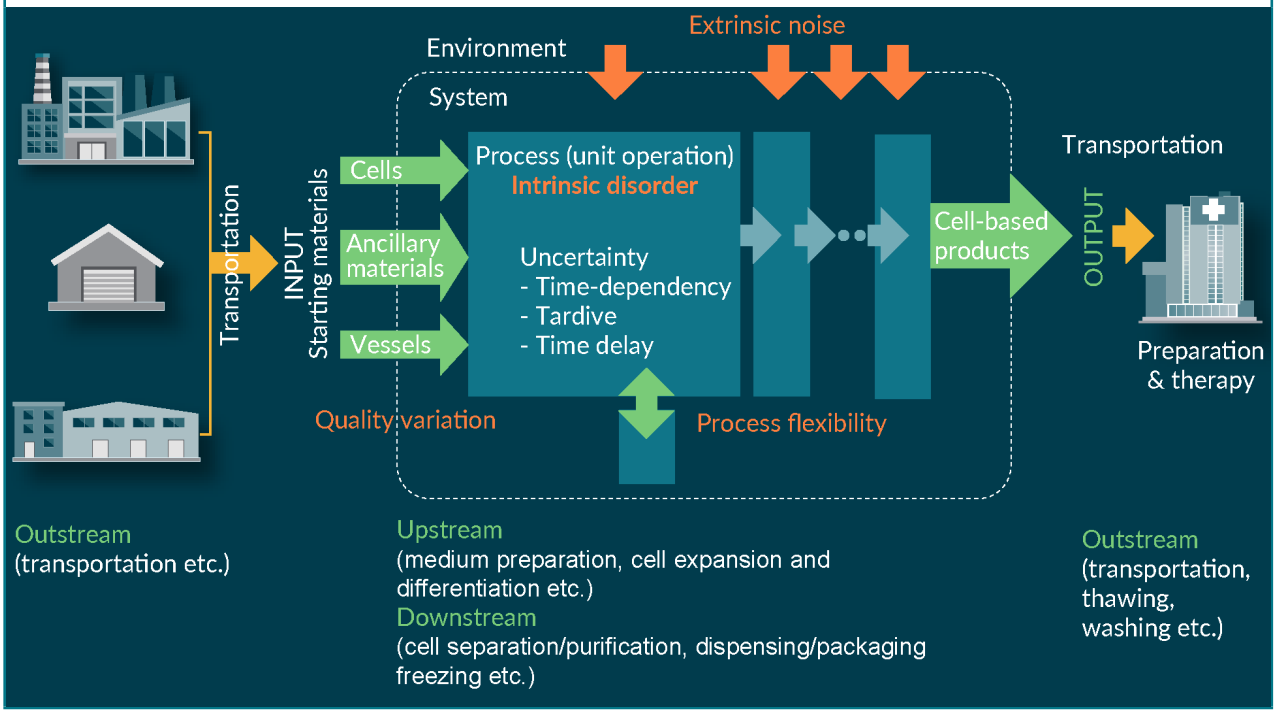
1. Environmental 'noise' (variable events outside the process arising from inadequate environmental control and not subject to operator control such as background room temperature during transfer operations and shocks during manual handling)

2. Variation in input quality, such as Working Cell Bank inoculum and materials (medium, reagents, vessel, pipettes etc.). In addition, there are factors inherent in the biological aspects;

3. Intrinsic disorders (uncontrolled in-process variation that arises from sources outside the operator's or the process designer's control such as

FIGURE 3

System in cell manufacturing and factors affecting fluctuation of cell product quality.



variation in the characteristics of any biological reagents)

4. Planned changes to the process(es), such as introducing a novel technique and redesign for process scale-up. These factors arise from events within and without the factory environment and so their presence is determined by the choice of operational design for manufacture and delivery. If this choice is made at a late stage in development then a risk arises that the process re-design to make the product reproducible will lead to a loss of comparability with respect to the product that was studied in early efficacy studies. In this context, early consideration of manufacturability can be regarded as a form of insurance against process development risk later on. This aspect, and a method to address it, are considered elsewhere in this Special Edition [10].

The biological aspects or intrinsic variation component, as shown in Figure 4, allow the cells to introduce uncertainty between process steps in three different modes:

1. In a 'time-dependent manner' where the cell states change sequentially as intracellular events occur

2. In a 'tardive manner' in which there is a time lag from the start of cell signaling to the appearance of the phenotypic result

3. In a 'time-delayed manner' where the perturbing event occurs but there is no ability to detect it immediately due to the technical limitations of the production system.

(This last feature prevents control via real time detection of the actual cell event.) The intrinsic sources of

FIGURE 4

Modes of cellular events in process that cause intrinsic disorder.

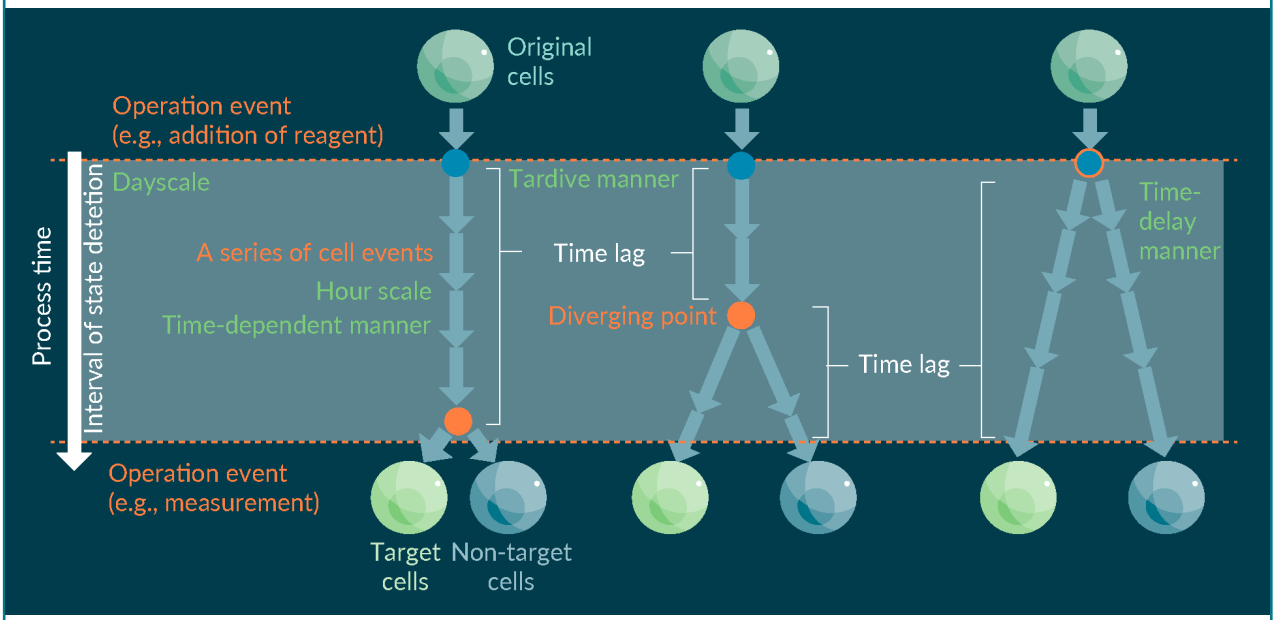


Diagram reads from the top, where an event triggers a cell response, through the interval in which the event is transduced, to the bottom where the impact is realized.

DOI: 10.18609/cgti.2019.140

disorder may accumulate in serial processes, leading to a compounded impact on the stability of the process. Such cumulative influences can increase process instability during scale-up to an extent that appears disproportionate to the initial deviation from control.

In this context the manufacture of a cell product may be characterized as follows:

1. The cell quality is incompletely understood at the molecular level.

2. The production manager is obliged to make subjective judgments during production about whether a given batch should progress according to menu-driven procedures prepared in advance or whether corrective action is needed at any point and recorded as a deviation. The decisions will be informed in real-time or near real-time by in- or at-process analysis. Analytical methods for this are, ideally, non-invasive (such as spectrometric) or based upon instruments whose working sensors may be included in the aseptic environment and discarded along with the disposable bioreactor (such as scanning impedance tomography).

3. During long-term manufacturing with serial batch cultures it is easy to introduce fluctuations in the product quality. Such fluctuations can be self-reinforcing due to autocrine signaling. Deviation from the control state can begin with small differences in phenotypic behavior and can propagate in a geometric progression to give gross changes in the cell population. This effect is seen in, for example, the generation of chondroprogenitors for engineered tissue and in the isolation and purification of sub-populations of mesenchymal stem cells.

4. There are fewer options for technology for downstream processes such as separation and purification than are available for, for example, manufacture of proteins and as a result the manufacturer must manage the risk that the proportions of cellular impurities in each batch will result in failure of the entire lot because downstream re-work may be impossible.

5. There are many cases where preparation takes place in a hospital after transportation of the product and quality is altered after the shipment ('out-stream processes').

6. Most cell manufacturing in the future will be autologous and will not begin with a Master Cell Bank that would allow a degree of reproducibility in the starting material.

7. Some cell manufacturing uses starting materials for which there is no possibility of verifying asepsis.

8. Some manufacturing processes must be run on a make-to-order basis due to the short shelf-life of products.

9. The batch scale for autologous manufacturing depends on each patient.

These features lead to a lack of alignment between process events and cell events, increasing intrinsic variation in the process and resulting

in variation in product quality within lots as well as between lots. The need to build concepts of process capability that are different from those used in more established manufacturing is unavoidable. In the future, the analysis of factors that impact upon and alter the system, the categorization of such factors, and systematization of methods for analyzing the permissible range and thereby constructing specific processes for cell production will be vital.

In the current context, it is tempting to allow cell processing to rely on small-lot manufacturing by experts and to manage the high fluctuation rates with 'craft' know-how in the same way as cottage industries, in which a number of manual procedures rely on the empirical knowledge and proficiency in manipulation of the most experienced operators. Such an approach leads to earlier market access but it is not scalable. In all but the smallest markets technical development is the key for reaching a state of effective production and realizing large-lot manufacturing with high stability. In addition, the standardization of environmental, material, and operational process features is required to realize a consistent process. Introduction of a systematic approach is needed to guide progress in developments in engineering, including cell engineering and culture engineering.

AN ILLUSTRATION OF FLUCTUATION IN CELL CULTURE & DISPENSING

Design for manufacture requires an awareness of the sources of variation must be backed up with practical investigation. The principles can be illustrated using the example of the production of human induced pluripotent stem cells (hiPSCs) in the large quantities that are required to realize clinical and industrial applications. Culture as suspended aggregates is an attractive route, particularly for allogeneic products but also for autologous. However, very little is known about the mechanisms governing the formation of the aggregates. The factors governing their stability in suspension culture are not fully understood. The formation of 3D cellular aggregates is widely accepted as a dynamic process regulated by differential cellular adhesions, matrix synthesis, and remodeling [11]. After the establishment of cell-cell interactions under physical forces or spatial proximity, the 3D aggregate self-assembly involves the adapted cadherin interaction and/or integrin binding to the extracellular matrix (ECM) proteins, enabling the formation of contacts between cells [12]. The ECM is synthesized and secreted by cells from the earliest stages of culture and provides structural and biochemical support to the surrounding cells. The ECMs in the aggregates not only function as signaling molecules in cell adhesion but also play a biomechanical role that influences the force balance and biomechanical signal transduction between intracellular cytoskeleton and extracellular microenvironment [13]. These changes in aggregate morphology could result from an active internal process, such as rearrangement of a cytoskeletal system. The cell-secreted ECM plays a key role in cell aggregation, spherical aggregate formation, and cohesion in suspension culture systems that will influence aggregate stabilization and compactness.

DOI: 10.18609/cgti.2019.140

Differences in cell aggregation capacity and ECM secretory capacity exist between hiPSC lines, leading to important differences in initiation and progression of aggregate formation. With a hiPSC aggregate suspension culture system, hiPSCs formed multicellular aggregates that could be classified as 'large compact' and 'small loose' aggregates at different hiPSC lines based on size and morphology of aggregates. These differences are correlated with differences in ECM secretion capacity and indicate that cells differ significantly in the regulation of the morphological and biological features of cellular structures and mechanisms related to cell-cell and cell-substrate interactions in process of aggregate formation and stability [14].

The stability of cell aggregates under fluid flow varies depending on their size and structure. The ECM is remodeled and synthesized on cell aggregates and covers their surface [15], preventing fluid flow from damaging the cells [16]. Several techniques have been developed to characterize cell aggregate properties [17], but the mechanisms are only beginning to be understood.

The impact of machine handling during medium exchange on the stability of two types of hiPSC aggregates has been demonstrated [18]. Machine handling leads to less variation in aggregate shape due to its more constant shear and it does this by preventing excessive maxima and minima in fluid flow, with accompanying shear forces, that would otherwise occur during medium exchange. Machine handling therefore introduces less intrinsic disorder. In addition, the aggregates exhibit a slow process of deformation arising from cellular protrusion from the aggregate surface after medium exchange with high flux, indicating a tardive phenomenon that must be prevented. Additional studies are needed to clarify the relationship between changes of ECM, cell adhesion and individual cells within hiPSC aggregates in order to fully optimize conditions for large-scale culturing. For the present it is sufficient to note that active measures to contain the fluid shear rate within a suitable range must be designed into the process.

As large-scale culturing methodologies have matured upstream of the cell-production process, scrutiny of critical steps has shifted downstream. For successful expansion in lot size, development of scalable downstream processes that enable high yield and high-quality production are essential. A typical downstream process consists of cell harvesting, clarification, concentration, formulation, filling and cryopreservation. In larger-scale production, the number of vials to be filled increases and the downstream process time is increased as a result. A longer processing time has an adverse impact on the quality of cell products. Therefore, understanding the related cell-decay kinetics is a major challenge for the development of robust and scalable cell-manufacturing systems. The impact of these effects will be most evident in the larger number of product units that will be made from an allogeneic batch and the impact will also play a role in autologous products due to any hold steps between operations.

The time-dependency of variation in cell viability was investigated in hiPSCs suspended in a cryopreservation solution [19]. It is essential to understand and to quantify the kinetics of cell decay cryopreservation solution when developing

robust and scalable cell-manufacturing systems.

A new evaluation methodology is needed for a cell-manufacturing system design because of the intrinsic heterogeneity and uncertainty in cell populations, the incomplete understanding of the biological characteristics the product and technical difficulties in analysis. The properties of cells in aggregate, as noted above, give rise to emergent properties that are not evident from the individual cells and that arise as a result of combinations of deterministic events from cell-cell signaling and in response to their surroundings. It is not usually possible to determine the historical path by which a cell batch arrived at its eventual composition based upon analytical techniques alone. Some form of quantitative, deterministic, population-based modeling is needed to evaluate the possible causes of a batch composition. This requires an alliance of mathematician, process engineer and biologist.

CLOSING REMARKS

As an increased number of cell products for cell therapy and regenerative medicine are developed, treatments using various cell sources and a variety of differentiated cells derived from ES cells and iPS cells are expected. Further developments of manufacturing techniques and operating guidelines will be essential by considering cell manufacturability, together with human resources development. These activities will lead to a decrease in manufacturing costs and to an increase in health care reimbursement in keeping with the profit needed to sustain the cell manufacturer.

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Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The authors declare that they have no conflicts of interest.*

Funding declaration: *The conceptual development of the article was partially supported by Japan Agency for Medical Research and Development (AMED). Grant Number JP19be060400.*

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited; externally peer reviewed.*

Submitted for peer review: *Sep 3 2019;* ***Revised manuscript received:*** *Oct 9 2019;* ***Publication date:*** *Oct 21 2019.*

CELL & GENE THERAPY INSIGHTS

DECENTRALIZED MANUFACTURE

SPOTLIGHT

INTERVIEW

Challenges in demonstrating comparability in the decentralized manufacturing environment

JONATHAN CAMPBELL obtained his PhD from the IRC in Biomedical Materials at Queen Mary University of London investigating the role of mechanics on MSC osteochondral differentiation before taking up post-doctoral positions at both QMUL and Cambridge, optimising biomaterial scaffolds for tissue development and disease modelling applications. In his current role at the National Measurement Laboratory hosted at LGC Ltd, he has responsibility for delivering cell measurement research and standards projects and inputting more widely to the strategic objectives of the NML. He is active on several UK and international standardisation committees including ISO TC276.

Cell & Gene Therapy Insights 2019; 5(10), 1267–1274

DOI: 10.18609/cgti.2019.133

Q Can you provide some more background on your and LGC Group's activities in the cell and gene therapy space and how they have evolved?

JC: LGC hosts the UK National Measurement Laboratory and designated institute for chemical and bio-measurement, which is tasked with enabling government, industry and academia to understand and address the measurement challenges they face, and to help meet existing and future national measurement needs. Our centrally funded research programs are administered by the UK government

Department for Business, Innovation and Skills (BIS) and all the outputs are freely available, generally in the form of open access publications such as white papers.

We've been active in the field of ATMP characterization and standard developments since the early 'noughties' and measurement research in this area has been conducted at times across analytical teams at LGC, to develop tools to help understand these highly variable, complex products. In the life sciences area we have high value and in some cases, unique (to the UK) measurement technology capabilities in chemical purity and structural analysis, which can support verification of starting materials, raw materials, metabolites, processes and product characterization.

The work principally involves describing and quantifying contribution in error, to measurement (measurement uncertainties) for various analytical techniques, which enable the community to better understand and control measurement processes. Our expertise also feeds into the documentary standards space – we're presently active in the BTI/1 committee in the UK and internationally at ISO/TC 276, supporting UK standards priorities for the biotechnology sector but we're also heavily involved in standards right across chemistry and healthcare more widely.

In developing analysis tools to support discovery biosciences and the identification of product critical quality attributes (CQAs) for a number of cell models such as T cells and MSCs, and characterizing their drift during manufacturing, we have collaborated with research sector partners and private companies to help them realize their products to market. However, although the pursuit of discovering CQAs is both challenging and rewarding, our focus is really on understanding variance in the measurement process and producing tools for customers to understand their product.

Additionally, we've been active validating novel measurement techniques, methodologies and control materials, often deploying comparative measurement approaches. More broadly, as a designated institute, we're able to value assign reference materials – both our own and others – to the highest metrological order, being part of the core framework of metrological traceability for the UK National Measurement System.

We offer a number of ISO 17025 accredited calibration services in chemistry and now in the molecular biology space, too. We also offer training consultancy packages to government linked or private industry groups.

Q Can you frame for us the chief challenges in establishing a workable decentralized manufacturing model for the cell and gene therapy space, as you see them?

DOI: 10.18609/cgti.2019.133

JC: Decentralized models, although having advantages of flexibility, responsiveness to surge in demand and being better able to meet stability constraints for starting materials and final products, will increase the burden of need for comparability in processing measurement systems.

"We are beginning to see the development of technologies in the transportation space that can improve the traceability of samples..."

The distributed network of such models increases the global number of unit operations and quite possibly will drive the miniaturization of production, presenting further challenges to measurement systems that are ultimately the key confirmative output in production. Measurement validation and instrument performance are further issues to be addressed in this regard.

Decentralization also increases the number of individuals needed to carry out manufacturing operations, which places emphasis on GMP, management and other human and social factors. Automation is another important related factor here.

Comparability in production is needed right across the manufacturing and raw materials space. To enable right-first-time manufacture, sources of variation in the process need to be fully quantified and where possible, designed out-patient-derived starting material is rare and could be assumed to be compromised in some way; the patient's health may also be assumed to be deteriorating, meaning we have one shot to get it right.

Manufacturing systems need to be integrated at the bedside, allowing the minimal amount of manipulation to the starting material. However, the healthcare setting is not necessarily compatible with a manufacturing environment and the associated changes to infrastructure, materials, equipment and staffing. These two schools therefore need to be housed together and made to appreciate each other's requirements for success. (In reality, technology development will ultimately address many of these issues through the advent of closed, GMP-compatible systems – devices that are shielded from deleterious agents, and that offer standardized, automated procedures and plug-and-play features that limit operator variability).

Finally, there is the need to reinforce supply chain logistics to enable delivery of consumables right on time, thus limiting stability issues for biologics. We are beginning to see the development of technologies in the transportation space that can improve the traceability of samples – for example, through the use of chip-based tracking devices, and devices that monitor ambient conditions.

Q Can you go deeper on what would be required to make comparability demonstration a viable proposition in the decentralized manufacturing environment?

"...we need to perform the basic discovery science for the various biomarkers that inform product quality control..."

JC: Expanding on the need for greater comparability, there are two fundamental components.

Firstly, there are precisely measured physical quantities (control materials). At the highest level, we have certified reference materials, which are traceable to the system of SI units. These are certified by an international consortia of national laboratories and can be employed at the peak of a traceability chain, which is a system of related physical quantities and measurement methods to ensure true standardization in measurement.

The workable output of these measurement systems is laboratory certification through instrument calibration and related expertise. Although a huge effort is underway within the measurement community to perform enough characterization to be confident of the measured quantity and the measurement process for biological entities (i.e., viral particles, microbes and cells), we are in reality far away from achieving complete traceability, due to the dynamic properties or stability of these components under test, or the inadequacies of the majority of measurement processes. Thankfully we can utilize counting as a unit of quantity, provided enough characterization of the quantity can be achieved and we are confident enough of the contribution to error in its measurement. That's related to the analyte under test and measurement technique deployed – for instance, molecular biology is now fully quantitative through digital PCR for specific sequences under test and we are starting to see measurement and ISO accredited calibration services in this area.

Since biologics characterization is in itself challenging, what is the best that can be achieved in the cell and gene therapy area? It will be up to individual manufacturers and supporting networks of national laboratories with a standardization remit – for instance, national measurement institutes such as ours – to validate in-house materials that conform to an ideal specification for a specific product in question, or more realistically, for an exemplar class of product.

The task before us as a community is daunting. Firstly, we need to perform the basic discovery science for the various biomarkers that inform product quality control – what can broadly be classed as cell health markers – in the most robust fashion. Where does characterization end for cell and gene therapy products? Certainly, for a cell therapy product the answer is 'we just don't

DOI: 10.18609/cgti.2019.133

know' – either we select a minimal number of markers of the most informative outputs, which allows testing in an efficient manner, or we come up with a robust analysis process that allows for inclusion of essentially an unlimited number of characteristics. The total amount of characterization will also be dependent on the type of product under development. We should also be mindful that certain QC characteristics will only be measurable during a limited number of process stages, and similarly, certain instrumentation or measurement approaches will only be able to be deployed in certain phases of the production process.

Secondly, we need to be able to meet the particular characterization challenges of cell therapies.

Cell therapies are living products which bring their own set of measurement challenges. They are adapted to and influenced by the environment. They often exhibit a target phenotype that is atypical in a population of cells, meaning the measurement of these cells is limited to rare populations which effectively fall outside the boundaries of a Gaussian distribution. In turn, that means that Six Sigma production strategies cannot necessarily be applied to them, or that the measurement of the target analyte is beyond the limit of detection or the limit of quantification for the technique available. This will become more of a factor with equipment miniaturization.

Thirdly, we would then need to translate this knowledge into control material production. This is often where there is a shortfall in developer expertise to allow reference material manufacturers to work for the good of the community. There are many issues here, but a clear challenge comes from the need to meet stability considerations and the need to select a robust format for the preservation of this control material by the laboratory. For example, using lyophilized materials may be our best bet in the cell therapy space in the near to mid-term.

We then need to proceed to a full validation of the measurement of selected quality control markers within the development process of the product in question, and to relating the real product to the exemplar material, so that manufacturers can define the limits of specification for the product.

Once all that has been navigated, full confidence in the CMC statement can be achieved, because the CMC document is valid for the lifetime of the drug product and will be needed for change control purposes.

A particular issue to overcome in reference to production is the need to balance protecting the proprietary techniques of the private sector with the standardization needs of the community - again, this is where the more agnostic community of reference laboratories might be able to help. Furthermore, the production of reference materials is an extremely expensive process. And finally, these are custom-made products, so there is a need to find exemplars for the community to work with that will be broadly applicable to their specific production needs.

Beyond physical materials, the second fundamental component in overcoming comparability challenges is procedural. This takes many forms.

Clearly, this is where documentary standards can have a potent effect, allowing identification of common language – particularly important where distributed networks such as those for decentralized manufacture reach the international context.

To realize the success of decentralized models of manufacturing we should reflect on their applicability to autologous therapy, meaning quality control for starting materials reaches across into the diagnostics space and therefore, there's a greater need to involve healthcare professionals within the manufacturing process.

This may very well produce new job descriptions and vocational training opportunities. Additionally, future standardization efforts may well reach down into identification of healthy donors from an analytics perspective. However, we do have to recognize that these therapies are very often for the critically or terminally ill, so intervention may proceed as a final resort. I think that's worth considering in the healthcare space, particularly in autologous therapy: that clinicians will often just go ahead and proceed in the patient's best interest. As a standards community we need to remain cognizant of this and maintain an adaptive environment.

Training to meet the analytical challenges at the bedside, or within the manufacturing environment wherever it may be located, will be provided through enhanced proficiency training (PT) schemes that should involve the clinical space as much as the manufacturing space. Furthermore, the sharing of best practice is an advantage of centralized manufacture so in a decentralized setting, the hub should take control of document management, training, and data control and archive.

Q Can you tell us about the state-of-the-art in enabling technology for the cell and gene therapy space as you perceive it – particularly tools applicable to decentralized manufacture?

JC: From the measurement community perspective, although we interface an awful lot with new technology, our primary focus is on finding the most robust measurement so that we can produce reference methods and offer calibration services most effectively. So we're not always interested in the 'fancy sport car': to us, robustness is vital – we tend to buy solid workhorses (although highly accurate ones, needless to say). We are most interested in contribution to variance so above all, our technology has to be stable – that doesn't often translate to miniaturized systems and the latest shiny device.

DOI: 10.18609/cgti.2019.133

That said, you can see the way things are going. Two particularly important areas are the development of analytics that are going to meet GMP requirements and the closing of processing systems. We also need to close the gap in analytical technology available in the manufacturing setting – that still measures gross metabolites or biomass, for example – to some of the state-of-the art technology available in the laboratory that allows single cell level characterization. And then a further theme or direction of travel is the combination of analytics – I suppose you could call it multidimensional analytics. That's actually what is needed at the bedside: bringing together different modes of analysis will be important for decentralization.

> "Training to meet the analytical challenges at the bedside ... will be provided through enhanced proficiency training..."

A classic example of this is flow imaging, which is a really great tool for things like rare cell detection. Firstly, flow cytometry can in a reasonable amount of time take you down to identification of something like 1 in 1,000 cells. Then you use imaging to take it down still further and identify the characteristics of a given cell. This is whether user intervention and subjective analysis and training becomes more important.

From the standards community standpoint, I hope we will see standardization of plug-and-play tools – that will be important in the healthcare setting, boosting ease of use for healthcare operatives.

And then of course, on the analytics side, we have the automation issue. Automation will obviously trim out operator variability, but it is also a source of problems in itself. For example, we're seeing issues with software version control – what version is the best version? What's the best algorithm of all the different algorithms that the software developers make for actually detecting what you need to detect, or being optimal analytically speaking? In measurement we have a term known as 'commutability'. Mathematically, how closely does the measurement of a reference material conform to the measurement of natural phenomena? In a similar manner, there is a task here to help AI and automation meet the spread of data likely in nature, and this will help with meeting the final specification of these complex products.

Q Looking to the future, where across the broad spectrum of distributed manufacturing models do you expect cell & gene therapy manufacture to eventually find its 'sweet spot'?

JC: A reasonable amount of centralization will be needed for administration, training, technology rollout during change control,

traceability of data, metadata archiving, etc. Plus, you will need a central organization point for logistics and raw material supply. Administration issues with healthcare coordinators and trusts will also need to be centrally managed, ideally. (In the UK, we actually have a big advantage in this regard with the NHS organization making things somewhat easier). So I do think that ultimately, there will be central hub activities that are needed in coordination with PT schemes.

If you take CAR T cell therapy as an example, I think we're going to find a situation where it's going to find its way into the university and teaching hospitals – the major central hospitals – but probably not into district hospitals and clinics. One key element of this is that the diagnostics part has to fit - certainly, for autologous therapy, it's as much about the diagnostics as it is the production and final product quality control. You do need to have that expertise at the clinical site. And of course, you will have to reinforce distribution networks to those major centers that will ultimately produce the therapies.

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AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The author declares that they have no conflicts of interest.*

Funding declaration: *The author received no financial support for the research, authorship and/or publication of this article.*

ARTICLE & COPYRIGHT INFORMATION

Article source: Invited.

Interview conducted: Sep 11 2019; Publication date: Oct 16 2019.

DOI: 10.18609/cgti.2019.133

INTERVIEW

Pros and cons of point of care manufacture of cellular cancer immunotherapies

DR LINDA KELLEY, Cell Therapy Facility Director, is a Senior Member at Moffitt Cancer Center and Professor at the University of South Florida. Dr Kelley has provided leadership for cellular therapy facilities for over 20 years at three institutions, University of Utah, Dana Farber Cancer Institute and Moffitt Cancer Center. She received graduate and post-doctoral training in immunology and hematology from Vanderbilt University, Nashville, TN. Her scientific career evolved from a fundamental interest in immunological mechanisms of T-lymphocyte function, growth mechanisms of hematopoietic stem and progenitor cells and molecular changes associated with malignant transformation. Knowledge of the hematopoietic system led to an interest in stem cell biology and therapies. As director of the Cell Therapy Facility at the University of Utah from 1994 to 2011, she was responsible for developing and expanding a Cell Therapy and Regenerative Medicine Laboratory. During her tenure she was responsible for pre-clinical and clinical cell therapy product development to support IND applications for the production of allogeneic mesenchymal stromal cells (MSC), autologous bone marrow-derived mononuclear cells and allogeneic fetal-derived oligodendrocytes. As director of the Cell Manipulation Core Facility at the Dana Farber Cancer Institute at Harvard from 2011 to 2012, she oversaw management of 20 FDA-approved INDs for the manufacture of gene-modified $CD34^{+}$ cells, tumor cell vaccines, dendritic cells, MSCs and others. As director of the Cell Therapy Facility at Moffitt Cancer Center, she oversees 22 active INDs for a variety of cell therapy products largely to support immunotherapy for adult and pediatric patients. She currently serves as the Principal Investigator for Production Assistance for Cellular Therapies (PACT) – Cell Processing Facilities to perform pre-clinical cell therapy product development in collaboration with NHLBI and other PACT Centers and as Core Laboratory Technical Director for the Moffitt Cancer Center Support Grant. Dr Kelley excels at bridging the gap between laboratory-based discoveries and new therapies for patients.

Cell & Gene Therapy Insights 2019; 5(10), 1109–1115
DOI: 10.18609/cgti.2019.118

Q What are you working on right now?

LK: We are a large academic cell therapy manufacturing facility. We are providing manufacturing services for our own investigator-initiated cell therapy clinical trials as well as for industry-sponsored projects.

Our main focus right now is on technology development – technology transfer – and then moving those new technologies into manufacturing for clinical trials.

"When it comes to assays, there is a continuous flow of new technology coming through – novel PCR assays, fluorescent assays, functional assays, etc. It is tough to gain access to all of those methods and tools as they become available and established – they are not easily acquired or obtained in a decentralized environment."

Q You have run cell therapy manufacturing facilities at some of America's foremost academic institutions – can you firstly frame for us the key pros and cons as you see them in terms of conducting manufacture relatively close to the point of care?

LK: The pros chiefly relate to providing more timely access to the therapeutic product. It leads to much better patient management and care if the manufacturing can occur close to the patient.

Cancer patients who have advanced malignancies are at risk of disease progression and any time spent sending a cell product out of the city, the state, or even the country for bioprocessing can prolong treatment. Likewise, when the manufacturing process can only be performed in specified, limited facilities, then issues may arise regarding facility capacity limitations and/or operational restrictions that could lead to further delays.

With point-of-care manufacturing there is less risk of a shipment mishap, which doesn't happen often but could potentially occur. Most of

today's cellular cancer immunotherapy products are autologous. Collecting each patient's cells, either by apheresis or as a tumor sample and labelling, packing and shipping them off to the manufacturing site, processing them there, sending them back to the patient's location… That's a lot of logistics to manage error-free.

In addition, the manufacturing costs are lower when the manufacturing can be done locally. Usually, some of the overhead costs are at least shared if not fully covered by the parent institution, so the cost for manufacturing the product can be significantly reduced.

The cons are the availability of the technical and regulatory expertise that would be required at each point-of-care manufacturing site. There are also capacity limitations – there is a dearth of laboratories that have the capabilities and capacity to manufacture large volumes of cell-based therapies.

Q Cellular immuno-oncology agents involve some of the more complex bioprocesses in the cell and gene therapy world – are there any particular steps or requirements in the manufacture of such products that present challenges in the decentralized environment?

LK: Yes. For one thing, many of the early-stage, novel cell therapy products have to be manufactured in open systems and therefore require GMP manufacturing suites, which are not readily available in most hospital settings. Likewise, some of the new gene editing techniques require specialized equipment which is not readily available.

When it comes to assays, there is a continuous flow of new technology coming through – novel PCR assays, fluorescent assays, functional assays, etc. It is tough to gain access to all of those methods and tools as they become available and established – they are not easily acquired or obtained in a decentralized environment.

Q What for you would be the key innovations or advances that might help decentralized manufacturing models for cellular immunotherapies become more established?

LK: The first one that comes to mind, which we all recognize as rate limiting, is the availability of closed systems that are automated for cell manufacturing.

"Another rate-limiting issue with regard to FDA-approved, commercially available cell therapy products is that the individual companies involved are using different IT systems to manage the logistics of shipment, scheduling, etc."

I think this is a need in the industry as a whole. There are some solutions available now, or that are just coming onto the market, but the types of cell products we are manufacturing are not all the same. Not every cell therapy in clinical trials right now is a CAR T cell product and they don't all require the same types of equipment. Even for those of us who are eager to have automated systems, currently there are no one-size-fits-all manufacturing solutions for multiple cell therapy products. As the field evolves it will become more clear which types of automated systems are efficient and economical for a given cell therapy. Academic facilities manufacturing different cell products will likely need to employ different techniques. The availability of resources, including capital funds as well as physical space will drive those decisions.

New assays are rapidly being developed for defining critical quality attributes and lot release testing for cell therapy products. Standardization of assay results from lab to lab is greatly needed yet does not exist even for commonly performed assays such as cell counting, viability and flow cytometry. Reference standards are needed for these assays as well as knowledge of how to perform appropriate assay validation to determine purity, potency and sterility. An understanding of when and how to test for accuracy, precision, sensitivity, specificity, robustness, etc., would greatly facilitate transition through the FDA approval process for new cell therapies.

Another thing that would be very beneficial is the application of rapid microbiological sterility testing to cell therapy products. That is moving forward quickly in the blood industry – testing blood cultures by using molecular techniques, for example – but it's not yet being done on cell therapy products. In many cases, we are having to release products based on a Gram stain, which we know is insensitive. And the current automated systems are still taking 7 days – in fact, people often have not validated them for a 7-day culture, so they are still having to wait 14 days for the result. So I do think that being able to conduct rapid turnaround sterility testing of cell therapy products using molecular techniques will have a significant impact.

Another rate-limiting issue with regard to FDA-approved, commercially available cell therapy products is that the individual companies involved are using different IT systems to manage the logistics of shipment, scheduling, etc. Having a universal information management system would greatly facilitate the learning curve at the clinical sites for the people who are responsible for scheduling the patients and making sure they get their cells back

DOI: 10.18609/cgti.2019.118

for timely infusion. Having a solution that works for all companies and all products would be very beneficial.

On a general note, I would also highlight the current lack of availability of FDA-approved, clinical- or GMP-grade reagents. There's still a dearth of approved reagents. If we can get the commonly used reagents – media and growth factors, cytokines, etc. – to GMP-grade, then they can be used early on in product development, facilitating the transition from Phase 1 to 2/3. That would in turn help get these products approved and into patients faster.

Availability of a trained workforce is certainly another rate limiting factor right now. Most of the people that come into the cell therapy workforce are required to have a bachelor's degree in a biological science, but what we really need are people who have been specifically trained in aseptic cell processing and culture techniques. Maybe a 4-year bachelor's degree is not required in all cases – a certification course that is more focused on the exact techniques we use in the laboratory might be more appropriate.

Finally, I look forward to global harmonization of regulatory requirements. It's becoming more and more commonplace to have products manufactured in the USA being sent to Europe or other regions/countries, and vice versa. However, facility requirements and standards differ between countries and that limits the potential for international exchange of these products. If we could get to a state of global harmonization, that would move the field forward much faster.

Q Can you point to a single future bioprocessing innovation that would make the greatest difference to you?

LK: I think the biggest challenge we face today relates to the volumes of the cell products we are dealing with. Because most of the cells we are after need to be isolated and then expanded *in vitro*, we end up with large cell volumes, which are difficult to maintain in closed

"...facility requirements and standards differ between countries and that limits the potential for international exchange of these products. If we could get to a state of global harmonization, that would move the field forward much faster."

systems. Genetic modification of fewer cells, perhaps isolated from peripheral blood, and modified such that they could then be expanded *in vivo* would reduce the *ex vivo* cell volumes. This could be accomplished by introducing a growth factor receptor, for instance, or a receptor for some other stimulant that could then be given to the patient systemically. That would really be the ideal way to get from vein to vein quickly.

Q What degree of decentralization do you think will prove the most feasible for widespread commercially available cellular cancer immunotherapies as the space matures further?

LK: In order to provide the best possible patient care, manufacturing is going to have to be available at the point of care, or at a minimum, at regional facilities closer to the patient.

Americans, in particular, have become accustomed to having the very best healthcare available. As long as our healthcare system stays the way it is, patients are going to demand that level of patient care and service providers are going to strive to provide it.

Of course, this does depend on a lot of things: it depends on whether or not allogeneic cell therapies will replace autologous, and on whether or not bioprocessing techniques can be shortened, simplified and reduced in cost. But surely, as all of that moves forward, it will get easier and easier to move manufacturing to the point of care.

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DOI: 10.18609/cgti.2019.118

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The author declares that they have no conflicts of interest.*

Funding declaration: *The author received no financial support for the research, authorship and/or publication of this article.*

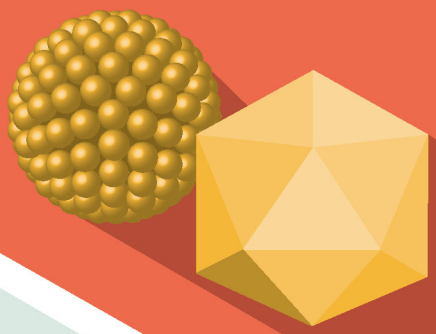
ARTICLE & COPYRIGHT INFORMATION

Article source: Invited.

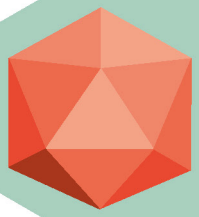
Interview conducted: Sep 8; Publication date: Sep 13.

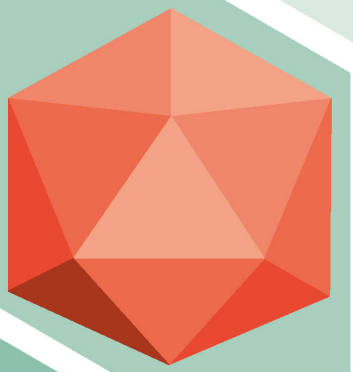
CELL & GENE THERAPY INSIGHTS

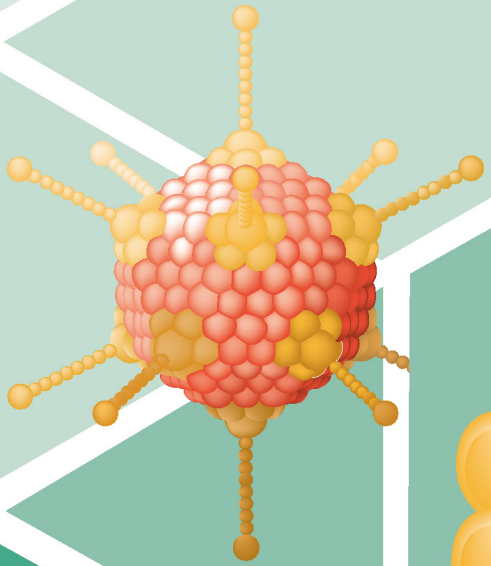
Viral Vector Channel

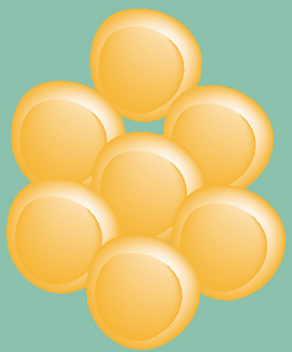


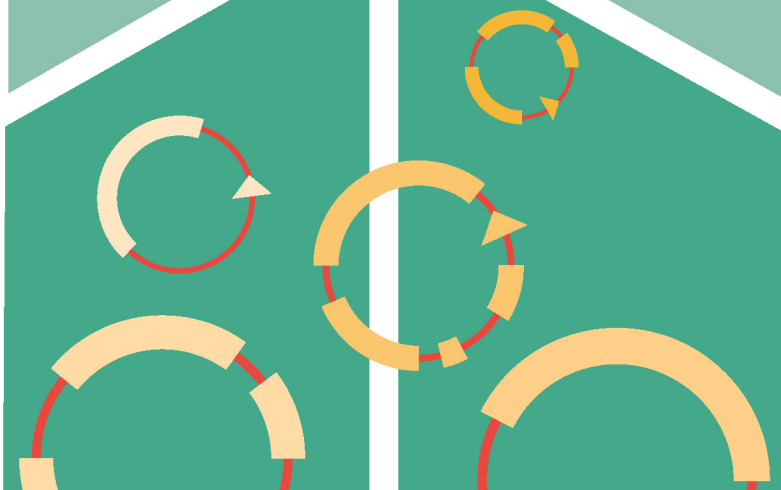
RAW MATERIALS EDITION

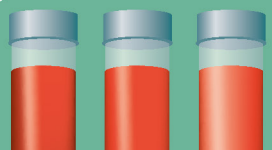




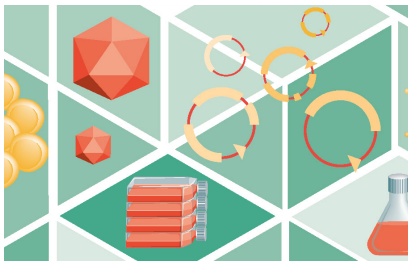








IN FOCUS:
Highlights from our Vector Channel



Raw Materials

EXPERT INSIGHT

ATMP Raw materials – "the plasmid conundrum"
Alan Griffith

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Identifying and mitigating risks in the viral vector supply chain
Claire Wartel &
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CELL & GENE THERAPY INSIGHTS

VECTOR CHANNEL: RAW MATERIALS

EXPERT INSIGHT

ATMP raw materials: 'the plasmid conundrum'

Alan Griffith

Plasmids and plasmid DNA (pDNA) have been key components in recombinant DNA molecular biology for decades. One of their uses as a precursor raw material represents a cornerstone of viral vector ATMP manufacturing. Here we provide a synopsis with regard to their own manufacturing lifecycle, limitations, demand, regulatory expectations and supply chain, as more and more companies join the gene and cell therapy clinical trial races to market in this fast-paced sector.

Cell & Gene Therapy Insights 2019; 5(10), 1259–1265
DOI: 10.18609/cgti.2019.132

After a lull period, Advanced Therapy Medicinal Products (ATMPs), prominently gene and cell therapies, are making a comeback. Attempts to treat disease by inserting DNA into patients' cells all but ended in 1999 after the death of an 18-year-old from a severe immune response to the virus used to deliver a corrective gene. Potential Companies and investors left the field in droves [1].

Arguably, the sector was never truly gone, pockets of groups and academics in particular stayed true to their vocations and continued in this research area, realizing gene therapy's inherent potential to provide a permanent cure for any of the more than 10,000 human diseases caused by a defect in a single gene. Fast forward to today and after remedying some limitations, a new wave of viral vectors (adeno-associated virus [AAV], adenovirus, lentivirus, etc.) have become prominent again due to the trojan work of these resilient groups.

Over the last few years, huge investment from astute venture capitalists and investment consortia such as Syncona in the UK has led to accelerated progression towards market authorization for many emerging GCT companies (many of which were spawned by academic institutes as mentioned).

Adding to the underlying expertise, and blurring the lines between academia and industry somewhat, industry partners and biotech professionals have piggy-backed on this initial development (initial development having ambiguous meaning here: development remains in its infancy in places whereas it actually

more accurately reflects decades of work, which was proceeding at a glacial pace towards clinical translation) and in turn put huge resources into facilitating these 'start-ups' getting from preclinical development into clinical trials, often in return for substantial equity.

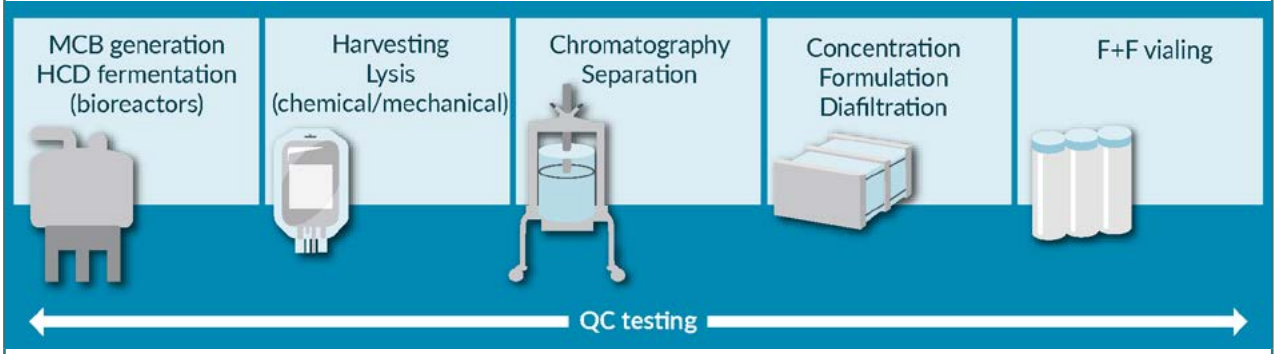
With testimonials of clinical success flooding the scientific social media newswire platforms over the last few years, the sector is continually being hailed as the next biotech revolution. Furthermore, with the progression of products (AAV viral vectors being one of the most abundant) into late-phase clinical studies, the GCT industry will see an inevitable need for increased amounts of plasmid DNA (pDNA), which is used as a starting raw material for viral vectors, to be made at larger manufacturing scales.

Since its discovery in 1952, plasmid DNA (pDNA) has become one of the most important tools in genetics and recombinant molecular biology and, more recently, in gene therapy and vaccination in medicine [2]. They are self-replicating extrachromosomal elements that can allow genetic transposition between animals, other plasmids and Genetically Modified Organisms (GMOs). Plasmid preparations using commercially available kits are useful for the small-scale bench top scientists but are not applicable for efficient multi-milligram or gram-scale plasmid productions. Frustratingly, the resulting plasmid concentrations and purity are often not reproducible. As many readers will understand, this should be a prerequisite, especially for therapeutic applications. Therefore, manufacturing facilities need to be utilized to manufacture in a standard way (Figure 1).

It is worth noting that for direct gene transfer into humans, good manufacturing practice (GMP)-grade plasmid DNA is mandatory. The same holds true if the drug substance contains a genetically modified cell – for example, chimeric antigen receptor (CAR) T cells – where these cells as well as the contained plasmids are used. According to the responsible regulatory agencies, they have to be produced under full GMP as the pDNA comes into contact with the patients' 'actual' cells via *ex vivo* intervention [3]. Conversely, for GMP production of viral vectors (lentiviral vectors, AAV vectors), it was previously assumed that, High Quality Grade

FIGURE 1

Plasmid manufacturing process. QC testing is done at all unit operations.



MCB (Master Cell Bank), F+F (Fill and Finish) represents the final formulation and final vialling step for the pDNA as its own manufactured product, which in turn is ready for use in viral vector manufacture as a starting raw material. During the pDNA lifecycle, it is subjected to appropriate Quality Control (QC) for its intended use.

DOI: 10.18609/cgti.2019.132

(HQ or GLP grade) manufactured plasmid DNA was acceptable as a starting material due to its categorization. Research-grade plasmid material has been routinely used in early-stage clinical trials, particularly those led by academic groups, but changes to FDA guidance mean that sponsors are now encouraged to treat even early studies as potentially pivotal – and so the use of GMP manufactured pDNA is now modus operandi [4].

Going back a step, one could see the rationale here. The pDNA starting material undergoes significant processing and does not itself make up the final therapeutic product. However, the risk factors exist where extraneous pDNA may not be sufficiently cleared during viral vector manufacture [4] and may actually hint that the processing of the viral vector is at fault, not the pDNA starting material processing (GLP or GMP) upstream. Additionally, as more and more clinical trial data presents itself to the MHRA/FDA/EMA agencies, they are slowly starting to implement greater stringency as plasmids are arguably the most important component in the viral vector manufacturing process, and they are in and of themselves biological entities that are subject to variability.

The manufacturing processes used (depending on vendor of choice) can represent different production steps. To ensure the right conditions are used for the plasmid, a pilot run must be conducted at the beginning. In this pilot run, steps must be taken to ensure reproducibility, range-find key process attributes, and establish the suitability of precursor pDNA (starting material of the plasmid manufacture process, as it is not created from scratch). Subsequently, once incoming testing is done on the precursor pDNA, a cell bank of the transformed *E. coli* strain is established and characterized. This cell bank is used for the cultivation/fermentation process. After cell harvesting and lysis, several chromatography steps are conducted to deliver a pure plasmid product. Depending on the respective required quality grade, the plasmid product (and its MCB) is subject to several quality control assays (such as sterility, purity (260/280 nm), full sequencing, enzymatic digestion, and also % supercoiled form homogeneity – highlighted lastly here to emphasize its importance in this article) to characterize and evaluate the end pDNA product. Once this pDNA has been QA released it is ready to be used in viral vector manufacture or T-cell tissue engineering.

To meet rising demand as companies successfully navigate clinical trial phases, it is no secret that production processes and platforms will need to be scaled-up significantly. It is difficult to get a clear picture of each GCT companies processes and implemented technology at their respective sites, or indeed if they use a Contract Manufacturing Organisation (CMO) service provider to manufacture. This makes perfect sense as the sector is highly competitive and many companies have numerous indications in direct competition, thus the need to keep their capabilities and trade secrets close to their chest. Basing assumptions on the existing market authorized viral vector GT products (*Glybera* from uniQure, *Zolgensma* from AxeXis and *Luxturna* from Spark Therapeutics), it may be possible to meet the demands for niche therapies of

<10,000 patients with small-scale production platforms making <10 g/batch. However, this value may only suffice as suitable for clinical stage batches for larger indications. A reasonable prediction is that 100–500 g/year of pDNA may be required (highly dependent on each companies' proprietary production process) for each plasmid vector for a marketed product. This calculation may further be adjusted depending on factors such as GMP suite occupancy/availability, patient access and instance rates, competitive products, process development and disruptive technologies.

Here lies a twofold problem: firstly, with pDNA being such a key starting material in ATMP manufacture and with ever-increasing demand, plasmid manufacturers may start to offer overly inflated service costs (due to demand for suite occupancy). Secondly, regulatory bodies (EMA, FDA, MHRA in particular) are playing catch-up with governance surrounding various aspects of viral vector manufacturing to GMP. Previously, these aspects were very much assessed on a case-by-case basis, as was the case with the three marketed products listed above. This second point is worth developing in the context of using pDNA manufactured to GMP: global guidance (being purposefully general here) portrays that to increase success rate of clinical trial authorizations (CTAs) via Investigational New Drug (IND) approaches, a GT company must make pDNA to GMP standards to get the best grade material prior to starting viral vector manufacturing.

Furthermore, the impact of this increased need for pDNA material is that a road map detailing plasmid quality attributes and standardization must be attained quickly. Working closely with the regulatory authorities may help with this. The road map critical elements are of course driven by the guidance literature and compendia, because as many will agree, there may be room for improvement based on the Sarepta [4] issue seen in 2018. However, the main issue with this is that the cost of GMP manufactured pDNA is often ~200–300% higher than that of research grade, HQ grade or GMP-s grade, as anyone who has received a proposal from the main pDNA global suppliers will testify. This may prove detrimental to early-stage GCT companies trying to manage strict budgets and having tighter bankrolls from less committed venture capitalists and investors. This puts the 'already strong' elite companies at an advantage, or the companies that can afford to build purpose built pDNA manufacturing facilities to feed their respective viral vector platforms. Another alternative is perhaps to find the middle ground by finalizing a pDNA 'grade' which appeases the authorities as well as the financially astute, but whether this is even achievable remains to be seen.

Manufactured pDNA to other grades can meet QC/QA requirements, depending on the vendor used and how specialized they are. This is an aspect potentially overlooked during IND submissions for Phase 1 indications. This is needed in order to guide the GMP approach to plasmid consistency, long-term stability and their intended use in viral vector manufacture. These road maps (driven by compliance to regulatory compendium and

DOI: 10.18609/cgti.2019.132

expectation) also need to demonstrate comparability with regards to safety and functionality. As you may imagine, these attributes are often overlooked and hard to implement in academic settings at the beginning of a therapeutic target's journey, and once a Phase 1 trial has been assessed, any changes would need to undergo comparability. If this comparability exercise could be avoided at the early stage of development, it would represent a substantial 'win'. This may in fact offset the cost implications mentioned above.

One aspect that may help with the standardization of pDNA in the sector is process development (PD). PD already plays an important role for viral vector manufacture to reduce Cost of Goods (COGs), increase quality attribute robustness and instill a get-it-right-first-time approach. Naturally, then, plasmids should be exposed to PD in their own right, as one feeds the other. We are seeing early movements on this globally, with key companies such as Aldevron, Cobra Bio, Boehringer Ingelheim, Biomay AG and VGXI all expanding their plasmid operations and facilities to position themselves for the looming spike in plasmid demands. Whether viral vector companies also start to bring this capability in-house remains to be seen, but it would create an end-to-end supply chain to final product, as briefly mentioned above.

QC/QA demands on plasmids remain an uncertain aspect of plasmid manufacture for viral vectors. This must translate into different QC/QA demands not only from one regulatory agency to another, but also one viral vector manufacturing company to another. Added complexity arises from the fact that plasmids can be used either as a direct therapeutic or indirectly via a starting raw material, and the guidance provided between EMA and US FDA appears to have some gaps in this regard. One clear example of this is that in the US, the FDA guidance points towards >80% Supercoiling (aka plasmid form or homogeneity) specification, which appears to come from a vaccine guidance repository 'Considerations for Plasmid DNA Vaccines', whereas in Europe (Eu.Ph 5.14 monograph), it is not specified at present.

One could argue that the effect supercoiling has on viral vector production is only realized at the transfection stage of its manufacturing lifecycle. It is often alleged that supercoiling can impact the transfection efficiency of plasmids being used in the transfection unit operation at scale. In other words, with a lower percentage of supercoiling, less plasmid gets successfully integrated into host cells (normally HEK293 mammalian cells). This in turn theoretically means less AAV titer coming out the back end after downstream bioprocessing (DSP). Data supporting this remains minimal and it appears to be a case-by-case basis, as each starting plasmid (especially the transgene or GOI plasmid) is inherently different by virtue of its intended therapeutic use. Conversely, it makes sense to have a reasonably high supercoiling value in cases where the plasmid is used as a direct treatment – however, the guidance does not seem to demarcate this. By complying with the guidance, viral vector manufacturers may safeguard their process and increase yields, but there does not seem to be any added benefit to the end patient from a

Safety, Integrity, Strength, Purity and Quality (SISPQ) point of view. That the FDA (or any agency) would be concerned with manufacturers' yields rather than the SISPQ may be an overgeneralization, but effectively, this is how the governance around certain QC tests is portrayed from the outside looking, specifically for indirect pDNA use in ATMP manfacture. This may be an avenue for providing a sensible agenda point when companies and agencies convene at early IND stages. With the accelerating development of GCT, the regulators are trying to keep pace and sensibly appear to be working more closely with GCT companies on a more informal basis, which may assist with the flow of information and choosing the most quality-assured path.

Sector growth is also forcing dedicated plasmid manufacturers to overhaul and invest in better facilities and QMS systems, which they appreciate their clients will require as the regulatory agencies start to implement and request more quality-driven data. This can only be a good thing globally. There is also a synthetic revolution occurring where companies such as Molecular Assemblies, LinearX, Touchlight Genetics and DNA Script are forging a path for the use of plasmid alternatives in the form of synthetic analogues, which can replicate the mode of action of plasmid DNA but are manufactured in a more scalable and consistent way. Plasmids are inconsistent by nature and can be difficult to make at very large scale, thus hindering commercial supply chains. They also require labor-intensive purification and testing, so the assumption is that the more you move away from the complexity of biological systems (you remove, for example residual RNA/DNA/proteins from QC testing), the more attractive the product becomes as a starting raw material. Having analogous DNA which behaves the same, yet can be made in a 'cleaner', more consistent way, is a triumph for that aspect of viral vector manufacture.

In conclusion, there does not currently seem to be an overnight fix or convention that early stage companies can adopt to ensure that pDNA consistency and quality can be attained in a cost-effective way. There is disparity between guidance repositories globally, which can be both time consuming and confusing for clinical operations and quality teams and departments. Plasmids are not your conventional non-biological starting material. This is not helped by the FDA, MHRA and EMA struggling to keep pace with the influx of clinical trial submissions.

Alternatives to pDNA exist which may augment these issues and make standardization of quality easier, but these are relatively unchallenged. Furthermore, if the solution does not lie with synthetic DNA alternatives, then stable integration may be another means for viral vector production. For example, the baculovirus system employed by Vigene (OneBac™) system simplifies this procedure by using Sf9 cells that have been genetically modified to carry rep and cap genes from native AAV. This would partially negate the need for the transfection unit operation and reduce reoccurring costs of dedicated pDNA manufacture and subsequent QC testing.

On a final note, once upon a time, plasmids were a means to an

DOI: 10.18609/cgti.2019.132

end for viral vector manufacture and not many people delved into all the nuances plasmids bring and more importantly, how these nuances can impact large scale viral vector manufacture. Now with a handful of GCT products reaching the market, added scrutiny has created this pseudo-space where plasmids are taking center stage and their characterization is needed for longer term use in the sector. However, trying to standardize and regulate a raw material which confers so much legacy intellectual property and competitive advantage between GCT companies may present a difficult hurdle to overcome. Like the circular clock shape that plasmids represent, only time will tell.

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AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The authors declare that they have no conflicts of interest.*

Funding declaration: *The authors received no financial support for the research, authorship and/or publication of this article.*

Article source: Invited; externally peer reviewed.

Submitted for peer review: Aug 23 2019; Revised manuscript received: Oct 1 2019; Publication date: Oct 17 2019.

CELL & GENE THERAPY INSIGHTS

VECTOR CHANNEL:
RAW MATERIALS

PODCAST INTERVIEW

Identifying and mitigating risks in the viral vector supply chain

CLAIRE WARTEL has a PhD in Molecular Pharmacology and Pharmacochemistry from the University of Strasbourg (France, 1999). After several post-docs in different prestigious universities, Claire joined Polyplus-transfection in 2004 as Cell Biology project leader and participated in the development of our flagship product jetPRIME®. Claire has taken Quality responsibility since 2007, and nowadays manages the department of Quality and Regulatory Affairs.

ULISES VILLAVICENCIO attended California State University, Long Beach (CSULB) where he earned a Bachelor's Degree in Anthropology and focused on Archaeometry. Ulises participated in numerous archaeological research projects, domestic and international, and assisted in various analytical projects at CSULB's Institute for Integrative Research in Materials, Environments, and Societies to further analytical research in Archaeometry via chemistry-based applications. Ulises applied his education and experience in Quality test environments where he then expanded into the auditing field in 2015. Since then, Ulises has focused his attention on improving Quality and Compliance programs for the security and assurance of patient safety, where he manages the Supplier Qualification program in his current role.

Cell & Gene Therapy Insights 2019; 5(10), 1339–1346

DOI: 10.18609/cgti.2019.139

Q The commercial scale manufacture of viral vectors presents a number of challenges for cell and gene therapy companies. What do you view as the critical pain points in this transition?

CW: As a key supplier of transfection reagent for the cell and gene therapy market, we are currently facing an increase in demand in terms of volume of supply and also in terms of supplier qualification process and regulatory support.

These aspects are manageable, but in the near future, with more and more companies moving to commercial-scale manufacture it could become a critical pain point. As you can imagine, moving to commercial scale means a higher quantity of raw material for the scale up of the manufacturing process, and a greater level of regulatory support for submission of market authorization.

That's why gene and cell therapy companies need to organize themselves in order to secure their supply chain of raw material.

UV: I believe some of the key components are not just those associated with shortages of key raw materials but also in final yields obtained due to inefficient downstream processes. For example, some of your purification processes, and ultimate potency are currently creating pain points for many cell and gene therapy companies.

Q There's a great deal of discussion around the quality of raw and starting materials that are required at the different stages of product development. What impact can the quality of your starting materials have on vector production?

UV: Throughout the field the quality of starting materials can have a significant impact on the final product. A rather simple example that comes to mind is contamination. Raw and starting material manufacturers typically offer more than one product, therefore understanding their manufacturing and process contamination controls is critical. For example, human interactions with a manufacturing process and how well you change over at the end of each manufacturing run is a key indicator of positive quality output.

So this is one significant impact that's going to have on the process and quality.

> "We launched the very first global GMP transfection reagent for the gene and cell therapy market ... and immediately received a great level of interest from all of our customers."

CW: At Polyplus we have regular discussions with our customers around the quality of raw materials for the different stages of product development.

DOI: 10.18609/cgti.2019.139

We provide a transfection reagent called PEIpro® at three different quality levels: PEIpro®, PEIpro®–HQ and PEIpro®–GMP.

You have to know that each quality grade has its own market from process development going through clinical trials and up to commercialization.

We guarantee the same vector production yield whatever quality of PEIpro® is used, ensuring a smooth transition from the process development through to commercialization.

In fact, the different qualities of the transfection reagents we propose are related to quality control, traceability, quality environment and regulatory support. But definitely our customers have to be assured that they will get the same vector production level when using one or the other quality grade PEIpro® products, otherwise they would have to fine tune the manufacturing process at each step of the product development, and this is definitely not manageable.

Q At what stage do you typically see companies starting to think about using GMP grade materials in their manufacture? Is it early enough in your opinion?

CW: This question is really interesting, and the answer is really customer dependent. The vast majority of our customers request a GMP-grade transfection reagent.

We launched the very first global GMP transfection reagent for the gene and cell therapy market, less than 1 year ago and immediately received a great level of interest from all of our customers, independent of their product development phase.

Regarding the potential reasons that influence a company's decision to move to GMP-grade raw materials, we have observed that when a gene and cell therapy company decides to use a GMP-grade transfection reagent, it's very often linked to a mature risk-based approach on their side. They deeply need to decrease the risk of their raw material supply chain.

Manufacturing GMP-grade raw materials ensures that the manufacturing process has been validated. As such, customers are assured of high lot-to-lot consistency and reproducibility, which greatly limits any impact on their own manufacturing process.

In addition, using GMP-grade raw materials is linked to a stronger relationship between gene and cell therapy manufacturer and the supplier. For example, the qualification process of the supplier, signature of quality and supply agreement, and having a secured supply chain allows the gene and cell therapy manufacturers to reduce risks relating to the sourcing of raw materials such as shortage of supply or any other critical issue.

UV: I second Claire's response for the first portion of that question; however, it's difficult for me to fully address this question without understanding the specific goal of the company. Perhaps it may sound a little cynical, but it's no surprise that some companies seem to bring a product beyond Phase 1 to ultimately become acquired by a larger entity.

With this in mind I believe some companies tend to shift to GMP-grade materials at a later phase. Now that being said a company with a strong focus on scaling up to commercial grade manufacturing will surely seek GMP-grade material much sooner rather than later.

I often receive feedback from manufacturing stakeholders that budgeting seems to be a key factor as to why they may opt for non-GMP grade solutions.

Q What guidance is provided by the regulatory agencies in terms of the quality requirements for your raw materials? Is there any confusion around this issue?

UV: There's certainly plenty of guidance that can be referenced, for example you look at 21CFR 211 and 210.A4, ICHQ10, and the EU Commission directive 2003 94EC.

However, I think we can all agree that when considering the requirement for raw materials, some of the requirements can be rather vague or high level. I strongly believe that the ticket to changing or improving raw material requirements is via risk assessments.

By performing assessments of materials based on risk, a manufacturer is able to soundly and objectively justify the raw material program, and assign criticality. One obvious implication of confusion around requirements can be an inadequate incoming testing and acceptance program and a situation such as this can be detrimental to the final product.

"...the ticket to changing or improving raw material requirements is via risk assessments."

CW: From the European point of view I can highlight the Part 4 of the GMP guidelines specific to advanced therapy medicinal products (ATMPs), adopted by the European Commission in November 2017. Here you can find a many of the current requirements concerning the quality of raw material, for example in sections 7.10 and 7.13, where it is written that the quality of starting and raw material is a key factor to consider in the production of ATMPs.

DOI: 10.18609/cgti.2019.139

It is also written that particular attention should be paid to avoid contamination and to minimize the variability of the starting and raw material. Using GMP-grade raw material will definitely address these two requirements. In the same section of these guidelines it is also clearly stated that while raw materials should be of pharmaceutical grade, it is acknowledged that in some cases only raw materials of research grade are available. And also that the risk of using research grade materials should be understood, including the risk to the continuity of supply when larger amounts of products are manufactured. Meaning that using research-grade raw materials is a risk taken by our customers. As soon as GMP-grade raw material is available on the market they should switch to this.

I think it is critical for the gene and cell therapy manufacturer to comply with this requirement in order to obtain their marketing approval and certainly we see no confusion at all around this topic.

Q The cell and gene therapy supply chain is incredibly complex when compared with traditional biopharma, how can developers mitigate some of their risks across the supply chain?

UV: I think auditing agreements can serve as a strong tool to assist in the mitigation of supply chain risk. While ensuring robust controls in a supply chain process amongst adequate resourcing should consist of strong forecasting, redundancy in suppliers wherever possible of course, accurate cycle counting, material controls, and training, which should also be assisted by a solid inspection program that shall detect potential risks prior to the manufacturing stream.

CW: Sourcing GMP-grade raw material is associated to a deeper interaction and closer cooperation between gene and cell manufacturers and suppliers. We at Polyplus adapt our support according to the needs of each of our customers, as Ulises highlighted, we are used to entering into supplier qualification process, meaning that we are qualified either through paper-based questionnaire or more and more through on-site audits.

We are also used to signing quality agreements but also supply agreement if needed. It is true that more and more customer want to secure the supply chain by sharing annual forecast with us. It really is a good way of mitigating risk.

For us, it is easier to plan manufacturing campaign having this annual forecast in mind. And from a customer point of view they are assured they will be delivered on time, meaning that they will not delay their cell and

gene therapy product manufacturing. While other, less organized customers, will take the queue for the supply of their transfection reagent.

Q How does Polyplus work with clients as they move through to commercialization? And can you share with us any future development plans to further support the growth of this industry?

CW: At Polyplus we build strong relationships with our customers from the very beginning. And it is visible in different departments, scientific and technical support, business, quality assurance, supply chain and logistics.

Usually it starts at the very beginning of their product development, so when they move to commercialization a strong partnership is already in place. They are used to contact our amazing scientific support team in order to get optimization advice for their transfection step for example. They have secured their supply chain by sharing annual forecast with us, quality and supply agreements are in place in order to fulfil regulatory requirements, qualification process of Polyplus as an approved supplier is finalized, etc.

And regarding future development plants, our outstanding R&D team is actively working on new generation transfection reagents in order to increase the vector production yield and decrease the volume of DNA needed, with still high-quality environment. And it is true that we are also developing more and more analytical methods around our transfection reagent in order to address regulatory requirements.

UV: I would like to add that I fully recognise the committment Polyplus has invested into our working relationship - Claire's quality team at Polyplus have been highly transparent and accommodating to ensure Audentes continues to be supported with the supply of quality material. I know from my experience with other vendors that this is not always the case and so working with Polyplus has been a breath of fresh air.

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DOI: 10.18609/cgti.2019.139

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The authors declare that they have no conflicts of interest.*

Funding declaration: *The author received no financial support for the research, authorship and/or publication of this article.*

Article source: Invited.

Interview conducted: Sep 16 2019; Publication date: Oct 15 2019

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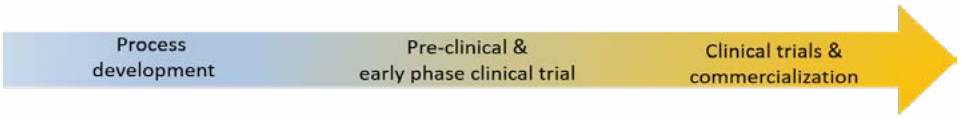

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Quality Grade	R&D grade	Pre-clinical grade	GMP grade
Composition	Ready to use, chemically defined and animal derived component free		
Packaging	Bottles	Bottles	Bags (closed system)
Fill & finish manufacturing process	Sterile filtration	Sterile filtration	Sterile filtration Validated aseptic process
Quality Controls	Standard QCs	Extended QCs to assess Identity, Potency, Purity and Safety	Validated QCs according to European Pharmacopeia assessing Identity, Potency, Purity and Safety

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CELL & GENE THERAPY INSIGHTS

VECTOR CHANNEL:
RAW MATERIALS

INTERVIEW

Challenges in viral vector raw materials procurement & management

KATHLEEN SZCZUR, Senior Specialist in the Vector Production Group at Cincinnati Children's Hospital Medical Center (CCHMC), has over 21 years of experience in both basic science research and Phase 1/2 GMP manufacturing. She began her career in production of GMP clinical supplies and analytical chemistry at a small firm working with biodegradable polymers to develop long-acting delivery systems of various molecules. She continued her career researching immune function at Shriners Burns Hospital, Cincinnati, OH, in the lab of Cora K Ogle, PhD and hematopoiesis with the Experimental Hematology and Cancer Biology group at CCHMC in the lab of David A Williams, MD and Marie-Dominique Filippi, PhD. Her current position involves manufacturing of viral vectors for both academic and commercial customers to advance the field of gene therapy.

Cell & Gene Therapy Insights 2019; 5(10), 1305–1310

DOI: 10.18609/cgti.2019.136

Q What are you working on right now?

KS: Manufacturing clinical grade Retroviral Vectors and Lentiviral Vectors for a variety of indications, for both internal and external sponsors.

Q Can you give us some background on the Cincinnati Children's Hospital Medical Center's specific activities and capabilities in the cell and gene therapy field?

KS: The Cincinnati Children's Hospital Translational Core Laboratory (TCL) has been assisting investigators in translating

innovative processes from bench to bedside since 2003 with a focus on manufacturing and testing for cell and gene therapy clinical trials. The TCL is operated under controls that ensure compliance with current Good Manufacturing Practices (cGMP) and Good Tissue Practice (GTP) in support of early phase INDs. Clinical manufacturing is performed in ISO Class 5, 7, and 8 cleanroom environments in accordance with aseptic processing guidance and occupies approximately 10,000 sq. feet on the 11th floor of CCHMC Research Building S.

"When sourcing materials, we examine the Certificate of Analysis to assure that critical material attributes will remain within specification at all stages of manufacturing."

Our Cell Manipulation Labs (CML) are focused on the translation of gene and cell therapies into clinical trials and performing the cell manipulation for these trials. For these studies, they can either develop the cell manufacturing process from early stages or they can be transferred directly from a Sponsor. For processing of patient material for a clinical trial, the cellular products are manufactured in cleanroom facilities. Since 2017, the CML have manufactured more than 30 products in support of clinical trials. The CML are compliant with GMP (21 CFR 211), GTP (21 CFR 1271) and hold a Type V Master File (MF-BB) with FDA.

The Translational Trials Development and Support Lab (TTDSL) is a CAP/CLIA certified and GMP laboratory that provides support for early phase cell and gene therapy clinical trials. Its services include assay development and qualification, biological product characterization, and specialized patient monitoring assays. Available technologies are flow cytometry, absorbance/luminescence plate readers, qPCR, digital PCR, and protein HPLC. The TTDSL holds a Type V Master File (MF-BB) that may be used as a cross-reference in support of IND submissions.

Last but certainly not least, we have our Vector Production Facility (VPF), which provides technology transfer, process development and scale-up using cGMP-compatible methods. Additionally, the core competency of the VPF is cGMP manufacturing of gamma-retrovirus and lentivirus vectors and the generation of Master and Working Cell Banks in compliance with FDA guidelines. The VPF is compliant with GMP (21 CFR 211) and holds a Type V Master File (MF-BB) with FDA. Since inception, the VPF has produced and certified more than 68 GMP vectors for both internal and external clients, with the majority of these vectors currently being used in ongoing clinical trials.

DOI: 10.18609/cgti.2019.136

Q The rapid increase in viral vector production at CCHMC mirrors that across both academic and industrial spheres in recent times – can you share how you have dealt with the 'growing pains' in seeking to keep up with rising demand?

KS: The Translational Core group has expanded its staff to provide resources dedicated for raw materials intake, manufacturing campaign staging, scheduled cleaning of the non-critical manufacturing areas, facility and equipment maintenance and calibration and various other support operations to allow our highly trained staff to focus on manufacturing. CCHMC is evaluating options for increasing manufacturing capacity, including improving operational efficiency, shift pattern optimization and expanding operations to multiple shifts. We are also improving our production planning and scheduling process to balance efficiency versus flexibility in alignment with the customer's needs while maintaining high-level quality standards. For example, depending on the customers' individual product requirements, increasing manufacturing campaign size, from single batch to multiple batches, allows for reduced downtime of the manufacturing suites for changeover operations.

Q This particular special edition of CGTI focuses on raw materials for viral vector production – can you firstly outline your particular requirements in this regard?

KS: We strive to identify materials that are compendial grade (e.g., USP/EU) whenever possible. When sourcing materials, we examine the Certificate of Analysis to assure that critical material attributes (CMAs) will remain within specification at all stages of manufacturing. For example, raw material endotoxin levels must be carefully considered to assure that, where appropriate, concentrated finished product remains within release specification. We also source materials from established distributors, where possible, to minimize supply chain issues and have established standing deduct and hold orders for critical items to ensure availability. Lastly, we evaluate dual sourcing of critical materials and components as a means to hedge against interruption of supply.

Q What quality systems and processes do you have around your raw materials?

KS: Our raw materials identification, intake, approval and use are managed by Standard Operating Procedures. Following vendor selection of a specific component, it is assigned a raw material number by QA. A Raw Material (RM) specification is created by Operations according to the CMAs, then reviewed and approved by QA. Depending on the nature and criticality of the item, it is assigned a particular Quality Control level as part of the RM specification. This level assignment dictates whether a vendor on-site audit is necessary for supplier qualification or if a self-survey may be sufficient. The level assignment also determines the intake process and the level of QA review for approval. These reports and assessments are handled by our QA department in partnership with the TCL management.

In terms of raw material intake, quarantine and approval, these processes are managed by SOPs and executed by trained individuals.

Regarding the use of raw materials, everything is documented on the Bill of Materials in the BPR and verified by a second person, except for those items identified as support items. These entries are then checked by QA during executed document review.

Q What for you are the most challenging or concerning areas of raw materials procurement and management at the moment?

KS: Currently, one of our biggest challenges is warehousing and storage. As we are increasing our output, storage for refrigerated and ambient materials has become a constraint. As we move toward increasing our use of custom-built component systems which have larger footprints, we must adapt our warehousing and storage facilities accordingly. We are partnering with CCHMC support groups for practical short-term options within existing facility constraints.

Another challenge is procurement of certain materials that are in high demand. We leverage our relationships with certain vendors to provide off-site warehousing of select components. Specifically, we enter into deduct and hold agreements. Such arrangements serve not only as external warehousing, but also guarantee the availability of inventory.

"As we are increasing our output, storage for refrigerated and ambient materials has become a constraint."

Another challenge is on-site raw materials inventory and control, which is currently done via a manual process. We are in the midst of transitioning to an electronic inventory system that includes features such as inventory tracking and minimum inventory reorder levels.

DOI: 10.18609/cgti.2019.136

Q Can you go deeper on where specifically you feel innovation is currently missing in this area?

KS: Generally speaking, as the demand for clinical lots of LV and RV gets larger in terms of both individual lot size and the total number of lots required, the procurement and use of the raw materials becomes even more susceptible to procurement challenges and disruptions in supply chain management. This is primarily due to the nature of our current manufacturing process being viral vector manufacture via transient transfection of adherent cells grown in Fetal Bovine Serum (FBS)-supplemented media in multilevel Cell Stacks. This platform is limited in terms of the total number of cell stacks which can be manipulated and a handled within a single run and cannot be readily scaled-up, but rather only scaled-out. This necessitates additional equipment such as incubators to house the cell stacks, cleanroom suites, and personnel to perform the manufacturing, thereby increasing manufacturing costs overall.

Additionally, the use of FBS in the media poses several challenges, with one being zoonotic transmission of adventitious agents possibly present in the FBS as a contaminant. A second challenge is a reduction in herd size due to changing weather conditions brought about by drought or climate change impacting price and availability. And a third is societal pressure to eliminate or reduce the collection of fetal animal sera as social norms around this practice evolve and change.

While reiterative batch manufacturing of multiple smaller lots of the same product could be performed, this strategy is also not an ideal long-term solution: it does not address the challenges already described and is also subject to extended time required for completion of manufacturing as well as increased certification costs from the requirement to test and certify each individual batch made. For these reasons, the development of a manufacturing platform which uses suspension cells grown in larger bioreactors in serum-free defined media is needed.

One further area of major interest for us is the development of high-titer novel gene editing vectors (sgRNA/Cas9 orthologues driven by tissue-specific promoters) expressed in specific serotypes of AAV cassettes for *ex vivo* and/or *in vivo* applications – not least due to increased safety profile from the promotion of homologous recombination integration.

Q Finally, can you share your and CCHMC's chief priorities and goals relating to gene therapy for the remainder of 2019 and 2020?

KS: Specifically speaking for the Vector Production group, our top priority is to manufacture safe and high titer vectors for our customers who in turn, will administer them to their patients in need. Another priority is to strengthen our reputation as a consummate gene therapy group, able to offer a 'one-stop' experience, from manufacturing and product release testing to cell manipulation and integrated patient therapy. Our short-term goal is to increase our manufacturing capacity by at least two-fold in the near term, trying to release the bottleneck that is plaguing the manufacturing sector. Our second priority is to develop novel processes to increase effectiveness and enable our group to continue improving titers and safety controls in the production of challenging vectors.

AFFILIATION

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AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The author declares that they have no conflicts of interest.*

Funding declaration: *The author received no financial support for the research, authorship and/or publication of this article.*

Article source: Invited.

Interview conducted: Aug 27 2019; Publication date: Oct 17 2019.

DOI: 10.18609/cgti.2019.136

CELL & GENE THERAPY INSIGHTS

VECTOR CHANNEL:
RAW MATERIALS

INTERVIEW

Major bioprocessing challenges & considerations with gene therapies and *ex vivo* gene-edited cell therapy

ANDY RAMELMEIER currently serves as Executive Vice President and Chief Manufacturing and Quality Officer and is responsible for Technical Operations at Sangamo, including manufacturing, quality supply chain, and process and analytical development. Dr Ramelmeier has 25 years of experience in the biopharmaceutical industry, developing and transferring biological processes, designing and building manufacturing facilities, and directing contract manufacturers as well as internal manufacturing operations. Prior to joining Sangamo in January 2018, he served as Senior Vice President, Technical Operations at Portola Pharmaceuticals, Inc., where he was responsible for tech transfer, bulk and drug product manufacturing, technical support and supply chain of Portola's pipeline products. From 2006 to 2014, Dr Ramelmeier served as Vice President, Manufacturing, Process Sciences and Facilities at BioMarin, overseeing multiple commercial biologics products, clinical pipeline, and facilities in Novato, CA, and Shanbally, Ireland. Earlier in his career, he held roles of increasing responsibility at Johnson & Johnson and Merck. Prior to joining industry, Dr Ramelmeier conducted post-doctoral work in Germany. He received a BSc in Chemical Engineering from Johns Hopkins and his PhD in Chemical Engineering from the University of California, Berkeley.

Cell & Gene Therapy Insights 2019; 5(10), 1225–1227

DOI: 10.18609/cgti.2019.128

Q It has been a busy period for Sangamo: can you firstly bring us up to speed on the company's major current activities?

AR: Our focus this year has included progressing our Phase 1/2 gene therapy trial of SB-525 in hemophilia A, which is partnered

"...our next steps for HemA are to complete regulatory and manufacturing preparations for Phase 3."

with Pfizer, and our Phase 1/2 *ex vivo* gene-edited cell therapy trial of ST-400 in beta thalassemia, in partnership with Sanofi. We recently presented updated results of SB-525 at ISTH (more at [1]), announced that we have completed our enrollment commitment to Pfizer, and that manufacturing transfer from Sangamo to Pfizer has already been initiated. Further, we initiated our first clinical trial site for our Phase 1/2 gene therapy trial of ST-920 in Fabry disease. Lastly, we continue to sustain momentum toward the long-term goal with *in vivo* gene editing and gene regulation, while focusing on our gene and cell therapies in the clinic.

Q What can you share in terms of any specific challenges or considerations relating to raw materials that you currently encounter?

AR: There are unique considerations with regards to raw materials and supply chain in the relatively new and quickly evolving gene and cell therapy space. Demand for many raw materials is increasing at a rate that suppliers are not always able to match and inventory levels can fluctuate significantly. Additionally, the scheduling and consistency of apheresed human cell products can be quite variable, requiring a high-touch approach to every order. Raw materials suppliers are a mix of large and small players, each with their own strengths and weaknesses. The former are not always sensitive to the customized, low volume and high value nature of this space and the later do not always have the robust business processes or GMP controls of their larger counterparts. It's important to remember that both the companies and the CDMOs are learning as this field develops. And, in response to this uncertainty, the companies often want greater visibility and control over their supply chains. These are all elements that contribute to the dynamic ecosystem.

Q What is your approach to minimizing their impact?

AR: There are a number of ways these challenges can be addressed. Sangamo has partnered with strategically aligned CDMOs to complement our expertise. We look to companies like Brammer Bio, now Thermo Fisher Scientific, to contribute unique capabilities like late stage and commercial manufacturing for viral vector products, which will augment our new Phase 1/2 cGMP manufacturing facility that will be operational in 2020. This

DOI: 10.18609/cgti.2019.128

strategy provides us with our own capacity to flexibly supply our early clinical trials while complementing our dedicated capacity at Brammer Bio.

Q Finally, can you summarize Sangamo's key priorities and goals for the remainder of 2019 and 2020?

AR: Looking ahead, we are excited to complete our in-house manufacturing facility and for it to be operational in 2020. With regards to our programs, in gene therapy, our next steps for HemA are to complete regulatory and manufacturing preparations for Phase 3, which will be run by Pfizer. We also expect to dose the first patient in our Fabry disease gene therapy trial this year. In cell therapy for beta thalassemia, we expect to complete patient enrollment in the Phase 1/2 study this year and look forward to clinical results. In the longer-term, our partners at Kite-Gilead expect to initiate a clinical study of KITE-037, an allogeneic CD19 CAR-T, in 2020.

AFFILIATION

Andy Ramelmeier
Executive Vice President & Chief Manufacturing & Quality Officer, Sangamo

REFERENCE

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AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *R Andrew Ramelmeier is a current employee of Sangamo Therapeutics and a shareholder.*

Funding declaration: *The author received no financial support for the research, authorship and/or publication of this article.*

Article source: Invited.

Interview conducted: Sep 4 2019; Publication date: Oct 9 2019

COMMERCIAL INSIGHT: SEP 2019

Commercial insight: cell and gene therapy

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

CELL THERAPY

Mark Curtis. Financial Portfolio Manager, Emerging Technologies, Lonza AG, Switzerland

Certainly, the disruptive news this past month was the acquisition of Semma by Vertex in an all-cash deal worth $950 million. This deal puts Vertex head-to-head with Sigilon and Eli Lilly, which are also developing a beta cell therapy for Type 1 diabetes. While beta cells are generally produced using a similar mix of cytokines gated at different time points *in vitro*, the modes of transplant remain quite differentiated, including medical devices and encapsulation. On the financing front Beam, Nkarta, and Achilles were all in the news as well with their fundraising efforts. Beam has filed for a $100 million IPO, Nkarta closed a $114 million Series B round, and Achilles closed a $120 million Series B round.

GENE THERAPY

Richard Philipson. Chief Medical Officer, Trizell Ltd, UK

It's been a busy month for Rocket Pharmaceuticals, with the publication of data from its Phase 1/2 trial of first-generation RP-L102 for Fanconi Anemia in *Nature Medicine*, the treatment of the first patient in its Phase 1/2 registrational trial of RP-L201 for leukocyte adhesion deficiency-1, and the announcement of IMPD clearance of RP-L301 gene therapy for pyruvate kinase deficiency. The publication in *Nature Medicine* of data from its FANCOLEN-1 gene therapy trial in Fanconi Anemia (FA) are particularly noteworthy, showing effective engraftment of transduced hematopoietic stem cells without the use of

pre-conditioning – something that has not been achieved in previous similar trials in FA. Patients with the highest levels of gene marking showed an arrest of bone marrow failure progression, and there is no evidence so far of gene integration at potentially oncogenic sites. Elsewhere, Alnylam has released data showing that the benefits of Givosiran in acute hepatic porphyria continue during the open label extension period of its Phase 3 study; the treatment is currently under Priority Review by FDA and accelerated assessment by EMA.

CLINICAL/REGULATORY

ROCKET TO INITIATE GENE THERAPY TRIAL FOR PYRUVATE KINASE DEFICIENCY

Rocket Pharmaceuticals has announced that the Spanish Agency for Medicines and Health Products (AEMPS) has approved its Investigational Medicinal Product Dossier (IMPD) for RP-L301.

RP-L301 is Rocket's lentiviral vector (LVV)-based gene therapy developed for treating pyruvate kinase deficiency (PKD). The planned Phase 1 clinical trial will investigate the safety, tolerability and preliminary clinical efficacy of a single-administration of RP-L301 in PKD patients.

PKD is a rare red blood cell disorder and is caused by a mutation in the *PKLR* gene. *PKLR* gene codes for the pyruvate kinase enzyme, a key component of the red blood cell glycolytic pathway, mutation of which results in increased red cell destruction leading to severe anemia. Currently available treatments include splenectomy and red blood cell transfusions, which are associated with immune defects and chronic iron overload.

RP-L301 was shown to reduce anemia in preclinical models, where at least 20–30% of bone marrow progenitor cells were genetically corrected. The gene therapy was licensed from the Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT), Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER) and Instituto de Investigación Sanitaria Fundación Jiménez Díaz (IIS-FJD).

The trial will enroll a total of six adult and pediatric transfusion-dependent PKD patients in Europe and the USA. The trial will have three cohorts of patients: older pediatric, younger pediatric and adult age groups. Upon completion of an initial adult cohort, the company plans to move to the pediatric cohorts.

DOI: 10.18609/cgti.2019.148

T-CELL IMMUNOTHERAPY SHOWS PROMISE IN TREATING PATIENTS WITH MULTIPLE SCLEROSIS

Early results from a Phase 1 trial which is testing the safety and efficacy of an allogeneic T-cell immunotherapy show promise in treating multiple sclerosis. Results were presented at the annual meeting of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) at Stockholm last week.

Multiple sclerosis (MS) is an acquired autoimmune central nervous system disease, resulting in axon loss and myelin damage. Epstein–Barr virus (EBV) is thought to play an important role in the pathogenesis of MS. San Francisco-based Atara Biotherapeutics' T-cell therapy, AT188, is designed to target and attack EBV-infected B cells for treating MS.

The study is a multi-center, open-label, dose-escalation study evaluating the safety and efficacy of ATA188 in patients with progressive forms of MS. In this study, patients were treated across four dose cohorts (5×10^6, 1×10^7, 2×10^7 and 4×10^7 cells), with six patients per cohort.

The preliminary results presented were those from the first two cohorts and clinical outcomes of ATA188 were assessed at baseline and approximately 3, 6, and 12 months follow-up from initial dose using recognized scales for MS symptoms, function and disability.

Safety results showed that ATA188 was well tolerated in the patients with no evidence of cytokine release syndrome, graft versus host disease or dose-limiting toxicities.

Data showed that all six of the patients in the second cohort who received 1×10^7 cells showed at least a partial improvement in MS symptoms at 6 months, while four of the six patients on the smaller dose showed a clinical decline and it was maintained at 12 months.

The trial has just completed dosing of patients in the fourth and final dose escalation cohort. Additional efficacy and safety results from cohorts 3 and 4 are expected in 2020.

Professor Amit Bar-Or, Chief of MS Division, Department of Neurology, Perelman School of Medicine at the University of Pennsylvania commented:

"I am encouraged by the well tolerated safety profile as well as early findings of potential efficacy in the ongoing ATA188 Phase 1 study. The outcome classification using multiple clinically recognized MS scales is an innovative approach, and I look forward to advancing the study alongside my colleagues for progressive MS patients who have limited treatment options and where continual clinical decline is expected."

CAR-T THERAPY SHOWS PROMISE IN TREATING HEART DISEASE

Researchers at the University of Pennsylvania's Abramson Cancer Center have developed a CAR-T therapy to target cardiac fibrosis, a

type of scarring commonly associated with heart disease which blocks the proper functioning of the heart.

Upon injury, cardiac fibroblasts in the heart deposits excess extracellular matrix to remodel the myocardium, resulting in increased stiffness of the tissue. Excessive cardiac fibrosis contributes significantly to the progression of cardiac disease and heart failure. However, there are no therapies that could target cardiac fibrosis.

In the present study published in *Nature*, using gene expression analysis, researchers first identified a specific protein, fibroblast activation protein (FAP), associated with fibrosis scarring in mice.

They then engineered CAR-T cells to target FAP and transferred them into mice with cardiac fibrosis, first at one week and then at two. Data showed that, after a month, the mice showed a reduction in cardiac fibrosis and improvements in heart functioning. The study provides proof-of-principle for the development of immunotherapeutic drugs for the treatment of cardiac disease.

The team will now run additional studies to determine if FAP is the best target for CAR-T therapies in heart disease. In addition, they will also research the possibility of adding a switch to the CAR-T treatment they developed to minimize side effects.

BLUEBIRD BIO PROVIDES UPDATE ON ITS PHASE 2/3 STEM CELL-GENE THERAPY

bluebird bio has presented long-term follow-up results of its investigational Lenti-D™ gene therapy in patients with cerebral adrenoleukodystrophy (CALD) at the 13th European Pediatric Neurology Society (EPNS) Congress in Athens, Greece.

The Starbeam study (ALD-102) is investigating the efficacy and safety of Lenti-D in boys 17 years of age and under with CALD. Long-term follow-up of 32 patients showed that the 88% of patients treated were free of major functional disabilities (MFDs) at 2 years, and continued to remain MFD-free at up to 5 years of follow-up.

X-linked adrenoleukodystrophy, also known as Lorenzo's Oil disease, is caused by mutations in the *ABCD1* gene that encodes a protein of the peroxisomal membrane named ALDP. It affects one in every 21,000 male births worldwide. The cerebral form of the disease, CALD, is characterized by demyelination and neurodegeneration and is fatal.

The primary efficacy endpoint of the study is the proportion of patients who are alive and free of MFDs at month 24. MFDs are six severe disabilities commonly attributed to CALD and thought to have the most profound impact on a patient's ability to function independently. These include, loss of ability to communicate, cortical blindness, need for tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement.

Data showed that, 88% (N=15/17) continue to be alive and MFD-free in a long-term follow-up

DOI: 10.18609/cgti.2019.148

study. The 14 patients currently on study have less than 24 months of follow-up and have shown no evidence of MFDs. The longest follow-up of the additional 14 patients was 20.4 months. Three out of the 32 treated patients did not meet the primary efficacy endpoint; two patients withdrew from the study at investigator discretion, and one experienced rapid disease progression early on-study resulting in MFDs and death.

The safety profile of Lenti-D was consistent with myeloablative conditioning with busulfan and cyclophosphamide, the standard preparative regimen completed prior to HSCT. Three adverse events related to the gene therapy treatment were reported, including viral cystitis and vomiting and all resolved using standard measures.

Dr David Davidson, bluebird bio's CMO commented:

"With the longest follow-up from the Phase 2/3 Starbeam study now up to 5 years, the data show that all boys with CALD who were treated with Lenti-D and were free of major functional disabilities (MFDs) at 24 months continued to be MFD-free. Importantly, there were no reports of graft failure or treatment-related mortality, and adverse events were generally consistent with myeloablative conditioning," said. "These results support the potential of Lenti-D as a treatment for CALD, which we hope may become an option for the boys and their families affected by this devastating disease."

Long-term follow-up data from bluebird bio's Phase 2/3 clinical study of Lenti-D™ gene therapy for cerebral adrenoleukodystrophy (CALD) look impressive, with all boys who were treated with Lenti-D and were free of major functional disabilities (MFDs) at 24 months continuing to be MFD-free during the follow-up period. CALD is the most severe manifestation of adrenoleukodystrophy, a rare, X-linked, metabolic disorder. Approximately 35–40% of boys diagnosed with ALD will progress to CALD, typically between the ages of 3 and 12 years, which is characterized by a rapidly progressive neurologic decline leading to severe loss of neurologic function and death, in most untreated patients. Lenti-D™ gene therapy uses myeloablative conditioning and ex vivo transduction of the patient's own CD34+ stem cells prior to re-infusion, and therefore carries significant risks relating to the pre-gene therapy chemotherapy; nevertheless, it appears to compare favorably with the alternative of allogeneic stem cell transplantation, which also requires myeloablative conditioning but which carries additional risks of graft-versus-host disease. – Richard Philipson

AKOUOS DISCLOSES LEAD GENE THERAPY PROGRAM FOR HEARING LOSS

Precision genetic medicine company Akouos has disclosed details of its lead program, AK-OTOF, a gene therapy developed for restoring hearing in individuals with sensorineural hearing loss due to mutations in the otoferlin (OTOF) gene.

Sensorineural hearing loss is the most common form of hearing loss and one of the most common of all sensory disorders. It results from dysfunction or damage to sensory cells and/or nerve fibers of the inner ear.

Otoferlin, a protein which functions by enabling the sensory cells of the ear to release neurotransmitter in response to stimulation by sound to activate auditory neurons is crucial for hearing. Without functional otoferlin, auditory signals received by the ear cannot be transmitted to the brain. Mutations in the *OTOF* gene are reported to be a major cause of genetic hearing loss, affecting an estimated 200,000 individuals worldwide.

Akouos' gene therapy uses an AAV vector to deliver a healthy copy of the *OTOF* gene to cochlear hair cells. Following a single administration of the vector to the inner ear, the therapy is expected to restore long-term physiologic hearing in individuals with sensorineural hearing loss due to mutations in the *OTOF* gene.

Dr Manny Simons, CEO of Akouos commented:

"Together with leading scientists and clinicians around the world, we are working with urgency to advance AK-OTOF for individuals with sensorineural hearing loss due to mutations in the otoferlin gene. We have already begun interacting with the US Food and Drug Administration about our IND-enabling studies to support first-in-human clinical trials, and we will provide an update on commencement of our first clinical trial as soon as possible."

The disclosure by Akouos of its lead gene therapy program for patients with sensorineural hearing loss casts an important light on a somewhat neglected area of research. The AAV-based treatment, administered using a minimally invasive technique, will deliver the vector to the sensory epithelium of the inner ear, with the potential to restore hearing in individuals with sensorineural hearing loss due to mutations in the otoferlin gene. Over 60 mutations in otoferlin have been linked to hearing loss, with an estimated 200,000 patients potentially amenable to treatment worldwide; interestingly, a number of missense otoferlin mutations cause hearing defects but only at higher body temperature. As affected patients are profoundly deaf from birth, it will be interesting to see whether there is a 'window' for treatment in infancy, after which intervention is not effective. The company has a very long way to go from these preclinical beginnings, but nevertheless these are important initial steps for patients with sensorineural hearing loss. – Richard Pllilpson

CAR-T THERAPY TARGETING B CELL-ACTIVATING FACTOR COULD CURE BLOOD CANCERS

City of Hope scientists have developed a CAR-T cell therapy targeting the B cell-activating factor receptor on cancerous cells and the new therapy eradicated CD19-targeted therapy-resistant human leukemia and lymphoma cells in animal models.

DOI: 10.18609/cgti.2019.148

20 to 30% of cancers in leukemia and lymphoma patients who achieve remission after receiving CD19 CAR-T therapy are thought to relapse after a few years. The effectiveness of those CAR-T cells, which target the CD19 protein on cancerous B cells, starts to wear off and the cancer returns.

But the new study published in *Science Translational Medicine* provides hope for those patients who relapse after receiving the FDA-approved CD19-CAR T cell therapies, and another type of CD19-targeted immunotherapy, blinatumomab. The study developed a CAR-T cell therapy targeting BAFF-R which was tested in animal models.

Animal models with CD19 therapy-resistant human-tumors (including Burkitt, mantel cell, and other non-Hodgkin's lymphoma subtypes and acute lymphoblastic leukemia) were used in the study and the animals received BAFF-R CAR-T therapy. Significant tumor regression and prolonged survival were observed after treatment with these CAR-T cells. In animal models with human Burkitt lymphoma, BAFF-R CAR-T therapy achieved a cure (complete tumor regression with 100% long-term survival) after a single treatment.

In addition, the study also compared BAFF-R CAR-T therapy with CD 19 CAR-T therapy. Animal models which had a mixed population of CD19-positive and negative human tumors were administered with either CD19 CAR-T cell therapy or BAFF-R CAR-T cell therapy. Results showed that the BAFF-R CAR T cells were able to eradicate both tumor populations while treatment failed in those receiving CD19 CAR-T cells.

Tumor samples from patients who relapsed after receiving CD19-targeted immunotherapy (blinatumomab) were also investigated. The study demonstrated that BAFF-R CAR T cells were consistently active against these tumors, whereas CD19 CAR T cells had greatly diminished responses to each patient's relapse tumor compared to the pre-therapy samples.

City of Hope plans to open a clinical trial next year using the BAFF-R CAR T cell therapy for B cell leukemia and lymphoma patients who have relapsed after receiving CD19 CAR-T cell therapies or blinatumomab. The institute will manufacture the CAR-T cells at its own facility, the Cellular Therapy Production Center. City of Hope licensed the BAFF-R CAR-T to Pepromene Bio Inc.

ALNYLAM'S GIVOSIRAN SHOWS POSITIVE RESPONSE

Alnylam, a Cambridge, MA-based biopharmaceutical company specialized in developing RNA interference (RNAi)-based therapeutics has provided updates on its two ongoing clinical trials of Givosiran. Data was presented at the 2019 International Congress on Porphyrins and Porphyrias (ICPP), in early September in Milan, Italy.

Givosiran is an investigational subcutaneously-administered RNAi

therapeutic targeting aminolevulinic acid synthase 1 (ALAS1). Monthly administration of givosiran was shown to have the potential to significantly lower induced liver ALAS1 levels in a sustained manner and thereby decrease neurotoxic heme intermediates, aminolevulinic acid (ALA) and porphobilinogen (PBG), towards normal levels. By reducing accumulation of these intermediates, givosiran has the potential to prevent or reduce the occurrence of severe and life-threatening attacks, control chronic symptoms, and decrease the burden of the disease. The safety and efficacy of givosiran were evaluated in the Envision Phase 3 trial with positive results.

Presentations included additional results from the ENVISION Phase 3 study and the Phase 1/2 open-label extension (OLE) study of givosiran, an investigational RNAi therapeutic targeting ALAS1 in development for the treatment of acute hepatic porphyria (AHP).

Envision Phase 3 OLE study: 93 patients from the Envision Phase 3 study of givosiran were rolled over into the OLE phase of the study. Interim data showed that porphyria attack reductions observed in the Envision Phase 3 study were sustained with continued dosing in the OLE phase of the study.

ALA, an intermediate responsible for causing both porphyria attacks and ongoing symptoms in between attacks, was also reduced with continued dosing. Rapid and sustained lowering of attack rates and ALA levels was also observed in placebo patients who crossed over after the 6-month double-blind phase of the Phase 3 study to receive Givosiran in the OLE phase of the study. Regarding the safety of Givosiran, the safety profile in the OLE phase remained consistent with the profile observed in the double-blind phase of the Envision study.

Updated Phase 1/2 OLE Results: 16 patients in the Phase 1/2 study continued in the OLE extension study and Givosiran treatment of up to 30 months demonstrated sustained or enhanced clinical activity with an over 90% decrease in mean porphyria attack rate relative to baseline with continued dosing. 5/12 patients (42%) who received givosiran during the Phase 1 study and continued with givosiran dosing in the OLE study and 2/4 patients (50% had been in the placebo arm of the Phase 1 study and crossed over to givosiran treatment in the OLE study achieved an attack rate of zero for a mean of 18.1 and 24.9 months, respectively.

ROCKET'S STEM CELL GENE THERAPY HOLDS PROMISE IN TREATING FANCONI ANEMIA

Long-term follow-up data published from Rocket's ongoing Phase 1/2 trial of RP-L102 has shown the potential of lentiviral vector-based gene therapy in treating Fanconi Anemia (FA). The study was published in the journal *Nature Medicine*.

The Phase 1/2 trial, FANCONI-I, is designed to assess the

DOI: 10.18609/cgti.2019.148

therapeutic safety and preliminary efficacy of a hematopoietic cell-based gene therapy consisting of autologous CD34+ enriched cells transduced with a lentiviral vector carrying the *FANC-A* gene in patients with Fanconi anemia subtype A.

The data included in the manuscript were obtained from four pediatric patients (ages 3–6 years) who received RP-L102 utilizing fresh or cryopreserved CD34+ cells that were collected and transduced. Follow-up for each of the initial four patients was 18–30 months from administration of RP-L102. Data demonstrated progressive increase in engraftment in peripheral blood leukocytes and in the bone marrow following administration of RP-L102 without the use of conditioning.

Data from our first trial of RP-L102 demonstrate increasing levels of bone marrow engraftment, leading to stabilization and restored bone marrow function. These data highlight the natural selective advantage that uniquely exists in FA for gene corrected stem cells over diseased stem cells, which potentially obviates the need for conditioning," said Jonathan Schwartz, MD, Chief Medical Officer and Senior Vice President of Rocket. "At the end of the year, we will have a first look at initial data from our Phase 1 trial of 'Process B' RP-L102, which utilizes fresh cells and incorporates a modified stem cell enrichment process, transduction enhancers, and commercial-grade vector and final drug product. We are also excited by the prospect of starting our global registrational trial incorporating recent alignment on endpoints from both the US Food and Drug Administration and European Medicines Agency."

Progressive increases in the total number of corrected leukocytes were observed shortly after the initial administration of RP-L102 in all treated patients.

Favorable safety profile with no serious adverse events associated with infusion of the investigational product in these initial four patients.

In additional news this month, Rocket has announced that it has dosed its first patient in the Phase 1/2 clinical trial of RP-L201, a lentiviral vector-based gene therapy developed for treating Leukocyte Adhesion Deficiency-I (LAD-I).

LAD-I is a rare, autosomal recessive pediatric disease caused by a mutation of the *ITGB2* gene that encodes for the Beta-2 Integrin component CD18. Absence of CD18 leads to decreased leukocyte adhesion and extravasation from blood vessels to combat infections. As a result, children with severe LAD-I are often affected immediately after birth. Without a successful bone marrow transplant, mortality in patients with severe LAD-I is 60–75% prior to the age of 2 and survival beyond the age of 5 is exceedingly rare.

RP-L201 will evaluate the safety and efficacy of the infusion of autologous hematopoietic stem cells transduced with a lentiviral vector encoding the *ITGB2* gene. In November last year the FDA had accepted its IND application and earlier this year The California Institute for Regenerative Medicine (CIRM) had awarded the company with a $6.5mm CLIN2 grant award to advance the clinical trial. Proceeds from the grant will be used to fund clinical trial costs as well as manufacture drug product for the Phase 1/2 trial.

LICENSING AGREEMENTS & COLLABORATIONS

OCUGEN MERGES WITH HISTOGENICS TO DEVELOP OCULAR GENE THERAPIES AND BIOTHERAPEUTICS

Ocugen, a clinical stage biopharmaceutical company developing biotherapeutics for rare eye diseases, has announced the completion of its merger with Histogenics Corporation, and the change of the combined company's name to "Ocugen, Inc."

The executive team of Ocugen has become the executive team of the combined company, and is led by Dr Shankar Musunuri, Ocugen's CEO and Co-Founder.

Ocugen's pipeline includes OCU300, an orphan drug candidate for ocular graft versus host disease in Phase 3 clinical trials, a modifier gene therapy platform, and OCU400, a gene therapy product with two distinct orphan drug designations for patients with inherited retinal diseases, and retinal disease programs in wet age-related macular degeneration and retinitis pigmentosa.

Immediately prior to the merger, Ocugen completed a private placement financing of approximately $25 million under the terms of the securities purchase agreement previously announced in August 2019. Additionally, immediately prior to the merger, Histogenics effected a reverse stock split of its common stock at a ratio of 1-for-60. As a result of the merger, after taking into account the reverse stock split, stockholders of Ocugen prior to the merger received shares of common stock of the combined company at an exchange rate of 0.4794.

Following the merge, Ocugen, Inc. has entered into a strategic partnership with CanSino Biologics on Ocugen's gene therapy pipeline product candidates for inherited retinal diseases, which are currently in development with Schepens Eye Research Institute of Massachusetts Eye and Ear, an affiliate of Harvard Medical School.

Under the terms of the collaboration, CanSinoBIO will provide all CMC development and clinical supplies for developing OCU400, Ocugen's first gene therapy product candidate. CanSinoBIO maintains the option to support commercial manufacturing for Ocugen. The agreement also provides commercialization rights to CanSinoBIO in Greater China.

OCU400 uses a modifier gene therapy platform which was initially developed by Dr Neena Haider at the Schepens Eye Research Institute of Massachusetts Eye and Ear. Ocugen later obtained an exclusive worldwide license to develop and commercialize ophthalmology products based on this platform.

DOI: 10.18609/cgti.2019.148

The platform uses an AAV vector to deliver a functional copy of the nuclear hormone receptor gene *NR2E3* to target cells in the retina. *NR2E3* being a potent modifier gene in the retina is believed to help reset retinal homeostasis, stabilizing cells and potentially rescuing photoreceptors from degeneration. The US FDA has granted two different orphan drug designations for OCU400; for treating *NR3E3* mutation-associated retinal degeneration and for treating *CEP290* mutation-associated retinal disease.

Dr Xuefeng Yu, CEO of CanSinoBIO commented:

"We are delighted to partner with Ocugen as they advance their portfolio of AAV-based gene retinal diseases. Our expertise in viral vector platform technologies, product development and manufacturing capabilities will play critical roles to advance OCU400 to the clinic and ultimately to serve patients in desperate need for retinal disease therapies."

VERTEX TO ACQUIRE SEMMA THERAPEUTICS FOR $950 MILLION

Vertex Pharmaceuticals Incorporated has announced that the company has entered into a definitive agreement under which Vertex will acquire Semma Therapeutics, a privately held biotechnology company developing stem cell-derived human islets as a potentially curative treatment for Type 1 diabetes, for $950 million.

Semma Therapeutics uses a differentiated approach to treat Type 1 diabetes, a serious disease affecting over one million people in the USA alone. Semma has made two major scientific advances: the ability to produce large quantities of functional human pancreatic beta cells that restore insulin secretion and ameliorate hypoglycemia in animal models and a novel device that encapsulates and protects these cells from the immune system, enabling durable implantation without the need for ongoing immunosuppressive therapy.

Most recently, together with Harvard University researchers, the company developed a strategy to differentiate pluripotent stem cells into insulin producing-pancreatic beta cells. The research was led by Prof. Doug Melton who for the first time in 2014 showed that stem cells could be converted to functional beta cells.

Semma Therapeutics was founded in 2014, raising $44 million in a series A funding. In 2017, it partnered with Novartis and other investors to raise $114 million in series B financing to advance therapies for diabetes.

Semma will now work to determine whether a mixture consisting of 80% beta cells will be sufficient for treating people with diabetes. In addition, identifying the optimal cell mixture will also be a priority.

Dr Jeffrey Leiden, Chairman, President and CEO of Vertex commented:

"This acquisition aligns perfectly with our strategy of investing in scientific innovation to create transformative medicines for people with serious diseases in specialty markets. We are excited to work with the talented scientists at Semma to build on their

significant progress toward providing effective and potentially curative cell therapy options for people living with Type 1 diabetes. We see a substantial opportunity to transform the treatment paradigm for Type 1 diabetes, a specialty disease cared for by endocrinologists, both by advancing the development and manufacturing of the cells themselves, as well as through the highly innovative cell/device combination."

ENTOS PHARMACEUTICALS ENTERS INTO R&D AND COLLABORATION AGREEMENT

Entos Pharmaceuticals, a healthcare biotechnology company focused on developing next generation nucleic acid-based therapies using their Fusogenix drug delivery platform, has entered into a research, development and collaboration agreement with a clinical stage biopharmaceutical company developing novel biotherapeutics for autoimmune and inflammatory diseases.

Under the terms of the agreement, the undisclosed partner has the option to exclusively license candidates developed under the agreement from Entos for further development and commercialization. In return, Entos will receive research funding and is eligible for option exercise fees, research, development, regulatory, and sales milestone payments of up to US$109 million. In addition, the partner will pay Entos undisclosed royalties on sales of products resulting from the collaboration.

Deloitte Corporate Finance Inc. acted as exclusive financial advisor and Norton Rose Fulbright Canada LLP acted as legal counsel to Entos on the transaction.

FINANCE

ACHILLES RAISES £100 MILLION IN SERIES B FINANCING

Achilles Therapeutics, an UK-based biopharmaceutical company developing personalized immunotherapies for cancer has raised £100 million in Series B financing.

Achilles will use the funds to begin two human proof-of-concept studies using its personalized T cell immunotherapy to treat non-small cell lung cancer and melanoma. The trials are expected to begin this year. The financing will also support the company to build its manufacturing capabilities

DOI: 10.18609/cgti.2019.148

and extend its growing product pipeline.

The company has thus far raised approximately £114 million, including a £13.2 million in Series A financing in 2016.

Achilles is developing T cell therapies targeting clonal neoantigens that are specific to each individual's cancer cells. These unique protein markers are expressed on the surface of every cancer cell, but not on healthy cells. Using DNA sequencing data together with bioinformatics technology, the company identifies clonal neoantigens specific to each patient and develops personalized T cell immunotherapy. Because the therapy targets only cancer cells, the treatment is believed to leave the healthy tissues intact.

Achilles Therapeutics was launched in 2016 by Syncona Ltd, the lead investor and the CRT Pioneer Fund, UCL Technology Fund, Cancer Research Technology, UCL Business (UCLB) and the Francis Crick Institute.

The finance round was led by Syncona along with RA Capital Management and new investors including Forbion, Invus, Perceptive Advisors and Redmile Group.

Achilles is the latest player in the growing field of using personalized cancer neoantigens to target solid tumor cancers. Other notable companies including Neon Therapeutics and PACT Pharma. Achilles differentiates itself by identifying clonal neoantigens, rather than sub-clonal mutations, which are mutations that are found across the entire population of cancer cells. It now has the money to put its platform to the test in human proof-of-concept studies. – Mark Curtis

NKARTA SECURES $114 MILLION IN SERIES B FINANCING

NKarta Therapeutics has raised $114 million in Series B Financing to advance its natural killer (NK) cell therapy portfolio and initiate clinical trials.

Although currently cell therapies for cancer has centered around T cells, for instance, CAR-T cells, Nkarta believes NK cells offer advantages that T cells lack. Since NK cells are part of the innate immune system, they can identify and hit a broader range of targets presented on tumor cells.

In addition, CAR-T therapy shows limited success in blood cancers and are associated with unwanted side effects such as cytokine release syndrome. NKarta believes NK cell therapy, could overcome these hurdles.

Proceeds from the finances will be used to conduct clinical programs in blood cancers and solid tumors for Nkarta's allogeneic NK cell therapy. The treatment, NKX101, targets a cell surface receptor called NKG2D found on various immune cells. It will also support IND-enabling and clinical studies of its CAR-NK program targeting CD19 in B-cell malignancies.

The company will also finish building a GMP manufacturing

site in South San Francisco that will supply treatments for its early-stage studies.

Nkarta CEO Paul Hastings commented:

"Since the company's founding, we have worked to bring our potentially transformative, engineered and off-the-shelf NK cell therapies to patients. With multiple INDs expected in the next year for an array of hematologic and solid tumors, now is the time to fund the company for its next stage of growth."

Samsara BioCapital led the round, with Amgen Ventures, Deerfield, Life Science Partners, Logos Capital, RA Capital Management and its existing backers NEA Ventures, Novo Holdings and SR One joining in.

With a healthy injection of cash, Nkarta is poised to make headway into the clinic with a series of allogeneic natural killer (NK) cell therapies for both blood and solid tumor cancers. While the T cell landscape has become increasingly crowded, there remain a relatively limited number of companies pursuing NK cells. Nkarta's most notable competitor is NantKwest. Nkarta also recently announced it will build-out its own manufacturing facility. – Mark Curtis

BASE EDITING FIRM BEAM AIMS FOR $100 MILLION IPO

Nearly 7 months after raising $135 million in Series B Financing, Beam Therapeutics has filed an S-1 filing with the Securities and Exchange Commission to raise up to $100 million in its Nasdaq IPO.

Headquartered in Cambridge, MA, Beam Therapeutics is focused on developing precision genetic medicines through base editing. The company was launched last year and Prof. David Liu of Harvard University, inventor of the base editing technologies is a cofounder of the company. He was also a cofounder of one of the original CRISPR companies, Editas Medicine, along with Feng Zhang, an inventor of CRISPR gene editing at Broad Institute, and Keith Joung, a gene editing researcher at Massachusetts General Hospital and Harvard Medical School. Zhang and Joung are cofounders of Beam Therapeutics too.

The new funding will be used for discovery-stage research and push the company's three delivery methods – electroporation, liquid nanoparticles and adeno-associated viruses – through preclinical proof of concept.

Currently one of the best available genome-editing tools is the CRISPR-Cas9 system, but it results in imprecise correction of mutations due to double strand break in DNA. The base editing platform developed in Liu's laboratory can overcome this by correcting a single base at a time, without causing double-stranded breaks. Liu has developed technologies that could convert all the 4 bases- C to T, T to C, G to A and A to G.

According to a database, 33000 single point mutations are associated with disease and Beam's novel approach to base editing could

DOI: 10.18609/cgti.2019.148

correct 63% of them in principle. Beam now has 10 active programs underway.

Beam's most advanced programs are in blood disorders and oncology, with treatments for beta thalassemia, sickle cell disease, acute myeloid leukemia and acute lymphoblastic leukemia all at the lead-optimization stage. It also has programs in liver disease and disorders of the eye and central nervous system in the works.

SANGAMO APPOINTS BETTINA COCKROFT AS ITS NEW CMO

Sangamo Therapeutics has appointed Dr Bettina M Cockroft as its new CMO and Senior Vice President. In her new role, Dr Cockroft will oversee all clinical development activities and operations and will report to Dr Adrian Woolfson, the Executive Vice President of Research and Development.

Dr Cockroft has over 20 years of experience in clinical development and has worked across multiple therapeutic areas in several countries. Prior to joining Sangamo, she was a member of the senior leadership team at Cytokinetics, Inc., where she was responsible for clinical development of fast skeletal muscle troponin activators in diseases such as Amyotrophic Lateral Sclerosis and Spinal Muscular Atrophy. Before that, Dr Cockroft held various leadership roles at Auris Medical AG, Merck Serono S.A., Novartis Consumer Health and Menarini Ricerche.

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