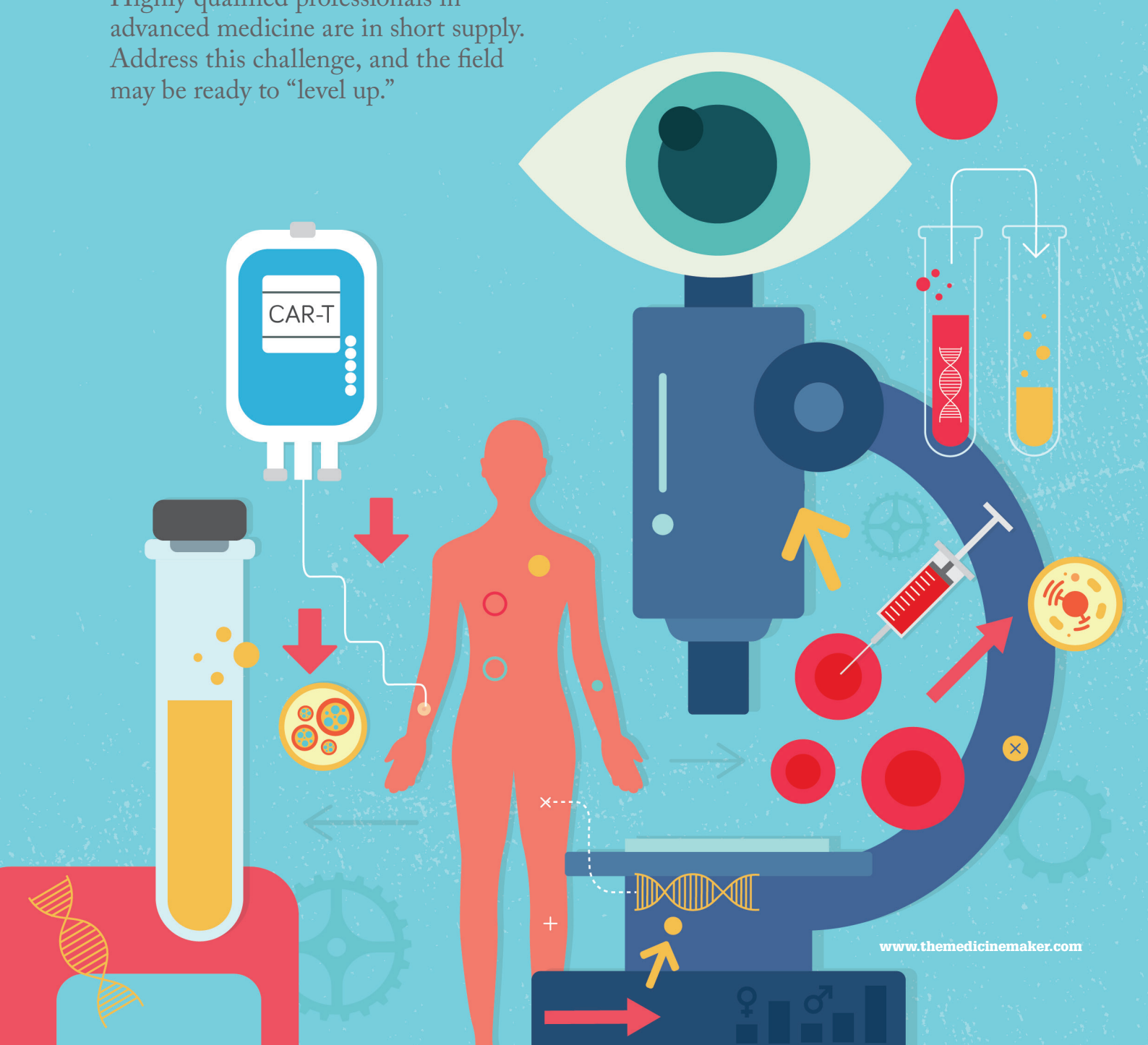
NEXT LEVEL
Cell and Gene Therapy

Highly qualified professionals in advanced medicine are in short supply. Address this challenge, and the field may be ready to "level up."



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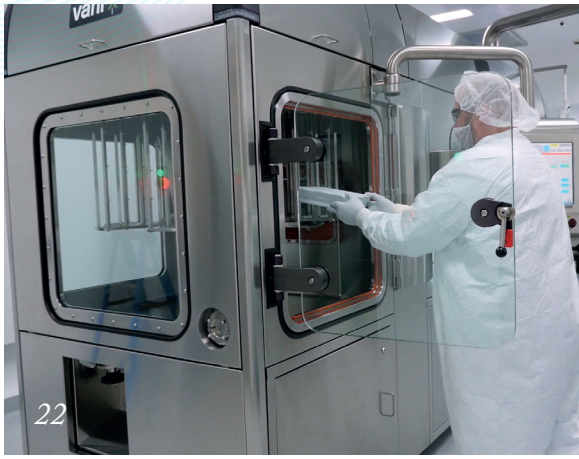
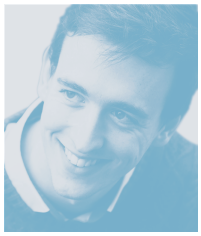


A Conference Season's Greeting

Glad tidings of progress and confidence this (conference) season! But let's not dismiss the emerging skills challenge as "humbug."



It is the holiday season! But many in the industry will not be preoccupied with full stockings at this time of year, but rather full schedules – with many conferences to attend in the weeks leading up to Christmas. Sitting in various cell and gene therapy talks and roundtable discussions in recent months, my focus has been to glean an overview of the current state of the field.

At the Cell and Gene Therapy Manufacturing conference in Twickenham, UK, there were several interesting case studies demonstrating how processes can be effectively scaled out – from late-stage solid tumor clinical trials to lentiviral vectors. Pernille Linnert Jensen from Novo Nordisk, also offered an example of how to transition from large molecule (antibodies in this case) to stem cell manufacturing. For Pernille, training and education was crucial to the endeavor.

The challenges raised in last year's cell and gene therapy supplement (namely, manufacturing, standardization, logistics and pricing) remained a central theme in Twickenham, and were also a hot topic of discussion at this year's Pharma Integrates conference in London. However, my sense is that strong progress is being made and optimism pervades. For example, advanced medicines were frequently compared to the early days of the monoclonal antibody (mAb) field – one delegate asked me consider the myriad challenges overcome by the mAb industry to grow to its current size.

But, excuse my humbug, this difficulty in finding and retaining staff arose in many talks. Matthew Cobb of Miltenyi Biotech, for example, said that this could be a major pinch point for industry over the next two years. A recent report from the UK's Cell and Gene Therapy Catapult (we interview their CEO, Keith Thompson, on page 24) supports this claim. They found that of the 70 UK companies in the field that they interviewed, 83 percent were concerned that recruitment and/or retention of skilled individuals will be an issue for growth (1). We delve into this topic on (page 17), featuring experts from the International Society for Cell and Gene Therapy (ISCT).

However, on the whole, I'm pleased to report good tidings for the cell and gene therapy field. The skills shortage is arguably another "good" problem to have – the natural result of the industry's meteoric rise and the inability of institutions to keep up.

James Strachan
Deputy Editor

Reference

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In My View

In this opinion section, experts from across the world share a single strongly held view or key idea.

Breaking the Bottleneck of Affordability

Could the daunting costs of cell and gene therapies be reduced if research hospitals developed and processed therapies in house to treat their patients?

By Vered Caplan, Chief Executive Officer, Orgenesis Inc., USA

Advances in cell and gene therapies offer the potential to transform medicine. But current pricing structures are unsustainable – and they are severely limiting the introduction of new, potentially life-changing or life-saving therapeutics.

Though research and development in this sector is moving at an impressive rate, the complexities of scale for growing, sourcing and transporting cells and other components of cell and gene therapies are evident – and this is clearly feeding into costs.

Part of the solution to the cost conundrum when treating patients is point of care automation – particularly, closed automated systems for processing cell therapies. The introduction of closed systems allows the services to be delivered from a less expensive (lower grade) clean space, requiring fewer and lower-skilled workers. Equally, these developments mean that multiple systems can co-exist in a single area. Once you have real-time quality-control testing at each different stage in the process, for instance, in taking blood delivery, isolating, propagating, testing, and harvesting, the time to deliver a product back to a patient can be reduced.

However, processing and technology are only one part of the problem. The business structure for developing and commercializing cell and gene therapies also increases costs (potentially unnecessarily in my view). The typical lifecycle of a new therapy begins with a research institute or group producing a potential new treatment. Often, in this sector, this research is being undertaken at a research-intensive hospital. The new therapy is then developed in house for as long as is feasible, before ultimately being either spun-out into a traditional biotech company. Further development – fuelled by intensive fundraising – is then followed by recruiting the services of a commercial CMO. This process is costly at all levels and erodes the core value of the treatment as ownership is diluted as development progresses.

But what if research hospitals could keep things in house, and fully develop and process the products themselves – even taking products all the way to the patient?

Typically, hospitals either don't have the capabilities or the expertise to work to the GMP standards required for cell and gene therapies, which are highly regulated very specialized. In some cases, where hospitals have facilities, they are simply not able to make use of them as they do not have staff with the required know-how. Notably, this latter point is certainly not a criticism of the hospitals but a reflection on the technically challenging nature of the process.

An exciting alternative would be to build a network of hospitals around the world that are equipped to develop and process cell and gene therapies. And that is something Orgenesis is creating.

The proposed consortium would evolve

a network or a partnership model, where external experts would be brought in to set up and run a series of hospital-based GMP facilities on behalf of the host hospitals. The model gives incoming experts direct access to onsite researchers, where they will see the new and innovative research programmes that are ongoing and be in a position to assist in turning these treatments for direct patient care at the hospital site.

If the expertise was derived from a single external source – ideally an established specialist in the field with the capacity to take on such a wide-reaching project – it could become the overarching "management company." This entity would bring together all the capabilities of the network hospitals, streamlining the whole program and providing a commercial window into the services for external clients, as well as for the research and development groups within the consortium.

The concept is akin to the Uber model. Uber gives drivers the technology (a standardized app) that allows them to work as a taxi driver, using their own car. Here, the specialist entity would provide the technology (licenses for closed automation systems and streamlined, specialist processing services and treatment therapies) to hospitals so that they can develop and commercialize advanced therapies. The key objective is to ensure that the same high standards of processing are maintained throughout the network – using harmonized, automated systems for patient treatment and care throughout would be key to success in this regard.

"An exciting alternative would be to build a network of hospitals around the world that are equipped to develop and process cell and gene therapies."

Hospitals would clearly benefit from this model by retaining ownership and the value of the product. And as that value is retained, rather than being diluted through the development and processing methods, overall costs will be lower, and therapies should be cheaper.

I also believe that large biotech and pharma companies would benefit from this model. If a hospital were to approach such a company and ask whether they would like to take on the marketing license for a new therapy that the hospital is processing, to a high standard, as part of an established network, I'm sure they would be delighted.

Overall, I believe this model, if integrated with modern, automated, closed systems at the point of care for treating patients, has the potential to reduce the currently overbearing costs associated with taking cell and gene therapies through to market.

Unprecedented Growth – and Challenges

Gene therapy is a rapidly growing area in healthcare but, now the promise has been shown, we must focus on improving the manufacturing process and reducing costs

By Philip W. Wills, Chief Commercial Officer at Catalent Paragon Gene Therapy

Since the first market approvals of gene therapy products in 2017, growth in the sector has accelerated. There is now an abundance of gene therapy-related activity, a clinical pipeline in a high growth phase, and an influx of venture capital funding for gene therapy companies. Frost & Sullivan recently reported that, "There are more than 400 cell and gene therapies in preclinical to phase 3 development" (1). In 2018, there was a 27 percent year-on-year increase in the number of clinical trials involving gene therapies,

"The growth in the field has naturally led to a dramatic increase in demand for viral vector manufacturing."

and the FDA's Commissioner of Food and Drugs predicted that by 2020 the agency will be receiving more than 200 investigational new drug applications per year, and approving 10 to 20 cell and gene therapy products every year by 2025 (2). The regulatory landscape for gene therapy products is not all that different from standard biologics, with the exception that they mostly target rare, orphan diseases. The FDA has proven to be very collaborative for products with this focus, and often designates products for priority review and accelerated approval because of unmet needs.

The growth in the field has naturally led to a dramatic increase in demand for viral vector manufacturing. A number of companies have risen to meet this need, offering access to experts and assets for the development and manufacturing of products. Because of the relatively low volumes required to fulfil demand, outsourcing the manufacturing and downstream processing stages has become a common strategy for innovators rather than spending time and money building a dedicated in-house facility. As gene therapy is a new and relatively undefined means of treatment, compared with other therapeutic modalities, chemistry, manufacture and control activities are "gating factors." There are challenges with dosing, undefined analytics, and unanswered questions about long-term traceability, which all contribute to the gene therapy regulatory landscape. Trying to build expertise to cover all these bases from scratch can prove very challenging.

Of the viral vector types open to gene therapy innovators, adeno-associated virus (AAV) vectors have proven to be a safe vehicle for getting genetic material into cells. AAV genetic material does not incorporate into the host genome, and maintains long-term expression (10-30 years) due to its episomal nature. Though its manufacturing is rather complex and challenging (compared with traditional monoclonal antibodies) – scalability challenges and non-standard expression systems being just two of the complications – it is still simpler than many other viral vector types and produces higher yields. AAV manufacturing also allows for sterile filtration so a fully closed process is not required, which increases the safety profile and decreases manufacturing complexities. Additionally, AAV has multiple serotypes, and both wild type and engineered serotypes have been successfully used as vectors with a preference for the tissue type being targeted.

It looks as though AAV will continue to dominate the market, as other vectors, such as traditional adenovirus or lentivirus, have not shown as much promise. Critically, however, the field will need to evolve; reaching higher production yields is currently the major challenge associated with manufacturing. Consumables and raw materials used in manufacturing currently make up a high percentage of the cost of gene therapy production, so decreasing these is pivotal. When monoclonal antibodies were in their infancy, there was a point in the development at which yields suddenly increased logarithmically; with viral vectors, we are already seeing incremental improvements, but it feels like a similar step-change increase is some way off. Right now, even a 30 percent increase in yield is counter-balanced with 30 percent increase in demand.

"As gene therapy is a new and relatively undefined means of treatment, compared with other therapeutic modalities, chemistry, manufacture and control activities are 'gating factors.'"

Overall, the cost of gene therapies remains high for two main reasons: one, they are curative; and two, the cost must compensate companies for development and manufacturing costs. With such a high cost of goods, bringing down the price of the final treatment is a huge challenge facing the industry. But as processes and platforms are optimized with new disruptive technologies (including more stable producing cell lines over today's plasmids), manufacturing costs will be reduced, which will allow the gene therapies of the future to be even more widely embraced.

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Going Viral

The gene therapy sector is booming, but can the industry address all the teething problems?

By Gabriel Festoc, Chairman of the Executive Board at Polyplus-transfection

Like mAbs before them, gene therapies have grown in popularity for their potential to treat life-threatening and rare diseases. And with a market estimated to grow to $11.96 billion by 2025 (1), it's clear that stakeholders believe these therapies are worth investing in.

Though the rapid growth of the sector has been positive for biotechs and patients alike, it doesn't come without challenges. Increased demand for these products is reshaping the manufacturing landscape. From Pfizer's recent $500 million cash injection into one of its facilities in North Carolina (2) to Fujifilm Diosynth's plans for the expansion of its upstream, downstream, and analytical development technologies for gene therapies (3), there is a ubiquitous awareness that manufacturing practices will have to adapt to appropriately handle the growing field.

A major (and valid) concern for the budding sector is the dissonance between the growing need for high production capacity of viral particles and the current manufacturing capacities. The manufacturing bottlenecks are two-fold: increasing upstream productivity and overcoming downstream purification challenges in order to increase yield recovery. Increase of upstream productivity is dependent on the transfection of one or more plasmids into host mammalian cells like HEK-293 cells and derivatives, a process that puts a significant amount of strain on the manufacturing process, resulting in struggles to produce them at scale, within designated time frames and with the degree of reproducibility needed to satisfy the expectations of regulators.

An additional challenge for manufacturers is the fact that starting raw materials for the production of virus particles (plasmid DNA and transfection reagent) must be manufactured in compliance with GMP guidelines for their use as advanced therapy medicinal products (ATMP). There are few companies providing cGMP grade plasmid DNA and there were none providing cGMP grade transfection reagent until end of last year with the launch of PEIpro-GMP by Polyplus-transfection. Moreover, switching suppliers (from non-cGMP to cGMP grade reagents) often involves changing technologies, which can be expensive and time consuming – extending development timelines by months, potentially years.

But new technology is emerging to help the field progress. For example, from a transfection point of view, we are focusing on new transfection technology to improve product titers and drive down cost.

Though the issues mentioned are a cause for concern, it is important to remember that the gene therapy field is young and the challenges it faces, in my opinion, aren't insurmountable. As a more seasoned workforce develops, so too will the technology to support it. The recent wave of investment in facilities, capabilities and staff has been a positive step forward, but whether it is happening fast enough to address this widely felt problem is another question.

"New technology is emerging to help the field progress. For example, from a transfection point of view, we are focusing on new transfection technology to improve product titers and drive down cost."

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The TCRs Are Coming

It's time to fine-tune the way we target solid tumors

By Miguel Forte, Chief Executive Officer, Zelluna Immunotherapy, and Chief Commercialization Officer and Chair of the Commercialization Committee at the International Society for Cell and Gene Therapy (ISCT)

In 2017, the industry shook with excitement at the news that the first CAR-T therapy, Kymriah, was approved for use by the FDA. The industry's elation didn't quieten quickly, as the approval of Yescarta came hot on its tails. But with time and room to think about the next step of the industry's immunotherapy journey, many are beginning to consider how we can fine-tune treatments to better target solid tumors.

The recent clinical success seen in the CAR-T therapy space exemplifies the leaps in progress being made in the field, but such success has only been seen in a small number of tumor types. The selectivity of CAR-Ts for both tumor and normal cells also raises questions about whether they can (or will) adequately address cancer types beyond hematological malignancies, where tumor penetration is required.

Like criminals, different types of cancer have different levels of sophistication. The low level criminal is easy to target and tackle, but the organized criminal can hide in plain sight and evade all attempts to stop them. The same can be said of law enforcement personnel. For the inexperienced officer of the law, catching certain offenders will be easier than others. Similarly, CAR-Ts are best suited to targeting cells in suspension rather than solid tumors, which are known for their hostility. Their inability to penetrate cells means we can't get significant results in using CAR-Ts against solid tumor types. Certainly, research is improving the functionality of CAR-Ts, but there is still much to be done before they can be used to combat a wide range of cancers.

But CAR-Ts aren't going anywhere soon – from industry to academia, people are vested in developing CAR-T based therapies to address a broader range of needs. Dual CAR-Ts and armored CAR-Ts are only some of the latest offerings coming out of the oncology space. But TCRs (T-cell receptors), unlike CAR-Ts, can recognize tumor-specific proteins within cells and are also able to target a wider range of antigens than their counterparts. Their potency is reliant on their interaction with peptide-major histocompatibility complexes (p-MHCs) and a great deal of promise has been shown when TCRs form interactions with MHC class II, as they are not only able to target cancer cells, but change the tumor environment through their interactions with other cells.

These therapies are beginning to shape expectations of how immunotherapies should work. CAR-Ts s have been shown to affect remission rates by 90 percent in hematological malignancies and the industry is beginning to wonder if similar levels of efficacy will be seen in solid tumors – preclinical and clinical testing will provide the answer. If we are able to achieve significantly higher success rates with TCRs than with current alternatives, I think we will be able to help patients achieve a better quality of life.

Adaptimmune, a clinical-stage biopharmaceutical company, is an example of the headway being made in the TCR space. Their lead candidate, ADP-A2M4, is currently in a phase II, open label, dose escalating study to examine the effect of the drug in synovial sarcomas. The compelling data so far lead me to believe that we will see the first TCRs come to market within the next two to three years.

But a lingering challenge for TCRs is their binding affinity to tumor antigens. Though companies have, for some time now, moved toward the development of affinity-enhanced TCRs, issues pertaining to cross-reactivity and self-reactivity are still likely to rear their heads, resulting in adverse events.

Zelluna, like someother companies in the immunotherapy space, are now taking TCRs from humans after immunization to help improve safety profiles. Because the TCRs are selected in vivo, the opportunity for cross-reactivity is low. But I suspect that the current issues with affinity and antigen targeting will be ironed out within the next five years as the field matures and interest grows.

Beyond these challenges, the coming years are bursting with potential. The industry is turning its head toward the use of multiple TCRs in cells and exploring the effect of phenotype on cancer cells. If companies are able to deliver benefit to patients by exploring these avenues, the treatment of solid tumors will be revolutionized. Until then, we must all focus our efforts on developing more advanced TCRs so that we can realize similar (if not better) levels of success than have been achieved with CARs.

The CRISPR Toolbox

Can we move beyond Cas9 to reduce unintended off-target effects of CRISPR technology?

By Garrett Rettig, Research Scientist at Integrated DNA Technologies (IDT)

Since CRISPR (clustered regularly interspaced short palindromic repeats) gene editing was discovered in 2012, its ability to make precise and permanent changes in the DNA of both animals and plants has been generating excitement. The focus of medical science research to-date has been on diseases caused by a single gene mutation, such as sickle cell anemia (SCA) and beta thalassemia, and the improvement of anti-tumor immunotherapy. The first use of an investigational ex vivo CRISPR-based therapy to treat SCA and beta thalassemia is already underway in at least two patients in clinical trials.

CRISPR gene editing makes use of enzymes, particularly nucleases, that have been programmed to target specific sequences in the genome and then introduce edits. However, DNA cleavage and editing may occur at additional off-target sites in the genome that have similar but different DNA sequence from that of the intended site.

Although Cas9 is the most commonly used CRISPR nuclease, others do exist, and applications are being developed. In fact, over the last few years, more than 10 different CRISPR/Cas proteins have been engineered for gene editing and there are many more known and being discovered across bacterial species. These other enzymes can work alongside Cas9 or be used to serve different functions – and there will likely be no shortage in the variety to satisfy the targeted nuclease application.

Though Cas9 remains the best-characterized and most widely used nuclease for gene editing, Cas12a has recently emerged as an alternative (1). There are several unique features of Cas12a that distinguish it from Cas9 – most notably the fact that it works across a broad range of temperatures, including lower temperatures. Additionally, it targets AT-rich regions of the genome, which makes it suitable for editing plants, which are AT-rich. Until recently though, Cas12a was not very efficient at cutting DNA. However, our team has isolated a new and improved variant, Cas12a Ultra, which provides specificity and efficiency as good as that of Cas9, as well as different targeting characteristics.

However, with all gene editing, whether it be in plants or in animals, off-target effects remain an important consideration. Despite its advantages in potency, DNA cleavage and editing may occur at unintended sites throughout the genome that have a similar DNA sequence and differ by typically one to three bases. Often, these events occur in areas of the genome thought to have no function, nevertheless there is always a risk of unintended, adverse consequences. Generally, the longer Cas9 persists in cells, the more opportunity there is for unintended side effects, like off-target effects. My work has focused on assessing the newly engineered Cas9 and Cas12a enzymes that have improved targeting specificity and thus reduced off-target effects.

"Although Cas9 is the most commonly used CRISPR nuclease, others do exist, and applications are being developed. In fact, over the last few years, more than 10 different CRISPR/Cas proteins have been engineered for gene editing."

As CRISPR technology advances, it is important to balance perspectives on both the potential benefits and risks. It is paramount that we have not only the tools to edit more precisely and effectively, but also tools to check for and eventually address off-target effects.

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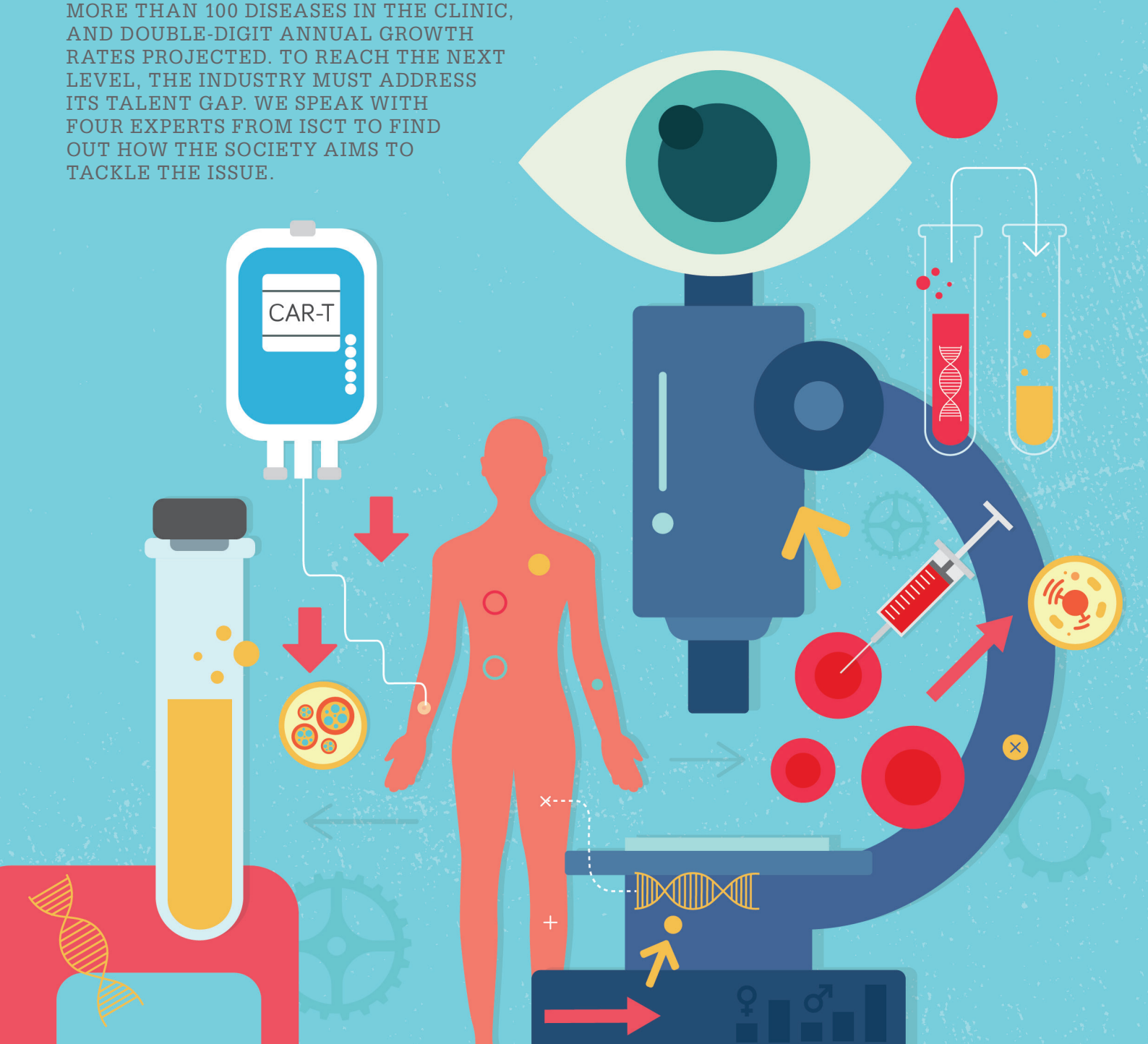
NEXT LEVEL
Cell and Gene Therapy

THE CELL AND GENE THERAPY INDUSTRY HAS AMAZING STATISTICS: ALMOST 1000 COMPANIES, 300-PLUS THERAPIES FOR MORE THAN 100 DISEASES IN THE CLINIC, AND DOUBLE-DIGIT ANNUAL GROWTH RATES PROJECTED. TO REACH THE NEXT LEVEL, THE INDUSTRY MUST ADDRESS ITS TALENT GAP. WE SPEAK WITH FOUR EXPERTS FROM ISCT TO FIND OUT HOW THE SOCIETY AIMS TO TACKLE THE ISSUE.



KEEPING UP WITH THE USAIN BOLT OF BIOTECH

WITH MANY CELL AND GENE THERAPIES SKIPPING PHASE III TRIALS ENTIRELY, ACADEMICS MUST GET TO GRIPS WITH GMP EARLY

By Emily Hopewell

When I started working as a medical technologist in academia in the cell therapy field, it was like being part of a small family. The space was very exciting from a research perspective but there were few trials taking place and we seemed to have plenty of time to learn about the science and manufacturing processes. When I returned to the field following my time at graduate school, everything had changed. There were many trials involving CAR-T and other new cell and gene therapies. Although this was fantastic news, I could see that academia was struggling to train enough people to meet the needs of investigators who wanted to carry out an increasing number of trials.

The 21st Century Cures Act in the US also changed things for academia. Traditionally, academics would carry out phase I and II trials before handing over to industry for phase III and commercial scale up. But cell and gene therapies often skip phase III trials entirely, which means academics must be far more rigorous in terms of their approach to GMP. Academic training rarely covers what it takes to manufacture a product to GMP standards – my medical technology training didn't, for example.

It isn't just the approval process that is different for cell and gene therapies – the variability is also radically different to small molecules and biologics. Cell therapy alone encompasses T-cells, mesenchymal stromal cells, iPS cells and many more, all of which are manufactured using a variety of techniques. In the gene therapy space, there are different types of viral vectors to consider, which often work very differently. Standardized processes are rare and starting on a new therapy often means starting afresh when it comes to manufacturing.

Another challenge for academia is that once someone gets to grips with the manufacturing and is able to work to GMP standards, they will inevitably be drawn to industry. Many early stage cell and gene therapy companies have been successful in raising capital; in fact, R&D companies are probably better capitalized than they've ever been before. Biotech has the funds to offer lucrative salaries, so academic centers can struggle to compete for individuals with the right skills – and it can be a real challenge explaining to human resources why our work differs from traditional clinical research.

And so we see an exodus of skill away from academic centers and into industry. Though this situation isn't inherently bad, it creates a real challenge for us in academia. We need a robust system in place that allows us to train the right number of people, while accepting that many won't be in academia for the long term.

PASSING THE MANTLE

In 2014, ISCT started its Early Stage Professionals Subcommittee to plan for the future. We realized that many of the leaders in the field were getting older and that we needed new members to take on the mantle.

First, we conducted a survey to characterize the scale of the problem; we found that nearly half of the training programs were not accredited by a regulatory body, which meant there was a real lag between the demand for programs and appropriate regulatory insight (this is a gap that ISCT is aiming to help fill). Another interesting finding was that the majority of respondents had PhDs. This is all well and good, especially on the process development side, but the majority of workers in manufacturing don't require PhDs – those are the people the industry is lacking.

A key finding was that the respondents who had participated in training programs said they benefited from them, suggesting that we need to provide more such opportunities. And while ISCT has a cell therapy training course that is great for investigators who want to run trials, we must meet needs on the manufacturing side too. We intend to broaden our survey in the future so that we can determine how ISCT can move forward to strategically contribute to workforce development. This initiative is part of a wider drive by the organization to take the industry to the next level by addressing gaps in education. This grass-roots movement has been pushed by various subcommittees and embraced by ISCT's leadership (see The Medicine Maker's interview with ISCT President, Bruce Levine on page 20, for that perspective).

I consider myself an early stage professional – fewer than 10 years have passed since my PhD. But I have seen the field develop at an incredible pace – so fast that it can be difficult for some segments to keep up. But with the right resources and people in place, I believe we can meet the challenge. And let's be honest, these are great problems to have! We know the science is sound and exciting – we just need to ensure we have the people available to take it to the next level.

Emily Hopewell is Director of Cell and Gene Therapy Manufacturing at Indiana University and ISCT Interim Global Treasurer, USA.

REINFORCING REGULATION

HOW AN UNDERSTANDING OF THE REGULATORY FRAMEWORK IS ESSENTIAL FOR THE FUTURE GENERATIONS OF CELL AND GENE THERAPY PROFESSIONALS

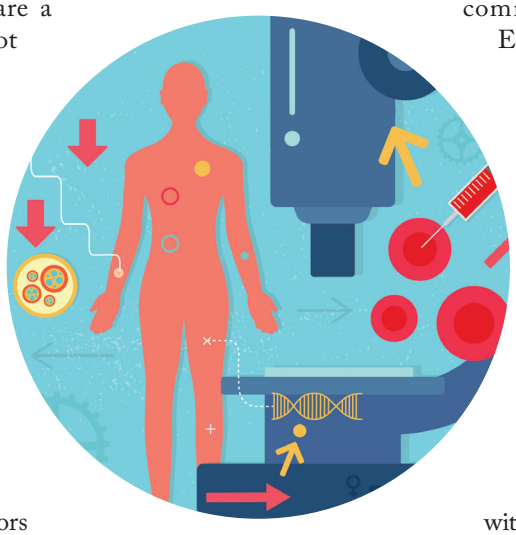
With Karen Nichols, VP Regulatory and Quality at Magenta Therapeutics, and Chief Regulatory Officer at ISCT

WHAT IS YOUR TAKE ON ISCT'S EDUCATION AND TRAINING INITIATIVE?

We put a high degree of visibility to the care of those just entering the cell and gene therapy workforce. They have mentors – giants in this industry – to guide them, and in turn they will pass their own skills back to future generations.

The Cell Therapy Training Course is really important to ISCT. Of course, the core reason for the program is that it provides technical skills. But it also provides the participants with an understanding of the larger environment of which they are a part; they need to develop skills not only in manufacturing, but also a regulatory knowledge base, and an understanding of everything from supply chain to commercialization. As the industry advances, we will develop this training further to meet the key needs of our members.

We also have a rich offering of annual meetings and conferences. People come to see and hear what's advancing within this rapidly changing field. Again, these don't just present a technical perspective, but also offer insights into what the regulators might be thinking.



HOW ARE REGULATORS COPING WITH SUCH A FAST-MOVING FIELD?

The field is advancing rapidly. Researchers are doing novel work at a level that the regulators may be unfamiliar with – but their broad view of submissions and approvals invariably means there are very few things that they have not seen or heard of before.

In the US, the legislative changes from the 21st Century Cures Act have driven and supported regulatory optimization. But there is also acceleration across different technologies that, in turn, the regulatory environment needs to adapt to or learn how to approach.

We also have different peripheral technologies – offshoots from the cell therapy space – that create novel regulatory situations to resolve. Humans are very imaginative creatures – as long as we have our wits and our science, we will continue to advance – and change is likely to follow an exponential trajectory!

HOW DO YOU WORK WITH REGULATORS?

There are certain formal pathways by which you engage with a regulator. But, at the same time, we have opportunities to meet regulators at events, giving us the opportunity for more informal and broad conversations. We have a very privileged relationship – and we don't take it for granted. Regulators have many years of experience, and we learn a lot from them.

In a nutshell, the regulatory aspect is essential to industry development; it provides the crucial guidance and the guardrails. And that allows the technologies to demonstrate their safety and efficacy for broader application into humans.

Our network of legal and regulatory affairs committees includes North America, Europe, Australia, and New Zealand. Each of these committees has local relationships depending on the initiatives that might be underway.

FROM A REGULATORY PERSPECTIVE, WHAT DIFFERENTIATES CELL AND GENE THERAPIES FROM MORE TRADITIONAL THERAPIES?

Fundamentally, it's the fact that we are dealing with "living drugs."

Small molecules specifically interact with a genetic site or vehicle in the body. You know pretty much exactly what they will do based on where they are going, their PK and PD, for hundreds of thousands of people. It's an organic chemistry process.

We have a product with a life of its own. We are harnessing or modifying that, which drives a different mindset in terms of how you look at the regulatory structure.

CAN YOU ENVISAGE THE REGULATORY CONSIDERATIONS FOR A TREATMENT THAT

Invest in Knowledge

By Patrick Rivers, Principal, Aquilo Capital, and Co-Chair, ISCT Business Models & Investment Subcommittee, USA

We know that manufacturing and process development are critical to the future of the industry. But another important factor in success is attracting investment funds. The investment community is not very attuned to looking at manufacturing or process development as critical parts of a product's profile. To be fair to investors, companies can be reluctant to talk about manufacturing – it is often viewed as part of their competitive dynamic and something that they do not want to reveal to competitors. But that can make it hard for investors to ascertain what's going on behind the scenes or understand why development or scale-up might be delayed.

I am a scientist by training – mostly in protein engineering – but now I oversee research for a biotechnology investment fund based in San Francisco. I also serve as one of the chairs of ISCT's business model investment subcommittee, which is part of the society's Commercialization Committee. The goal is to increase the industry's ability to raise capital from the investment community. To achieve this goal, education is essential.

A big part of our focus within the subcommittee is directing information to the investment community with a view to showing investors how to think about the way in which manufacturing is tied to the value of a therapy. And that's why we have created an initiative called "Investigators to Investors" – to facilitate a bi-directional flow of information from investors to and from key opinion leaders within the cell and gene therapy community. The central aim is to educate the investment community on the core challenges in developing cell and gene therapies, and how they might be similar or different to more conventional (and more familiar) therapies. We hope the initiative will lead to a flow of capital from the investment community and into the development of new therapies.

The ISCT takes a holistic approach to addressing gaps in education and skills in the cell and gene therapy field – and investors play an important part. To evaluate what the gaps are in the investment community, we carried out a survey. We had over 160 respondents, including venture capital groups, crossover funds, public markets and investors, and the results highlighted that manufacturing and the associated challenges were not as prevalent a concern as they should be. And that reflects the educational gap that we're trying to fill.

We're in the process of putting together a webinar and/or white paper that gives investors a roadmap on how to conduct due diligence on cell and gene therapy manufacturing processes. What are the right questions to ask? How do I assess this form an external perspective? And how can I look at a company with a different lens so that I'm not surprised when issues arise during manufacturing? In the end, it's an understanding of the challenges that we want to convey.

USES A MACHINE TO PROCESS A PATIENT'S CELLS IN A HOSPITAL SETTING?

The concept of bedside treatment using devices that select and return cells as therapy is not far in the future; people are talking about it now. I would say from a regulatory perspective it is really a question of conscience.

The equipment and the process needs to operate in a validated way that delivers the service as safely as possible. Risk to benefit is really a common sense question. What do you need to do to make sure the patient is properly and safely treated using the technology?

FROM A REGULATORY PERSPECTIVE, WOULD SUCH A CONCEPT BE CLASSED AS A DEVICE OR AS A THERAPY?

It would likely be classified as a device rather than a therapy – there's a precedent. But such topics are a constant source of debate. At the core of the debate are the autologous cells themselves and the degree to which they have been modified or manipulated as a result of this procedure.

Understanding the technology, the biological material, and the purpose and integration for use all come together for a regulatory person. They have to ask many questions to determine what makes the most sense.

STIRRING THE TALENT POOL

WIDESPREAD TRAINING INITIATIVES AND A SUPPLY OF EXPERIENCED PROFESSIONALS ARE VITAL TO KEEP THE INDUSTRY MOVING FORWARD

By Bruce Levine, Barbara and Edward Netter Professor in Cancer Gene Therapy, Perelman School of Medicine, University of Pennsylvania; and President Elect of ISCT USA

When people ask, "Do you teach?" I tell them that most of my teaching is actually outside of the University – and not only by virtue of our program here, but also through my position as President Elect of ISCT. There are many reciprocal invitations from collaborative societies around the world. In August, I was in Korea for a week, speaking at an innovation and biotechnology conference, and meeting biotech companies there. In March, I was in Taiwan, where I met with the Vice President at a conference. To be global, to engage, and to really move the needle forward as this technology progresses is an essential part of who we are as a society.

AN ADVANCING FIELD

Looking out of my window, I can see three floors of cancer immunotherapy researchers at the University of Pennsylvania, probably the largest collection of such researchers at an academic institution in the world. But consider where we came from: a very small group of researchers going to meetings scheduled on the last day of a session, in a room nobody could find, with only the speakers and two or three others attending. Now the sessions are packed!

When you start a research project or design of clinical trial, you have in your mind what would be an amazing outcome. We achieved our amazing outcome in 2010 and in 2012 with our early CAR T-cell patients. I have a graph of the results on my filing cabinet like a parent would put up their kid's artwork – I just could not believe it. We've had quite a ride.

I am excited by so many things that are going on in the cell and gene therapy space at the moment. As an immunologist by training, it is not only seeing the science and the clinical trials advance that I find incredibly exciting. It is also the fact that we are talking about things like reimbursement, ethics, and patient education. When we began to investigate these therapies, I did not appreciate what would happen if we were successful – that we would be thinking about all of these issues, and speaking with the media and the public. That transition from early research and development to having a broad impact on a new pillar of medicine is exhilarating.

INDUSTRY-WIDE SHORTAGES

Despite our advances, the field still suffers from a lack of capacity in terms of facilities – space in laboratories and academic centers; space to manufacturer vectors for gene delivery or manufacturing of cells; and our tools and technologies. But progress is being made.

The area of highest priority right now is the severe shortage of people with experience in the field – technical, regulatory, and even at the higher levels. When we bring someone on who may not yet have much experience, it takes longer to train them. It takes longer for them to make an impact, and it takes time from a mentor.

Less than 20 years ago, we were working in a niche field, so we did not expect to find people with experience, but we could take our time. Now, the rate of acceleration in the industry has put a gold rush on talent. Talent is scarce, which means you may train someone and then lose them – there is extensive recruiting and cross-recruiting. Although academic centers can offer the a-to-z of discovery, development, translation and clinical trials, they lose people to higher-paying industry, which has a cascade effect.

Higher-level departures also feed into the issue we have with a shortage of talent. We need to recognize and identify key roles, and plan who might fill that role, if the need arises. This is good practice in both industry and academia. But as the field has been moving so fast, firms and centers have not paid as much attention as they should.

So how else do we adapt? We have looked into adjusting pay and compensation scales to compete in this area, with the argument that these positions are not research positions, they are clinical manufacturing positions. And we have been adjusting our onboarding and training programs, including the Early Stage Processionals (ESP) Committee Mentoring Program, the Cell Therapy Training Courses, and several other education and training initiatives.

THE ESP COMMITTEE MENTORING PROGRAM

Education and training at all levels are vital to bring the industry forward. I have been involved with the ESP Committee Mentoring Program for the past couple of years. In short, the ESP Committee has recruited a number of mentors that can be accessed by early stage professionals for a mentoring cycle that lasts almost a year. (Two or three mentees are paired with one mentor.) It's a hands-on process that reviews career status and progress, and delivers direct advice from people with experience.

We've just announced the next cycle of this program; notably, it will be open to a greater number and wider range of people – those with an interest in clinical, research, or regulatory aspects, in both academia and industry.

TRAINING COURSES

We also run the Cell Therapy Training Courses for early stage

investigators with an MD or PhD (we have one coming up in Philadelphia shortly). We hope to expand the scope and number of these courses, as the demand exceeds supply! Currently, they run every two years in the US for a very select group of scholars that have been admitted from a larger cohort of applications. We have 16 scholars – six North American, six international, and four institutional – with an equal number of faculty, maybe more. It is a five-day intensive course, which begins with the proposal of a translational and clinical project. The course then covers a huge range of topics, including the design of clinical trials, statistics, quality assurance, regulatory affairs, manufacturing, testing, FDA speaker correlative studies, funding, and team science. Based on what they have learned during the course, they revise their initial project proposal to present on the last day for feedback. This year we will record these lectures for a webinar for ISCT members, and stream some sessions to the FDA.

We engage FDA staff so that we can increase our relationship and provide them with training. FDA reviewers need to be trained in the field and any way that we can assist in that training benefits both the FDA and the field as a whole. We see this as a global need – especially in regions of the world where staff are not trained to the levels that we see in the US, the UK, and elsewhere in Europe.

EDUCATING THE PUBLIC...

Our public-facing education is incredibly important. We hold meetings and other activities, but it is primarily conducted through the ISCT Presidential Task Force (PTF). The PTF arose from the absolute need to differentiate scientifically- and clinically- validated therapies from unproven and unethical "therapies." These so-called clinics sell a mess of things purported to be "stem cells", and claim that they can treat everything from Alzheimer's to autism. But these therapies have had harmful financial and medical effects on patients.

... AND BEYOND

We also have scientific committees for various cell types and disease areas, as well as commercialization, lab practices, and legal and regulatory affairs committees. Each of those committees itself has activities – from white papers and publications to webinars and meeting sessions – for those interested in the various scientific, commercial, operations, regulatory and quality areas. These committees and the committees' education initiatives are the original foundation of the ISCT.

If you think about cell therapy professionals, you're thinking about laboratories and clinical programs. But now that some therapies have received approvals, they are being administered by nurses, pharmacists, and professionals in hospitals. We had a meeting earlier in the year where there was huge interest from nurses and pharmacists in transplantation and cell and gene therapy – and so we've also come up with an education initiative to meet that demand.

Participants get so much out of our training courses; it is often a turning point in their ability to translate, manage and lead clinical trials. We believe our courses are geared towards professionals that will make an impact – a little like those elite diplomatic or business courses... But as a society, we recognize that this is a small slice of our membership, and we want to offer education and training in different flavors to different audiences… You will see more coming in the near future.

PATIENTS AS EDUCATORS

The role that our patients have as educators is crucial. Many have joined the board of patient advocacy organizations, or have even started their own foundations. We often have patients speak at ISCT meetings, which serves to motivate our membership and investigators. The impact of patients is not mentioned enough; not only do they volunteer for our clinical trials, but they commit themselves to represent and educate others about how their therapy has enabled them to beat their disease.

You may have heard of Emily Whitehead and her father, Tom. Emily is an icon. In 2012, at the age of seven, she was the first child to receive CAR T-cell therapy, which put her leukemia into remission. People know Emily around the world, and her picture is on the desk of the Director of the National Institutes of Health. She has met with celebrities; Steven Spielberg even wrote her a get-out-of-school note. It's nice to meet famous people, but they are doing it for the purpose of advocacy. You don't see such a connection with chemotherapy.

Hope is one of the most powerful words in the English language (and possibly other languages, for all I know). The incredible levels of patient involvement are not only because we are seeing success in "untreatable" cancers, but because these therapies are uniquely personal. The empowerment that patients feel from using their body's own cells to fight their disease can only be sufficiently conveyed by hearing them speak about it themselves. And it is very different to poisoning yourself with chemotherapy.

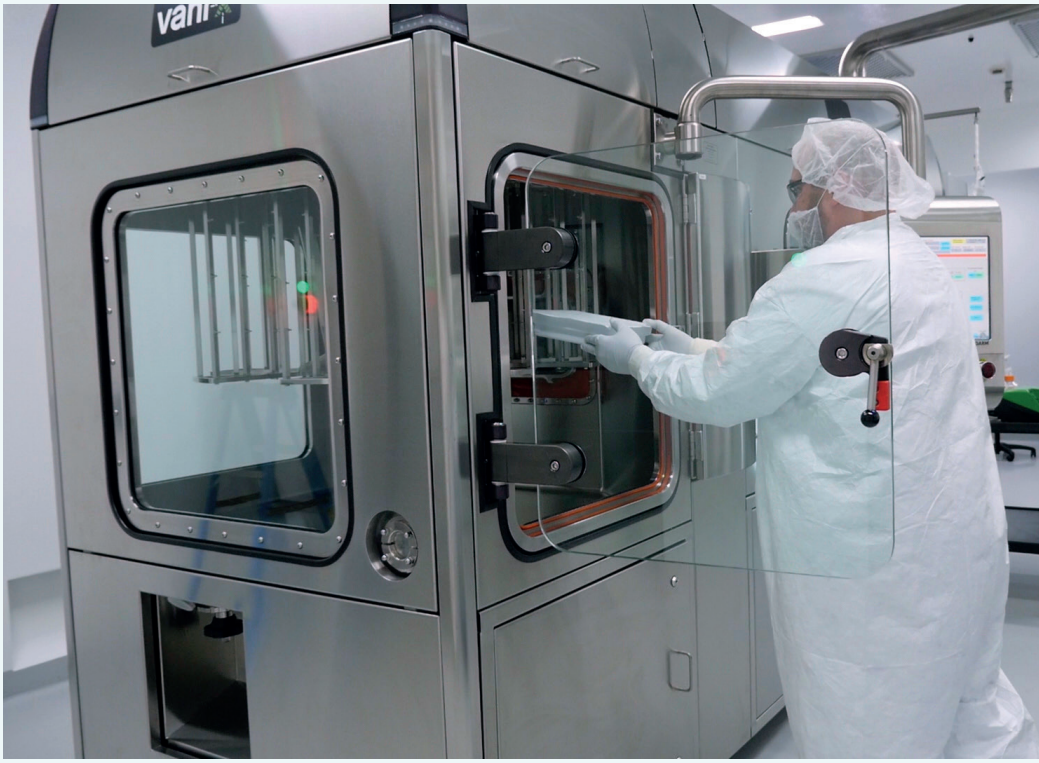
ISCT MARCHING FORWARD

At some conferences, there are leaders and regulators who are not only saying they have a shortage of staff and are looking to establish a framework for appropriate regulations, but they are also asking, "Where do we start?" These countries are looking to the FDA and the EMA for guidance, but they are also looking for certain advice that the ISCT is best-placed to provide.

We are the only global cell and gene therapy society that is engaged in translational and clinical development. We have a very strong relationship with the FDA, and we are the lead society in the cell therapy liaison meetings. We have members with expertise all around the world. My vision for the society is to continue to engage professionals, to enhance our relationships with regulatory agencies around the world and, most importantly, to substantially enhance our education and training platforms.

Collaboration at Work

When looking for a new fill-finish solution for its gene therapy manufacturing operations, CDMO FUJIFILM Diosynth Biotechnologies turned to isolator technology offered by Vanrx Pharmasystems. We speak with Thomas Page, Vice President, Engineering and Asset Development, to learn why.



How involved is FUJIFILM Diosynth with gene therapy?

It's been a major focus for us for several years; in fact, our College Station (Texas) site is a center of excellence for gene therapy. We have two facilities in Texas, with a total of around 200,000 square feet dedicated to advanced therapy manufacture, and we plan to deploy another $120 million into these products in the next few years. One of our goals was to create a vertically integrated CDMO for gene therapies, so we've had to ensure we have incredibly strong process development, and expertise in early and late phase manufacturing. The last piece of the puzzle has been to integrate the drug product offering as well because it's really critical for some of these products to avoid additional freeze-thaw cycles.

What are the key challenges and considerations during manufacture?

A lot of senior people have had careers based on recombinant protein manufacturing and this can leave them with blind spots – because they have good solutions and want to apply that to other product types, but it's not always appropriate. One of the challenges of operating in the advanced medicine field is that it's incredibly diverse in the number of ways people want to manufacture these products, scale-up, and present the final drug product, so there are big differences in formulations, batch sizes, and operations like fill-finish. This means that for us as a CDMO, flexibility is crucial.

These therapies also require the very highest levels of quality. Some of them use live viruses and you need containment for contamination control, as well as for protecting the operator. Isolator technology is crucial for this. We use advanced mobile clean rooms, which you can think of as a piece of equipment – like an isolator that you can walk into. Product changeover is also crucial to consider. Early on, we opted for single-use, completely disposable fluid paths, and to make our rooms completely VHP-able.

How did FUJIFILM Diosynth and Vanrx come to work together?

We put together a venture team of senior people with various different areas of expertise, including quality, operations, commercial, engineering, and technical specialties. The team outlined what technologies and solutions we'd need to serve the market and decided that they would only consider isolator-based filling systems. We also wanted to be able to fill syringes, vials, and cartridges. The team opened discussions with a few different companies and then did a really deep failure mode and effects analysis (FMEA) dive to understand the ins and

"We scored each vendor and Vanrx scored twice as high as the next closest competitor."

From Making Medicines to Making Machinery

With Chris Procyshyn, CEO and co-founder of Vanrx Pharmasystems

What's the story behind Vanrx?

Before starting up Vanrx, my co-founder and I were involved in developing biologics and creating manufacturing solutions. It was clear that manufacturing processes were becoming more complicated, and that batch sizes were getting smaller – new technologies were needed! We started Vanrx about 12 years ago to design automated fill-finish technologies that met the need for faster changeover and implementation rates, while greatly reducing all associated risks from a process and sterility standpoint. Essentially, our technology is about putting liquid into small containers. That sounds very simple, but if you can't get it into that container perfectly, and with every variable you could possibly imagine, then you have nothing.

How do manufacturing processes vary for cell and gene therapies compared with traditional biologics?

There are many different methodologies, formulations, and processes, but, as Thomas explained, one of the biggest challenges is the diversity of approaches for gene therapies. Each product is different from the last. In terms of equipment, traditional biologics manufacturing makes medium to high volumes of products that are all the same. Changeover periods, involving sterilization, preparation, and cleaning, might happen once or twice a week for a given product. But for cell and gene therapies, you may have a different batch of products every hour, each for a different patient – the difference in total changeover time is dramatic.

To adapt, we have utilized the flexibility of our machines. They are much more software-based than traditional systems, with a lot more interoperability. But a lot of work goes into making the system so simple to use. We have more people working in controls and software than we do in the actual machine building.

What advantages does your technology have over other systems that are available?

The largest competition in this space is manual filling – a person in an isolator suit filling containers by hand. It's well accepted, but it is slow and cumbersome, with much greater risk in terms of sterility. And frankly, it's just not scalable. A regulator once told me that it breaks their heart to see brand-new therapies with so much science built into them being piped by hand into a vial!

How do you work with FUJIFILM Diosynth?

We work with FUJIFILM Diosynth as a partner. Working together continuously allows skills on both sides to be applied in new ways, and we have constant feedback to start working on long-term challenges. At the moment, we are completing a second system for the company that uses our new high-accuracy peristaltic pump technology – offering around six times better accuracy than traditional pumps, which is essential for the new process they are implementing.

outs, the hazard pathways and the risk controls with different approaches within the industry. We scored each vendor and Vanrx scored twice as high as the next closest competitor, so the choice of who we should work with was very clear. We chose to use the company's SA25 Aseptic Filling Workcell.

We have found that we are a good match in terms of how we like to work and our ultimate goal: to improve patient outcomes and patient access.

What are the benefits of Vanrx's SA25 Aseptic Filling Workcell?

We have used the system for numerous fills for different live viral agents. We chose the system based on minimizing risk to the patient, as well as minimizing product loss. We have been working through several different iterations of components for a client to screen different approaches to filling – taking advantage of the fact that the unit does not have a hazard pathway that involves contact surfaces. All of the components are held by the nest; for example, there is no stopper bowl. This allows us to take earlier developmental material and fill it into an array of components, performing screening efficiently and giving the client the best primary container possible. The elimination of gloves has also been a bonus.

I think this type of technology is very beneficial for manufacturers and regulators alike. Simple designs that eliminate whole hazard pathways are easier to regulate, easier to understand – and reduce risks to the patient by many orders of magnitude.

What advice would you offer to other gene therapy companies who are starting to think about manufacturing?

Assess the blind spots that you might be carrying, if you are not experienced in this space. Step back and look at your risks from first principles and design your risk controls. Also, choose partners that align with your philosophy of quality and risk control.

Business

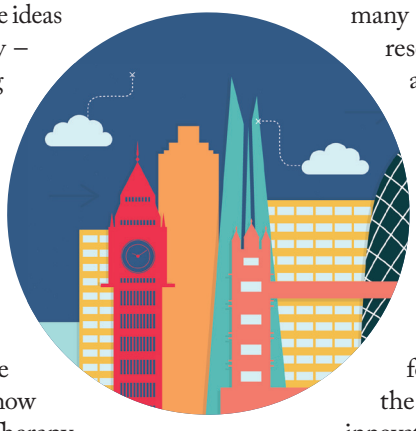
Economic drivers
Emerging trends
Business strategies

A British Success Story

The UK's Cell and Gene Therapy Catapult has played a significant role in building the strong advanced therapy ecosystem in the UK – the largest outside the USA. Keith Thompson, Chief Executive Officer, explains how the Catapult has tackled the challenges of the field.

By James Strachan

The Cell and Gene Therapy Catapult is part of a network of centers designed to transform the UK's capability for innovation in the advanced therapy sector. They were formed in 2012 as part of a larger program – established by Innovate UK (a government-backed, innovation-championing agency) – that provides a functional network to support innovation by UK businesses. How? By providing access to expert technical capabilities, equipment and other resources required to take ideas from concept to reality – in particular, focusing on the bridging the gap between university research and industry. The result, according to Keith Thompson, is the largest cluster of cell and gene therapy activity outside of the US. Here, he explains how the Cell and Gene Therapy Catapult works and shares his view on trends in the sector.



Why is the Cell and Gene Therapy Catapult so important?

Before this initiative was set up, the cell and gene therapy sector was relatively small, particularly in the UK, and certainly much smaller than it is today. This class of therapy is mostly considered as a one-time treatment. In some cases, however, it requires more than one dose of medication to completely cure the target disease. In the early years, gene therapy was considered to be impossible on a commercial-scale, but through a number of innovative technological breakthroughs, it has become mainstream, with many companies ploughing resources into research and development. Indeed, many of the smaller companies have been successful in bringing a few molecules to market with the backing of larger companies. The Catapult focuses its efforts on the lifecycle that takes innovation from the research bench, through development within a smaller biotech company, and finally out to market via a large pharma. In 2018, the global gene therapy market size was valued at around $536.43 million – and it's set to grow by 33 percent (CAGR) a year.

"In the early days, gene therapy was considered to be impossible on commercial-scale, but through a number of innovative technological breakthroughs, it has become mainstream."

How does the Catapult work?

Since being established through the Innovate UK grant, we have built an exciting range of unique people-assets – we have experts in regulatory affairs; clinical trial design and implementation; reimbursement; and clinical adoption. Our critical core skill or centerpiece, however, is the wealth of expertise we now

have in industrialization, manufacturing, and the specific supply chain for this sector. Companies are able to access and leverage this expertise, accelerating their development and allowing them to grow more quickly than perhaps they would have on their own. We have a large development center in central London, which has 70 scientists working on industrialization technologies, including everything from analytical techniques to scale up of viral vectors, CAR-T and allogeneic cell therapy.

We also have a manufacturing center in Stevenage, which is designed specifically to help companies develop their manufacturing at a scale sufficient to satisfy the requirements, both in terms of purity and quantity, for clinical trial materials. This center has really been central to our success story, as it directly drives these therapies out towards patients, through a network of advanced therapy treatment centers that we have also strategically identified and pulled under our umbrella of support.

We are now at nearly 200 people. We took on over 100 projects last year, partnered on 28 collaborative research and development projects, and assisted 13 research partners from academia in the translation of their research into top performing private companies. To date, we have worked with 45 SMEs, opened the manufacturing center and obtained regulatory licenses from the MHRA for both clinical trials and commercial production. We have five companies working at the center (four from the UK), and over 60 partnerships or collaborations. Alongside the CAR-T manufacturing, we now host a company working on large scale viral vectors and also T-cell receptor (TCR) manufacturing systems supplemented by a cryo-hub facility.

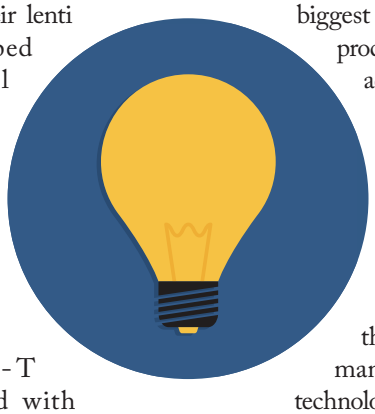
What does a typical project look like?

One of the main strategies we employ is to anticipate where help will be required within the industry. For instance, we may identify a future need for some particular process, or analytical methodology or a novel vector scale, and we will target our research and development capabilities to provide a solution. We do this in conjunction with companies out there in the industry, either through collaborative research and development grants (for example, Horizon 2020 or UK research charities) or directly through commercial collaborative programs, where companies fund the work to access our resources and capabilities.

Around 60 percent of our current work is within the viral vector space – mainly because there is a global shortage of both the capacity and technologies required to scale up production to an appropriate level. There is also the burden of cost, which is not insignificant. We recognized the cost problem early on and have been working to address some of the complex issues surrounding it. For scale, you have to be able to improve productivity whilst

"Taking a process developed by pioneering academics and turning it into a reproducible system is very difficult indeed."

ensuring adequate and successful growth of healthy cell lines and techniques to improve extraction – and you must comply with GMP guidelines, of course, which presents further complications. All companies involved in gene therapy face these issues, and so it's an important focus for the Catapult. To give some specific examples, we've worked with Cobra, Pall and Combigene on AAV processes. We've supported Adaptimunne in the scale up of their lenti process and developed process analytical technologies with Oxford Biomedica. We've also helped a Scottish company called Symbiosis on the scale up of their supply chain (particularly, fill finish).



In the CAR-T space, we've worked with Birmingham University on a project to direct CAR-Ts to a vasculature target within solid tumors and helped reduce an Oxford-based company's process time. We also worked with a Chinese company to automate CAR-T production with a modular bioreactor.

What are the main trends?

The majority of our work is in the viral vector space. But overall, the scaling out of autologous processes is probably the biggest trend right now. Taking a process developed by pioneering academics and turning it into a reproducible, scalable system is very difficult indeed; and organizing the flow of materials in a GMP system with a quality management system is enormously complex. And though we're helping with the manufacturing processes and technologies on the one hand, we're also helping with the massively complex delivery of the therapies – logistics – where no detail is too small.

Finally, by way of a further example, we are investing time and effort into factors that affect the scalability of embryonic/induced-pluripotent stem cells. Here,

it is not just scalability, but also how to deliver a controlled differentiation process in parallel that presents challenges. The requirement for this is not yet critical, but we believe it will be in the near future.

What are the main advantages of the Catapult model?

The full program reaches into a wide variety of sectors including renewable energy, satellite applications, compound semiconductors, and medicine to name but a few. Within this, the high-volume manufacturing theme features across a number of areas. However, these sectors are well established, whereas scale up in cell and gene therapy is still new, with some unique challenges that make it extremely challenging. The Catapult program has allowed us to build a unique set of assets, both physical and intellectual, to help companies simplify this difficult process. Our range of operations is not normally seen within any one company. Equally, we have insight into the whole of the product development lifecycle, so we can tackle issues that arise from regulatory hurdles, clinical trial design and implementation, and even as far as understanding eventual reimbursement opportunities once at market. On top of this, we are able to provide a skilled workforce that is absolutely necessary to run these processes, and we are in an ideal position to provide specialist training. To this end, we have recently opened an advanced therapy manufacturing apprenticeship.

The Catapult program has allowed us to create a fantastic ecosystem in the UK, which has developed into the largest cluster of cell and gene therapy activity of its kind globally outside of the US. We have over 70 companies developing products, supported by a deep supply chain and about 85 clinical trials. Remarkably, the NHS was one of the first adopters of a clinical CAR-T project. We are very proud to have been part of this process, accelerating the development and acceptance of these new medical approaches.

Why does the UK appear to be a leader in this space?

It all begins at the research bench, and we are lucky to have a wealth of research in our universities that focus on advanced therapies – and that's been wholeheartedly supported by the Government and medical charity initiatives. Following a number of national wealth and scientific reviews, advanced therapies were identified as one of the emerging core strengths of our future economy and, as such, became the focus of a number of Government-led incentives, including Catapult. With the backdrop of a definite industrial strategy that is supported from the top down, coupled with strong innovation in our universities and within smaller biotech companies, a tried and tested mechanism to spin technology out into vehicles that can be supported by risk capital (for example, venture capital), the UK has been given every opportunity to grow a world-leading base in advanced therapies.

What's next for the Catapult?

The Catapult is by necessity inquisitive and forward looking, with an aim to solve tomorrow's problems for this industry. Without a doubt today's advanced therapies will become a normal part of the medical toolkit, with the concomitant need to simplify the pathway from bench to patient. We have a privileged vantage point from which to identify potential roadblocks early, and provide solutions, reduce costs, reduce risks and increase efficiency, encouraging more companies or institutions to work in this field.

How do you see the field as a whole evolving?

Firstly, we're off to a great start! There is a self-generated momentum in the industry, but we need to accelerate the modernization of our manufacturing processes – especially by incorporating process analytical technologies, and analytical technologies more broadly to support rapid release and characterization.

Looking a little bit further out, we're seeing the second and third waves of technologies snapping at the heels of existing technologies. Companies are already planning to cannibalize and advance their own products even before they've gone to market, which really speaks to the pace of change in the industry.

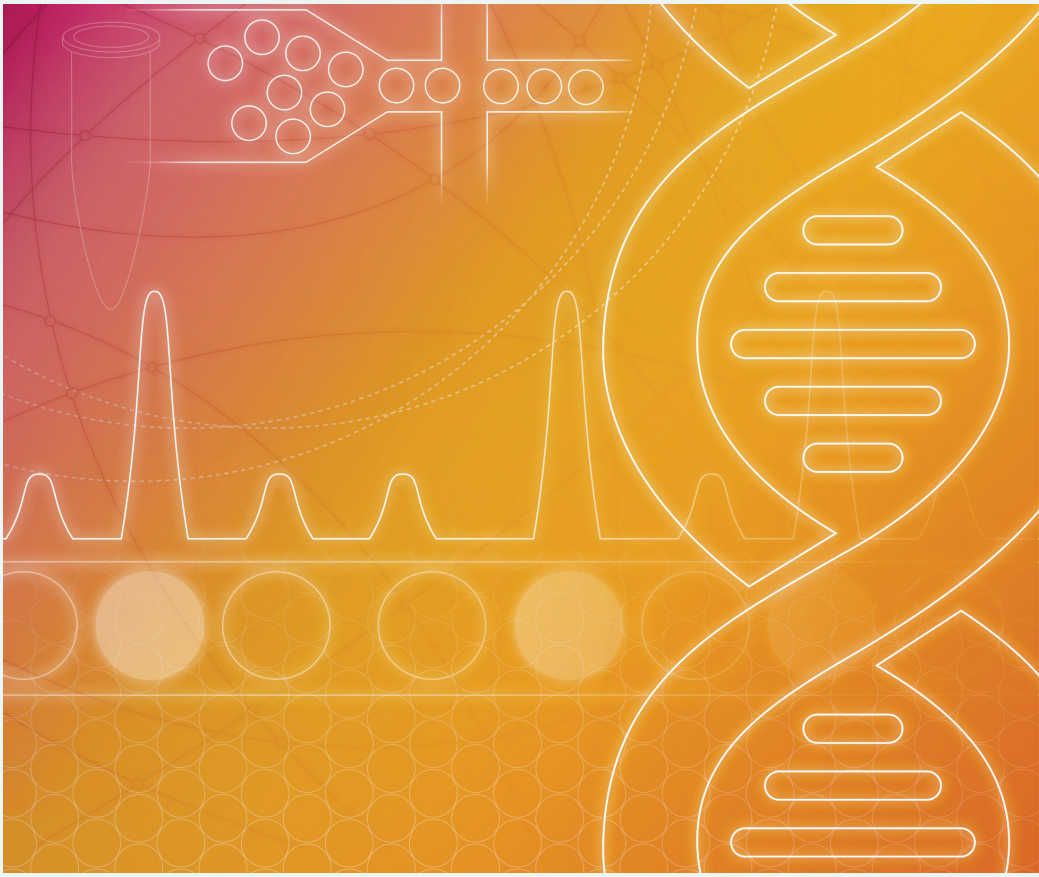
Thinking even further – decades perhaps – into the future, I think we will see cell and gene therapies becoming completely mainstream treatment options – just as biologics have become. Most big pharmas manufacture small and large molecules, as well as vaccines. Soon, these companies will all have a range cell and gene therapy platforms. If the current size for the pharma industry across existing modalities is around one trillion dollars, we'll see cell and gene therapies going on to represent around 10 percent of that.

"The Catapult program has allowed us to create a fantastic ecosystem in the UK, which has developed into the largest cluster of cell and gene therapy activity of its kind globally outside of the US."

Technology Leads the Way

Can new tools lower the hurdle of high manufacturing costs for cell and gene therapies?

By Dawne Shelton and Eli Heffner



Cell and gene therapies are rapidly establishing themselves as one of the most exciting areas within the biopharmaceutical sector. The number of cell and gene therapy clinical trials rose by 37 percent in the UK alone in 2018. However, as with any new therapeutic modality, there are challenges, and it's fair to say that these advanced medicines are some of the most complex medicines to work on. Patient-specific cell and gene therapies need to be manufactured using a one-batch-per-patient method – success relies on the manufacturer's ability to edit genetic material and manipulate the patient's cells safely and in a time-critical situation. This leads to a lot of process and manufacturing challenges.

Access for all

The right technology and processes are essential to develop and deliver these therapies to patients – but often the solutions can be complex. One of our objectives is to make relevant technology as easy to use as possible. For example, one important technology for cell and gene therapy development is Droplet Digital PCR (ddPCR). At Bio-Rad, we believe in making technology accessible to everyone, not just the specialist. As such, ddPCR is accessible to a broader audience. If we can bring a little simplicity into an already complex system, the operators can concentrate less on technology and more on generating the biological results.

ddPCR technology is a high throughput and flexible technology which partitions target molecules into roughly 20,000 droplets per well. This yields a dynamic range of 0 to 150,000 copies per well, or higher by simply merging multiple wells. This high number of partitions yields greater precision and accuracy when checked against standard WHO reference materials. The methodology is particularly good for measuring exact copy numbers, especially in the lower copy ranges, which is critical for these therapies.

The precision of quantification can make a significant difference in manufacturing processes and help companies address concerns raised by regulators. Our ddPCR System is being used by drug developers to precisely and accurately measure the biological dose of an edited virus or cell, and establish how many genes per cell are successfully integrating on target. ddPCR is accurate at very low, "rare event" numbers, measuring down to between one in ten thousand and one in a million. The ability to perform precise rare event detection means ddPCR technology serves as a critical analytical QC assay for cell therapy bioprocessing through its ability to measure the amount of mycoplasma, bacteria or host cell contaminants in the manufacturing process, where ddPCR's strengths in precise rare event detection will serve as critical QC assays for cell therapy bioprocessing.

Going with the flow

When manufacturing cell and gene therapies, it is critical to be able to measure the physical and chemical

"It is critical to be able to measure the physical and chemical characteristics of a large volume of cells rapidly and consistently."

characteristics of a large volume of cells rapidly and consistently. Flow cytometry has been the standard method since the 1970s and has been constantly enhanced over the years, resulting in ever more sophisticated ways to analyze cells. Currently, high-end cytometers can measure more than 25 parameters per cell and between 10,000 and 30,000 cells per second. For example, at Bio-Rad, we have developed the ZE5 Cell Analyzer. This system can be configured with up to five lasers and 30 detectors, with an optional small particle detector. The ZE5 Cell Analyzer was designed for the translational biology and biopharmaceutical community with the ability to easily integrate automation. This allows our customers to perform multiple analyses including high-resolution immunophenotyping and exosome analysis.

Getting highly specific

One of the challenges of CAR-T cell therapy development is the measurement of cellular kinetics in the patient. It is crucial to be able to discriminate between CAR-T cells and normal T cells at several stages, and this can be done with a specialized antibody. Our custom recombinant antibody service uses HuCAL technology to generate an antibody that is highly specific to the chimeric antigen receptor. This unique antibody is a critical reagent needed for the quantitative assessment and tracking of CAR-T cells in patient blood using flow cytometry. The provision of custom services using HuCAL technology is unique to Bio-Rad in the research antibody field. It is an in vitro technology, using phage display to select antibodies from a naive synthetic antibody library consisting of 45 billion antibodies. The in vitro method enables us to select antibodies that meet very specific criteria and deliver them in as little as eight weeks; antibody generation can take six to nine months using traditional animal immunization methods. Because we are not relying on the immune response of an animal, we can generate antibodies to challenging targets, such as drug antibody variable regions, post translational modifications, protein complexes, non-immunogenic proteins and toxins, as well as the more usual proteins and peptides. The sequence of every antibody is known from the outset, and this coupled with the recombinant production method means scientists can be confident of a long-term secure and consistent supply for research projects or clinical studies. Every custom project is designed in collaboration with the client, and carefully managed by our antibody experts from beginning to end.

Working with regulators

It is particularly important in these early days of cell and gene therapies that authorities, researchers and commercial companies work closely to provide a rational regulatory framework. We've been delighted to be invited to discussions with a number of different internal divisions at the FDA, regarding areas where our technologies can impact research and manufacturing processes. As the provider of a new technology that is being pulled into many research and manufacturing processes, we find ourselves partnering with both the regulators and the practitioners, and providing support and education to both. For us, being part of that dialogue early on has been extremely productive and we look forward to the outcomes from these discussions and being able to have a positive impact on the research and manufacturing of these important therapies.

As a company deeply embedded in this sector, it is exciting to see how rapidly the field is evolving in multiple ways. The notion that we are able to produce tailor-made treatments that originate from an individual patient took time to be accepted as a viable, commercial-scale option but the various challenges from R&D through to those now being faced in manufacturing and scalability have helped drive innovation in the field. We are proud to be part of this process by providing the field with innovative tools and technologies, and we expect to see the momentum continue to grow in the years to come. By providing systems that can be operated by anyone from entry-level to highly experienced researchers, we're helping to bring next-generation technology to a wider audience – and ultimately helping manufacturers bring revolutionary new therapies to patients who desperately need them.

Dawne Shelton is Associate Director for ddPCR IVD products, and Eli Heffner is R&D Manager III, both at Bio-Rad Laboratories.

Ahead of the Curve

Sitting Down With...
Ravi Nalliah, Chief Executive Officer and Cofounder of TrakCel, UK

Who inspires you?

I've always been inspired by the way Steve Jobs conducted himself in business. From Apple's early days, instead of trying to be all things to all people, Jobs and his team focused on a niche market that allowed the company to thrive and develop into what it is today. I've tried to apply that principle to my own working life – and that's why TrakCel caters to such an exclusive section of the pharmaceutical industry.

What's the story behind TrakCel?

I left university with a degree in biochemistry and molecular biology, and though a career in science might have seemed a natural progression, I spent a significant portion of my early working life in the financial industry. As a chartered accountant, I provided services to mid- to large-corporations, but having the opportunity to interact with varied clientele, particularly those in the pharmaceutical industry, led me to believe that my calling lay elsewhere.

In particular, I was constantly interacting with companies who needed alternative solutions to the issues they faced with low temperature storage, packaging and distribution. I set up TrakCel in 2012 to help address these issues, but the CDMO arena was dominated by heavy-hitters who had resources, manpower and money, so we had to find a way to stand out from the crowd. We focused our energy on becoming a specialist provider of cloud-based software to support the complete visibility of supply chain management for the biotech industry.

What were the initial challenges you faced?

We were distributing primary products to international clients, which meant that we had to find ways to deal with both language and legislation barriers.

Certain challenges were out of our control. For example, we might transport a product to a site in Singapore, but after delivery it may inadvertently be stored in a fridge at the wrong temperature – instantly destroying it. The smallest deviation in temperature is enough to make a difference to a cell therapy. Of course, there are financial consequences to these situations, but the serious repercussions are for the patient. Our real-time track and trace technology helped iron out these problems; we are able to determine the status of any given product and any point during its distribution.

Why is supply chain management so important for cell and gene therapies?

Compared with the supply chain for traditional small molecule drugs, there are further considerations that supply chain management companies must make in terms of the storage, packaging and distribution of both allogeneic and autologous therapies. With such therapies, which are often for patients living with rare disease indications, any mistakes in supply chain management could result in devastating consequences.

The industry, however, is rapidly adapting to manage the pressure of dealing with personalized therapies. People are looking at ways to improve processes, and we're seeing the introduction of advanced IT systems, smart technologies (including geo-fencing and data location tracking), and a more decentralized approach to supply to help cope with the unique demands.

As the market continues to expand, I hope that the push for standardization continues. Trying to harmonize standards internationally will undoubtedly be challenging – every market has its own attitude when it comes to CGTs, but there is an inherent and pressing need for practices to be become uniform so that patients, wherever they are in the world, receive the best care possible.

What is the biggest lesson you've learnt over the course of your career?

Every interaction with every customer and every stakeholder will be different. Understanding that every market has its own attitude to dealing with the complexities of the CGT supply chain and being able to adapt to these nuances is important. And it has also influenced TrakCel's technology; we've had to adapt our solutions to ensure they are highly configurable and adaptable to the challenges that come with working internationally. My aim is to see the standardization of the CGT supply chain across markets but, until that time, having a grasp on the culture of the global marketplace is what will help build long lasting relationships.

Why is the cell and gene therapy space so exciting to work in?

We're on the cusp of a new era in medicine. When YESCARTA and Kymriah gained market approval, it wasn't only a huge moment in terms of science, but it marked the start of a new outlook on life for many patients. I remember watching a video explaining what the therapeutic could do for patients' lives; I felt utterly moved by the fact that patients finally had access to a curative medicine that could take them from a state of blindness to the point where they were able to see.

At the end of the day, I want to see these therapies be a success. And I want to help draw more talent into this exciting area so that we have experts within every aspect of the supply chain who can help pull down the red tape that prevents CGTs reaching their potential as quickly as possible.

Where does the future of the industry lie?

Allogeneic therapies. A lot of attention is given to autologous therapies but, as the field develops and changes, more people are beginning to consider the specific challenges and benefits that exist when bringing allogeneic therapies to market – and there's a lot of investment in this area.

The industry is also expecting the approval of several CGTs by the FDA over the course of the next two years. The evolution of the industry is happening at such a fast pace; we all have to work extra hard to stay ahead of the curve so that we are able to successfully deliver these novel life-saving products to patients.

the Medicine Maker

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