CELL AND GENE

FROM the Medicine Maker

Presenting our special supplement to celebrate the fast-growing field of cell and gene therapies

The Champions Speak Out

We asked leaders across advanced medicine to answer the field's toughest questions

A Not So Rare Problem
How do we manufacture enough doses for tens of thousands of patients?

Candy, Chimps, and Chocolate Cakes
ISCT's new leader, Jacques Galipeau, shares his recipes for future-proofing the field

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A Year in Review, A Year in Flux

Twelve months spent covering the raging torrents of the cell and gene therapy space have left me emotionally invested… and anxious

In the summer of 2021, I was given the helm of The Medicine Maker's coverage of the cell and gene field. Since then, so much water has passed under the bridge.

I've been immersed in the history, status quo, and possible futures of these remarkable therapies. Online and offline, I've picked the brains of the vanguard and figureheads of the field, learning their stories and building a more complete picture of advanced therapy and where it is going.

Flicking back through our newsletter archives, I see wave upon wave, strata upon strata of achievements reshaping a steadily expanding landscape. New sites built, new deals inked. Square meters filled in the thousands, currencies spent in the millions and billions, binding companies across continents and oceans. Starts and stutters of trials launched, paused, completed, and shut down following "miracle" cures, tragic deaths, and less dramatic – but still crucial – partial alleviations in human suffering.

One question facing cell and gene therapy that remains a constant – one that we should all care about – concerns cost. For my entire lifetime, the gap between the world's richest and poorest people has been expanding. And, as that gulf yawns wider, the utopian promise of cell and gene therapies surely means little if only the wealthiest nations and individuals can afford them.

In our weekly cell and gene newsletter (subscribe at tmm.txp.to/cg-reg), I launched a series called "The Cell and Gene Champions," in which I pitched thought-provoking questions to the community, sharing the strongest answers. The question closest to my heart was – unsurprisingly – "How do we ensure that not only the rich benefit from cell and gene therapy?"

In this special supplement to The Medicine Maker, you will find thoughts on how we bring cell and gene therapies to the many and not the few – as well as other contributions from our Cell and Gene Champions. You will also gain access to a wealth of additional insight into this high-stakes field from visionaries such as Bruce Levine of the University of Pennsylvania, Miguel Forte of BioSenic, and Marianthi Psaha of Santen.

Perhaps you will walk away from it with your curiosity sated. Perhaps you will be full of nervous energy and eager to learn more. In either case, I will consider my mission accomplished.

Angus Stewart
Associate Editor, The Medicine Maker

The Pros and Cons of Lentiviral and Adeno-Associated Viral Vectors

Demand for gene therapies is rising, so all the more reason to better understand the properties of their delivery devices

By Suparna Sanyal, Head of Commercial Development for Viral Vector, Cell and Gene Technologies (CGT) at Lonza

Demand for viral-vector-based gene therapies has risen to unprecedented levels, thanks to their potential to help treat previously incurable diseases. The two vectors most in the spotlight? Lentiviral (LV) vectors and adeno-associated viral (AAV) vectors – due to the increased research and positive clinical results they are seeing across a wide range of applications, including cancer, heart disease, and hematologic and genetic disorders. The more drug developers look to expand this range of therapeutic areas, the greater the demand for commercial-scale development. So it's important to understand not only how these two vectors can be applied to drug development, but also the capabilities required for scale-up that allows us to bring these innovative therapies to patients.

LV vectors are derived from the single-stranded RNA retrovirus HIV-1, and have been used extensively because of their ability to infect non-dividing cells, efficiently integrate into the host genome, carry large transgene loads, and allow for long-term transgene expression. They are predominantly used as delivery vehicles for introducing genetic modifications into cell therapies, such as CAR T, and HSC gene therapies. Importantly, recent regulatory approvals and clinical successes with LV vectors are spurring even more interest among drug developers.

Let's look at the benefits of LV vectors in more detail:

- Volume. LV vectors can carry a high volume of transgenes – up to 8 kilobytes – into the DNA of host cells, which helps address more indications.
- Gene delivery. The viral genome is passed onto daughter cells during division, leading to long-term and stable expression of exogenous genes.
- Applicability. Unlike other types of retroviruses, lentiviruses can infect cells whether or not they are dividing, which allows them to transduce and genetically modify cells that do not replicate.
- Immunogenic profile. The recent lentiviral vector designs have low negative side effects; an advantage they share with AAV vectors.

"Manufacturing each viral vector currently requires different processes, so companies cannot apply a one-size-fits-all-approach to their upstream and downstream processes."

However, LV vectors also present two major risks to safety.

The first is a risk of accidental exposure because HIV can self-replicate during manufacturing thanks to the lentivirus's high mutation and recombination rate. Though research shows that the risk is low, it remains a major safety concern for lab engineers and workers during development. Before using a lentiviral vector system, a risk assessment must be completed and documented. Typically, lentiviral vectors may be safely handled using either BSL-2 or BSL-2 enhanced controls, depending upon the risk assessment.

The second risk is the potential for oncogenes to occur in cells through insertional mutagenesis. For this reason, lentiviral vectors are predominantly used for cell therapy applications with genetic modification of cells ex vivo. Only limited use is seen for direct in vivo therapies.

Unlike their LV cousins, AAV vectors are single-stranded DNA parvoviruses that can replicate only in the presence of helper viruses, such as the adenovirus, herpes virus, human papillomavirus, and vaccinia virus. Following several landmark approvals, AAV vectors are currently being used for in vitro, ex vivo, and in vivo research. AAV therapies predominantly target rare genetic disorders for which the patient population tends to be highly limited. As the market is so small, drug developers feel immense pressure to be first to market to commercialize their therapies.

The biological elements of AAV vectors make them a very attractive candidate for gene therapy for several reasons:

- Safety. AAVs do not produce any known human diseases and thus have very low pathogenicity and require less equipment to handle.
- Immune response. AAVs have a low immunogenic profile, complementing their low pathogenicity during gene delivery and reinforcing their biosafety.
- Infectivity. Thanks to their ability to deliver genetic material to dividing and non-dividing cells, AAVs can be applied across different indications – an advantage they share with LV vectors.

As with LV vectors, AAV vectors come with several drawbacks that affect their applications and efficiency.

Firstly, AAV vectors are limited by their restricted capacity for insertion of transgene DNA; because of their relatively small transgene size, they are unable to deliver genes larger than 4.8 kilobytes. Secondly, the generation of neutralizing antibodies against AAV in non-human primates (NHP) and humans may attenuate the curative effects of AAV-mediated gene therapies and limit the size of patient populations suitable for these therapies. Thirdly, there are several different serotypes and capsids for AAVs, all of which have different production and purification requirements and vary greatly with respect to function and efficacy. Fourthly, AAV drug products have varying degrees of empty and partially filled capsids, and these have implications for safety and efficacy. Generally, the highest possible percentage of AAV particles with the full transgene DNA is desired, and this varies significantly depending on the production method, AAV serotype, and the transgene itself. The latter two factors introduce significant manufacturing challenges for AAV therapies.

Overall, the industry's collective ability to successfully scale up LVV and AAV vectors faces two challenges:

i. Manufacturing each viral vector currently requires different processes, so companies cannot apply a one-size-fits-all approach to their upstream and downstream processes. Therefore, manufacturing requires immense scientific and market expertise to make the informed decisions necessary for developing a robust plan.
ii. Given the industry's limited experience with commercial-scale viral vector supply, companies need to work closely with regulatory agencies. This can be especially challenging during the transition from preclinical to commercial, where complexities arise that can cause potential delays resulting in increased costs.

As demand continues to rise, pharma companies must understand how to navigate these challenges to continue delivering their life-saving medications.

A Not So Rare Problem

Efficient manufacturing – and a little innovation – can help bring gene therapy into the mainstream

By Timothy J. Miller, CEO, President, and Co-Founder, and Erandi De Silva, Co-Founder and Vice President of Product Development, both at Forge Biologics

There are multiple pathways to overcome gene therapy manufacturing challenges at the small scale. But a solution that addresses the production bottleneck for the whole field – unlocking therapies for dozens of diseases, each encompassing tens of thousands of patients – remains elusive.

Gene therapies were initially developed to find treatments for patients with "rare" diseases and few (or no) treatment options available. It's still a struggle in the field to appreciate the scope of the challenges ahead as this therapeutic approach moves from rare to not-so-rare patient populations. We often get asked "what does rare really mean?" When you consider these five observations, you'll realize that rare is not so rare after all (1):

Today, there are thought to be over 7000 distinct rare diseases – and this figure is likely an underestimation.

- Globally, 400 million people are affected by rare diseases (there are 30 million people in the US alone – that's one in ten of the total population).
- Rare diseases impact more people than cancer and AIDS combined.
- About 50 percent of people affected by rare diseases are children.
- Over 80 percent of rare diseases have identified genetic origins.

That's a lot of patients to develop and manufacture treatments for! Clearly, there are many people – hundreds of millions around the world – who might benefit from access to gene therapies. Yet treatments remain woefully underdeveloped; in the US, over 90 percent of all rare diseases do not have a single FDA-approved treatment.

The first step is to forget about the concept of rarity, instead focusing on removing obstacles so that all patients with genetic diseases receive attention. Enabling access to therapies to the greatest extent possible can be a resource problem – particularly when we consider the scope and scale of manufacturing. Right now, it takes a great deal of time and effort to develop, scale, and manufacture a gene therapy.

Let's work through an example: one 1000 L bioreactor can produce sufficient material to treat 10–20 patients using the most common form of gene therapy. From start to finish, it can take 6–12 months and millions of dollars to manufacture one 1000 L lot of drugs in a bioreactor. If we consider the 7000 different rare diseases known today, and the 400 million people globally who need treatment, we can quickly see how demand so easily overwhelms current manufacturing capabilities.

Compounded by demanding analytical and quality specifications, the obstacles to manufacture drugs for just one clinical trial can make it hard for companies to focus on a single gene therapy, let alone develop a pipeline for multiple rare diseases. Manufacturing is highly capital intensive, requiring specialized buildings, rooms, and equipment. And, on top of that, the pool of talent and expertise in current gene therapy "good manufacturing practices" is limited. It's fair to say that supply–demand mismatches are significant across the entire industry.

"Clearly, there are many people – hundreds of millions around the world – who might benefit from access to gene therapies."

Despite all these issues, we have seen successes in gene therapy. There are many novel drug candidates in the preclinical stage, and many others in clinical trials – each one offering hope for patients who may have no other option. But what good are they if there is nowhere to produce them in a timeframe that makes sense, given that time is the enemy for patients?

Scientists and doctors worldwide are working on solutions for millions of patients who need new treatments, and companies need innovative manufacturing solutions to bring their therapies to market. Let's turn their hope into reality by enabling the solutions we know exist.

Reference

1. *Global Genes, "Rare Disease Facts," Global Genes (2021). Available at: https://bit.ly/gg-rdf*

The Early Bird Gets the...

All decisions have a ripple effect throughout your cell sourcing supply chain; you must adopt a commercial mentality right from the start

Joy Aho, Senior Product Manager at Be The Match BioTherapies

When it comes to your supply chain for cell sourcing, you must embrace a commercial mindset whatever phase of development your cell or gene therapy is in. And that means starting with the end goal in mind and working in reverse. Why is this important? With the anticipated trajectory of cell and gene therapy development and approvals, you need a resilient cell sourcing infrastructure from the start, including suppliers that can meet your long-term demand.

What does this mean in practice? Let's look at each step of the supply chain in reverse starting with the patients who will receive the therapy. First of all, you need to think about your indication. The supply chain for a cell therapy treating a rare disease has far different needs than one that will be delivered to thousands of patients per year. Equally important is where the patients will be treated. Here, I'm specifically referring to the country where the therapy will be delivered. Different countries have different regulatory requirements for starting material collection and manufacturing. If you expect your therapy to have international distribution, you need to think beyond where your initial clinical trials take place. This is particularly important for allogeneic therapies (where the same starting material may be used to create therapies for multiple patients).

Consider the following scenario. You collect starting material for your allogeneic cell bank in a manner that is compliant with FDA regulations in the US. Later, you decide you want to distribute your therapy in Australia. The US and Australia have different regulations when it comes to donor screening and product testing for use as allogeneic cellular source material. The differing regulations could render your FDA-only compliant material ineligible in Australia.

You can avoid this by thinking about distribution – and varying global regulations – from the start.

Next, what type of cells will you use as your therapy starting material? This decision impacts how you transport the material. Some cell types are very sensitive to cryopreservation so fresh shipments are necessary, but regardless of method (cryopreserved or fresh), you need to keep an eye on your vendor and make sure they know what they are doing when it comes to moving time-sensitive starting material or cell therapies around the globe. Numerous obstacles can stand in the way of a product delivery – from weather delays to a global pandemic… You need to make sure your vendor is up to the job.

The decisions you make upfront, such as fresh versus cryo, will also impact which apheresis centers can collect for your therapy. Different centers have different cell processing capabilities. And that's also true for capabilities beyond cryopreservation, which is why you need to determine the requirements for your protocol as early as possible; not doing so will cost you development time – and your ability to scale up collections quickly.

Finally, for allogeneic cell therapies, you must know the donor attributes that are critical to the safety and efficacy of the end product as you develop a cell bank that can meet the needs of future patients once your therapy is commercially approved. The more requirements you put on donor characteristics, the larger your donor pool needs to be. Each donor attribute eliminates some portion of the donor population – and the size of the donor pool you need may surprise you. Therefore, it is essential to ensure that the supplier you select to provide allogeneic starting material has a donor pool large enough to meet your needs – especially as you scale.

I worked with our team on an analysis of frequency data for different genetic types within our donor registry to learn the starting pool size needed for 10 qualified HLA-matched donors for a therapy. In the case of the fiftieth most common HLA genotype for donors who self-reported being Hispanic or Latino (which may not seem common but is out of 462,000 genotypes), the donor pool would need to be over 600,000. And that's before taking other demographics, such as age or sex, into account.

I hope I've persuaded you of the extreme importance of keeping future commercial scale in mind. By adopting a commercial mindset, you can think about your potential needs from a clinical and commercial standpoint from the very beginning. That's the mindset you need to help set your therapy up for success.

CHAMPIONS *of* CELL *and* GENE THERAPY: *The* GREATEST HITS

Throughout 2022, we posed a series of questions
to great minds working in the cell and gene field.
Here, we share some of the most thought-provoking answers.

The cell and gene therapy industry is beset by some quite serious problems. Right now it is flourishing, but what does the future hold and what challenges do we need to address as a matter of urgency? To find the answer, we created the Cell and Gene Champions series and ended up covering some of advanced therapy's biggest challenges: skills, mRNA, equitable access, and supply chains. Here, we curate the very best of those answers, taking care to spotlight perspectives from people of different sectors, backgrounds, and schools of thought. Metaphor, minutiae, and mastery – our champions deal in them all!

WHERE DO THE BIGGEST SKILLS SHORTAGES EXIST IN THIS FIELD – AND HOW SHOULD WE ADDRESS THE PROBLEM?

CARL TAYLOR OF TRAKCEL SAYS:
"Talent is tight, so be enticing"

I'd like to offer a different perspective on the skills problem. Economic expansion and a swell of therapies approaching commercialization have increased the pressure on many aspects of advanced therapies. In response, companies are turning to IT and technical solutions to help them automate, streamline, and increase the productivity of their processes. Unsurprisingly, the field now faces a growing shortage of programmers, test engineers, analysts, and product development positions.

There is high competition for tech talent across all industries, amplified by a pandemic-induced rush for software to manage a world in lockdown. The situation is tight, but also hopefully inspiring more young people to consider careers in the field.

Inspiring those young engineers early to turn to life sciences and advanced therapies will be key.

Organizations will need to be aware that the competition for talent is tight. Organizations should also bear in mind that they will constantly be assessed by talented and in-demand employees. It will be critical to attract and retain these people by maintaining and cultivating in company culture, development and training, and – of course – remuneration.

BRUCE LEVINE OF THE INTERNATIONAL SOCIETY FOR CELL & GENE THERAPY SAYS:
"Build and protect the Rosetta Stone"

I believe that we need a virtual Rosetta Stone for the cell and gene therapy field. To explain what I mean, here's a quick history refresher.

The Rosetta Stone was a tablet created in 196 BC and inscribed with a decree rendered in three languages: traditional Egyptian hieroglyphics, Egyptian demotic (or language of the ordinary people), and the Greek text of Egypt's then-ruling elite, the Ptolemies. These parallel texts allowed modern Egyptologists to decode the previously-uncracked hieroglyphs.

Here, we can think of those three languages as the three totems of advanced therapy: science, regulation and quality operations, and commercialization. We need forums of exchange that allow these three tribes to work together. To be proficient and agile in cell and gene therapy translation, one needs to be conversant in all three languages. And this means that education and training will be crucial.

At ISCT, we've been working to promote regional and global interactions between early stage professionals, and we've even set up mentorships to cultivate future leaders. We have an early stage professionals committee that works to provide opportunities for new talent. Scholarship opportunities and training will also be important to address the unfulfilled need for cell therapy training.

HOW COULD THE SPOTLIGHT ON MRNA IMPACT THE CELL AND GENE FIELD?

CHELSEA PRATT OF BIO-RAD SAYS:
"Make sure it works"

The coordinated effort of governments around the world to curb the impact of the COVID-19 pandemic brought about the largest vaccination campaign in modern history, with over 11.3 billion vaccine doses already administered around the globe.

Data is what propels scientific progress. While the pandemic brought about grim and unprecedented times, one upside we've seen over the last two years has been ample data on biodistribution and persistence, which has advanced our understanding of mRNA technology. Compared with viral vector-based vaccines (Oxford-AstraZeneca and Janssen), COVID-19 mRNA vaccines (Moderna and Pfizer-BioNTech) were more cost effective, easier to manufacture, and had fewer severe systemic side effects. This triple success reignited commercial interest in the development of mRNA-mediated therapies for genetic disorders and malignancies.

The key challenge to using mRNA-mediated therapeutics extensively across the cell and gene therapy field is how to ensure these particles reach the targeted cell type while prolonging efficacy and maintaining safety. Studies using mRNA-based therapeutics to treat genetic disorders, such as cystic fibrosis, have shown great promise and have brought us significantly closer to achieving effective delivery and producing proteins for days or weeks at a time. This technology has opened the door for additional treatments beyond infectious diseases and helped increase the already-bright spotlight on the cell and gene therapy field.

Applying lessons from recent developments in mRNA will empower cell and gene researchers to progress effective and affordable treatments for a multitude of diseases.

ANIS H. KHIMANI OF PERKINELMER SAYS:
"The advantages of mRNA far outweigh those of DNA"

The transient message bearer has been in the limelight over the past decade. It served as a candidate vaccine template during the COVID-19 pandemic, with two of the multiple leading vaccine manufacturers (Moderna and Pfizer-BioNTech) using RNA encoding of the SARS-CoV-2 spike protein as a powerful immunogen to elicit an immune response against the virus.

Advances in the study of mRNA structure, target activity, packaging, and delivery have opened up multiple new therapeutic approaches. The corrected and modified mRNA delivery into cells to generate normal or immunomodulatory proteins not only has the potential of being used in vaccines against infectious diseases and other chronic disorders, but also offers the option of treating disorders such as cancer via cell therapy. Furthermore, gene editing functionality can also be delivered via mRNA encoding an enzyme, Cas9, to facilitate targeted corrections at the genome level to treat inherited diseases. Conversely, abnormal mRNA can be shut down by silencing RNA designed to block the message and inhibit abnormal protein expression responsible for a disease state.

In cell and gene therapy, the advantages of mRNA far outweigh those of DNA. Transfected mRNA in a cell localizes within the cytoplasm, which enables immediate and efficient expression. In addition, mRNA-based expression for gene correction or cell modulation is safer since it does not integrate into genomic DNA, eliminating the risk of mutagenesis. Hence, the recent evolution of nucleic acid-based modalities, such as mRNA, evaluation of their stability, and packaging that leverages various vector designs have empowered cell and gene therapy approaches and continue to advance this novel frontier of therapeutics.

HOW DO WE ENSURE THAT NOT ONLY THE RICH BENEFIT FROM CELL AND GENE THERAPY?

ROB COLLISON OF CAMBRIDGE CONSULTANTS SAYS:
"It's about more than cutting costs"

Great question! It is vital that we strive to democratize the availability of these therapies, and, for me, the answer lies in three key strands: reducing costs, providing better access, and conceiving new payment options.

Let's start with costs. They can be reduced significantly through manufacturing innovations that incorporate automation, AI/machine learning, and other emerging technologies to allow the scaling out and scaling up of therapies with reduced labor and minimized controlled environments – both of which are key cost drivers. Such innovations will allow biopharma companies to develop robust manufacturing platforms that produce multiple therapies – each for a wider range of clinical indications – and benefit from economies of scale. I envision a plug-and-play model that uses the same process and has the ability to modify cell types, viral vectors, and/or genetic modifications; for example, a CAR platform that is able to produce CAR T, CAR NK, and CAR M for varying targets, such as CD19, BCMA, and so on.

Turning to improved access, we'll need new hospitals and treatment centers in economically diverse areas, equipped with specialized resources and trained clinicians. Hospital systems – benefiting from government subsidies or directly from biopharma – will need to invest to provide greater local access. Individuals on low incomes may not have the means to travel and access currently limited treatment facilities.

Finally, I see unique payment models from both healthcare and biopharma as an option to serve broader populations. Government/socialized healthcare and insurance providers need to evaluate the upfront costs of curative cell and gene therapies versus the total long-term costs of treatment and medication. New reimbursement strategies could then be implemented.


Carl Taylor


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Edwin Stone


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Miguel Forte


Chelsea Pratt


Bill Vincent


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Perhaps biopharma will develop a performance-based payment approach, recouping costs through recurring income based on therapy performance and longevity rather than a single initial price. This could reduce the barrier to entry for cell and gene therapies by defraying costs.

EDWIN STONE OF TTP SAYS:
"Reform the structure"

The cell and gene therapy industry has some structural challenges. Currently, the eco-system is fragmented. Early stage developers often call on CMOs to make therapies that are then acquired by big pharma. Equipment companies develop systems and sell consumables into this ecosystem, trying to respond to not only shifting requirements as a therapy moves through the pipeline, but also to demands that change over time in a fast-moving field. All this comes before we consider payers, regulators, logistics, local governments, and the multitude of other interested parties. Each stakeholder wants a seat at the table, but, at present, there are many opportunities for objectives and motivations to misalign.

One solution is massive vertical integration. Everywhere from mobile phones to ophthalmics, vertical integration has helped drive down prices and increase access. But this approach is not without flaws, especially when a limited number of players become too dominant. The alternative is deep collaboration. Here, our field's greatest strength is the alignment of our core motivation: the desire to bring therapies to as many patients as possible.

So how can we deepen collaboration? Grand solutions may seem attractive, but achievements built from small, stacked bricks are the better bet. We are in an industry that is simultaneously innovative and cautious. Standardization in everything – from shipping though digitization and even into fluidic connectivity – could greatly simplify new therapies' entry to market. We should also look at how creative use of payer models can be used to lower the cost of entry. Finally, we need to analyze and develop the talent pool to meet the needs of the industry. Unless we all invest in growing that pool, we will be stuck as a boutique industry for the few.

Despite every hurdle, I am confident that our field has the people, motivation, and resources to solve all of the above, and make good on the incredible promise that we all know lies in cell and gene therapy.

DAVE SEAWARD OF 3P INNOVATION SAYS:
"One word: automation"

To answer this question, it may be worth considering an analogy from the early years of the automotive sector. Before the introduction of the moving assembly line in 1908, the Ford Model T was priced at $825. By 1925, after Ford had revolutionized the method of manufacture, it was priced at $260. At the same time, Ford's employees saw their weekly working hours shrink and their wages rise.

During this period, the British company Rolls-Royce employed large teams of highly skilled artisans to hand craft their Silver Ghost chassis. We should remember that, while Ford produced complete cars, Rolls-Royce only produced a chassis and engine. They left it to other companies to produce the coachwork. Over a two-decade period, Ford produced around 16 million cars. How many Rolls-Royces? Eight thousand.

Cell and gene production is currently analogous to those beautifully hand crafted Rolls-Royces – and the highly skilled laboratory technicians and PhD graduates are the "highly skilled artisans."

Cell and gene therapies are revolutionizing the treatment of many life-limiting diseases, but the growth of this nascent industry is constrained by a worldwide lack of skilled staff for their development and manufacture. Throughout human history, automation has reduced the costs of goods by reducing the number and skill level of operators. Automation has also improved the consistency of the product (with reductions in faults and scrap) and, in many cases, it performs tasks that humans simply cannot.

Cars revolutionized transport and Ford revolutionized their manufacture. Today, we need a "Ford" of cell and gene. And that's why the new paradigm will almost certainly include significant automation – both physical and digital.

WHAT IMPROVEMENTS DO WE NEED TO SEE IN CELL AND GENE SUPPLY CHAINS?

BILL VINCENT OF GENEZEN SAYS:
"Brace for impact"

When predicting challenges that the cell and gene therapy industry would face in 2022, it was no surprise that many drug developers consistently identified supply chain issues as a big area of concern. In the years leading up to 2020, the global viral vector manufacturing capacity had expanded in response to increased demand for these advancing technologies. The onset of the COVID-19 pandemic then magnified the supply burden that manifested.

Increased demand for vaccine manufacturing supplies was seen worldwide, in parallel with supply transport and delivery

disruptions. Additional issues stemmed from the reduced availability of raw materials, like fetal bovine serum (FBS), used in the upstream processing of many biologics.

With some items subject to a one-year lead time, developers and manufacturers came under further pressure to increase stockpiles or find alternative suppliers to prevent disruption. This challenge persists to date and is particularly prominent for projects at clinical phases, where speed is of the utmost importance for success.

Although those in the cell and gene industry are hopeful that supply issues will be resolved with the world coming out of COVID "lockdown," the impact of future global events will never be easy to predict – from natural disasters to new pandemics or conflicts. However, we can foresee that continued high demand for COVID-19 vaccines and growth in the cell and gene market will only add to future supply challenges.

To overcome these issues, a growing burden will be on suppliers to invest in manufacturing capacity and offset this bottleneck. By making all the necessary technical, quality, and safety information easily accessible, as well as being proactive in identifying potential solutions, suppliers could further ease the difficulties biopharma manufacturers face. If major suppliers do not adapt quickly, we can expect alternative competitor vendors to fill the void.

JESSICA MADIGAN OF BIOVECTRA SAYS:
"Prioritize plasmids"

Perhaps the biggest supply issue for cell and gene therapies is a lack of reliable sources of GMP-grade plasmid DNA. The supply of pDNA – and, therefore, mRNA – is constrained by both manufacturing issues and short supply of consumables and starting materials. These constraints result in at least year-long lead times for pDNA made under GMP conditions.

The industry should adopt established manufacturing platforms that have been through the drug approval process for cGMP plasmid production. For example, plasmid manufacturing has not been designed and scaled to create a reproducible, reliable process for both alkaline lysis and purification. We need a large-scale manufacturing process that can lyse cells as quickly as possible to avoid the buildup of impurities. An optimized lyzing process would lead to higher yields by eliminating the need for additional purification steps with a goal of delivering shorter timelines and reduced manufacturing costs. Since the technology for plasmids and vectors is continuously changing, cGMP manufacturing will need to be flexible and supported by a supply chain and production capacity that can keep pace.

We need to see additional suppliers in the overall supply chain for critical starting materials and consumables to meet the demand of the many manufacturers who have invested in single use fermenters, only to be challenged by months-long lead times for filters, bioreactor bags, and diafiltration cassettes. Another good example of necessary improvements are the anion exchange resins used during plasmid purification to remove host cell DNA, RNA, and proteins. Currently, the best options for high specificity at large scale are low-capacity chromatography resins, requiring large columns and slow cycling times. The industry needs to develop higher capacity ion exchange resins to make purification more reproducible and decrease lead times.

These advances should help relieve the strain on supply that currently bottlenecks the cell and gene therapy market.

MIGUEL FORTE OF BIOSENIC SAYS:
"Tech and talent – you can't have just one"

The supply chain is the route by which well characterized and functional cell and gene therapy products reach patients. It plays host to products ranging from very challenging (and now mostly outdated) single-patient, autologous therapies to large-scale cryopreserved allogeneic products for multiple patients. In all cases, three aspects remain critical for a successful supply chain – technology, process control, and readiness to manage the unforeseen.

We continue to see great developments in the technologies that enable the supply chain, but improvements are still needed. These include wider and less stringent cryopreservation requirements with the possibility of reduced necessity for lower temperatures and increased flexibility with local and point-of-care storage options.

Tight control and management of the supply chain process is vital for the quality of the product, and a general readiness to manage exceptional and urgent unforeseen circumstances remains critical. Well adapted processes and suitable operator talent are still necessary assets for a successful supply chain. It should work smoothly and mechanically but enable quick reactions to inevitable surprises.

In the near-future, more patient bed-side manufacturing technologies will be considered and developed and "micro supply chain" options will be needed. This area will certainly see growth.

Overall, it is always about the interface between the technology and talent and experience of the operators. We will need to develop both.

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In recent years, new technologies have emerged to improve human living conditions. Two popular examples are cell therapy, where cells are enriched or modified *ex vivo* then re-introduced to the patient, and gene therapy, where genes are introduced, replaced, or altered within the body. Consolidated as cell and gene therapy, both are projected to revolutionize the treatment of genetic or acquired diseases, such as cancer.

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Our bioprocess solutions support the upstream bioprocessing cycle from early development to scale-up to pilot-scale production. Powerful hardware and software tools for process monitoring, control, and analytics help to build process understanding and facilitate standardized process control.

Eppendorf and its 5000 employees use their broad knowledge and experience to support laboratories and research institutions around the world in our mission to improve human living conditions.

With our equipment, training programs, and application services, we support scientists in resolving cultivation bottlenecks during development and help to stimulate the growth of your cultures and cultivate solutions tailored to your challenges.

www.eppendorf.com/bioprocess

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Get to know OmniaBio, Canada's largest CDMO focused on CGT manufacturing

Launched in 2022, OmniaBio Inc. enables focused manufacturing for cell and gene therapies (CGTs), from clinical to commercial scale. As a subsidiary of CCRM, OmniaBio builds on an established reputation built over a decade, with proven expertise in process development and good manufacturing practices (GMP)-compliant manufacturing.

The OmniaBio campus, opening in a scaled launch between 2024-26, will cover up to 400,000 square feet, making it Canada's largest contract development and manufacturing organization (CDMO) for CGTs.

Taking a collaborative, extended team-member approach to project management, OmniaBio works with clients to produce a comprehensive manufacturing plan that identifies opportunities to build in efficiencies, saving time and money.

With teams experienced in generating and characterizing over 200 induced pluripotent stem cell (iPSC) lines, OmniaBio can deliver high-quality iPSCs that meet the unique requirements of each client, with GMP-compliant reprogramming platforms to produce therapeutic-grade iPSC lines. OmniaBio is built upon leadership in iPSCs, lentiviral vectors, and immunotherapy – and these are just three of our 11 areas of extensive expertise.

Visit omniabio.com to find out more about our expertise, and how we can support CGT manufacturing projects.

OmniaBio

The Gibco™ CTS™ DynaCellect™ Magnetic Separation System enables closed, fully automated, and rapid cell isolation and bead removal for cell therapy manufacturing.

When used with Gibco™ CTS™ Dynabeads CD3/CD28, users can consistently achieve >85% cell isolation with 95% purity, with no effect on viability. Recovery of cells after CTS Dynabeads CD3/CD28 removal is >91%.

The CTS DynaCellect System can process cells in ~100 minutes when used with CTS Dynabeads CD3/CD28, while other instruments may take 4–5 hours. Furthermore, the system shortens bead removal time from ~5 hours to under 1 hour. The combination of shortening cell isolation and bead removal time is key to streamlining the workflow.

The system is also highly scalable, allowing for 10 mL–1 L of reaction volume for cell isolation. The continuous flow process for bead removal means the volume is potentially unlimited. With flexible software for optimal protocol design and a documentation functionality for increased quality control, the CTS DynaCellect System helps ensure manufacturers can move toward commercialization with confidence.

The CTS DynaCellect system combines scalability, flexibility, and automation with high-speed proven performance and modularity, helping cell therapy manufacturers get their essential therapies to the patients quickly.

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Memories From the Start of the Gene Therapy Wave: Lessons Learned with Alan Boyd

The remarkable story of gene therapy drug development during the 1990s and early 2000s

Featuring Alan Boyd, CEO of Boyds

When adults asked what I wanted to be, I would reply: "A doctor." In the post-war council estate in Blackpool where I grew up, this type of aspiration was unheard of – and I think my parents were horrified! People would say to my parents, "Don't worry, he'll grow out of it."

But I did not! I worked hard and I attended the local grammar school. The school bus had to change its route to pick me up because I was the only one from my area who attended. It was known as a "rugby school" in England, which means that everybody played rugby rather than soccer, and nearly everybody was good at it. Except me. I was absolutely hopeless at rugby, but it didn't stop me from becoming head boy. In fact, I was the first head boy who wasn't also captain of the rugby team in over 100 years. After that, I moved from Blackpool to Birmingham to study medicine and biochemistry, waving goodbye to a dad who worked in a factory and a mother who worked as a cleaner. I like to think their horror had subsided at that point.

Mergers and acquisitions can change companies – and jobs – fast

For five years, I worked in hospital medicine, looking after patients with heart attacks, kidney failure, diabetes, strokes, and so on. I was on track to become an academic clinical pharmacologist, but in the mid-1980s I was recruited by Glaxo. Back then, it was a very different company to what it is today – they were nowhere near the top ten of big pharma. They made more money in baby food and other commodities than from their small range of medicines. As part of my new job, I set up their first phase I unit in Greenford, West London, on the floor of an old milk packing factory. Regulations regarding clinical trial approvals were less extensive than they are today. I managed many trials in human volunteers for products that brought Glaxo to where they are today, including fluticasone, cefuroxime, and ceftazidime, among others.

Then I moved to ICI where I developed their heart failure drug, lisinopril, before being promoted to head of cardiovascular research. In the early 1990s, they sent me to Toronto with the mission of setting up a research and development centre for their products. After a few (very fun) years, I returned to the UK and was promoted to global head of medical research for Zeneca, which by then had spun out from ICI. It was a huge job! Sitting one level below the board, I had over a thousand people reporting to me from all over the world.

Under my leadership at Zeneca, we got six major products approved, many in oncology. But then Zeneca merged with Astra, creating AstraZeneca. Being one

level below the board and with not enough seats at the table, I was made – to put it gently – redundant. Most of the R&D jobs went to Astra people, and most of the commercial jobs went to Zeneca people.

Some setbacks lead to new opportunities

In retrospect, the redundancy was probably one of the best things that ever happened to me. I wasn't short of job offers and I ended up taking the opportunity to help set up one of the world's first gene therapy companies: Ark Therapeutics.

Ark Therapeutics was a spinout from University College London and the University of Kuopio in Finland. The UCL scientist was John Martin, a professor of cardiology, and his Kuopio counterpart was Seppo Ylä-Herttuala. The two had previously worked together on research into gene therapies, eating up a €250,000 EU grant in the process. For their spinoff, they went to a prominent UK investor who was quite happy to back their startup – provided they could install proper leadership.

And that's where I came in. We took on a CEO and a CFO, and I became the R&D director. This all happened only four or five years after the very first clinical study of a gene therapy, so it was terra incognita for everybody.

Money talks. But that's not always enough

We raised millions in venture capital and came to float the company on the main London stock market in 2004, which raised another £55 million – taking the record for the biggest ever biotech float (and holding it for many years). Next, we built a manufacturing facility in Finland, with the assistance of the Finnish government. The gene therapy we developed was for the treatment of malignant glioma which included a large phase III study across 36 European sites, we also received a commercial license from the Finnish authorities for the manufacturing facility – the first ever in the world for gene therapy production. We achieved a great deal.

But when we took all this to the EMA, they didn't approve it. They were happy with the manufacturing and the toxicology work, but the medical reviewer was unsure about the endpoint we'd used. We had agreed upfront to go for progression-free survival, but the medical reviewer insisted upon us having overall survival. We went back for an appeal, but were denied.

It was a shame. We had raised about £150 million pounds to develop this project, but couldn't raise any further funds. By now, it was 2008, and we were in the start of the recession. Who would give any more money to a gene therapy company that just had a product rejected?

Companies in cell and gene need to prepare for a funding fight

Even today, where there is so much excitement around cell and gene therapy, funding is still difficult to access. In the US alone, there are over 500 budding cell and gene therapy companies. There are so many great ideas out there – but they need money.

There have been several cell and gene therapy companies that have raised a lot of money and floated on the New York Stock Exchange in recent years, but share prices have tanked over the last 12 months or so, and this is creating problems. It seems that the market is not particularly interested in new cell and gene therapy products right now. But we have to remember that things are cyclical.

When I was at Ark, big pharma was starting to show interest in gene therapies and I predicted they would get more involved, but then, in 1999, Jesse Gelsinger died after taking part in a clinical trial for a gene therapy. There were also a few other issues in studies – and big pharma left the sinking ship.

Many of us knew that big pharma would be back, which is exactly what happened. In recent years there have been a lot of deals and acquisitions, with big pharma snapping up cell and gene therapy specialists. However, many cell and gene therapy companies today will probably go to the wall because of the lack of funding. I think it will be survival of the fittest.

Every cloud really does have a silver lining

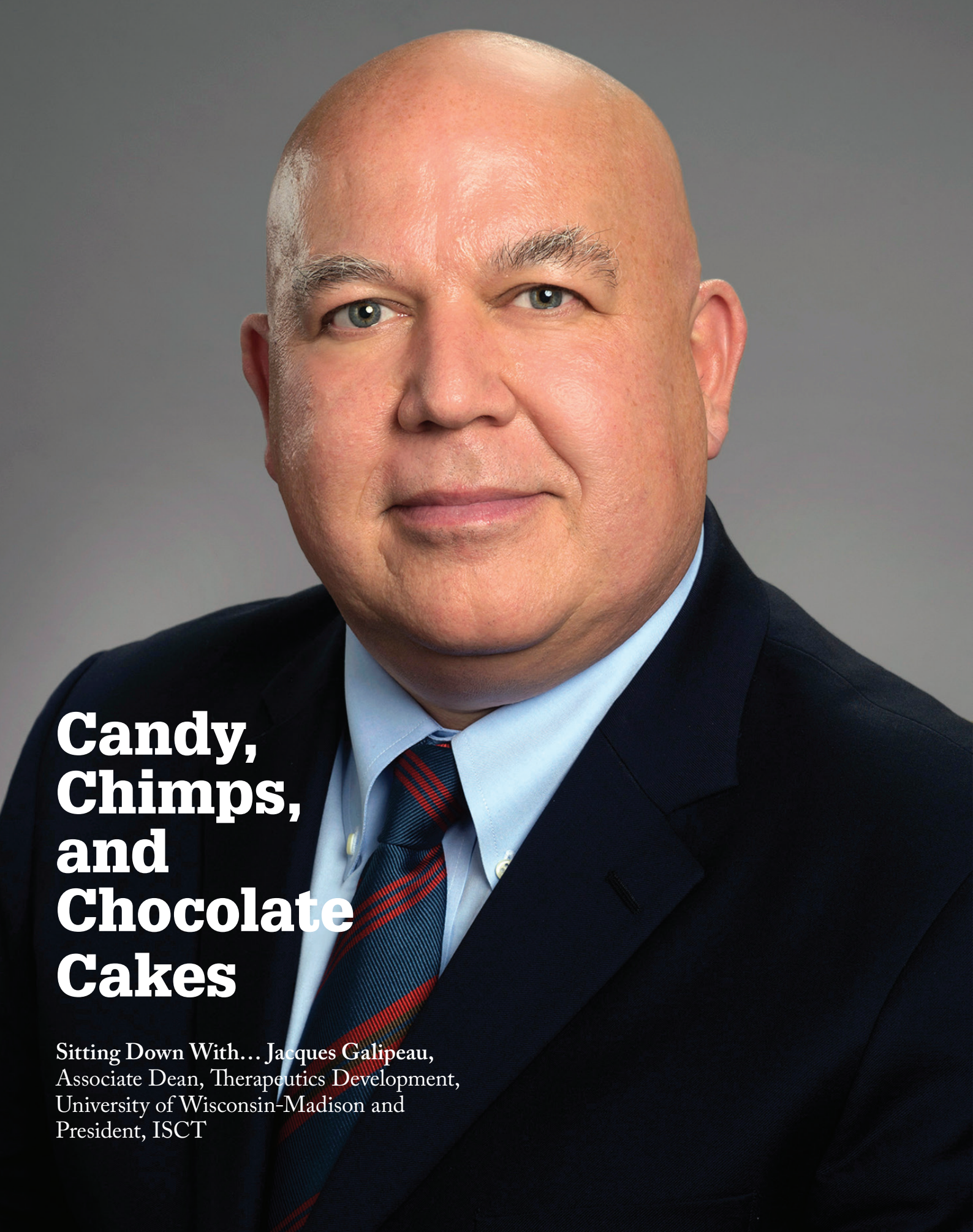
At Ark Therapeutics, we were able to take a DNA gene therapy product all the way through the development process and make a submission to the EMA – all by the book. We didn't get the product approved, but we'd still achieved something meaningful.

Prompted by encouragement from my investors, I then set up my consulting business, Boyd Consultants. My experience in both senior pharma roles and a biotech startup made me somewhat unusual at that time – in the best possible way.

The investors told me that I could offer them due diligence on their potential investments, and that they may well come to me seeking help with their developments at the board level. So I formed my consultancy solo but soon realized that I needed help. I started hiring, and after 17 years we now have almost 40 employees, just under half of whom make up the regulatory group. We have a global client base, and we've got two offices in England, one in Philadelphia, and – prompted by Brexit – one in Dublin, to keep us in contact with the EMA.

We do a lot of cell and gene therapy work because of my background – in fact, I'm proud to say that we have contributed at some time to eight advanced therapy products approved on either side of the Atlantic.

Looking back on this I know that to some extent I was lucky. My career is not one you could replicate starting today, because I was placed and working at a particular place and at a particular time. The moment has passed.



Candy, Chimps, and Chocolate Cakes

Sitting Down With… Jacques Galipeau,
Associate Dean, Therapeutics Development,
University of Wisconsin-Madison and
President, ISCT

Tell us about the work that you do…

At the University of Wisconsin-Madison, we have a special interest in virus-specific T cells and the "version 2.0" of mesenchymal cells. My work is in discovery – understanding how cells tick and how to make a better mousetrap out of them. We also work more boldly, testing first-in-human studies that may grow legs and march toward further development.

While wearing my ISCT hat, I'm like a kid locked in a candy shop! There are so many exciting platforms, especially in immunotherapy and regenerative medicine. For some, the latter term is a dirty word because it has so often been bandied about as a catch-all "everything for everybody." But now, we're hearing about ongoing, highly promising works like the clinical trials of induced pluripotent stem (IPS) cell-derived dopaminergic neurons for Parkinson's disease.

How was your time at the ISCT 2022 event? Did it feel good to be meeting up in person again?

Absolutely. We humans are gregarious simians. Chimps don't talk – it's all nonverbal. Humans deal in a great deal of nonverbal communication too, and that can't be replicated online. So much of the spontaneity and exchange is leached away through the virtual interface. Not to mention the drop in dopamine levels!

Offline serendipity can't be replicated either. Everybody has a story that proves it. You turn and say hello to the person behind you in a queue for lunch at an event, and the next thing you know you're launching a collaboration. That doesn't happen on Zoom, where everyone is just one rectangle in a grid of video feeds.

Was running an in-person event a major risk in the wake of COVID-19?

It was a bold bet. Between our CEO Queenie Jang, our outgoing president Bruce Levine, and myself, we knew that we would have to make the call by October 2021. Reading the signs, we made plans for an in-person event, and the result was a smashing success – the biggest turnout we've ever had at an international meeting. I also think it helped prove that in-person events should remain the gold standard, with virtual hybridity as a bonus that remains well worth considering. Recording events is another pandemic practice we'd like to keep alive. Having those recordings for future reference and wider access is really valuable. We want these international events to be absolutely optimal because they only come once per year and attending them isn't cheap – especially for our friends flying in from afar!

What's the current state of cell and gene therapy – and how far has it come?

The field has matured since the early nineties. It's worth remembering that the proof-of-concept for applying cell and gene therapies in humans arrived more than 30 years ago. Now, we have approved products! The first live cell vaccine approved by the FDA was Provenge in 2010. More recently, we've had the whole CAR T story, and in Europe we've seen the approval of mesenchymal cells for Crohn's-related skin complications. All in all, it's a very nice buffet.

There's a skills gap looming in the sector. Is there an answer?

The answer will be woven from different strands. In the case of established, repetitive approaches, automation is your most obvious ally. But during investigational development – when you're building the plane as you fly it – you may need some hands! Lab work can be a science in the same way cooking is a science. You need tactility, and more than a little artistry. Take the analogy of baking a chocolate cake. I might give the exact same recipe to Bob and to Bert. Bob makes a beautiful cake, and Bert makes a burnt mess. Good hands and good instincts; some people have them, and some people just don't.

Disruptive technologies are loose in this field, and the task of incorporating them is a hands-on affair. ISCT steps in here because we excel as a knowledge transfer and networking organization. We can't confer diplomas, but the way we pass on best practices is akin to a sort of cooking school, if I may stretch my chocolate cake metaphor a little further.

We bring in experts, and introduce them to "newbies" – people who may well be very clever and have excellent degrees, but who still need to learn the ropes. This is an ever-evolving field of ever-evolving platforms. Penning a curriculum is not much use because it will likely be out of date by the time you've completed the first draft.

Where is the field heading?

Right now, everybody is focusing on the highly impactful cell therapeutic platforms that have met marketing approval and are now commercially deployed. The challenges here really hinge on the different regulatory environments that shape them.

In Europe, success is dictated predominantly by universal payers and national entities. The US is more of a wild west. I have no magic solutions for my commercial friends, but I do aim to help them understand the best practices necessary for distributive justice. Balancing ROI and access is not just a moral question; if one overtakes the other, the platform may collapse.

Now, the relevant technologies are becoming increasingly simple, and the prices are ever more robust. It is becoming easier to imagine that hospitals could serve as a complement to large-scale manufacturing, especially for autologous cell therapies or one patient/one donor paradigms. There's a lot of new money in this space geared toward not only the traditional model, but also these complementary models of deployment. That's something I think we need to face, as the future comes knocking.

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