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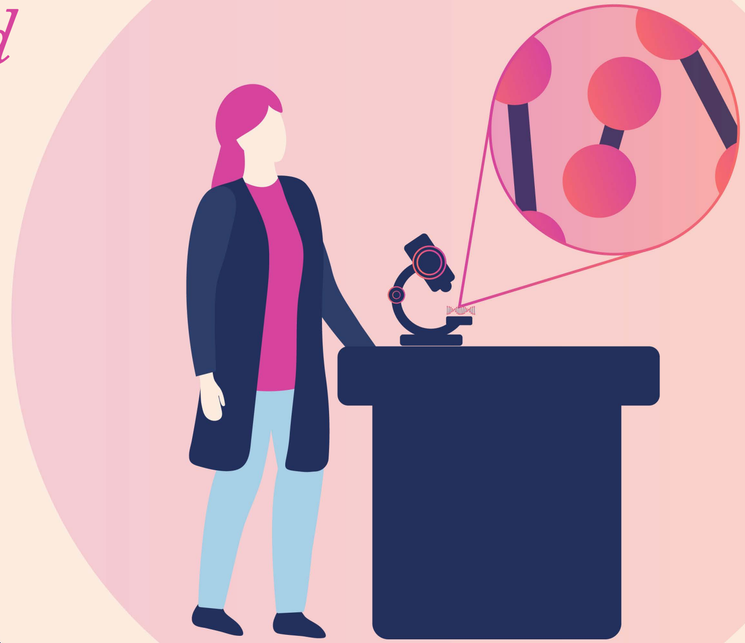

IN MY VIEW

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 at Forge Biologics and Erandi De Silva, Co-Founder and Vice President of Product Development 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:

- 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.

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.

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IN MY VIEW

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

By 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 a 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. And that's the mindset you need to help set your therapy up for success.

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Are you meeting safety standards for residual host cell DNA?

Meeting regulatory standards for cell and gene therapy products with absolute quantification and accurate sizing of HEK293 residual DNA

To realize the incredible potential of cell and gene therapies, scientists must overcome many challenges specific to creating these products. One persistent challenge is residual host cell DNA contamination.

HEK293 cells are a dominant platform for cell and gene therapy production. However, if traces of these host cells are not removed before the final treatment is administered, there can be dangerous immune responses or oncogenic effects.

To ensure patient safety when it comes to host cell DNA contamination, the Food and Drug Administration (FDA) published industry guidance for cell and gene therapy manufacturing:

"Limit the amount of residual DNA for continuous non-tumorigenic cells to less than 10ng/dose and the DNA size to below approximately 200 base pairs. If you are using cells that … have tumorigenic phenotypes (e.g., HEK293, HEK293T), the limitation of specific residual DNA quantities may be needed to assure product safety."

To ensure adherence to these rigorous guidelines, biopharmaceutical manufacturers need cutting-edge solutions. The traditional method for quantifying residual host cell DNA is quantitative PCR (qPCR), which relies on a standard curve and presents other limitations such as nonspecific signals and lack of reproducibility. In addition, BioAnalyzer technology, widely used for DNA sizing, fails to deliver cell line-specific results and is unable to analyze fragments larger than 7 kilobases.

In contrast, Droplet Digital™ PCR technology (ddPCR™) delivers the high-quality data you need to meet FDA standards. ddPCR technology provides an absolute count of target DNA copies per input sample without relying on standard curves. This capability makes the technique simpler, more precise, and highly sensitive.

The Vericheck ddPCR HEK293 Residual DNA Detection Kits are the first digital PCR HEK293-specific kits, providing an elegant solution that enables absolute quantification and accurate sizing of residual HEK293 DNA on the same instrument. In addition, the kits offer an extraction-free workflow—minimizing hands-on time and sample manipulation—and reproducible, quantitative readouts for precise measurement of residual HEK293 DNA.

With these easy-to-use ddPCR assays, you can confirm that the precise amount of residual HEK293 DNA in your cell and gene products falls within the FDA guidelines for every batch. Then, empowered with the knowledge that your products are clear of dangerous contaminants, you can have greater confidence in your work.

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IN MY VIEW

Solving Gene Therapy Challenges Using the Human Commensal Virome

Gene therapies have opened the door to a brand-new treatment landscape, but the field isn't without its troubles. Can the harnessing of our commensal virome help overcome bumps in the development curve?

By Tuyen Ong, CEO at Ring Therapeutics

Since their inception, gene therapies have held the promise of treating diseases that conventional therapies could not. Take Zolgensma, for example; developed by Novartis to treat spinal muscular atrophy (SMA), the drug's impact on young patients and their families since its approval has been profound.

Unfortunately, a large proportion of patients have pre-existing antibodies against the viral vectors used in gene therapies – a major challenge for gene therapy drug developers, as these patients cannot receive treatment or participate in clinical trials. However, if a patient is able to receive an initial therapy, current viral vectors cannot be repeatedly dosed due to the generation of antibodies that results in a robust immune response to any subsequent exposure.

The lack of tropism of certain gene therapies for tissues is another issue the industry has to contend with. The reduced capacity to "infect" cells and initiate treatment means that companies must, in some cases, increase the overall therapeutic dose to induce an appropriate response. But this decision comes with consequences; patients who receive increased doses of gene therapies may experience hepatic toxicity, liver inflammation, or even death.

Finally, there are documented instances where expression hasn't been permanent, so companies must also ask themselves how effective their gene therapies are in the longer term.

We need to embrace new approaches to gene therapy development for continued progress in the field. And with that in mind, examining the potential of our commensal viruses may help us understand how to overcome some of the impediments faced by the field.

"We need to embrace new approaches to gene therapy development for continued progress in the field."

Most of you have heard about the gut microbiome – the good commensal bacteria that coexist inside of us and influence how our bodies' function. But questions about the viruses that live within us without causing harm – the human commensal virome – often go unanswered. When we think about viruses – particularly now as the pandemic rages on – we associate them with illness. But I think there is a general lack of awareness about commensal viruses and the key role they play in human health. What if we could exploit such viruses to enhance gene therapies?

Ring Therapeutics was launched to take advantage of the viral residents of our bodies – the vast majority of which are anelloviruses. This particular class of virus can infiltrate cells without causing disease; they have evolved with us over millions of years and developed a genetic diversity that allows them to inhabit various organ systems. These evolutionary traits are a clear advantage over the more conventional viral vectors used today, which have not necessarily adapted to harmonious coexistence. Anelloviruses also exhibit strong tropism, making them even more compelling to use in gene therapies.

At Ring, we're using anelloviruses to create a new class of viral vector and deliver genetic payloads to patients. Importantly, studies have shown broad similarities between donor and recipient anellovirus. And that means redosing patients without triggering adverse immune reactions is a real possibility – with current gene therapy approaches patients can only be treated once.

Through harnessing the unique biology of anelloviruses, we've created a platform called Anellogy. The Anellogy platform is composed of four key pieces: AnelloScope, AnelloScreen, AnelloDesign, and AnelloBricks. Anelloscope is our primary discovery engine driving our platform growth which makes use of machine-learning strategies to identify and characterize the genetic make-up of the various anellovirus sub-types that exist within us. Thousands have been identified – all of which are potential candidates for further development.

AnelloScreen rapidly characterizes anelloviruses through screening for factors including tissue tropism, redosability, potency and immunogenicity. These results feed into AnelloDesign, our computational pipeline that uses this information to design a variety of AnelloVectors that that are capable of targeting specific tissues, are able to be redosed, and retain potency without unwanted immunogenicity. Our final platform component is called AnelloBricks, our in-house manufacturing system which works almost like Lego and allows us to assemble therapies exhibiting key intrinsic factors efficiently– testing the viability and success of different payloads and serotypes as we go. The programmability and scalability of this technology means that we can investigate how well these viral vectors work in a broad spectrum of diseases. Taken together, these components comprise a powerful new platform for building better programmable medicines – ones with the potential to be safely redosed and that can target a wide-range if tissues and conditions.

Gene therapies are undoubtedly a promising therapeutic modality, but the field is encumbered with pressing challenges. As a physician and drug developer, the science behind anelloviruses simply fascinates me. And I believe they give us a huge opportunity to have a meaningful impact within healthcare – providing a safe and effective option to add to the growing roster of advanced medicines.

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INTERVIEW

Towards Treatment for Leukodystrophy

Dan Williams, CEO of SynaptixBio, tells us the story of his career and how a colleague's ill child inspired the formation of the company

Can you introduce your company?

The story begins with a former colleague of mine at Immunocore.

Her daughter has a disease called H-ABC (hypomyelination with atrophy of the basal ganglia and cerebellum) – a form of leukodystrophy caused by the gene TUBB4A. After learning of her daughter's diagnosis, my colleague responded – not just as a mother but also as a scientist.

She investigated existing treatments and research, then set up a charity, all before sitting down with me to have a good think about how we could produce the therapy her child needed. That's how we ended up setting up SynaptixBio.

"Our aim is to alleviate the decline in quality of life faced by these patients – and potentially increase their life expectancy."

What's your background?

I'm a trained scientist. I spent the better part of 10 years at Dundee University in the UK, studying biochemistry and working toward my PhD. After my studies, I joined a very small start-up called Avidex. Over time, I progressed from the bench to leadership.

For the remainder of my first two decades post-academia, I worked in T-cell therapy development. I went from Avidex to MediGene, and then on to Adaptimmune, where my final role was vice president of research operations and technology.

After that came SynaptixBio.

Could you tell us more about leukodystrophy?

It's helpful to think of leukodystrophy as a spectrum of severity. At the severe end of the spectrum, babies born with the disease have developmental and motor issues.

With H-ABC – which is just as severe – the mutation forms within the children and they start to undergo myelin degradation, and again we see developmental delays and deterioration of motor functions. This usually starts at five to eight years old but it can continue through to the mid-to-late teens. Often, the disease is fatal.

There are also other forms of TUBB4A leukodystrophy that are less severe, but still affect quality of life.

Our aim is to alleviate the decline in quality of life faced by these patients – and potentially increase their life expectancy. If we can stabilize the disease outright that would be even better. Clinical trials will show us whether that level of success is possible.

How do you plan to tackle these diseases?

The starting point is our understanding of the root cause of the disease – in this case, a mutation in the TUBB4A gene. The mutation causes the formation of an abnormal protein, which then fails in its task of transporting various fats, lipids, and proteins used to produce myelin – a fatty substance that insulates nerves and causes the white hue in our brains.

Put simply, the formation of the myelin is compromised, meaning that the signals traveling back and forth along the central nervous system are disrupted. Patients start to suffer from problems with movement and can also experience seizures or developmental delays.

SynaptixBio is trying to develop a gene therapy that will silence the expression of the abnormal protein to allow another protein to step in to support production of myelin, in turn alleviating those symptoms.

The type of molecule under investigation is an antisense oligonucleotide (ASO), which binds to and inhibits the mutated TUBB4a messenger RNA encoding the abnormal protein. When bound, the cells cannot make the toxic mutant.

However, we don't yet know to what extent we can actually silence the gene, and we don't know the full mechanism of action.

What other challenges await SynaptixBio – and you personally as the CEO of a new company?

One key question we're trying to answer is: How many patients are out there? TUBB4A leukodystrophy is a rare disease, but it is not ultra-rare. As we examine the literature, we are finding that the numbers are higher than they first appeared. From personal experience, I can say that I've met a number of children in the south of England with the condition. And that's just one region in one country.

Pre-seed funding has been essential in helping us launch the company by paying for licenses and researchers. We currently remain privately funded, but we are gearing ourselves up for a further round of funding in the very near future, which would take us to the next phase, before being followed by the clinic.

Going down that road, we'll certainly encounter challenges, but also learning opportunities. We have good data, and we have our future spending mapped out, so I believe our position is strong. As CEO, I really enjoy contributing to every aspect of the business. I'm involved with the science, operations, development, and financial strategies. It is certainly a huge challenge, but I'm surrounded by incredible people.

How has your company navigated the pandemic?

Fortunately for us, we are a very small company, and we're almost entirely virtual. We don't actually have labs. We are outsourcing and partnering at the moment. Working from home and meeting in Zoom has worked well for us, but we did miss the upsides of face-to-face communication. I will also say that my dog deserves some of the credit. On a typical working day he's with me in my home office – either curled up on the sofa or demanding walks for our mutual sanity.

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Cracking mRNA's Manufacturing Code

With complex workflows to navigate, pharma companies must find trusted partners to rely on as they navigate the challenges of mRNA manufacturing

While mRNA is now widely known for being a central component in vaccines for COVID-19, a group of dedicated scientists and researchers have been studying the potential of this molecule for decades in hopes of developing novel cancer therapies. Despite steep challenges, the researchers persevered, which has led to advances in a host of mRNA-based therapies that are now in clinical trials. The biggest success, however, has been the development and approval of several mRNA-based vaccines against the SARS-CoV-2 virus. In fact, the pandemic played a crucial role in "cracking the code" of mRNA technology – and mRNA changed the course of the pandemic.

It's time to take those years of research and recent learnings and help scientists discover the next mRNA breakthrough. Before that can be accomplished, however, the industry must make certain investments to help alleviate logistical and supply chain bottlenecks and address the unique needs of mRNA-based manufacturing. Today's mRNA manufacturers require holistic solutions that can help reduce project risks, stabilize costs, maximize capacity, and help speed time to market.

As a provider of end-to-end solutions for mRNA, Cytiva has recently moved toward enabling the development, manufacture, and delivery of mRNA-based vaccines and therapies through its large-scale mRNA manufacturing workflow offerings. From plasmid DNA (pDNA) template manufacturing to mRNA synthesis and mRNA–lipid nanoparticle formation, mRNA solutions from Cytiva help enable sequence-to-patient manufacturing with a fast and standardized process.

Through its Enterprise Solutions division, Cytiva provides flexible start-to-finish solutions that are configured to support different product modalities. These include modular solutions for both pDNA and mRNA manufacturing by way of Cytiva FlexFactory™ platforms and KUBio™ facilities.

Whether you are just getting started, or want to grow to large-scale production, Cytiva brings a breadth of offerings to help you evolve or scale up your mRNA manufacturing.

Cytiva is a global life sciences leader that works with academic and translational researchers, developers, and manufacturers of biotherapeutics, cell and gene therapies, and new technologies such as mRNA, to enable the delivery of transformative medicines. Cytiva is a trusted expert with nearly 10,000 associates in more than 40 countries dedicated to customers' speed, flexibility, capacity, and efficiency in drug discovery, research, and manufacturing.

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OPINION

Addressing the Skills Shortages

We ask industry leaders to answer one big question: Where do the biggest skills shortages exist in this field – and how should we address the problem?

Matthew Durdy of the UK Cell and Gene Therapy Catapult says:

"We must train the workforce of the future."

In our 2021 Cell and Gene Therapy Skills Demand Survey, we found that between 2021 and 2026 the UK's cell and gene industry will need employees to be split across three main roles as following, with bioprocessing staff most in demand:

- 74 percent in bioprocessing
- 11 percent in research and development
- 7 percent in support services

Moreover, 62 percent of employers are intending to recruit to expand their workforces within the next two years, with most companies looking for skilled and experienced people. In my view, the greatest shortage will be in the demand for sector-specific skilled people.

In the UK and across the world, the current demand for talent is a good problem to have; it is a testament to flourishing investment and innovation. But we need new initiatives to help develop a new wave of talent in advanced therapy, such as apprenticeships that expose apprentices to the most cutting-edge developments in the field, to cultivate the skills that the market lacks. It would also be beneficial to look at how we can bring transferable skills from other sectors into our own.

At the Cell and Gene Therapy Catapult, we're doing our part with an Advanced Therapies Apprenticeship Community program.

Anshul Mangal of Project Farma says:

"Partnerships can help to overcome the problem."

The cell and gene therapy industry has experienced exponential growth in the last three years and, as funding for the field continues to break records, there are no signs of a slowdown. With 2,261 ongoing clinical trials in regenerative medicine, the FDA expects to approve between 10 and 20 new cell and gene therapies a year by 2025. However, this means that the need for solutions to the industry's biggest bottlenecks are growing daily.

The advanced therapeutic revolution has resulted in a significant talent shortage across the industry, particularly in manufacturing. Even with recent advances in automated technology for cell and gene therapies, the sector is still heavily reliant on manual processes, so these technological leaps cannot yet backfill the workforce gap.

Though the talent shortage is a complex problem, the industry is making great strides to come together to find solutions. Leveraging private–public partnerships and continuing to disseminate experiences and information across the industry will help elevate the current generation of skilled workers. In an effort to focus on the next generation of talent, funding is being poured into universities to support advanced degrees for the industry's incoming technical workforce. For example, last April the US National Science Foundation awarded a $573,347 grant to a Pennsylvania community college to support efforts in elevating the advanced technical workforce for the cell and gene therapy industry.

Matthew Durdy

Anshul Mangal

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 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.

Carl Taylor of TrakCel says:

“Companies must be aware that competition for talent is tight – and ensure they provide attractive places to work.”

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


Carl Taylor

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CCRM is expanding its CDMO offering. As a CCRM subsidiary, OmniaBio Inc. will extend CCRM's manufacturing capacity from Phase I/II clinical trials to Phase III and commercial-scale manufacturing. Benefitting from an ecosystem built over a decade, OmniaBio will be Canada's largest manufacturing facility for cell and gene therapies and will build on CCRM's training, infrastructure, manufacturing platforms, technologies and partnerships.

Operational	**120 employees**	**20,000 sq ft**	**11,500 sq ft lab (PD, MSAT, QC)**	**10 clean rooms**
Opening 2024	**500 employees**	**~100,000 sq ft**	**17,000 sq ft lab (PD, MSAT, QC)**	**15 clean rooms**
Opening 2025-6	**1500 employees**	**~305,000 sq ft**	**45,000 sq ft lab (PD, MSAT, QC)**	**32 clean rooms**

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CDMOs Are Enabling Therapy Developers to Save Lives

Jocelyne Cormier was out of options when she learned of a clinical trial for a CAR-T cell therapy to treat her cancer

It was 2014 and she was travelling regularly from Picton, east of Toronto, to the Princess Margaret Hospital in Toronto, Canada, to meet with her care team. She signed up.

By the time she participated in a corporate video for CCRM in 2017, her cancer was in remission and she was living a disease-free life. Now, in 2022, she is still cancer-free and is spending her retirement playing with her two young grandchildren. She remains very grateful for the care she received that saved her life.

Jocelyne Cormier, Emily Whitehead (celebrating 10 years cancer-free) and others like them, are the reason why cell, gene and tissue-based therapy developers exist. CCRM, a Toronto-based contract development and manufacturing organization (CDMO), exists to enable these developers – of which there are over 1,300, according to the Alliance for Regenerative Medicine.

CCRM launched in 2011 with a mission to generate sustainable health and economic benefits through global collaboration in regenerative medicine, and cell and gene therapy (CGT). In practical terms, CCRM is helping to build a regenerative medicine ecosystem by solving the big challenges that face the industry.

"When Peter Zandstra [Director of the School of Biomedical Engineering, University of British Columbia] and I conceived of CCRM more than a decade ago, we realized that manufacturing needed to be our sweet spot," explains Michael May, President and CEO of CCRM. "We've put considerable effort into building specialized infrastructure and teams, and now, with OmniaBio Inc., we have the capabilities to offer clinical to commercial manufacturing of CGTs."

The volume of clinical trials underway puts pressure on CDMOs to scale-up the production of cells and viral vectors needed for therapies, and worldwide demand is currently outstripping supply by at least five times. Based on the number of clinical trials in progress – 2,406 according to ARM – there could be 10-20 CGT products approved every year for the next several years needing CDMO services. OmniaBio Inc., located in Hamilton, Ontario, is just 50 miles from the US border and is accepting clients.

Jocelyne Cormier isn't thinking about viral vectors or automating cell manufacturing. She trusts that CCRM and others are doing that on her behalf. She's busy with all the things on her to-do list and doesn't understand how people can feel bored in retirement when her schedule is so full. That's a good problem to have.

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SITTING DOWN WITH

Time Will Always Tell

A lifelong passion for genetics led Dolores Schendel to Medigene, a German-based biotech company. But what lessons did she learn along the way – and how far does the immunotherapy sector, particularly the TCR-T segment, need to go before it becomes a mainstay in healthcare? Here, she shares her views on all things advanced medicine.

Why science?

Before my university experience, I had always dreamed of pursuing a career in medicine, but I ended up at a college that offered its students great research opportunities. Every summer, I would find myself in a different location, working on a new project alongside different colleagues. One year, I spent time on the Isle of Anglesey, Wales, studying barnacles! My research was acknowledged in a scientific publication and, from that point onward, I was hooked.

But, though I had cemented the idea of becoming a scientist in my mind, I still wasn't clear in what area of science I wanted to work. Because I had always had an interest in genetics, I decided to pursue a PhD in the subject with a subspecialty in immunogenetics. Throughout my doctorate, I explored the role of human leukocyte antigens (HLA) in cellular function and the genes that regulated the immune system – trying to find targets that would improve bone marrow transplantation. It was, and still is, an intriguing area of research – probably why I'm still involved with it today!

"I'm confident that pharma will find ways of bringing these important medicines to patients, but time will be an important consideration."

What advances in immunotherapy have stood out during your career?

Several events have imprinted on my life and impacted my career significantly. The emergence of synthetic biology and the discovery of the structure of T cells are just some examples of moments that have helped shape me as a professional within the industry.

But the crystallization of HLA molecules was like watching lightning strike across the sky. It was awe-inspiring. Not just because we could see the peptides at the heart of these molecules, but because it represented a huge milestone in the progression of scientific research. For the first time, we had a good understanding of these beautiful molecules. The discovery opened new avenues in research and development as we further explored the function of these proteins. The discovery meant that scientists and companies alike could embark on journeys that would help create solutions for areas of unmet need.

What lessons have you learned from working in different research environments?

Each scientific community is like an anthropological cluster. Science is very much a community activity, but the culture differs from country to country. I think it's important to travel and live with those differences. If you can take the best of the social and scientific cultures of each country you work in, you can contribute to the development of positive working environments that champion and celebrate the individual strengths of your team members.

What's the story behind Medigene?

Before my team and I joined Medigene, I was the head of a research institute at the Helmholtz Association – an organization with a clear interest in understanding the real-life applications of research. Of course, the researchers who worked there were all tackling problems that had a significant impact on society. This gave me the opportunity to explore both the use of T cells in transplantation and my interest in curing cancers.

My team and I had a successful run in the institution, but we realized that we would have to move into the commercial arena to test the tools and technologies we were working on. It was a huge step for us. We tested our platform in a way that wouldn't have been possible in an academic environment. Simply put, the world of industry was fascinating. The infrastructure and resources available brought an entirely new dimension to our work. Though there were many lessons to be learned and challenges to overcome, we have also had many successes during our time in pharma. For example, we were the first company in Germany to bring a TCR-T cell therapy to the clinical stage. I'm sure we will celebrate many more milestones as our journey continues.

What are your predictions for the future of immunotherapy?

I think it's important to look back at the achievements we have already made in the field before casting our minds toward future aspirations. Scientific research is a labor of love and, sometimes, breakthroughs are years in the making. Take antibodies, for example; it took several decades before the first products were commercialized to treat cancer. Finding the right target molecules and understanding the immune reactions to these products took years. But success breeds success. Once the first breakthrough occurred, there was no stopping the pharmaceutical industry from continued innovation. Now, there are antibody products not only for cancer, but also for autoimmune diseases. The field is ever-expanding.

We're seeing the same pattern emerge in the CAR T field. At the moment, companies and researchers are trying to find the right targets, elucidate cell structures, and navigate the complexities of delivering these therapies to patients. There are many questions yet to be answered, but the field is undoubtedly progressing.

TCR-T therapies are a little further behind, but developers can learn from the successes and failures that have affected other segments of advanced medicine and TCR-Ts open-up a whole new universe of potential target molecules to tackle. I'm excited to see what happens next!

What question does the industry need to address?

Cost is always a pressure in drug development, but for living therapies – particularly gene therapies and immunotherapies – we need to think of cost-effective ways to manufacture and distribute products.

The fact that living cells will remain a key component in the development of these products leads to difficult, but necessary cost considerations. I'm confident that pharma will find ways of bringing these important medicines to patients, but time will be an important consideration. As technologies develop, so too will our ability to create access. Who could have imagined the progress the pharmaceutical industry has made in the last 10 years? Imagine what the next decade will bring!

APPLICATION NOTE

Quantify HEK293 Residual DNA Without Extraction

Meet regulatory standards for cell and gene therapy products with absolute quantification of HEK293 residual DNA

Cell and gene therapy manufacturers are no longer limited to traditional methods of detecting potentially dangerous residual host cell DNA for quality control. Droplet Digital™ PCR (ddPCR™) offers the sensitivity, reproducibility, and cell line specificity needed to overcome the challenges faced by other tools such as qPCR. Now you can access the off-the-shelf validated solution for quantitative data generation and analysis providing confirmation on the quantity of HEK293 DNA in your therapeutic product.

The Vericheck ddPCR HEK293 Residual DNA Quantification Kit is designed to quantify residual HEK293 DNA in biotherapeutics with a novel 5-plex ddPCR assay that offers high specificity and reproducibility. The assay works with a broad range of sample types, from in-process samples to purified final product, using the extraction-free workflow of ddPCR technology.

The Vericheck ddPCR HEK293 Residual DNA Quantification Kit provides:

- High sensitivity and specificity
- Limit of detection (LOD) of 0.1 pg/µl (3 wells) and limit of quantification (LOQ) of 1 pg/µl (3 wells)
- Low cross-reactivity and low false-positive rate
- 99.9% specificity to HEK293 DNA when tested against Chinese hamster ovary, E. coli, and Vero cells

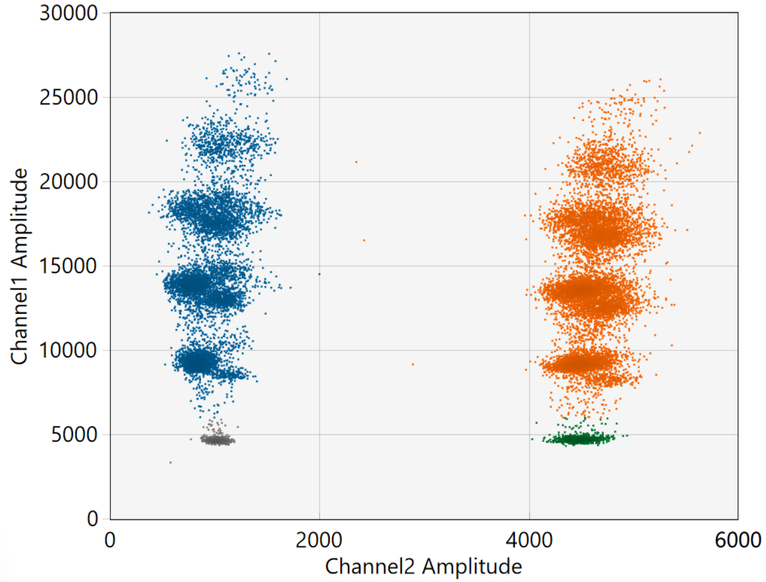
Extraction-free, easy-to-use protocol

- Broad range of sample types, including in-process samples (cell lysates, cell culture media, sonicated samples, and adeno-associated virus [AAV] vectors) and purified final product (phosphate buffered saline [PBS] with human serum albumin [HSA])

Positive control-based auto thresholding with regulatory compliant software

- Automated data analysis using in-kit positive control with QX Manager version 1.2/QX ONE version 1.2 Software
- Software includes tools to help with U.S. FDA 21 CFR Part 11 compliance, offering audit trails with tracked protocol changes

VISIT THE BIO-RAD WEBSITE TO LEARN MORE ABOUT THE VERICHECK DDPCR HEK293 RESIDUA DNA QUANTIFICATION KIT AND ORDER YOURS TODAY.



2-D amplitude plots showing data obtained by using the Vericheck ddPCR HEK293 Residual DNA Quantification Kit to test unextracted AAV sample with 25 ng residual HEK293 DNA contamination. The internal control is used as an inhibition control for unextracted samples. Plots show HEK293 signal in channel 1 (FAM) and internal control signal in channel 2 (HEX). The cluster in gray is double-negative for HEK293 and internal control, the blue clusters are positive for HEK293, the green cluster is single-positive for internal control, and the orange clusters are double-positive for HEK293 and internal control. The HEK293 Residual DNA Quantification assay is a 5-plex assay that detects five targets in the FAM channel. The higher amplitude FAM-positive clusters represent higher occupancy droplets that contain multiple HEK293 target molecules.

SPONSORED FEATURE

SPOTLIGHT ON...
DROPLET DIGITAL PCR TECHNOLOGY

QX200 Droplet Digital™ PCR (ddPCR™) System

The QX200 ddPCR System consists of two instruments: the QX200 Droplet Generator and the QX200 Droplet Reader. It provides absolute quantification of target DNA or RNA molecules for EvaGreen or probe-based digital PCR applications.

EXPLORE THE INSTRUMENT AND WORKFLOW

QX ONE Droplet Digital™ PCR (ddPCR™) System

The QX ONE ddPCR System seamlessly integrates a standard ddPCR workflow of droplet generation, thermal cycling, droplet reading, and analysis into a hands-free platform. Save time with walk-away automation and increase your throughput with advanced multiplexing capabilities.

SEE FEATURES AND APPLICATIONS

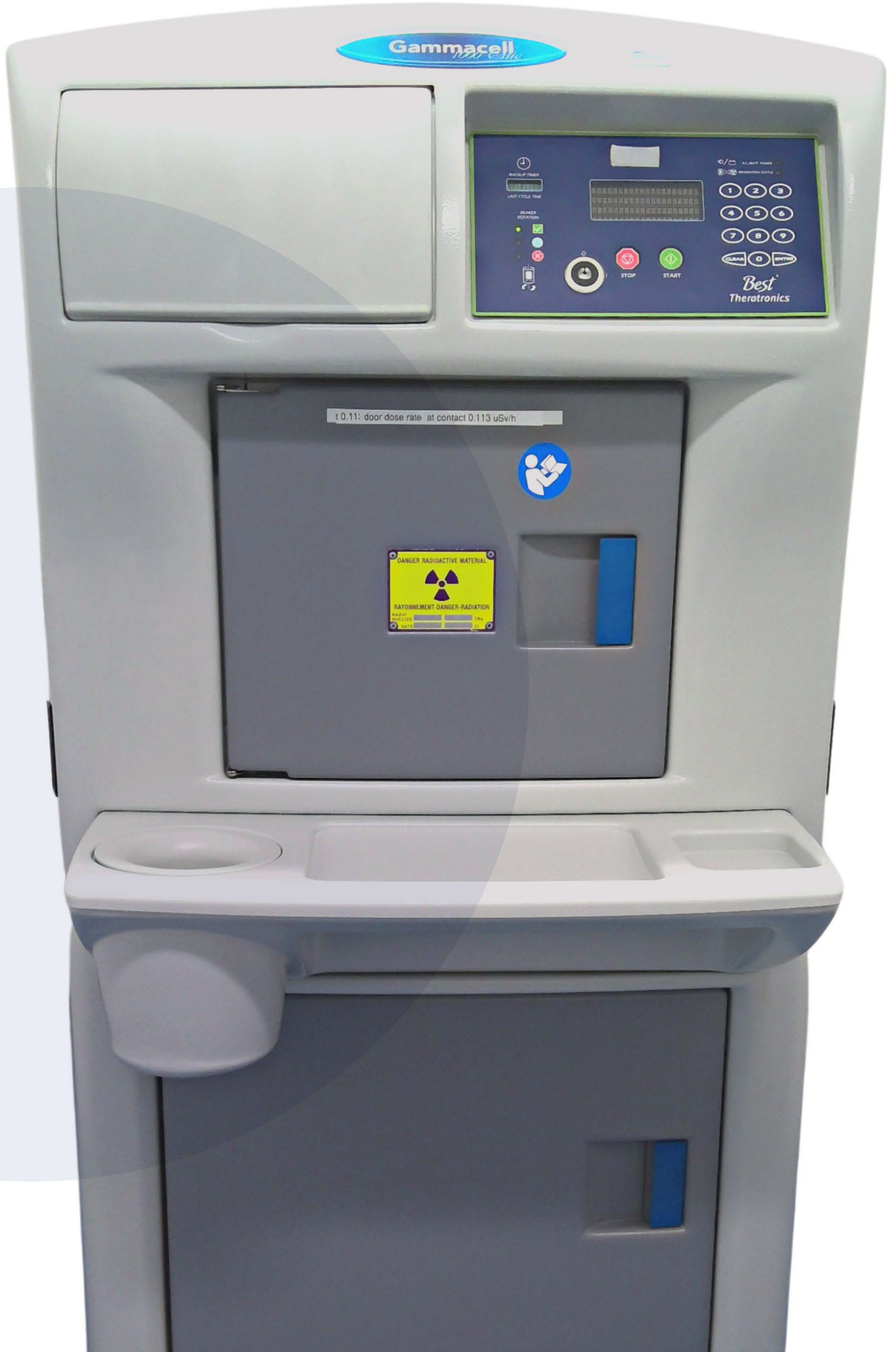
Vericheck ddPCR HEK293 Residual DNA Quantification and Sizing Detection Kits

These ddPCR-based assay kits are compatible with both QX200 and QX ONE systems, providing highly specific, sensitive, and precise quantification and provides sizing information of host cell DNA contamination in complex bioprocess intermediates. The workflow is extraction-free and regulatory software is available.

LEARN ABOUT DETECTING HEK293 DNA CONTAMINATION

SPONSORED FEATURE

SPOTLIGHT ON...
TECHNOLOGY



The Gammacell 1000 Irradiator: A Special Tool in CCRM's GMP Arsenal

Gamma irradiation is the most effective method to inactivate cell populations, including peripheral blood mononuclear cells (PBMCs) and cancer feeder cell lines. The irradiated cells become damaged and can no longer divide, but are still alive and can produce cytokines and other soluble factors that make them ideal for use as an activator during the drug product manufacturing process in the field of cancer immunotherapy.

FIND OUT MORE ABOUT CCRM'S ENABLING TECHNOLOGIES.