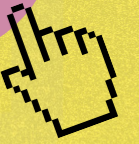


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# HAVING THE *Right Conversations*

To ensure the cell and gene therapy field advances with all stakeholders in mind, especially the patient, we need to talk – now

EDITORIAL

UPFRONT

FEATURES

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WITH

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EDITORIAL

UPFRONT

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Editorial

**E**



### No Rest for the Wicked!

*If there's one word that sums up the state of the field at the end of a challenging year, it's resilience – but another could be excitement*

In my editorial for our 2019 cell and gene therapy supplement (1), I suggested that many in the industry would not be preoccupied with full stockings in the weeks leading up to Christmas, “but rather full schedules – with many conferences to attend.” Oh, how times have changed! Last year’s overview was based on the conferences I’d attended that year. And though there have been many virtual events in 2020 – some excellent ones – nothing quite beats a few days away from the desk seeing people face to face. But in February this year we launched The Cell + Gene Curator ([www.texereneletters.com/cellandgene](http://www.texereneletters.com/cellandgene)) – a weekly newsletter covering the latest research, process innovations, and business updates in the field – and it has given me a different perspective and a different sense of connection.

In our third issue, I was already discussing “the global spread of the novel coronavirus,” and, to be honest, I was concerned there wouldn’t be much to curate. As it turned out, while there were difficulties (especially recruiting patients for new trials), the industry was able to adapt – the volume of research (as you can see from our roundup on page 10), business deals,

and announcements never ceased. As an Alliance of Regenerative Medicine report highlighted (see page 5), funding for cell and gene developers in the first half of 2020 was double what it was in 2019.

Such high levels of activity certainly speak to the resilience of the field. And perhaps that resilience is driven by results that generate true excitement.

In cancer cell therapy alone, we’ve seen the discovery of cells able to kill most human cancer types in mice (2), genetically engineered macrophages (3), and allogeneic T cells (4) that can kill solid tumors (also in mice), 78 percent response rates in an allogeneic CAR T trial (5), 25/29 complete responses in J&J’s anti-BCMA CAR T (6), and even another CAR T approval (7) – a peek into the future of oncology.

Despite the unusual lack of travel commitments for this time of year, it seems that the cell and gene therapy community isn’t about to sit back and relax with a large glass of eggnog – even if it is richly deserved.

**James Strachan**  
Deputy Editor

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## Spreading the Word

**Keith Thompson joins OVID Health in time for the launch of The Cell and Gene Collective, which aims to boost patient access and awareness of cell and gene therapies**

The development of cell and gene therapies has progressed with incredible pace, but are doctors and regulators ready? And are patients prepared for this new frontier of medicine?

To help ensure patients who could benefit from advanced medicines do so, specialist communications agency, OVID Health, is set to launch the Cell and Gene Collective in the new year. “The unifying force behind the Collective is patients” said Roudie Shafie, Director at OVID Health and former head of the Association of British Pharmaceutical Industry’s Government Affairs team. “What that looks like in the short to medium term involves raising awareness of cell and gene therapies, particularly among the policy making and healthcare professional community. We also need to overcome any barriers that occur from regulatory approval onward

in getting treatments to the patients who can benefit.”

Healthcare systems must be ready for cell and gene therapies, so Shafie, who is leading the project, sees a need for changes to the acute care environment – from workforce to supply chain to manufacturing – and even how they are procured and paid for. “We need a greater willingness by policy makers and payers to answer some of the difficult questions about how they value the life-changing potential of these new treatments,” she says.

Keith Thompson, founder and former CEO of the Cell and Gene Catapult, also recently joined OVID. “We are at a crucial moment in the evolution of cell and gene therapies where we want to reach out to explain simply the promise of these new treatments,” he says.

Thompson believes cell and gene therapies could be part of a fundamental recalibration of how we treat disease. “The UK has done a great job in bringing the first wave of cell and gene therapies to patients mainly with rare and orphan diseases, but we have a tidal wave of them coming and a step change is needed. There is little bandwidth to make this step up today,” he says. “But we don’t think hope should wait – OVID is bringing together like-minded companies and patient organisations who want to see patients get these life-changing treatments as soon as they become available.”

## Cross-Kingdom Collaboration

**Tissue engineers combine plant and human cells for the first time**

In recent years, 3D bioprinting techniques have been used to fabricate tissues for biomedical applications. But, despite advances in bioink technology, maintaining sufficient oxygen levels throughout remains a major limiting factor.

Now, researchers at Harvard Medical School have developed a 3D-printed algae-based biomaterial that provides a sustainable source of oxygen for the growth of human cells in engineered tissue (1).

The photosynthesizing algae supply mammalian cells within a volumetric matrix-like construct with a “natural, eco-friendly, cost-effective, and sustainable source” of oxygen, which supports the development of engineered tissues and tissue models.

“The study is the first true example of symbiotic tissue engineering combining plant cells and human cells in a physiologically meaningful way, using 3D bioprinting,” said senior study author Y. Shrike Zhang (2).

### Reference

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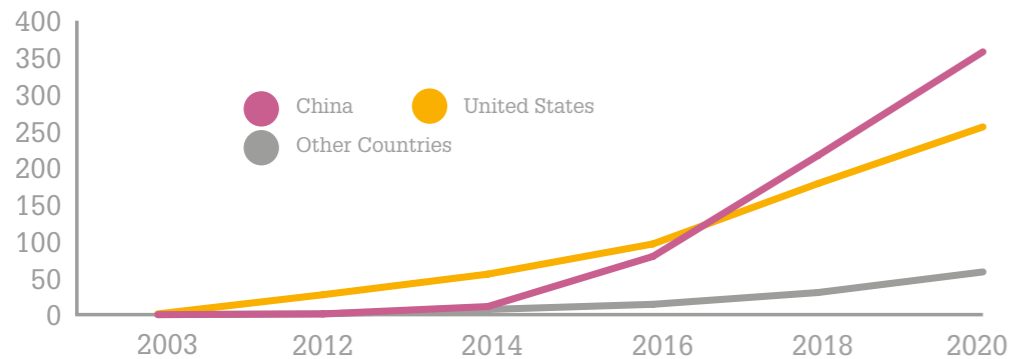


INFOGRAPHIC

# Surveying China's CAR T Boom

China has more CAR T-cell therapies in clinical development than the rest of the world combined

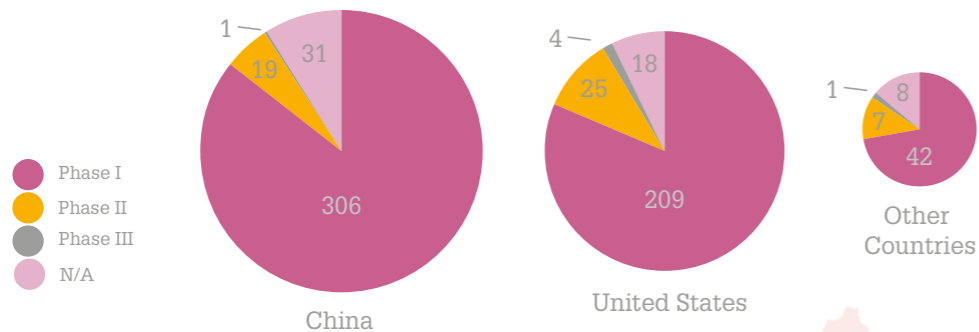
CAR T trials registered on [clinicaltrials.gov](https://clinicaltrials.gov)



Some complications (according to the authors)...

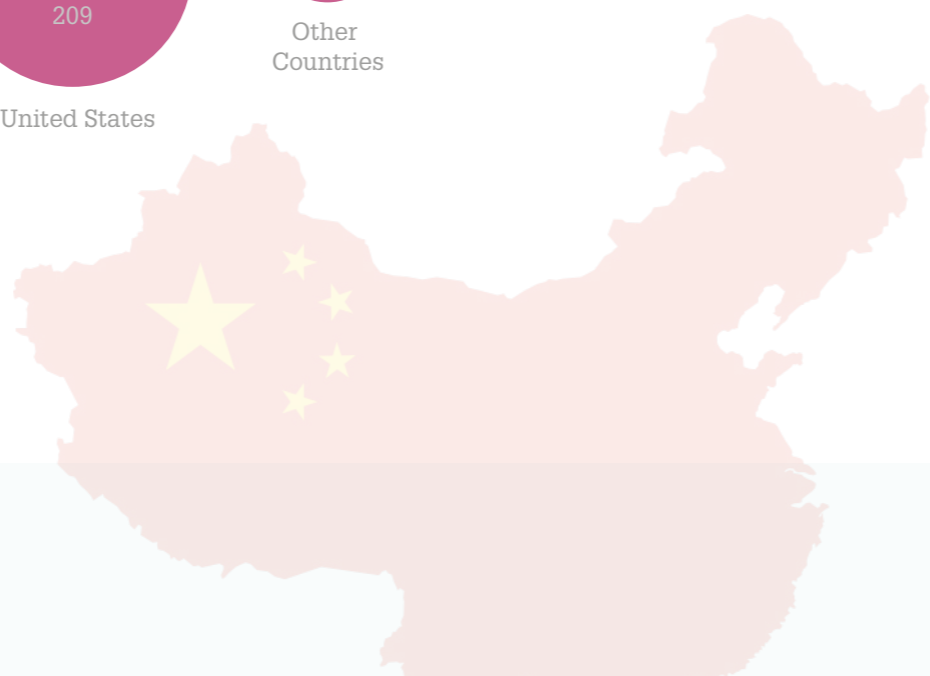
- ★ Most lack investigational new drug applications
- ★ Most trials small-scale and single-centered
- ★ Lack of “rationality and originality” in trial design

In 2020...



Source:

1. J Wei, “Clinical development of CAR T cell therapy in China: 2020 update” (2020). Available at: <https://go.nature.com/2HlycjH>.



## THE YEAR 2020: BUSINESS-IN-BRIEF

Bayer's big buy, a third CAR T, and the industry perseveres... Three business highlights from 2020.

- An Alliance of Regenerative Medicine report highlighted the resilience of the advanced therapy sector during the early stages of the COVID-19 pandemic. Global fundraising for cell and gene therapy developers during the first half of 2020 more than doubled compared with the same period in 2019. At the time of the report's publication, there were more than 1000 active regenerative medicine and advanced therapy developers worldwide – and over 400 of these companies had progressed to the clinical development stage.
- In July, the FDA gave the nod to Kite Pharma's Tecartus – a CD19 CAR T for adults with relapsed or refractory mantle cell lymphoma. The decision was based on results of the ZUMA-2 trial, in which 87 percent of the 72 patients responded, including a 62 percent complete response rate at a minimum follow-up of



- six months. Tecartus debuted with a list price of US\$373,000.
- Bayer paid US\$2 billion upfront and will pay up to US\$2 billion in success-based milestone payments to acquire gene therapy developer AskBio. AskBio has a pipeline of gene therapies, including programs for Parkinson's, congestive heart failure, and Pompe disease in early human trials. “Instead of going to Wall Street and every quarter trying to make milestones, we have one financial partner with which we're trying to bring this technology to fruition,” said Sheila Mikhail, AskBio CEO.

Want to stay up to date with all the advanced medicine news each week? Subscribe – for free – to *The Cell + Gene Curator*: [www.texereneletters.com/cellandgene](http://www.texereneletters.com/cellandgene)







## The Scale-Up Mindset

The Medicine Maker's Deputy Editor, James Strachan, hosted a panel discussion at Reuters Cell and Gene Therapy USA 2020 on scaling up ATMPs. Here, we pick out three key quotes from the session.

“If you think about needing to produce product for about 1000 patients a year, and our current batch records can run anywhere from 400-600 pages per batch, you start getting into the millions of pages of documents that you have to manage [...] There's a need to transition those to electronic batch records; but we can go even further towards a 'failure by exception' process, where there's a lot more automation in the sense of capturing the information that's coming out of your QC testing and filtering it effectively, so you're only stopping the disposition process when things are not obviously meeting your spec.”

~ Steven Goodman, Head of Drug Product Manufacturing, bluebird bio

“In taking the lens of the patient and the hospital provider, we were able to have real conversations about things that should be an industry utility. So when we think about labels and the data fields on labels, or the audit approach and how we reduce the level of impact [...] these were some of the areas we were able to align. And my hope is that the same mindset can transfer over to where you have cell and gene therapy publications, where there are people who have done really great work, putting it out there as open source code so that folks can build and iterate on that.”

~ Peter Olagunju, SVP, Technical Operations, FerGene

“I do think the cell and gene therapy industry will go a similar way to monoclonals, but I think it will be for very different reasons. Monoclonals had that inflection point when cell line engineering and cell specific productivities went through the roof. Cell and gene is so multimodal that I don't think there will be a single technical advancement [...] So as an overall industry, we are headed in the same direction, but our technical challenges – and the multiple different manufacturing modalities – are going to make for very different mechanisms of how we get there.”

~ Gary M. Pigeau, Director, Centre for Advanced Therapeutic Cell Technologies, Cytiva

*Steven Goodman, Peter Olagunju, and Gary M. Pigeau, were all speakers at Reuters Cell and Gene Therapy USA 2020: <https://bit.ly/2SLdu4D>*







## The More You Know...

### A decade-long AAV gene therapy study in dogs emphasizes the importance of long-term follow up

A 10-year study of AAV gene therapy in haemophilic dogs found genomic changes that may increase the risk of liver cancer (1).

Though none of the nine dogs administered with the AAV8 or AAV9 vectors (expressing canine factor VIII) in the study showed evidence of tumors or altered liver function, the team found 1,741 unique AAV integration events in genomic DNA and expanded cell clones in five dogs, with 44 percent of integration near genes involved in cell growth.

The authors pointed out that, though integration into the host genome has been observed in mice, non-human primates, and humans, previous studies for hemophilia B with about 10 years' follow-up haven't reported increases in transgene expression or vector-mediated serious adverse events.

They added that their data "emphasize the importance of long-term monitoring after AAV gene therapy."

#### Reference

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## Cell Engineering, Meet Big Data

### Big Data opens the door to "smart" cell therapies that remain inert unless triggered by cancer-specific protein combinations

In September, researchers from the University of California, San Francisco, assembled a catalog of protein combinations that could be used to precisely target cancer cells (1).

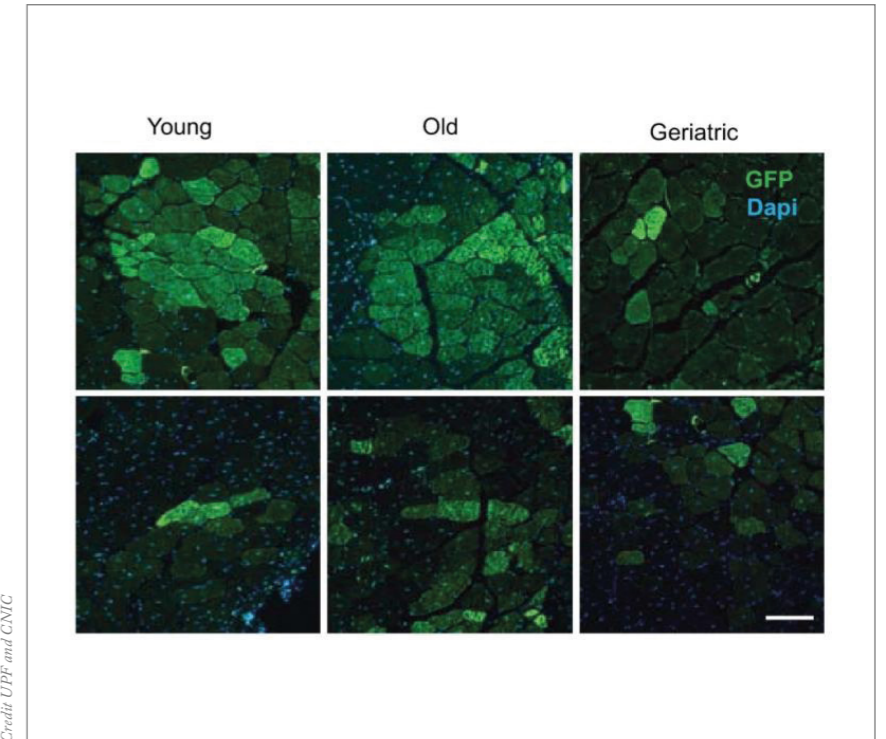
In their latest study, the team screened more than 2.5 million dual antigens and around 60 million triple antigens across 33 tumor types and 34 normal tissues, finding that dual antigens significantly

outperform the best single clinically investigated CAR targets and also predicted that antigen triplets could offer "close to ideal tumor-versus-normal tissue discrimination for several tumor types" (2).

To demonstrate the potential power of the data, the team programmed T cells to kill kidney cancer cells expressing a unique combination of antigens called CD70 and AXL. Although CD70 is also found in healthy immune cells, and AXL in healthy lung cells, the engineered T cells were able to kill the cancer cells while sparing the lung cells.

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Credit UPF and CNIC

## Still Alive and Regenerating

### Not all muscle stem cells are made equal...

Losing muscle mass is a significant problem for older people and is partly due to a loss of the regenerative functions of satellite cells. Now, an international team of researchers have discovered a subgroup of satellite cells that maintain their regenerative capacity over time, declining only at geriatric age (1).

Their superior regenerative capacity is via the activation of the FoxO signaling pathway – previously associated with longevity – which is lost in later life.

The scientists hope that their findings will help "harness the potential of stem cells for regenerative medicine in sarcopenia," with the door now open for therapeutic intervention targeting FoxO expression.

#### Reference

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## Collaborate to Accelerate

**A cell-therapy focused partnership between industry, academia, charities, and the NHS has launched in the UK; we spoke with Mike Hannay, Managing Director of Medical Technologies Innovation Facility (MTIF), and Academic Lead John Hunt to find out what it's all about**

What is MTIF?

A really big challenge in healthcare is getting innovations to patients quickly; it can take up to 17 years for a product to go from proof of concept to clinical use. MTIF aims to accelerate the development of innovative medtech products – including cell and gene therapies – that improve patient outcomes. As a partnership between two universities in Nottingham, UK, the NHS, investment groups, and industry networks, MTIF supports companies from “bench to bedside” in developing the next generation of medical technologies.

Why did you both decide to get involved?

*Mike:* I have spent my career developing new medicines and medical technologies that I hope have improved the lives of patients. Over 30 years ago, I was involved in developing treatments addressing the symptoms of AIDS; as science progressed, anti-retrovirals came along and we were able to treat AIDS as a chronic disease rather than a terminal one. We now understand the genetics associated with a number of diseases enabling the personalization of medicine and I was delighted to lead the pharmaceutical development of Lynparza as Vice President, Medicines Development at AstraZeneca. This scale of innovation is amazing – life changing – but it can also be protracted. And that led me to join the NHS and head up the Academic Health Science Network (AHSN), which is charged with accelerating the adoption of innovation within the NHS. The role involved discussions about MTIF with regional universities, hospitals, and government, and I recognized early on that MTIF was unique in approach, bringing together all the elements needed to enable quicker patient access to innovations. How could I not get involved?

*John:* With over three three decades of research and industrial experience developing and testing implanted medical devices and cellular therapies, I am very excited to be part of MTIF. This is a



great opportunity to unlock invention and entrepreneurship, and accelerate innovations in the healthcare arena. By uniquely bringing academic and industrial expertise together within its auspices, MTIF will help enable the delivery of next generation therapies to meet the increasing demands made on healthcare.

Why were cell therapies identified as an area that the MTIF could help advance? And can you tell me about the “memorandum of understanding” with UK charity Anthony Nolan?

Cell therapies offer an unprecedented opportunity to treat and cure patients with the most challenging diseases. Here in Nottingham, the universities have invested significantly in novel cell therapy development – from basic research into stem cell characterization and differentiation through manufacturing process optimization to conducting large scale clinical trials of both autologous and allogeneic therapies. MTIF is bringing together capabilities and expertise at every stage of the R&D lifecycle to support companies in bringing their ideas to patients.

Our partnership with Anthony Nolan is a great example of how, by collaborating with the right organizations, aligning goals, and bringing together unique capabilities, we can accelerate the development of innovative new cell-based treatments. Anthony Nolan is well known for its amazing work in saving the lives of thousands of patients with blood cancer since it was established as a charity in 1974. The AN cell and gene therapy service offers high quality blood products as starting materials and MTIF is uniquely positioned to maximize the potential of this material as new cell based treatments. MTIF and Anthony Nolan have

complementary capabilities, expertise, and research that enable us to support organizations looking to develop cell therapies.

What facilities will MTIF have with regard to cell therapies?

Working in collaboration with our partners, we have developed an integrated set of capabilities, facilities, equipment and, most importantly, people to support the development of cell therapies. MTIF has invested in the isolation, purification, characterization, differentiation, enrichment, and expansion of both autologous and allogeneic cell therapies. For example, we have tissue culture facilities able to process prokaryotic, eukaryotic, and co-cultures in 2D and 3D. We also have wave, hollow fiber, stirred, perfusion, shear, pulsatile, mechanically loaded, tubular, and anisotropic bioreactor capabilities. There is still a lot of debate about optimum sorting methods concerning throughputs, yields, viabilities, and processing times; we intend to test, develop and optimize sorting methods, such as fluorescence-activated cell sorting (FACS) and magnetic bead-cell sorting (MACS), as well as more passive affinity based substrate purification approaches.

A UK first is the availability of a Hamamatsu FDSS/ $\mu$ CELL system within MTIF. Various differentiated cells have recently been created from iPSCs, and this increasingly allows for the conduct of cell-based assays using human-derived native cells. The beauty of the FDSS/ $\mu$ CELL system is that it can perform high throughput toxicity screening and is available for single studies at MTIF, eliminating the need to make a major capital investment. MTIF has also established a number of 3D tissue analogues that offer huge benefits in minimizing the use of animal studies in the development of cell therapies.







## The Cell + Gene Curator

### Looking back on 12 months of cell and gene therapy research

The Cell + Gene Curator collates the week's discoveries, process innovation, and business updates – and delivers them straight to your inbox. Subscribe: [www.texereneletters.com/cellandgene](http://www.texereneletters.com/cellandgene)

Here, we roundup a selection of some of the most significant research studies – from preclinical studies to clinical trials – from the past year.

#### January

- A team from Cardiff University used CRISPR-Cas9 screening to reveal a TCR able to recognize and kill most human cancer types (in mice and in vitro) via MR1.

#### February

- Mice with diabetes were “functionally cured” by transplanting islet-sized pancreatic beta cells generated from human pluripotent stem cells.
- CRISPR was used directly in the body (the eye, in this case) for the first time in a patient with an inherited form of blindness called Leber congenital amaurosis.

#### March

- Researchers used stem cell transplantation in combination with chemotherapy to cure the second-ever patient of HIV.
- UPenn researchers genetically engineered macrophages to kill solid tumors in both mouse models and human samples – coining the term CAR M-cell therapy.

#### April

- “TriCAR” CD19/CD20/CD22 CAR T cell therapy was significantly more effective than T cells targeting CD19 alone in vitro and in an animal model.

- Researchers reprogramed skin cells into light-sensing rod photoreceptors used for vision and transplant them into blind mice – restoring vision.

#### May

- Allogene reported an overall response rate of 78 percent in a trial of off-the-shelf CAR T (ALLO-501) combined with ALLO-647 antibody in patients with non-Hodgkin lymphoma who had failed to respond to previous therapies.
- Chinese biotech Gracell announced 24-hour “FasT CAR-T” at AACR – and said early clinical results showed 20-40 times greater potency in B-ALL compared with conventionally manufactured CAR Ts.
- Researchers injected mice with the FST gene (using an AAV9 vector) to increase the production of follistatin, which helps grow muscle by inhibiting myostatin, resulting in a doubling of muscle mass and strength over four months.

#### June

- J&J's anti-BCMA CAR T for multiple myeloma achieved 25/29 complete responses.
- Sloan Kettering Institute team used “uPAR-specific CAR T cells” to “efficiently ablate senescent cells in vitro and in vivo” and reversed some surrogates of aging in mice, including liver fibrosis.
- Verve Therapeutics researchers knocked out two cholesterol-associated genes, PCSK9 and ANGPTL3, in cynomolgus monkeys, resulting in up to a 60 and 65 percent reduction in LDL cholesterol and triglycerides, respectively.

#### July

- Researchers from Baylor College of Medicine used off-the-shelf T cells to eradicate solid tumors in mice; the cells avoid immune rejection with an engineered 4-1BB-specific receptor (4-1BB is a cell surface receptor temporarily upregulated by activated lymphocytes).
- Auxolytic found that, when UMPS (which normally makes the nutrient uridine) is knocked out in human

T cells, the cells become inactive within a week; researchers could knock out the UMPS gene during cell therapy and give patients a uridine supplement, which they could stop taking if side effects emerge.

#### August

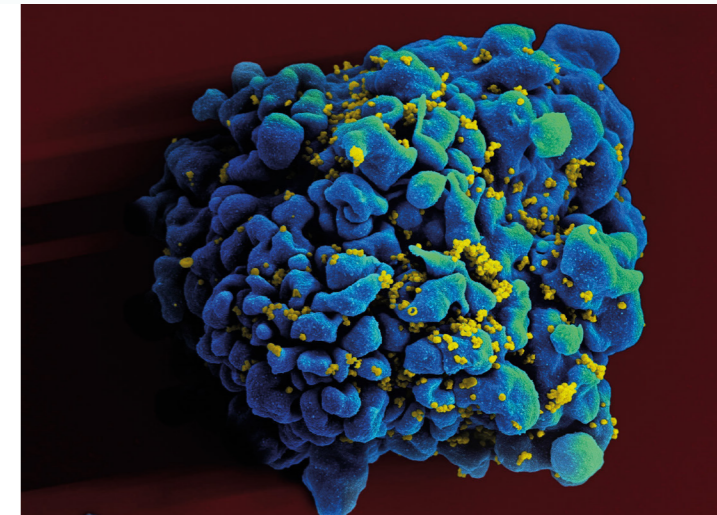
- Two brothers at Macquarie University, Australia, used gene therapy to reverse the effects of memory loss associated with Alzheimer's disease in mouse models of advanced dementia.
- Researchers used CRISPR to create brown-fat-like cells from progenitor white fat cells; they transplanted their “HUMBLE” progenitor cells into mice on a high fat diet and found that the mice put on less weight and had greater sensitivity to insulin and greater ability to clear glucose from the blood than the control group.
- A team from the UPenn designed HIV-specific Dual (4-1BB and CD28) CAR T cells that provide a strong, long-lasting response against HIV-infection in mice while being resistant to the virus itself.

#### September

- MSC-derived extracellular vesicles delivered via the nose alleviated behavioral phenotypes of PCP-treated mice in a model of schizophrenia.
- According to researchers, AAV2 vectors bind too tightly to HSPG and get trapped before reaching their destination; a naturally occurring AAV, using a different mechanism, is more successful at delivery into the liver.
- Researchers from the San Diego State University, USA, created a “CardioCluster” of three types of cells that reduce scar tissue and improve heart function in mice; the cells persist inside heart walls for as long as five months after transplantation.

#### October

- University of Wisconsin Madison researchers repaired Parkinson's disease-damaged neural circuits and restored motor function in mice using human stem cell-derived neurons.
- University of North Carolina researchers locally



- delivered GD2-specific CAR T lymphocytes into mice eyes using in situ grafting, and successfully, in combination with IL-15 and an injectable hydrogel, eliminated retinoblastoma tumor cells without impairing mouse vision.
- In a study of 43 subjects with B-cell acute lymphoblastic leukemia receiving allogeneic anti-CD19 CAR T after relapsing post allotransplant, 34 achieved complete histological remission; two died from multiorgan failure and cytokine release syndrome.

#### November

- Scientists discover that local tissue inflammation following allogeneic hematopoietic stem cell transplantation is caused by host-derived tissue-resident memory T cells.
- University College London's GD2-directed CAR T therapy was well tolerated without on-target toxicity in 12 pediatric patients with neuroblastoma – inducing rapid, but ultimately transient, reduction in tumor size in three patients.
- Researchers from Trinity College Dublin developed a gene therapy for dominant optic atrophy (DOA), which protected mice models of the disease and improved mitochondrial performance in human cells that contained mutations in the OPA1 gene.

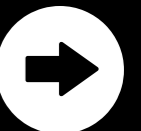
*A full list of references can be found in the online version of the article at [tmm.txp.to/1220/cellandgene](http://tmm.txp.to/1220/cellandgene)*





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Cell and gene therapies hold the promise to change lives. Even as the path to patients accelerates, manufacturing and regulatory complexity challenges remain. With limited process templates, evolving regulatory guidance, and urgent patient needs, finding a partner with experience is critical to success.

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# SARTORIUS







# WE NEED TO TALK

THE PACE OF INNOVATION IN THE CELL AND GENE THERAPY FIELD IS BREATHTAKING. BUT IS PROGRESS BEING MADE WITH THE NEEDS OF THE PATIENT – AS DEFINED BY THE PATIENT – IN MIND?

*By James Strachan*







**W**hen it comes to genomic medicine, do patients understand that they are consenting to a fundamentally different kind of treatment – one that may become part of their body for the rest of their lives? And are companies engaging all the relevant stakeholders early enough to avoid issues with commercialization down the line? Here, three industry leaders – Kelly Page, Head of Global Cell Therapy Commercialization at Takeda; Sandy Macrae, CEO of Sangamo Therapeutics; and David Meek, CEO of FerGene – explain what excites them most about cell and gene therapy today. And kick off some crucial discussion topics for a field looking towards the future...

#### WHICH AREAS OF CELL AND GENE THERAPY EXCITE YOU THE MOST?

*Page:* Overall, the story of our field has been the discovery of new ways to harness the immune system to fight cancer. The second chapter is going to be about optimization. We're going to move cell therapy from just a few haematological indications to a broader range – perhaps including solid tumors. One issue we face is that many patients can't get to an academic medical center – they often don't even know these therapies exist. The next chapter will be about putting these therapies within the reach of the average patient.

Starting with the first generation autologous CAR T cell therapies, the community has been dealing with very complicated products. Manufacturing delays are common, with patients' diseases progressing and requiring bridging treatment. After treatment, patients can end up in intensive care or require close follow up in or close to a hospital. And sometimes the manufacturing fails altogether.

With an allogeneic product, you aren't having to take live cells and manufacture the therapy within a constrained time frame, which is the root cause of many manufacturing failures and delays. Plus, as these allogeneic therapies move forward, we should be able to expand the range of hospitals that are able to deliver them. Autologous therapies require specialized hospitals, but perhaps regional or larger community hospitals that are currently offering transplants could also offer allogeneic cell therapy – patients won't

have to live next door to an academic medical center to access a treatment. That's an exciting development!

*Macrae:* Cell and gene therapy is all about delivery; in the case of autologous therapies that includes the whole supply chain, and it includes the delivery of vectors for gene therapy. There tends to be a focus on the liver, because that's where all the vectors go, but the next frontier is the brain. Everyone has been looking for a virus that can cross the blood brain barrier; and there have been some successes in small animals that have not been seen in primates. The field as a whole is getting more comfortable with neurosurgical interventions, which is opening up a whole range of diseases to new therapeutic intervention. Some companies are injecting into the cisterna magna – the reservoir for CSF in the brain. Another approach we're interested in, pioneered by David Ojala, involves evolving viruses to select for their ability to reach the brain. Essentially, you perform targeted mutagenesis to create a library of barcoded viruses that you put into the brain. You can then use the barcode to track where each virus goes and select for the most effective ones. Do this enough times and eventually (in theory) you'll find an effective vector for delivery across the blood brain barrier. It's fascinating work and I believe David is on the threshold of succeeding with this approach.

With regard to cell therapy, there's room for significant advances in process development. It might not be glamorous, but improving how we culture and grow cells, how we mobilize them, and how we create space in the bone marrow to put them back are all crucial to ensuring that cell therapies work. And if we listen to the people at Kite, a Gilead company, and Juno, a Bristol-Myers Squibb company, it's all about the supply chain for autologous therapies. The real problem is in oncology, where there's a danger that a patient may not survive the time it takes to manufacture the CAR T; I know Kite was pleased to be able to get the skin-to-skin time down to 17 days, for example. But that's still too long for some patients. And that's why I believe allogeneic is the right way to go (if we can figure out what allogeneic really means given the number of approaches today...). We use zinc finger nucleases to edit healthy donor cells and turn them into allogeneic therapies. We also have another program where we edit iPSCs and grow them up into allogeneic cell therapies. Finding allogeneic Tregs – particularly iPSC sourced – would be an enormous advantage because you would be able to treat anyone with an off-the-shelf product at any

time; for example, during an acute multiple sclerosis flare up.

*Meek:* Cell and gene therapies provide an opportunity to potentially cure rare and chronic diseases that have lifelong debilitating effects for patients and families – I don't think this can be said often enough! The pace of innovation is remarkable, particularly in areas like haemophilia. There are over 20,000 patients with this disease in the US and around 400,000 globally and it's not inconceivable that we might be looking at a cure in the not-to-distant future. This opportunity alone is exciting enough, but there are many other indications that could be cured with cell and gene therapies. And I'm enormously proud and excited to be a part of this community.

#### WHICH PROGRAMS AT YOUR COMPANY ARE YOU MOST EXCITED ABOUT?

*Page:* In 2015, Takeda made the decision to focus on partnerships with a number of world class scientists, including with MD Anderson and Memorial Sloan Kettering; it is the MD Anderson partnership that brought about our lead candidate, a CD-19 directed CAR NK therapy. Natural killer cells are designed to kill and destroy cells that are foreign to the body, so harnessing innate immunity to fight cancer makes a great deal of sense – and that's the line of development we're taking with MD Anderson. Put simply, we took the collaborative approach to stay ahead of the curve – the rate of innovation in the field is rapid and we believe partnerships help open the doors to innovation that patients are waiting for. We also believe that academics at research hospitals maintain a real patient-focused perspective, which is crucial for the success of such therapies. It's great to combine external innovation with our internal scientific experts and our ability to take a therapy through the approval and commercialization processes.

*Macrae:* In addition to our work in gene therapy delivery across the blood-brain barrier (which I've already touched on), I'm really excited about our work in Tregs. After our deal with Gilead, which took us into T cells and NK cells for oncology, it was obvious to us that Tregs (the cells that coordinate the immune response and regulate inflammation) were going to be next. The main advantage is that they localize to a certain antigen – but the antigen doesn't have to be causative. For example, you could use a myelin binding protein to localize the Tregs to the myelin sheath to treat MS,





without that particular antigen needing to be involved in the disease. Tregs are editable and we hope to soon be able to grow them up into allogeneic cells – even from iPSCs. There’s an emerging body of research accumulating to support their effectiveness and their ability to target areas of the body that could take us beyond the ultra-rare diseases. And that, I feel, is the next stage in cell and gene therapy. We’ve done a lot of preclinical work in this area and we’re hopeful of treating the first patient early next year.

*Meek:* Our lead program at FerGene is nadofaragene firadenovec – an investigational gene therapy for the treatment of high-grade, Bacillus Calmette-Guérin (BCG) unresponsive non-muscle invasive bladder cancer. This early form of bladder cancer presents in the superficial tissue of the bladder and has not yet spread to other parts of the body. In the US, there are approximately 81,000 cases of bladder cancer every year and 20 percent of those present as non-muscle invasive. BCG is the current recommended treatment, but in 30–50 percent of cases, high-grade disease reoccurs. In other words, there is an unmet need in a significant proportion of patients. Notably, patients that don’t respond to BCG are usually recommended for cystectomy (the removal of the bladder) – clearly, a life-changing procedure.

Nadofaragene firadenovec is an adenovirus containing the gene interferon alfa-2b, administered by catheter into the bladder every three months. The vector enters the cells of the bladder wall, where it breaks down and releases the active gene, which then causes the cells to secrete high quantities of interferon alfa-2b protein – a naturally occurring protein the body uses to fight cancer. The therapy essentially turns the patient’s own bladder wall cells into interferon microfactories, enhancing the body’s natural defenses against the cancer. The Phase III study met its primary endpoint and we’re hoping for an FDA approval in the near future.

#### DO YOU THINK THE CELL AND GENE THERAPY FIELD WILL FOLLOW THE SAME TRAJECTORY AS THE MONOCLONAL ANTIBODY FIELD?

*Macrae:* I remember when the first antibodies were under development and how complicated it was to manufacture them. We’ve just begun to describe how to make cell therapies and therefore it’s going to take some years to perfect the processes.

But there are now lots of people who used to work in monoclonals entering the cell and gene therapy industry (because that’s where the jobs are); and they talk about how monoclonals went from having many different specifications to a few specifications, and the important role that development played in the efficiency of manufacturing. We still have many specifications in cell therapy and we don’t quite know which ones are critical for efficiency. In short, I see many parallels with the monoclonal antibody field and I believe we are on an analogous journey.

#### AND FINALLY, THE QUESTION THAT WE CANNOT AVOID: HOW HAS THE CELL AND GENE THERAPY FIELD COPEd WITH THE CHALLENGES OF COVID-19?

*Kelly Page:* Rather than “coped,” I’d say “pivoted,” as we’ve certainly had to pivot away from what we usually do to help our patients. We’ve seen a significant increase in digital and telemedicine approaches across the industry. Companies have also explored ways of treating patients at home – an especially complicated task for our industry given the nature of our therapies and the sometimes very ill patients we treat. There’s also been a push to make sure patients understand the importance of continuing with screening and treatments, which we’ve seen decrease due to COVID-19. Separately, we’ve been able to pivot through the opening of a new manufacturing facility in Boston to ensure we can continue providing treatments to our patients in ongoing and upcoming clinical studies.

*Sandy Macrae:* If you’d have asked me eight months ago whether I could run a virtual business, I would have probably said, “No!” And yet our labs have stayed open throughout, with non-lab staff working effectively from bedrooms and kitchens – often taking care of children at the same time. As for the lab, anyone entering must have had a negative test within the last week, and we also arranged shifts – along with social distancing – to reduce person-to-person contact.

We’re lucky that, in California, our business has been considered a critical part of the healthcare system, so we were able to stay open. That being said, hospitals were understandably focused on treating COVID-19 patients during the pandemic, so it has been difficult to

get new trials off the ground. One trial in Fabry disease was delayed by five months, for example. And I think this is a trend throughout the industry; existing trials, for the most part, have continued, but getting new trials underway has been difficult.

We’ve also seen a trend towards decentralized trials – even in the cell and gene therapy space. As an example, we worked out ways to send nurses out to patients in their homes to collect blood samples – saving them a trip to the hospital. Overall, I think the industry has done remarkably well given the circumstances. Necessity has indeed proved to be the mother of invention, and I can see some of these trends continuing post-COVID-19. However, I would like to get back to the office. Planned meetings are easy, but those chance occasions when you bump into someone at the coffee machine or in an elevator can’t happen virtually. And, in my experience, a great deal of progress and new ideas arise from those chance meetings and unplanned conversations.

*David Meek:* It’s certainly been an interesting year. But I would say that the pharma sector, and cell and gene therapy companies in particular, have been incredibly resilient. Though operating norms and timelines have required adjustment, as in all industries, the innovation and patient focus – which is at the core of what we do – has not waned at all. If anything, COVID-19 has actually accelerated the focus on the patient, as we’ve found ways of keeping in touch and even treating patients within their own homes. The pandemic has also highlighted the real benefit of a once and done cure, as offered by many cell and gene therapies, given the risks to immunocompromised patients of having to regularly go into hospitals to receive treatment. And though we’ve had to adapt – especially in March, April and May, with hospitals and clinical trial sites closing – I would say we’re now back on track.

*Kelly Page, Sandy Macrae and David Meek were all speakers at Reuters Cell and Gene Therapy USA 2020: <https://bit.ly/2SLdu4D>*







## Getting Everyone on Board

*By Kelly Page*

My dad is a cancer survivor. Twenty years ago, there weren't many treatment options and it was also very difficult to find the information we needed. Today, patient advocacy groups do a great job filling that void and are becoming increasingly important in helping patients find what they need at the beginning of their journey. For cell therapies, there's opportunity for this to continue through their treatment and recovery. These therapies are complex. It can be difficult to find out which treatments are relevant, where the treatment centers are located, and how to access them. In short, they have key roles in ensuring that patients are aware of – and can access – these therapies.

Patient advocacy groups also have a prominent part to play in ensuring cell therapies are developed with the needs of patients in mind. These groups are increasingly involved in clinical trial design – especially in helping to choose the endpoints that matter most to patients. A few years ago, we ran a study to compare the thoughts of Hodgkin lymphoma patients and physicians when it comes to therapeutic value. We found that patients and physicians had different criteria when selecting therapies. For example, a physician might have said that efficacy is what drives them to pick a particular treatment, whereas patients were more concerned with quality of life.

Similarly, we often find that regulators prefer a particular criterion of value (and with different endpoints) to a payer. It's crucial that we initiate conversations between the various cell therapy stakeholders to ensure that we meet the needs of patients and run the best studies we can. We all want patients to get better and find treatments that work, but are we all defining “better” in the same way? Different payers may have different definitions of value, which may differ from what patient advocacy groups prioritize, which might not align with what the regulators are saying.

Balancing all of these views when trying to determine what clinical study to run can be difficult, which is why getting together to discuss the best way forward is so important.



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## The Path to the Patient

By David Meek

The progress made in the gene therapy field over the past 20 years has been remarkable to watch, with a number of therapies steadily making their way through the FDA approval process to reach the patients that need them. Part of what makes gene therapies so transformative is their uniqueness – but that also brings new challenges. When Scott Gottlieb was head of the FDA, he noted that, for small and large molecules, 80 percent of the FDA's review was focused on clinical, with 20 percent on CMC and manufacturing. For cell and gene therapies, the weighting was reversed. I think that highlights the importance of focusing on manufacturing early to ensure launch and post-launch success.

Scaling cell and gene therapy capacity is a clear and present challenge. Limited vector capacity is a real issue; with 39 new gene therapy approvals expected by 2022, companies must plan for potential capacity problems. The key to success is setting up a cross-functional team – characterized by open collaboration – early in the preclinical stage. Who should be in such a team? Well, medical affairs, patient advocacy, market research, operations planning, marketing, CMC, program management, policy, and patient access... Ensuring that these groups do not form silos is part of what you could call horizontal collaboration. But don't forget that vertical collaboration is important too: your team leaders need to be speaking to their colleagues on the ground, who are working with customers day in, day out.

Listening to customers is something we take seriously – and we've been able to identify a number of issues that keep cropping up. For example, with treatment guidelines being relatively new, some healthcare professions have struggled to keep up with what the FDA is saying about first-line treatment unresponsiveness or understanding trial designs. We've also found that previous experience with high-cost "buy and bill" products has created skepticism of new treatments that require infrastructure and/or those that come with financial risk. Finally, differences in terms of

patient care between regions, academic centers, and community-based practices has also been a challenge.

To address these problems, we've taken a number of approaches, including:

- Analytics-driven segmentation of prescribers with early identification of early adopters.
- Establishing a market development team to understand customer needs.
- Sharing patient experiences and trial results with clinical stakeholders to demonstrate early impact.
- Using real world evidence and education to address unmet needs and drive insight generation.
- Segmenting payers to allow data-driven messages and evidence development for policies/guidelines.
- Using prescriber and market insights to tailor payer-based responses and go-to market models.
- Delivering a "white glove customer service experience" where you navigate the patient through the delivery of therapy, including support with the reimbursement process, if necessary.

My advice would be to begin these tactics two or three years before launch. And for complex diseases in particular, frequent and early engagement with payers is a must – we've found that payers are eager to learn more and to prepare for the introduction of new and innovative therapies. They want to understand the benefits of what your medicine offers, and that includes health economics and outcomes research, what it means for the patient, and the total value proposition. In the US, you might be speaking to different people, depending on the product – the government in the case of a Medicare patient or a private payer if not. But the fundamentals are the same for any payer, in any market – and the earlier you are able to have these conversations the better.

Companies are really charting their own paths and working out how best to commercialize these new and potentially revolutionary therapies. But we do now have the beginnings of a roadmap for ensuring the path to the patient is as smooth as possible.







## Understanding Consent

By Sandy Macrae

I am a physician and I've also worked in large pharma companies as the chair of the safety board, which helps decide whether a medicine is safe to be released into the population. And so understanding the benefit-to-risk ratio and how you transmit that information to the patient has been part of my life for some time. For example, imagine we were considering the release of tablets for diabetes; we knew that, if a patient had a bad reaction, they could stop taking the medication and would likely feel fine the next day. In contrast, genomic medicines potentially remain a part of the patient's body for the rest of their days. And that means you need to think about the benefits and risks differently. I've come to realize that this is a conversation that isn't happening enough.

I think it's clear many people struggle with rationally evaluating benefit vs. risk – we see this with debates around masks and vaccines. In the case of a dying child with no alternative, it's obvious that the benefit of a relatively safe and effective therapy far outweighs the risks. But when we're talking about a patient with several alternatives, the answer is less clear. When a patient consents to a gene therapy, they are consenting for life (or a parent is consenting for the entirety of their child's life).

The good news is that gene therapies appear to be remarkably safe. The biggest risk is usually at the moment of infusion (some patients can have a reaction to the virus) and inflammation or hepatitis of the liver (which can be treated with steroids). The vast majority of these therapies have had few adverse events. But we can't be totally certain about the safety of gene therapies in the (distant) future. And that's why it's important that we follow patients over the course of their lives. And if something does happen to a patient many years down the line, we must be prepared by asking ourselves: what benefit did the patient receive over their lifetime? Were they properly informed of the potential (or unknown) risks of the therapy?

The FDA requires that we follow up with patients for up to 15 years. Is that enough? I personally think we should be following up with patients for their entire lives in some way. It won't be easy, but we need to think about giving the patient a lasting form of certification that includes, for example: what treatment they had, when they had it, perhaps details of the DNA sequence that was



changed, and contact details of the developers.

Another element of patient consent, as Kelly discussed, is involving patients in the development of these therapies. Fortunately, the voice of the patient has become increasingly heard by developers – especially in the cell and gene therapy industry. We understand their disease, but we also need to understand our responsibility to them as people – and that means taking the time to improve consent processes and better explain risk management. An analogy: before you buy a house, how much time do you spend thinking about it – and then filling out forms?

Consenting to a gene therapy needs to be in the same bracket as these rare and big decisions – perhaps even in its own bracket; it truly could be once in a lifetime. We should be engaging with patient advocacy groups on how to get the right messages across to patients.

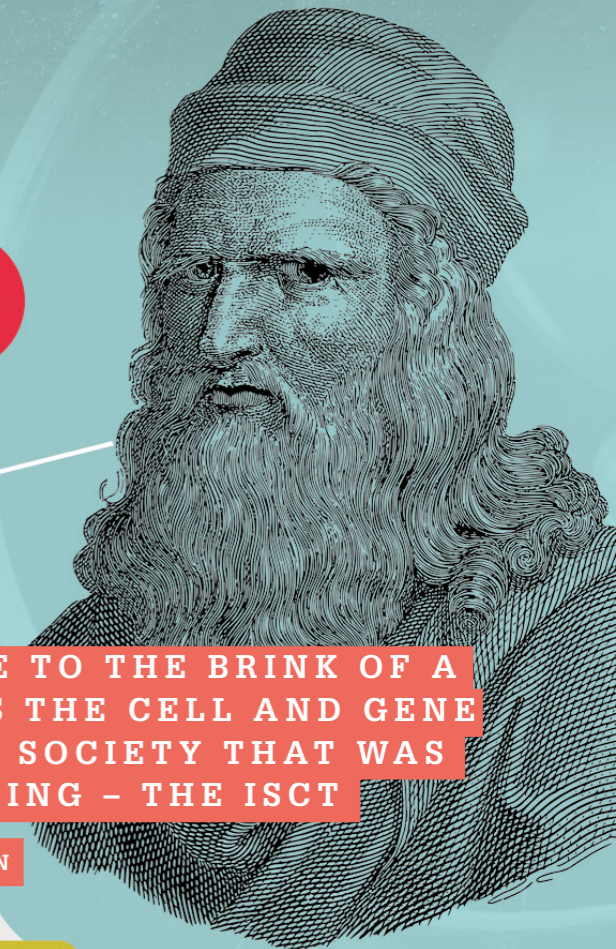
We're a field that's driven by the excitement of venture capital and groundbreaking science. And when you're at the cutting edge, it's like driving a car while simultaneously building the road in front... The key is to have essential conversations now to ensure we end up at the right destination.







# “CURING CANCER? THAT’S CUTE”



FROM THE FRINGE OF THE FRINGE TO THE BRINK OF A  
REVOLUTION IN MEDICINE; THIS IS THE CELL AND GENE  
THERAPY STORY AS TOLD BY THE SOCIETY THAT WAS  
THERE AT THE VERY BEGINNING - THE ISCT

BY JAMES STRACHAN







In the early 2000s, Catherine Bollard took the stage at an international scientific meeting to tell delegates about her work using T cells to treat cancer – an approach that would eventually be described by an FDA Commissioner as “revolutionary.” But she wasn’t presenting to a packed auditorium. She was in a small room away from the bigger sessions and recalls, “Pretty much everyone there was a friend.”

Cell and gene therapies may be an integral part of today’s treatment triumvirate: small molecules, large molecules, and advanced medicines. But it wasn’t long ago that today’s star researchers were seen as outsiders by the mainstream. “There wasn’t a lot of enthusiasm for cell therapy,” says Bollard, Professor of Pediatrics and Immunology at The George Washington University and Children’s National Hospital and Past-President of the International Society for Cell and Gene Therapy (ISCT). “Colleagues were either impressed that we were working on something so ‘out there’ or, more often than not, skeptical or dismissive. The idea of using the body’s immune system to kill cancer was like voodoo to many oncologists.”

“The scientific community would say, ‘Well, isn’t that cute, but will it ever work?’” says Bruce Levine, Barbara and Edward Netter Professor in Cancer Gene Therapy at the University of Pennsylvania and ISCT President. “That skepticism was always in the back of your mind.”

In the early days of cell therapy, researchers came together – escaping the back rooms of bigger conferences – to share their radical ideas at ISCT meetings. Back then, ISCT was known as ISHAGE (“ice age”): the International Society for Hematotherapy and Graft Engineering. “There were researchers looking at stem cell transplants, graft engineering, T cell depletion, and things like that,” says Levine, who joined in 1999, just after he and Carl June re-established their cell manufacturing facility at the University of Pennsylvania. “We saw the society as an important resource because there was no roadmap for cell therapy – you had to chart your own path.”

“They were quite small, boutique meetings back then,” says Bollard. “And they were more focused on stem cell processing, so we in cancer immunotherapy were actually on the fringes – the fringe of the fringe!”

“They were small in comparison with today’s meetings,” adds Levine. “But they were and remain a great source of support,

education, and monitoring. Perhaps most importantly, in those early days, they were eye-opening for attendees. They realized they weren’t alone in their institutions – there were people on all six continents working alongside them in the field.”

Miguel Forte, Chief Executive Officer at Bone Therapeutics and ISCT Immediate Past Chief Commercialization Officer, remembers being “flabbergasted” at the cultural difference between the ISCT meetings and the big oncology and rheumatology meetings. “When I first attended 10 years ago, it felt like a handful of people with different starting technologies ranging from reconstructing a lung to using mesenchymal stem cells (MSCs) to treat autoimmune diseases,” he says. “As Bruce said, it was seen as a ‘cute’ thing – like we were just playing with technology. But look where we are only a decade later...”

### GOOD SCIENCE, GOOD MENTORS – AND PASSION

At its core, the cell and gene therapy story is about innovation. For any innovation to succeed, you need something simple, yet crucial – belief. So what was it that made the early pioneers in advanced medicine believe that they, despite skepticism from colleagues, would bring about a revolution in medicine?

For Bollard, it came down to three things: mentorship, confidence, and passion. “This year’s ISCT annual meeting is a special one because I had the chance to present the Lifetime Achievement Award to my mentor and former boss, Malcolm K. Brenner,” she says. “If it weren’t for Malcolm being President of ISCT, I probably wouldn’t have joined ISCT in the early 2000s. His support was invaluable early in my career – and now I’m presenting his award as past-president. It feels like I’ve come full circle.”

Science was also of paramount importance. Bollard says that she was convinced of the merit of focusing on the immune system – and “wasn’t willing to take no for an answer.” The experience of watching a friend suffering from Hodgkin’s lymphoma go through multiple, ultimately unsuccessful, rounds of chemotherapy and radiotherapy solidified her belief that there had to be another way – and fueled her passion for finding it.

“The treatment was initially successful and she went into durable remission. She then got married, immigrated to America, and was getting on with her life before being struck with acute leukemia. She died within six months of her diagnosis,” says Bollard. “That

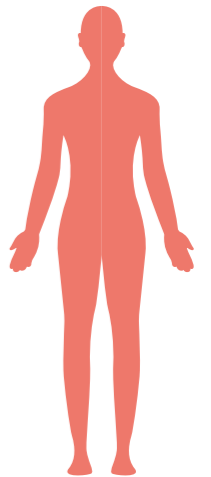
leukemia was the direct result of the previous bouts of chemo and radiation she had received, and I just thought, ‘There has to be a way to kill cancer without killing healthy cells.’ Even then, researchers knew that the immune system was our best natural defense against cancer.” With that, Bollard’s path was set. “When you’ve got strong beliefs in the science, fantastic mentors, passion, and drive, you’re going to be resilient and find new angles when you face challenges – even when people tell you that what you’re doing is crazy.”

Levine says one of the most impactful books he read early in his career was *Commotion in the Blood* (1997), which laid out the roller coaster history of the first 100 years of immunotherapy. “Throughout the book you can relive the disappointments of early investigators and the skepticism and scorn of the wider scientific community,” he says. “I read this just after Carl June had asked me to start a cell manufacturing laboratory to support an adoptive immunotherapy trial, and we were collaborating with Cell Genesys on the very first Chimeric Antigen Receptor clinical trials. Now Carl is the ultimate optimist and mentor. But, if the rest of science is putting you down, who is right? Well, into my career comes ISHAGE/ISCT, and I thought that if Carl’s crazy and I am crazy, we might as well be crazy together trying to get this technology to work.”

For Levine, it was meeting patients that most kept him motivated in the face of skepticism. “I will never forget going in to meet a patient on one of our myeloma trials to thank her for enrolling,” he says. “She kindly looked at me and said, ‘Why would I not volunteer?’ These patients placed their faith and hope in us and that was a great responsibility to them and to their families. Mix in the great team when we moved to the University of Pennsylvania and the support from colleagues and friends in ISCT and you have all the motivation needed.”

### COMPLETING THE REVOLUTION

As the years went by, cell therapy’s clinical results spoke for themselves. Early skepticism regarding therapeutic efficacy gave way to concerns about logistics and commercialization. All the while, the number of people entering the field increased substantially across various disciplines. “Traditionally, only bone marrow transplant doctors administered cell therapies,” says Bollard. “Now, the field is open to oncologists, cardiologists,





orthopedists, and many more disciplines – and this is reflected in the growth of ISCT membership and its annual meeting.”

Fast-forward through years of scientific advancements, hurdles, and setbacks to 2017, when Novartis pulled off the impossible: the first CAR T cell therapy approval – a huge moment for the field. But, according to Forte, economics was key: “Here, we had Novartis come in and say, ‘We’re going to do this at a large scale and spend a lot of money taking the products through clinical trials – and be successful with the approval.’ It proved to other big pharma and biotech companies that the business model was viable. It was game-changing.”

So far, where CAR T has been adopted, healthcare systems have coped well with the logistical challenges. Payers, too, have been generally willing to consider new pricing and reimbursement models to support curative (though often expensive) treatments. But, as the afterglow of the first approvals begins to wear off, the cell and gene therapy field is coming to terms with the fact that it hasn’t revolutionized medicine – yet. For that to happen, it will have to crack solid tumors – and to deliver at scale it will likely go down the allogeneic (off-the-shelf) route.

“We’re beginning to see success with allogeneic “off the shelf” approaches, which is great, but the next step for the field is for cell and gene therapy approvals to become more “mainstream”– that will really put advanced cell therapies on par with the more traditional approaches,” says Bollard. “But the real blue-sky potential is finding a cell therapy to routinely cure solid tumors. An approved therapy there could be groundbreaking for the field and, more importantly, for patients. We could potentially treat millions of people worldwide.”

“I’m excited about combination approaches to enhance the efficacy of CARs and the progress that is being made in solid tumors,” says Levine. “As the field evolves, we’re going to see an increase in the integration of diagnostics and biomarkers in determining which cell and gene therapy to give to a patient. We’ve already done some work on predicting responses in CAR T patients.”

Although looking forward to allogeneic cell therapy’s evolution in the coming years, Forte mainly wants to see the field optimize existing approaches. “Now that we know the cell works – and that it can be made into a commercial product – we need to optimize everything,” he says. “That means modulating cell function to make treatments more effective or off-the-shelf, improving how we source cells – induced pluripotent stem cells (iPSCs) will become increasingly important here – and how we deliver them.”

## HOLDING IT ALL TOGETHER

Forte says the growth of the society has mirrored the growth of the industry. “For example, ISCT’s commercialization committee was established to keep track of the challenges facing developers trying to turn these therapies into commercial realities,” he says. “There are many such challenges – but they’re good problems to have.” And over the years, the organization has further broadened its scope to include committees on legal and regulatory affairs and quality/operations, as well as other stakeholder committees, such as the Presidential Task Force (PTF) on the Use of Unproven and/or Unethical Cell & Gene Therapies, and Early Stage Professionals Committee.

In recent months, the field has joined countless others in facing the difficulties raised by the COVID-19 pandemic. In many countries, hospitals simply weren’t permitted by governments to conduct non-COVID-19 related trials. Elsewhere, patients have been more reluctant to travel to hospitals because of the risk of infection, which has affected trial recruitment. “Bone Therapeutics had two studies approved at the beginning of the pandemic; we had to halt recruitment and wait for the situation to improve,” says Forte. “We saw that things were improving in Hong Kong, which is where we recruited our first patients, but we have now (at the time of writing in July) started to recruit patients in Europe too.”

Investor attitudes have also shifted as the scale of the pandemic unfolded. “Investment by no means dried up, but the discussions did change with the onset of the pandemic,” Forte says.

Unscrupulous “clinics” preying on pandemic fear also popped up. And so, ISCT members have intensified their efforts against unproven cell and gene therapies for COVID-19 and led calls for proper clinical procedures for legitimate COVID-19 therapies (both of which you can read more about in The Cell Therapy Guardians on page 29). The pandemic also affected ISCT’s annual meeting, which was due to take place at the end of May in Paris. ISCT decided to go virtual; our “How to Deliver a Virtual Conference in Under Two Months” sidebar reveals how they did it – and how it went.

But, at the time of writing, economies are beginning to open back up, paving the way for advanced medicine development to resume. So, as the field continues to evolve, what will ISCT look like in the next 10 to 20 years?

Forte believes ISCT may have to play a greater role in the ethical debates that will take place as the field reaches its full potential. “The sky’s the limit when it comes to what you can do with cells in terms of reconstructing, modulating, and improving function,” he says. “The benefits for patients will be tremendous, but we’re not too far away from being able to go beyond restoring health to designing specific traits.” Cell and gene therapies could be used to change how we look, how we think, and even how long we live – raising a wide range of ethical questions. “We might be entering the realms of science fiction here, but CART cell therapy sounded like science fiction just 10 years ago,” says Forte. “ISCT is well placed to be part of these discussions and to take a position on them – we have to make sure there’s an ethical dimension to everything we do.”

Another interesting development is the rise of China as a hotspot of advanced therapy development. “China’s importance to the global cell and gene therapy industry is set to increase and that has important implications – especially as their regulations continue to evolve – for companies in Europe and the US,” says Levine. “Many discussions are taking place between Western and Chinese companies about potential partnerships. But challenges such as IP protection, movement of goods and people, and cultural differences must be overcome. ISCT is a global organization with recognition in China, but I think there is scope to increase our presence there and to engage Chinese players further to help facilitate collaboration.”

For Levine, as President of ISCT, the big challenge is having a global perspective and vision while also respecting local needs. “We need a global exchange of ideas and information, but cell therapy must also respect patients and physicians at the local level,” he says. “We recognize that not every country has the infrastructure or the expertise to review and regulate the conduct of translational and clinical research in cell and gene therapies. This is exactly where ISCT can serve as a resource and forum to connect researchers, clinicians, and regulators.”

For Bollard, it is amusing to discuss how we can bring together the global cell and gene therapy industry, given how different things were only a decade ago. “You could have never predicted back then, ostracized as we were, that we would be embraced by the scientific community and industry and talking about how to get proven technologies to millions of patients,” she says. “The whole thing just takes you by surprise. But the craziest part? The field is still in its infancy and we can still take it so much further.”







## HOW TO DELIVER A VIRTUAL CONFERENCE IN UNDER TWO MONTHS

By Queenie Jang

As soon as we heard the news of a viral outbreak, we began monitoring the situation very carefully as it spread first through China, then Europe, to Italy, Spain and France – where we were planning to host the ISCT 2020 Annual Meeting. As a global organization, we knew that many of our delegates would be flying in from the USA and elsewhere. We didn't know what government bans on group gatherings and international travel restrictions would be in place. Should we cancel the meeting? Could we postpone it, and if so, to when? What about a virtual meeting? These were the options everyone on the executive management committee (the three presidents, the global treasurer, the global secretary, and myself as CEO and chair) had to weigh up in our weekly discussions about the situation.

Other societies postponed their meetings and, for some, it seemed a no-brainer that we should do the same. But we didn't know what restrictions would be in place, how long the "peak" would last, or whether there would be a second wave. Would we end up in the same situation a few months later? We also had to keep in mind our members. The ISCT annual meeting is a business meeting, an educational forum, and one of the most important events of the year for our industry. In the end, after a lot of soul-searching, we decided in mid-March that the only viable option was a virtual meeting.

Making the decision was the easy part. Once we had chosen our path, we had just seven weeks and, like so many others, very little experience in delivering virtual meetings. Fortunately, we recognized early that this might happen (having world-leading immunologists in your team certainly helps during a pandemic!), so we had researched virtual platforms as early as January. This meant that we were able to sign a contract with our chosen virtual meeting platform provider 48 hours after we decided to go virtual.

One thing we didn't want was just a series of webinar streams. A lot of our members were working extremely hard during the pandemic – many on the frontlines – and most were dealing with screen fatigue. We wanted to offer people a bit of a break and a chance to learn and to engage with peers. But we also wanted to capture some

of the magic of the physical meeting and provide something that felt like ISCT. I've always believed that, when someone attends an ISCT meeting, it should be about the experience – people should know it's an ISCT meeting. And that's what we tried to recreate in a virtual setting.

When you enter the platform, you're greeted with a screen that looks something like the actual entrance of the convention center – with ISCT branding everywhere and even avatars of our meeting co-chairs, president, and president-elect greeting you. But the really interesting element is the "exhibition hall." We spent a lot of time working with our exhibitors to make each "stand" unique – they had their own customized branding and arrangement of chairs, posters, and so on. More importantly, attendees could chat via text (which could also be translated live into over 40 different languages) with exhibitors. We gamified the whole LIVE event so attendees could win prizes for interacting. We also had posters in the "poster hall," which were scored as they would be at the physical meeting – and you could chat with poster presenters. Networking sessions were planned during the meeting, but messages could also be exchanged for 12 months after the event. The same was true of sessions, many of which were panel discussions delivered live and available also as on demand pre-recorded sessions. We tried to use the same terminology and event structure we have always used. We did everything we could to make it quintessentially an ISCT meeting.

Putting this together in under two months was, to put it mildly, a real challenge! Even during the event, things were somewhat frantic behind the scenes. We'd spent hours brainstorming how things might go wrong – what to do if a speaker disconnected or people couldn't gain access or register properly – but we

still learned things after every live session. Going live across the globe was also tricky. We had people working 12-hour shifts so we could help with technical issues anywhere in the world. We also had to consider whether our bandwidth requirements were appropriate for attendees from across the world. Overall though, we were really happy with how the event went – in spite of the butterflies in our stomachs beforehand. For the two day LIVE: delegates spent an average of 19 hours on the virtual meeting platform during these two LIVE dates; over 32,000 views of the sessions and over 17,000 poster hall visits. Attendee numbers for the two LIVE dates are 2024.

That said, we could never totally recreate everything that happens at a live event – the chance meeting, the introduction from a colleague, going out for a meal or a drink. Plus, with people working from home, colleagues may act as though they aren't "really" at a conference – they'll still respond to emails and messages they might postpone during a physical event.







## THE CELL THERAPY GUARDIANS

*We speak with Laertis Ikonomou, Chair of the ISCT Presidential Task Force on the Use of Unproven and/or Unethical Cell & Gene Therapies, and Associate Professor of Oral Biology at the University at Buffalo, SUNY, and Dan Weiss, ISCT Chief Scientific Officer and Professor of Medicine at the University of Vermont, about the ISCT's work to combat unproven cell therapies and its drive to ensure that studies into legitimate COVID-19 cell therapies rigorously demonstrate safety and efficacy.*

### How widespread is the problem of unproven therapies?

*Laertis Ikonomou:* The problem of unproven cell therapies is a global one. A decade ago, this phenomenon was known as “stem cell medical tourism” in which patients in the USA and Europe would travel abroad to access unproven “stem cell” treatments. Now, there’s no need. Most Americans can find an unproven “stem cell” clinic within driving distance – and the same is true of Canada, Australia, New Zealand, Europe, and parts of Asia. Why? These clinics have undoubtedly benefited from the hype surrounding legitimate cell therapies.

### What procedures do the clinics offer and what are the consequences?

*Ikonomou:* Interventions include autologous bone marrow extracts and, until recently, stromal vascular fraction from adipose tissue. These have been reduced in the USA after injunctions against companies. Increasingly, companies are offering perinatal tissue-derived products and exosomes.

Patients have suffered serious injuries and even death because of these procedures. The time spent accessing an unproven therapy is time that could be spent receiving a proven therapy. Financial damage is important, too, as none of these unproven approaches are covered by insurance. Some clinics encourage people to take on debts or crowdfund to pay for expensive treatments, which can affect their ability to afford proven therapies and cause psychological harm.

### What is the main aim of the Task Force?

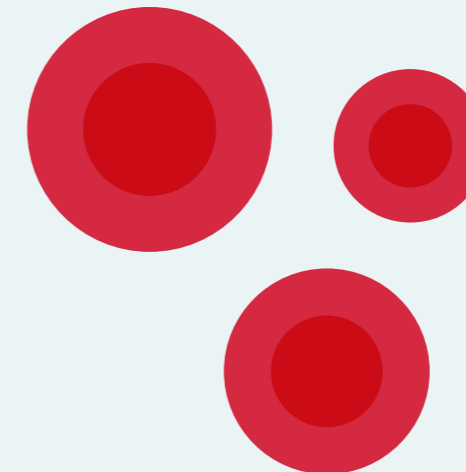
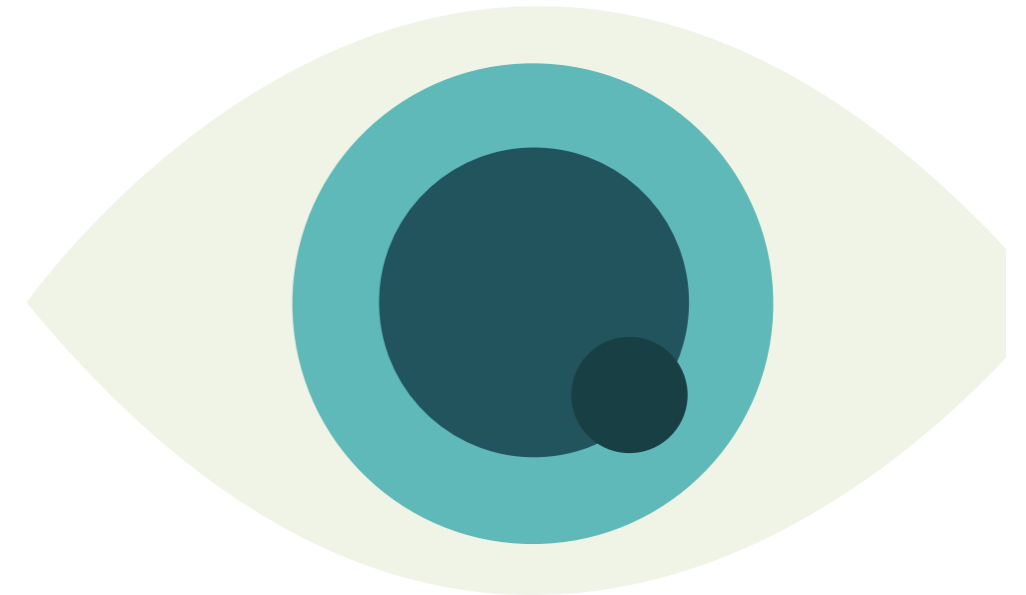
*Ikonomou:* The main aim of the Presidential Task Force on the Use of Unproven and/or Unethical Cell & Gene Therapies is to monitor the situation, educate all parties involved, and protect patients worldwide. Initially, we published an extensive guide – a series of articles in *Cytotherapy* – in which we defined “unproven therapy” and examined several aspects of the phenomenon. How are they offered? What are the regulatory implications? How does this impact legitimate cell and gene therapy development? We also actively monitor where these clinics emerge and what kinds of procedures they offer, and we send out regular press releases and issue statements jointly with other societies.

*Dan Weiss:* The ISCT is a nonprofit organization, which means we cannot lobby politicians to effect change. But what we can do is raise awareness and, most importantly, educate people – especially patients and their families – so they can make informed choices about their healthcare.

### What about clinics offering unproven treatments for COVID-19?

*Ikonomou:* A number of clinics have claimed to treat COVID-19 using unproven cell and gene therapies – particularly in the USA. Usually, they will simply add COVID-19 to the list of conditions their “therapies” claim to treat, obviously without proof of efficacy. The ISCT has issued statements to strongly condemn such practices. We recently released a statement with the International Society for Extracellular Vesicles to point out that exosomes are not a proven modality for COVID-19.

*Weiss:* In the USA, the FDA has taken a proactive stance against companies offering unproven COVID-19 treatments. They’ve sent out several letters a week essentially telling these clinics to stop advertising this garbage! I’m paraphrasing of course, but they clearly recognize that this is a growing problem.







# Building a Beautiful Biotech

Sitting Down With...  
Vered Caplan, CEO of  
Orgenesis, Israel



What attracted you to (biomedical) science?

I began my career in mechanical and biomedical engineering. Yet I always loved art. And, to me, science is the art of understanding reality. If you think about music, there are people who can break down and analyze pieces of music and understand what makes a given piece beautiful. If they're creative, they can then take what they've learned and create something new – something others can relate to and enjoy. Scientists do something similar when they seek to understand the rules underpinning reality – in the case of biology, the mechanisms of the human body. And so, developing new therapies that positively impact people's lives is artistic – and that's always been an attractive notion for me. People think of science and art as two separate things, but science is deeply creative and, I would say, beautiful.

Though mechanical engineering obviously has positive implications for human beings, nothing is quite as direct as improving health and saving lives. And that's a huge source of motivation for me – an obsession really. I've had to draw upon that source of motivation plenty of times as an entrepreneur, which has had its fair share of ups and downs. Building a biotech company is something that takes years and years of work, and I don't think I would have persevered with only financial success as a goal.

How do you balance the “art of science” – or the desire to do something positive – and the need to make money?

Good question! It's all well and good talking about creating a “beautiful biotech company” that will help patients around the world. But to be helpful you must be sustainable; and to be sustainable, you must make a profit! So, building a steady revenue flow is something we've tried to do at Orgenesis. For example, our POCare Platform includes several different arms, including therapeutics and our “POCare Network,” which brings leading research institutes and hospitals together and provides a pathway for their therapies to reach patients more quickly.

Please tell us more about Orgenesis and the POCare network...

The goal of Orgenesis is ultimately to make cell and gene therapies more accessible to patients. CAR T cell therapies can cost \$300,000–\$1,000,000; how many patients could we realistically treat given these prices? Developing cell and gene therapies is far from straightforward – cleanroom environments, several manual operations, complex logistics, and so on – so it's easy to see why

such therapies would be so expensive. We realized that the industry needed a way to automate production and move it closer to the patient. The POCare Platform sets out to do this by bringing three critical components together: therapy development (POCare Therapies), automation through processing and cell engineering technologies (POCare Technology), and the hospital site (POCare Network).

The idea is for Orgenesis to act as an open source biotech. POCare Network hospitals work with us to design and manage validated cleanrooms that implement our automated and closed technologies. And that allows them to affordably develop and commercialize therapies in-house – significantly reducing the cost of clinical trials, and ultimately the cost of the therapy. In return, Orgenesis gains access to new promising therapies and technologies. We currently have 16 centers in the POCare Network and we're looking to make our technologies available to as many hospitals as we can.

Can you talk about any recent additions to the Network?

We have announced collaborations with a few international institutions this past year. For example, we're supporting Johns Hopkins University's cell and gene therapy development and processing needs as part of a collaboration. The University of California, Davis, joined the Network too: we're working together to scale up and integrate their lentiviral vector process. I'm also excited about the establishment of a center at Hospital Infantil Universitario Niño Jesús in Madrid where we are working together on a treatment for solid metastatic tumors based on oncolytic virotherapy. Within the POCare Therapies portfolio, we recently acquired Koligo with a view to expanding their autologous pancreatic islet cell therapy for chronic or recurrent acute pancreatitis.

What is your hope for the near future of the cell and gene therapy field?

I can certainly tell you what I'd like to see. I want patients with diseases like cancer to have access to a treatment center not too far from their homes, where they get the best care possible at a reasonable price. And I want this to become routine – something we expect from our healthcare systems. This vision is achievable – even within the next five years. We already have all the essential elements; we just need the researchers, hospitals, and technology companies to come together and make it happen.

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