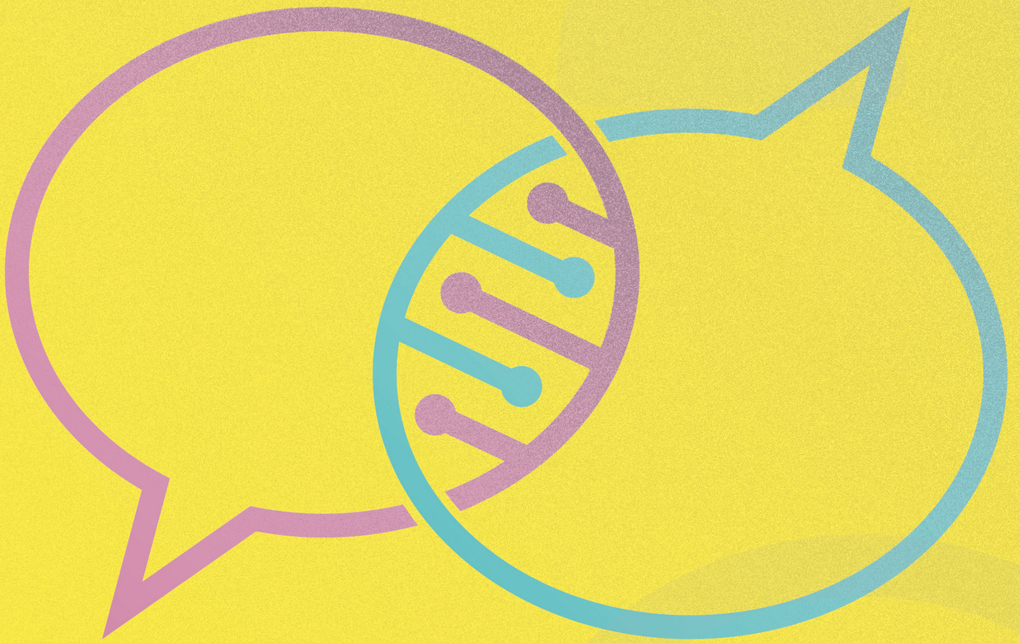
the Medicine Maker

SPECIAL SERIES:

Advanced Medicine



FOREWORD

Introducing The Cell + Gene Curator

The Curator distills the week's cell and gene therapy news – the latest discoveries, process innovations, and business deals – into a five-minute newsletter.

My background is in biomedical sciences and I distinctly remember one lecturer talking about the prospect of engineering the body's own cells to fight cancer during my degree. It sounded like science fiction – and I certainly didn't think it was less than 10 years away from being an approved product. But here we are!

When I joined Texere Publishing and The Medicine Maker magazine, we tended to think in terms of small molecules and biopharma – the latter including cell and gene therapies (CGT). Now, given the rapid rise of CGT, we see the pharma industry as a triad: small molecules, large molecules, and advanced therapies. Over time, while seeking content for The Medicine Maker, it became clear that there was more cell + gene therapy research and news than we knew what to do with. I remember someone asking a semi-hypothetical question: wouldn't it be useful if someone just collated – or curated – the most interesting stories each week? And that was the genesis of The Cell + Gene Curator.

The Curator delivers the week's cell + gene therapy news – the latest discoveries, process innovations, and business deals – into a five-minute read. The content is aimed at professionals working in the cell and gene therapy sector. But we also want the Curator to be a hub for the community – somewhere to share ideas and start discussions. I'm always keen to shine a light on the big issues by talking to leaders in the field.

Ever since the first CAR-T approvals in 2017, people have been discussing the shift from questions of scientific efficacy to manufacturing and commercialization. Now I think we're increasingly seeing a return to development – specifically, how can we crack solid tumors?

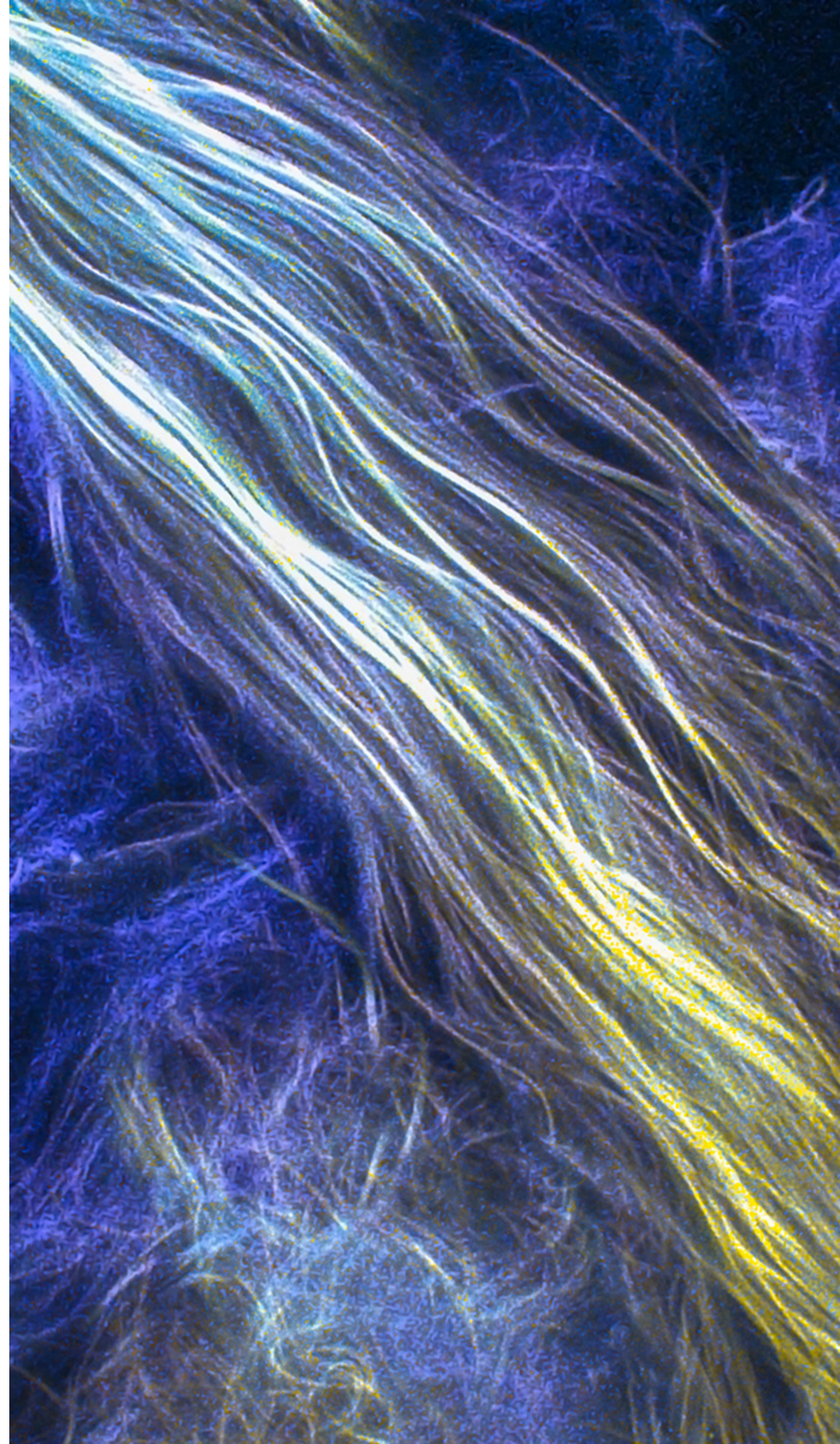
In short, it's an incredibly exciting time for a field that is really still in its infancy. And I'm delighted to be following all the twists and turns – and pulling everything together in a digestible format for our subscribers each week.

JOIN US BY SUBSCRIBING TO THE CELL + GENE CURATOR FOR FREE

UPFRONT

Welcome to our Cell + Gene Curator roundup

Hot topics in the field this month include using CRISPR to engineer cell therapies and recent advances in bioengineering – key to unlocking the potential of regenerative medicine and tissue fabrication



Walter Isaacson writes about people who change the world. His biography of Franklin shows how he brought together the passionate Adams brothers, the rectitudinous Washington, and Jefferson and Hamilton's intellects to create the Constitution and Declaration. Similarly, his book on Steve Jobs shows his lasting impact on cell phones, personal computers, music, publishing, retail – the list goes on.

So it's telling that his next subject is none other than Jennifer Doudna – who, along with Emmanuelle Charpentier, won the Nobel Prize in Chemistry for her role in developing CRISPR. From what I've heard, The Code Breaker details Doudna's remarkable personal story, as well as discussing the future implications for gene editing.

"Suddenly after a billion years of evolution one species had the talent and also the temerity to edit its own genes – to hack its own evolution," said Isaacson.

Deciding, as a species, what we're going to do with CRISPR may be the defining issue of this century. But, let's not get wrapped up in sci-fi dystopias and focus instead on the significant positives: the end of debilitating diseases.

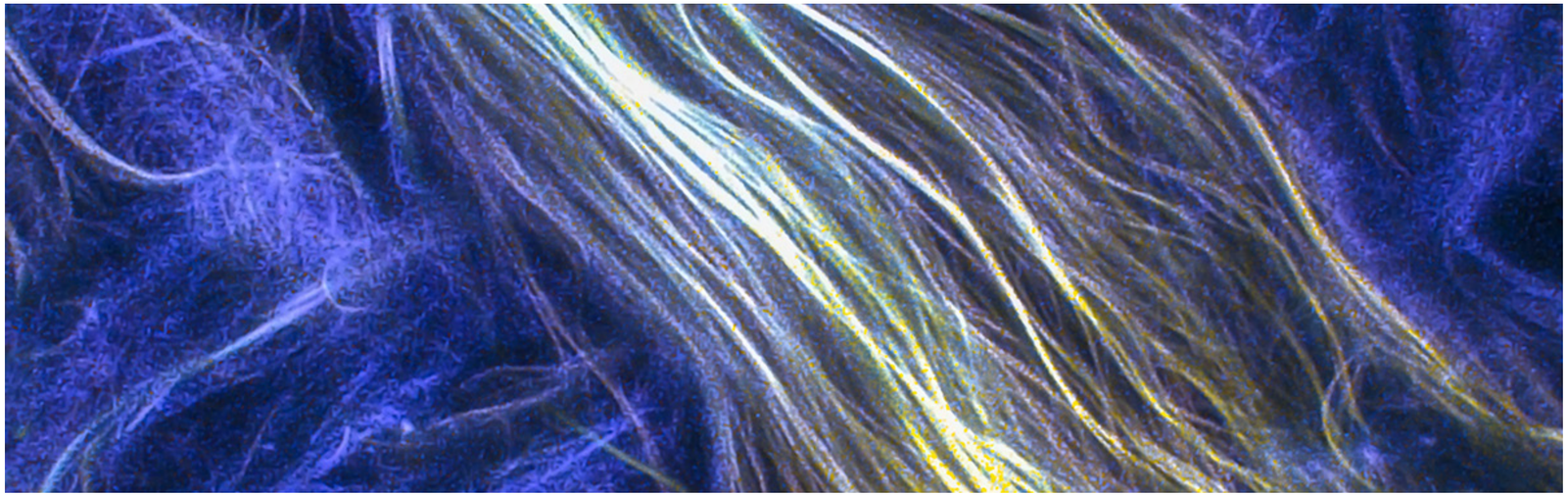
Engineering the future of oncology

A current trend is using CRISPR to engineer cell therapies. For example, AbbVie has entered into a collaboration with Caribou Biosciences – which will use its CRISPR gene editing platform to engineer off-the-shelf CAR T cells with the ability to withstand host immune attack (1). AbbVie will then continue the programs into clinical development and commercialization. Let's see if the deal – worth $40 million upfront and up to $300 million in milestone payments – will bear fruit as quickly as AbbVie's 2018 deal with CALIBR, which has already led to clinical trials (2).

Another example in the research comes from Guangxi Medical University: a team there recently used CRISPR to design nanobody-based anti-CD105 CAR T cells for solid tumors. The CAR T cells prolonged the survival time of tumor-bearing mice and human tumor xenograft models (3).

We're also seeing a lot of improvements to the CRISPR system and new applications for the technology. Fred Hutch researchers developed "T cell optimized for packaging" (TOP) vectors for delivery of CRISPR-Cas9 to primary T cells that showed ~5–9-fold higher transduction efficiency than the commonly-used epHIV7 vector (4).

Meanwhile, Rice University researchers have developed a CRISPR/Cas9-based tool for editing the human epigenome – specifically histone phosphorylation. Their programmable chromatin kinase, called dCas9-dMSK1, allows for site-specific control over histone phosphorylation for the first time, and potentially opens the door to cracking the "histone code" – in other words, understanding how histones control gene expression. The researchers were also able to use dCas9-dMSK1 to identify seven new genes linked to melanoma resistance (5).



And in a brief departure from cell and gene therapy news, researchers from Columbia University in New York are using CRISPR to encode binary data into bacterial cells. By assigning different arrangements of DNA sequences to different letters of the alphabet, the team were able to encode the 12-byte text message "hello world!" into DNA inside E. coli cells. "This work establishes a direct digital-to-biological data storage framework, and advances our capacity for information exchange between silicon- and carbon-based entities," said the study authors (6).

Mighty morphin' biomaterials

Elsewhere, a number of advances have been made in biomaterials and 3D printing for regenerative medicine. A Northwestern University team has discovered a new printable biomaterial that mimics the properties of brain tissue. In 2018, the group reported the phenomenon of molecular reshuffling, where molecules migrate over long distances and self-organize to form larger, "superstructured" bundles of nanofibers. Now, they've shown that these superstructures can enhance neuron growth (7). The ultimate aim is to grow healthy neurons from a patient's own cells using these superstructure-enhanced biomaterials, and transplant them into the brains of patients with neurodegenerative conditions.

In a related story, researchers at the University of Illinois at Chicago describe their new bioengineering material as "4D", which means it changes shape over time in response to stimuli – it can morph multiple times in a preprogrammed fashion or in response to external trigger signals. And that could allow the researchers to engineer tissue architectures that more closely resemble native tissues (8).
Finally, Carnegie Mellon University researchers have developed a new 3D-bioprinting method that could enable the fabrication of adult-sized tissues and organs (9). The Freeform Reversible Embedding of Suspended Hydrogels (FRESH) approach involves a yield-stress support bath that holds bioinks in place until they are cured. This prevents distortion of bioinks, which results in a loss of fidelity – a major barrier to advanced tissue fabrication.

REFERENCES AVALIABLE ONLINE

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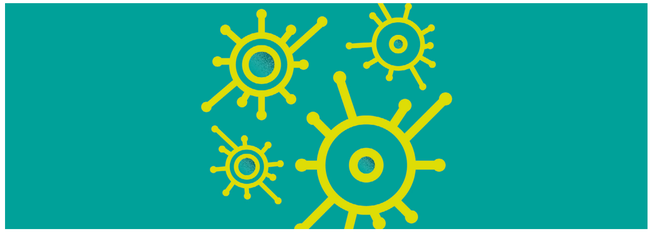
Advanced Therapies: New Year, New Challenges

We posed one big question to a selection of speakers at CAR-TCR Summit Europe 2021: What is the single greatest challenge facing the cell and gene therapy industry in 2021?



ONLINE

Cell and Gene Therapy: Learning from COVID-19 Vaccine Development

What can the advanced therapy sector learn from COVID-19 vaccine development? We ask winners of The Medicine Maker 2021 Power List.

IN MY VIEW

Cell Therapy on Demand

We must continue to make progress in developing off-the-shelf options

Over the course of the last decade, cell therapies have changed the cancer treatment landscape. Though autologous therapies, which require patients to undergo apheresis (immune cell harvesting), can be used to address patient needs, they are complex and time-consuming, especially when used for very ill patients. Having cell therapy products available when a patient needs them, without having to harvest and engineer a patient's own cells, would eliminate some of the complexity and speed up the time to treatment. The sooner a patient can be treated, the higher the likelihood of a better outcome for them.

These "off-the-shelf" allogeneic cell therapy products could be manufactured in bulk and given to a broad number of patients on demand. This approach could address the two major manufacturing challenges current autologous therapies face: no inventory and variable quality of starting material. Because autologous therapies use a patient's own cells, manufacturing cannot start until the cells are collected from the patient and delivered to the manufacturing site. The clock starts ticking as soon as the cells leave the patient, so any last-minute changes to the collection or delivery process can greatly impact manufacturing planning.

Patient populations, of course, are not homogenous – individuals will vary in age, immune status, and treatment history. This means that the quality of starting materials, like the patients themselves, will differ – making process validation and standardization difficult. When treatment can shift to allogeneic therapies, these challenges can be overcome. Cells could be manufactured, frozen, and stored in multiple doses ready for use, making process standardization a reality. Every patient would receive cells of the same type with defined characteristics.

But developing allogeneic therapies has proved difficult. The cells must not be rejected by the patient's immune system before they can get to work and must not harm patients by attacking healthy tissues. These two considerations require different elements of cells to be genetically modified to prevent rejection and toxicity (graft-versus-host disease).

There are also many choices along the way – do you start with stem cell lines? Cord blood or healthy donor cells? Which editing tools do you use? Each option has advantages and disadvantages. One major factor that introduces variability is the cell source used. In my view, gene-editing stem cells is a flexible approach that minimizes batch-to-batch variation. At my company, we use a stem cell line created from a single donor. We then edit it and use it to make stem cell banks. This gives us control over our starting material so that each manufacturing run starts with the same cells.

Though there are still challenges for the industry to examine and address, I'm excited by the progress being made across the industry in allogeneic therapies. These treatments hold tremendous potential for overcoming the main challenges of autologous treatments and can achieve the ultimate goal of being not only curative, but also mainstream for patients with cancer.

Jo Brewer, SVP Allogeneic Research at Adaptimmune, Abingdon, Oxfordshire, UK

IN MY VIEW

Keeping CRISPR On Target

The buzz around therapies based on gene editing is increasing, with clinical trials already underway. Let's not forget the scientists working to improve efficiency and accuracy of the technology – for they are key to unlocking its full potential.

Since the advent of CRISPR (as a reminder: clustered regularly interspaced short palindromic repeats) gene editing in 2012, scientists have worked on improving the technology, as well as our understanding of genetic diseases. The ultimate aim is the development of CRISPR-based therapies – which might not be too far away. In 2020, we saw the first human dosed with an in vivo CRISPR-based therapy, known both as EDIT-101 and AGN-151587 (1), in a phase I/II clinical trial in patients with type 1 Leber congenital amaurosis (LCA) – a genetic condition where a single point mutation causes blindness. Publication of the trial results is expected to be around March 2024 (2). LCA is just one of many diseases that could be treated using CRISPR-based medicines. Other targets for in vivo or ex vivo CRISPR gene editing include cystic fibrosis (CF), sickle cell disease (SCD), and severe combined immunodeficiency (SCID).

In addition to the development of new CRISPR-based therapies, the technology is also being used in research to explore the creation of new models of disease, which may indirectly lead to therapies by elucidating pathological mechanisms and creating new opportunities to test potential therapies. But to faithfully recapitulate many disease variants and to unlock CRISPR's full potential, gene editing must efficiently and precisely modify the DNA. One research team – led by Bill Skarnes at The Jackson Laboratory (JAX), USA, – has developed a refined CRISPR/Cas9 methodology to improve precision (3). Cas9 is the CRISPR enzyme that targets and cuts DNA. After being cut, the DNA is repaired by the cell's natural repair mechanisms – either non-homologous end joining (NHEJ) and homology-directed repair (HDR). For many CRISPR experiments and potential therapies, the HDR pathway is preferred, as it is less error prone than NHEJ; the JAX method promotes error-free repair of CRISPR/Cas9-cut DNA by shifting the ratio towards HDR.

The improved protocol is now being used by the JAX scientists to research and develop cellular models of human disease, generated through the CRISPR gene editing of induced pluripotent stem cells.

"As reporting of the first-in-human administration of an in vivo CRISPR drug follows hot on the heels of the first report of clinical results from an ex vivo CRISPR therapy (4), scientists worldwide are working to ensure that CRISPR technologies are as precise and controllable as possible in basic life science research and clinical applications."

As we move towards more testing and evaluation of CRISPR-based therapies for a variety of diseases, any potential off-target gene editing and their effects need to be carefully monitored and measured. Therefore, the measurement of off-target effects (OTEs) is another aspect of CRISPR research technologies that requires clear focus. Indeed, Integrated DNA Technologies (IDT) has developed a new research-use-only strategy for the quantification of multiple off-target sites in a single assay using rhAmpSeq technology (not intended for clinical or therapeutic applications).

Ayal Hendel – a pioneering researcher at Bar-Ilan University (Israel) developing CRISPR-based therapies for diseases, such as SCID – and his team have published a method to nominate potential off-target sites and then quantify them in cells using rhAmpSeq multiplexed amplicon sequencing. Notably, the same workflow can be applied to other model systems to characterize the off-target potential of CRISPR/Cas9.

As reporting of the first-in-human administration of an in vivo CRISPR drug follows hot on the heels of the first report of clinical results from an ex vivo CRISPR therapy (4), scientists worldwide are working to ensure that CRISPR technologies are as precise and controllable as possible in basic life science research and clinical applications. These ongoing and upcoming studies will certainly test and add to our knowledge of CRISPR genome engineering, eventually paving the way for a new class of gene therapy.

Mollie Schubert, Research Scientist, Integrated DNA Technologies, USA

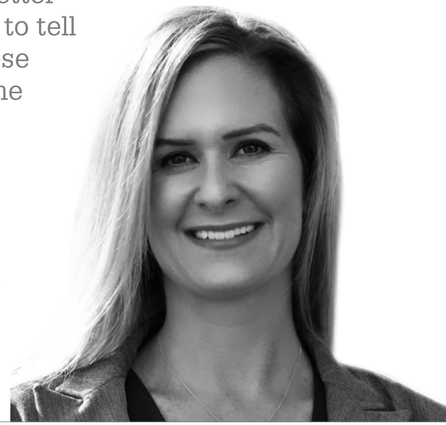
REFERENCES AVALIABLE ONLINE

ONLINE

What's in Your Capsids?

Are your capsids full, half full, or empty? We need better analytical techniques to tell us the answers to these crucial questions in the development of gene therapies.

Lori Stansberry, Senior BioPharma Marketing Manager at Thermo Fisher Scientific



ONLINE

Purifying Gene Therapy

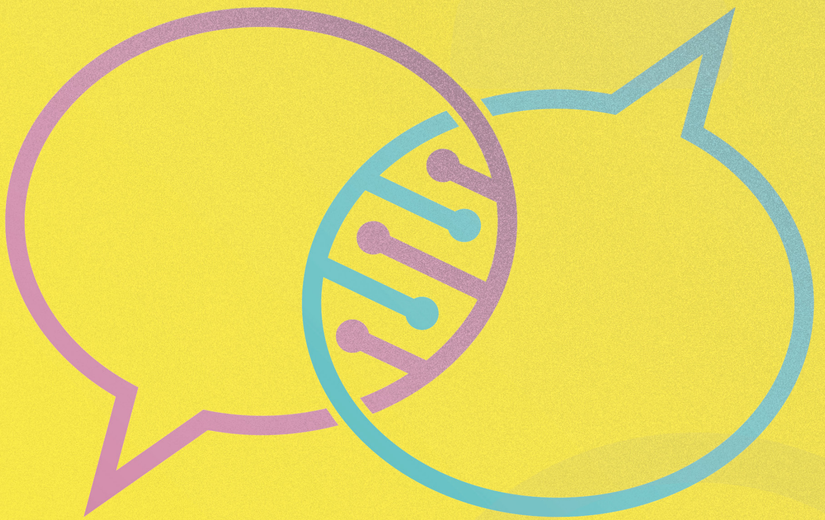
The gene therapy industry must maximize the amount of therapeutic gene payload being delivered with each vector to reduce the risk of immune reaction and, ultimately, cut costs. How? High-level purification.

Akash Bhattacharya, Senior Application Scientist at Beckman Coulter Life Sciences

FEATURE

We Need To Talk About Cell and Gene Therapy

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?



When 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 then 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.

ONLINE

Getting Everyone on Board

By Kelly Page

ONLINE

Understanding Consent

By Sandy Macrae

ONLINE

The Path to the Patient

By David Meek

"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."

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.

READ THE FULL FEATURE ONLINE

DEPARTMENT

Armored Tregs to the Rescue

How Treg-cell therapy could transform the way we treat autoimmune disease and transplant rejection.

In disease states such as autoimmune disease, chronic viral infection, and transplant rejection, the immune system responds inappropriately to self-antigens or doesn't resolve once the pathogen has been removed. Immunosuppressants may be used to reduce inflammation, but current biologic and small-molecule therapies must be administered over the long-term and can only alleviate symptoms. Regulatory T cells (Tregs) maintain a healthy immune response by suppressing inappropriate activation. And, in recent years, researchers have turned to Tregs to develop adoptive cellular therapies that can restore immune tolerance in autoimmune disease and transplantation – with minimal side effects.

Tregs are a subcomponent of the T cell compartment. Around five percent of circulating CD4+ T cells are Tregs, which can be identified by expression of the transcription factors FOXP3 and Helios, together with high expression of cell surface marker IL-2 receptor (CD25). In addition, the subunit α of the IL-7 receptor (CD127) is downregulated, which is inversely correlated to the suppression function of human Tregs (1). Lastly, the demethylation of the Treg-specific demethylated region (TSDR), an evolutionary conserved noncoding region of the FOXP3 locus, is the best marker for the stability of Tregs (2). Clinically stable Tregs are defined as a CD4+CD25+CD127low/- with over 80 percent of demethylation in the TSDR.

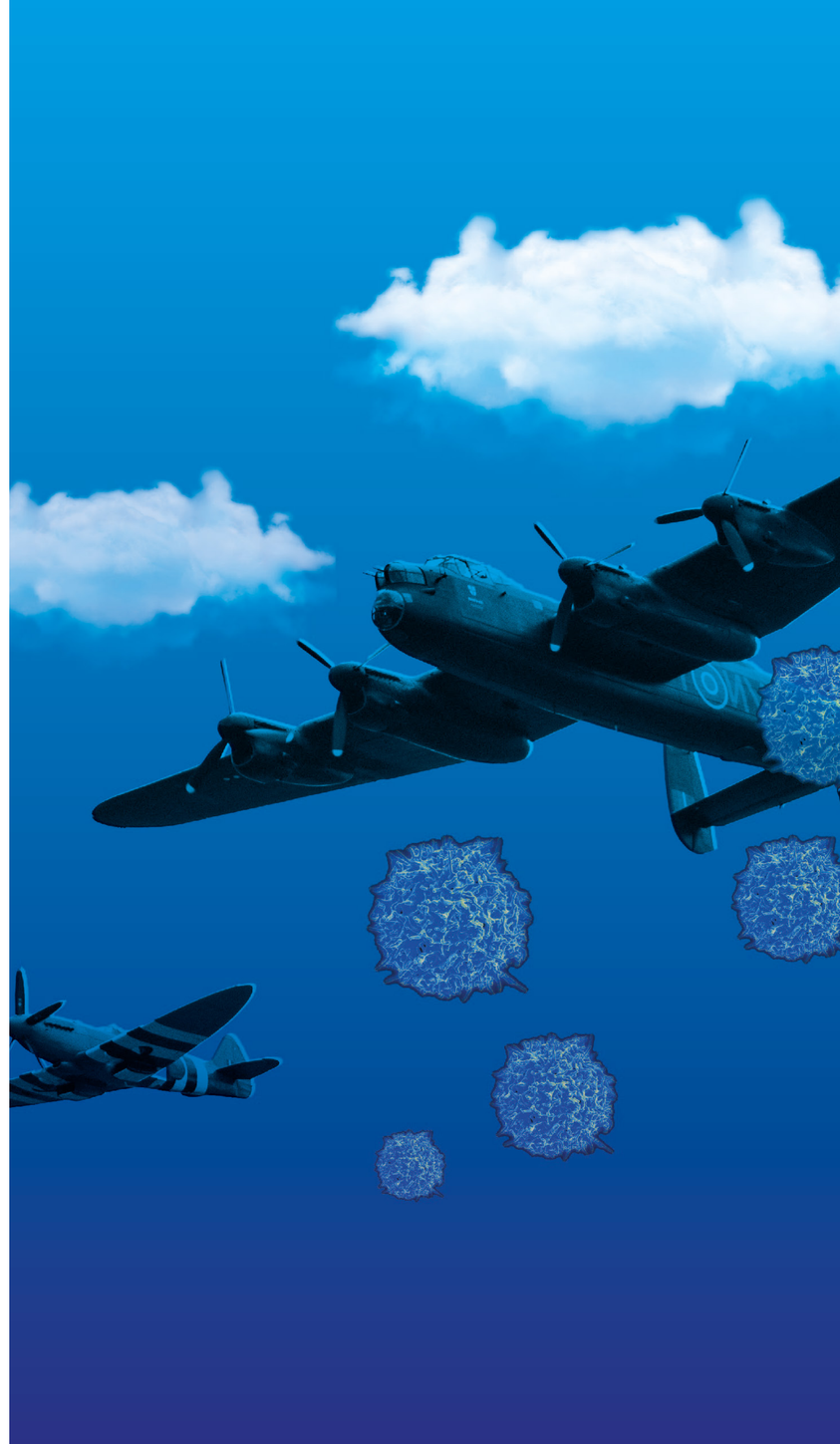
Once Tregs are activated via their cognate antigen, they suppress immune response by i) releasing inhibitory cytokines; ii) expressing suppressor cell surface molecules, such as CTLA-4, PD-1, Vista; and iii) depriving nutrients needed for T cell activation. These mechanisms block dendritic cell maturation and abrogate effector T cell proliferation and function. And that's why this subset of CD4+ T cells are showing promise in the development of cellular therapies for autoimmune disease and transplantation.

Current state of play

Currently, three main Treg-cell products are being developed for adoptive cell therapy: polyclonal Tregs, antigen-specific Tregs and chimeric antigen receptor (CAR) Tregs (see Table 1). In clinical trials, polyclonal Treg cells isolated from peripheral blood tend to be used, as these cells can be readily expanded in vitro. Polyclonal Treg-cell therapy has been found feasible and safe in different clinical settings, including kidney transplant and autoimmune type 1 diabetes (3, 4). However, these studies have failed to demonstrate efficacy – and this failure has been attributed to the low Treg specificity of the therapy.

In the context of transplantation, the second approach for adoptive Treg therapy is the use of antigen-presenting cells from donors to stimulate in vitro Tregs from recipients (5). This method provides greater specificity than polyclonal Tregs, but the yield of cells is very low in comparison, and it cannot be applied to expand Tregs from patients with autoimmune diseases. Therefore, this Treg product has not successfully moved forward into the clinic.

The third approach is the expansion of polyclonal Tregs genetically engineered to contain a chimeric antigen receptor (CAR) or a transgenic T cell receptor (TCR) expressed on the cell surface to increase the specificity of the therapy. In recent years, CAR T-cell therapy has been successful in the oncology field, but has seen significant cytotoxic side effects associated with cytokine release syndrome and neurotoxicity. In contrast, CAR Treg-cell therapy would be expected to have the opposite effect and dampen down inflammation in autoimmune disease and promote transplant tolerance. Transgenic TCRs and CARs should play an important role in the future adoptive



"Autologous adoptive cellular therapy is currently the most promising model of Treg-cell treatment, but there are challenges."

Treg-cell therapy clinical landscape, given the antigen specificity they are able to introduce.

What about allogeneic approaches?

Autologous adoptive cellular therapy is currently the most promising model of Treg-cell treatment, but there are challenges. First, the starting material required must be of high quality. In many cases, patients' T cells are exhausted and unable to be expanded or their numbers are too low for the manufacturing process. Second, engineering and expansion protocols are long and there is a risk of the patient deteriorating rapidly – shrinking the window of time where the therapy could be efficacious. Finally, the price per treatment tends to be high; for example, the cost of the CD19 CAR T-cell therapy for B cell lymphoma is currently around $475,000 (6). Thus, an alternative therapeutic approach is needed to reduce both the cost and time of the manufacturing process.

Allogeneic or "off-the-shelf" Treg-cellular therapy could be the answer. This approach involves generating CAR Tregs expanded from a bank of healthy donors with the best possible human leukocyte antigen (HLA)-match. In the short term, this may be sufficient to establish the suppressive environment in both autoimmune disease and in transplant tolerance. The isolation and preparation of Tregs from healthy donors is advantageous as it helps reduce variability in expansion, increases the quality of the starting material and reduces the treatment time. Nevertheless, this method is susceptible to host-mediated allo-rejection of the transferred cells, which will likely limit repeat dosing and long-term efficacy. Therefore, developing Treg cells that can evade host-mediated immune recognition will present exceptional opportunities in the creation of off-the-shelf therapies.

At this point, the use of human induced pluripotent stem cell-derived Tregs (hiPSC-Tregs) for allogeneic therapy appears an attractive alternative. hiPSCs can be expanded easily and could be an endless source of Tregs given that they are amenable to biotherapeutic manufacturing processes. Computational approaches to cell reprogramming are well placed to identify new genes needed to accelerate and improve the process of generating both consistent and well-characterized batches of hiPSC-Tregs (7). Importantly, hiPSCs would generate "rejuvenated" Tregs with longer telomeres which will improve expansion and prevent cell cycle exhaustion (8). Finally, the genome of hiPSCs can be routinely modified in the lab, bringing a wide range of possibilities: from adding CARs to editing HLA identity.

However, there is a clear need to establish robust protocols for the generation of Tregs from hiPSCs. Mohammad Haque and colleagues have developed a method based on the genetic modification of iPSCs with the FOXP3 transcription factor followed by in vitro stimulation with Notch ligand (9). The resulting Treg cells were able to produce suppressive cytokines, inhibit other immune cell activities and suppress arthritis development in an adoptive transfer context (9). Notably, this study was only carried out in a murine model, and efforts are now focused on unraveling how Tregs are developed in the human thymus and in defining protocols to generate phenotypically stable Tregs from hiPSCs. Here, the deployment of next-generation sequencing and gene regulator/epigenetic network data could play a key role. Through the systematic identification of gene regulators and soluble factors, we can expect to enhance the generation, maintenance and stability of hiPSC-Tregs for cellular therapies (10).

Raul Elgueta, R&D manager at Mogrify, UK

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SITTING DOWN WITH

Of Plumbing and Poetry

Sitting Down With… Sandy Macrae, Chief Executive Officer, Sangamo Therapeutics, USA

You started out in medicine, but what happened next?

I studied medicine and pharmacology at the University of Glasgow. During my time there, I did an internship at a pharma company, which completely changed my perspective of the industry. I was impressed by the professionalism and the way science was focused toward a clear goal. I then studied for a PhD at the University of Cambridge and a postdoc at Duke University Medical Center, and was offered a grant from the Wellcome Trust to set up my lab and my first PhD student. But I realized that I would never be able to compete as a full-time physician only working in the lab a couple of times a week. So I looked to industry and took a job at SmithKline Beecham (which of course became GSK). This move provided me with incredibly powerful training in how to carry out quality scientific and clinical research. I spent the next 19 years in industry, before being offered the chance to head up Sangamo in 2016.

Do you think your background in medicine and academia prepared you well for the job of leading a cell and gene therapy company?

It is rather unusual for a physician/scientist to lead a cell and gene therapy company, but I think it does help to coordinate the technology and development arms – especially important for advanced medicine. No matter the excitement around your technology, you must understand how to recruit patients with the specific disease you're trying to treat, inclusion/exclusion criteria, and ultimately how to meet your endpoints and validate your technology. But nobody knows it all. Leaders with my background will lean on a good chief business officer, with a real understanding of how to make our therapies available to patients – how to price them and how they'll fit into the various healthcare systems. Similarly, someone from a business background would require a strong head of R&D or chief medical officer. A good balance of skills and perspectives is a must.

Are there any leadership qualities you've found to be especially important?

My wife – a psychiatrist and a chief medical officer – gave me a book by James G. March, called On Leadership, in which he describes leadership as a combination of plumbing and poetry. A leader must inspire – think Henry V at Agincourt – and give people a real sense of purpose. Fortunately for us, most people in the pharmaceutical industry are inherently purpose-driven. To keep employees motivated and engaged, we need to join the dots between what they're doing and the patient. We spend a lot of time bringing patients into the organization – last week we had a couple of children with autism and before that we had men with BLS (an inherited immunodeficiency); meeting patients really helps people make those connections.

That's the poetry side, but the plumbing is a little more prosaic. Imagine you're staying at a hotel and the plumbing works – you don't go down and thank the staff. But if you flush the toilet and it doesn't work, there's a good chance you'll complain or never go back. My job is to ensure there are few obstructions - that the organization is balanced, that people are working well together and have good facilities, IT systems and benefits. In other words, I'm there to make sure the plumbing works. Leaders must listen for gurglings in the pipes and see that they are sorted before they burst!

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