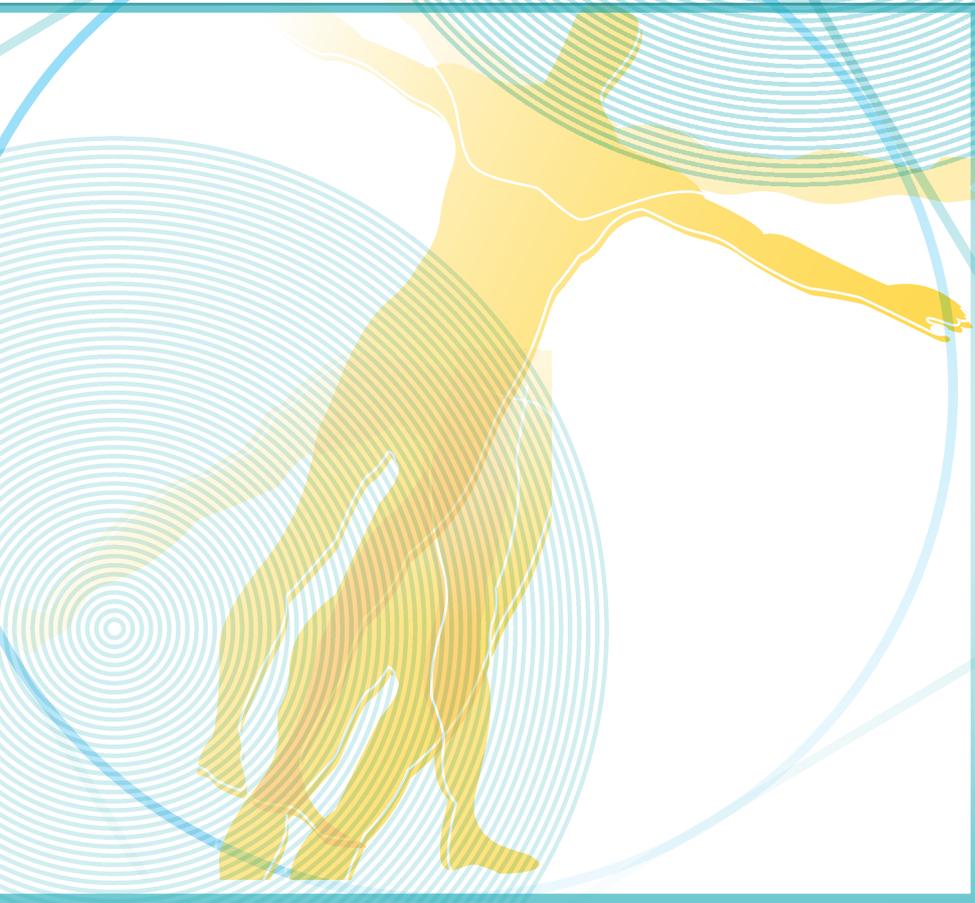


Advancing Medicine

Can cell and gene
therapies paint a picture
of perfect future health?

the
Medicine Maker

www.themedicinemaker.com



03 **Introduction**
Hype to Hope,
by Stephanie Sutton

On The Cover



Taking inspiration for perfect health from Leonardo Da Vinci's Vitruvian Man

In My View

- 04 We need to put a stop to unapproved cell therapies before they damage the field, says **Daniel Weiss**.
- 05 **Simon Ellison** offers his advice on conducting the supply chain orchestra for advanced medicines.
- 07 According to **Neil Hunter**, it's crucial to be seen and heard in the field to be a success.
- 08 Gene therapies are making real progress, says **Linda Randall**, but cost is still an issue.

Report

- 20 The Big (Bio) Freeze

Feature

- 12 **Gurus of Advanced Medicine**
Five esteemed gurus debate what's hot in the advanced medicines manufacturing field, and what is needed to help take the field to new highs.

Sitting Down With

- 22 **Steve Oh**, Director, Stem Cell Bioprocessing, Bioprocessing Technology Institute, Agency for Science, Technology and Research (A*STAR), Singapore.

Hype to Hope

Welcome to a special supplement focusing on one of the most exciting fields of medicine to emerge in recent years – advanced therapies.

Introduction



It is with great pleasure that I welcome you to this supplement to the July/August edition of *The Medicine Maker*. The EMA defines advanced therapy medicinal products as medicines based on genes or cells that offer “groundbreaking new opportunities for the treatment of disease and injury”.

When I first started out on my journalistic career in medicine and pharmaceuticals (many years ago), I made a mistake common to many young, inexperienced journalists – I went straight to the most dramatic headlines I could find, including miracle cures for cancer and Alzheimer’s, nano robots that could potentially patrol the inside of the human body, inventive ways to repair spinal cord injuries, and giving mice superhuman (or supermouse) strength.

My very patient manager at the time explained that certain research topics, while fascinating, were a very long way from the clinic. Included on that list were cell and gene therapies. It was early days for the field and at the time there was uncertainty over whether such therapies could ever make it to a patient’s bedside.

Now in the summer of 2017, things are very different. A handful of cell and gene therapy products have already been approved by US or EU regulators – and more are set to follow. There is much excitement around Novartis’ investigational CAR-T therapy, CTL019, which has recently been recommended by an FDA panel (1) for treating relapsed or refractory pediatric and young adult patients with B-cell acute lymphoblastic leukemia (ALL), the most common childhood cancer in the US. CTL019 is likely to be the first CAR-T therapy to hit the market, although Kite Pharma isn’t far behind (2), and other companies are also focusing on the CAR-T field

Cell and gene therapies are still a very long way from the hype of complete cures and revolutionary treatment options, but it is encouraging to see the field progressing. We know that cell therapies can have clinical effects; the questions now are what conditions can benefit? How do we maximize efficacy and safety? And how do we scale up manufacture to reach larger patient numbers?

In this supplement, we unite experts from across the field to discuss the progress being made in advanced medicines, and how the industry is approaching the complex challenges posed by the supply chain and commercial manufacture.

References

1. Novartis, “Novartis CAR-T cell therapy CTL019 unanimously (10-0) recommended for approval by FDA advisory committee to treat pediatric, young adult r/r B-cell ALL,” (2017). Available at: <http://bit.ly/2uTmQbC>. Last accessed July 18, 2017.
2. Kite Pharma, “Kite Receives U.S. Food and Drug Administration Priority Review for Axicabtagene Ciloleucel,” (2017). Available at: <http://bit.ly/2ql22kc>. Last accessed July 18, 2017.

Stephanie Sutton
Editor

Stephanie Sutton

In My View

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

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of pharmaceutical development or manufacture.

They can be up to 600 words in length and written in the first person.

*Contact the editor at:
stephanie.sutton
@texerepublishing.com*

Putting a Stop to Cell Therapy “Snake Oil”

We must close loopholes that allow patients to pay for unapproved cell therapies.



By Daniel Weiss, Chief Scientific Officer at the International Society for Cellular Therapy (ISCT), USA.

The last 10 years has brought about the development – and broader acceptance – of cellular therapies. But, as with many great breakthroughs, there’s a dark side – the selling of unproven cell therapies. Unfortunately, unscrupulous people are bold enough to take advantage of desperate patients, and there are countless clinics worldwide advertising cell therapies to treat a range of diseases including cancer, Alzheimer’s, Parkinson’s and more. A current core focus of the International Society for Cellular Therapy (ISCT) is to combat medical tourism and tighten up loose legislation.

The regulatory climate in the US suffers from loopholes that complicate the issue, specifically the fact that “minimally manipulated” cells are subject to different rules compared with

conventional cell therapies. According to the legislation – under section 361 of the Public Health Service Act – minimal manipulation means cells have not been chemically or biologically altered. For example, if a patient has a tissue sample removed and simply centrifuged to separate the components, it is considered minimal manipulation (despite potentially fundamental changes) – and the resulting cells are not subject to any other regulations. As such, it is currently legal in the US to isolate a patient’s own cells and inject them back into their body, without the need for extensive testing. Indeed, you may recall the ocular injection incident in Florida earlier in 2017; three patients paid at least \$5000 each for an unapproved cell therapy that involved injection of autologous fat cell-derived stem cells into their eyes in an attempt to treat macular degeneration. Two of the patients lost most of their eyesight and one patient was left completely blind by the procedure (1).

Such lax regulation is in complete contrast to section 351 cell therapies that are “meaningfully manipulated” – here, regulations are extensive; there are requirements for safety and efficacy tests, and the need for market authorization from the FDA along with an Investigational New Drug (IND) license to conduct research or commercialize the therapy.

To protect patients, the ISCT is trying to work with legislative and regulatory agencies to close these cell therapy loopholes. But it’s a long and tricky process – and even legislators can be convinced of the benefits of bogus unproven therapies by particularly talented sales people with “snake oil” pitches... In particular, the ISCT would like the United States Justice Department to play a larger and more visible role in setting these regulations; after all, it is a matter of public health and safety.

The ISCT is also taking a parallel route to address the issue from a patient perspective. People in desperate situations can make irrational judgments. And although we can't put ourselves in their shoes or tell patients or their families what to do, we can try to provide them with as much information as possible and make them aware of the potential dangers and lack of proven efficacy of unapproved treatments so they are able to make the best possible decisions. To that end, the ISCT has been reaching out to professional societies, creating patient education sheets and web statements, and using social media and other online

resources. In 2015, for example, the ISCT published a reference guide on the use of unproven cellular therapies (2). In fact, we're doing everything we can think of to get the message out there to make sure patients are as informed as possible before making any major health-related decisions.

Some people wrongly perceive stem cell therapy as a magic cure-all – and there are individuals out there who take advantage of that. Aside from the obvious aforementioned risk to patients, it also jeopardizes the future of the field. If unapproved cell therapies are allowed to exist without proper regulation, it could result in a stigma around the

field, which could affect legitimate research – or possibly stop legitimate cell therapies from reaching patients. If we truly want to help patients and allow the cell therapy field to proliferate, we need to act now and properly regulate unapproved treatments.

References

1. AE Kuriyan et al., "Vision loss after intravitreal injection of autologous 'stem cells' for AMD", *New Engl J Med*, 376, 1047–1053 (2017).
2. ISCT, "ISCT Presidential Task Force on the Use of Unproven Cellular Therapies: Reference Guide," (2015). Available at <http://bit.ly/1VT1xay>. Last accessed July 26, 2017.

Conducting the Supply Chain Orchestra

A coordinated supply chain management plan is crucial when developing advanced therapies.



By Simon Ellison, Senior Manager, Advanced Therapies, at Fisher Bioservices, UK.

Conducting the advanced therapy supply chain orchestra is more than waving a stick at people – it is an “end to end”, complicated, inter-related system that requires controlled, consistent management. For the purpose of this article, advanced therapies are seen as cell- and gene-based therapies. These therapies are showing fantastic clinical results and are now on the brink of becoming a commercial reality. Initially, advanced therapies are likely to be for small, orphan indications, but over the coming years I expect them to expand to address larger health challenges, such as stroke or diabetes. The value of advanced therapies is that they can potentially offer long-term solutions, and even cures, to unmet medical needs.

There are many challenges involved in developing an advanced therapy product – and rightly so, R&D is the main focus for any company in the field. While focusing on building a strong melody, however, it's important not to overlook how it will be delivered to the audience – otherwise you may find that your delivery is closer to a garage band than a full Philharmonic. In other words, it

is important to consider a coordinated supply chain management plan. In my view, this should be done as early as possible during the development of the therapy.

“A cell or gene therapy supply chain often has multiple time-critical components.”

Unlike more traditional biologics, a cell or gene therapy supply chain often has multiple time-critical components, needs to be shipped under controlled (often cryogenic) temperatures and is directly linked to the patient. During clinical trials, this is manageable as the

scale of operation is limited; however, as we move into global commercialization, the complexity will increase. Much like moving from a musician's demo tape into a fully produced Top-40 single.

It is surprising just how many companies fall into the trap of thinking that supply chain management is “easy” and something that can simply be grabbed off the shelf as required. The danger is that this viewpoint can lead to disjointed, ad-hoc supply chains that end up requiring extraordinary levels of manual intervention. To develop the capability to provide a harmonious supply chain management system, you need to think about:

- Choosing the right musicians. When I use the word “supply chain” I am talking about an entire supply chain, rather than just logistics. The supply chain involves the management of processes, whilst logistics is the flow between points (1). The local “busker”, no matter how talented, may be able to help with a small-scale Phase I project, but is unlikely to be able to offer what is necessary to commercialize a therapy on a global scale.
- Work together – or it’s just noise. Much like an orchestra, the advanced therapy supply chain comprises a mix of different people, skills and positions. This inter-relationship is what allows the music to flow. It is the same for the supply chain where challenges such as moving therapies between countries, or even provinces, can easily stop the music mid-verse and leave a therapy drifting out of temperature.
- Strong conductor. The art of a conductor is that he/she makes the job look easy. The “stick waving” at the front is all

that is visible, but the conductor has had to recruit the musicians and validate their capability; organize them so that one group does not over-power the other; build a system that allows all the instruments to work together; manage the cultural differences between the diverse groups of individuals; use their expertise to control the flow of the concert from one piece of music to another – or from one part of the supply chain to another.

“In a supply chain, you need to consider what will add value to your end consumer.”

- Meeting the audience needs. For advanced therapies, the audiences are clinicians and patients. These are the people who get the value from what you are producing. While there is no point playing jazz in a heavy metal venue, from a supply chain point of view, this critical component is often under-managed. Advanced therapies are often transported cryogenically. This means that they arrive at the clinical site in large containers that need specialist training to control. Additionally the therapy

within them, much like a famous soloist, needs to be managed very carefully. For example, until recently therapies were thawed in a water bath. This can lead to variation in the thawing cycle, which could impact therapy efficacy, and therefore the value to the patient.

Cryo shipping is the key to controlling cost in the supply chain but you also need to think about how the clinician wants to receive the therapy. Do they have to monitor water baths or can you provide digital thawers that control the cycle for them? Essentially, do they want to see the concert live or listen on line? In a supply chain, you need to consider what will add value to your end consumer.

These are really exciting times for the advanced therapy industry. Some life-changing therapies are already on the market, but more will follow – many large investments are being made in the industry after promising clinical results. When thinking about manufacturing, don't forget about your supply chain. Considering a supply chain early on will give your company a competitive advantage (2). If you don't have a plan, then you risk sitting down to listen to your favorite tune and finding that the loudspeakers are missing.

References

1. Lummus et al., “The relationship of logistics to supply chain management: developing a common industry definition,” *Industrial Management and Data Systems*, 101, 426–32 (2001).
2. Li et al., “The impact of supply chain management practices on competitive advantage and organisational performance,” *Omega*, 34, 107 (2006).

Being Seen and Heard

In the bustling world of cellular therapies, effective communication is essential.



By Neil Hunter, Life Science and Corporate Communications PR Director at Image Box PR, UK.

The cell therapy sector is widely recognized as having moved from a state of promising, fledgling future ambition to achieving real therapeutic potential – all thanks to brilliant science, major clinical results and key regulatory approvals. Many individuals have played a role in developing this exciting sector, including communication professionals like me, whose work is often in the background.

It wasn't that long ago that many people, including journalists, investors and analysts, considered cell therapies as medicines of an idealistic future rather than a potential reality. And so it's taken a great deal of hard work, science and public relations (PR) efforts to prove that cell therapies are here and now – and ensuring that this message was heard has helped generate greater collaboration, investment and funding for the field.

For some companies, the overall success of the sector has a downside from a business perspective. The big headlines – and subsequent industry, investor and media attention – are

taken up by the companies making the biggest noise (which at the moment is Novartis and CAR-T therapies), and it's easy for smaller voices (particularly those of suppliers and support partners) to be lost amidst the clamor. Many companies have exciting propositions and promising clinical data; unfortunately, if nobody knows about them, they aren't much use...

If you want to be successful in this sector (or any other sector for that matter), you need to build long-term communications into your business plan to be seen, heard and noticed by the market. That includes the companies developing therapies, the suppliers, the investors, the grant and fund providers, the potential academic or commercial partners, and, last but not least, potential pharma buyers inundated with offers when investors seek an exit.

But what is "effective communication"? Contrary to the belief of some, a communication strategy is not just distributing occasional magnolia press releases. Business revolves around competition – you need to compete for investment or the best research partnerships. And it's the same with communication. In key publications, there is limited column space written by a limited number of journalists with a limited number of hours in the day. And social media is also saturated with posts about cell therapies and other advanced medicines. You need to work out how to be ahead of the competition by asking a simple question: "Why would people want to write, read and talk about my company and innovations?" As well as getting your management, company and achievements noted by the market and stakeholders, you need to generate excitement. You need to persuade people to agree with you. You need to shape the market and landscape to your advantage. You need to highlight how your key achievements will affect the wider

sector. It's also important to bear in mind that many stakeholders – investors, for example – will not understand technical jargon or scientific language, so information must be communicated in more widely understood terms.

"You need to highlight how your key achievements will affect the wider sector."

Wise companies choose to invest in communications by working with a PR agency – and there are many different types to choose from. My advice is to be wary of the agency that says "yes" too often. PR agencies are on the frontline of life science communications and their job is to give you their advice, not what you want to hear. In return, the PR agency will need to understand what you do, what differentiates you, and why your work will be exciting to the wider community.

Right now, cell therapies and advanced medicines are in the media spotlight; there is great deal of excitement and many investors are moving into the field. But honeymoons have surprisingly short life spans... Cell therapies must take advantage as soon as possible, because it won't be long before another evolving field steals the excitement. Darwinism dictates that strong individual organizations will survive and weak ones will fail or be absorbed. Each and every organization needs to give itself the best chance of success.

What About Gene Therapies?

Gene therapy has come a long way since 1990 and the industry is seeing real advances, but there is an elephant in the room: cost.



Linda Randall is Director, Process Sciences R&D, at Allergan Biologics Limited, Liverpool, UK.

When discussing the potential of precision or personalized medicine, cell therapies are often the first to spring to mind – and such therapies are certainly causing a stir in the industry. But there is also another contender in the precision medicine field that potentially offers significant benefits: gene therapy. Gene therapies work in one of three ways: i) replacing a mutated (improperly functioning) gene that causes disease with a healthy copy of the gene, ii) inactivating a mutated gene, or iii) introducing a new gene to the body to provide a treatment or cure.

The first gene therapy was administered to a human in 1990 but, since then, gene therapies have faced several challenges and setbacks, including unexpected side effects and, in one case, a tragic death. Over the years, knowledge and understanding of the field has increased, along with relevant technologies and regulatory acceptance. From 1990 to 2015, more than 2000 clinical gene therapy trials were approved worldwide. Data from the Gene Therapy Clinical Trials Worldwide database shows that the number of trials has risen steadily from 102 in 2012, to 163 in 2015. And

in 2017, a handful of gene therapies are expected to move into the EU and US approval processes.

The increase in gene therapy activity is attributed, in part, to the first EU approval of a gene therapy agent in 2012 – Glybera for the treatment of lipoprotein lipase deficiency, which leads to severe or multiple pancreatitis attacks. Many challenges faced Glybera and uniQure has since decided not to seek market authorization renewal in Europe, but the fact that it was approved signals to researchers, drug makers and investors alike that the regulatory pathway for gene therapy for rare diseases is open.

Gene therapy is most commonly delivered via viral vectors, with recombinant adeno-associated virus (AAV)-based vectors being the most widely used. One significant advantage of AAV vectors is the availability of different recombinant serotypes, which means that therapy can be targeted to specific tissues or organs in the body. For example, the AAV2 serotype is being used in early phase clinical trials to deliver a gene that encodes channelrhodopsin-2 (ChR2) – a light sensing protein – to the eyes of patients suffering from blindness due to retinitis pigmentosa.

Research around gene therapies is now moving at a rapid pace, and scientists have a number of techniques in the toolbox to help identify mutations and create therapies to correct them. But what about manufacturing? It's still relatively early days for gene therapy commercialization, so it's fair to say that manufacturing is a big challenge. Current processing methods have been well placed to provide early clinical trial material for proof of concept (typically tens of patients), but these processes are frequently low yielding, laboratory-scale processes that are difficult to scale up. At later stages of development, drug product demand escalates as material is required for analytical method validation and product stability, as well as late-stage clinical studies – and, at this point, the manufacturing challenges become very

apparent. As an industry, it is important that we continue to develop scalable, robust process technologies, as well as orthogonal analytical techniques that ensure the right balance of quality, yield and manufacturing costs. At the moment, there is a shortage of GMP manufacturing capacity and routine manufacturing expertise for gene therapies, but more contract manufacturing organizations and companies are now seeing the dawn of a new era of commercialized therapies and subsequent investment in internal capabilities will help to drive the field forward.

As more gene therapies reach the market, manufacturing will become more efficient as companies learn through repetition. So, does that mean we are poised to overcome the major gene therapy hurdles? The elephant in the room is cost – a highly controversial topic that is common to all precision medicines. Many say that the price for a single dose of Glybera (\$1 million) is extraordinary, but others believe that a life-changing therapy – that only requires one dose – is surely worth the cost, particularly given the fact that Glybera treats an inherited, chronically disabling diseases for which there is no other cure. Like Glybera, most gene therapies in development also target rare diseases and conditions of unmet medical need, and R&D investment and the cost challenge associated with small scale production of a single-dose administration for a small patient population will force health economists, drug companies, insurers, and health service providers to re-think their approach. Perhaps in time, these discussions will lead to innovation in healthcare provision.

Nevertheless, I believe that we are on the edge of a major transformation in the biopharmaceutical world. With increased collaboration and investment in developing manufacturing platforms for these therapies, as well as innovation in health economics, I think gene therapy has a real chance to make a difference to medicine.

*Producing quality content requires
considerable time and resources.*

*This supplement would not have been
possible without the support of our sponsors.*

By exploiting the strong synergies in bioreactor technology and polymer manufacturing, Eppendorf has emerged as a global player and valuable resource to its customers in the bioprocess marketplace. With a comprehensive offering of single-use and traditional products for the growth of mammalian and microbial cells, and working volumes of 60 mL – 2,400 L, the Eppendorf bioprocess portfolio can satisfy the demands of process development through production.

Many labs trust Eppendorf as an expert partner for stem cell bioprocessing. Eppendorf fosters close relationships with researchers from the stem cell field all over the globe to fully understand their needs. To support scientific exchange, Eppendorf brought together experts from industry and academia at the 1st Stem Cell Community Day in April 2017 to discuss recent achievements, challenges, and chances in stem cell bioprocessing for research and commercial manufacturing. The event was very well received and will be repeated in spring 2018.

www.stemcellday.de

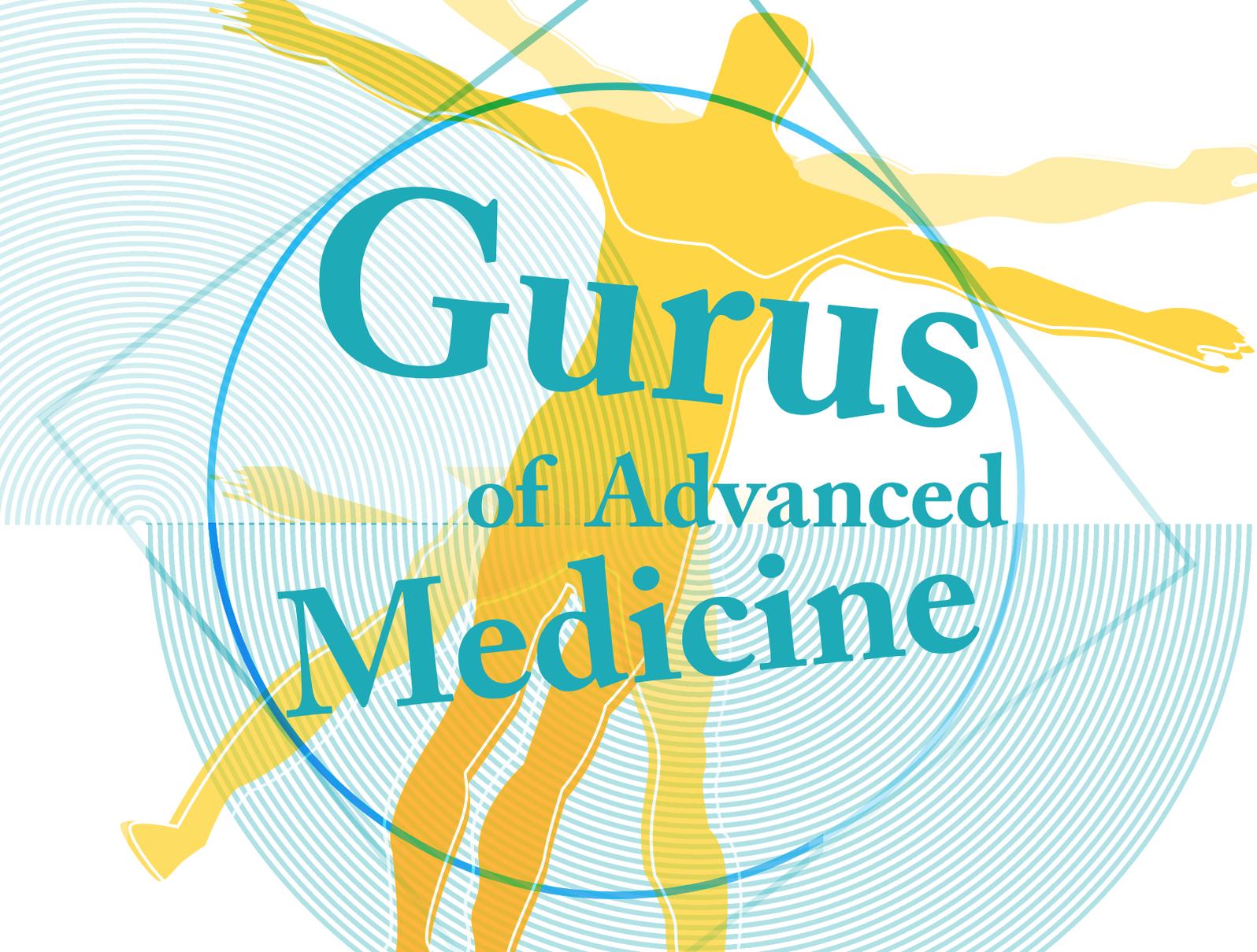
eppendorf

At GE Healthcare's Life Sciences, we accelerate precision medicine by helping researchers, pharmaceutical companies, and clinicians discover and make new medicines and therapies. We provide expertise, technology and services for a wide range of areas within the life sciences industry, including the manufacture of contrast agents for diagnostic imaging, basic research of cells and proteins, and technologies that enable large-scale manufacturing of vaccines, biologics, and cell therapy.

The emergence of cell therapy as a frontline treatment for challenging diseases, including cancer, is rapidly changing the healthcare landscape. Our Cell Therapy business provides the tools, technology and processes to enable customers from pharmaceutical manufacturing as part of our Cell Processing segment, to clinicians and technicians in our Cell Banking and Point of Care business segments. We are investing in the field for the long-term, and partnering with pharma, biotech and clinical researchers. GE brings expertise in quality, global distribution, R&D, and regulatory that will transform cell therapy from small-scale treatment to a globally-accessible personalized medicine.

www.gelifesciences.com





Gurus of Advanced Medicine

Advanced medicines, such as cell-based therapies, have the potential to revolutionize treatment, but the field is in its infancy and there are many barriers to break through.

Is the pharma industry and the scientific community up to the challenge?

Five gurus discuss the emerging products leading the field – and debate the future.

How is the advanced medicine field currently shaping up?

David Williams: One of the key developments is simply the recognition that these science-led – but incredibly challenging – medical therapies can deliver, from a clinical point of view. In recent years, there has been a resurgence of gene therapies and the use of induced pluripotency stem cells – and successes are finally being seen. More companies are now engaging with these therapies and investing to reach patients at scale. Increasing clarity in the regulatory environment is also helping to create successes in the field, and there is growing national strategic support from a number of countries worldwide to help the medical profession and industry move cell therapies and other regenerative medicines forward.

Timothy Allsopp: The dominant therapeutic concept being tested

clinically was once mesenchymal stromal cell therapy (MSC), but this approach lacked efficacy in many diseases (although undoubtedly success exists in bone and cartilage repair). Concomitantly, the field has experienced an evolution, with new paradigms emerging, such as gene-modified immunotherapies and previously identified concepts, such as embryonic stem cell and induced pluripotent stem cells (collectively iPSCs), and complex tissue engineered products, finally reaching clinical-stage testing. There has also been notable progress in first market approvals for gene therapy, ex vivo stem cell gene therapy, a number of pivotal clinical studies, and unprecedented levels of investment for biotech companies.

Thomas Heathman: The cell therapy industry, as a whole, is finally moving from the discovery stage, where the challenges are

THE GURUS



Timothy Allsopp is the founder and Managing Director of consulting and strategy firm, Consilium, UK. Until recently, he was the Head of Stem Cell & Cell Therapy Lead at Neusentis, a Pfizer research unit.



Thomas Heathman has a PhD in regenerative medicine from Loughborough University, UK, and today is Business Leader in the Technology Development, Manufacturing Development & GTP Services, at PCT, a Hitachi Group Company, USA, a global contract development and manufacturing organization for the cell therapy industry.



Stéphane Boissel has experience in investment banking and the biotech immunotherapy space. Today, he is CEO of TxCell, France, which focuses on personalized T-cell immunotherapies.



Catherine Bollard is President of the International Society for Cellular Therapy. She also leads a research laboratory focusing on the development of novel cell therapeutics as Director of the Program for Cell Enhancement and Technologies for Immunotherapy within the Children's Research Institute of Children's National Health System and George Washington University School of Medicine & Health Sciences, USA.



David Williams is Professor of Healthcare Engineering at Loughborough University, UK, and was founding Director of the Loughborough-led Engineering and Physical Sciences Research Council Centre for Innovative Manufacturing in Regenerative Medicine. He was awarded an OBE for services to science and engineering in the Queen's Birthday Honours List in 2014.

mainly biological, to a stage where cell therapy developers and manufacturers are facing engineering challenges in terms of truly industrializing and commercializing therapies. This leap forward has been buoyed by the efficacy demonstrated by chimeric antigen receptor T (CAR-T) cells, and recent announcements of filings with the FDA from Kite Pharma and a positive recommendation for Novartis' CTL019 from an FDA advisory panel. Generally speaking, the increasing body of positive clinical data has led to increased investment in the field, and placed higher priority on tackling manufacturing and scalability issues, which currently contribute to the high cost of goods for advanced therapy products. Changes in regulations to specifically cover advanced therapies have also been significant. For example, in November 2014, Japan

passed a new regenerative medicine law which enables therapeutic development sponsors to receive conditional marketing approval and generate revenue from regenerative products while clinical trials are being conducted, after safety and an early indication of efficacy have been established.

What have been the field's biggest success stories so far?

TA: By far the most impressive early progress concepts involve using a patient's own ex vivo CAR-T cells to target blood cancers. Near complete molecular remission from disease was reported for a few patients and significant improvements in disease status for many others. European Medicines Agency approval for Glybera, a gene therapy to restore lipoprotein lipase deficiency, and the first ex vivo

stem cell gene therapy, Stremvelis, are also major landmarks. Stremvelis, in particular, represents a success for the technology sector for a number of reasons. It stems from a successful public-private partnership between GlaxoSmithKline and the San Raffaele Institute in Milan, highlighting the key role that collaboration can play in the sector. Stremvelis also exemplifies how a novel paradigm – using a patient’s own bespoke cells – can be pursued by big pharma, querying the assumption that pharma prefers a business model based on the historical practice of providing mass produced, “off-the-shelf” medicines.

Stéphane Boissel: Regenerative medicine has been a dream of scientists for more than 30 years. It is now a clinical reality with a new generation of CAR-T products yielding incredibly promising data in some hematological disorders. In 2017, CAR-T therapies will likely become a commercial reality, with the impending launch of the world’s first two products. Both Novartis and Kite Pharma have filed Biologics License Applications for their separate CAR-T products with the FDA, and both received Breakthrough Therapy designation. Considering that Kite was founded eight years ago, it’s amazing that KTE-C19, their lead product, could reach FDA licensure in B-cell lymphoma after less than five years of clinical development. The company has built the appropriate manufacturing, logistic and commercial infrastructure, and from a timeline viewpoint, I’m not sure there is any equal precedent in the biopharma industry.

Catherine Bollard: I’m with Stéphane and Timothy, and am really excited by advances in cellular immunotherapy, such as those for hematologic cancers. Successes seen so far include using tumor-directed T-cell therapies, such as CD19-CAR-T cells for CD19+ B-cell leukemias and lymphomas, and virus-specific T-cells for virus-associated cancers. There is a lot of science emerging in the T cell therapy field and I think we will see numerous breakthroughs for patients with unmet medical needs.

What are the biggest misconceptions about cell therapies?

DW: Many in the industry believe that the manufacture of advanced medicines and cell therapies is very special compared with other products. For the last decade or so, my team has been working hard to understand where we can transfer techniques from other areas that involve making things at scale with demanding precision; for example, my personal background is in the manufacturing of drug delivery devices within the pharmaceutical supply chain and in consumer micro-electronics for computing and telecomms – and many of the problems are the same. We’ve also been looking at the

“We disrupters need to emphasize the continued requirement to address unmet medical needs.”

significant differences, so that we can decide on what the field really needs to focus on to flourish.

TA: There is an unrealistic expectation that donor MSCs can treat everything. MSC therapies will continue to be tested, and have demonstrated some effect for symptom modification in early stage trials for anti-inflammatory and musculoskeletal repair mechanisms. In the last decade, however, only two MSC-based products have received approval, Procyhmal and TemCell for Crohn’s and GvHD, respectively, which is the very thin edge of

a large wedge of basic and non-clinical research effort with this technology. Frequently, assumptions have been made that non-clinical evidence of efficacy will successfully translate into major symptom modification, via a predominant class of therapeutic action for the majority of patients diagnosed. Large-scale clinical studies are demonstrating that this is not the case. Another major misconception is that advanced medicines should only be tested in patients for whom approved medicines are failing – this is often not the best scenario for demonstrating efficacy, and the risk-benefit analysis needs to be re-evaluated.

TH: I would add that another misconception is that patient-specific (typically autologous) cell therapies are too expensive to commercialize, and that the future of cell therapy has to lie in off-the-shelf cell therapies (always allogeneic cell therapies, where the manufacture of doses for multiple patients is possible from a single donor). We must keep in mind that rigorous industrialization efforts have not yet been applied to patient-specific cell therapies. I believe that there will be a commercial future for both autologous and allogeneic therapies – as long as the clinical and economic value proposition can be developed, on a case-by-case basis.

SB: There are still some who are skeptical about whether cell therapies will ever take off because of manufacturing and pricing issues. Developing cell therapies and other advanced medicines is certainly challenging – and we don’t yet know how pricing will play out – but, in my view, cell therapies will be a success. And we won’t have to wait for long to see who has been right or wrong about the field’s potential!

CB: One of the biggest misconceptions we encounter at the International Society for Cellular Therapy (ISCT) is the belief that all successful T-cell therapies are CAR-T cells. It is better to publicize the fact that there is a wealth of highly successful clinical data being seen in the T-cell therapy field: antigen specific T-cells (for example, targeting viruses) and other genetically modified T-cell strategies, such as abTCR-transduced T-cells, suicide gene

CAR-Ts A Go?

By James Strachan, Associate Editor of *The Medicine Maker*.

CAR-T cell therapies have caused much excitement in the scientific community, but could such therapies pass regulatory muster? Things are looking very good for Novartis' CAR-T cell therapy, CTL019, for pediatric acute lymphoblastic leukaemia (ALL). In July, the FDA's Oncologic Drugs Advisory Committee unanimously recommended CTL019 for approval (1). A Biologics License Application is under FDA priority review – approval is by no means guaranteed, but the FDA will take the comments of the committee into consideration. And the therapy received glowing recommendations, according to media reports. Tim Cripe, an oncologist with Nationwide Children's Hospital in Columbus, Ohio, and a temporary member of the committee, reportedly said, "I think this is the most exciting thing I've seen in my lifetime", while another panel member, Malcolm A. Smith, said the treatment is "a major advance, and is ushering in a new era" (2).

CTL019 was first developed by the University of Pennsylvania, but in 2012, Novartis and Penn entered into a collaboration to further research and commercialize the therapy. CTL019 uses the body's own immune system to identify and kill cancerous cells, making the manufacturing process for this type of therapy a new paradigm for the FDA – involving multiple rounds of cryopreservation and shipping. A patient's white bloods cells are first separated from the blood (leukapheresis), cryogenically frozen, then shipped to a manufacturing facility. After thawing, monocytes and B-lineage lymphoblasts are removed, and the remaining T cells are activated using antibody-coated beads, which are transduced with a vector containing the anti-CD19 CAR transgene – this enables the resulting "CAR-T" cells to identify and eliminate CD19-expressing cancerous cells. The transduced T cells are subsequently expanded *ex vivo* and then washed, formulated, and again cryopreserved, before being shipped back to the clinical site and administered to the patient (3).

The advisory committee reviewed evidence from a study showing that, of the safety analysis population (68 patients), 32 experienced the potentially life-threatening cytokine release syndrome – but there were no deaths (4). In its report, the FDA said that post-marketing considerations for long-term safety monitoring may be necessary to address the potential safety concern, since the study was too short to fully consider potential long-term side effects. A follow-up study is planned to monitor patients for 15 years post-treatment.

Kite Pharma CEO, Arlie Belldegrun, said in a blog post (5), "I will be Novartis' biggest cheerleader today... Today is not about business or competition. Today, we are not rivals. Today is about advancing an exciting technology that has the potential to transform cancer treatment."

The FDA is currently reviewing Kite's CAR-T for the treatment of adults with advanced aggressive lymphoma and a decision is expected by November 29, this year.

References

1. Novartis, "Novartis CAR-T cell therapy CTL019 unanimously (10-0) recommended for approval by FDA advisory committee to treat pediatric, young adult r/r B-cell ALL," (2017). Available at: <http://bit.ly/2uTmQbC>. Last accessed July 18, 2017.
2. C Dietz, P Goldberg, "ODAC unanimously recommends approval for CAR T-cell therapy for relapsed and refractory B-cell ALL in kids and young adults," *The Cancer Letter*, 28 (2017).
3. FDA, "FDA Briefing Document Oncologic Drugs Advisory Committee Meeting", (2017). Last accessed July 17, 2017. Available at: <http://bit.ly/2vtaVGM>.
4. FDA, "Oncologic Drugs Advisory Committee Briefing Document", (2017). Last accessed July 17, 2017. Available at: <http://bit.ly/2u0RoOq>.
5. A Belldegrun, "CAR-T in the Spotlight", (2017). Last accessed July 17, 2017. Available at: <http://bit.ly/2vbNTEf>.

modified T-cells, and/or T-cells engineered to resist the immune-suppressive microenvironment.

Why has progress with allogeneic cell therapies been slow?

DW: Early approaches to allogeneic therapies may have been conditioned by a big pharma/blockbuster vision of what our field should or could be. Blockbuster opportunities tend to be occupied by incumbents who have become very good at what they do, and it can be tough for an unproven, high-cost disrupter to make their case. We disrupters need to emphasize the continued requirement to address unmet medical needs and must be exact about the

medical needs we aim to meet, understand how our approach will meet these needs, and be able to communicate all of this in a way that is convincing to busy clinicians.

TA: I believe there will be a future for allogeneic-based therapies, and exciting concepts based on restoring cell function using hPSC are currently being clinically tested. Using orthotopic transplantation of hPSC-derived products to regenerate replacement healthy, functioning tissues may be a more reasonable mechanism to test next, as the paradigm of systemic transplantation of cells to modulate local inflammatory or tissue repair processes (as with MSC) has not proven to be a success on the whole. Time will tell

Collaboration is Key

By Robert Zweigerdt

On page 18, Catherine Bollard from the ISCT states that collaboration is crucial to advance the cell therapy sector – and she is correct. TECHNOBEAT (Tools and Technologies for Breakthrough in Heart Therapies), funded by the European Commission's Horizon2020, is one example of a collaborative project that is addressing unmet medical needs in cardiovascular disease. The unlimited proliferation potential of human embryonic stem cells (hESC) and their ability to differentiate into, in principle, any somatic cell type in vitro, has opened a whole new universe of exciting possibilities in regenerative medicine, pharmacological research, human developmental biology and basic stem cell research. The possibilities were further stimulated by the derivation of induced pluripotent stem cells from mice (2006) and humans (2007) by Shinya Yamanaka and his team, through a technology enabling the so called “reprogramming of somatic cells” from adult patients into an ESC-like state. These discoveries revealed that human pluripotent stem cells (hPSC; an umbrella term for hESC and hiPSC) can serve as a universal cell source for the derivation of unlimited amounts of functional somatic cells to help, for example, with disease-induced cell loss in organs.

Cardiovascular diseases, particularly ischemic cardiomyopathies, remain the major global causes of morbidity and mortality affecting millions of patients worldwide. The obstruction of coronary arteries, which normally supply the heart with oxygenated blood, triggers ischemia in areas downstream of the occluded vessel, a condition known as myocardial infarction. The condition often leads to the terminal loss of billions of heart muscle cells, which are not replaced by endogenous repair mechanisms and may result in reduced heart function and ultimately heart failure.

TECHNOBEAT aims to develop new treatment options for patients suffering from heart failure caused by the loss of heart

muscle tissue following a heart attack. The consortium calls on the expertise of a network of leading European entities in the cardiovascular field, including Hannover Medical School – a medical center with a strong focus on translating cell-based regenerative medicine for several organs; Leiden University, which offers leading expertise in basic mechanism of cardiovascular differentiation of hPSCs; and Utrecht Medical Centre, which brings top expertise in experimental cardiology and development of pre-clinical animal models. The consortium also involves partners with leading know-how in clinical stem cell production: Paracelsus University in Salzburg provides expertise in the derivation and clinical application of adult stem cells (in particular, mesenchymal stem cells, an important cellular component for organ repair) and Kadimastem, located in Rohovot, Israel, is developing protocols for the clinically compliant manufacture of hPSCs and their progenies, as well as expertise in handling the regulatory requirements of regenerative medicine. In addition, technical innovation in hardware development for stem cell bioprocessing, monitoring and analysis is essential to our project – as well as the whole cell therapy field. In the area of bioreactor development, Eppendorf provides their support, while OVIZIO provides innovative solutions in the monitoring of cells and more complex cell aggregates.

Finally, it also goes without saying that safety is of great importance in cell-based organ repair – which specifically requires monitoring of the genomic integrity of mass-expanded and differentiated stem cells to avoid process-induced cell transformation and the potential development of tumors. Thus, our project partner at the University of Sheffield in the UK is applying its long-standing expertise in analyzing the genomic stability of hESC lines to the field of hiPSCs manufacturing.

Read more about TECHNOBEAT at <http://tmm.txp.to/0717/technobeat>

whether an allogeneic approach proves to be more or less efficient than other types of therapies in delivering novel, disease-modifying treatment options to patients and their healthcare providers.

SB: Allogeneic technologies will be an important component of the field in the future. The only question to me is: “when?”

What are the main challenges involved in moving cell therapies into commercial manufacture?

DW: The manufacture of these therapies involves two principal challenges: making the same thing more than once, and making the same thing in more than one place. There is a lot of understanding

and experience in manufacturing already gained from high-volume production, but personalized, autologous cell therapies are driving the industry to better understand the latter point, as they need to be made close to clinical settings.

TA: There are three main challenges when it comes to developing cell and tissue therapies. First is the challenge of developing suitable analytical assays to define and monitor the consistency of a therapy's functional attributes for product release after manufacture. Appropriate analytics are especially needed for autologous therapies to assess potency and to be used for comparability across batches for a single patient, or across multiple patients. It is essential that

these analytical techniques be non-destructive, or at least do not use up too much of the product. The second challenge relates to sample processing and the need for scalable, affordable production platforms. There are currently no “one-automated-platform-suits-all” approaches for commercial-scale development, and manufacturers are instead dependent on manual, skilled specialists working in accredited cleanroom facilities – which inevitably makes manufacture prone to human error and processing variability. A number of pioneering, approved autologous therapies have found overcoming the barrier of major inflexion problematic in terms of scaling between clinical production and commercial manufacture, but most suspect that the hard lessons learned so far will benefit the future of the whole sector. The third challenge is the overall cost of production and reimbursement. At this time, there are no clear or consistent global-scale examples that exemplify how therapies should be reimbursed.

TH: Today’s cell therapies, including autologous and allogeneic therapies, are manufactured using highly manual and often open processes, which pose significant commercialization challenges in terms of maintaining consistent quality, supply chain sustainability and minimizing costs. Furthermore, because patient-specific therapies cannot be scaled up but instead must be scaled out, there are specific challenges when it comes to achieving economies of scale. Solutions, however, may include:

- rigorous understanding of the desired product quality profile
- minimizing the number of unit operations in the manufacturing process
- avoiding peak capacity by evenly distributing labor requirements across the process
- driving development to minimize variation and maximize product yield
- closing and automating process steps
- sharing infrastructure across multiple product manufacturing processes (in-house or externally)
- demonstrating product comparability following process modifications.

Cell therapy developers need to look closely at the drivers for commercially viable manufacturing of their product, with an eye to establishing processes, as early as possible, that deliver high quality and robust products that can scale to meet demand over the commercial life of the product. And, importantly, they need to do so with a reimbursable cost of goods.

CB: I believe that the Holy Grail for the industry is the development of “off-the-shelf”, universal products. In time, I think we will see advances in this area, but patient-specific cells are the way forward for now and these need to be manufactured

on demand in a viable timeframe. For gene-modified T-cells, there have been challenges regarding scale up. Looking at the cell therapy field as a whole, I believe that a key question is whether to move to centralized manufacturing facilities versus individual centers for product manufacture on a larger scale.

What improvements in manufacturing technologies are needed?

DW: All unit processes need to be made more robust and repeatable. There is also the question of how we grow the supply chain for the key enablers, including process automation and mechanization, and robust characterization – especially given that instruments developed for research laboratories do not always work well in settings that are determining manufacturing quality. New advanced technologies are emerging, but we also have to generate business models that permit viable machine supply businesses, without pushing up prices for media and consumables that result in unacceptable cost of goods.

TA: The scale out of more than minimally manipulated autologous therapies poses a major challenge for developers. There is a regulatory requirement to demonstrate comparability of measurements for the therapy across many decentralized production sites or from a single, near-to-patient production site. For therapies with a potentially short shelf life, generating data on safety, sterility, purity, identity and potency before release of a patient-specific dose is challenging. As many of these measurements currently depend on the use of assays that are destructive, it can also be a hindrance if material is limited (though less of a problem if patient bio-samples can be banked for later use). Sensitive assay technologies that provide reliable results for sterility and potency in turn-around times that meet clinical demand are needed.

TH: Firstly, online monitoring and control systems need to be integrated into cell therapy manufacturing. Secondly, we need harmonization to allow more seamless integration of technologies within a single process. I would also like to see the introduction of devices which, rather than being designed as “magic boxes” customized to one specific product’s manufacturing process, are designed to handle a range of unit operations, providing a true manufacturing platform, common to an entire category of cell therapies. There is a defined market need for flexible, automated and closed-system solutions like this, for which the cost should be much more economical for each developer than an entirely customized device.

CB: Members of ISCT also believe that the industry needs to move to closed, automated manufacturing systems. We also need more attention on “GMP-in-a-box” concepts so that centers can manufacture therapies without needing a physical “GMP space” – such a move would help to broaden the applicability of cell therapeutics beyond boutique centers.

SB: I agree that many companies developing cell therapies or other advanced medicines need more automated and closed systems

– and I would add that there has been a lot of investment pouring into cell therapy manufacture over the last five years from sponsors, contract manufacturing organizations and equipment makers. Already, manufacturing lead-time and failure rates have decreased significantly. I'm cautiously optimistic that processes will continue to improve so that we can routinely manufacture cell products at a commercial scale, and claim that they are close to being off-the-shelf products.

What should the field be prioritizing?

DW: A key area for the field to focus on is the interaction between regulation, standards and manufacturing strategy. Underlying this is the need for the community to address its approach to comparability. There is increased level of informed discussion here, including the recognition by regulatory agencies that the practicalities of decentralized manufacture should be explored. The development of standards is also a significant area for international collaboration.

TA: The design of advanced therapies needs to be more tightly aligned with improved understanding of disease development and individual patient profiles. We must also consider prevention rather than symptom modification as a goal. A fresh look at companion diagnostics would be beneficial to more closely tailor a patient's advanced therapy. We should also consider the fact that advanced therapies are being approved, but not adopted and reimbursed in healthcare systems. There are several reasons linked to this, but a principal one is affordability. All stakeholders involved in developing advanced therapies are responsible for finding an appropriate solution – and perhaps a radical rethink is needed rather than attempting to evaluate cost-effectiveness in the traditional way.

TH: The industry needs to set standards that will speed up development efforts across the field, and accelerate the process of innovation to resolve key manufacturing constraints to commercial viability. For example, with common standards for T-cell characterization – agreed upon by the FDA – each developer stands to benefit by reducing the cost of development. Efforts are under way to look at setting these standards, through the Alliance for Regenerative Medicine and other groups.

CB: Collaboration is crucial. ISCT is working with organizations to help establish standards that ensure quality in the clinic, as well as in the laboratory. Such priorities will be critical to improve the safety for patients receiving cell-based therapies. To that end, ISCT is one of the co-parent societies for The Foundation for the Accreditation for Cellular Therapy

“We can use the autologous route to establish a track record and trust in the clinic, as well as ways forward for reimbursement”

(FACT), a voluntary organization that sets practice standards for cellular therapy, including transplant and regenerative medicine.

SB: We first need to prove that these therapies can be safe and efficacious in a range of indications. At the moment, successes with CAR-T cells, for example, are being seen in LAL and B-cell lymphomas.

If we can get results in a wider range of diseases, it will create more awareness about the potential of advanced therapies with broader scientific, physician and patient communities. We then need to continuously invest in improving logistics and manufacturing, and finally work with payers to find the most acceptable reimbursement system that fulfills the needs of all stakeholders: patients, payers and drug development companies – who need a good return on investment to continue to invest and innovate in this challenging field.

What are your predictions for the field?

DW: I have always believed that cell therapies will be like other similar fields in medical technology; we can expect a few big products, as well as a variety of smaller ones. We can use the autologous route to establish a track record and trust in the clinic, as well as ways forward for reimbursement. I don't expect to see many big wins in the field, but the big products that do emerge will make a significant difference.

TA: In the near future, there will be several gene-modified, patient-specific immunotherapies on the market. Promising clinical data from early stage studies using allogeneic immunotherapy platforms will also have been generated. There will also be a surge of new gene therapies in development, categorized as defective protein replacement strategies, as improvements in vector design and a better understanding of how to deliver these more precisely arise from optimizing approaches to cell tropism.

I think the long-term horizon is tremendously exciting. If the science translates successfully and safely, future prospects include approaches for stimulating local tissue regeneration, in trauma and degenerative disease, and using precision genome editing to repurpose the function of somatic cells in vivo.

TH: Most cell therapies today are manufactured in cleanrooms, but in the future closed and automated systems will dominate. These systems mitigate the risks of cross-contamination and therefore allow concurrent processing of multiple batches, in lower grade clean rooms, which results in enormous savings in terms of facility operation and efficiency, as well as reduced labor costs. Remember – every hour of labor saved in a patient-specific

Advanced Medicine News-in-Brief

Business

- A report from Roots Analysis on the cell therapy manufacturing market has predicted an annualized growth rate of around 42 percent over the next 10 years – estimating that the market will be worth more than \$4 billion by 2027. Near term demand for cell therapy manufacturing is expected to be primarily driven by clinical candidates.
- The Cell and Gene Therapy Catapult is selling its Catapult Therapy TCR subsidiary to Cell Medica for an undisclosed amount. The subsidiary has been developing a gene-modified WT1 TCR T cell therapy that actively targets certain blood cancers and solid tumors.
- Oxford BioMedica has signed a deal for the commercial and clinical supply of lentiviral vectors used to generate CTL019 (tisagenlecleucel) and other undisclosed CAR-T products for Novartis' CTL019 therapy, which is expected to launch later this year. The supply agreement is for three years and could see Oxford BioMedica receive in excess of \$100 million from Novartis.

Research

- An Intent to Grant Notice – given to parties that have met the requirements for a patent – has been assigned to Bone Therapeutics by the European Patent Agency. The patent relates to Bone Therapeutics' first-in-class allogeneic cell therapy technology and the technique used for the manufacture of biologically active osteoblastic cells.
- Researchers from the UK's University of Sheffield have discovered a new mechanism behind the genetic causes and altered functioning of nerve cells in motor neurone disease – and hope it will eventually lead to new gene therapy treatments. The team have pinpointed why repeated RNA sequences are able to leave a cell's nucleus to cause cell death.

- Silicone Valley entrepreneur Jeffrey Rothschild and his wife, Marieke, have provided \$10 million in funding to help launch the Stanford Center for Cell Therapy, which will mainly focus on cancer cell therapy. The center will be led by Crystal Mackall, professor of pediatrics and of medicine at Stanford – and one of the pioneers in the field of cancer cell therapy.

Regulation

- The FDA has granted priority review to Spark Therapeutics' voretigene neparvovec – a potential one-time gene therapy candidate for the treatment of patients with vision loss due to confirmed biallelic RPE65-mediated inherited retinal disease. A decision is expected by January 12, 2018.
- Regenerative advanced therapies in the US have been re-designated by the FDA as Regenerative Medicine Advanced Therapies. To be eligible, therapeutics have to fall under the following categories:
 - a) The drug is a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, except for those regulated solely under Section 361 of the Public Health Service Act and part 1271 of Title 21, Code of Federal Regulations;
 - b) The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition;
 - c) Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition.
 - d) The FDA hopes that the new designation will make the path to approval easier for serious/life-threatening diseases.

process is one hour saved on every single dose you manufacture (as each batch is made for one patient).

Automation and integration will also play a role in the future of cellular therapies. Just think about the personal computer industry. Computers used to be massive because all the different functions were in separate modules, but the functions have been progressively integrated into smaller, unitary pieces of equipment. The same thing will happen in cell therapy manufacture; all the different steps involved in cell therapy will one day be integrated so that a single, closed unit can execute multiple operations.

CB: I'm really confident about cell-based immunotherapies and

I can't wait to see them advance even further. As accessibility and toxicity management improve, it's possible to foresee a future where chemotherapy and radiotherapy are no longer the mainstays of cancer treatment, replaced instead by new therapies that focus on enhancing anti-tumor immunity. It would make a tremendous difference to patients.

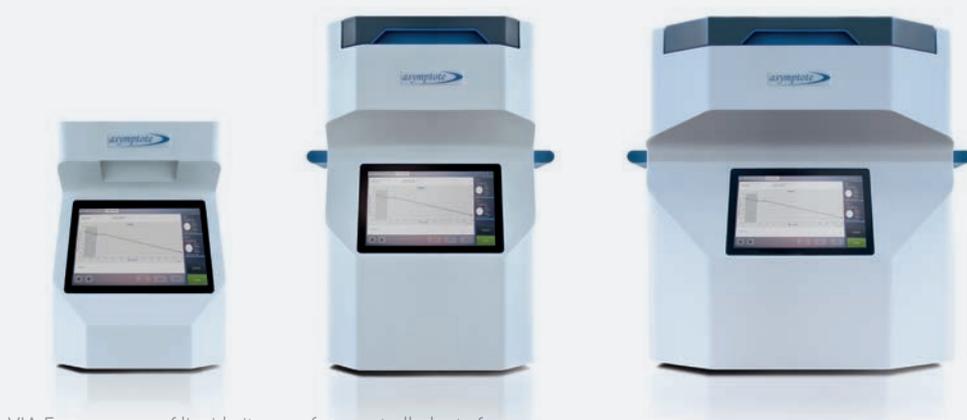
SB: Ours is an industry in the making and we've already come so far. A few years from now, we will be talking about cellular therapy as we now talk about other biotherapies, such as monoclonal antibodies. Cell therapies will just be one part of the medical arsenal used daily to efficiently treat serious disease.

The Big (Bio) Freeze

When it comes to cryopreserving cell therapies, there's a right way – and a wrong way...

The potential of cell therapies has been recognized for some time, but commercialization is a relatively recent endeavor. Cryopreservation is a crucial part of the manufacturing process because it allows cell therapies to be efficiently stored and transported; however, it is only beneficial if cell viability is maintained. Here, we speak with Asymptote (Part of GE Healthcare Life Sciences) CEO John Morris, who has been freezing cells for over 40 years, to delve into the good, the bad, and the icy aspects of cryopreservation.

How did you become involved with Asymptote and GE Healthcare? Back in the 1970s, my PhD focused on the freezing of T and B lymphocytes, which was widely ignored at the time. I was fascinated by the field and I worked for various research councils on freezing-based issues, such as how organisms grow in the Antarctic or on high-altitude mountains. Soon after, I dabbled in the academic world before joining Asymptote in 1989, where I worked on a range of freezing/solidification challenges across a wide range of industries, from food products such as ice cream, to freeze drying of pharmaceuticals and oil and gas industry projects. Earlier this year, after identifying the work we were doing, GE Healthcare Life Sciences acquired Asymptote to fill a critical gap in the GE Healthcare end-to-end ecosystem of products and services for cell therapy production, and form an important piece of their cell therapy portfolio.



VIA Freeze range of liquid nitrogen-free controlled rate freezers

How have cell therapies changed the approach to cryopreservation? Cryopreservation was developed in the 1950s, mainly for shipping livestock sperm worldwide. In time, it was applied to other cells, such as human sperm, embryos, and blood cells. Around 10 years ago, regenerative medicine became a reality and cells were being classified as medicinal products, which led to a need for better control over the freezing and thawing process. For example, when freezing many different samples, you have to ensure that each sample has the same activity once thawed. Each sample also has to be free from contamination, and you have to be able to track everything to ensure the patient gets the right cells.

We spoke with Innovate UK, a funding body, about the changes taking place in the field, and they identified clinical delivery of cells in regenerative medicine as a gap in the industry. Cells were being grown and created for therapeutics, but people weren't putting much thought into the post-manufacturing steps of getting cells to the patient. To help fill that role, Innovate UK awarded us several grants to develop equipment and consumables that help deliver cryopreserved cells for clinical use. We also teamed up with the UK's Cell and Gene Therapy Catapult to work on the final stage of the chain – a device to thaw the cells for clinical application.

How is the industry reacting to commercialization pressures and the need for cryopreservation?

We've been working with leaders in the cell therapy field for around 10 years, and it's been interesting to watch the field develop. Right now, it's exciting to see immunotherapies close to reaching healthcare systems, with companies like Novartis and bluebird bio looking to get immunotherapies approved in the US. However, now that the research is coming to fruition, the industry is suddenly realizing that the cryochain – cryogenic cold chain - will be critical to its success.

One of the main reasons for cryopreservation is quality control. For example, when producing immunotherapies, you need to test that the T cells you've grown are the correct type, that they do not contain bacteria, and that they are fit for use. This takes several days – and cryoprocessing helps buy back time. It is also important to consider the patient. Patients, by definition, are often very ill, and complications may mean that they are unable to receive immunotherapy on the planned day. Frozen therapies can easily be stored, allowing for more flexibility in terms of when they are administered. Cryopreservation also has benefits from a financial perspective – shipping fresh cells is far more expensive than shipping a frozen product.



What cryopreservation pain points are cell therapy manufacturers likely to face? Companies can get so caught up in the intricacies of the biology that the cryopreservation and shipping aspects become an afterthought. Freezing a few cells in the lab is easy for research applications, but freezing cells that will be injected into patients as therapeutic drugs is more challenging – and often underestimated. Now, many big companies are realizing that they have to get the cryogenic cold chain correct, and are hiring PhD cryobiologists. Some think that refrigeration at 4°C is a good short-term alternative, but it's actually significantly more expensive to refrigerate cells and maintain a regular cold chain than it is to cryopreserve cells and ship them at cryogenic temperatures. Cell therapies are already expensive to produce so I don't believe that refrigeration is a sustainable solution.

“Companies can get so caught up in the intricacies of the biology that the cryopreservation and shipping aspects become an afterthought.”

Retaining cell viability and function on thawing is one of the biggest challenges, which means that you need to plan your cryopreservation strategy at an early stage. In other sectors of cryopreservation, peak viability isn't necessarily crucial. For example,



there are around 200 million calves born every year following artificial insemination with cryopreserved sperm. Whether 100 percent or 10 percent of the sperm are viable is irrelevant so long as one of them can fertilize the ovum. With cell therapies, however, low viability is not an option; it essentially means that the patient gets a lower “dose” of therapy, which can prevent treatment from working effectively.

There are many factors that come together to help maintain high cell viability, including experience and the equipment used. Asymptote has been working with cells and cryopreservation for years, so we understand the ins and outs of the process. When somebody approaches us with a clinical treatment that they want to develop, we look at how best to tailor the cryopreservation process to their particular cells. Controlling the temperature of ice formation during cooling or using the right cooling rate, for example, can double or triple viability compared with other techniques. It's all about knowledge and experience – understanding and controlling what works in terms of cooling, storing, and thawing.

How has cryopreservation equipment evolved over the years?

Until about 10 years ago, equipment was based on liquid nitrogen, which worked well for many types of cells. When we're effectively dealing with medicines, however, it is not the right solution –

liquid nitrogen is often contaminated with particles and biologically active bacteria. Because of this – and the fact that liquid nitrogen is quite hazardous to operate with – we turned to Stirling cryocoolers. Not only do they provide more control over the processes, they are also safer and simpler to use than liquid nitrogen. A huge amount of engineering and refinement has gone into optimizing these cryocoolers (they were previously used by NASA and the European Space Agency for use on the space station) and Asymptote has pioneered their application in cryopreservation.

At the moment, scaling is one of the main limitations with equipment. We're currently performing batch freezes of small samples at a time, which is adequate for today's needs, but in the not-too-distant future I believe there will be a surge in demand, and equipment will need to keep up. For example, continuous processing of large batches will be required as allogeneic therapies come to market. I also expect equipment to advance in terms of tracking capabilities. We can already track cells to an extent but, in time, it should be possible to obtain a complete history of the cells from creation to patient. This digital backbone will allow us to further control the temperature and condition of the samples in real time. We may even get to the point where patients can watch their therapeutics move through the supply chain towards them.



Banking on Cell Therapy

Sitting Down With... Steve Oh, Director, Stem Cell Bioprocessing, Bioprocessing Technology Institute, Agency for Science, Technology and Research (A*STAR), Singapore.

How did you end up working in the stem cell field?

Science has always been something I loved. As a child, I really enjoyed reading about the universe and the world we live in, but my interests turned towards chemical and biochemical engineering – particularly how cells work. During my university studies, I looked at the issues associated with using animal cells to make antibodies for the biologics industry. After receiving my PhD in Engineering from the University of Birmingham in 1990, I returned to Singapore and ended up focusing on bioprocess optimization in the National University of Singapore's Bioprocessing Technology unit, with a focus on improving the productivity of antibody production in hybridomas. From there, I jumped to Pall – and it was fascinating to see the bioprocessing industry from the point of view of a vendor. My work with stem cells didn't start until 2001, when I joined the Agency for Science, Technology and Research (A*STAR) as a principal scientist. At the time, embryonic stem cells had recently been discovered by Jamie Thompson, and my director suggested looking into stem cell bioprocessing. It was a really early time to start focusing on this area – and it was very exciting.

What is your current focus?

The field has changed significantly over the years. Rather than stem cells, researchers and the biopharma industry are now looking at non-stem cells, such as T-cells and immunotherapy, which has also changed how we need to think about bioprocessing. With cell therapies, each patient needs a billion cells – even with 10,000-liter bioreactors it would be challenging to meet those needs. We must work on bioprocess intensification.

Our research initially focused on pluripotent stem cells in 2001, but later we moved into mesenchymal stem cells

(MSCs). In the past two years, we've moved into immunotherapy. We haven't published anything in this area yet, but we are preparing a grant proposal to build a self-contained, fully disposable bioreactor that can make personalized cells for 15-20 days.

Our main focus right now is on controlled expansion and controlled differentiation of cells. Once we've hit that target, we will work on obtaining good yields, and then use assays to predict how the cell culture will perform in vivo. Developing these assays will be a major challenge over the next five to 10 years.

“We will start to see a few blockbusters in the coming years.”

What is the regulatory viewpoint on cell therapies?

With every medicine – including cell therapies – regulators are concerned about safety. I like to constantly engage with regulators – and I bring them to my labs every quarter to show my progress, and to ask what else I should be thinking about in terms of patient safety. MSCs have been very well received by regulators, despite the fact that it can take time to see results in the clinic. For example, one company in Phase II/III trials using MSCs to help stroke victims recover faster only saw a significant improvement in symptoms one year after administration, which was well outside of the original three-month trial window, but now they are in Phase III trials. If everything goes well, it could be a big win for the field – we are all waiting for more therapies to be approved.

You've also founded your own company...

That's right. There is a huge amount of interest in stem cells right now from the public – and with good reason as I think it's clear that there is huge potential. In 2015, I founded a company called Brilliant Research, which specializes in the development of stem cell research products, production tools and therapy products. I'd also like to move the company in a new direction by offering personalized stem cell banking. We've recently found that we can select stem cells more effectively than using traditional reprogramming methods, and we're going to work with a company to develop a robotic, automated solution. The aim would be to take a drop of a person's blood, reprogram the cells into induced pluripotent stem cells (iPSCs), and then bank them. The banked cells could then be used years down the line and differentiated into other cell types.

When will the cell therapy field really take off?

The field is full of exciting developments and there are a number of very promising studies that I am keeping my eye on. When I graduated, the big biopharma companies were just starting out with antibody therapies. We're now at a similar point with stem cells and I think we will start to see a few blockbusters in the coming years, particularly in ophthalmology; for example, using retinal stem cells to treat blindness caused by macular degeneration – we should see results from a study later this year. There have already been promising Phase I studies so if the later stage results are good, I think we'll see the field really take off because macular degeneration affects so many people. There is also much research on how cell therapies could potentially help diseases like Alzheimer's and Parkinson's – but there is a long way to go. Such diseases are highly complex and treating them will not be easy.



the
Medicine Maker

www.themedicinemaker.com