The Science Huddle

Sparked by biopharma excellence by PHARMALEX

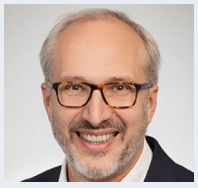
Cell & Gene Therapy: Maximizing Commercialization Potential

How to Navigate the Less Obvious Barriers to Bringing Advanced & Highly Targeted Treatments to Market

Practical takeaways from a new panel debate on how those at the forefront of cell and gene therapy development can maximize their commercialization potential through optimized planning.

With so many exciting novel treatments emerging from the labs, particularly in the field of cell and gene therapy, biotechs and pharma companies need to understand the potential unknowns as well as the known considerations if they are to successfully commercialize their innovations.

In April 2023, in a second live **Science Huddle** debate, big names from the forefront of the industry, as well as regulatory and commercialization experts, came together to advise on some of the poorly understood barriers to commercialization, and the most effective strategies to ensure a smooth and viable path to market.



Participants in this Science Huddle event were:

Moderated by **Dr. Christian K. Schneider, Head of Biopharma Excellence at PharmaLex,** an ex-regulator and the former Chair of EMA's Committee for Advanced Therapies.

Keith Thompson, CBE, Chairman, Natural Killer (NK) cell therapy company, NK:IO

Michael May, President & CEO, The Centre for Commercialization of Regenerative Medicine (CCRM)

Sven Kili, CEO, Antion Biosciences

Panelist bios:

Moderator Christian K Schneider, M.D. is Head of Biopharma Excellence, Chief Medical Officer (Biopharma) at PharmaLex and a former regulator. He was previously interim Chief Scientific Officer at the UK's MHRA. He has also held leading positions at the Danish Medicines Agency and at the Paul-Ehrlich-Institut, Germany's Federal Agency for Vaccines and Biomedicines. At EMA, he has chaired the Committee for Advanced Therapies (CAT) as well as the Biosimilar Medicinal Products Working Party (BMWP), and served as a member of the Committee for Medicinal Products for Human Use (CHMP).

Keith Thompson, CBE is the chairman of a Natural Killer (NK) cell therapy company, NK:IO, and Chair of the Pharma Advisory Board of Deep Science Ventures. He is also the former CEO of UK accelerator, Cell and Gene Therapy Catapult.

Michael May is President & CEO of CCRM (The Centre for Commercialization of Regenerative Medicine), a not-for-profit in Toronto, Canada that develops technologies, supports the launch and scaling of enabling and therapeutics in new companies and catalyzes investment in the field of regenerative medicine.

Sven Kili is CEO at Antion Biosciences, a Geneva-based Multiplex Cell Engineering company developing 'Smart-Data' driven allogeneic cell therapies for under-served patients suffering from recalcitrant diseases. He was previously the Head of Development for the Cell and Gene Therapy division of GSK.

What keeps the panel awake at night?

Moderator Christian Schneider of Biopharma Excellence opened the discussion by expressing his own deep interest in gene and cell therapy, across a regulatory career that's included a period chairing European Medicines Agency's Committee for Advanced Therapies (CAT) – in the days before the potential of cell and gene therapies had translated into authorized products.

He began by asking each of the panelists what they perceived to be the main obstacle to the commercialization of advanced therapies today.

Finance, value & manufacturing capability

Speaking as a developer of advanced therapies, **Antion Biosciences' Sven Kili** said he felt there remained a myriad of challenges in bringing cell and gene therapies to market. The two most prominent barriers, however, are financing – especially for small companies like his; and how to get ground-breaking cell and gene therapies to the patients that most deserve them around the world.

"There are a lot of very similar therapies addressing the same target, so this is about how we direct our efforts to ensure we address more patients with fewer therapies," he said.

Other issues he highlighted include how to keep the costs of treatments down, particularly so that they are accessible by patients in low- and medium-income countries, and how to work with manufacturing colleagues, regulators, payers and transport and logistics organizations to make therapies available to patients globally.

This, in turn, highlights the importance of demonstrating how such therapies generate value – something requiring collaboration with health technology assessment organizations.

Michael May, who heads up a not-for-profit in Toronto, Canada that develops technologies, launches new companies and catalyzes investment in regenerative medicine, concurred that there are numerous challenges to bringing niche, novel therapies to market. But, for him, the number one issue is access to capital – even though more funds are entering the system now.

"We work at the front end of development, with startup companies, and there's always been a challenge with catalyzing investment at that stage," he noted. "Access to capital is worrisome on many fronts. There are so many uncertainties, so many aspects of development that need to be de-risked. We're seeing a number of companies going bankrupt or succumbing to mergers/acquisitions, with the result that a number of tech developments will be halted," he said.

Bridging the skills gap

Other challenges involve talent gaps, particularly now that cell and gene therapy manufacturing is maturing. "Manufacturing is now a key gatekeeper for success in cell and gene therapy – that is, robust, scalable clinical and commercial-scale manufacturing," Michael explained, based on his experience building process development and clinical GMP-compliant manufacturing at CCRM. This means having GMP-trained operators and high-quality process development. Optimization and targeted automation can help bring down the cost of goods, but talent is still an issue - which comes back to accessing the funding to hire and train people, he noted.

Keith Thompson, chairman of cell therapy company NK:IO, and the former CEO of the UK's Cell and Gene Therapy Catapult biotech accelerator, echoed the concerns about finance access for fragile but promising startups. "There is a general chill in the markets," he commented. "Although there's plenty of money out there, it doesn't want to find homes in biotech risk at the moment."

Speaking from many years of experience, he said, "I've been through these biotech winters several times and they do come to an end. What will trigger this is the thirst for breakthroughs. Some of the technologies in the clinic now will show or are already showing outstanding results, which will stimulate interest and start to unlock the investment freezer".

Access to funding isn't just a problem for young biotechs either, he noted. "All companies at all stages are having problems because venture capitalists and other investors are tending to support their current portfolios currently."

The bigger issue is differentiating the various therapies – being clear about how they are unique and liable to move the needle in the sector, whether that is clinically or through meeting unmet need, then how well it meets that need and how deliverable the therapy is. This last point, along with a treatment's affordability, will be the critical factors that influence commercialization potential, Keith suggested.

Moving the needle: the measurable impact of advanced therapies

Probing the issue of differentiation and value, Christian asked the panel to expand on the concept of competition among similar gene and cell therapies. Would relative success be determined by speed to market, for instance, or could it be argued that even the umpteenth CAR-T cell product would still add value? And what about more traditional treatments as part of the competitive landscape?

From a biotech perspective, **Sven** felt this was a multi-faceted issue, where once being first to market would have seemed the critical determinant of success. "From a cell and gene therapy perspective, this hasn't necessarily been borne out," he said, speaking both from a personal and professional viewpoint. Sven was involved with MACI (matrix-induced autologous chondrocyte implantation), a tissue-engineered product for the repair of full-thickness cartilage defects of the knee - the first combined advanced therapy to reach the market.

"It was used very successfully, had phenomenal track record, but when it came onto the market, particularly within the EU, it didn't do so well - which was down to costs," Sven noted. When he subsequently led the commercialization and launch of a pioneering ex-vivo gene therapy for GSK, again this was very successful clinically but less so commercially, he recalled.

For all the activity and patient benefit then, the traction is not what it could be.

Competitive positioning

Although more and more cell and gene therapies are being developed, particularly for rare diseases, issues remain, including access to patients with the particular condition when populations are often small, **Sven** lamented. In such situations, it probably does pay to be the first - at least to be able to secure the patients for studies.

"If we think particularly about CAR-T, discussions with investors often revolve around whether we really need another CD-19 therapy, or are we getting to the iterative stage of the new one being cheaper, or having a better side-effect profile, etc? And I don't think that's what's going to drive the thawing of the financial markets," Sven noted. "Rather, we need the big wins - the really strong clinical results; the hard science that's going to make a measurable difference to patients' lives."

Competition with non-cell and gene therapies becomes absolutely critical, here," he added. "For so long we've been talking about the massive benefits of cell and gene therapies, particularly within rare diseases, when we've got no real comparators. Sometimes the comparator is some form of minimal therapy that runs out after a number of years, or a surgical procedure that potentially has a low incidence of working, or a bone marrow transplant that is limited to a certain number of donors. "

"Now we're starting to get into some of these bigger use cases, not - even if these are rare disease indications – such as haemophilia; diabetes; sickle cell disease – where, from a payer perspective, this is a relatively well-controlled disease with a long, associated lifetime cost due to medical symptoms and complications. Here, the onus is on us to show the value against these much lower-priced therapies that manage patients lives, if not cure them."

Whatever the potential for enhanced patient convenience or comfort, Sven explained, payers aren't going to be overly concerned about how far the patient has to travel once a week or once every two weeks for a blood transfusion.

"They're more concerned about the reimbursement side of things - so we need to be thinking very carefully about how we're positioning our therapies. Yes, this is really cool science, and cool technology, but the real criterion is how we positively influence a patient's life, and make a positive contribution in the particular country or to the payer or the reimbursement authority?"

"In other words, how are we positively driving value within that environment and making a positive contribution to society as a whole? As we get into more common indications, this is something that we really need to start thinking about. We need to stop being so inward-looking."

Clinical efficacy: the key to unlocking investment – as long as clinicians & payers buy in

Arguably there has never been such a broad and rich spectrum of opportunities for differentiating novel therapies from existing products, compared to a decade ago. As **Michael** put it: "It's the era of the super cell now - all cell therapies will be genetically modified in some way for specific purposes," he noted. "Go back 10-12 years, and yes, there was a lot of innovation happening, but there wasn't clinical demonstration in cell therapy. That's all changed now, led by the CAR-T therapies that illustrated real clinical efficacy, giving rise to extensive investment and growth in the field."

It's important not to lose sight of this link, he warned. "Ultimately, clinical efficacy is the driver of investment, commercialization and the successful pathway to patients."

Bringing clinical considerations, regulatory approval and reimbursement into early decision-making is paramount. "We don't always ask the questions at the early stages of development, because we're often dazzled by the science," Michael said. "Currently, these are expensive therapies, so we really need to be factoring in the question, 'Is this advanced, complex, costly therapy really going to make a difference against standard of care, and will someone pay for that?'."

"There is a lot of focus on oncology right now, where CAR-T has driven investment," he added. "And now people are starting to think about what are the non-oncology applications for cell and gene therapy, not – for treating autoimmune diseases and so on. But when we are driving those commercialization pathways, we need to ask not so much what is the technical differentiation (because I think that's easy in this environment), but rather, will someone pay for it?"

Market expansion: broadening the technology's reach

Christian wondered whether others recognized the potential of a shift in focus from rare diseases to high-prevalence conditions as a therapeutic indication, or whether with fewer direct incentives or tolerance of 'smart statistical solutions', there might be other hidden challenges.

Speaking for a 'Natural Killer' cell therapy company, **Keith** said he suspected that new therapies would generally start in areas of high unmet need, which by definition suggests low prevalence, but that depending on their maturity the emerging treatments would migrate to higher prevalence indications once shown to be safe, durable and cost effective.

He noted: "Where you're looking at new technologies, which are unproven, whether they're new cell therapies, new gene therapies or new techniques like in-vivo gene editing, you're effectively starting again, in very small subsets of populations, to prove some efficacy and safety.

"Before that migration to larger/more general populations, these therapies will command high prices," Keith added. "There's now a general acceptance that both cell and gene therapy are viable, if costly, therapies."

Keith understands the investment perspective, both as chair of a young biotech working on Natural Killer (NK) cells to target solid tumors as an unmet need, and as an advisor to Deep Science Ventures (Investors in Pharma). Of NK:IO's work, he referenced the historical poor outcomes for patients with most solid tumors, and the considerable potential for transforming results using cells from the innate system – first for patients with high unmet needs, before migrating to larger clinical populations. That's as long as the reimbursable price/cost-benefits ratio is achievable, and clinicians actually want the treatments.

Advancing the science: technology progression & treatment options

Looking at the scientific/technology pathways, **Michael** pointed to lingering confusion over when and whether one modality of treatment is superior to another. "I remember 10/15 years ago having the debate about autologous [using a patient's own cells] versus allogeneic [cells from an external source], as though there was a clear-cut answer as to which is better, when it's more likely that one scenario will be more suited to rare diseases and the other to more mainstream use cases."

As allogeneic manufacturing platforms are demonstrated, and can scale, Michael believes there will be a transition to the higher prevalence diseases.

Sven agreed that specific applications are likely to vary. "Ultimately, we need to think about how we develop the best therapy for the patient at the time that they need it," he said. "We need to get away from this, 'I have a hammer and everything looks like a nail' way of looking at the options. It's more about having a toolbox, and learning how to use each option effectively and efficiently. Only once we start doing that will we be able to create value for the payers and for society."

Matching modality to context

Keith noted the importance of autologous therapies in cooperating with the human immune system, rather than trying to 'fool' it. "The human immune system is not passive," he said. "So, while it may suit everybody's investment desire to favor allogeneic delivery, because it simplifies the logistics and the cost, there is a balance to be struck. Just as there can't be a purist approach to technology just for its own sake, it's more about an equation: what's going to work; what's deliverable; and can it be delivered in a cost envelope?"

Michael drew an analogy with treating heart disease. "There are expensive, complex transplantation units which need specialized infrastructure and doctors when the situation requires it. In other cases, patients are stented using products made by a medical device company – a significant intervention, this time in a hospital setting, again requiring specially-trained doctors. The pharmacy, meanwhile provides drugs that treat heart disease. Similar choices will apply to cell and gene therapy, in time. In the pharmacy of the future, patients will be able to pick up a prescription for an allogeneic cell type suited to certain diseases; at the same time there will be cell therapy suites in hospitals that provide autologous care whose products may or may not be manufactured on site. In other words, there will be a cost range and spectrum of therapies that accommodate the various indications, depending on what the patient needs."

Christian noted that the criteria for commercialization success was much broader than clinical efficacy, in the light of different options suiting differing contexts. "This is a really exciting train of thought," he said. "The different treatments might all be similarly efficacious, but it's the relative added value that makes each unique, and potentially better, more usable, faster to manufacture and deliver. The role of speed of manufacture is particularly interesting as a differentiator."

Communicating value across the healthcare ecosystem

Moving the discussion on, **Sven** noted the importance of effective communication which is often missing in the whole discipline of new drug commercialization.

"Up to now, we've been pretty poor at communicating – by which I mean marketing," he said. "As fanatics we rave about the particular cell and gene therapy, assuming that everyone's going to clamor for it just because of the technology. But the wider medical community including payers and regulators aren't all quite as enamored with cell and gene therapy as we are. So we need to learn how to communicate better across the whole value chain. And that's where details such as more rapid manufacture might have a bearing, as a potential commercial benefit."

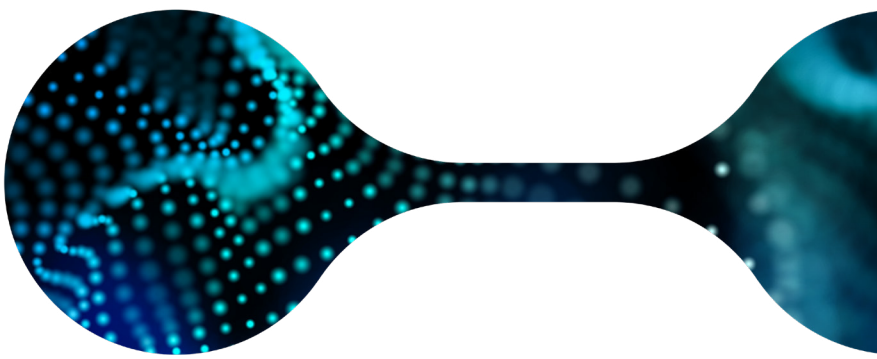
"For very severe, end-stage cancer patients, a 17- or 21-day manufacturing run for a CAR-T can be too long, and sadly patients do expire in the meantime. This raises the question of whether we should really be using these therapies (which are very expensive) as a last-ditch effort, or introducing them and using them to treat patients earlier - which, importantly, the data does suggest is more effective. So all of that needs to be part of the communication. Also, the longer it takes to manufacture something, the higher the costs associated with that product."

Indeed, some of the benefits of allogeneic therapies could occur here as treatments are scaled and batch sizes increased to achieve a better cost-per-cell ratio, Sven noted. "If you can use that comparison, and you can store the cells – e.g. 20 or 30 doses at a hospital – then the cost model improves. All of these are important considerations. But we're going to struggle to achieve the comparison unless we learn how to talk more effectively about the entire value chain."

Product characterization

Michael pointed to the importance of *characterization* of advanced products, which again is too often neglected until much later in a therapy's development. "There are still many gaps in product assay development identity, purity and, in particular, potency assays for these unique, living products," he noted, adding that automation could help here.

"When people talk about this, they're usually referring to the liquid side/the processing side of manufacturing," he explained. "But automating the release, and the assays associated with these products, is a major gap that could be addressed. I raise this because there's also a large technical component to scalable characterization of cell-based products. There remain challenges with the biology, and connecting a potency assay to clinical outcomes, for instance. So, for me personally and for my organization, I'm keen to develop an analytics strategy which will help control costs and drive success as well as adoption. I don't think this issue gets enough attention in the marketplace."



The 'wild west' of royalty distribution

Christian then opened up the discussion to include questions from the debate's audience. One concerned royalty stacking (where a licensee must pay royalties to multiple parties to commercialize a product) and whether companies are no longer investing in essential components such as vectors, promoter cell lines, and other genes unless there is clear ownership of the assets.

Keith noted that, while generally investors are willing to invest in the enabling technologies required to unlock a potential therapy, the tendency is to go after the biggest slice of the action. **Michael** pointed out, however, that as cell and gene therapy is an emerging field, with a lot of enabling technologies coming online rapidly, the market hasn't yet been normalized in terms of the expectations for each of those therapies in a single product. "There probably needs to be some level of correction as more and more products come online," he said. "When you know you have complex products that are highly modified, the licensing can be an issue, but I think this will be dealt with as in any other industry."

Sven proposed defining appropriate royalty stacking. "Sadly, there are companies out there that feel they're in the wild west – there's a bit of a money grab, with some organizations demanding very high royalties that are probably unwarranted," he said. "And there's not enough openness about who's paying what. Standardizing this to an extent is going to be critically important."

Bluebird's curtailed flight path: overcoming systemic barriers to commercialization

Finally, Christian brought the discussion back to funding of the commercialization journey, referencing the health technology assessment and the developer of a cell and gene blood disorder treatment, Bluebird's departure from Europe, "which suggests this is still a considerable hurdle," he said. "Is there something we can do about this during the development," he asked.

Michael suggested that, as the industry evolves and matures, and cost of goods come down, health assessment should become more standardized and prices will be more reasonable. Noting that different markets have different payer systems, he emphasized the importance of considering reimbursement early in development - in the given context, and based on the expected outcomes.

"It's still a work in progress, and these are very expensive therapies," he conceded. "And if, a CAR-T came online tomorrow for solid tumors, it would disrupt healthcare systems around the world – demand would be high and money would need to be available for a large market cure". "I have no doubt that these therapies represent the future of medicine, but challenges remain," he said.

From a practical perspective in the meantime, **Keith** recalled advice issued during his time heading up the UK's Cell and Gene Therapy Catapult accelerator. "We used to preach the importance of establishing a target product profile very, very early on, and running a 'skinny' health technology assessment," he said. The aim was to understand the reimbursable prices - across the different markets too - and embed these considerations within the strategy.

With reference to Bluebird's withdrawal from Europe, **Sven** felt this represented a failure of the EU system, but added that both Europe and the US have major changes underway in their approaches to health technology assessment. Although the issue persists in the EU, where each member state expects to perform its own assessment and determines its own payment conditions, the emergence of the US Institute for Clinical and Economic Review (ICER) bodes well for more reasonable assessments across the Atlantic, he said.

Final recommendations, agreed by the panel, included planning the target product profile (TPP), and understanding the patient pathway, especially as advanced therapies are applied to more mainstream use cases and are compared against more common therapies. Tracking pharmacoeconomic indicators from the start is vital too – in other words, balancing the costs and benefits of an intervention towards the use of limited resources, aiming at maximizing value to patients, healthcare payers and society, supported by data.

The recording of the full Science Huddle panel debate is available to watch or download on the Biopharma Excellence website. Future Science Huddle events will take place quarterly.

The Science Huddle, Sparked by Biopharma Excellence, are thought leadership panel discussions featuring key stakeholders from across the life sciences ecosystem, focusing on the complex challenges in the race to bring critical, cutting-edge treatments to patients.

About Biopharma Excellence

Biopharma Excellence partners with biopharmaceutical companies on their journeys toward the development and delivery of scientific advances and product breakthroughs. Its worldwide team of experts comprises multidisciplinary scientists; specialists in cell and gene therapies, vaccines, monoclonal antibodies and process development; clinicians; and former regulators. Biopharma Excellence has a proven track record in developing solutions to the scientific, regulatory and commercialization challenges that are unique to biopharmaceutical companies. These global solutions are grounded in major regulatory markets across Europe, the United States and Australia.

More at www.biopharma-excellence.com.

biopharma excellence by PHARMALEX