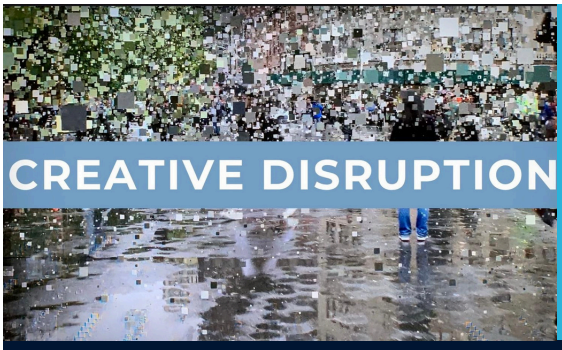

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Newsletter

FOR BUSINESS AND R&D LEADERS OF LIFE SCIENCE INNOVATION

AT A GLANCE

Making CGTs Investable

what are the key ingredients to make your CGT company investable

Creative Disruption Forum (CDF) - Cell & Gene Therapies

This CDF took place on the 22 May 2024 at the Wellcome Collection in London. Although most participants were from the UK, this CDF featured a notable transatlantic line-up of cell and gene therapy (CGT) experts. Lively and engaging sessions and workshops discussed "what makes CGT biotech's investable and highlighted numerous ways in which startups can help fast-track their innovative technology - from lab to market to patient." With so many new ideas and technologies in development and en route to market, getting the attention of investors at the right time and ensuring your company is differentiated is more critical than ever.

Chatham House Rules

Continuing the tradition, the Creative Disruption Forum observed the Chatham House Rule whereby participants are free to use the information received, but neither the identity nor the affiliation of the speakers, nor that of any other participant, may be revealed—the aim of which is to encourage inclusive and open dialogue at the Forum. ***To this end, highlights of key takeaways and trends that emerged from the discussions and workshops do not attribute specific statements to any of the attendees.***

The top picture features our investor keynote, Domonic Schmidt of Advent Life Sciences. The second picture is a snapshot during the workshop presentations highlighted in this newsletter.

Takeaways from keynote sessions

The topic of conversations derived from the CDF morning keynote sessions

Planning, derisking, and the 'self-amplifying loop'

Exciting movements in the CGT space continue post-commercialization of CAR-T cell therapies. Examples discussed include continued work in Duchenne's muscular dystrophy, the 2023 approval of two sickle cell gene therapies and the recent development of dual-vector gene therapy for hearing loss. When investing in CGT companies, the most significant risk is the science and robust clinical data, as is the leadership of an experienced team. Companies can flourish within a 'self-amplifying loop', whereby a tremendous initial team leads to greater derisking and more capital, which leads to the team continually being strengthened and able to close the loop by completing a milestone or funding cycle. Crucially, companies must have a considered development plan in place and the ability to respond and pivot agilely as new information comes into play.

Overcoming CGT development and manufacturing hurdles

"A solution applied by a scientist can cause a deviation in GMP, for example, leading to further problems in future commercialisation – this is why early external support with people with different disciplines can be essential and accelerate progress long-term"

In CGT, as in other areas of biotech and pharma and across different industries, solutions do not always have to come from within the company. There are significant advantages to partnering with innovative contract development and manufacturing organisations (CDMOs) with an established track record because they have often navigated similar problems with other programs. Ultimately, it's about the product. Fast-tracking lab to market is about shifting thinking to overcome the technical difficulties that arise along the way. One real success story shared at the Forum is BioNTech's partnership with Rentschler Biopharma, which led to the production of over 2 billion mRNA doses of its critical COVID-19 vaccine under extreme time constraints during the recent pandemic.

Off-target toxicity in gene therapy

Safety profiles are crucial when developing CGTs, although these are currently not very well understood during early-stage development. Minimizing the risk of off-target toxicity is critical, particularly as CGTs are beginning to compete with other treatment modalities like small molecules. Patients also expect clear understanding of the risks and how these treatments might affect them in twenty years' time. Due consideration needs to be given to off-target toxicity, as can be the case with some gene therapy technology, known to cause hepatotoxicity or possible long-term effects. This could potentially arise with CRISPR - especially as more treatments become available and potentially expand into indications currently treated with more conventional small molecule drugs or lifestyle changes.

Upfront analysis of off-target toxicity can help better understand potential long-term risks. To that end, AI is poised to play a larger role in toxicology by mapping out protein expression and signalling pathway interactions. For this to be achievable, more data is needed, highlighting the continued role of conventional toxicology methods and data being used to answer new questions that are being asked as CGT therapies are developed. While plenty of data already exists within companies, using it to inform AI models while maintaining data security and privacy remains challenging.

The CGT commercial journey

From a UK perspective, by the end of 2023, five cell and six gene therapies were in regular use nationwide in clinics. These treatments were offered by 22 hospital providers, covering 1700 patients. The NHS and NICE are currently considering a further 80 advanced therapy medicinal products. Five therapies are reimbursed to treat an unmet need; however, payers demand lower prices due to the uncertainty in the long-term efficacy and safety data. Companies should incorporate the costs of such long-term uncertainty into their product pricing when going to market.

Challenges and opportunities in CGT

Delivery of the therapy is a critical factor in CGT development programs. Each delivery agent - be it viral, non-viral or synthetic biology-based - has its challenges. Often, a simple design that works in cell culture and small animal models produces a different outcome in humans. Overcoming these challenges will frequently require novel solutions. Laverock Therapeutics, for example, have utilised whole cells in their innovative approach to delivering biologicals to the site of interest. This is an exciting concept, allowing for programmable delivery as the cells can be made to produce the biological therapeutic agent in response to environmental stimuli.

The future of CGT

Discussions turned to what the next 50 years have in store that will take CGT to the next level. Several thoughts were put forward such as enhanced safety and greater standardisation of CGT therapies. In addition, there will be advances in reliable means of delivery and gene expression, as well as targeted delivery to organs, tissues and cells. Alternative delivery systems will also likely be developed as there is a cost-of-goods ceiling in terms of what adeno-associated viruses can deliver. As CGT become more embedded in routine patient care pathways, the future should also see decreased hesitancy and increased acceptance by patients, as time allows for better understanding of long-term effects.

Key Takeaways from Workshops

In the afternoon we held eight workshops; here we highlight key learnings

Investment challenges

The valley of death in investment remains a challenge for companies starting out. Often, investors want to see clinical proof of concept before funding, which makes it difficult for companies that need funding to generate the proof of concept data. The current focus in investment appears geared towards the clinical stage and larger companies, with early-stage investments lagging. Venture capital money is also more targeted suggesting that the honeymoon period has come to an end; however, the positive spin is that investment should return.

As it stands, companies often scale up too quickly, leading to funding constraints. This has led to mission creep, whereby early-stage funding has more advanced companies applying. This money typically only lasts a short period before companies return to apply for more funding. Outsourcing can help overcome these challenges, but it depends on how specialised the innovation is. Smaller CDMOs can offer solutions that are less structured and more piecemeal.

Raising finance challenges

A common mistake when approaching venture capital is pitching too complicated ideas, which can make it difficult for investors to see the opportunity and business potential. It's important to ensure that the pitch is realistic. Investors want to see that the company has a strong understanding of its technology, its value proposition, the potential opposition, the funding inflexion points, and a team that can make it happen.

Toxicology challenges

CGT companies are concerned about off-target toxicity, with the current focus being first to assess liver toxicity - much like the assessments used for small molecules. As a result, traditional assays continue to drive the standard for regulatory agency assessments. One solution has been to build upon existing liver models by incorporating immune cells, although the predictive values are disputed. Long-term chronic exposure and acute toxicity assays are recommended, but for these to be reliable, there is a need for better models. AI could also be employed to identify potential risks, which may aid the development of biosimilars. There is a need for greater standardisation, which allows data to be compared across a more extensive set – this is an area where the US is ahead.

View this webinar to learn more about assessing tox risks in CGT therapies. Click below:

How Conventional ADME Test Systems Can De-risk CGT Studies - Webinar (bioivt.com)

Manufacturing challenges

Manufacturing small batches is expensive and a challenge for companies limiting the costs associated with producing Phase I materials while ensuring all the testing is performed. Using academic labs to manufacture small batches has its risks, as scale-up will eventually require the move to a commercial CDMO – this can be more costly when planned and carried out at later stages. Discussions also focused on decentralised manufacturing, which is considered difficult to achieve. Chemistry, Manufacturing, and Controls should be factored in from an early stage.

Legal challenges

A key legal challenge for CGT companies of achieving balance between IP rights and exclusivity with a view to potential infringement issues that could arise much further down the line. A common issue seen is companies using technologies during development that may come with additional licensing restrictions applicable at the clinical stage. It's essential to have internal processes in place to manage legal risks associated with technological improvements and changes. Careful attention is also needed when drafting contracts with CDMO to delineate ownership throughout the relationship and beyond.

Regulatory challenges

Regulations around CGTs are still being developed, providing opportunities for stakeholders to engage regulators and shape the guidelines but highlighting the crucial need to engage regulators as early as possible. Being first-to-market in this space currently comes with regulatory challenges, often due to the mismatch between current safety and toxicology assays and animal models commonly used for small molecule development but sub-optimal for cell and gene therapy applications. At the same time, this provides opportunities for more informal discussions. There is a clear need for an international committee focused on harmonisation, which could aid in reducing differences in the requirements between regulatory agencies and clarify regulatory guidelines applicable to this space.

Market access challenges

Patient access to CGTs is hampered by the slow pace of trials, which is affected by limited treatment facilities and the evolving payer landscape, which creates uncertainty. Discussions centred on greater stakeholder engagement in the early stages to identify challenges and work towards mitigating them. Players should take a proactive and realistic approach when considering the commercial challenges. Development and scale-up budgets should factor in the costs of the additional outreach essential to creating market access.

Key takeaway

One major takeaway from the Creative Disruption Forum workshops was to identify challenges early in the company journey and start putting in place strategies, the right ecosystem, and experts to help mitigate them before they arise—and to be able to move agilely and pivot should unpredictable issues arise.

About the Sponsors

BioIVT ADME Products and Research Services

BioIVT is the global leader in providing products for *in vitro* ADME research. They pioneered the cell isolation and cryopreservation techniques used in the industry and continue to set the standard for hepatocytes, subcellular fractions, and recombinant enzymes. They offer proprietary technologies, including pooled hepatocyte products, and long-term cultures, as part of their comprehensive portfolio, and their R&D efforts focus on application development. Their commitment to innovation, quality, and supply chain logistics has led to a reputation as the best-in-class provider. They offer:

· Large lot sizes

· Extensive inventory

· Full characterization

· Technical support from ADME scientists

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About Rentschler Biopharma

Rentschler Biopharma is a leading global CDMO, focused exclusively on client projects. Thanks to their 50 years of proven scientific expertise in biotechnology, they count themselves among the leaders in the industry. From their headquarters in Laupheim, Germany, and their sites in Milford, USA, and Stevenage, UK they offer end-to-end solutions including biopharmaceutical and viral vector process development and cGMP manufacturing.

Located in Europe's largest cluster for cell and gene therapies (CGTs) in Stevenage, their advanced therapy CDMO facility provides high-quality viral vectors for advanced therapy medicinal products (ATMP). Their experienced teams are dedicated to advancing your viral vector programs from early development to cGMP manufacturing for their clients' clinical and commercial needs.

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About Mills & Reeve

Mills & Reeve are lawyers with one of the largest full-service life sciences teams in the UK. Renowned lawyers with extensive expertise in the industry will provide the solutions to enable you to seize the opportunities open to you.

About SciTribe

SciTribe offers strategic communications advisory services focused on science, technology, and the environment. It combines professional corporate and scientific communications expertise with lab-based research experience. It is driven by a deep understanding and enthusiasm for your science, technology, and impact, applying strategic thinking, listening and roll-up-your-sleeves, "get it done" know-how.

SciTribe provides focused and flexible bespoke support to a variety of organisations big and small. Their services include strategic consulting, problem-solving, messaging, copywriting, and digital services that provide the clarity and style that effectively tells your story - through the right channels, to the right audiences.

About the CDF Organisers

Prof Tony Sedgwick, Founder, Henry Sedgwick Ltd

Prof Tony Sedgwick, the self-professed www.ThoughtDisruptor.com, facilitates the Creative Disruption Forum. Tony has an esteemed career in life sciences, academia and industry; he is a trained pathologist. His accolades include being the global head of clinical trials at Roche AG for 10+ years, CEO of four life science companies, and chairman of 10 companies. He has held many positions within the academic community and is a strategic consultant for various business leaders. He published a book called “Mighty Advisor” in 2022, which topped the best-selling Amazon charts within the STEM Management category.

Graham Combe, Founder, Biosell

Graham is an experienced strategic consultant with a demonstrated history of working in publishing, marketing and events within the life sciences and science-led industries. He spent ten years working with Nature, where he pioneered Nature's BioPharma Dealmakers quarterly publication and developed Nature’s SciCafe, amongst other things. In May 2011, he started BioSell, which works with many of the world's leading life science publishers, marketing and event organisations - and runs its own stand-alone events. The stand-alone events include #BiotechBuddies evening networking, the #AgileLeaders Forum, the #CreativeDisruption Forum and the online #coffeebuddies events.