CELL & GENE THERAPY 2020 A LOOK AHEAD

Part of Proventa International's EU Cell & Gene Therapy Strategy Meeting 2019 Radisson Blu Zurich Airport, Switzerland - October 9, 2019

Attendee Statistics - Who Went and What They're Investing In
The Top Strategic Challenges for Cell & Gene Therapy, 2020 and Beyond
Highlights from All Our Tracks
An Expert Look at the Next Five Years in CGT

INTRODUCTION

Proventa's EU Cell & Gene Therapy (CGT) Strategy Meeting came to a successful conclusion recently, with delegates and sponsors both satisfied with the unique roundtable format and fantastic networking opportunities on offer throughout.

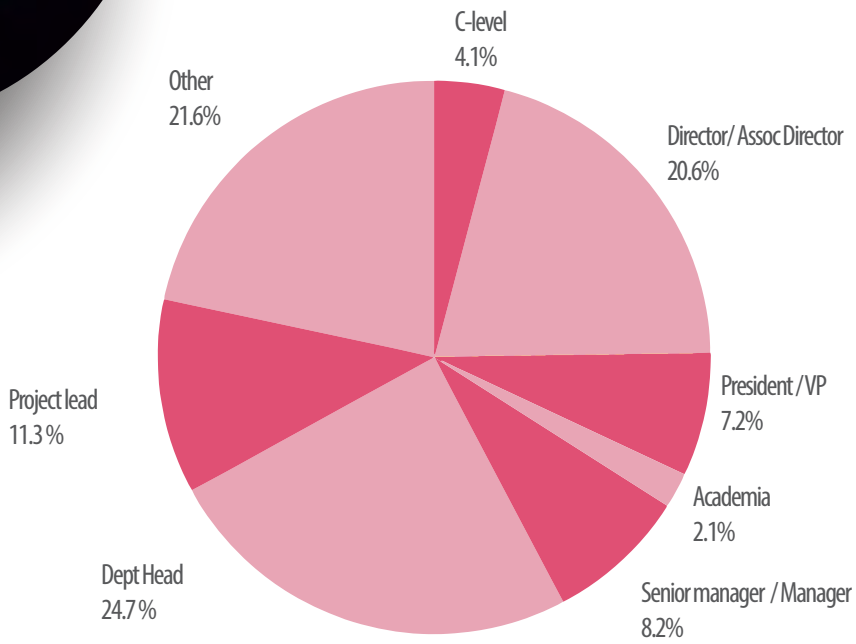
The event showcased a number of expert industry facilitators talking about a wide range of forward-thinking topics within the area, including building a robust supply chain for personalised therapy, technical and commercial complexities of recombinant viral vector production and the automation of CAR-T cell product manufacturing procedures, and addressing the challenge of clinical manufacture of modified cells.

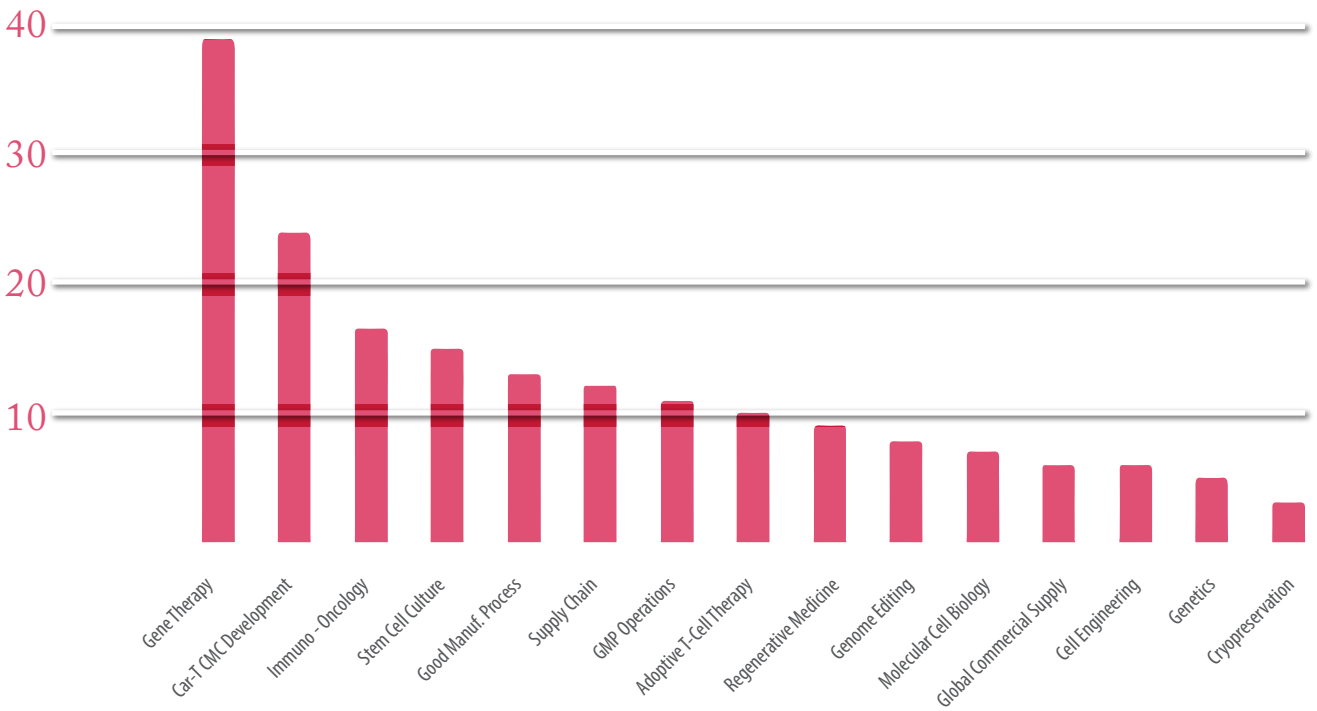
THIS REPORT - THE FUTURE OF CGT

This report, looking both back over the 2019 CGT Strategy Meeting in Zurich and - more importantly - to the future of the sector, contains quality information both for those who attended and those who may attend in coming iterations: it lays out not only statistics showing job titles and the investments of this year's delegates, but highlights from the event roundtables themselves and even our facilitators' impressions of how CGT will evolve and change over the near future.

We hope you enjoy this report, and take away information that will be of use to you and your company whether you attend our future events or not.

THE STATISTICS: CELL & GENE THERAPY STRATEGY MEETING 2019





2019 EVENT HIGHLIGHTS

The 2019 CGT Strategy Meeting saw five high-quality tracks covering almost all our delegates' areas and interests. The five tracks were: oncolytic viruses & MRNA-based technologies; CGT vectors (I.E. AAV and Lentivectors); CAR-T & TCR Cell Immunotherapies; Cell & Gene GMP Manufacturing; and Global Logistics.

ONCOLYTIC VIRUSES & MRNA BASED TECHNOLOGIES

Tobias Speck, Scientific Project Manager at CanVirex, began this track by facilitating a fantastic roundtable on preclinical development of next-generation oncolytic viruses (OVs) for use as immunotherapies. The roundtable initially discussed certain area-specific facts, including that there are around 3,000 IO clinical trials currently underway around the world today, and that in preclinical and clinical development today around 80% of OVs are genetically modified to increase or alter tumour selectivity, enhance viral replication or improve cancer cell killing.

From there, the discussion moved to the topic of immunity against the vector, looking at vector design and route of administration. Participants decided that IV delivery was a more applicable and advantageous system, at least when treating metastatic diseases. Further discussion suggested that IT administration could also deliver a high concentration of the OV into a tumour, though questions were raised around how an IT dose is defined.

The topic then moved on to the risk-to-benefit profile, and arming and targeting of OVs. It was noted that OVs tested in trials have generally had an excellent risk-to-benefit profile, though study sizes have at this time been limited. At this point it was noted that targeting virus tropism could increase tumour selectivity, with delegates talking about engineering viral attachment proteins to both redirect and ablate unwanted attachments.

The talk then moved on to arming with toxins, prodrug convertases or immune modulators, with points raised that there was limited benefit when dealing with highly-immunogenic tumours, or tumours which are sensitive to the applied toxin or agent.

Over the course of the roundtable, a number of important facts about the area were made clear:

- The choice of transgene depends on the patient's immunological needs, so there won't be only one virus encoding one immune modulator that will be most successful
- There will ideally be a platform of viruses encoding different immune modulators, which can be given to cancer patients as monotherapy or in combination
- Selection of armed viruses will be based on predictive molecular signatures which determine the patients' immunological need to induce or enhance a lasting, potent anti-tumour immune response
- Although IV delivery of OVs is currently more clinically applicable, IT delivery will in the future dominate

Professor Andre Gerber of the University of Sussex finished the track with a talk on mRNA therapeutics to reprogramme and determine cell fate.

CELL & GENE THERAPY VECTORS (IE AAV & LENTIVECTORS)

Paul Carter of GSK started the CGT vectors track with a discussion on biosafety risk of replication competent lentivirus to users from recombination events during viral production.

After this, Novartis' Global Head of CGT Technical R&D, Otmane Boussif, headed a roundtable looking at the technical and commercial complexities of recombinant viral vector production. Some of the conclusions to come out of this talk included:

- that while most pharma companies shy away from using T antigen cells for anything except AV work due to a perception of regulatory disapproval, no guidelines actually prevent it: in essence companies are stopping themselves from increasing titer levels via this method
- that new processes and innovations are coming most from hospitals and small biotech companies, rather than big pharma

After that, Ricardo Hermosilla of Roche ended the track with an enjoyable discussion on avoiding inflammation and liver toxicity when administering large doses of a virus.

CAR-T & TCR CELL IMMUNOTHERAPIES

The CAR-T and TCR Cell Immunotherapy track began with Sarah Warren of NanoString Technologies Inc leading a roundtable on addressing challenges in CAR-T manufacturing with standardised characterisation.

She was followed by Lothar Germeroth, SVP and Managing Director of Juno Therapeutics, who facilitated a talk on automation of CAR-T cell product manufacturing procedures. This talk looked among other things at CAR-T versus TCR; the importance of team integration and working together; and change in processes and how they can be controlled.

The delegates began by discussing the benefits of using CAR-T versus TCR. It was noted that TCR is a cumbersome process, but one which could better address tumour cells in a more powerful way, while CAR-T and omitting of expansion can result in better cells placed in the patient.

From here, the discussion moved on to the importance of research and manufacturing teams working together, with leadership also mentioned as vitally important to bring together the right professionals to ensure a process is handled well. Next the question was raised of which metric or element in production is most vital for reducing goods cost: delegates largely agreed that scaleable off-the-shelf products were useful in this regard, though they had some downsides.

One of the final takeaways of the roundtable was the suggestion that manufacturing must move away from viruses, due to their random integration when compared with CRISPR processes.

Following this, Geert Mudde of TYG Oncology facilitated a discussion on addressing the challenge of clinical manufacture of modified cells, which ended the track for the day.

CELL & GENE GMP MANUFACTURING

In the Cell & Gene GMP Manufacturing track, the day began with Oliver Bartelen of Miltenyi Biotec delivering a roundtable discussion on standardisation in manufacturing of autologous CGT products. He was followed by Eric Halioua, working for PDC*Line Pharma, who led delegates in talking about the opportunities and challenges in manufacturing bioreactors-based scale up.

The track's final roundtable of the day was led by Niklas Engler, Global Head of Technical Development Portfolio, Projects and External Collaborations at Roche, and focused on in-housing versus outsourcing manufacturing and process development, looking particularly at the benefits and risks involved.

Initial thoughts from many delegates seemed to suggest a mixture of outsourcing and in-house recruitment was needed to deal with manufacturing and process development. While it was generally agreed that process development and production could not be given out of hand, vectors and other areas still needed to be outsourced. One large company suggested that more than 50% of its development was handled in-house.

Generally, it was agreed that out-sourcing development, and the need for supply chain insurance that came with it, was a risk to most companies. Delegates agreed that the risk of outsourcing to smaller companies was primarily one of proprietary knowledge: there can be a steep learning curve when such companies act alone.

The roundtable ended with discussions around AI's ability to reduce the gap in the need for talent, for example ensuring successful and accurate filing of information. The delegates agreed that while there was a definite place for AI to ensure accuracy and avoid human error, a certain level of human involvement would always be needed as oversight.

GLOBAL LOGISTICS

Timo Simmen, Director of Technology Innovation & Standardisation at J&J, kicked off this track with his roundtable on building a robust supply chain to deliver personalised cell therapy, looking at the key challenges from end to end and how to provide a safe product to patients.

Much of the talk focused on ensuring the supply chain was safe and secure at every point, with delegates noting that some hospitals or pharmacies lack suitable standards, and that often with CGT, delivery is unreliable, with clinics and pharmacies subsequently demanding that drugs are already on-site before patients are treated.

A possible answer lies in the shipment model, with a need to put in place quality processes, though due to the variance and differences in maturity level between hospitals no single solution currently presents itself. Standardisation was strongly heralded as the answer to this issue, but due to a lack of communication between pharma and the clinic, and particularly between individual pharma companies, such standardisation seemed at present remote.

The discussion then turned to working with health authorities, particularly when exporting from the US, with delegates determining that such a process can either be done quickly or done thoroughly, with the latter much preferred for a robust and definitive outcome. After this delegates discussed cross-contamination, noting that automation would address this issue in the near future but until then that delegates should carefully choose supply chain partners and monitor all aspects of the chain closely, particularly during the hospital hand-over.

The track concluded with Ricardo Hermosilla facilitating a discussion on how to set up a CGT supply chain with a focus on logistics.

KEY DELEGATE CHALLENGES 2020 AND BEYOND

One of the most important resources available to any senior figure in biotech or pharmaceuticals is an understanding not only of the field at present but where the field is going, and the key obstacles that any company in the sector faces.

Proventa International surveyed a number of major players in the field, using expert opinion and insider knowledge to uncover out of the many obstacles on the horizon the major challenges to overcome in the next few years.

MAJOR CHALLENGES 2020 AND BEYOND

Organisational changes and growth
The major challenge cited by our delegates related to growth and change at an organisational level: despite a number of smaller, more field-related issues within the sector, it appears that fundamental structural problems are still number one on the list of challenges to come.

Manufacturing
Manufacturing challenges were also a critical issue cited by delegates, with areas discussed ranging from ramping-up of CAR-T manufacturing abilities to capacity and manufacturing costs.

Clinical and preclinical trials (set-up)
The set-up and successful execution of clinical trials, trial recruitment and the translation of preclinical data into clinical results were all mentioned as challenges for a number of companies in the field.

Optimising and Streamlining Processes
Similarly to organisational change and growth, many companies stated that the high-level streamlining and optimisation of their processes was a key challenge in the years ahead.

Commercial
The commercial side of cell & gene therapy was one of the key challenges mentioned by some delegates, with mention of commercial support, global commercial supply and setting up commercial models for launching genetic therapies, suggesting challenges ran along the entire breadth of the commercial business aspect.

CAR-T / TCR Cell Therapy
The relatively new CAR-T and TCR immunotherapies were both mentioned as challenges by several delegates. Specific comments noted CAR-T logistics, CAR-T blockchain technologies, and TCR generally as issues which will need to be addressed in the years to come.

Supply chain
Supply chain was also noted as a critical issue for several companies, including comments on building a new supply chain for gene therapy and supply chain set-up in Europe.

Recruiting and training staff
Recruiting and training staff, and finding individuals with the correct skill set, was a repeating challenge for a number of delegates. Developing cell therapy teams and hiring talent in commercialising genetic therapy were particularly mentioned as important for experts surveyed.

Finding product and technical innovation
Finally, finding the newest technology and critical innovations were mentioned as a vital challenge for the next 12 months: delegates voiced concerns around developing innovative payment models and supporting the establishment of innovative production platforms in the business, among other areas.

A LOOK AHEAD: EXPERT OPINION ON THE FUTURE OF CELL & GENE THERAPY

THE FUTURE OF CELL & GENE THERAPY

Despite a decade of setbacks and tribulations, the last few years have seen CGTs come into their own. Advances in clinical safety and vectors have seen both R&D and manufacturing pipelines filled with potential new therapies, promising breakthroughs for even some of the most obscure and complex diseases.

Now, though most research is still focused on oncological disorders, extensive evaluations are occurring across the CGT space, looking at varying diseases, technologies and formats. We spoke to some of the experts present at our 2019 CGT strategy meeting to find out their views on how the sector will evolve and grow over the next five years.

FUTURE EVOLUTION

A Project Manager facilitating at the event reiterated the idea that CGT has shown "unprecedented curative outcomes" in cancer therapy and inherited diseases. Based on this potential, he believed the field would increasingly evolve and grow outwards in the next five years, becoming a clinical reality for more and more patients. He said that for CGT to become mainstream enough to affect a large part of the patient population, however, a much longer time would be needed.

Looking at the specific instrumentation of change in the field, the facilitator said that the two main focuses for any new technology or process would be safety and efficacy, as has continued to be the focus of the last 30 years.

WIDER AUDIENCES

The facilitator also noted that, at present, a major challenge is moving the focus of CGT from rare diseases or single patient subpopulations to a wider audience, though manufacturing and other technological breakthroughs would be needed before this occurred.

CAR-T VERSUS T-CELL THERAPIES

Another delegate in the role of CSO & Managing Director suggested that the current sector focus on CAR-T cell areas was possibly misplaced, and noted that major results from the therapy would not be seen for at least ten years, and in some cases - such as in solid tumours - perhaps never. He argued that the industry should instead be focused on T-cell engagers, whose problems are easier to solve and will be considerably cheaper.

REGULATORY APPROACH

One Vice President in charge of Regulatory Affairs offered a more regulatory perspective on the field of CGT and the possible future as he saw it. He said regulation around the area was still just beginning, and noted that at present the challenge was very complicated, with many regulators still working on a case-by-case basis.

What was important, he suggested, was that manufacturers make contact with regulatory agencies early in the process to align operations and exchange information, as is done in other areas such as biomanufacturing or biotech products.

He added that the most difficult task for regulators was in production, and how pharma companies can demonstrate from a clinical point of view that their outcomes could be repeated.

AGNOSTIC TREATMENT

Finally, another facilitator suggested that one area professionals would slowly move towards in the next five years would be agnostic treatment, as opposed to indication treatment: he thought the industry would move more towards an understanding of a diseases genetic or molecular features, as opposed to looking only at what the specific disease is and treating that alone.

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