CELL & GENE THERAPY INSIGHTS

SUPPLY CHAIN FOCUS: GLOBAL COMMERCIAL STRATEGIES

CHANNEL CONTENT

PODCAST INTERVIEW with:
Brandon Fletcher, Cell and Gene Therapy Principal;
Tamie Joeckel, Cell & Gene Therapy Business Lead;
Martin Lachs, Vice President, Project Management, Oncology & Cell Therapeutics;
Olivier Saulin, Cell & Gene Therapy Principal at ICON, plc




Enabling clinical development of cell and gene therapies on a global basis

Cell & Gene Therapy Insights 2020; 6(2), 373–385
DOI: 10.18609/cgti.2020.047

Q Could you provide an introduction to your roles and activities at ICON?

> "...every new study will probably have ... risks that we never thought of, so we try to be reactive and build processes in order to mitigate those risk as much as possible."

TJ: As the Business Lead for the ICON Cell and Gene Therapy Group. I assist with the overall strategy for our cell and gene therapy focus, and help manage and identify strategic alliances that we have with specialized service providers. I'm also involved in connecting sponsors to the correct ICON resources for the opportunities that we pursue.

ML: As VP of Project Management I run the Oncology and Cell Therapeutics Group here at ICON Clinical Research, and I work with Olivier, Tamie and Brandon in executing strategy and making sure that we run a tight ship and have a strong, forward-looking operational strategy.

BF: I'm a biochemist and cancer immunologist by training. My role as a cell and gene therapy principal is to provide scientific-based strategic and thought leadership, and to support education and training throughout all of our cell and gene therapy projects and teams.

OS: I'm a biochemist cell and gene therapy expert in the oncology group. I also have a role as program manager; I oversee operations of clinical programs with adoptive cell therapy for two clients. In the last 5 years I've built significant hands-on expertise in cell and gene therapy clinical development, and I work with Brandon to support our operation and clients in executing projects.

Q When it comes to designing and running trials, what are the biggest operational issues to consider, and how can they be addressed?

ML: I'll start with design. With any good design in any clinical trial, having the endpoint in mind is going to be a critical factor: the target product profile (TPP). In cell and gene therapy, when we talk about design, the difficulty is in making sure that scientific enquiry is balanced by practical execution – and this overlaps with the operational component of it.

Whether you're considering the end-to-end chain of custody of a living therapy, or the basics of how hospitals can set themselves up in order to actually run effective clinical trials, the design has to be built in line with operational reality. This is one of the biggest challenges in an ever-emerging field, where more complex and innovative designs are being brought to bear all the time. And of course, there's the regulatory component to consider too.

Q What are the main issues surrounding data generated from trials?

BF: This is the gorilla in the room, indeed. In the cell and gene therapy world, data management continues to be an ongoing challenge; it is magnified by diminishing site resources and increasing competition for them, leading to overburden and overburn at the site level. Not to

DOI: 10.18609/cgti.2020.047

mention the overwhelming amounts of non-traditional data that are generated. In response, one of the key strategies we have adopted is to use predictability in our favor.

It is imperative to understand and manage the fact that cell and gene therapies simply do not correspond with standard metrics. They must be planned, resourced and managed differently. To mitigate the negative impact of the blinded approach to data, we created and use a technology to vet out these unique expectations for strategic planning, both for us and our sites. For example, if you were to visualize the standard metric on a non-cell and gene therapy trial – such as recruitment, which could be in parallel with the Site Initiation Visits (SIVs), or data accumulation, which could be paralleled with on-site monitoring – then those graphs would be quite predictable. However, when compared to the metrics graphed for cell and gene therapies, they're drastically different. Thus, data intelligence has become the foundation of our planning, communications and resourcing in order to help us better manage high volumes and unpredictability.

OS: Due to the nature of these living therapies and the unique safety requirements of these processes, the trial sponsor usually requests a lot of data deliverables and data cuts throughout the life of the study. This can be for independent review – for example, a committee to review radiology data, or the Data Safety Monitoring Board (DSMB) to review AE/SAE (Serious Adverse Event). We also have the Biological License Application (BLA) submissions, which are a very important milestone in a study. These are important timepoints at which to review the efficacy and safety data and as a company, we have been involved in multiple BLA submissions. We have observed the intensity of those data transfers, which often require 100% of the data to be clean. We also need to ensure that the transfer is compliant to the FDA-accepted CDISC standards.

Submitting this data involves a lot of coordination between our clinical, data management, statistics, and medical writing teams. This is a real challenge because these products need quick approvals and very frequent reviews of their safety.

ML: You could summarize these issues by saying that very often cell and gene therapy studies are like clinical trials on steroids. They may involve some of the elements you expect in regular oncology clinical trials, but they're magnitudes greater in terms of intensity, and the speed at which you need to make decisions.

Q What strategies can help to mitigate predictability challenges?

BF: The importance of proper and thorough education and training in the realm of cell and gene therapies cannot be stressed enough. This is a complex area, and even the heavily seasoned clinical care and clinical research desks have often never worked with cell and gene therapies. Going a step further, a good portion of those on the development and sponsor side have very little experience in the field. It's still quite new to the mainstream,

> "...data management continues to be an ongoing challenge; it is magnified by diminishing site resources and increasing competition for them..."

> "Our training academy is a repository of our best practices and tools that we have developed to execute the trials."

and has been mostly managed through the National Cancer Institute (NCI) and other top tier centers. Very few of us can say we have a lot of experience in this.

Therefore, taking the time to understand the science and technical modalities behind these therapies is critical for aligned and effective drug management and development. A deep and thorough understanding of what you're working with, along with the need for flexibility and what that may mean operationally, is key to mitigating predictability challenges. One of our primary ways to manage this is through our grassroots, proprietary 6-month training program called the Cell and Gene Therapy Academy. We have roughly 300 dedicated cell and gene therapy colleagues enrolled, and this serves as the backbone of our knowledge base.

As mentioned earlier, using predictability in our favor here is key, and it's what we try to build our strategies around. In the case of data management on a site level, we have developed strategies along with predictive modelling to support proactive planning and effective communications for efficient data management to help reduce site overburden and overburn, which is a big problem in this field. The technology creates an evidence-based prediction of the site's anticipated data volume, to properly assess the data needs which lie ahead. This helps us ensure that the project is prepared and resourced appropriately, and provides tangible evidence for resource redirection.

Q What are the unique challenges posed by manufacturing and developing cell and gene therapies?

ML: We've already touched on the issue of predictability. You've also got very large numbers of individual stakeholders, more than you would expect in any other kind of oncology development program.

Another challenge is that no two technologies are necessarily alike. For example, you can't assume that autologous studies are the same as allogeneic studies, or that the needs within them are the same. There are lots of commonalities, of course. You're still talking about a living therapy. But when it comes to processes such as apheresis, there are different nuances which have to be taken into account.

There's also the notion of access. For example, familiarity with administering cell and gene therapies both in the marketed products space and also in the trial space is limited to accredited sites, for the most part. This means sites themselves have to have the appropriate infrastructure in place. We're able to help with that as part of our role, but currently there are a finite number of sites that have the capability and capacity to undertake this kind of drug development.

DOI: 10.18609/cgti.2020.047

Very often we are working in uncharted territory as new technologies, vectors and gene editing aspects come to light. Because some of the translational models are not highly predictive, we don't necessarily know what the outcomes will be. Therefore, we are in a constant phase of stopping and starting. Manufacturing is a major issue in this space as it can be limited, and it is also subject to numerous halts owing to emerging safety data, as well as to ensuring maintenance of purity of cells.

There's a whole raft of challenges in the development space – from logistics, to manufacturing, to patient safety, to the limitation on facilities that can actually administer these drugs. The unique challenges are expressed through limitations on who can actually execute studies of this nature, because of the highly coordinated and complex interactions.

Q What patient recruitment issues have you faced, in particular for oncology and the rare diseases?

ML: Most of the development thus far, and the products that are marketed currently, are in the hematology-oncology space, specifically lymphoma and leukemia.

When we started doing these trials about 5 years ago, it was very easy to find willing patients because the results were looking to be very hopeful; and they continue to be in terms of response rates and durability. But now, everyone has jumped on to this bandwagon for perfectly good technical and scientific reasons – hematology-oncology indications have been shown to be the most straight forward indications to target. This means the space has become quite congested in a way, and as we are increasingly moving these treatments closer to the frontline, there are alternative and cheaper treatments knocking at the door which are more accessible to a broader number of physicians and hospital institutions. This competition, not just from the cell and gene space but from other therapies such as immunotherapies and so on, is putting pressures on enrolment capabilities and capacities.

> "Whether you're considering the end-to-end chain of custody of a living therapy, or the basics of how hospitals can set themselves up in order to actually run effective clinical trials, the design has to be built in line with operational reality."

There's also a burgeoning interest in solid tumors, but it's more difficult to actually develop or find targets with which you can demonstrate the same level of response and durability as we've had in the lymphomas and leukemias. Once you get into other indication areas that are not oncology – rare diseases, CNS, etc. – you're in an area where physicians may not be as familiar with the particular challenges and requirements for cell and gene therapy studies. This places

> "We learned the hard way never to assume anything when you're dealing with a new therapy, especially related to cancer."

you in novel territory in terms of educating sites, and actually setting those sites up with the capability to access and treat patients themselves.

TJ: The implications of rare disease patient recruitment are obvious: we're looking at an extremely small patient population. Not only rare, but in many cases ultra-rare. It's really important to understand where these patients are located. Often there are pockets of patients found geographically, so being able to identify the sites that treat those patients is key to build awareness of the trial.

For example, when we were starting a study on severe combined immune-deficiency (SCID), we worked very closely with patient advocacy groups. These groups are already proving support services to these patients and know where these families are. We learned that there are pockets of communities inside the United States where there's a relatively high occurrence of that disease state. Advocacy groups can also help us build awareness within the community about the availability of the trial.

Q Once a client gets past their first in human trials, what are the next big hurdles they face?

ML: Scalability would be number one when operating a first in human study with a small number of patients, and being able to manufacture enough product for the treatment of a small number of patients. Let's remember that for autologous treatments the patient is effectively the main source of the drug. In allogeneic studies, that's a different story again. Scalability is an issue in terms of manufacture, in terms of organizing the logistics of getting the therapy to the patient, and something that comes with engaging with specialist organizations and specialist platforms that allow workflow management to actually get the patients through the trials.

Many development companies with these innovative and ingenious ideas are smaller, and they may be venture capital funded or be in collaboration with larger pharma. Cost is a very sensitive issue as you scale up for a larger patient population, and then you start rubbing up against the competitive space as well.

TJ: The lack of standardization is a big issue in this space, which is exactly why ICON formed a dedicated center of excellence for cell and gene therapies. We understood very early on that these trials had to be delivered differently. We have learned along with our sponsors, and we've also learned from our own mistakes. Those experiences have become best practices that are now the foundation of how we execute these trials. Our training academy is a repository of our best practices and tools that we have developed to execute the trials. Additionally, every protocol has unique requirements and each site has its own standard operating procedures (SOPs), and these have to be integrated into our required workflows.

DOI: 10.18609/cgti.2020.047

The lack of standards, combined with the sheer number of stakeholders required in these trials, dictates the need for very detailed training and defined workflows. This becomes even more important as sponsors move from early phase to Phase 2 and 3, and on to commercialization. As the number of patients and number of sites grow, it only exacerbates the issues and challenges we face.

We're doing a lot of work with standards. We work with the International Society for Cellular Therapy (ISCT), the Alliance for Regenerative Medicine (ARM), and standards coordinating bodies. The field is constantly evolving and there's still so much work to be done. Not to mention the reimbursement hurdles from a commercialization perspective that can impact patient access.

Q How do these challenges evolve when you then consider not just scalability, but running multinational trials? What would you say are the most important considerations?

ML: Regulations are heterogeneous. What goes on in Japan is different from what goes on in the US or European countries, or Australia or China, which are all big centers for cell and gene therapy development. Navigating this heterogeneous regulatory field is something we have a lot of expertise in, both through experience and the ability to database the information.

The other component is moving materials, which are also subject to regulatory and safety considerations, across borders. For example if you look at allogeneic cell therapy and developments in specific areas like gamma delta T cells, you might have to source tissue from which you extract cells, which are then going to be the source of some of the components for your therapy. How do you move those across borders? You're not talking about just the cells themselves, you're actually talking about tissue – possibly from plastic surgeons, for example. Again, coordinating those activities, having a strong knowledge base about how that can be affected, is something that a CRO has a big part to play in.

TJ: As Martin says, these are living therapies. Therefore, you have a chain of condition that has to be monitored, because there's temperature sensitivity. Therapies are shipped in liquid nitrogen dry vapor shippers, and you have to monitor those for temperature excursions. The chain of custody has numerous hands-offs, and end-to-end traceability and trackability has to be maintained and documented between all of the stakeholders involved.

Then there's the unpredictability of customs clearance. If you're moving these therapies between countries, you can ship something 20 times via a specialty courier and have it pass through customs just fine. But then there may be a time there's a particular person at the border that holds up the shipment because of insufficient documentation,

> "Cost is a very sensitive issue as you scale up for a larger patient population, and then you start rubbing up against the competitive space as well."

or some other issue, and at that point you've got to make sure you can mitigate the risk of temperature excursions. It's an extremely complicated process – it's not a case of just putting it on a plane and assuming it's going to reach the destination.

Q How is trial design evolving to meet the needs of the cell and gene therapy space, and what are the biggest innovations you are seeing in this area?

OS: One of the most innovative trials we worked on recently involved evaluating patients based on the presence of cancer specific antigens in solid tumor, regardless of the tumor type. The study tested the effect of drugs in a variety of cancer histologies, which allowed us to test a lot of different tumor types, which then leads more rapidly to results on which specific tumor type to concentrate on.

This type of design is reducing patient exposure to these drugs and allows us to have quicker results than if we're doing one study for each Phase 1, 2, 3. I think we will see more and more of this type of adaptive design in the future, and that's going to really help with the specific challenges of this space – for example, looking at CAR-T in multiple solid tumor.

ML: In common with much of oncology development and beyond, because you're not talking about mass manufacturing, we're seeing that trials are becoming more registration-focused at an earlier phase. There's a move towards more adaptive designs, such as basket type trials, umbrella trials and platform trials. We're trying to combine as many possible treatment groups within the framework of a single trial.

Long-term follow up studies are becoming increasingly important. Subjects and patients who are receiving these treatments are effectively becoming genetically modified organisms, and we're still in a position where we have to follow through with patients for a very long time after they are treated. Designing long-term follow up protocols to allow us to accrue data for an extended period of time is also challenging.

Q Looking beyond trial design, what would you consider to be the hot topics and biggest hurdles cell and gene therapy development is facing, and how can CROs in particular be involved in addressing them?

"...we are focused on building solid risk assessment categorization tools, or risk management plans..."

TJ: As we move from an autologous 'one and done' dose therapy to an allogeneic therapy that may be multiple doses, these patients are going to be discharged and going back into their own communities. ICON has been a leader in this area: we acquired a home health services group and bringing the trials to the patients within their communities is something we're

DOI: 10.18609/cgti.2020.047

> "The chain of custody has numerous hands-offs, and end-to-end traceability and trackability has to be maintained and documented between all of the stakeholders involved."

working to anticipate. A lot of these patients are very sick, and the four or five-hour long drive to a site to be administered a dose may not be practical for them. We're really looking at how we can support our sponsors in doing this not only in the clinical trial phase, but potentially in the commercialization phase.

ML: Cost is probably the largest tangible challenge if you look into the commercialization of what are otherwise extraordinarily exciting technologies. Not just the cost of doing trials, which is not trivial, but also the cost of the product once you get close to commercialization. We've seen from the two marketed products out there at the moment, Yescarta® and Kymriah®, that they don't come cheap. When you factor in the additional costs of hospitals administering treatment and general care for the patient, they have an even higher price. A lot of development is targeted towards managing that cost downwards, whether it's through allogeneic therapies, which arguably should be a lot cheaper, or in other ways. There are other approaches to patient treatment that are a lot cheaper. If they can be proven to be as effective – which may or may not happen – that is going to be the threat for the further development of cell and gene therapy.

Realistically, we can work to support companies as we do because we have our own pricing, market access, and commercialization groups who are experts at looking at things like net present value and doing full evaluations on potential. They take into account patient groups that would benefit at an international level, and also look at the market as a whole in terms of what is out there, what has got the greatest chance of success, and what that means for payers in terms of the long-term benefit for patients. Bringing that level of expertise in helps drug developers visualize where they may be going with their particular assets.

Q What have been your most educational mistakes when supporting the development of therapies in the cell and gene therapy space?

BF: Looking back, we've certainly had many blind spots along the way! In the beginning, we kept trying to frame this area and create boundaries with clear definitions, so that we could frame our own work. For instance, in our work with CAR-T: this area of cell and gene therapy is itself definitely unique, but as soon as we got our heads around this concept, developed our systems and processes and deployed our troops, the field changed. New scientific modalities such as TCRs, tumor infiltrating lymphocytes (TILs), marrow infiltrating lymphocytes, and multiple tumor associated antigens, *et al.*, emerged. We reframed again, adding the allogeneic realm. Then we reframed it all again for solid tumors. This process of tearing down and

rebuilding shed light on how easy it is to take a limited view, and the importance of keeping our minds extremely open.

In clinical research we're programmed to standardize processes, but with cell and gene therapies, we had to look to the learning and listening aspects, and the challenging of our processes, because there are no standards. And it's too soon to make standards just yet because it's moving at lightspeed.

We had to plough our way through the dark and there were a lot of educational mistakes. A lot of that was trying to put boundaries around this area, which is massive – we just didn't know it at that time. Trying to create process and standardizations within something that is exploding is a very difficult thing to do. We learned the hard way never to assume anything when you're dealing with a new therapy, especially related to cancer. And we learned not to assume that all cell and gene therapies are created equal, or would bring similar challenges or similar results.

OS: I agree. With cell and gene therapy trials, we have built a culture of lessons learned and tried to learn from every error or mistake in order to apply and refine our processes. We do this for every study and we are focused on building solid risk assessment categorization tools, or risk management plans, to ensure that we mitigate the risk related to manufacturing processes changes, limited capacity, logistical issues, and the unexpected volumes of data. We also know that every new study will probably have other risks that we never thought of, so we try to be reactive and build processes in order to mitigate those risk as much as possible.

Q Looking to the future, what do you predict as the key challenges and opportunities for the cell and gene therapy sector within the next 5 to 10 years?

BF: We have already spoken on the challenges of expanding access to these therapies, and this further challenges CROs and sponsors to lead the guidance and support for community centers to manage these safely and accurately. A strong focus will be on streamlining logistics and reducing cost to truly support the opportunity of access.

In oncology, the field still awaits a clear demonstration of clinical efficacy of cell and gene therapies in solid tumors. This challenge is becoming a defining issue in cellular immunology as the new decade begins. Solid tumors make up almost 80% of all cancers, and the key challenge is creating and managing therapies which can manipulate and/or withstand the inhospitable environments of these tumors, known as the tumor microenvironment (TME). In the future we'll see a focus on bringing these therapies to solid tumors in a meaningful and effective way.

Persistence of these therapies, whether they be hematologic, oncologic, or rare diseases, is also a key driver. The primary challenge is understanding and combatting the mechanisms that act against our cells, including these therapeutic cells, and decrease their ability to persist once they're active against their target. This is an area where we've not had a breakthrough yet, and I think that's going to be one of the major focuses moving forward.

DOI: 10.18609/cgti.2020.047

Most importantly, from a broader perspective, our knowledge of disease, the genome, and tissues still far outweighs our ability to respond from a medical technology perspective. We're going to be playing catch-up for quite some time. In the cell and gene therapy world, the emergence and elevation of gene editing technologies is key. We have the ability to modify genes *in vivo*, and the potential here is mindboggling. We also now have the ability to recreate our starting materials from, for example, master induced pluripotent stem cells. This is extremely exciting. As gene therapies and genetically modified cell therapies leverage these emerging gene editing technologies, coupled with ever more optimal material resources, the future of cell and gene therapies is more than just promising – it's tangible.

ML: Brandon has summed it up beautifully: there is going to be expansion. In the same way that we have moved to mark 1 and 2 of immunotherapies, whether it's through antibodies or immune checkpoint inhibitors, I think the potential here is vast. This is not limited to oncology, hematology, or solid tumors. I think we will see a raft of indication spaces for rare diseases, ophthalmology, and even CNS.

There's a huge mountain to climb and we're not even at base camp yet, but we're going to have increasingly accelerated progress. The knowledge base is vast – it's how you tailor the application to address that knowledge base that is the real challenge. In a way, it's a different kind of translational medicine.

TJ: A few years ago, Dr Tim Cripe of the FDA said that cell and gene therapy represented the most exciting new therapeutic breakthrough he had ever seen. I think it truly is, and it's going to continue. When I joined ICON, I really appreciated how we internalize what an honor it is to work on these trials, and the importance of the hope that we are able to bring to patients. I expect to see the space continue to grow and flourish.

BIOS

Brandon Fletcher

Brandon Fletcher is a Biochemist and Cancer Immunologist with over 27 years of research experience; 23 in hematology-oncology and four in infectious disease. She has held roles in broad immune-oncology and cell and gene therapy research within academia and industry. Brandon is a collaborator with NCI's origination of cancer CGTs and co-founded a global immune-oncology research training and support organization.

Tamie Joeckel

Tamie Joeckel started her career with Arthur Andersen & Co (now Accenture) as an ERP manufacturing and distribution systems consultant, and has over 20 years of experience in specialty biologics working in both clinical and commercialization sectors. A former senior executive at one of the largest drug distributors, she specialized in distribution, patient hub services and reimbursement support for newly approved therapies for oncology and rare diseases. For the last 6 years, Tamie has worked with cell and gene therapies as a global logistics and ecosystem expert. At ICON, she supports the Cell and Gene Therapy Solutions Group with ongoing strategy and innovation.

Martin Lachs

With over 28 years' experience in clinical development, Martin has worked across a number of therapeutic areas whilst specializing in oncology. Martin heads up ICON's Oncology and Cell Therapeutics Project Management Group, lending operational and indication expertise across a group of over 260

international project management staff globally, dedicated to oncology and cell therapy drug development. He has worked in developing key oncology site networks in the US and the UK and in 2020 was a member of a clinical trial review panel for University of Sydney affiliated hospitals. Martin has produced a number of position papers in the Pharmaceutical Press as well as hosting / presenting at numerous international events at scientific and pharma industry meetings. Recently the key focus of his publications has been thought leadership related to cell therapies in oncology, e.g., CAR T.

Olivier Saulin

Olivier Saulin has over 18 years of research experience in oncology and rare disease and holds a MS in Bio-chemistry. His expertise includes extensive roles in DM and project management for both sponsors and CROs; including large CAR-T programs in Phase 1 to Phase 3 trials. He has also worked on GMO studies involving gene therapy (AAV vector) and cell therapy products (CAR-t/lentivirus). Olivier is the EU cell and gene therapy expert for ICON supporting CGT teams. He co-developed the adoptive cell therapy training academy for the company and authors the internal cell and gene therapy newsletter.

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The authors declare that they have no conflicts of interest.*

Funding declaration: *The authors received no financial support for the research, authorship and/or publication of this article.*

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited.*

Interview conducted: *Mar 20 2020;*

Publication date: *Apr 21 2020.*

DOI: 10.18609/cgti.2020.047

Transforming Oncology Trials in Cell and Gene Therapy

Cell and Gene Therapy (CGT) trials present unique challenges requiring thoughtful planning and innovation. ICON's extensive experience in executing CGT trials delivers proven solutions in:

- Site support and patient recruitment
- Regulatory strategy for expedited development & filings
- Tissue and blood procurement protocols
- Orchestrating complex logistics requirements
- High volume data management
- Bioanalytical laboratory services
- Commercialisation and outcomes product placement and pricing consultancy

ICONplc.com/CGT