CELL & GENE THERAPY INSIGHTS

NEW HORIZONS IN CELLULAR IMMUNOTHERAPY

SPOTLIGHT

INTERVIEW

Working together to safely advance cell & gene therapies




David McCall, Editor, *Cell and Gene Therapy Insights*, speaks to (from left to right), **John Maher,** Scientific Founder & Chief Scientific Officer, Leucid Bio Ltd, **Francisca Neethling**, Head of Cell & Gene Therapy, Eurofins Discovery, **Alastair J King,** Head of Biology, Eurofins Discovery & **Andrea Bisso**, Associate Director Pharmacology & Pre-Clinical Development, Gadeta B.V.

"Drug development is a costly and time-consuming process associated with a significant attrition rate in the clinic. Safety is an important factor in this, and is a particular issue for cell and gene therapies. This point is illustrated by the fact that around 40% of all clinical holds in 2021 were attributed to this particular class of pharmaceuticals."

– **John Maher**, Scientific Founder & Chief Scientific Officer, Leucid Bio

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Q What do the panel think are the primary safety considerations at the preclinical stage?

FN: Primary considerations for gene therapy are vector safety, target efficiency, and feasibility. Is the target efficiently druggable, with the least amount of concomitant damage?

The same can be said for cell therapy, but using different testing systems, and somewhat different discovery processes and preclinical testing. The key is to make the drug as specific as possible to treat the condition. There is a significant amount of *in vitro* investigation that can be done to ensure that.

The most important consideration for both approaches is whether the treatment would be toxic to the patient, and whether there may be unintended on- or off-target side effects. Unintended cytotoxicity is also a real concern for any drug treatment, and one that is not always predictable *in vivo* in animal studies.

AK: Some of the aspects of biologics drug discovery are already being dealt with in the form of things like immunogenicity. We are all familiar with assays that are traditionally designed to evaluate the potential immunogenicity or activation of the immune system upon administration of a foreign agent to the body. For cell and gene therapies, we need to think of these therapeutic modalities with the same mindset.

We do have simple assays in place for examining the effect of a variety of agents on peripheral blood mononuclear cells, whole blood, cell samples, etc. But, in the case of cell therapies, they can elicit their own effects and, in some cases, immune responses, especially when they are of T cell origin. Do we need more complex predictive *in vitro* models to accommodate the evaluation of these kinds of off-target activities?

Genotoxicity is another thing that could potentially be a concern on the gene therapy side. We have standard assays to look at genotoxicity in anti-cancer agents, but these may not be enough in the context of cell and gene therapies. This raises the question of looking at key tissues that could potentially be liabilities. We want to be able to target therapies to get to the tissues where they are designed to act, but do we need to put in place assays and platforms that can evaluate off-target activities within the context of those specific tissues? This may also be dependent on where the target is expressed.

JM: My own particular area is chimeric antigen receptor-T (CAR-T) cell immunotherapy, particularly focusing on solid tumors. In that setting, the three major toxicities we have concerns about are cytokine release syndrome, various forms of neurotoxicity, and on-target off-tumor toxicity.

At the early stage of development of a new CAR-T, it can be helpful to consider establishing a target product profile for that particular drug, thinking particularly about where you wish to position it in the clinic. It may raise issues such as regional delivery being a more appropriate route to get these cells to the site of disease, which may have an impact on the safety of that drug.

In the context of preclinical modeling in animal models, often a CAR-T that you have designed will not recognize the ortholog of the human target in the animal model you are using.

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You must think carefully about how to get around that problem, sometimes with the use of homologous modeling systems.

AB: We are all aligned with the importance of understanding the safety profile of the cell-based therapies that we are developing, particularly the importance of on-target or off-target effects.

We have not yet defined the minimal level of characterization–in terms of safety–that we should provide for a candidate product. We are still looking for a consensus between the leaders in the field, including scientists from industry, biotech, and academia, in addition to regulators. We have some general guidelines, but there are no established or unique assays that should be included in this characterization.

There is a boom of additional systems to consider, following great improvements in *in vitro* tissue engineering, including 2D versus 3D models, organoids, and organ(s)-on-a-chip. All these should provide new models that we can evaluate for their capability to predict product safety. We should also define the minimum dataset required to prove safety.

In March, the US food and drug administration (FDA) provided two updated guidelines for industry, for the development of human cell and gene therapies, in particular (for) CAR-T. These documents included some of the aspects that we need to address, such as the characterization of antigen recognition and the domain of the target antigen of cellular components. They also deliver a degree of flexibility in that they encourage continuous communication between sponsors and authorities. It is difficult to define the details required and the models that should be used to assess the safety, because cell-based products have unique biology.

JM: Some predictive assays for small molecule adverse impacts, such as the BioMAP® Toxicity Signature Analysis, drew from published literature and clinical findings. One of the critical safety issues for gene therapy is the occurrence of unpredicted death of subjects treated with these advanced therapies. We cannot wait for that body of literature to accrue on this matter. How do we create more predictive approaches for these types of biologic agents?

AK: The BioMAP Platform is a translationally relevant and predictable *in vitro* model platform. We have demonstrated the ability to use this platform in a highly predictive manner both for small molecules and more traditional biologic agents such as antibodies. These kinds of *in vitro* models can be set up in a way that is clinically relevant. The key here is to be able to learn from some of the existing data we have around clinical evaluations for cell and gene therapies, and build that into models that are more relevant to those particular therapeutics.

Many of the models contained within the BioMAP Platform are more related to specific tissue biology and biological effects. In some ways, that platform is agnostic of the therapeutic modality, because it focuses on the effect on the surrounding tissues in a clinical situation. Capitalizing on this kind of approach is the way to take this forward.

However, a key aspect would be to establish systems with 'the right biology'. This means modeling the kinds of biology where we see potential liabilities with cell and gene therapies, and modeling biologies that are relevant to the target tissue types for those therapies.

The platform and the approach have already been proven with other therapeutic modalities. We now need to pay attention to aspects that are more unique to cell and gene therapies, and couple that with the existing and growing body of data we have from clinical evaluations to put in place similar models for the cell and gene therapy field.

> "The BioMAP® Platform is a translationally relevant and predictable *in vitro* model platform. We have demonstrated the ability to use this platform in a highly predictive manner both for small molecules and more traditional biologic agents such as antibodies."
> - Alastair King

FN: There is a lot we can do *in vitro* for gene therapy. We can simulate the clinical setting and assess the effect of the therapy in these *in vitro* models, whether by functional assays or methods such as western blot, enzyme-linked immunosorbent assay (ELISA), or quantitative polymerase chain reaction (qPCR) to determine the amount of expression in cells.

The choice of viral vector depends on many factors, including the disease being targeted, the amount and type of genetic material to be delivered, and the location and characteristics of the cells being targeted. Viral vectors have been around for quite some time, so there is a significant amount of literature available, with more being published regularly. We cannot wait for new literature, but we can use the basis of this published literature to build on for safety and efficacy studies in gene therapy.

Humanized mouse models or xenografted models can be used for greater accuracy in assessing the efficacy of viral vectors in humans, but they do not always translate into the human setting. With 3D cultures of different tissues or organoids becoming more common, and the field growing fast, *in vitro* data is (*sic*) becoming more relevant.

AB: I would like to stress the importance of a better understanding of the physiology and behavior of an organ or tissue, both in normal conditions and in the alteration of disease. This will be key to directly recapitulating the complexity of an organ or tissue in an *in vitro* system that considers the microenvironment in a certain setting. This is the first step to predicting the safety of a candidate product. By learning from these data, we can then go back and redesign and optimize the product to reduce any possible toxicity, in a way that can increase patient safety.

JM: In the context of CAR-T, preclinically, one of our CARs exhibited unpredictable, on-target, off-tumor toxicity. We found that reconfiguring the CAR so it was co-expressed with a chemokine receptor, which preferentially trafficked the CAR-T cells into the tumor, not only boosted efficacy, but also enhanced the safety profile because there were fewer of these cells in organs where they could cause toxicity.

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AK: The key here is thinking outside the box. We have many standard safety pharmacology assays which traditionally have been used for things like small molecule drug discovery, and these outline toxicities we know and understand well.

As we move towards more complex aspects of cell and gene therapies, there is the potential for the occurrence of toxicities that we cannot currently predict. We need to be open-minded about that, and take new data to constantly refine our approach. This might provide a second-generation of safety pharmacology approaches, looking at the cellular level rather than the biochemical level.

JM: Animal models have had a somewhat inconsistent profile of success in predicting clinical toxicities of cell and gene therapies. What have been your experiences here? How do you think that non-animal alternatives could be employed for safety testing and how may these evolve over the next decade?

Q Considering the recent FDA Modernization Act, what do you think will be the greatest challenges to implementing non-animal alternatives in preclinical testing?

AB: We are faced with growing scientific knowledge and terrific technological development, with more and more sophisticated *in vitro* non-animal models that will be helpful in predicting the safety and efficacy of our cell and gene therapies.

From the perspective of cell-based therapy for tumors, we are also experiencing increased use of more complex *in vitro* models and assays to assess safety and efficacy. For example, culture organoids and spheroids can recapitulate the specific microenvironment of a tumor to allow the *in vitro* investigation of the efficacy of a cell-based therapy. We also use a lot of primary tissues or organoids to assess the safety and toxicity of products and even more complex pharmacology/toxicology models with a mix of normal healthy cells, which can then be cultured together with primary tumor cells: the effect of a product can then be simultaneously measured on both components, to better recapitulate the real situation of a patient.

These *in vitro* assays will gain more space in the next five to ten years, although we are still bound to the use of animal models for specific questions. We are indeed limited in the type of answers we can gain from *in vitro* models and, while there are huge limitations in animal models–such as the lack of human cytokines that support cell survival, homing, and expansion, and the lack of cross-selectivity for mouse targets–they have a value, though. For instance, the trafficking of a cellular product into an organ or tissue can only be studied using these models.

I envision that the development and application of more advanced techniques, such as omics and single-cell technologies, coupled with *in vitro*, multi-cellular cultures, may allow us to closely capitulate the physiology of a tissue and its microenvironment, and will probably represent the future to minimize testing in animal models.

AK: Especially as we aim to move away from animal models, we are reducing, refining, and improving the models that we do have. The Eurofins BioMAP® Platform is

an excellent way of illustrating how we can do this *in vitro* in a highly translational, relevant, and predictable manner. The key here is understanding what is happening in the complexity of an animal system.

Sometimes there are events that occur within the context of a disease that are not immediately obvious prior to using that therapeutic within the context of an *in vivo* model. Building that back into those *in vitro* models will give us a more accurate model of the biology, in a constant process of refinement. We often talk about initiatives to reduce and refine animal models; we should do the same thing for *in vitro* models, and use the data that we can generate from *in vivo* models to help boost their predictability.

We are at an exciting point in the development of models to support drug discovery, from the perspective of having a vast number of omics capabilities available, including proteomic modeling, metabolomics, and transcriptomics. We have a wealth of data that can potentially be generated. This, coupled with the fact that we are now more able to evaluate larger datasets, puts us in the unique position of being able to look at the complexity of these biological systems in response to cell and gene therapies. This will allow us to generate more safety or toxicology fingerprints. For any therapeutic, even for the same target, there may be different safety profiles generated.

Beyond that, machine learning and artificial intelligence can assist in evaluating the large datasets generated from *in vitro* models, and we could then move towards more in silico approaches in terms of safety and toxicity issues. We would still need to evaluate whether those safety and toxicity effects do occur, but I think this can capitalize on some of the technologies that we currently have at our fingertips.

FN: There is relatively little guidance from authorities for cell and gene therapy, considering that it has been around for quite some time now. We can help build the body of data to allow clients to have conversations with the authorities that can help to shape guidance in the future. Eurofins and other contract research organizations (CROs) have done so in the past for other therapeutic modalities, so there is no reason we cannot do that for cell and gene therapy.

We already have various capabilities up and running routinely, and we can deliver the type of data that clients will need to present to the authorities at a pre-Investigational New Drug (IND) application conversation, for instance, regarding reduced need for animal testing.

JM: From my own experience in the CAR-T space in the UK, the feedback I have received from regulators is that they want to see data surrounding the safety and efficacy of therapeutic drug products. For human CAR-T cells, the only way that can be done *in vivo* under existing guidelines is by using animal models. I am heartened by the recent moves the FDA and others have made to begin to broaden this, so that animal models are no longer a compulsory component of preclinical testing. We have a wealth of *in vitro* models to choose from, from organotypic cultures, induced pluripotent stem cell-derived differentiated cell types, and elegant organ-on-a-chip cultures. For example, a pulmonary organ-on-a-chip can have lung epithelial cells in an air channel, separated from endothelial cells in a blood channel using a semi-porous membrane. This gives all the components in the system

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to infuse CAR-T cells in through the blood channel and examine if they can be incited to traffic into the epithelial layer, and what kind of damage they could do. I can see great potential for some of these *in vitro* model systems in satisfying some of these questions in the not-too-distant future.

> "From my own experience in the CAR-T space in the UK, the feedback I have received from regulators is that they want to see data surrounding the safety and efficacy of therapeutic drug products" - John Maher

Q We are all agreed that the need for innovation is enormous in this space. How does the panel envisage that existing platforms could be modified, thinking not only about the technologies themselves, but also target-related issues?

AK: We need to further explore some of the learning that we have from clinical failures. From looking at previous clinical evaluations, failure comes from three sources. First is a lack of efficacy, which often is related to the target or the validation of that target. There is also the occurrence of off-target toxicity, which may not necessarily have been seen or predicted from existing assays that are put in place. Finally, there is target-related toxicity.

Off-target toxicities is where we need more complex, predictive platforms to help address whether there would be expected off-target activities. Because they are off-target, there is going to be some degree of not necessarily knowing what is going to happen–the effects are agnostic by nature. This is where having models in place becomes even more important. They can generate data that can be predictive in terms of how these toxicities may manifest themselves.

Traditionally, we have tended to look down certain avenues, such as conventional cytotoxicity of cell types and electrophysiology relating to hERG and targets. The existence of more complex platforms, such as omics, provides a way to be able to address the off-target toxicities that are not traditionally seen with some of the existing models. This will go a long way towards addressing those issues earlier in drug discovery, to mitigate the risks when declaring a candidate and going forward into clinical trials. The technological advances will undoubtedly enhance our ability in the off-target toxicities area.

Target-related toxicity advances will more than likely need to come from other avenues, such as in partnerships with academic research–for example, looking at how modulation of a given target can manifest not only in disease tissues or in target tissues, but in other tissues. Academic research where one is potentially looking at a whole range of different tissues and systems can provide tremendous value in terms of helping validate the target from the perspective of safety.

FN: As a CRO, we are well suited to being able to work with clients to adapt what already exists. We can optimize, customize, and innovate, to help clients meet their

goals. Some of that innovation can also lead to building guidance and aiding regulators in the industry. While addressing safety, we can work with clients to optimize their methods to build a more efficient process. Several of the gene therapy programs have had problems with producing enough viral material to be able to characterize it appropriately. There is room for improvement, and we can help with that by optimizing methods and expanding processes. All of this is done by monitoring new innovations and considering implementation, so that when a client comes to us with a request, we can do the innovation for them.

AB: The great technological development of these omics techniques, from transcriptomics to metabolomics, will allow us to gain unprecedented molecular characterization and understanding of the behavior of cell products, and a better understanding of the on-target and off-target unwanted effects. The combination of omics with single-cell technologies would allow us to make a further step. We will hopefully be able to investigate for instance the potential heterogeneity within our cellular products, and whether this is a potential issue in terms of safety or lack of efficacy.

All this would lead to maximizing the safety and efficacy of these products. For example, the identification of a specific sub-population of product cells that can cause unwanted toxicity can allow us to adopt strategies to reduce the impact of this population within the product. This could be achieved by tweaking the conditions of manufacturing to exclude this population or expanding a different, more effective population.

JM: This highlights one of the issues we have in many forms of cell therapy, which is the lack of standardization of these products.

When it comes to CAR-T, I struggle to keep up with all the innovation going on. There is so much activity in this space. An example of this is that we are seeing the advent of many forms of controllable CARs, such as CARs whose expression is dependent upon the presence of a second pharmaceutical, or CARs that are only expressed under conditions of hypoxia, so they are preferentially switched on in the hypoxic tumor microenvironment.

There is a tremendous amount of innovation around the development of so-called gated CARs, which are not just recognizing a single target but are instead recognizing a signature associated with the tumor microenvironment. There are many variations, including dual-sensing CAR systems and SynNotch systems. We are also seeing the advent of CARs which are being used as drug delivery devices in their own right. They can be armored either to produce cytokines with the capacity to modulate the tumor microenvironment, or to produce oncolytic viruses, for example.

Another area of enormous innovation is the refinement of the signaling properties of CARs. For example, calibrating the activation signal by mutating Immunoreceptor Tyrosine Activation Motif (ITAM) units in the activation module, and potentiating co-stimulation by the placement of co-stimulatory units in their natural location close to the plasma membrane. This is just the tip of the iceberg in terms of tweaking the CAR itself.

CARs need a cell within which to work, and modification of the cell host–for example, by selecting different subsets of long-lived T cells *in vivo*–to give the greatest therapeutic impact. The cells could also undergo manufacturing in the presence of chemicals, which can

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retard the differentiation of the cells, thereby ensuring they have a greater capacity to proliferate and persist in the patient.

We are seeing the advent of a huge toolbox of genome editing technologies, which also further the potential for innovation in this space. For example, the advent of base editing allows us to modify gene expression without the introduction of double-stranded DNA breaks, thereby potentially reducing the genotoxicity of the approach.

A final area of innovation that I am excited about is in manufacturing. For anyone in the cell therapy field, manufacturing is the core business. The advent of automated platforms to reduce the human factor in manufacturing has shortened the duration of the manufacturing process, and reduced the cost of goods, to achieve a fitter, less differentiated cell product. We are now seeing some manufacturing processes that are shorter than 24 hours, as well as *in vivo* delivery of vectors to transduce T cells in the patient rather than manufacturing *ex vivo*.

Q How do the panel members go about choosing an outsourcing partner, and what is the primary role of the CRO?

AB: I can speak from the perspective of a small biotech, but this may hold true for bigger organizations. Our main reason to go for an outsourcing partner is to get access to complex assays and services that do not make sense for us to set up in-house, due to a lack of resources, narrow capabilities, or access to material.

In other words, we look for a balance between costs and having access to high-quality, complex, translational assays, coupled with proper advanced bioinformatic analysis when needed. We also value the possibility to customize assays based on the goal or experimental needs of a specific study. For example, assays like the BioMAP® Platform, or high-throughput assays based on the use of advanced imaging or the use of primary material from patients, require a lot of setup, know-how, and access to patient material.

For a small biotech, having the possibility to perform these assays in collaboration with a CRO will allow to test what we need, whether that is a higher number of variables, multiple replicates, or a greater number of patients or donors. This will lead to the acquisition of valuable data to allow risk reduction for the company.

The final consideration is the importance of the timing of the experiments. We need to get the results as soon as possible, and as early as possible in the development of a product. This is another important parameter when selecting a CRO. The possibility of fast and agile communication and fast execution of the experiment are relevant parameters that we consider when we decide on a partner.

FN: As a CRO, we work in a highly consultative way with the client throughout the execution of a project. We need a clear understanding of what the needs are and then together with a client, we decide what the approach is going to be. We can either customize what we already have within our versatile catalog of capabilities, or we can develop new approaches and assays, if required. We communicate regularly and keep the client up to date on progress.

As Andrea said, quality, cost, and speed are of the utmost importance to our clients, and we are aware of that. While we do not focus on the cost of a project, we do try to increase efficiency both in terms of cost and time, so that we can deliver the right data to our clients to allow them to move their projects forward in an efficient manner. Reduction of risk in the execution of the project is also a key consideration, with a focus on risk reduction in the clinical setting.

> "As a CRO, we are well suited to being able to work with clients to adapt what already exists. We can optimize, customize, and innovate, to help clients meet their goals. Some of that innovation can also lead to building guidance and aiding regulators in the industry"
> - Francisca Neethling

AK: Thinking about the role of a CRO from a more global, overarching perspective, one of the fundamentals is to listen to our client's needs. From a strategic perspective, we are in the position of seeing trends in the industry in terms of safety and toxicology aspects. Understanding where the same kinds of toxicities or safety issues are coming up time and again becomes the need in the field. We not only listen to our individual clients on a project-by-project basis but listen to the industry and see where those needs are changing. As we develop newer therapeutic modalities, cell and gene therapy being a perfect example, we are uncovering new needs in the field, in a whole variety of different aspects of drug discovery.

The other aspect is listening to the regulatory authorities as we gain greater understanding of how cell and gene therapies work. We want to understand where some of the key issues that need to be resolved are. As with any therapeutic, regulatory agencies will eventually formulate their own framework for what they would like to see as part of the vetting of an agent before declaring a candidate or approving it for clinical trials.

From a CRO's perspective, listening to the client, the industry, and the regulatory requirements are some of the key aspects of being able to provide services that are relevant and appropriate for the needs of the industry.

One of the powers of CROs comes from having not only a wide range of technologies but platforms available. We are in the privileged position of seeing things from a 10000-foot viewpoint. We can see a broader picture of safety and toxicity issues that are becoming more recurrent. Every study that we conduct with each one of our clients is under the strictest confidentiality, but there are trends that one sees from the perspective of safety and toxicity that are of a non-proprietary nature. We have seen this before with some of the safety pharmacology consortia that have been set up, that have provided tremendous value in outlining practices and assays that are needed, in particular for small molecule drug discovery. Being able to bring sophisticated bioinformatics and analytical approaches to the table can then provide additional value and impact to the kinds of services we provide in addressing the potential liabilities of a particular agent with respect to safety, pharmacology, and toxicities.

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Q JM: What is the view of the panel on virtual companies? Can they succeed in this space as well as they might do for small molecules, for example? Do virtual companies have special needs regarding assay and safety considerations?

FN: As a CRO that can offer a full range of services, we see that the needs of the virtual company and small biotech are essentially the same. There could be different levels of input from either. Some small biotechs might have assays or materials they want to transfer to us, while a virtual company might have intellectual input based on previous experience that their team has had. They may have a larger need for assays to be built or established, and we can certainly do that for them.

We can customize assays that we already have up and running to meet client needs. We are all in this together and we can work together to accommodate the needs of both virtual companies and other partners that might need our services. We are their lab, so they do not need to establish or expand one of their own.

AK: We are not working in pursuit of new therapeutics in isolation. A key way to view the CRO dynamic, which pertains to virtual companies, is that we are effectively part of the client's drug discovery team. The question of what differences there might be between the needs of virtual companies versus more traditional drug discovery companies with internal assets and lab space is an interesting one.

When one considers the needs of drug discovery, they are generally very similar, only differing in terms of the therapeutic modality being developed. Cell and gene therapies do however have different things that need to be explored compared with more traditional biologics.

As the drug discovery paradigm is the same within a certain area – for example, in the development of a specific cell therapy – it remains the same whether one is functioning with a virtual company, a small biotech, an academic institution, or even big pharma. As a result, the same needs exist within that program regardless of where it is situated. Although the challenges are the same, the real difference between a virtual company and other companies is simply the existence of labs.

Being able to contribute both intellectually from an advisory perspective and leveraging the experience that we have is important. People within the CRO world are experts in the context of the assays and services that they provide. Many also have pharma industry experience, myself included. That helps to get rid of some barriers in some of those areas where there might be less opportunity for cross-pollination between the companies.

Q JM: How can we all work together to safely advance cell and gene therapies? What are your closing thoughts on this?

FN: CROs work with clients not only to assess and ensure safety for cell and gene therapies but to optimize their processes with the goal of a faster and safer

path to the clinic. The CRO industry is there to work with any client that needs us to execute complex assays that they do not routinely run in-house, freeing up their scientists to do other aspects of research and development, or allowing them access to technology that they may not have available. We can work collaboratively to get their therapeutics to patients as quickly and as safely as possible.

"Working together as academia, CROs, and industry with the final goal of creating novel products and better characterizing the features and safety profile will be the key to success. "
- Andrea Bisso

AB: Working together as academia, CROs, and industry with the final goal of creating novel products and better characterizing the features and safety profile will be the key to success. We should never forget that we started from biology and pathology. A better understanding of the context in which a cell should work will allow us to develop better models and knowledge around the product itself, allowing movement toward better safety and efficacy *in vivo*.

AK: I am looking forward to seeing how some of these aspects play out with the continuing success of the cell and gene therapy field. It all starts with the biology, and there are processes that need to be followed as part of drug discovery that can differ from one therapeutic modality to another.

Everybody has something to bring to the table with respect to drug discovery, whether they are present in a pharma company, an academic organization, a CRO, or a biotech. The fundamental nature of any drug discovery team is that everybody has different areas of expertise, whether it's located within one organization or matrixed across multiple organizations.

The shared goal of everyone working in the field is to see the successes and ultimately, to get therapeutics to patients who are in need. We truly are all in it together, and I am looking forward to seeing how we can develop newer, more efficacious, and safer medicines in this interesting therapeutic field.

BIOGRAPHIES

JOHN MAHER, MD & PhD is the Scientific Founder and Chief Scientific Officer of Leucid Bio. He is also a clinical immunologist who leads the "CAR Mechanics" research group within King's College London. Dr Maher played a key role in the early development of second generation (CD28) CAR technology while a visiting fellow at Memorial Sloan Kettering Cancer Center, an approach that has achieved clinical impact in haematological malignancies. His research group is focused on the development of adoptive immunotherapy using CAR engineered and gamma delta T-cells, with a primary emphasis on solid tumour types. In addition, he is a consultant immunologist at Eastbourne Hospital.

FRANCISCA NEETHLING, PhD is the Head of Biotherapeutics Discovery at Eurofins Discovery. She brings over 20 years of academic, start-up and pharmaceutical Industry experience to support portfolio and program strategy for large molecule drug discovery. Dr Neethling holds a BSc

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in Microbiology and Genetics and a MSc and PhD in Transplantation Immunology. She was a Postdoctoral Fellow at the Transplantation Biology Research Center at Harvard Medical School and at Oklahoma State University. Prior to joining Eurofins Discovery in 2021, Dr Neethling spent almost 10 years as a Sr. Principal Scientist in the antibody discovery group at Boehringer Ingelheim, developing novel biologics across a broad range of therapeutic areas.

ALASTAIR KING, PhD is the Head of Biology at Eurofins Panlabs, Inc., a part of Eurofins Discovery. He has over 20 years of scientific research experience, with a specific focus on drug discovery in the oncology and inflammation therapeutic areas, and use of cellular assays to profile and advance drug leads. Dr King holds a BSc (honors) and a PhD in Biochemistry, and completed his postdoctoral training in the field of mitogen signaling at the Indiana University School of Medicine/Walther Oncology Center in Indianapolis. Dr King has deep experience in all stages of drug discovery, gained from previous positions he has held at SmithKline Beecham, GlaxoSmithKline, and Johnson & Johnson, where he has led drug discovery programs, international teams, and strategic initiatives in the pursuit of both small molecule and biologic therapeutic agents.

ANDREA BISSO, PhD is Associate Director at Gadeta BV. There he oversees the investigation of the efficacy, safety and mechanism of action of the new proprietary candidate cellular products, by leading the Preclinical Pharmacology team and managing the collaborations with external partners and CROs. He joined Gadeta at the end of 2020, after a nearly 15 years career in academia, during which he gained extensive experience in the cellular and molecular mechanisms at the basis of cancer. Working as Scientist at the European Institute of Oncology (Milan, Italy), he contributed to the understanding of the role of the MYC, WNT and Hippo pathways in tumorigenesis, by performing functional genetic screenings and by developing new preclinical mouse models of B-cell lymphomas and liver tumors. Dr Bisso received his PhD in Molecular Medicine from the University of Trieste (Italy), focusing on the role of microRNAs regulating the activity of the p53 pathway and on novel potential therapeutic approaches to block the oncogenic functions of p53 tumor-associated mutants. He holds a patent covering the application of peptides and aptamers as specific modulators of mutant p53.

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AUTHORSHIP & CONFLICT OF INTEREST

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*ADCP=antibody-dependent cellular phagocytosis, ADCC= antibody-dependent cellular cytotoxicity, CDC= complement-dependent cytotoxicity