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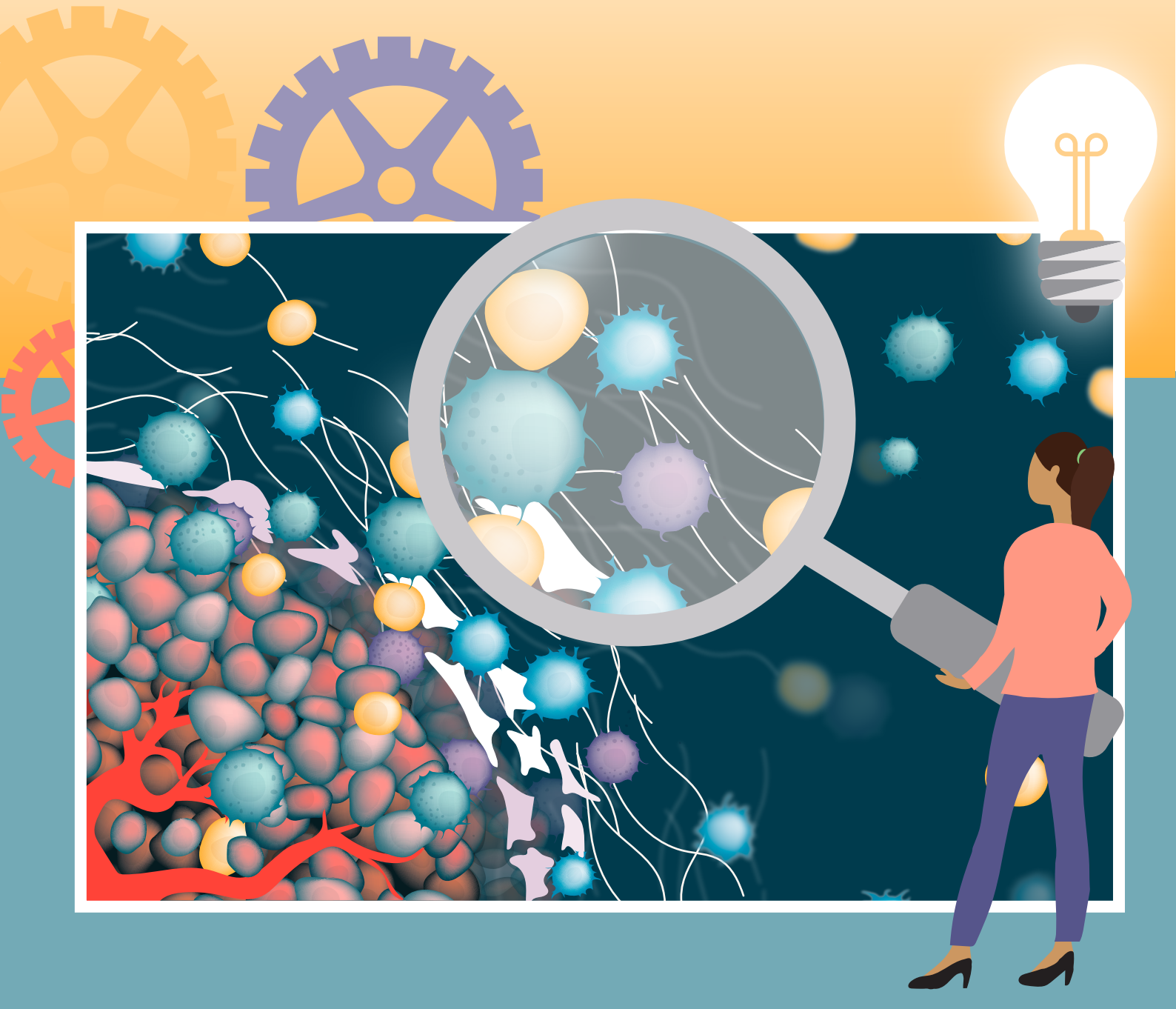
IMMUNO-ONCOLOGY INSIGHTS

SPOTLIGHT ON

Overcoming mechanisms of tumor resistance part 1: breaking into the TME



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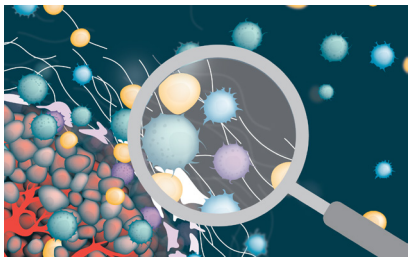

Overcoming mechanisms of tumor resistance part 1: breaking into the TME

SPOTLIGHT

INTERVIEW

Developing better CARs for solid tumors

CAR-T cell immunotherapy has proven to be highly effective in the treatment of blood cancers. But how can that success be recreated in solid tumors? **Roisin McGuigan,** Editor, *Immuno–Oncology Insights*, speaks with **John Maher,** Scientific Founder and Chief Scientific Officer, Leucid Bio, about his work in developing innovative therapies for solid tumor applications, including the lateral CAR platform, which adopts a more natural configuration of CAR molecules.

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Q Can you tell me a bit about the work you do, and what led to the founding of Leucid Bio?

JM: I am mainly focused on developing new chimeric antigen receptor (CAR)-T solutions, primarily for difficult-to-treat solid tumors. This is something that I have been doing for about 25 years. Along the way, the generation of new intellectual property around CAR-T solutions for solid tumors led to the birth of Leucid Bio.

One of the most important starting points for a new company is to have a new technology over which you have exclusive rights from an intellectual property point of view. We have developed what we refer to collectively as lateral CAR technologies. The idea here is very

simple. Instead of building up as people have been doing previously in the construction of newer CARs, we are building out.

This allows you to have a more natural configuration of the signaling components of these molecules. In turn, this allows you to achieve a more natural activating signal in the immune cells that you are trying to direct against the cancer. We also develop new ancillary technologies, which support the CAR to do its job in certain circumstances. Those are the main activities that are going on at Leucid right across the spectrum, from basic research and development (R&D) right through to the design and implementation of clinical trials.

Q Can you expand on what differentiates Leucid's approach to treating solid tumors from others in the space?

JM: The general approach of the competition has been to attempt to use existing CAR platforms by armoring those CAR-T cells—for example, to make additional cytokines or other immunostimulatory molecules. By that means, they hope to bridge the gap into solid tumors.

We, on the other hand, feel that it is very important to think about the CAR itself. We have aimed to build different types of CARs, which deliver a more natural and balanced signal to the cells. You want these cells to work hard—but not too hard. If they work too hard they become exhausted and are useless. However, if they do not work hard enough, they are not going to be effective. It is about trying to strike that balance between these two extremes in terms of the right design of CAR, in order to achieve sustained performance without over-activating and exhausting the cells.

Q Can you provide an overview of Leucid's pipeline for solid tumor indications?

JM: At the moment, the pipeline is very much based around the two core CAR technologies which collectively we refer to as lateral CARs. The first is something we call a parallel CAR, in which we have two chimeric molecules expressed side by side. The second we call an adapter CAR. In the adapter CAR you have two or more components which associate with each other in the plane of the plasma membrane, which is reminiscent of the structure of many natural immune receptors. Traditional CARs are single polypeptides in which you build different modules, one on top of the other. The adapter CAR means that you have at least two separate polypeptides.

First on the list in the pipeline is an asset that we refer to as LEU011. This is an adapter CAR targeted against eight different targets—the NKG2D ligands. These molecules are upregulated on stressed cells. Cancer is full of stressed cells, not just in terms of the malignant cells but also the stromal cells that are in the hostile environment of the tumor. We are trying to target that stress using the LEU011 CAR.

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"Traditional CARs are single polypeptides in which you build different modules, one on top of the other. The adapter CAR means that you have at least two separate polypeptides."

LEU011 also has a second molecule, which is a homing receptor. This molecule is designed to sense small molecules released by tumors. It acts as a kind of a 'travel guide' for these cells, directing them to enter the tumor rather than to sit, for example, in vital organs such as the liver and the spleen where they otherwise might go. It is a combination therapy: in other words, LEU011 consists of the adapter CAR and the homing receptor which are all co-expressed in the same T cell using a single vector.

The first trial has a basket-type design, meaning that we would recruit patients with any type of solid tumor in which the targets—i.e., NKG2D ligands—are expressed in the tumor. We plan to follow that up with an expansion cohort, which is effectively a second trial in which we go after a single indication. At the moment, that single indication is colorectal cancer, a disease in which NKG2D ligands are widely expressed.

Although we are primarily focused on solid tumors, we also have a hematological trial in our pipeline, using the parallel CAR technology. This one is directed against CD19, which is the best-validated target for CAR-Ts. We view this as a good opportunity to test our platform in a setting where there is a lot of clinical experience with the target. It should give us a good feel as to what we have in terms of the parallel CAR technology.

We are also working on a number of targets which are not disclosed as yet. In fact, in some cases, the reason they are not disclosed is that we are still trying to figure out what they should be. We are weighing the pros and cons of different targets, particularly in the context of the parallel CAR technology.

Another element we have in our pipeline is an off-the-shelf clinical trial. This is currently based upon the use of a T cell subset known as γδ T cells. Most T cells in the peripheral blood are conventional αβ T cells. However, this subpopulation of γδ T cells have many unique attributes, such as the fact that they do not cause graft-versus-host disease (GvHD). They also have a number of other attractive properties, particularly the fact that they have intrinsic antitumor activity, and they are a very nice cellular chassis to introduce CARs into. We will be testing lateral CARs of various configurations in these γδ cells with a view to having a trial which would involve an off-the-shelf or a healthy donor-derived cell therapy product to be tested in patients.

The first big milestone for us will be to actually initiate the first of those trials; the LEU011-01 basket clinical trial. Our target for starting this trial is August of this year. The clinical trial application has been submitted to the regulators, and we are hoping—with a fair wind—to get into the clinic with this product in late summer.

Q Outside of your own work, what innovations do you see in the space when it comes to immunotherapy approaches to solid cancer?

JM: Immunotherapy is transforming the landscape of cancer management and has been since the dawn of the new millennium. There are a lot of very interesting developments going on. Bispecific antibody drugs are being developed at quite a pace, and some of them have achieved really impressive clinical data in recent years. Another good example is a HER2-directed antibody-drug conjugate called Enhertu. It has essentially made HER2-low cancer a treatable disease with a HER2-targeted therapy. The data in HER2 expressing but not amplified breast cancer is very impressive indeed.

There are a whole range of bispecific antibodies out there which can essentially recruit T cells, natural killer (NK) cells, or invariant natural killer T (NKT) cells to the tumor and harness those cells in the patient to direct immune attack against the tumor. Immune checkpoint blockade drove all the initial excitement around immunotherapy, and was initially focused around CTLA-4 and PD-1. Now, as people are identifying ever more immune checkpoints, this focus is broadening, and there is quite a list of them now. The smart money will be on which of these is going to emerge to be key immune checkpoints in specific solid tumors. Across the spectrum of immunotherapy, we are looking at very exciting times for the field and the development of better treatments for patients.

Q What are your hopes—and fears—for this area in the next few years?

JM: I have a few interrelated fears. These are extremely expensive therapies, so there is the question of who is going to pay for them when they are developed. They are also complex to manufacture, particularly in the autologous setting, and the off-the-shelf products currently do not seem to work as well as the autologous ones. The delivery of these therapies is also a concern. They are very complicated to administer to patients, so GPs or local hospitals are not going to be delivering these drugs to patients in the near future! Instead, they are going to be delivered in tertiary referral centers where there is an active stem cell transplantation program. These patients can get very sick, and can block up intensive therapy units. The whole delivery issue, especially when somebody does develop a CAR-T or cell therapy that is effective for a common solid tumor, is going to be a real challenge.

However, I am a very strong believer in cell therapy for cancer. What we have learned about CAR-T is that it is a highly effective therapy for blood cancers. We know that, in general, blood cancers are probably easier to treat than the more common solid tumors. Therefore, the technology needs to be adapted in order to make the leap into solid tumor immunotherapy. I am optimistic that that leap will be made by CAR-T. Some of the data emerging with TCR-engineered T cells are also very encouraging, and I think that we are going to see progress there as well.

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BIOGRAPHY

JOHN MAHER is a clinically active consultant immunologist at Eastbourne Hospital and King's Health Partners. While a visiting fellow in the laboratory of Michel Sadelain, Dr Maher was the first to engineer and test second generation CAR-T technology in human T cells, building on the pioneering work of Helene Finney in the Jurkat model system. He established CAR-T cell research at King's College London in 2004 where he leads the 'CAR Mechanics' group, which is focused on the development of adoptive immunotherapy using CAR engineered and gamma delta T cells. He is chief investigator of a Phase 1 clinical trial in which a pan-ErbB targeted CAR-T that he developed is being evaluated in patients with refractory locally advanced/ recurrent head and neck cancer.

AFFILIATION

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AUTHORSHIP & CONFLICT OF INTEREST

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OVERCOMING MECHANISMS OF TUMOR RESISTANCE PART 2. WHAT PROGRESS IS BEING MADE IN SOLID TUMORS?

SPOTLIGHT

INTERVIEW

Evolution by innovation: improving TCR-Ts for solid tumors

How can TCR-based therapeutics learn from the field's experiences with CAR-T, and better tackle the complex challenges posed by solid tumors? **Roisin McGuigan,** Editor, *Immuno–Oncology Insights*, speaks to **Dolores Schendel,** Chief Scientific Officer, Medigene, about current and future applications of TCR therapies in solid cancers.

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Q Can you tell me about your current role and the work that you do?

DS: I'm the Chief Scientific Officer of Medigene. We are an immunotherapy company that has developed an end-to-end platform for T-cell receptor-engineered T cells (TCR-Ts), and we are developing differentiated, best-in-class therapies for patients with solid tumors. Embedded in our platform is an approach that we call evolution by innovation, in that we aim to use science-driven knowledge to sequentially improve every module that you need for TCR-T therapy development, from the very beginning of antigen identification through to

clinical trials. We use analytical tools to understand the impact that we're having at each step of TCR-T therapy development and work to bring those improvements into clinical studies as fast as we can.

Q How would you sum up the current state of play for TCR-based therapeutics?

DS: There is a perception that TCRs are at a disadvantage compared to CARs because you need an HLA match between the T-cell receptor and the target on the patient's tumors. However, I actually see this as an opportunity. It opens up a much broader world of target antigens, from overexpressed molecules inside the cell to specific mutations. The HLA restriction does constrain the patients that you can treat with any individual TCR-T therapy, but you can make T-cell receptors that are restricted by different HLAs in order to expand the population of patients that can be treated.

The ability to capture this broader world of antigen diversity and specificity is a real advantage. You can get highly specific differential recognition of tumors versus healthy tissues, giving you a much higher level of safety in developing a drug product. In comparison, with CD19-targeted CAR-Ts you take out natural B cells as well. There is no differential recognition for that drug product between tumor cells and healthy cells, which you need when you address solid tumors, because now you're dealing with healthy cell types from which the tumor is derived that you cannot eliminate because they are not replenished by the body. You can't destroy normal cells of the liver, kidney, or brain, and those are the kinds of tumors that come into play for solid cancers.

Q How can TCR-based approaches benefit from the successes—or the mistakes—of CAR-T therapies?

DS: The tremendous success and clinical impact of CAR-Ts has spurred all kinds of accompanying industries around manufacturing and supply. This means that reagents, assay systems, and instruments needed to develop drug products have become more readily available, making it much easier for players in the field coming in a little bit later. This is the status for TCR-Ts now—we can piggyback on deep knowledge gained from studying CAR-Ts.

We are currently seeing some remarkable data on moving CAR-T therapies into earlier lines of treatment. First, they were approved for third line treatment, and now important data shows improved efficacy in second line. I've also seen some of the first data for first line treatment, which is another major leap forward. As regulatory authorities see the advantages of using these therapies in earlier lines of treatment, it will be easier to initiate studies that will likely reveal better efficacy. The T cells that you harvest from the patients to make the drug products will be fitter, the patient tumor load will not be so extensive, and perhaps even the heterogeneity in the tumors may not be so extreme. These advances will all help TCR-T therapies that are being applied in the challenging context of solid tumors.

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"If you can apply therapies earlier, you … have more effective ways to treat solid tumors and overcome the constantly evolving mechanisms of immunosuppression that solid tumors employ."

Additionally, if patients have also taken I–O drugs like checkpoint inhibitors that modulate and change the tumor microenvironment (TME) this may up-the-game in terms of what a TCR-T therapeutic needs to accomplish. If you can apply therapies earlier, you can interfere in negative aspects of such processes as well, to have more effective ways to treat solid tumors and overcome the constantly evolving mechanisms of immunosuppression that solid tumors employ.

Q What unique advantages do TCR therapies offer for solid tumor applications?

DS: The last year has been very good for the TCR-T arena because the first TCR-based therapeutic, KIMMTRAK, was approved. KIMMTRAK binds to uveal melanoma cells using a TCR binder and its second arm binds to CD3 on T cells. It is a soluble drug product, but it still addresses an HLA-restricted peptide target. One saw an interesting phenomena in trials of KIMMTRAK with clinical benefit not observed using standard RECIST criteria, but clinical benefit was seen in overall survival of patients. This showed that treatment initiated a process in the patients with long-term benefit, and is a real glimmer of success for the TCR-based field of immunotherapy.

We now have new data constantly emerging, for example, from Immatics targeting PRAME in solid tumors. After testing their TCR alone, their next step was to combine the TCR with CD8 to enable both the CD4 and the CD8 cells to contribute to the immune response. They already announced that they will also test a combination of their TCR-T therapy with a checkpoint inhibitor. So those are sequential steps that are moving quite rapidly. Adaptimmune is following a similar approach in their studies of MAGE-A4 TCR-T therapy.

This rapid development is an important dimension that will hopefully impact the regulatory point of view as well—as authorities understand that these sequential developments should move faster, we would be able to gain information more quickly on improved clinical efficacy. If the specificity and safety of the T-cell receptor is established, then you can start to evaluate what happens when additional enhancements are used to improve efficacy, either in the TCR-T cells themselves or through combination therapies.

We're taking such a route in our TCR-T therapy development and that's why we made the transition from blood cancers to solid tumors. We started to work with switch receptor technologies that allow us to examine the potency and impact of a costimulatory switch receptor

that has the natural PD-1 binding domain, but switches intracellularly to the 4-1BB signaling domain, yielding a PD1-41BB switch receptor. In a solid tumor interaction with a T cell, the peptide-HLA is presented by the tumor cell. The T-cell receptor sees that target antigen and gets activated. But if this happens repeatedly, as occurs in a solid tumor microenvironment, the constant delivery of a T-cell receptor signal without co-stimulation will eventually drive the responding T cells into exhaustion, anergy, and often apoptosis.

PD-1/PD-L1 upregulation on tumor cells also contributes to natural downregulating mechanisms for T cells. So with this switch combination of PD1-41BB, we are tricking the tumor cell into providing a source of co-stimulation through its expression of PD-L1 that binds to the PD-1 switch receptor on the TCR-T cells. Here we keep the natural extracellular interaction of PD-1/PD-L1, but we interfere with the inhibitory pathway and instead switch to co-stimulation through 41BB. We are essentially killing two birds with one stone, by providing co-stimulation to the T cells while blocking the inhibitory PD-1/PD-L1 pathway. This is done with a single drug product. Those two receptors—the co-stimulatory PD1-41BB switch receptor and the T-cell receptor—are combined into the same delivery vector, so patient T cells that express the TCR will co-express the switch receptor.

We also have a safety mechanism coupled in the process because the 4-1BB pathway has to have a starting signal through the T-cell receptor. That means that these TCR-T cells, will not be active through the switch receptor alone. They need to see their target ligand—which is present on the tumor cells to bring the T cells into the first stage of activation—and then the switch can play the role in co-stimulation. Having both combined in a single drug product simplifies the whole approach.

Down the line, this dual receptor approach should also be cheaper because you're not using two expensive drug products (the TCR-T and the checkpoint inhibitor), and you're going beyond just inhibition of the PD-1/PD-L1 pathway. You're now turning it into a positive signal. Dosing, scheduling, and related processes therefore become simpler. What we see in our *in vitro* and *in vivo* models convince us that this could be a real game changer for solid cancer because through this co-stimulation and a high-quality TCR, we're getting very strong proliferation and very high polyfunctionality. We have cells that are making up to fifteen individual cytokines at the single-cell level. We're seeing enhanced killing both *in vitro* and *in vivo* and we're maintaining metabolic fitness in the cells. This combination brings advantages in multiple ways. I call it an intrinsic combination therapy—it's not two externals coming together, but one combined drug product.

Q What are your hopes and predictions for this space in the next few years?

DS: So many different industry players are now coming together with each providing critical pieces of the puzzle. I predict that we'll see the complexity of manufacturing be reduced and the whole manufacturing process set-up will be simplified. We will use automation in a much broader framework, and we will introduce it earlier in the process. It may be a complex system at the very beginning, but a fast transition to an automated system could then

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be a stepping stone to scale out for patients in far-reaching locations. Some smaller automated systems are opening that door, showing that you can try it very early, before there are needs to commit to a manufacturing process for large trials.

We're also seeing people sharing their in-depth analysis of biomarkers and what's happening in patients in their clinical trials. Those results start to impact how we would go about generating TCR-T cells. The question has always been about persistence and proliferation in patients. However, questions are now arising as to whether persistence might not as critical as previously thought. Rapid proliferation—really early expansion—is what starts the process that can lead to complete responses in blood cancers, and that is happening in the first couple of weeks, so one needs to get this step right at the start and understand what is then needed for solid cancers.

For example, growing TCR-T cells for 2 or 3 weeks may have been overshooting to obtain high cell numbers and perhaps the aim should be to get early cells with naïve-like and stem-like qualities that can rapidly proliferate and differentiate *in vivo* in the patient. If this is the case, then you'll dramatically reduce manufacturing times and costs, because you will need fewer cells. Novartis is developing a 2-day manufacturing protocol, using 1/20th of the cells that they used to manufacture for earlier trials. You can already see a tremendous opportunity if we learn more about how to manufacture the best cells.

At Medigene, as part of our end-to-end-platform, we have a very unique set of tools for drug product assessment. We look very extensively at the starting materials, what the apheresis looks like, and what impact that has on our final drug product. We investigate all of the qualities of our drug products at multiple levels through the manufacturing process. Then when TCR-T therapies are given to patients, we use fit-for-purpose assays to look at what's happening to those cells within the patients. You can already start to derive some hypothesis-generating questions even in a small cohort of patients. We took advantage of the situation in our first TCR-T trial in acute myeloid leukemia to not use additional IL-2. So our results were not confounded by the impact of a second drug applied with the TCR-T cells on driving proliferation and mediating a response that could shape a repertoire in a different way than what TCR-T cells would do on their own. These kinds of approaches rapidly deliver information that helps us design our next trials to answer the next round of critical questions.

In the years that I have participated in this field, the reduction in the challenges for manufacturing has been enormous. That's something that a company like Medigene, which develops tools and innovations at a much earlier and fundamental level of the development process, benefits from. Seeing this peripheral growth in the industry is exciting because it makes it likely that it will become much easier and more realistic to save on manufacturing costs and time.

Q What will be your own chief goals and priorities in the same timeframe?

DS: We are currently trying to bring our switch receptor technology into the clinic using an additional innovation that improves how we select T-cell receptors. I'm very much a proponent of copying evolution, and that's why we talk about evolution by

innovation. We try to pull out of natural repertoires the best TCRs that we can get that do not need to be mutated to improve their sensitivity. We do not use affinity maturation, but rather bypass central tolerance by using an allo-restricted form of antigen presentation. In this way we can get natural, high-affinity receptors that have been scanned against other HLAs. They've had to pass through the thymus and so they're not generally alloreactive but we get very high affinity receptors to self-antigens. That's our fundamental building block for TCR-T cells. Then we add co-expression of PD1-41BB into the TCR-T drug products. We are now moving to take into clinical studies a TCR specific for the NY-ESO-1 cancer-testis antigen, which is a well-validated target antigen, with indications known to respond to TCR-T therapies. Our highly-specific TCR gives us specificity, sensitivity, and a good safety profile. This, in combination with our PD1-41BB switch receptor, provides an optimal basis to assess how this intrinsic combination therapy impacts clinical results. We hope to have an IND/CTA filing made in the second half of 2024.

BIOGRAPHY

DOLORES SCHENDEL has been researching T cells and their abilities in immunotherapy since the 1970s, and has accompanied the scientific and therapeutic turn of era in this field. Prof. Schendel served as a University Professor for Immunology at the Ludwig-Maximilians-University in Munich, is the author of more than 200 scientific publications and has spent several decades as a scientific review board member in various research organizations such as the German Research Foundation, German Cancer Aid and the European Research Council among others. From 1998–2013, Prof Schendel was Director of the Institute of Molecular Immunology of the German Research Center for Environmental Health at the Helmholtz Center in Munich. Following this, she founded the Trianta Immunotherapies GmbH (today Medigene Immunotherapies GmbH). With the acquisition by Medigene in 2014, Medigene Immunotherapies GmbH was integrated into the Medigene Group and Prof. Schendel became Chief Scientific Officer (CSO) and, in 2016, also the CEO of the Group. With the new CEO joining in July 2022, she again focuses fully on her responsibilities as CSO and Head of Research and Development at Medigene as well as Managing Director of Medigene Immunotherapies GmbH. Prof. Schendel completed her PhD in Genetics at the University of Wisconsin, USA, followed by post-doctoral training in immunology at University College London, UK. She developed her interest in tumor immunology while working at the Sloan-Kettering Institute for Cancer Research in New York. She is a recipient of the German Federal Order of Merit and the Bavarian Order of Merit and received the 'Deutsche Krebshilfe Preis', the award of the German Cancer Aid.

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OVERCOMING MECHANISMS OF TUMOR RESISTANCE PART 1: BREAKING INTO THE TME

SPOTLIGHT

INTERVIEW

Understanding T cell dysfunction & exhaustion in the context of solid tumors

Roisin McGuigan, Editor, *Immuno–Oncology Insights*, speaks to **Gary Lee,** Chief Scientific Officer, Lyell Immunopharma, about the barriers to effective cell therapy approaches in the solid tumor setting, and Lyell's strategy for tackling them.

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Q What is your current role, and how has your career led you there?

GL: I'm the CSO of Lyell Immunopharma, and I've been in the field of gene and cell therapy for more than 20 years. For the majority of my career, I've been working on technologies geared toward engineering T cells and other cell types for various diseases, including cancer. What attracted me to Lyell is their focus on the cells. I love the fact that Lyell's mission is first to better understand T cell biology and to fundamentally understand why T cells don't work in solid tumors like they do in liquid tumors, and then develop technologies to address these barriers.

"Syngeneic model studies allow us to better understand the reasoning and the timing of how T cell exhaustion occurs. Now we know that T cell exhaustion is one of the key barriers for T cells working in solid tumors."

Q What are the barriers to successfully applying cell therapy in the solid tumor setting?

GL: There have been great successes with chimeric antigen receptor (CAR)-T cells and cell therapy in general in the liquid tumor setting. For example, the response rates in B cell malignancies and multiple myeloma with B cell maturation antigen (BCMA)-targeted chimeric antigen receptor CAR-T therapies have been remarkable. However, it would be naive to think that this success can be easily translated into solid tumors, and to date, it has been much more challenging.

One of the questions that we want to ask is whether we have a hypothesis based on clinical trial results and preclinical studies in relevant models like syngeneic models, where we actually understand the immunology. Lyell's founding story comes from that. One of our scientific founders, Stan Riddell, conducted a study with ROR1, which is a target that is expressed in both the liquid and solid tumor setting. When he used CAR-T cells in a liquid tumor patient as a control arm, he saw what you would expect to see. The T cells expanded, were functional and cleared the tumor. They were still active when taken out of the patients and—based on cell surface markers—weren't exhausted. When stimulated *ex vivo*, they made cytokines and behaved just as you would hope and expect. But when performing the same process in the solid tumor setting, for example in triple negative breast cancer and non-small cell lung cancer, the results were different. Within days, when the T cells were taken from the patients, they showed signs of dysfunction and exhaustion, including the overexpression of TIGIT and LAG-3. More importantly, the T cells that were extracted from the solid tumor patients were not functional. They didn't produce cytokines and didn't respond to any stimulation, confirming that T cells experience a very different fate when they go into liquid versus solid tumor patients.

Syngeneic model studies allow us to better understand the reasoning and the timing of how T cell exhaustion occurs. Now we know that T cell exhaustion is one of the key barriers for T cells working in solid tumors.

Discovery of the second barrier comes from clinical experience as well, and some of this work can be credited to researchers at the National Cancer Institute surgery branch who, after decades of studying tumor-infiltrating lymphocytes (TILs) in the melanoma setting, realized that having stem-like qualities in your T cell product is really important in the solid tumor setting. This is likely because these qualities give the T cells persistence. It takes a long

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time for T cells to find and kill tumor cells, so the T cells need to have persistence in order to not get exhausted. That persistence is gained through stem-like qualities.

To summarize, the two barriers that we are trying to solve at Lyell are to endow T cells with the ability to resist exhaustion in the tumor microenvironment. Secondly, we are trying to achieve a subset of cells that are truly stem-like in that, even after they get stimulated by antigens on the cancer cells, they could retain a subset of stem-like population that can continually drive T cell persistence in the patients.

Q Could you give me an overview of Lyell's current development strategy?

GL: We have two programs looking at T cell reprogramming technologies in the ROR1 CAR-T setting: LYL797 and LYL119. LYL797 is a CAR-T cell product enhanced with our c-Jun overexpression, which is the technology that endows T cells with the ability to resist exhaustion, as well as our Epi-R epigenetic reprogramming technology, which is designed to create populations of T cells with durable stemness. LYL797 is currently in Phase 1 clinical development and enrolling patients with relapsed or refractory triple-negative breast cancer or non-small cell lung cancer (NSCLC), two types of cancer where ROR1 is highly expressed. LYL119 stacks two additional technologies, NR4A3 knockout and Stim-R, on top of those two technologies. Each of those further provides T cells with greater ability to resist exhaustion and we have presented nonclinical data demonstrating these cells further improve CAR-T cell antitumor efficacy *in vitro* and *in vivo*.

We also have two programs in TILs. The first one is built on what the NCI has done, showing that TILs have clinical responses in patients with advanced melanoma. But, as I mentioned before, the clinical evidence suggests that we really need to be able to make TIL products with these stem-like qualities, so we are applying our Epi-R technology in our lead TIL product candidate, LYL845, which is currently in Phase 1 clinical development. We take the T cells from a tumor resection, where you would typically find a few million T cells. Using our proprietary Epi-R protocol, we expand the number of T cells to approximately 10 billion or more. We expand these cells in a specific way so that they do not become differentiated T cells, and retain as much stem-like quality as we can get in the product.

That Phase 1 study was recently initiated and we are actively recruiting patients now. We are starting with patients with relapsed and/or refractory metastatic or locally advanced melanoma, but expect to expand into NSCLC and colorectal cancer.

We also have a second generation TIL program—we have not disclosed what technology we are incorporating yet, but it will be both genetic and epigenetic reprogramming.

Q How would you sum up the current state of play when it comes to cell therapy approaches for solid tumors?

GL: There are different approaches being taken by different groups, which all provide valuable next steps in terms of what the field can do. Some people are focusing on targets; they are trying to find targets and indications where maybe the bar is a little bit lower.

The problem we are tackling at Lyell is trying to fundamentally improve the cells so that they are more functional. We believe that by accomplishing this, we can broadly apply this technology to many different targets and indications. If we are successful in making cell therapy efficacious in the setting of solid tumors, then the next step is to broaden the field further by looking at all the allogeneic technologies people are developing for the liquid tumor setting. We already see efficacy there, and hopefully we can maximize the utility of these technologies to benefit as many patients as possible.

Q Looking toward the future, what are your hopes for the space in the next few years?

GL: There is emerging evidence that we can find targets that are suitable for solid tumors, both in cell therapy and in biologics. There appears to be some cancer antigen targets that may have a therapeutic window we can take advantage of for CAR-T cell approaches. This is true for the TCR-T cell and TIL space as well. We are seeing some initial efficacy, at least. One of the challenges we have faced is that it's been more difficult to get a durable response in solid tumors in comparison to liquid tumors. Again, we hope that our technologies can benefit patients by providing persistent T cells that have durable efficacy and potency. I hope that in the next three to five years, we can get a good response rate as well as durability. I believe that by chipping away and overcoming different barriers to making T cells functional, we will get there step by step.

BIOGRAPHY

GARY LEE has served as Lyell's Chief Scientific Officer since January 2022. Dr Lee is a veteran biotech executive with over a decade of experience leading cell and gene therapy programs for human applications. From October 2018 to January 2022, Dr Lee was the Chief Scientific Officer at Senti Bio. From August 2005 to October 2018, Dr Lee held positions of increasing scientific and leadership responsibility at Sangamo Therapeutics, including last as the Vice President of Cell Therapy. Dr Lee earned his PhD in Chemical Engineering from the University of California, Berkeley, and his BSc in Chemical Engineering from the California Institute of Technology.

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AUTHORSHIP & CONFLICT OF INTEREST

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