Dr Ira Mellman on the Cancer Immunity Cycle, new research and his style of mentorship

Dr Roy Baynes shares his experience leading Merck’s oncology portfolio during the pandemic

Next-generation strategies to make a meaningful clinical impact on solid tumors.

Recent developments in CAR-T cell therapy, T-cell exhaustion research, clinical trials for brain cancers, and more
Welcome to the IO360° Summer 2021 newsletter.

In this newsletter, we are pleased to share brief, but in-depth interviews with IO leadership and the work they are advancing in immuno-resistance and rational combinations, strategies to expand the CAR-T cell therapeutic window, next-generation engineered T-cell therapies, recent developments in the field of T-cell exhaustion, ongoing CAR-T cell therapy clinical trials for brain cancers, managing through the pandemic and new research to better understand and develop cell therapies.

The interviews in this issue are:

**Ira Mellman, PhD**, VP of Cancer Immunology at Genentech

**Marcela Maus, MD, PhD**, Director of Cellular Immunotherapy at the Mass General Cancer Center

**Roy Baynes, MD, PhD**, SVP Global Clinical Development and the CMO of Merck Research Laboratories

**John Wherry, PhD**, Director of the Institute for Immunology at the Perelman School of Medicine at the University of Pennsylvania

**Christine Brown, PhD**, Deputy Director of the T Cell Therapeutics Research Laboratory at City of Hope

**Rafael Amado, MD**, EVP of R&D and CMO of Allogene Therapeutics

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How has the Cancer Immunity Cycle framework evolved in the last eight years?

We got it right the first time to a large extent; I suppose that happens sometimes. There have been two major differences. In the first incarnation we did not really consider the contribution of the tumor stroma as an independent player. We updated the framework a few years ago and the stroma was entered as a major player. Based on new data collected, we changed the positioning of where we know or anticipate different agents to work. For example, the PD-1/PD-L1 blockade had uniquely been assigned to the lower right-hand part of the cancer immunity cycle acting on the tumor. We now believe that there is a second and possibly even predominant role in the upper left-hand corner which is the stage of T-cell expansion in lymphoid organs.

This is why this construct is so useful to work with. It organizes concepts based on a common construct informed by data as it is generated. It has served its purpose and helped communicate not only internally but to the field that there is a conceptual change afoot and what that change means.

Can you speak to some of your current research in immuno-resistance and rational combinations?

One workstream is to study the things that we already know about and try to understand how they work. For example, we did not stop trying to understand how PD-1 works as a negative regulator of T-cells just because the molecule has reached the clinic and has had multiple approvals. We dove into the basic immunology and cell biology of what this pathway does and how the agent works. As a consequence of that research and the research of others, we decided to prioritize TIGIT as the next major target. We then expanded the effort to understand how PD-1 and TIGIT interact and what we should do next. One aspect of running the research program is that you build from what you know and try to understand it as best you can because knowing why something works and not just that it works gives you important insights into what to do next and the actual limits of your knowledge.

The second approach is informed by the patient data that we and others generate. The stroma is a good example. As more samples from patients in clinical trials were examined, we realized that a large fraction of the patients who were not responding to therapies had an immunological phenotype referred to as the immuno-excluded group. There were a lot of T-cells but they didn’t make it to the tumor because they were stuck in the stroma. We reasoned that if we could get them out of the stroma they would do their job. This turned out to be the case in mouse models. That led us to think more analytically about the stroma from a mechanistic perspective that could give us some guidance as to what types of therapeutics to make. The problem starts with understanding the basic immunobiology of the tumor stroma. We decided to study the role of TGF-beta, the role of collagen, how T-cells interact with the stroma and the role of cancer-associated fibroblasts, which is the main cell type responsible for establishing and maintaining the stroma. That defines a huge area of investigation that is led by my colleague, Dr Shannon Turley.

A third area of research focuses on the basic biology of tumors. As tumors mutate and diverge from self, they become potential targets for immune attack. When we took on this research around ten years ago, we wanted to know how to understand and make use of that information to generate the basis for a vaccine or cell therapy. That involved an enormous amount of basic immunology and biochemistry to understand what neoantigens are, how to deal with them on a computational basis, which ones are important and which aren’t and why, how to make a vaccine and how to develop an optimal cell therapy. We want to make...
therapies that are effective so anything that we do must be founded in a sufficiently well-understood aspect of basic science that we can trust to make sense.

“I personally have long felt a moral imperative to honor patients in clinical trials as they have been so generous with their time and effort to help us understand and develop our drugs. As scientists, we owe it to them and to their courage to get as much information out of their generosity as possible.”

Also, as we gain an understanding of human responses to therapy in cancer and elsewhere, many extrinsic factors come into play including genetics, the microbiome, diet and other pharmaceutical agents. For example, a data analysis we performed on patients who did or did not take antibiotics during immunotherapy showed that patients responded less well to therapy if they had been given antibiotics in a certain time window of the therapy. The implication of that analysis is that the microbiome is important and the immediate application is that if you want your patient to have the best response to an immunotherapeutic, you shouldn’t prescribe antibiotics. We are also looking into whether other drugs used for palliative purposes in cancer patients exhibit negative or positive interactions to take into account. These are really difficult studies to do because, from an epidemiological perspective, we don’t want to publish this information based solely on some weird association. We want to understand if there is a potential biological basis. We are taking this information and going back to mice and cell cultures to see if “concomitant medication A” could be interfering or enhancing an immune response before we decide that we believe it is the case.

You can also factor patient genetics into that and find different genotypes, adverse event profiles and response profiles. The unifying message here is that we’re starting to generate enough information from patients to establish an invaluable database. I personally have long felt a moral imperative to honor patients in clinical trials as they have been so generous with their time and effort to help us understand and develop our drugs. As scientists, we owe it to them and to their courage to get as much information out of their generosity as possible.

What is the biggest issue that needs to be solved for cell therapy to make a meaningful clinical impact on solid tumors?

The context of the question is that CAR-T therapy can be extremely effective for hematopoietic tumors but so far it has been completely ineffective in solid tumors. On the other hand, there is a cell therapy that works really well in solid tumors: TIL therapy, which is the process of taking tumor infiltrating lymphocytes (TILs) out of a patient’s tumor, growing them in culture and then re-injecting them into the patient. It’s labor-intensive and expensive and it cannot be applied to a majority of patients for technical reasons. But when the stars align, you can see spectacular results in solid tumors. As a result, I think we have a good proof-of-concept to say that cell therapy can work in solid tumors but the question is how.

When I compare CAR-T therapy and TIL therapy, the first and most glaring difference is not even the cells that are used but rather how the cells you’re injecting/re-administering are targeted to the cancer cells. In the case of CAR-Ts for hematopoietic tumors, you’re targeting them with an antibody that is specific to a lineage that is limited to blood cells. That means that you can treat lymphoma and leukemia and it doesn’t really matter that the target is also expressed by normal cells. For example, in the case of lymphoma, you can take out all of the B-cells in your body with the CAR-T therapy because they will repopulate from stem cells present in the bone marrow that don’t have that antigen. That’s why CAR-T therapy and bispecifics work extremely well for heme disorders. That situation does not apply to almost any solid tumor. You can’t make an antibody to a solid tumor and then have that antibody only react to the tumor cells. It will also hit the normal cells. But in the case of solid tumors, the normal cells it hits aren’t going to grow back. That then immediately limits your therapeutic index because you are always going to have on-target unwanted toxicity.

TILs work by capturing those T-cells that are already specific to tumor antigens that the body has identified. If you were able to target the T-cells only to see these tumor-associated mutations or other forms of neoantigens, then you may have something. Then the question is, can you generate a cell therapy that is based on targeting the cells to neoantigens that are expressed uniquely by a patient’s tumor? A large part of our effort is to figure out how. I’m invested in the idea that some day this will work. I hope to see it. It will be a long-term effort but I think we’ll start seeing the approach bearing some fruit fairly early on. There are already some interesting hints. It will involve an enormous amount of screening, technical skill and machine learning and artificial
intelligence based approaches to help navigate the path but we’re already seeing that there are paths forward.

The other question is how to scale these therapies. You’re removing cells from patients, modifying the cells, engineering them and then putting them back in the patient. It’s difficult for the patient. Many times patients can’t give you a sufficient amount of blood to generate the cells that you need and the companies that are working on CAR-T therapies now have yet to figure out how to simplify that process.

To me, the process forward is to make use of iPSCs (induced pluripotent stem cells) where you can engineer a recipient cell line to use as a universal cell line for all patients so it won’t be nearly as burdensome and expensive as going through the whole process. That will provide enormous cost savings and make it more accessible and scalable.

“I learned early on in my own career that it is as much work to do something that is highly impactful and conceptually new as it is to do something boring. Why not do the most important thing you can think of doing?”

How have you fostered an environment that has led to such success among your students and mentees?

The trick is to create a situation where you let each person get the maximum amount out of themselves. I learned early on in my own career that it is as much work to do something that is highly impactful and conceptually new as it is to do something boring. Why not do the most important thing you can think of doing? That doesn’t mean you’re going to succeed all the time but at least you will have a chance of doing something that is truly important. And even if you don’t succeed, you will learn something important and of value rather than doing something nobody is interested in or really cares about. Continuously, my role has been to challenge people to do the most important thing they can think of. I am pretty much open to anything, but it’s up to them to come back and explain why their idea is indeed an exciting one.

Anyone can do science. All you need is motivation. But you must realize that however smart you think you may be, you are not going to be as smart as a room full of people who have been motivated to think about problems in important and creative ways. Some scientists may feel threatened by this realization because they need to be in intellectual control. I gave that up long ago because I don’t think I have the intellect to do it.

How do you see the field of immunotherapy evolving over the next 1-3 years?

Over the next 1-3 years, we are probably going to see incremental improvements. When you say 1-3 years, I’m looking at therapies in clinical development that are fairly far along. There are a few molecules that will undoubtedly bring really good benefit to patients. But they are not going to change the bar because we are focused on a series of approaches directed by checkpoint inhibitors to solve a particular narrow set of problems associated with T-cell biology. It’s important to understand and build on what works.

There is much more out there from a conceptual point of view like stroma. We believe around 50% of patients don’t respond to checkpoint inhibitors because they have a stromal barrier. If we could solve the stromal barrier, we would open up the doors to two times more patients than we can currently treat. That would be transformational and we will solve that problem. Bringing forward the next generation of cell therapies and vaccines will also cause that kind of transformative benefit, but we aren’t there yet. I think it will be 3-10 years before these next generation approaches become part of standard oncology practice.
Can you speak about your recent research in mechanisms of response of CAR-T cells and diagnostics?

We have spent quite a bit of time looking at potential mechanisms of resistance and developing robust assays to measure persistence and phenotypes of CAR-T cells derived from patients. We think CAR-T cells kill by convincing the target cell to kill itself in some way. We are looking at how the interaction between the CAR-T and the tumor cell drives the response. We think that different kinds of tumors interact with the CAR-T in different ways, which results in different outcomes. There was a group at University of Pennsylvania led by Nathan Singh that did a CRISPR screening in leukemia cells and found that molecules involved in apoptosis in the tumor cells were important for CAR-T cell efficacy. We are doing a similar type of work but looking across different liquid and solid tumors and different kinds of cell death and what mechanisms of resistance look like in different tumors.

In addition, we are looking at the more common factors that have already been described, like antigen loss variants, and generating multi-targeted CARs to avoid the antigen loss. Loss of persistence can happen lots of ways: the cells can be exhausted or unfit. But another way persistence can be lost is that the CAR-T cells are actively rejected by the host. We are looking at how often that happens and ways to overcome that as well.

Each of the companies that makes CARs has their own diagnostic assays for measuring expansion and persistence. Once these CARs are approved and used commercially, we no longer have access to those types of assays. You might have a patient with fever or hypotension and not know if it is due to CAR-T expansion or if it is an infection or whether the CAR-Ts are going up or down. In collaboration with some colleagues in the UK, we have done some work in trying to develop ways to measure the CAR-T with non-proprietary assays. In the long term, it would behoove the community to develop assays and make them available to hospital laboratories so that healthcare teams taking care of patients can measure the CAR-T cells and help them figure out if the presenting symptoms are ones that could be related to the CAR-T cells. There is also some work going on in development of point-of-care cytokine measurements. We are looking at some targeted areas in that space.

“**We are driven to look beyond the typical safety measurements, and even beyond the MRI’s, to try to understand what is actually happening at the CAR-T interface with the tumor.**”

What are the implications of your recent studies on EGFRvIII CAR-T cell treatment?

A couple of years ago, we did a phase 1 study of CAR-T cells targeting EGFRvIII which is an oncogenic mutation that happens in about 20% of patients with glioblastoma. We found that CAR-T cells are really good at getting across the blood brain barrier and into the tumor parenchyma. Unlike a lot of chemotherapy or many targeted therapies, CAR-T cells don’t have a hard time getting past the blood-brain barrier. We also found that there is a lot of tumor heterogeneity, so going after one mutated antigen is not enough to wipe out all of the tumor that is there. Additionally, at least in glioblastoma, there are active mechanisms of immune suppression. We saw a really significant infiltrate of regulatory T-cells that shut down immune responses.

**Strategies to Expand the Therapeutic Window of Engineered T-Cells**

**Marcela Maus, MD, PhD,** is an Associate Professor of Medicine at Harvard Medical School and Director of Cellular Immunotherapy at the Mass General Cancer Center.
That seemed to happen after we gave an immune therapy. There is a compensatory immunosuppression after you give something that is immunologically active.

In our next-generation trials that we are now developing at Mass General, we are trying to address both of those concepts by targeting wild-type EGFR, which is expressed on most brain tumor cells at high levels but not in other parts of the brain. We think that this strategy will target more of the tumor. At the same time, the method that we are using actually converts T-regs into killers. Even if we get this compensatory T-reg infiltrate, we will be able to turn them into assistants to actually kill tumor cells. This is how it worked in immune deficient mice but we don’t know for sure how it will play out in humans. We are driven to look beyond the typical safety measurements, and even beyond the MRI’s, to try to understand what is actually happening at the CAR-T interface with the tumor. We hope to collect blood samples and CSF samples to measure activity of the cells and, where patients need a biopsy or resection, so we can learn from that experience to then prepare and design the next version if needed.

“Everybody talks about CAR-Ts but these can actually include engineered T-cell receptors, NK cells and CAR-Ts for lymphoma, leukemia and myeloma. It is a class of therapies – engineered immune effector cells – but I think that optimizing the strategies is going to be different for each product and even potentially for each disease.”

How can we optimize strategies to expand the CAR-T cell therapeutic window?

There are different issues with different CARs. Everybody talks about CAR-Ts but these can actually include engineered T-cell receptors, NK cells and CAR-Ts for lymphoma, leukemia and myeloma. It is a class of therapies – engineered immune effector cells – but I think that optimizing the strategies is going to be different for each product and even potentially for each disease. For example, there was a recent publication from Kite Pharma about their ZUMA-3 trial in adult ALL where it turned out that they needed to use lower doses of chemotherapy and got great responses. Everyone has seen good responses of CD-19 cells in that disease. The issue has been that the toxicity levels have been significant in most people’s hands. Kite seemed to overcome it by reducing the lymphodepleting chemotherapy.

On the other hand, in an allogeneic CAR-T product in the same disease, you needed to jack up the lymphodepleting chemotherapy. One of the findings from a study using allogeneic UCART-19 published in The Lancet was that you needed not only Cytoxan and fludarabine, but also alemtuzumab for even more lymphodepletion. What you need for an autologous CAR versus what you need for an allogeneic CAR is very different even in the same disease. And what you need from the same product in mantle cell lymphoma is going to be different from what you need in leukemia.

There are ways to optimize these strategies. For that we need the field to grow even more, especially at the clinical investigator level so that we can optimize chemotherapy combination regimens. We can design ways to perhaps prevent some of the toxicities. We have some studies using anakinra, which is a biologic that competes with IL-1 signaling. We think that by giving this subcutaneously at the time of the infusion of the CAR-Ts and then continuing for a couple of days afterwards may be enough to prevent the cytokine release syndrome and the neurologic toxicity that currently makes this therapy only feasible to do in a hospital setting. We may not need that for a different CAR-T product but there are advantages and disadvantages to all of these and you need to optimize and mitigate those windows differently based on the product, disease and perhaps even the patient.

What does the next-generation of engineered T-cells look like?

The field is growing so much and there is a lot of variance as to what comes next. One thing we can probably all agree on is that in a lot of diseases we need to target more than one antigen. In lymphoma, where there has been tremendous progress in terms of availability of CAR-T and how many patients get into these durable responses, 40% of patients do not need any other therapies for more than two years. That said, I think everyone can agree that we need to target more antigens in leukemia, lymphoma and definitely in solid tumors.
“I think that there are almost two dipoles in the field. One is the optimal personalized therapy, identifying neoantigens and neoepitopes of a patient’s tumor to design T-cell receptors or CARs that are very specific towards a patient’s own tumor. The exact opposite is to have the off-the-shelf therapy manufactured in mega bioreactors so that it is ready to go for whomever walks through the door.”

Beyond that, what the next-generation change of engineered T-cells looks like is a bit of a philosophical question. As the field grows, you are going to have a lot of different ideas about where it should go and there will be some natural selection depending on the data that comes out. Some people are looking at how to make therapy off-the-shelf, large-scale, cheaper and faster. I think that is one possibility. It certainly has a lot of commercial advantages because that is the way that most drugs get distributed and it is a process that we know works at a healthcare system level.

I am unsure if that is how it will work best on the biology level. Will that be the optimal product for a patient seeking cure? In that setting, I suspect that autologous products will always have an advantage over allogeneic products on a pure biologic basis. I think that there are almost two dipoles in the field. One is the optimal personalized therapy, identifying neoantigens and neoepitopes of a patient’s tumor to design T-cell receptors or CARs that are very specific towards a patient’s own tumor. The exact opposite is to have the off-the-shelf therapy manufactured in mega bioreactors so that it is ready to go for whomever walks through the door. Biologically one of them makes a lot of sense but is probably very difficult to scale and the other is appealing to have a large scaleup but I’m not convinced that it will have that same therapeutic window, toxicity level and biologic efficacy. The field is trying to find out where each disease fits in and what the right cell type may be.

I am partial to T-cells. I suppose it’s partially a bias because it’s what I’ve worked on for so many years but I think this is based on the biology. You can do a lot of genetic engineering on T-cells. They live a long time. We understand their biology quite a bit. We have a lot of tools and reagents to study them. And they proliferate, persist and form memory. Their own biology is favorable because they grow in response to how much antigen there is and then they contract and stay around for a long time. It is a very dynamic system. That’s why I’m so in love with the T-cell itself.

Anything else?

I think we need to be open to building on what we’ve already learned. There is a lot of step-skipping and jumping into what is going to happen ten years from now, like jumping into off-the-shelf therapy for solid tumors. Although I have no criticism of off-the-shelf therapies and I strongly favor designs of early trials, I would say that that is not a reason to give up on the idea of autologous products. There are patients that have blood cancers that are not CD-19 positive who could benefit from this kind of therapy. I see a lot of people wanting to be forward thinking and only focus on allogeneic products for solid tumors. But we have proof of concept in liquid tumors in one target with autologous cells. Let’s use autologous cells for a different antigen in a different liquid tumor and also autologous cells in a different solid tumor. I think there is a role for all of those ideas. If we really want to help patients, we need to make those investments.
Leading Merck’s Oncology Portfolio Through the Pandemic

Roy Baynes, MD, PhD, is the Senior Vice President of Global Clinical Development and the Chief Medical Officer of Merck Research Laboratories.

What was the experience like to get multiple oncology FDA approvals during the pandemic?

As a company dedicated to trying to improve the lives of patients, we recognize that the pandemic presented some unique challenges to the oncology community. The oncology community has adapted quite quickly in terms of how to care for patients. During this critical time, we have had some guiding principles. Firstly, we wanted to ensure that our staff was safe. Secondly, we wanted to ensure that our healthcare providers were safe. And we were also committed to the notion that patients really do need to get their cancer care because that is the best way of addressing cancer in a given patient. We had a very simple choice to make. Do we pause programs or do we keep going? After a rapidly convened discussion, we decided that there was only one way forward, and that was to keep going and to ensure that we met all deliverables. So we issued no blanket pauses. We did not put any trials on hold. We dealt with the circumstances on the ground as they arose.

For example, China shut down early on so we deployed continuity plans. China recovered and then East Asia had a general shutdown. This then moved around the world. We were able to leverage best practices to keep trials on track. We did not miss any critical database locks. Filings were delivered on time. And we made a conscious commitment to stay open for business with no patient left behind and, preferably, no scans or blood tests left behind. While there was some disruption, we believe that we managed pretty well and we’re very fortunate to have completed our files and approvals on time. It has been a very intense period for everyone in the company.

How were you able to lead a team through the pandemic while continuing your portfolio of trials?

We have a very experienced cross-functional team. In developing a drug there are many key functions that all have to be delivered on time and in an organized way to ensure that the evidentiary package to support approvals is presented. We operated by having everyone in the Western world work remotely for a given time. We had a number of leadership meetings on a regular basis. The cadence was as often as once or twice a week to ensure that we were addressing issues as they arose. Functional leadership and teams were also kept apprised on developments in real-time. Communication was really important and there were certain things that we had to do differently. For example, at many centers in the United States, we were not able to get onsite to verify data. So we had to develop a system of remote monitoring. In the US, that is facilitated by the electronic medical record (EMR) and we were able to do a tremendous amount of source data verification and documentation using remote methods. Teams also displayed remarkable creativity in jurisdictions where EMRs were not available and we were able to develop workarounds to verify data while ensuring that patient privacy was protected. The regulatory agencies understood that this was going to be disrupted and generally provided guidance which allowed for flexibility but required documentation and also plans that accounted for changes in the operating model during the pandemic.

One vignette that gives you a sense of what could be accomplished: We had a 17 year old patient enrolled in an oncology clinical trial who returned to his home in Romania and was unable to reach the trial site in Italy due to the COVID-19 travel restrictions. The team rapidly found an experienced local study site in Romania, developed a special route for the drug transfer, and trained local staff on how to follow the protocol. Ultimately the patient was able to access treatment on time at this site in Romania and continue participation in the trial. There are many similar stories like this of remarkable creativity. We had many examples of people being transported over hundreds of miles to get to a site that was open. In various parts of the world we had novel sites set up. We also used...
alternate imaging sites. There was a tremendous amount of coordination, and all of this was carefully documented. Temporary operating procedures were put in place so that we could document what happened. It was an enormous effort, but I think that people are extremely encouraged and humbled by the experience and it is a testament to the incredible teamwork that we have been able to keep things on track.

“We had many examples of people being transported over hundreds of miles to get to a site that was open. In various parts of the world we had novel sites set up. We also used alternate imaging sites. There was a tremendous amount of coordination, and all of this was carefully documented.”

Aside from the current activity that Merck has, what might be next in the oncology pipeline?

For many decades, we knew that the immune system could potentially be important to the treatment of malignancy. With the advent of checkpoint inhibitors, we realized that natural immunity to cancer could be revealed and in so doing, actually address really grievous disease in a large number of patients. The evaluation of our checkpoint inhibitor as monotherapy, or as a single agent, has been extensively explored. We deployed a tremendous amount of precision medicine around the monotherapy to ensure that we select the patients who are most likely to benefit and then, by inference, identify those patients who might need a combination or something other than monotherapy. At the same time, these precision medicine tools have allowed us to understand mechanisms of resistance.

As we looked at the next wave of innovation, we moved from salvage treatments, which was where we studied monotherapy initially, into earlier lines of treatment. We are starting to see a number of adjuvant and neoadjuvant studies read out. Next, we applied combination approaches. The simplest combinations involved immunotherapy with standards of care, such as radiation, chemotherapy and surgery. A number of those trials have been deployed and read out, and many have been transformative in different types of cancer. Importantly, we find that while precision medicine tools are helpful in identifying potential combinations to pursue, many times the combination therapy is strong enough to overcome any precision medicine limitation.

Consequently, a part of the combination work has been for broader populations. In other words, the benefit of combination approaches to treat cancer is seen regardless of the precision medicine tools that helped predict how the treatment worked as a monotherapy.

We then moved on to additional combinatorial efforts. Within the company, we have more than 20 novel mechanisms that we are exploring. Many of these will be destined to be combinations with our checkpoint inhibitor, pembrolizumab. The agents we are working with include additional checkpoint inhibitors, immune agonists, personalized cancer vaccines and oncolytic viruses, tumor microenvironment modulators and targeted therapies. Here we can point to a number of the VEGF tyrosine kinase inhibitors (TKIs) as well as two targeted agents, which in combination have shown remarkable activity in certain tumor types. We are pretty early in the full exploration of immunotherapy. It is certainly my belief that for the next decade, we are going to see an extremely rich vein of data and communications relating to these various combinations. At the moment, most of the combinations have been doublets: chemo-plus-something or TKI-plus-something. There is now the idea that certain triplets may turn out to be important. Just recently we received an accelerated approval for HER2+ gastric cancer, where we combined chemo with pembrolizumab together with trastuzumab, and showed remarkable efficacy. Other triplet approaches will be coming along after that. We are early in this course and I think we are going to learn an awful lot about the immune system and how to add to it as time goes on.

What do you look for when seeking combination partners?

One of the wonderful aspects of drug development is when you have a powerful drug like pembrolizumab, you have a tremendous amount of interest from the external environment. An enormous number of companies come to us to see if it makes sense to explore a combination of their preferred drug with ours. We typically consider a couple of factors before agreeing to that type of combination. We want to see preclinical data. The hypothesis needs to be plausible. It’s excellent if we have molecular epidemiology or signals that support the notion. And if there is any clinical data that speaks to remarkable efficacy, that is an even stronger point.

I want to emphasize that today, we have 200+ combination trials ongoing where the combinatorial drug is not ours. We have over a hundred different company collaborations ongoing. This has allowed us to have an early readout of potential strong efficacy signals. It has also allowed us to enable quite a lot of business development activities, where we have been very active. For example, we have executed a
collaboration agreement with AstraZeneca, where we have partial ownership of the product olaparib. That has been a very fruitful collaboration. We have also signed agreements with Eisai around the TKI, lenvatinib. We have done collaboration agreements with Seagen around their HER2 targeted TKI, tucatinib. We are also working on a number of antibody drug conjugates. One of these is in collaboration with Seagen around the LIV-1 targeted antibody drug conjugate (ADC). We acquired VelosBio for the ROR1 ADC, which we think will be an important addition in the hematologic malignancy space. We also acquired Peloton for their HIF-2-alpha antagonist, belzutifan. We have the great privilege of already presenting monotherapy data with that agent in renal cell cancer of VHL disease and we are exploring that further in sporadic renal cell cancer and combination therapies extensively. Additionally, we acquired ArQule for a non-covalent BTK inhibitor. And we have over 20 internal assets which look as though they will be important additions to pembrolizumab. We are very active in external collaboration in the licensing arena, as well as, potentially, the acquisition arena.

What can be done to better achieve precision immunotherapy?

I think we’ve made a lot of progress there already. From a very early time point, we have been very active in the precision medicine arena. Early on, we had three key underpinnings. The first was that since pembrolizumab interdicted the interaction between the ligands of PD-L1 and PD-L2 and their receptor, PD-1, it made sense to look at tumors that had a significant expression of PD-L1. There is also a notion that the immune response that we are able to reveal with checkpoint inhibition for patients with cancer relates to neoantigens. It’s thought that mutations of genes in cancers lead to the elaboration of these neoantigens. That combination of mutations as well as PD-L1 expression has been explored very extensively across our program. Our initial screening phase 2 program for monotherapy looked to tumors that had either high PD-L1, a lot of mutations or both. Having screened more than 30 different major cancers, we have unequivocal evidence of activity in greater than 26 of those. That strategy has worked very well.

The question becomes, can we learn more about biology using precision medicine tools? There are many ways you can think about this. If you think about a graph where on the Y-axis you have the number of mutations and on the X-axis you have the inflammation of the tumor, which can be measured either as PD-L1 expression or gene expression profile for inflammation, you find that a given cancer will resolve into four quadrants. You can have a highly-inflamed, highly-mutated cancer. These generally have markers for numerous immune active agents. This is where checkpoint inhibition combinations or combinations of immune stimulators may be active. If you look at patients who are inflamed but are not highly mutated, these typically have angiogenesis signals so you may predict that these tumors would be very responsive to the addition of a VEGF TKI to pembrolizumab. When we look at the non-mutated, non-inflamed tumors, we often find unusual biologies, such as mutations that portend resistance. These may be abnormalities of signaling pathways. These may be approachable with specific targeted therapies. Finally, when we look at the uninfamed but highly-mutated population, these often have a proliferative staple and so combinations with conventional therapies like chemo and radiation may make a lot of sense. We have tested this prospectively and the prediction seems to be generally accurate. Precision medicine will help us resolve combination decisions and understand mechanisms of resistance. Circulating DNA measurement will have a number of applications and specific tumor markers are going to be important where a targeted therapy is required. It is an exciting time. Precision medicine revolutionized immunotherapy and continues to revolutionize the combinatorial approach.

“It is an exciting time. Precision medicine revolutionized immunotherapy and continues to revolutionize the combinatorial approach.”

What will the conversation around immuno-oncology sound like in five years?

Since our initial approval for pembrolizumab in 2014, we have seen incredible progress in monotherapy, combination therapy and novel targets. I cannot wait to see the next five years. It will be even more exciting. With each new discovery we learn an enormous amount about biology and the power of the immune system. With the tremendous technology that we’ve deployed, the investment we’ve made and the vastness of the clinical trial program, we will continue to see major advances in this important research area for many years to come. It is quite an exciting time. I have given you a flavor of directionally how this is going to be studied. Not everything is going to succeed but I think a high proportion of projects might.
What have been the most important recent developments in the field of T-cell exhaustion research?

There are four points that are worth mentioning here. The first and most important is the very clear recognition that exhausted T-cells play a key role in human disease. The first evidence for that was from infectious disease. Others in the field identified exhausted T-cells in HIV, hepatitis B and hepatitis C infections in humans. But the real event that crystallized the importance of exhausted T-cells in disease was the recognition that exhausted T-cells responding to PD-1 blockade first in pre-clinical infection and tumor models and then in human melanoma patients are associated with clinical benefit. From there, we now recognize exhausted T-cells in a large number of cancers and in many other disease settings. We have started to appreciate how important those cells are in those diseases.

A second important development in the field was the recognition of heterogeneity of exhausted T-cells. They are not all the same and they have different roles not only in steady-state disease but also in therapeutic interventions. There is a subset of exhausted T-cells that respond to immunotherapy and another subset that does not. We now know a lot about this biology.

The third thing is that we can define the underlying epigenetics of exhaustion that help explain how different exhausted T-cells are from other types of T-cells, really defining them as their own immune lineage distinct from other types of T-cells like effector T-cells and memory T-cells. This also allowed us to understand their lack of reprogrammability. These cells are locked into their fate and it is going to be challenging to take cells that are fully exhausted and turn them into something else. Many of our therapeutics may actually avoid that path. Once the cells are exhausted it is difficult to reverse because they are epigenetically locked in.

The fourth point is that through CRISPR engineering and other approaches, we see the opportunity to use our knowledge of the biology of exhausted T-cells to engineer around some of the deficiencies. This fourth point is quite nascent while the other three are pretty well established developments in the field. The idea that you can use genomic engineering to engineer around some of the problems with exhausted T-cells has been a big step forward in the last year and a half.

How has our understanding of exhausted T-cell types evolved and what are the implications?

My thinking of this has evolved quite a bit over the last 20 years. To take a macro view first, exhausted T-cells are not bad. That is counterintuitive given their name and the historical literature on this, even from our own group. They are simply one evolutionarily selected solution to the problem of persistent, high-level stimulation faced by the immune system. It is difficult for a cell type to manage the physiological stress of needing to respond to constant stimulus for regeneration.

Exhausted T-cells have done a couple of things. They have managed to thread the needle evolutionarily to maintain some form of homeostatic balance, even in the setting of a chronic infection or tumor. Tumors are often in a meta-stable homeostatic balance where they slowly progress but if you remove the immune system then they progress much faster. Exhausted T-cells are able to manage that constant stimulation and yet maintain some level of moderate control. Tumors often
escape that by mutation or evading or suppressing those responses even further. We should think about what it is about exhausted T-cells that has allowed them to survive and apply pressure to the disease in this particular setting and if we can exploit that to increase the therapeutic pressure on the tumor. Over time, we have learned which subsets of exhausted T-cells are mediating which part of that biology.

We now know that there are progenitors of exhausted T-cells that can self-renew. They have all the therapeutic response to PD-1 blockade and they have managed to withstand the stress of constant stimulation and yet also give rise to cells that put some pressure on the tumor or infection to maintain a host balance with the disease. We then learned that the more terminal subset, which is numerically more abundant, mediates some of this containment and is able to populate peripheral tissues and take advantage of some of the biology of tissue resident memory to maintain some balance. Our understanding has evolved to get out of this framework of thinking that exhausted T-cells are bad to thinking about a developmental biology map where progenitor cells need to maintain several different layers of function to establish some sort of host-pathogen or host-tumor pseudo-equilibrium.

What outstanding research questions in T-cell exhaustion that are most important to work on next?

One of the first things for us to understand and define properly is the modular nature of exhausted T-cells. We think this is important because of the overlap of the program of T-cell exhaustion and the program of tissue resident memory T-cells. If you look at the gene expression of T-cells in a tumor and you happen to come from our lab you would call them exhausted. If you happened to come from one of my friend’s labs who studies tissue resident memory, you would call them tissue resident memory. The reality is that both signatures are there and they happen in the same cell. We get into this blind men and the elephant equation where we see the thing right in front of us because that is what we think about. But it is very likely that those cells are using different components of biology in a modular way to generate a composite cell type that has features of both cells. If we understand the composite nature of what is happening for exhausted T-cells in different settings, we will better be able to therapeutically exploit them. We probably want a tissue resident memory program combined with an exhaustion program to help us mediate beneficial effects in lung cancer or tissue tumors. It’s probably different for CLL. Understanding the modular nature allows us to pick apart our therapeutic targets better.

The second thing is that we need to understand this process of reprogramming cells and taking them backwards in their epigenetic history. The picture we envision is that there are certain one-way valves in the process of cell differentiation. Once you get past one of these valves, it is very difficult to go back to the previous state. We need to understand where in these differentiation processes are these big inflection points that are hard to reverse through. We then need to find mechanisms either to avoid those steps or to step back through that valve somehow. This idea of reprogramming links both into the epigenetics I’ve mentioned, the transcriptional programming and also these modules. We may want to reverse back for one module but keep the other. We may want a tissue residency program but we may not want repression of effector function. Can we actually reprogram these cells or do we have to avoid this process altogether? From a therapeutics standpoint that changes whether you think about interventions after the immune response has started or interventions to prime new immune responses and divert them down the right path.

The last thing that we really need to understand from a basic science standpoint is the signaling architecture that gives rise to these outcomes. We still don’t really know what it is about how the T-cell perceives antigen in the early parts of priming that causes it to become exhausted versus productively activated. We know Tox is involved but we don’t know what happens between the cell membrane and the T-cell receptor. And the reinforcing architecture of Tox is still sort of a black box. If we knew that, we could guide T-cells down paths of differentiation much more effectively.

“If you ask ten T-cell immunologists what an effector memory cell is, you will easily get ten or more definitions based on which flow cytometry markers the lab used. We are using high-dimensional flow cytometry combined with transcriptional profiling and epigenetic profiling to ask about cell identity across three layers: protein expression and phenotypic markers, RNA and transcriptional identity, and epigenetic access and the potential of cell response or behavior.”
Can you share some of your current research in high dimensional immune profiling?

We are very interested in this topic and this has been driven by some of our translational needs to identify and profile exhausted T-cells in cancer. Our questions go way beyond exhausted T-cells. We need a holistic picture of how the immune system is in all of these settings. We built large high-dimensional profiling approaches to do this and have initiated a new project at Penn called the Immune Health Project with the idea that if we profile the immune system with enough depth and precision, we should be able to define why your immune system behaves differently than my immune system. The vast majority of those differences will be sub-clinical and won’t really matter but the way your immune system has experienced other infections in life will be different than mine. Those all leave an imprint on your immune system. We are using high-dimensional profiling to define that landscape view across individuals and diseases to ask whether there are fundamental immunotypes or immune fingerprints that predict how an individual will respond to future diseases or therapies.

We also recognize, even among ourselves, the blind men and the elephant problem. We are all fumbling around with limited information looking at T-cells with a handful of markers and flow cytometry and calling the same T-cell phenotype different things or different T-cell phenotypes the same thing. If you ask ten T-cell immunologists what an effector memory cell is, you will easily get ten or more definitions based on which flow cytometry markers the lab used. We are using high-dimensional flow cytometry combined with transcriptional profiling and epigenetic profiling to ask about cell identity across three layers: protein expression and phenotypic markers, RNA and transcriptional identity, and epigenetic access and the potential of cell response or behavior.

This highlighted the observation that cells can exist in a very similar epigenetic state and yet have a different transcriptional program. It can even have a similar transcriptional program and exist in two different protein phenotypes. It gets to this idea that many of the things we see by protein phenotype or by RNA are reflecting the same cell type responding differently to different environmental cues. When you put an effector memory cell in a dish and give it IL-2, it will look different transcriptionally and by protein phenotype than if you give it TGF-beta. That allows us to make predictions about which cell types play a role in which disease settings and whether those cell types are fundamentally locked in or they have the potential to behave differently. We are combining three layers of high-dimensional profiling to build an atlas with data from different diseases to find what cell types are there and their potential. We then want to use high-dimensional flow cytometry approaches to build a landscape map of how different humans manifest their immune fingerprint, link that to disease outcomes and ask if we can predict how different people will respond to different diseases and treatments over time.

How has COVID affected your oncology research?

It’s been a challenging year on many fronts. The biggest thing for those of us who do immuno-oncology work but who are T-cell biologists or focus on areas of basic or anti-pathogen immunology is that we now have a second full time job. The amount of time and energy spent on COVID as a disease and on vaccination is absolutely enormous. For a period of time, we couldn’t do anything else because oncology research was shut down. Now everything else has come back online and yet the time, energy and effort spent on COVID-19 work remains. Even for those who are not doing as much active lab work, keeping up with that literature and information has been extensive. We had to open another part of our lab focused entirely on COVID-19 and SARS-CoV2 vaccination with the same people doing the immuno-oncology work. This has really strained the infrastructure. There isn’t the bandwidth to do everything.

For a good period of time last calendar year, a lot of our basic immuno-oncology research was shut down. This caused a lot of discovery and translational efforts to slow. We are now playing catch-up and making up for lost time because both COVID patients and cancer patients need these research efforts.

On the other side of the equation, we have learned a lot from how we’ve done pandemic-style research. The pressure to have answers now has pushed us to do things that we didn’t do before. We have platform-level science in patients that operates more quickly at a higher proficiency and precision than what we were doing prior to the pandemic. We can now run a high-dimensional immunological analysis on a cohort of patients and have data analyzed, knowledge results and production-quality figures in a week. This is a turnaround time that we’ve never seen before. Part of this is because we have learned how to code and template much of what we needed from this kind of approach and standardized many of the assays yet keep them adaptable enough to incorporate new ideas in real time. The big take home message is that COVID has given us opportunities to redefine our efficiency, questions and even the precision with which we do research. We’re moving that in real time, back and forth between applying it to COVID-19 research and immuno-oncology. The bottom line is that doing human immune research during the COVID-19 pandemic has transformed our ability to understand the human immune system and has set a new standard for mechanistic, real-time immune profiling leading to new treatment opportunities. Immuno-oncology will benefit tremendously from these changes as we gain control over the pandemic.
Can you speak about your ongoing CAR-T cell therapy clinical trials?

It’s an exciting time at City of Hope and in the field of CAR-T cell therapy for both primary brain tumors and tumors that metastasize to the brain. These are very difficult to treat tumors. Most other therapies fail. There is a huge opportunity to improve outcomes for patients using cell-based therapies. Oftentimes when I give presentations, I start off by showing that CD-19 CARs can traffic to the brain and eliminate leukemia and lymphoma in the CNS. That was a surprise to all of us but it gave hope that this type of therapy can make a significant impact in these really difficult cancers.

I think City of Hope has more trials treating malignant brain tumors than any other institution at this point. We’re running seven clinical trials. Six of those are in primary brain tumors, either pediatric brain tumors or glioblastoma (GBM) or grade III gliomas. One is for HER2 malignancies that have metastasized to the brain. My laboratory is focused on accelerating learnings from the bench through City of Hope’s translational infrastructure to the clinic and to patients as quickly as possible. We have been doing that in many exciting ways since we started this program.

We have been looking at optimizing the route of CAR T cell delivery for patients based on my preclinical research. We are also evaluating combination therapies and new CARs. We now have trials testing CARs that recognize three different antigens: IL-13 receptor alpha 2, HER2 and a chlorotoxin-directed CAR. We are also looking at different agents that modify the tumor microenvironment. We are combining CAR-T cells with checkpoint inhibition. We’re looking at CAR T cell therapy with and without lymphodepletion. We’re testing a lot of these variables that we are hoping will come together to change how we think about treating brain tumors with cell-based therapies and CAR therapy.

What are some of those recent learnings from the bench that you’re translating to the clinic?

One important learning goes back to a New England Journal of Medicine publication from 2016. We had a patient with multifocal GBM. At that same time, my research laboratory was investigating different routes of administering CAR-T cells and how best to address the challenge of multifocal tumors. In mice, we were implanting tumors on each hemisphere of the brain and looking to see which delivery routes were most effective. We found that if we delivered these cells to the cerebrospinal fluid (CSF) we got better trafficking to multifocal tumors. When one of our patients seemed to have a local response but his tumors far from the injection site progressed, we were able to meet with the clinical and research teams and show that the data in mice suggested the utility of delivering these cells in the CSF, which no other group was doing. We went to the FDA and asked for permission to administer CAR T cells into the CSF in that patient and this individual had a dramatic clinical response where all of his lesions regressed and the therapy mediated a complete response in that setting.

Now there have been publications from other groups looking at other types of brain tumors and they are finding that administering CAR T cells into the CSF has clinical advantages. Many institutions are now using this route of delivery for their clinical trials. That is one example where we pivoted for a specific patient based on learnings from the research bench.

“We’re testing a lot of these variables that we are hoping will come together to change how we think about treating brain tumors with cell-based therapies and CAR therapy.”

Christine Brown, PhD, is the Heritage Provider Network Professor in Immunotherapy at City of Hope Comprehensive Cancer Center and the Deputy Director of the T Cell Therapeutics Research Laboratory at City of Hope.
How has the pandemic impacted both your preclinical and clinical research?

During the pandemic, it has been challenging to move these complex therapies and translational programs forward. I’ve been proud of our institution and my research lab. The institution at City of Hope really prioritized patients. We did not shut down our CAR-T cell trials even during the pandemic. We continued our GMP manufacture. We continued to enroll patients. I’m thankful for that because these are important therapies that mean a lot for patients not just in our trials in brain tumors but across all cancer types.

There are no borders for these innovative therapies. We often get patients coming across state lines or from out of the country to receive these innovative therapies and enroll in these trials. That’s where we did see a difference. There seemed to be more resistance for patients to travel during the pandemic. We had a little more difficulty in enrollment because these are immunocompromised patients and it is difficult to travel under those circumstances. But we did still have individuals come from out of state to enroll. Now our enrollment and manufacturing seem to be coming back to pre-pandemic levels and we’re happy to see that.

On the research side there were challenges because individuals needed staggered work schedules. I was amazed by the flexibility of the researchers to continue to progress their research. It also gave us some time to step back and publish some papers we’ve been meaning to get out. We have some really exciting work doing a CRISPR screen for both CAR-T cells and GBM cells that was just published in Cancer Discovery. We have a new paper just coming out in Cancer Discovery looking at how CAR-T cells remodel the tumor microenvironment through the production of IFN-gamma. And we’re about to publish a new study developing CAR-T cells through iPSC-differentiated T-cells for an off-the-shelf type approach. While it took people being flexible on the research side, it gave us the opportunity to get some of these stories out that we’ve been meaning to publish.

What are some of the challenges with taking an allogeneic approach for brain cancer?

We’re really excited about moving toward an allogeneic approach for brain tumors. These patients can’t wait. Median overall survival at first diagnosis is just a little over a year and a half. Once those tumors recur, which is the setting we’re treating at, it’s 6 months. Waiting 3-4 weeks for your autologous therapeutic product to be manufactured is a critical time for these patients. Off-the-shelf therapies will be important for all cancer types but will have a real opportunity for brain tumors. Also, the brain is an immunospecialized organ and so you might potentially have a greater therapeutic window before the allogeneic cells are rejected. Quite a while ago City of Hope was one of the first institutions to evaluate an off-the-shelf approach for CAR-T cells in collaboration with Sangamo Biosciences.

The iPSC platform gives us a new opportunity. We have really encouraging and exciting preclinical data for our ability to differentiate these iPSCs into a T-cell lineage but we now need to scale-up the process and make this GMP compatible so it can be administered to patients. There are some unique aspects to the cell product. Our publication will show that these cells look very T-cell-like. They have a conventional T-cell phenotype but the majority of cells are more CD8 in the product versus CD4. We’re trying to use that to our advantage to build out a potent therapy and combination therapies that will be geared to promoting the therapeutic activity of a CD8 CAR product.

“We are now looking at other ways to promote trafficking of the cells and creating an environment in the tumor to better recruit these immune cells. That’s true of all solid tumors but brain tumors represent a unique challenge because of its location.”

What are the biggest challenges to have a meaningful clinical impact on brain tumors?

I wish there was just one challenge. In all cancers, there are many challenges that we are trying to overcome and in brain tumors, all of them are really critical. The first is how to get the cells there. That is a huge challenge in brain tumors because these are regional cancers protected by the blood-brain barrier. How do you get these cells to infiltrate and penetrate these tumors? A lot of our work has been focused on that question and we have started out by focusing on optimizing the route of delivery to address this challenge. We are now looking at other ways to promote trafficking of the cells and creating an environment in the tumor to better recruit these immune cells. That’s true of all solid tumors but brain tumors represent a unique challenge because of its location.
The second key challenge for solid tumors is figuring out how to safely target without compromising or targeting normal tissue. In the brain, again, it is critically challenging. We cannot tolerate any off-tumor targeting in the brain. At City of Hope, we are evaluating three novel CARs for GBM and hoping to build out trials combining them to have a multitargeted approach to address the challenge of heterogeneity.

You want specificity but also broad targeting. A year ago we published in Science Translational Medicine a novel CAR using the chlorotoxin peptide. Chlorotoxin is a peptide that was identified in the venom of scorpions and has had a long history in neuro-oncology showing the ability to bind to malignant brain tumor cells. We built a CAR using the chlorotoxin peptide and are now looking to evaluate the utility of this CAR in the clinic and whether it will be tolerated by patients and if it will broadly target tumors as our preclinical data has suggested. We have treated the first dose cohort and are dose escalating. We are excited to get that data to add to the learnings for targeting IL-13 receptor alpha 2 and HER2.

In addition, another important question is: How do we make the most potent CAR product we can? We can optimize manufacturing, optimize how we genetically engineer, optimize the CAR design and innovate in many other areas. In all settings, when you administer these cells, there are always many more malignant cells than there are therapeutic cells so how do you optimize this therapy so that it can kill multiple rounds of tumor and proliferate once it kills the tumor.

Lastly is the tumor microenvironment. How do you co-opt the microenvironment to become more anti-tumor? Our publication that is coming out and is online shows how CAR-T cells not only kill the tumor but through production of inflammatory cytokines like IFN-gamma can reshape the tumor microenvironment and actually promote endogenous immunological memory. That is really exciting because it shows that the CAR-T cells can kill and, under the right conditions, stimulate a host immune response. I think that the engagement of endogenous immune cells will be critical as we try to develop therapies that are highly effective against solid tumors. There is evidence that CAR-T cells can convert a tumor from “cold” to “hot” and recruit in more immune cells. How do we put that together and ensure that the CAR T-cells are potent enough to tilt that balance in favor of the endogenous immune system?

If you can not only target malignant cells with CAR-T cells but engage the host immune system, you have opportunities of addressing tumor heterogeneity with the therapy. Opportunities to create a whole system that targets these tumors. In our New England Journal of Medicine paper where we saw that CAR T cell therapy mediated a complete response in a patient, one reason that patient responded so strongly, based on our correlative studies, was not only because the CAR-T cells targeted the antigen -- because the recurrent tumor came back antigen negative -- but because there seemed to be engagement of the host immune response. The possible induction of an endogenous immune response by CAR T cell therapy has potential to improve outcomes for patients with GBM and other solid tumors.

**What will the next generation of therapies for GBM or brain tumor in general look like?**

Most of our trials are focused on GBM. If you can crack the nut of curing GBM, you have a good likelihood of helping patients with any type of malignant brain tumor. Most of my studies and research has focused on GBM as the model for malignant brain tumors. It’s the most common and it’s an intractable tumor with few efficacious therapies.

The next generation of therapy will be a multipronged approach that targets tumors in a way that engages the host immune system. We hope these therapeutic cells will act as micro-scalpels that are able to go throughout the brain parenchyma and other areas and eliminate these sites of malignant disease. It’s not going to be easy. We spoke about the challenges. But I am optimistic. I think that there are a lot of exciting innovations going on in the field and bringing together other fields to make a meaningful impact for this patient population and other solid tumors.

**Anything else?**

We are still at the early stage of building out and optimizing cell-based therapies for solid tumors. We have had some early wins like developing CD19 CARs against B-cell malignancies. The power and capability of this therapy is clear. Solid tumors have clearly been a greater challenge but I am very optimistic that we will solve it and provide patients with new options and approaches that have meaningful therapeutic impact.
Advancing Allogeneic Cell Therapy During COVID: Leading in a Pandemic

Rafael Amado, MD, is the Executive Vice President, Head of R&D and Chief Medical Officer at Allogene Therapeutics.

Can you speak about the work you are leading at Allogene Therapeutics?

Our teams at Allogene are leading a paradigm shift in the science of adoptive cell therapy which consist of the use of normal donor T-cells engineered to fight both hematologic malignancies and solid tumors. Our allogeneic CAR T-cell therapy (AlloCAR™) addresses the logistical challenges, availability – including insufficient T-cell yields from low baseline absolute lymphocyte count – and variabilities in the products associated with autologous CAR-T therapy. The fundamentals of allogeneic therapy are the ability to avoid causing graft versus host disease (GvHD) and preventing the allogeneic cells from being rejected. At Allogene, our clinical programs are investigating the use of TALEN gene editing to disrupt the T-cell receptor alpha constant gene and the CD52 gene to reduce the risk of GvHD and permit the use of ALLO-647, our anti-CD52 monoclonal antibody designed to selectively and transiently induce host lymphodepletion. Our goal is to have product available on demand for all patients in need of CAR-T therapy across a variety of tumor types.

As EVP of R&D and CMO, I view my role as the person overseeing the benefit/risk for the products the company develops. As such, I lead a team of professionals involved in the discovery and development of these products. I oversee the advancement of our products across various trials, and various functions such as pharmacovigilance, safety, regulatory, and other aspects of drug development. I see my role as someone to ensure that products are being developed in a safe and effective manner throughout the continuum of the evolution of each of the compounds towards approval.

How have you managed to maintain momentum throughout the pandemic?

The diseases we are treating are life threatening. From the inception of the pandemic, and in collaboration with our investigators, we made the decision to keep our studies open in order to continue to provide these investigational products to patients with advanced lymphoma and myeloma who were refractory to standard therapies. Investigators remained interested in gaining access to our clinical trials as some studies from other sponsors were closing or access was becoming more restricted. We relied on the judgement of investigators and provided guidance to use testing and vaccination to protect patients. Accrual remained active through the pandemic. Across our programs, we have treated over 100 patients with allogeneic cell therapy, many of them in the last 18 months. We have added two additional INDs during this period to test our first TurboCAR™ named ALLO-605 and ALLO-316, our first allogeneic CAR-T in solid tumors for the treatment of renal cell carcinoma. Organizationally, we have maintained the presence of personnel in our laboratories and manufacturing facilities to enable continuation of the discovery research activities and to reach our manufacturing goals, while putting in place measures and policies to minimize the risk of COVID in the workplace.

“The pandemic has not spared the cancer population.”

Were there any specific challenges that came up running the trials during COVID?

Some hospitals had patients with COVID and if a patient came in contact with someone who had contracted the
disease, we observed that patient for infection prior to treatment through the quarantine period. The guide to care delivery during the COVID pandemic issued by ASCO is a useful resource. Unfortunately, much like many in the industry and as part of normal patient care, a few patients acquired COVID in the community months after treatment. The pandemic has not spared the cancer population.

How has COVID affected Allogene’s expansion, with a cGMP manufacturing facility opening in Newark, California?

The manufacturing personnel have continued to come to work with all the measures that we organized to minimize the risk of infection. We had some initial delays in construction early in the pandemic but that was quickly remedied given that this was a facility dedicated to making medicinal products dedicated to saving lives. We completed construction of the facility at the end of last year and we are on track to initiate GMP clinical manufacturing by year-end. We will have to go through all the comparability processes that are required independent of the pandemic. Our role in R&D is to make sure that the clinical trials are ready to introduce the products made in this facility utilizing the final process into the ongoing and future clinical trials.

How do you prioritize while leading a portfolio with multiple programs?

This is always a challenge in any R&D organization, as we must balance multiple programs with finite resources. In terms of prioritization, we work on both products and technologies. We make decisions based on what we see in our trials and preclinical research, what the results are with standard of care and what the competitive space is like.

Our lead program is ALLO-501A, to be developed as the first allogeneic therapy in non-Hodgkin’s lymphoma. Our goal is to initiate a pivotal trial in patients with relapsed/refractory large B cell lymphoma and plan for studies in other lines of therapy and other indications. We also factor in unmet medical need, which guided our entry into solid tumors, and the benefit:risk gaps of existing technologies.

In terms of technologies, we look at areas that may enrich our allogeneic platform such as improvements in the control of rejection or alloreactivity, as well as enhancements in cell function such as our TurboCAR™ technology. Even though autologous therapies are incredibly exciting and can cure patients who heretofore were incurable, many patients either don’t respond or fall out of response. In in vitro experiments, TurboCAR™ technology decreases exhaustion, improves the phenotype and activity of the CAR upon rechallenge, and allows the use of targets in tumors while sparing normal tissue. In the setting of myeloma, which is where our first TurboCAR™ has been introduced, we are investigating whether these CARs can resurge, expand, and combat tumors including those outside of the bone marrow. We are also looking at novel sources of allogeneic cells such as iPSC-derived CAR-T cells through our partnership with Notch Therapeutics, and we continue to make progress on T-cell differentiation.

While allogeneic cell therapies have potential benefits beyond that of autologous products, and clinicians have indicated that there is likely some room for equivalency with regard to efficacy, it’s about trying to increase the clinical benefit. For instance, in multiple myeloma our initial results with ALLO-715 have led to RMAT designation. But there are autologous products that have raised the bar in their performance. So we launched our ALLO-605 product, an anti-BCMA CAR with a TurboCAR™ that has the potential to be more active, to see whether we can get a higher number of patients in deeper responses and prolong their durability of response. This is just one pillar of our BCMA strategy along with consolidation and the use of nirogacestat, a gamma secretase inhibitor which may increase the activity of ALLO-715 by decreasing the turnover of BCMA in malignant plasma cells.

Can you speak about the results of the ALPHA and ALPHA2 studies and your plans for your pivotal phase II trials with ALLO-501A?

We have been incredibly gratified by the results. As reported at ASCO in June 2021, with a single dose, the overall response rate for ALLO-501 in the ALPHA trial has been 64% with 46% complete responses in large B-cell lymphoma autologous CAR-T naïve patients. The complete response rate at six months was 36%, which is on par with what is seen in the autologous CAR-T therapy setting. As we also discussed at ASCO, we have introduced consolidation dosing where we give a second dose approximately at day 30. At the time of the first and subsequent assessments post second dose, we have seen promising results both in follicular lymphoma as well as large B-cell lymphoma, with a number of patients converting from partial responses at day 28 to complete responses by day 56. We are considering the use of consolidation in our Phase 2 clinical trial but we are still awaiting more durability data as we plan meetings with regulatory authorities. We are working full speed.
ahead with regards to regulatory interactions as well as preparatory activities in clinical development, operations, and other functions to get the study of ALLO-501A initiated by the end of the year.

“The ability to treat everybody without intervening bridging therapy, have off-the-shelf availability, and have outcomes that are at least similar to the autologous setting make allogeneic cell therapy a very attractive proposition and we are very proud to have treated a high number of patients in multiple clinical trials.”

Can allogeneic therapy have the same therapeutic window, toxicity level and biologic efficacy as autologous therapies?

Absolutely. I am convinced that allogeneic treatments can match the performance of autologous treatment. We are seeing that in non-Hodgkin’s lymphoma based on initial results from our studies with ALLO-501 and ALLO-501A. The advantages of allogeneic therapy represent an important advance in adoptive cell therapy. We can treat patients within days of entering the study, which may lead to activity that is very similar whether you take all the patients that are treated versus all the patients that are enrolled. That is not the case in the autologous setting where there can be up to 30% attrition of patients who are enrolled. These patients are then excluded from the response assessment, but attrition and disease state are not fully independent variables, so the results to date may represent some selection bias. The ability to treat everybody without intervening bridging therapy, have off the shelf availability, and have outcomes that are at least similar to the autologous setting make allogeneic cell therapy a very attractive proposition and we are very proud to have treated a high number of patients in multiple clinical trials.

What are the biggest challenges to be overcome for allogeneic cell therapy to make a meaningful clinical impact on solid tumors?

Solid tumors represent the majority of malignancies in humans. While using TCRs presenting neoepitopes is a promising strategy, it may be hampered by the paucity of shared antigens among tumors, which requires personalized therapies of engineered cells. Responses in solid tumors with CAR-T have proven elusive due to a variety of factors including lack of targets that are exclusive to the tumors and other factors that may prevent adequate expansion, migration of CAR-T cells to tumor deposits and avoidance of the suppressive effects of the tumor microenvironment. The advent of gene editing is making possible testing targets that are shared with normal tissue, such as the use of dual CARs that utilize logic gates to spare non-tumor tissue. In addition, it is possible to engineer CAR-T cells to respond with stimulatory intracellular signals when they encounter immunosuppressive ligands and some of these ideas are already being tested in clinical trials. If the tumor microenvironment is inhibiting CAR-T cells, one can work to genetically engineer allogeneic cells around these inhibitory steps. The use of allogeneic cells can represent an advantage as these are cells from healthy donors which can have enhanced functionality in response to antigens, provided that both GvHD and rejection are controlled by genetic engineering. Allogeneic therapy has enormous potential not just because of the convenience and the ability to treat everybody but also because you can take advantage of gene editing technologies that are emerging in the cell therapy space, unlike autologous therapies where genetic editing is limited as it is based on patient specific products.

Anything else?

The enthusiasm behind this field is palpable. What’s exciting about AlloCAR T™ therapy is that this paradigm shift could be on the market in the next few years. This truly has the potential to be the next step in revolutionizing treatment for patients with cancer and we are excited to be leading this breakthrough area of development. Over the longer term, the field will continue to grow and expand, and we will work to maintain pace with existing technologies, and to lead the way of novel ones, so that we create the cellular therapies of the future that may transform the way we treat patients with cancer in need of novel treatments. ●
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IO360° 2022, February 16-18

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