Allogene’s Dr Arie Belldegrun shares his vision on biotech innovation

Dr Lisa Butterfield on how PICI is changing the model of cancer research

Adriana Comprelli, BMS on how clinical operations are evolving through COVID-19 and beyond

A patient’s journey Steve Hamilton’s experience participating in an IO combination therapy clinical trial
Welcome Letter
September 2020

Welcome to the inaugural interview issue of the IO360° quarterly newsletter.

In June 2015, we launched the first Immuno-Oncology 360° Conference to combine business and clinical development strategies with scientific updates to help prepare the market for accelerating IO clinical trials. Building on the success of the last six years, the IO360° quarterly newsletter continues the conversation and raises the voices of inspiring people fighting cancer on all fronts in the IO space, including patients.

In this newsletter’s inaugural issue, we are pleased to share a feature an in-depth interview with Arie Belldegrun, MD, FACS, Executive Chairman and Co-Founder, Allogene Therapeutics and Co-Founder and Senior Managing Director, Vida Ventures, as well as the following incredible interviews:

Lisa Butterfield, PhD, VP, R&D, Parker Institute for Cancer Immunotherapy, talks about cancer vaccines and collaboration.

Dimitris Skokos, PhD, Senior Director, Cancer Immunology Research, Regeneron Pharmaceuticals, discusses costimulatory bispecifics and future development strategy.

Adriana Comprelli, Therapeutic Area Head, Clinical Operations Strategy, Bristol Myers Squibb, describes adapting clinical operations to COVID-19 and innovations in the area.

Steve Hamilton, Cancer Veteran, shares his journey participating in a clinical trial with an IO combination therapy.

John Connolly, PhD, CSO, Parker Institute for Cancer Immunotherapy, speaks about immunometabolism and how PICI is revolutionizing cancer research.

If you are interested in contributing to a future newsletter, please contact andrew@tcflc.org

Enjoy the interviews.
What’s Inside?

Arie Belldegrun, MD, FACS, Executive Chairman and Co-Founder of Allogene Therapeutics and Co-Founder and Senior Managing Director of Vida Ventures, explains how he is innovating in allogeneic CAR-T and investing in the future of biotech.

Lisa Butterfield, PhD, Vice President of Research & Development of the Parker Institute for Cancer Immunotherapy, talks about cancer vaccines and collaboration.

Dimitris Skokos, PhD, Senior Director, Cancer Immunology Research of Regeneron Pharmaceuticals, discusses costimulatory bispecifics and future development strategy.

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Steve Hamilton, Cancer Veteran, shares his journey participating in a clinical trial with an IO combination therapy.

John Connolly, PhD, Chief Scientific Officer of Parker Institute for Cancer Immunotherapy, speaks about immunometabolism and his new role with PICI.

Recommended Podcasts

Cancer Immunotherapy Debate: Bispecifics vs Cell Therapies

How AI, Machine Learning and Big Data are Used to Inform Combinations

New Opportunities for Cell Therapy Combinations

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What does it mean to you to light the fire of biotech innovation?

I gave that title for my presentation at a conference last year and I’m not sure that’s the right title anymore. There is no need to light the fire now. Biotech innovation is more on fire now than anything that I recall in the last 25 years of my experience in the life science business. If one just looks at the last quarter of 2020, there were $6.4 billion of new investments in life science, the highest ever in biotech.

People realize that when there is a major medical problem in the world, the best scientists and drug developers jump in and come up with solutions that save lives. Therefore, drug pricing and other issues that usually come before election time take a backseat to the issues that we can solve in life sciences.

How do we capitalize on that fire and make sure the innovation creates lasting change?

This process of innovation is now unstoppable. The Human Genome sequence project was completed 17 years ago. Once the scientific community started understanding the different molecular dimensions of human health it gave rise to precision medicine, gene therapy, immunotherapy, the development of molecular markers and other important translational discoveries. The biotech world then moved away from the traditional trial-and-error strategies to evidence-based discoveries. Once the genes are cloned and their function understood, the rest is straightforward and the process can run fairly quickly.

Today, science drives innovation. These innovations are then translated to medicines. If you look at cell and gene therapy, gene repairs and CRISPR gene editing, these are all revolutionary and life-changing discoveries. That’s also why more and more young researchers are moving to work on true translational science. We are definitely in the right space in 2020.

What do you see as some of the critical success factors for the many companies in the cell and gene therapy space?

Undoubtedly, impressive early clinical data was the driver for the proliferation of companies in the space. In 2009, when we founded Kite Pharma to devote a company to engineering the human immune system, it was the only company I am aware of that was dedicated to the field. Over the following years, others joined the field. Today, there are over 400 cell therapy companies. It became a truly exciting field where each company believes that they have something unique and better than the others.

The early success in the field was really driven by a small group of leaders in cellular therapy. There were only a handful of centers dedicated to engineered cell therapy who continued to develop the science despite lack of funding or interest by the biotech world. They brought it to a place where Kite and others were able to successfully translate it to patients. That was the seed. Without them, the entire field would have never proliferated as is the case today.

Once the proof-of-concept for the technology was recognized, it started to gain the interest of the clinical and the scientific communities. What excited them most was the fact that within 3-4 weeks from infusing the cells, major tumor masses melted away and patients dramatically improved. The patient’s own engineered lymphocytes home to the tumor and destroy it. This is done with a single infusion and treatment, rather than chemotherapy for life.

“I like the challenge of being at the cutting edge of medicine and being able to predict where the science will go based on the clinical needs.”

Staying Ahead of the Scientific Curve

Dr Arie Belldegrun, MD, FACS, is the executive chairman and co-founder of Allogene Therapeutics as well as the co-founder and senior managing director of Vida Ventures. Dr Belldegrun has been closely involved with the founding and advancement of several successful private and public biopharmaceutical companies including Cougar Biotechnology, Agensys, and Kite Pharma. Dr Belldegrun holds the Roy and Carol Doumani Chair in Urologic Oncology, and is Director of the UCLA Institute of Urologic Oncology at the David Geffen School of Medicine at UCLA.
The early trials started with leukemia and lymphoma and then moved to other blood cancers, such as multiple myeloma. The next challenge is solid tumors. What drives excitement is the ability of patients to achieve complete responses. This is the first time we can almost talk about the “cure of cancer.” When I was in residency at Harvard, we used to say, “the C word doesn’t exist.” But today, you can talk about “cure” in a growing subset of patients. Each company will expand on these results and hopefully we will move in the right direction.

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

Having established the proof-of-concept of cell therapy in hematologic oncology, the next frontier is solid tumors. This is a more challenging problem because of the host immunosuppressive environment that is generated by the cancer. Tumor-infiltrating lymphocytes (TILs) are getting to the tumor but become immunosuppressed and lose their power to kill cancer cells. Initially, we tried to take these TILs and activate them outside of the body and give them back to the patient. This was clearly not the answer.

The full solution is to work on reversing the host immunosuppression while activating the T cells to become more powerful. On the one hand, you need to increase the activity of young T cells. On the other hand, you need to decrease the immunosuppression around the tumor and create an environment where the adult T cells, NK cells and macrophages can work in concert to create a full effect against cancer cells. This is the next challenge for the field of cell therapy.

“It’s tempting to do a lot of things at the same time but in order to create something unique, one must focus”

How have you managed to stay ahead of the curve when it comes to what’s coming up the pipeline?

That is really the fun part for me. I like the challenge of being at the cutting edge of medicine and being able to predict where the science will go based on the clinical needs. I started attempting to predict where the science was going when working with Dr Steve Rosenberg at the NIH and then as a professor at UCLA, where I ran my own laboratory and could identify the areas in which I wanted to focus my research. Later on, I moved to create our own biotech companies to bring real products to benefit patients. This is a highly satisfying feeling.

Being among the first in a space is challenging but at the same time relatively simple. You do what you believe is right. Now life in the space of cell therapy is much more complicated. One needs to know what 400 or so companies are doing and find ways to differentiate yourself from the others. Not always easy. It’s gratifying for me to see how much excitement cell and gene therapy are generating today compared to just a decade ago.

What was it like to transition from the autologous space to the allogeneic space?

It was a natural process for us. At Kite, we took blood from immunosuppressed patients who already had chemotherapy, radiation and bone marrow transplants. We took the blood from the patient, sent it to our manufacturing plant, processed the cells, engineered them and then shipped it back to the hospital to give to patients.

It was exciting and the responses were dramatic but it created several issues. Number one: Manufacturing. Nobody before had built an engineered cell therapy processing facility. We had to design our own factory for cells with GMP and FDA inspections, and with no prior experience. But it worked and became a success. This year at Kite, they produced over $500 million worth of product in that facility we designed in 2015. Now at Allogene, we are building a facility that could potentially produce billions worth of product for allogeneic CAR-T therapy.

Number two: Off-the-shelf therapy. With the autologous approach, if the doctor wants the cells to be infused into a patient on a given Monday morning, the team needs weeks to produce the therapy, including weekends, in order to process and ship it to them by that day. Therefore, we started thinking about how we could make manufacturing scalable and more efficient, reduce the time a patient had to wait for therapy, and make the therapy accessible to more people all over the world.

Kite was a small company and very focused. Our mission was first and foremost to open the door for engineered cell therapy approval with the FDA. Next was to improve the therapy and make it more accessible for patients. That is how the allogeneic approach got our attention. With an allogeneic approach, we are taking blood from a healthy volunteer – not from a patient – and engineering and gene editing the cells to create CAR-T therapy that is stored in a liquid nitrogen freezer. From one patient, we can generate more than 100 treatments. When the patient needs therapy, it’s readily available.

For us, the sequence of events was very logical in moving from autologous to an allogeneic approach. After Kite was acquired by Gilead in October of 2017, we identified an opportunity at Pfizer. They had been working internally and built an amazing team of experts focused on an allogeneic approach. It whetted our appetite and we moved to partner with Pfizer and acquired these assets to create Allogene Therapeutics.

Allogene received 17 potential products from Pfizer, at different stages of development. We took 40 employees from Pfizer to Allogene and created a company dedicated 24/7 to only allogeneic product development. David Chang, CEO of Allogene Therapeutics, is doing a phenomenal job in moving these products from our labs to patients as fast as possible.

How do you stay flexible and adaptive in new areas?

Always look for the right people who can help you build a new industry and try to predict where the field is moving and how it is going to change. When building a
manufacturing plant for engineered cell therapy, we found people with experience in building manufacturing for antibodies to adapt that expertise for this new space.

It was also clear to us that it could not remain a static manufacturing plant. Technology would change rapidly. The equipment will change. It’s not much different than what happened in the computer business. What is now a laptop once took up half a room. We needed to take the future into account and remain flexible. And that’s what we’re doing with what we’re building for allogeneic now.

What advice do you have for small and emerging biotechs navigating the cell & gene therapy field from early stage through commercialization?

The name of the game is focus, focus and focus. It’s tempting to do a lot of things at the same time but in order to create something unique, one must focus. Surround yourself with the best people in the industry that you can find. You need to be able to attract talent with expertise in science, in process development, in translational medicine, and clinical development, as well as experienced regulatory people who understand how to interact and gain credibility with the FDA. Finally, remember that in the business of cell and gene therapy it’s all about the “art” and science of manufacturing the product.

Cell therapy is different than any other pharmaceutical product, and given its complexity it has to be a group effort, rather than a one-man show. It’s not about a star CEO. It’s about bringing the best people and the best technology together. Technology is rapidly changing and it must constantly be under consideration.

As someone who has founded biotechs and also has invested in biotechs, what do you look for in companies to invest in?

Three years ago, we founded Vida Ventures, a venture capital group that focuses on investing in cutting-edge technologies and companies. Since then we had the privilege of evaluating many hundreds of opportunities that were presented to our team. We therefore have quite a good understanding of what is out there in the world of Life Science.

How do we try to select the winners? We first evaluate the science. If I don’t believe that it will make a major change in the life of patients, I am personally less excited. I want to see a technology that eventually translates to a product that will make a difference.

The second criterion is people. How experienced are they? What’s their scientific level and experience? How’s their integrity? Have they brought a product to the market? Are they good drug developers? Then there is evaluation of the intellectual property. So science comes first but there is also a bit of an art component to good investing.

Different VC groups have different investment philosophies. The size of the investment per company also dictates the selection process in which companies to invest. At Vida Ventures we limited how much money we took from investors because we wanted to focus on which type of companies we were interested to invest in. In our fund 1, we wrote checks anywhere between $10-20 million per company. In fund 2, we are now investing up to $50 million per the life of a company. So that’s also an important component and dictates the type of company in which to invest.

“It’s not about a star CEO. It’s about bringing the best people and the best technology together.”

Speaking of the next generation, is there anything coming down the pipeline that really excites you?

There are a lot of areas that personally excite me these days. But mainly I can see great promise in the near future in the areas of cell therapy and immunotherapy, gene therapy, precision medicine, transcription regulators and undruggable targets.

The field of engineered cell therapy started with developing products for blood cancers, since it was felt that they represent the lowest hanging fruits for success and FDA approval. Next are solid tumors and non-oncologic indications such as autoimmune diseases, HIV and inflammatory bowel disease. At Vida, for example, we are founding investors, together with Gilead, in a company called Kyverna to focus on that area.

Beyond cell and immunotherapy, the prospect is fantastic for correcting genes in monogenic disorders, using gene therapy. Currently, the focus is on rare diseases, as they are caused by a single gene defect. Cancer is a more complicated story, where multiple gene defects and mutations exist. But with gene editing technology we are going to see exciting developments in cancer and other more complex diseases.

Precision medicine, for both oncologic and non-oncologic indications, is also an exciting area. Understanding the precise molecular mechanisms and the science behind a given disease opens the opportunity to either block, activate, or manipulate the defect of the disease based on precision approaches.

Finally, the area of transcriptional regulatory networks and protein degradation or inhibition of undruggable targets is quickly coming up as an intriguing new field of drug development. We are involved in that area with more than one company, but the more advanced one is Kronos Bio, under the leadership of Norbert Bischofberger.
Can you tell us about the work you are leading at the Parker Institute?

Most of what I’m doing in the Parker Institute is facilitating research programs and in particular, those around cell therapies. PICI has a major interest and real belief in the power of cellular therapies, specifically engineered adoptively transferred T cells. We want to support those efforts and also coordinate research in multiple aspects of cancer immunotherapy, including cell therapy.

How do you facilitate that collaboration?

We have really terrific scientific retreats twice a year, where we bring all of the network investigators together. Because of the nature of the network that has been built, people are open about what they’ve seen in their trials and in their labs. We have young investigators who are on the projects, but we also fund a group of scholars and fellows who also openly interact with each other, presenting updates, spending 2-3 days together. Collaborations can spring up spontaneously, and also everyone can come together and recognize a particular area that needs some more work.

The agreements among the sites created an atmosphere with IP protection, confidentiality and collegiality that help people collaborate. That has led to very exciting clinical trials. Investigators can bring their best knowing that there’s true impact for patients through PICI network projects and trials.

What about you personally, what are you working on in your own research?

I run an independent research lab that moved to UCSF a year and a half ago. When I moved, I had completed a dendritic cell (DC) vaccine clinical trial in melanoma. We had performed a lot of pre-clinical studies after the previous trial to see how to improve our DC vaccine. We tested a combination that had a lot of literature behind it, and in vitro rationale. It turned out that this trial was similar to some past trials in that 5-10% of patients had objective tumor regressions, some durable responses and most had induction of antitumor immunity. Very good, however it wasn’t a big home run.

Now we’re finding out why. We are learning what did and didn’t work, and really refocusing efforts utilizing the amazing technical capabilities we have now to identify real improvements and take the important lessons forward to the next trial.

Do you have any findings or any ideas as to what your next trial will look like?

We had a paper come out a couple of months ago in the Journal of Experimental Medicine led by Patricia Santos and Juraj Adamik. They dug into the T cell responses in those patients and we looked for an exhausted T cell story. That’s not what we found.

When we started the trial, checkpoint blockade was just becoming standard of care. We found that patients who received PD-1 or CTLA-4 checkpoint blockade first had increased baseline frequencies of melanoma-specific T cells, but it didn’t change the response to the vaccine. We looked in vitro at stimulating the T cells with the vaccine simultaneously with PD-1 blockade and that didn’t make anything better either. But patients who received checkpoint blockade by standard of care after the vaccine had a huge increase in their functional melanoma-specific T cells. It was small patient numbers but it points us in a direction in terms of therapy sequencing. We found that within a DC vaccine, the antigen dose doesn’t make any difference. We also tested IFN-alpha as a combination and it was also not an improvement. We checked a number of good ideas off that we will not test again, because they weren’t good enough, so, the sequencing of checkpoint blockade is going to be one important finding.

We also looked at the DC vaccines themselves. This is in a manuscript in revision from Deena Maurer and Juraj Adamik. We measured many things about them that don’t turn out to correlate with the induction of T cells or clinical regression of tumors. We looked at all phenotypic markers of co-stimulation and the relative amounts didn’t make any difference. IL-12 p70 production by those cells didn’t correlate with outcome either.

We’ve identified ICOS ligand as something that looks important. Cells made from melanoma patients have dysfunction in NF-kappaB that can lead to reduced levels of ICOSL, and impact shedding of the ICOS ligand.
on the DCs. So, we’ve homed in on one molecule that we think is important so far and there are a number of other pathways we’re looking at. In vitro, cancer patient cells look just as good as healthy donor cells if you use standard measures, but I think we haven’t been measuring the right things to really identify what is critical of those vaccine cells.

What challenges are associated with cancer vaccines?

One is how to incorporate them into checkpoint blockade. There’s a rationale to go in different directions, and it may differ with the platform of the cancer vaccine. I think there’s a complexity around combinations and how to build on these different components that we have to address.

Another challenge is the antigens. People like me have been focused on shared self-antigens that are not mutated for a very long time. Once in a while they can cause tumor regression and durable response. But they haven’t been home runs. So the field has shifted to neo-antigens. Those have been shown to be very immunogenic. They’re shown in murine models to be superior in a number of ways. We’re watching for human data that shows what they’re capable of doing against patient tumors.

The last one is about who to vaccinate. A standalone vaccine is not enough in a late-stage patient even if we optimize it in a number of ways. There may be settings where cancer vaccines would be enough as a prevention step in a high-risk patient who already has precancerous lesions (colorectal polyps, pancreatitis, or a long-term smoker with lung tissue problems). That’s an important area for investigation.

What other developments and advancements are being made in the area to address the challenges of cancer vaccines and improve responses?

One important hurdle is trafficking. If you create a systemic immune response you can detect in the blood, how can we better get those cells to the tumor? How can we tell who will benefit from receiving a cancer vaccine? What can we learn about a given patient’s tumor that will instruct us about the unique issues that we need to address? Some patients’ tumors are immune deserts so trafficking or changing that microenvironment is the main challenge. Other patients have an infiltrated tumor but there is also very active immunosuppression. Maybe we have to do something about regulatory T cells or differentiate their myeloid-derived suppressor cells to allow the T cells to work for them. There’s a patient-specific component to this that needs to be addressed for us to make the vaccine piece work better.

What made you passionate about immunotherapy and cancer vaccines? How do you maintain that motivation today?

Initially, in junior high, I decided that I wanted to do gene therapy and started looking at majoring in molecular biology. When I got to graduate school, the field looked like I would spend ten years in the dark corner of a lab engineering a viral vector. That would not have been a very satisfying way to be a scientist. When I started looking at cancer, it looked like molecular biology could be a tool but cancer was a disease that was incredibly important, common and a place where a research scientist like myself could partner with clinicians and really have an impact on human health.

I got interested in the immune system in my first post-doc. In my second post-doc, I had a fabulous time in a laboratory at UCLA run by a surgical oncologist who wanted to do bench-to-bedside cancer gene therapy. We all performed five clinical trials together in 8 years. You carry on even when the field stalls. When I joined SITC, there were around 200 people at the annual meetings, and everyone was a true believer despite limited data. The revolution that started ten years ago when we started getting data on checkpoint blockade really showed us that there’s clinical impact from cancer immunotherapy. Things wax and wane and you can’t jump from field to field just because you had a bad year. People keep plugging away, trying to understand what’s working and what’s not, why it’s working and what the mechanisms are.

While that’s going on, technology has evolved. Then you get a period like now where the data are phenomenal. It’s amazing to be able to see what cancer immunotherapy can do in a cancer patient.

What’s the best advice that you’ve ever received or lessons you’ve learned throughout your career?

On a simple level, seize opportunities when they are presented to you. Say what you’ll do, and then do it, and do it on time so that people know that they can count on you and that you’re a good colleague. Then they will reach out to you again for the next opportunity. Environment is incredibly critical. I’ve gone to universities that have strong clinical and translational science. That quality environment allowed me to be the scientist I was capable of being, adding to that environment and supporting it and being supported by it.

I think you have to understand so much about what your field is in order to make an impact. I’ve mostly studied two different cancer types. I focus on a piece of the puzzle that is vaccination. That focus allows you to understand the critical questions you are posing. The other side of that is collaboration outside of your focus. That brings new perspectives and ideas to you and to your collaborator.

How do you see the Immunotherapy field evolving over the next 5-10 years?

I’m very excited to see what comes next. We’re going to learn more from every patient, from every blood cell and tumor cell that we get. We’re capable of doing much smarter engineering of the elements that we want to test clinically and then more thoroughly analyze the outcomes. Just like we have immune-infiltrated “hot” tumors and immune-excluded “cold” tumors, we’re going to identify additional themes so that immunotherapy becomes increasingly personalized. We’ll be able to bring a more personalized approach based on tumor biology and immune function, and a greater technical ability to create smart therapies and perform smarter analytics on them.
How are you working to be more collaborative and build those cross-functional groups?

Regeneron is built around revolutionizing technology platforms. That's one of the key ingredients that can set us up for success. The idea is to bridge the technology platform folks together with the people from different functions such as Oncology and Angiogenesis, Therapeutic Proteins, Bispecifics and Cancer Immunology, amongst many others, under the same goal to push it to the next level.

You published a study recently about using costimulatory bispecifics with anti-PD-1. Could you talk about that?

Our CD28 costimulatory bispecifics are designed to bridge T-cells to cancer cells, thereby selectively activating T-cells at the tumor site and synergistically enhancing the anti-tumor activity of foundational drugs such as anti-PD-1 therapy and CD3 bispecific antibodies.

Our study published on June 24th was the first to demonstrate the benefit of combining a CD28 costimulatory bispecific with anti-PD-1 therapy. Our preclinical research found this combination overcame resistance to anti-PD-1 monotherapy and endowed long-term T-cell memory in multiple preclinical cancer models.

Importantly, we did not observe systemic cytokine release syndrome in our animal studies, which has historically been a challenge with CD28 superagonists. We believe this pathway is important. Therefore, we invested the time to understand it, generate high-quality preclinical data and carefully move this therapeutic combination into the clinic.

So what comes next after this study?

We remain focused on better understanding how CD28 costimulatory bispecifics can enhance our immuno-oncology treatments. To that end, we are looking holistically at the quality and the characteristics of T-cells generated after treatment with combination therapies involving our CD28 costimulatory bispecifics using deep-immune profiling and single-cell sequencing technologies to help us optimize our therapeutic options and boost discovery.

Were there any challenges or difficulties with the study or the costimulatory bispecifics?

To provide some background, back in 2006, in a Phase 1 trial conducted by another company, a CD28 superagonist overactivated T-cells throughout the bodies of healthy volunteers. This caused life-threatening levels of cytokine release syndrome (described as a cytokine storm), leading to multiple organ failure. That set the field in a situation where everyone was afraid to touch this particular pathway, despite its promise.

This led us to carefully select CD28 costimulatory bispecific candidates that would only activate T-cells when they were bridged to cancer cells and after having received the first “recognition” signal via the TCR/CD3 complex. We also tested the safety of our CD28 costimulatory bispecifics in several animal models.
and showed they did not induce cytokine storm when administered as monotherapy or in combination. That was an important aspect that we discussed in the June 24th publication but also in another study published also in Science Translational Medicine on January 8th, 2020.

You also recently published a study characterizing the TCR repertoire of CD8+ T-cells in MC38 tumors and the spleen. Could you talk about that and its implications?

That paper offers a window into how we are developing cancer therapies at Regeneron and the closely integrated way in which R&D and clinical teams work. This study showed the impact of novel combination therapies on T-cell biology both on the intratumoral and peripheral level. It provided essential information on assays needed to translate the R&D into clinical trials.

Our goal is to develop and apply relevant, systematic and comprehensive assays to better understand how our combination therapies affect the quality of intratumoral and peripheral T-cells. This methodology, and the subsequent data generated, influence how we approached our experiments with, for instance, PSMAxCD28 + anti-PD-1, which is the first costimulatory bispecific going into the clinic, as well as other interesting and exciting combinations we are exploring. This study provided essential information to our clinical colleagues and helped them with the clinical trial design. At Regeneron, our preclinical efforts are hand-in-hand with our clinical neighbors. There is no firewall between departments. We always look for this cross-functional interaction.

Can you tell me a little bit about the costimulatory bispecific that’s going into the clinic?

In 2020, Regeneron plans to enroll patients in clinical trials investigating three different CD28 costimulatory bispecific candidates. The first trial is already underway and involves a combination of PSMAxCD28 (REGN5678) and our anti-PD-1 therapy Libtayo® (cemiplimab) is prostate cancer. To date, we have treated patients in several dose-escalation cohorts in this trial.

Before the end of the year, we also plan to begin a clinical trial with EGFRxCD28 (REGN7075) and Libtayo in solid tumors for non-small cell lung cancer, head and neck squamous cell carcinoma, cutaneous squamous cell carcinoma and colorectal cancer. Further, MUC16xCD28 (REGN5668) in combination with either Libtayo or MUC16xCD3 (REGN4018) will be tested in ovarian cancer.

At this year's IO360 you said that “The game is trying to anticipate what are the limitations of existing treatments and bringing something new.” How do you anticipate the limitations of existing treatments?

Despite the immuno-oncology revolution and the encouraging and sometimes impressive clinical results to date, this field is still in its infancy and there is still significant room for improvement. We need to invest the time and the resources to understand why some immunotherapies succeed in certain tumor types and why others fail, on a biological level. The idea around that is to use this knowledge to develop medicines that will further increase the response rate across multiple tumor types and also drive more durable responses.

What are the next steps in that investment? What should we be investing in?

One of the examples that we just discussed is investing in the next wave of cancer immunotherapeutics like the development of costimulatory bispecific antibodies. While innovations in the field overall mean that we have a growing plethora of immunotherapies, we have to recognize their limitations and better understand the resistance mechanisms that cancer uses to evade current treatments. This information will help us to make educated choices on how we can develop the next wave of combination therapies and tailor them to specific indications. Then we may be able to change the course of this devastating disease.

What made you passionate about entering the field?

I grew up in a middle-class artistic family in Greece, an environment that instilled in me the freedom of thinking. The catalyst was when my father got diagnosed with lung cancer. What excites me about my job is that innovation happens when knowledge meets intuition and imagination. At the end of the day, our goal is to understand the biological phenomenon in order to find cures and save people’s lives. That’s what we do in science. Passion will always be there until we find the cure.

What’s the best advice you’ve ever received?

During my postdoc studies at The Rockefeller University, I was fortunate enough to be groomed by an immunology luminary, Ralph M Steinman, recipient of the 2011 Nobel Prize in Physiology or Medicine for his discovery of dendritic cells as an orchestrator of the immune response, linking the innate with the adaptive immunity. Ralph taught me to tune out people without imagination, not to get discouraged, and to keep working to prove the importance of scientific discovery. At the end, this is our commitment to science itself.

Where do you see immunotherapy evolving over the course of the next 5–10 years?

We are in a unique position as a field. The foundations of immuno-oncology have been established over the last decade, and we have a variety of new therapeutic options available for patients. Moving forward, we need to identify and develop optimal combinations to improve the response rate across multiple indications and enhance the durability of the anti-tumor response.

Is there anything else you wanted to highlight?

Every single day counts in the fight against cancer. At Regeneron, we are motivated by the hope generated by the recent clinical breakthroughs. Another important thing is the investment in synergistic thinking and working together in a cross-disciplinary manner with aligned goals. This mentality combined with our proprietary and robust technology platforms, which can generate high-quality antibodies, will be an important ingredient to reach our goals and expectations.
How has COVID-19 disrupted your clinical trials and how have you adapted to it?

Immediately, we recognized patient and provider safety in our clinical trials as the primary goal for our research and development organization, and looked to find ways to manage ongoing patient treatment until we could understand the scope of what was happening at the centers and clinics. Once we put controls for patient and provider safety in place, and options for compliant data, dose administration and patient care were determined, and we reopened activities.

We had to do a prioritization exercise by looking at the health impact to patients. We looked at what was most important to get patients their drug product or to start enrolling and randomizing those patients at most risk. Safety, patient care and access to the study drug have been our primary goals.

Personally, our own work-life balance was something we all had to understand. It wasn’t our typical work-life balance, but we all needed to assess our family and self-care needs first and then determine, "how does my workday fit into this?" As leaders in our businesses, demonstrating that it is okay to step away, to have a noisy background and to connect personally with our colleagues brings a sense of security and acceptance to our teams.

How were you able to balance work and life?

I prioritized my family in the morning with homeschooling and getting them set up for the day. I focused on being present with my family, making sure that they were set up and had what they needed and had some down time for them in the afternoon so I was able to focus on work. It was messy in the beginning but we got into a groove.

What will clinical trials look like when things “go back to normal?”

There will be components that we learned and adapted to during the pandemic that will remain in place afterwards. Potentially across industry, you can imagine that resource modeling will be adjusted to accommodate the upswing in remote access and technology-based solutions used to manage site and patient access during the pandemic. It would have to either be additive, in that a role to manage these solutions will have to be present but then also we will have attrition in those traditional on-site roles. It may ultimately even out because of the creation of new roles to manage technology, but would definitely shift.

Although technology typically moves metrics and timing to faster outputs, I imagine that the additional need for patient and healthcare worker safety will temper that speed, and until COVID-19 is controlled, technology in operational activities will not drive an increase in speed and metrics.

Additionally, sites, institutions and ethics committees will have to accommodate cloud- and remote-based activities as the norm, many of which were limited in the past due to conservative approaches to patient data and cloud-based technology. I think they will become more open to those formats where they weren’t in the past.

Where do you see the direction of clinical operations going in five to ten years?

There are so many things that will impact what we do. One of the most tangible evolutions would be the drug product. I’m seeing so much innovation in manufacturing and drug technology where there won’t be that very long chain of custody. Ideas such as direct-to-patient supply, whether at the hospital bedside or at home, are possible, which cuts out a lot of components that need to be managed with regard to compliance and monitoring. These changes in drug products and technologies will spur change in how our business operates.

The other piece is the evolutions of our health and data systems. Within the pharma industry, we’re seeing a shift for data management and patient data access. With electronic medical records, data availability and data sharing, we will be able to work faster and make faster clinical decisions and have virtual trials because patients will have the ability to access ways to give us data, whether it’s clinical data with tools or entering data. This will also allow for meta-analysis trials where we use Big Data functionality to run analyses on data that we already have and use that to do submissions. We will need the flexible resources and processes to manage these diverse study types and data sources.

Innovations in Clinical Operations

Adriana Comprelli, is the Therapeutic Area Head, Clinical Operations Strategy at Bristol Myers Squibb. Ms Comprelli is responsible for the operational strategy and planning for a portfolio of innovative assets in early clinical development.
How can clinical trials be more innovative for new molecules that may not have a regulatory history?

There is much to be gained in viewing the agility and innovative thinking in spaces such as early clinical development. Moving through uncharted territory for new molecules inherently drives the need for innovation through limited spend on process and increased spend on delivery of smaller, more frequent milestones.

Health authorities or regulatory agencies are open to discussion for novel options. Operations holds the key to innovative potential in drug development options, and a highly regulated environment should be the guide but not the rate limiter.

What inefficiencies do we need to leave behind?

In the IO and cancer therapy space, one of the most important components of our clinical research are pharmacodynamic and biomarker samples that we collect from patients. Some patients are very ill and really give a lot of their time and themselves to give those samples. As an industry, we need to improve sample management, analysis, getting results and returning that data (e.g., for approved markers) back to physicians and patients.

There are some archaic medical systems and disparities in data systems. These systems need to be resolved and aligned to get these trials out to patients. We need to figure out how to provide easy-to-use, inexpensive platforms, such as devices and web access, and their training for patients who typically don’t have them.

What innovations in the clinical operations space are you most excited about? For those and other innovations, what foundation needs to be built?

Virtual trials would be so life changing to many patients who have trouble leaving the home or wouldn’t typically get access to innovative or novel medicines that haven’t been approved yet. The development of those modalities for virtual trials would be very impactful to patient populations.

There are some archaic medical systems and disparities in data systems. These systems need to be resolved and aligned to get these trials out to patients. We need to figure out how to provide easy-to-use, inexpensive platforms, such as devices and web access, and their training for patients who typically don’t have them.

What can we collaborate better?

In my experience, if teams or functions are afraid to put forth realistic feasibility and presentation of their risks and capabilities then it doesn’t work. You have to give the options and trade-offs but be very realistic in your what-if scenarios. At times, we must work with the full dataset and the full end goal. But if there are opportunities to make decisions on a smaller subset of data, those should be considered in the trial planning. That multifunctional input and scenario planning can work if everyone agrees to be accountable for that shared decision.

How can you balance speed, success and cost?

Frequent check-ins and progressing in a stepwise fashion allows you to go quickly through and fund some phases and then review where you are at different points, measuring success and determining if you need to make a change. Be willing to be agile with your scenario planning and know that you will most likely have to account for change. This way, you aren’t building the entirety of a five-year protocol plan but working against a nine-to-twelve month goal. That allows you to move faster at less cost upfront. Additionally, having decisional brakes gives you allowance for change based on new technology and new data.

What’s the best advice you’ve ever received?

A little bit of nerves are good. It was so early in my career, but it meant that those nerves keep you accountable, humble and present, without causing you to slip up.

Keep your presence of mind in gratitude that although this is a big industry, a big business, you are working in service to patients and the health and safety of potentially thousands of people.

What made you passionate about entering the field? How do you maintain that motivation?

My father passed away at the very young age of 45 from lymphoma. Cancer destroys so much in families: the loss of a loved one, financial insecurity, mental health impact. But it can also spur resilience. I wanted to do whatever possible to work against cancer and serious illness hurting other families or my own. Research and science were always a passion for me, and I was fortunate to be a part of the clinical trials and approvals in immuno-oncology. The innovation and hope that it spurred showed all of us what is possible in drug development.

There will always be a need to help patients who are very sick. That will never change or go away. So many of us who work in research and development are inherently tuned towards helping people. Seeing that you can create a successful treatment that extends a patient’s life and provides them better quality of life allows us to not yield in our motivation. There is always a new treatment and there is always more research being done to help patients. The idea that through our research we are impacting people’s life is omnipresent and very motivating.
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Can you tell us about your diagnosis and your experience?

I was originally diagnosed in October of 2006. I noticed a bump on the top of my head one night after taking a shower. I went in to see my dermatologist. She took a biopsy but wasn’t overly concerned at the time. She called me the next week and told me that I had melanoma. That set course from 2006 to today in terms of everything I’ve gone through from treatments and surgeries and all that good stuff. Things were good for almost two years. Then, I went in for a routine x-ray of my lungs and saw some shadowing. Over the next 18 months, I had 3 lung surgeries to keep outpacing it. The cancer would metastasize in my lungs and the doctors would perform a wedge resection to take out part of my lung where the tumor was. I also did a month of Interferon, which is a form of chemo.

In May 2011, I went in to get my results for some scans and my oncologist sat me down and told me that the scans showed that I had tumors on my liver, pancreas, lungs, and one behind my heart. A lot of metastasizing had taken place and he basically told me that there was nothing he could do for me.

This was at the time that immunotherapy was very new and no one was really talking about it. After that diagnosis, I went on a very exhaustive search on where to get treated and landed at MD Anderson. My doctor there, Dr Patrick Hwu, and I discussed treatment options and that’s when immunotherapy hit my radar.

I went through the process of getting tested to qualify for some trials taking place. There were a few that I did not qualify for. Basically the last one that was available for, I tested for and was a match to the trial. That’s when I started my treatment.

How did you do that research that led you to MD Anderson?

The biggest thing was really reading up on potential treatment options, success of medical centers as it related to treating melanoma specifically. There were other options but after really doing research and reading up on some doctors who represented melanoma treatment, I found MD Anderson.

MD Anderson’s name speaks for itself. Their success speaks for itself. Not just prior to me getting there but even between my being there until today. I was very fortunate to get connected to Patrick as my oncologist. He had a very forward-thinking approach. If you know anything about MD Anderson, you should know that Dr Jim Allison just won the Nobel Prize; he’s the godfather of immunotherapy. It was a great situation to get in and Patrick was out in front of that in terms of treatment options and looking at me as a good candidate to go through a trial.

What led you to decide to participate in an IO trial and this specific trial?

The research was limited to the extent that there were not many immunotherapy trials taking place at the time. A lot of my knowledge was based on the information I was getting from MD Anderson in terms of what trials they were connected with and what was available for me. A lot of my research was predicated on what they could provide me. I was learning enough about the trials in terms of what they entailed and some of the treatment but that was the extent of it.

“**I would encourage those conducting the trials outside of the presiding doctor to spend some time with the actual patient to gain an appreciation of what the trial entails.**”

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**Steve Hamilton**, is a stage IV melanoma cancer survivor who participated in an IO combination therapy trial. Mr Hamilton will be joining IO Combinations 360° to share his clinical trial journey with an IO vaccine involving the MAGE-A3 protein paired with IL-2 that ultimately saved his life.

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A Big Swing: Going from Stage IV Melanoma to Full Remission
The biggest thing is that you can’t just show up, raise your hand and say “Yea, I’m going to do this trial.” You have to go through a litany of tests to make sure that your body is going to be even remotely receptive to the treatment with some level of success. People may not realize that it is not just a volunteer basis. There is a qualification and testing process before you can get into a trial.

The treatment was high dose IL-2 combined with a MAGE-A3 vaccine. The IL-2 treatment was inpatient. I was administered as many doses as my body could handle over the course of a week in an ICU and I would get the vaccine to go with it. The IL-2 would take my immune system down and the vaccine would recharge it.

“You can’t just show up, raise your hand and say “Yea, I’m going to do this trial.” You have to go through a litany of tests to make sure that your body is going to be even remotely receptive to the treatment with some level of success”

How was your clinical trial experience?

Physically and mentally, it was very intense. It was very hard. But the trial itself did what it was supposed to do for me. I made it through the trial and got out on the right side and I am now 6 years into full remission. Going from stage IV to full remission is obviously a big swing and I am well aware how fortunate I am to be where I am today health wise.

There’s a lot to it. Not only the physical and mental pieces of it but there is a lot of information to be aware of and trips to the doctor and the scans and all the things that are a part of the trial. It’s not just showing up and getting your treatments. You have to answer questionnaires every time you go in to see your doctor for follow-ups. I’m talking 50+ questions because that’s part of the trial and the checkpoints. It’s a detailed, rigorous process. It’s not just showing up and taking your treatment and going on your merry way. You are in the trial and you are an important part of it because they want the trial to succeed. Patients have a vested interest in the trial and doctors want to see a level of success to move the treatment into the approval process for other to be able to take advantage.

What were some of those challenges and difficulties?

The biggest side effect was the violent shaking when I got the IL-2 treatment. I had severe rigors. Think of a time when you had the flu and the shakes and then multiply it by about 20. I had a rapid heartbeat to the point where my heart rate would go to over 200 bpm. My taste buds would go away and eating was somewhat a challenge. And every time I was in treatment, I gained 20-30 pounds of water weight. Those are the physical side effects that are etched in my memory.

What would you want researchers and physicians to know about the patient experience?

I would want them to understand how much of a grind it is. It is not easy going through a trial. There are lots of unknowns along the way. Trials are very rigorous in that you have to hit certain milestones and you have to follow the trial to the letter. I think anyone going through a trial understands that because that’s the only way it can go from a trial into production from a treatment standpoint. I would want them to understand that while the trials are difficult, they truly are an investment in your future as well as other patients who could benefit from the treatment.

I would want them to have the opportunity to spend time with those going through the trial. I didn’t ask to see anybody representing the drug company or running the trial. But I would encourage those conducting the trials outside of the presiding doctor to spend some time with the actual patient to gain an appreciation of what the trial entails. When you can walk in someone’s shoes who is going through something so mentally and physically demanding, having that type of an appreciation is beneficial.

What advice would you have for newly diagnosed patients?

A diagnosis is just that. It’s the current state, not a long-term prognosis. I know it’s difficult when you are hearing such hard words about your physical well-being. Your mind races and you can’t think quickly. Take a step back, digest the information and realize it’s a current state and not a future state. I also recommend getting a second and third opinion. When it comes to one’s health, knowledge is power.

I also think when you are open to what is possible, and are willing to explore options and educate yourself, you put yourself in the best possible position for making that future state what you want it to be. There is a lot to it and it is easier said than done. Having gone through everything, I can tell you that that is one of those things that I believe helped me tremendously. When I heard that initial diagnosis, it was difficult, however I did not let that be my final diagnosis. I sought out treatment options and the best doctor possible. You are your own best advocate! Adopt a positive mindset and attitude of determination so you can put yourself in the best position for survival.
Can you tell us about your new role with the Parker Institute?

PICI is a completely new model that revolutionizes the way we do cancer research. It removes a lot of the barriers that exist in industry and academia, and creates a safe space for groups to collaborate across research institutions. My role as CSO is to amplify collaborations among scientists to accelerate the development of immunotherapy.

I’ll also work closely with our center directors and the PICI team to develop our research strategy and determine our scientific priorities. My background is in human immunology and cell therapy, and I think these will be two areas of focus moving forward.

If you focus on the patient, no matter what you’re trying to build, whether an academic career or a company, everything else, including success, will follow.

What are some of those barriers to collaboration that you’re breaking down?

I’ve had the pleasure of working in academia and industry, so I’ve seen the barriers of both firsthand. In academia, there is limited funding. The opportunities for things like tenure and growing a lab are wholly dictated by the ability to publish research and write grants. Given the current funding situation, only a small fraction of those grants are funded.

The other barrier in academia is that as you move forward with great ideas, you’re competing with everyone around you. Your likelihood of local collaboration is limited because of limited opportunities to advance your career. We unfortunately still have this idea of the lone brilliant scientist in the corner who is able to solve problems. Though individual creativity will always play an important role, this model ultimately stops scientists from working together and making a big impact.

In industry, young biotechs are focused on the fundraising and inflection points. The opportunities to bring technology between companies is really difficult, even if they know that the possibility for synergy is right in front of them.

PICI exists to break through these barriers. If there’s a PICI investigator from MD Anderson Cancer Center who wants to work with a PICI investigator from Stanford Medicine, we’re here to make that happen. We also make sure they have the tools and resources they need, like informatics, clinical trials support and translational medicine capabilities, to accelerate their research.

Can you talk about your personal research?

My background is in immune monitoring, which means monitoring human immune responses to recognize the mechanism of action or mechanism of resistance in therapy. During clinical trials with experimental medicine, we try to deeply investigate the human immune system over the course of the disease and the therapy. If a therapy is working in our patients, how is it working? And when it stops working, what is the mechanism of resistance? We’ve come to some interesting conclusions that have led to new, next-generation therapies, technology development and real exploration.

“*If you focus on the patient, no matter what you’re trying to build, whether an academic career or a company, everything else, including success, will follow.*”

The Future of Immune Monitoring at the Parker Institute

**John Connolly, PhD**, is the CSO of the Parker Institute for Cancer Immunotherapy. He is also an Associate Professor at National University of Singapore; an Adjunct Associate Professor of Immunology at Baylor University; a Senior Principal Investigator and Director for translational immunology at the Institute of Molecular and Cellular Biology A*Star; and serves as Director for the IMPACT Cell Therapy Program.
What are some next steps to overcome the challenges of solid tumors in terms of their mechanisms of resistance?

The human immune system itself is a complex, dynamic system. We look for big concepts like “protection” and “durability of response.” These are emergent behaviors in that complex system. But you can’t design a product that just does that. You need to have a completely different mindset on inducing these responses. The best way to approach the problem is to ask how nature does this.

This is reflected in the solid tumor space in some of the successes we’ve seen with natural T cells, like TILs, tumor-antigen specific T cells and virus-specific T cells. These reorient the entire immune system through recruitment of secondary effectors and not the T cells themselves. There is also a huge role for synthetic biology here. In my mind, you start with the right cell and then you build upon that with synthetic biology. That’s the direction for solid tumor biology.

What is immunometabolism?

The immune system as we know it was built upon a pre-existing metabolic system. We had metabolic pathways long before we had an immune system. As we evolved, those metabolic switches were at the core of how the immune system functions. We’re just now beginning to understand this. If you look at the mechanisms of resistance in the solid tumor space, many of those mechanisms converge on metabolic pathways.

The research around how we can use immunometabolism to modulate the tumor microenvironment is tremendously exciting. This is also true in cell therapy. We’ve found that metabolism is at the core of T cell persistence in the context of CAR-T biology. Particularly, the metabolism of the T cells allows them to persist longer and have durable responses. This is a good example of how you can use synthetic biology along with that core metabolic switch in order to push research forward.

“From what I see happening every day, I feel like real solutions and breakthroughs are right around the corner.”

What do you see as next steps there?

Manufacturing is the biggest challenge in the cell therapy field. This includes everything from NK cell therapy and TIL therapy to T cell therapy and iPSC-derived cell therapy. In the next few years, we’ll find a lot of routes to carefully manipulate the conditions used in cell culture, formulating media to provide nutrients to the cells at certain stages. We will also find ways to use pharmacological modulation of cell cultures to improve the quality of the cell product.

Another step is the rise of rationally designed combinations to address the lack of consistent efficacy in solid tumors. These compounds target key pathways of immune suppression in the tumor microenvironment and represent targets of opportunity, particularly in the context of adoptive cell therapy. For example, we can use drugs that modulate the glucose dependence to limit the proliferation of the tumor but also improve the memory differentiation of T cells.

What got you passionate about entering the field?

It's the opportunity to solve problems. Whether it's a small problem like figuring out a molecular mechanism or a big problem like how to build large structures to treat thousands of patients, it’s the reason I get up every day. It comes down to focusing on central questions in biology and the impact of our efforts on patient care. From what I see happening every day, I feel like real solutions and breakthroughs are right around the corner.

How is research conducted differently internationally and what can we learn from each other?

Different countries have different models of research, and all of them have their strengths and weaknesses. Singapore is different in that there is a consensus that the biomedical sector is central to the long-term success of the nation. The investment in research funding and infrastructure reflects this. When I arrived, there really weren’t any existing models for translational research. We were able to be very creative in how we built the translational immunology program, building on our experience in Texas. Biobanking, deep immunophenotyping and relational databases for clinical trials are open to both companies and academic researchers. This willingness to accept new models in order to solve problems is key to the Singapore strategy. It’s also one of the things that attracted me to the Parker Institute.

What’s the best advice you’ve ever received?

A mentor of mine, Jacques Banchereau, PhD, who I had the pleasure of working with for quite a while at the Baylor Institute, told me to always focus on the patient. If you focus on the patient, no matter what you’re trying to build, whether an academic career or a company, everything else, including success, will follow. I’ve never seen that fail.

Is there anything else you wanted to highlight?

I’m tremendously excited about Sean Parker’s vision for PICI and the team that he has built. I am looking forward to working with the team and with our investigators to realize our mission of making all cancers curable, while always putting the patient first. 