WOMEN LEADERSHIP IN IMMUNO-ONCOLOGY

Kelly Clark
Merck

Stacey Adam
Foundation for the National Institutes of Health

Teresa (Teri) Foy
BMS

Laura Johnson
Verismo Therapeutics

Shana Kelley
CTRL Therapeutics

Barbara Lavery
Alliance for Cancer Gene Therapy

Lauren Halloran
Halloran Consulting Group

Wei Li
Cytovia Therapeutics

Elaine Long
GE Healthcare

Marcela V Maus
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Women Leadership in Immuno-Oncology 2023 celebrates

Celebration Issue 2023

The official newsletter of the Immuno-Oncology 360° Conference

www.io360summit.com
Welcome to the IO360° newsletter’s fourth annual “Women Leadership in Immuno-Oncology” Issue.

We are living in an exciting time as the field of immuno-oncology advances. More women than ever are working in the space and leading a wide range of scientific programs and initiatives. This issue highlights 17 incredible women, ranging from executives, directors, heads of department, and development leads.

This issue is a sampling of the many incredible women who are working to advance the field of immuno-oncology; we honor all the women who are working to make a difference in fighting cancer.

These women share their career journeys and give their perspectives on a wide range of immuno-oncology topics, as well as offering advice to women in science careers. We are honored to highlight the IO360° women speakers, and thank them for participating in this issue of our annual series. We thank them for their achievements and their contributions in immuno-oncology to fight a wider range of cancers.

Enjoy the interviews.

Sincerely, the IO360° team,

Danny McCarthy, Multimedia Editor
Kate Woda, Senior Director
Valerie Bowling, Executive Director
BreAnna Bugbee, Senior Marketing Manager
Meredith Sands, Executive Director, Business Development

If you would like to nominate a woman leader in the immuno-oncology space to be featured in the 2024 issue, write to us at service@tcflc.org with the subject headline “IO360° Women Leadership Nomination.”

Recommended Media & Events

Enjoy more media and events around immuno-oncology.

Event:
SITC Spring Scientific - Host Immunity in Immunotherapy Responses: From Discoveries to Precision Oncology (Denver, CO or Virtual)
March 15–17, 2023
From sessions on clinical trials with novel IO targets, to sessions on aging, sex hormones and microbes, we take a holistic approach in addressing factors that affect the host and response to immunotherapy beyond the TME. Keynote by Douglas Hanahan, PhD.

Podcast
IO360° Podcast: What to Expect at the IO360° Summit in 6 Minutes

Newsletter
IO360° Newsletter: The Cell Therapy Issue

Newsletter
IO360° Newsletter: The Business Development, Investment and Analysis Issue

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IO360° Newsletter: The Women Leadership in IO 2022 Issue

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Kanya Rajangam, MD, PhD, Chief Medical and Development Officer, Senti Bio

Isabelle Rivière, PhD, Director, Cell Therapy and Cell Engineering Laboratory, Memorial Sloan Kettering Cancer Center

Ana Rosa Sáez Ibáñez, PhD, Research Analyst, Clinical Accelerator and Venture Fund, Cancer Research Institute

Barbra Sasu, PhD, Chief Scientific Officer, Allogene Therapeutics

Leah Sibener, PhD, Co-founder, VP, Head of Therapeutic Discovery, 3T Biosciences

Shivani Srivastava, MD, VP, Development Program Lead, Cell Therapy Development, Bristol Myers Squibb
What is the work you’re currently leading in your role at your company?

I lead and develop high-quality programs to develop research-naïve and less experienced clinical trial sites with a focus on oncology. I am responsible for building and sustaining partnerships with key sites across the United States. That involves sharing knowledge of future clinical trials, proactively consulting site personnel to better understand their needs, and providing the necessary training and support to enable them to efficiently execute clinical trials with the highest quality. I also help sites engage with community-based organizations and patient advocacy groups with the goal of building trust and clinical trial access.

How does that contribute to immuno-oncology work?

The high saturation of oncology clinical trials in the US, in conjunction with historically low representation of diverse people in oncology trials, requires sponsors to expand their community site footprint.

By developing research-naïve hospitals and clinics in diverse communities, we anticipate increasing diverse representation in our clinical trial populations to help bring new IOs and IO combinations to all people. We also recognize the importance of growing and diversifying the clinical research workforce to enable the IO advancements of the future.

What made you passionate about entering the field?

My passion stems from the desire to help others. I knew from a young age that I wanted to work in a helping profession. I chose nursing. That opened opportunities for me to work on clinical trials as study coordinator, where the foundation of my knowledge of clinical trials, and my skills and passion for the work were established.

I’ve witnessed, firsthand, how clinical trials saved lives and advanced medicines and vaccines. Being part of that then, and now, even in a small way, drives my passion.

What is the best piece of career advice you received that you’d like to share?

My parents did not have advanced degrees or illustrious careers, but they instilled the importance of benevolence, hard work and doing good work and in the community. When I have done all of these, good things follow.

I would encourage people to find a mentor. Having role models or mentors, someone you can channel when you’re not feeling confident or worthy, has helped me enormously too.

Do you have any book recommendations?

*Born A Crime*, by Trevor Noah
What role does FNIH play in advancing oncology research through its partnerships?

We oversee a number of public-private partnerships in oncology research that are consortia-based style projects. They range across multiple cancer types and research fields, including, but not limited to, biomarker development and assistance in regulatory evaluation of important targets for pediatric cancer. Some of our partnerships include clinical trials.

For all of these partnerships, we bring the private sector to the table to provide resources that will work alongside government resources to amplify the potential of the joint project. The partnerships can either leverage government projects that are in flight, or those in the planning phase that the partnership can help to shape. We act as a neutral third-party broker. We act as that central hub for all the spokes to mediate project design and facilitate implementation. That includes project management, to contractual work, to whatever else is needed.

Can you give an example of a consortia-based project?

I can put it into the context of our large IO partnership, PACT (Partnership for Accelerating Cancer Therapies). The focus of that partnership is to standardize and harmonize assays and biomarkers within immuno-oncology trials.

Between the NCI portfolio of trials and private sector trials, we have about 45 trials that we’ve recruited. In those, we are deploying a set of additional standardized correlative assays. These are assays that the four core laboratories we put together spent a year harmonizing. That way, all of the data coming out of those labs are uniform. They’re deploying these assays across all the trials: a set of about six assays in as many trials as we can get them in, as well as some very specific assays, depending on the biology needed to study IO.

What is the goal of this collaboration?

The hope is we will put together all of the data from the 45 trials and be able to do a cross-trial analysis that no one company could do. We will be able to cross-compare PD-L1 agents, novel IO mechanisms, etc., and boil down the potential biomarkers that can target treatments to patients much more effectively.

What’s lacking in the IO field right now is that there are not good biomarkers. There are TMB, microsatellite instability, and PD-L1, but not much else. The overall goal is to increase biomarkers for IO to push treatment in this space to join the precision medicine paradigm.

What are the modalities that are being looked at in FNIH partnerships?

We have a lot of efforts in liquid biopsy, trying to develop assays or standards for assays that would allow for more accurate and less invasive patient testing, thereby minimizing patient burden.

We have efforts in imaging biomarkers, as well. We had a project called Vol-PACT (Advanced metrics and modeling
with Volumetric CT for Precision Analysis of Clinical Trial results), working with Drs Larry Schwartz and Geoff Oxnard as our PIs and with financial and data support from nine companies, that was aggregating imaging data from existing trials, in particular in the IO space, to see if they could develop either a 2- or 3-dimensional imaging algorithm that could beat the performance of iRECIST. When using iRECIST, there can often be false progression detected in the early phases of IO treatments, forcing the doctors to stop a treatment that may actually be benefiting a patient. The group that has been working on a new algorithm has actually come up with what seems to be a better algorithm that actually outperforms both RECIST for normal tumors and iRECIST for those being treated with IO.

What drew you to this role?

I was a bench researcher for cancer for 12 years. In fact, I went through five-and-a-half years of a postdoc, thinking that I would become faculty. I got to the end of that, and I was having conversations with some mentors, and they said, “Team science isn’t ultimately rewarded in academia.” This was almost a decade ago, and things have changed a lot since then. But I began to think that if the type of science I wanted to do wasn’t going to be rewarded in academics, I should find somewhere else that would allow me to make the impact that I wanted to see.

Most postdocs when they leave academics make the lateral move into industry. I decided to try something new. I went into corporate consulting; I worked for Deloitte’s Federal Healthcare and Strategy practice. I had been there for three-and-a-half years, when a friend of mine sent me the job for the Foundation for the NIH. The job with FNIH was a balance of my past science life and all the soft skills I learned in consulting. I took the job with FNIH and it’s been about seven years in a role I have enjoyed immensely.

What is your favorite part of this job that has kept you there for seven years?

Every new partnership that we start is another puzzle to solve. I am a scientist at my core. I still love to problem-solve; I still love to figure out how things work. Oftentimes we’re approached by a pharma partner or by our government partners to help solve a problem.

And so we go out and assemble all of the needed partners, evaluate all the existing and necessary resources, and then begin putting the puzzle pieces together into a functional partnership. Every partnership looks different. We have models that we have proven work, and obviously we try to replicate those things that have been successful. But there isn’t a single partnership that is identical to another. I love the variety and the challenge of making each partnership function at its highest level.

What piece of advice has been impactful to you in your career?

When I took this job, the then-president gave me a piece of advice that I still love to this day. She said, “There will be challenges and unpleasant parts of every job. What you have to figure out in life is what challenges and unpleasantities you are willing to accept.” It sounds really simple, but it was just a nice, gentle reminder that yes, you should be happy in your job, but you have to set expectations that no job is going to be perfect. You will have to fight for what you want in every job. The challenges are part of what can make it rewarding.

Oftentimes people are always looking for the next greener pasture. Not that we shouldn’t, but you can’t always expect it to be smooth sailing. If you’re willing to put up with the challenges, you can find a really rewarding position.

What is a piece of advice that you give out?

Advice that I love to give people, especially people coming out of their PhDs, is that once you have your PhD, people are going to hire you for jobs that you never dreamed you’d be qualified for, or that you necessarily are qualified for. But it’s a great reminder, especially for women, that you shouldn’t feel limited by past experiences. Look at what you really want to do with your life and know that with all of those past experiences, you can parlay them into a job that isn’t exactly what you were trained to do, but you’re completely qualified to achieve.

I read recently that women only tend to apply for jobs that they’re overqualified for, because they feel like they have to check every box. We just need to keep reminding each other that with all of those past experiences, you can parlay them into a job that isn’t exactly what you were trained to do, but you’re completely qualified to achieve.

How can we better support women in science careers, from those just joining the industry to those rising the ranks?

I have always found that both formal and informal mentorship have always been a huge bonus in my own career. Formal mentorship is one thing; there are a number of organizations that do a lot of great things. But I also encourage women to reach out and find informal mentors on topics of interest to you. I’ve done this throughout my career. I still have contacts with many of the informal mentors that I’ve developed. Finding somebody that isn’t necessarily assigned to you, but that you could look up to and would be willing to coach and counsel you through the steps in your career.

Do you have any book recommendations?

Right now I’m reading Never Split the Difference by Chris Voss. He’s an FBI negotiator, and this book goes through his experiences taking those FBI negotiation tactics out into the world of business to see how well they work. I’ve also been reading Michelle Obama’s The Light We Carry on the side.
What are your biggest concerns around rising costs for cell therapies?

What’s important to think about concerning the costs of cell therapies is that bringing costs down will increase our ability to deliver these therapies to more patients. The biggest challenge with the current generation of cell therapies is that they are very labor-intensive to manufacture, in three ways. Firstly, they are autologous products made for each individual patient, which adds time and complexity to manufacturing. Secondly, much of the process is manual; it relies on individual manipulations of cells. And thirdly, it’s dependent on viral vectors to deliver the genetic materials needed to engineer the CAR and the other features to the cells. Each of those things adds to the expense of manufacturing: when you scale up to deliver to thousands of patients, you compound those costs. So as we’re working to reduce costs, we’re looking at each of those different pieces to try to reduce those costs.

What are the topline hurdles in addressing cost for the next generation of cell therapies?

If we take autologous versus other cell sources: one of the biggest hurdles is in biology. When using a patient’s own cells, you don’t have to worry about those cells being rejected by the patient because they are their own cells. If you’re using an allogeneic cell therapy, those cells come from a healthy donor, but you have to figure out how to engineer them such that they’re given to the patient, they’re not rejected, or that they don’t attack the patient’s tissues. Even when we go to iPSC-based therapies, which offer some advantages in that we are able to build a master cell bank which enables additional manipulations and engineering; you still have to engineer out those foreign, allogeneic components. Saying “off the shelf” sounds great, but there are big biological hurdles to overcome for “off the shelf” therapies to be as successful as autologous therapies. We’ve seen companies moving forward with allogeneic products, and we’re seeing decent efficacy. The question is: will it be durable? It’s not yet demonstrated that it’s as good as autologous therapy. Will we be able to bridge that gap?

What questions are you asking to be able to move forward with reducing costs?

Can we do more automation? Can we look at ways to decrease the cost of the viral vector or eventually move away from dependency on viruses to deliver the cargo? Can we engineer cells using non-viral delivery mechanisms? Can we move away from autologous cells as the source of cells? Each of those pieces could contribute to driving down the costs eventually. But with that goal of reducing costs is maintaining and even increasing the efficacy and safety profile of the cell therapy.

Why do you think we need to examine the potential for non-viral vectors to get costs down?

In some ways, we have been a victim of our own successes with CAR T cell therapies. Vector manufacturers have been
challenged to supply the market at pace with the demand from manufacturers, so we are trying to figure out ways to diversify our supply.

Then, automation. While there are components of automation already, end-to-end automation that is reliable, closed and offers stability takes a while to build. I feel like the success of the first commercial products perhaps got ahead of the infrastructure needed to support scaling for the demand.

**Do you think we’re on the right track to lowering costs?**

We’ve made good progress. Each of the companies launching a CAR T cell therapy, from the first one until now, has learned from the previous ones. We as BMS are learning from our manufacturing experiences and clinical translational data. We’ve learned that while the data you collect during a clinical trial can absolutely inform and predict which patients could benefit, when you get into the real world, there is much more patient heterogeneity. Doctors can prescribe CAR T to any patient who fits into the label.

It is an opportunity to serve more patients, but those patients may be more sick than the patients in your clinical trials, or they may have different disease characteristics and profiles. We’re learning what needs to be overcome to serve patients who may not be responding, as well as how to improve our manufacturing to make sure we are delivering the best products we can.

**Abecma and Breyanzi are both for blood tumors. BMS recently announced building on its partnership with Immatics for the development of their candidate IMA401 for solid tumors. Can you tell us about BMS’ work in solid tumors?**

The success of cell therapies in blood cancers is tremendous and transformational for patients. We are excited to build on those learnings and move that success into solid tumors. We have a number of programs and a number of partnerships, Immatics being one. They have identified T-cell receptors for different solid tumor targets. They’ve actually gone as far as to show that those antigens on the tumor cells are there in high-enough density so the T cells can recognize them.

Instead of a CAR T cell, where you’ve got an antibody-like binder recognizing a cell surface protein, here you’ve got a TCR binder recognizing an intracellular protein that’s presented on a tumor cell. That gives you an opportunity to look at different kinds of targets. Only about a quarter of targets are present on the surface of tumor cells, but the vast majority of targets are intracellular targets and are present on the cell surface in a different way that allows them to be recognized by TCRs. That gives us an advantage in solid tumors to look for different targets.

**What is a challenge you’re facing in solid tumors?**

One challenge is finding good targets. A lot of the antigens expressed on solid tumors are also expressed in normal tissues. In blood cancers, the antigens that CAR T cells target are also on normal cells, B cells and plasma cells, but these cells can be regenerated.

That’s not as true in normal tissues; you don’t necessarily want to hit a normal tissue with your CAR T cells. For solid tumors, it’s often difficult to find a target that’s not expressed on the same normal tissue, and you don’t want your CAR T cells to kill that normal tissue. Therefore, you have to look for ways to differentially recognize the tumor tissue from the normal tissue.

**How do you solve a problem like that?**

One thing you can do is use a logic gate: “I’ll look for a target that is here, but not there.” Or “If it is here, it will only trigger expression of the CAR if it’s also on the tumor.” That’s what we’re doing with our partnership with Arsenal. They’re looking at building logic gates to help give better selectivity on targets that are on the tumor and not the normal tissue.

Another factor is the solid tumor microenvironment is more complex. You have more suppressive factors in the tumor. In addition, access to the tumor is more difficult than in blood.

**What do you view as the biggest knowledge gap in tackling solid tumors?**

Targets and trafficking of the CAR T cell are both big challenges. Trafficking is important because if the cells stay in a patient’s bloodstream and don’t get to the tumor, they’re not going to expand. In myeloma and lymphoma, they expand hugely, because they’re seeing the target antigen right away. After CAR T cell infusion, 70-80% of T cells in the blood can be CAR T cells. In solid tumors, we don’t see expansion like that. Now, you might not need 70-80% of cells to be the CAR T cell, but you need a good portion of them, at least initially, to be able to see the antigen in the right spot and expand to be able to kill the target tumor cells.

Target selectivity is the other challenge. Some of the very early work in CAR T cells with a target like HER2 showed on target/off-tumor toxicity in the lungs. It was known that HER2 was expressed there, but it was the extent of the inflammatory response due to CAR T activation that was unexpected.
What does Halloran Consulting do in immuno-oncology?

Our expertise is strategic program leadership, clinical development planning, regulatory affairs, and regulatory operations to early-and late-stage biotech and pharma companies with immuno-oncology assets. In some cases, we act as interim staff to alleviate a financial burden of the company who may not yet have the payroll or capacity to assume full-time hires. We've worked on numerous immuno-oncology products resulting in a bedrock of relevant and current thinking about how FDA operates in this space. We can save a company valuable resources and potentially costly mistakes by adding our insights to their regulatory process. For larger pharma companies, we bring the small company nimbleness, and we help them adopt what might be perceived as too risky. For example, if an organization is evaluating a risk-based quality management (RBQM) system, considering adopting technology for managing decentralized trials, or thinking outside the box organizationally, we're able to add constructive value based on what has worked at other companies.

What are the areas you most help biotechs to supplement?

We provide senior-level executive thinking for biotech startups. Experienced industry players often are hesitant to join and commit to a small biotech until there is good clinical data because they don’t want to frequently change jobs due to uncertainty or potential company failure. There’s a real talent shortage for deeply experienced people which can be a huge impediment to a young company because they won’t necessarily get the senior-level thinking if they bring in more junior people. Critical thinking and planning early on is essential.

With the current funding challenges, small biotechs need to find a more efficient path. They want to save as much money as they can and be as laser focused as possible. Time equals money in a drug development lifecycle. So, if they can bring on a person that commits five-to-twenty hours a week, it’s less expensive and they’ll ensure a deeper level of experience.

From Halloran’s experience, what is unique about an early stage IO biotech versus other biotechs, and the challenges they face?

One unique challenge to the IO biotechs is time. With lots of “me-too” products and similar targets under development, it is a race to the finish line of accelerated approval or traditional regulatory approval. Further, time impacts the patients for whom we are trying to impact their survival and treatment outcomes. That is why having a vetted strategic development plan with heavy considerations towards the competitive and regulatory landscapes is essential.

With respect to the regulatory landscape, early stage IO companies will need to closely watch the evolving programs and perspectives emerging from the FDA Oncology Center of Excellence (OCE) including Project Optimus and Project FrontRunner. Project Optimus is beginning to reshape the landscape of early stage clinical trials, particularly with respect to dose exploration and optimization, in oncology settings. Project FrontRunner is a more recent initiative and may create an opportunity for certain companies/products to explore efficacy in early line settings much more rapidly.
than the traditional paradigm, where products must begin in a treatment refractory setting.

What should IO biotechs be aware of in regards to changes in the approval process?

IO biotechs must be aware of the evolving landscape for accelerated approval. Historically, small biotechs would take product through a conditional approval through the accelerated approval process before initiating a confirmatory RCT. Often these small companies were not properly funded to support a large global RCT and this development approach was the only viable option. However, recent messaging from FDA (and the OCE in particular) suggests that the agency will expect a confirmatory trial to be fully enrolled by the time accelerated approval is granted.

This is a major change in regulatory expectations, but one that is focused on reducing that window of uncertainty between accelerated approval and standard/confirmatory approval to avoid continued distribution of products that do not demonstrate clear benefit and efficacy. In addition, identifying and implementing biomarkers in IO is a major challenge and given the increasing pressure that the accelerated approval is facing, the use of reliable biomarkers will become increasingly important for these programs.

What is your advice to young IO companies, to get through the hurdles facing early biotechs?

To successfully get through the many obstacles that early stage IO biotechs will face, execution of the development program will need to be thoughtful and deliberate. Strong leadership and communication is a requirement, and this is not only internally facing, but also in collaboration with the FDA. Forming a collaborative and transparent relationship with the FDA will help to align expectations on the necessary data package to support a future marketing application and mitigate the risk of designing clinical trials that will not produce robust clinical data.

Before you got into helping small biotech companies, how did you get into the industry?

I no longer wanted to be on-call as a nurse. I answered an ad because I needed a new car and it said “50% travel.” That’s it. When you take care of a patient, they either get better and go home, or they don’t. That was devastating for me, especially in the pediatric ICU.

I saw the opportunity to develop new products as a much bigger way to make a difference for patients. That’s what turned me on to it, and what still makes me passionate about this industry. I’m not interested in working on the second or third generation of an existing drug. We’re gravitating towards diseases with no treatments because this will change lives.

What experiences did you draw on to create your company?

When I was at Parexel, we went from 40 people to 5,000. I really learned a lot about what organizations are like at different sizes. The first biotech company I worked at had only five people in the U.S. and they eventually spun out and licensed off their lead product. The second company I worked at was a later stage biotech; there was nothing put in place before I joined.

I realized you have to have big company thinking to put systems in place at an early-stage company because you can’t “fake it till you make it.” It just won’t work. You need quality and infrastructure every step of the way. If you don’t, you won’t have a high-quality product. You need senior people who know what they’re doing to save time and money. There’s a need for right sized process and discipline to be ingrained into a young company from the get-go. Our consultants, like me, come from the industry, have learned how to be better, and we take our collective knowledge and framework to a company with the confidence and understanding of having walked a mile in their shoes.

What is career advice that you find impactful?

My number one piece of advice would be: “If you want to, you can do it.” Women often think that they can’t do things or feel they need to be an expert at everything. That’s not true. Figure out what you’re good at, and then find somebody else who can be good at the things that aren’t aligned with your skills.

We see this with our clients – they believe they need to know everything – and we recognize a limiting mindset will be an impediment down the road. To be successful, you have to have a high level of self-awareness and not feel guilty about saying, “I don’t know this.”

How do we better support women in science careers, from those just entering and those rising the ranks?

For a lot of young women in science, they have to recognize that to grow within their career and ultimately get into a position of executive leadership, they have to give up some of the science because they have to be good at management. You can’t be down in the weeds, while also thinking about the vision and the future. That is where I’ve seen people face significant challenges because the person who gets stuck in the data will struggle to be the ultimate leader.

Dig deep to understand your strengths and weaknesses. Pick up skills to be a leader or find a mentor. The biggest part is recognizing that you have to grow.

To learn more, visit www.hallorancg.com
What is the work you’re currently leading in your company?

I oversee the research and development of a paradigm-changing new CAR T technology, guiding our KIR-CARs from discovery through to translation into the clinic to treat patients with advanced cancers. Our team was founded by those who originally invented the first globally registered CAR T therapy for cancer, Kymriah.

Killer immunoglobulin-like receptor (KIR)-CARs are a new platform of CAR T therapy inspired by a more natural immune-cell dual receptor design that separates tumor binding from T cell activation. This dual receptor system allows KIR-CAR T not only to engage and destroy tumors, but also to rest and recover in between tumor encounters, preventing the T cell exhaustion seen in other types of single-chain CAR T treatments.

How does incorporating KIRs into CAR T therapy improve a patient’s chances of getting benefit from treatment?

While current CAR T have been effective in treating patients with hematologic malignancies, they have failed to work in solid tumor indications, with CAR T becoming prematurely exhausted and losing the ability to function. KIR-CARs use a more natural, dual receptor/signaling pathway that has been successful in treating preclinical models of solid tumors, with prolonged KIR-CAR T cell function, and no evidence of T cell exhaustion.

Verismo’s work on KIR-CAR technology takes learnings from the interactions between the immune system and cancers and applies them to enable a patient’s own T cells to redirect to recognize and destroy their own tumors, in the same way that it eliminates pathologic viruses and bacteria.

What made you passionate about entering the field?

When I was a child, my favorite aunt was diagnosed with metastatic cancer. She was one of the strongest women I have ever known. Watching her embrace life and live to her fullest while she was fighting a battle whose outcome was already decided inspired me to want to make a difference for people like her.

Laura Johnson, PhD, is CSO of Verismo Therapeutics, overseeing the company’s research and development. Dr Johnson brings over 20 years of experience in molecular and cellular immunology, including 16 years of gene-engineered T cell immunotherapy translational expertise.

Laura Johnson, PhD
Chief Scientific Officer, Head of R&D at Verismo Therapeutics

The CSO Working to Overcome T-Cell Exhaustion
What has surprised you about working in immuno-oncology?

The resilience and amazing positive attitude that patients who volunteer for clinical trials has amazed and inspired me. When I was in training at the National Cancer Institute, postdoctoral fellows were given the opportunity to attend the weekly clinical rounds, meeting the patients and learning their stories.

At first I was very nervous, and worried that this would be a sad experience, since these patients all had advanced Stage IV metastatic cancers; in fact it was exactly the opposite. While being hopeful, patients would remain realistic about their low chances of benefiting from the trial. They felt proud and empowered that, by their involvement and contribution, the trial results could one day benefit someone else.

What would be your advice for young women who are entering science careers?

Work to become the person you want people to think you are and stay true to what you hold important. You do not need to fit some preconceived mold of what a scientist, or a doctor, or a businesswoman “has” to be. You can be kind and smart. You can be pretty and professional. You can be compassionate and successful. You can have a family and a career. At the end of the day, it is being part of something larger than oneself that brings happiness.

“KIR-CARs use a more natural, dual receptor/signaling pathway that has been successful in treating preclinical models of solid tumors, with prolonged KIR-CAR T cell function, and no evidence of T cell exhaustion.”

Is there anything else you would like to share with our readers about your work?

I love working in immuno-oncology as there are so many opportunities to really make a difference. Following the science, enjoying each day one day at a time, looking forward to work and to home, the camaraderie with colleagues, and loving what I do is the ultimate reward.

Do you have any book recommendations?

Best fiction book I’ve read this decade: Project Hail Mary by Andy Weir. It’s an incredibly realistic science-fiction story that just feels good.

Best non-fiction book: This Naked Mind by Annie Grace. The neuroscience behind addiction and alcohol-misuse and the need to fill a personal void with good marketing.
What can you tell us about your new company CTRL and what it’s aiming to achieve in Immuno-Oncology?

CTRL stands for Circulating Tumor Reactive Lymphocytes. It is based on a discovery that was made in my research labs of tumor-reactive cells that can be identified in the blood. These are T cells that we believe are resident in tumor tissue and then return to the circulation. We have a very high performance cell isolation technology that is able to comb through milliliters of blood and isolate those cells in quantities that are large enough that you can envision using them as a therapeutic.

This is different from anything else that’s out there. We have TIL therapy, which has a really good safety profile, and then we have engineered cell therapies that are still being optimized to be effective and safe. The CTRL approach is right in the middle. By harvesting the cells out of the blood, it’s not invasive. You don’t have to do surgical tumor resection. We’re in the midst of trying to take that forward, scale it up and take it to the clinic.

Is the idea that it could deliver a payload into a tumor and then leave?

Potentially, but what we’re pursuing right now is isolating those cells, multiplying them or expanding them to a level that we can take them back into the body to really go after a solid tumor, the way you do with TILs. In TIL therapy, you harvest cells from tumor tissue, multiply them, and bring them back into the patient. That has been shown to be very effective in some cases, for example people with advanced metastatic melanoma that are essentially cured of with a complete response.

With these circulating cells, we have the potential to do the same thing, but without the need for surgery and tumor resection.

Earlier this year, you were the corresponding author of a paper about TIL-isolating technology. What is that technology?

That technology platform – MATIC – is the same platform that we use at CTRL to isolate these tumor reactive cells out of the blood. It’s a magnetic isolation technology and it’s very good at finding rare cells. If you have 1,000 rare cells – like a tumor reactive T cell – that you’re trying to find, and you have billions of normal blood cells, the platform is able to isolate the tumor reactive cells with very high efficiency. It can process about a billion cells in an hour, which is a much higher level of throughput than can be achieved with fluorescence sorting or other ways of doing magnetic sorting. Having the MATIC platform allows us to do really high performance cell isolation and is core to our approach.
You used that technology to identify phenotypes of successful TILs. Can you speak on those findings?

We used it to get cells that were in the sweet spot, not too exhausted, not naive, but tumor reactive and cytotoxic. We did that using a marker, where if it is really high, you probably have an exhausted cell. But if it's too low, you have a naive cell. You can think of the active T cells as “Goldilocks” cells: right in the middle. In exploring how this could be used for autologous cell therapy, we were able to take a cut of cells, get rid of the exhausted ones, get rid of the naive ones, and only bring forward the ones that would have beneficial activity for a patient.

How did you develop the MATIC technology?

That technology platform was originally developed to look at a different kind of cell: circulating tumor cells in the blood. We worked in that area for a little while. But it was clear that liquid biopsy was going in a different direction. So we started applying that same platform to different things. I had always been a little scared of tumor immunology given how complex it is, but during the pandemic, it just seemed like a good time to learn something new.

We looked at different applications where a high-throughput, high-performance cell profiling approach could allow you to do something different. TILs were an interesting first application in that area to take those cells and find the really good ones. But the fact that the logistics are so complex for TILs bothered us. We wondered, “How are we going to fit this into an already complicated workflow?” That’s what prompted us to look in the blood. Many hospitals already processed blood and cell suspensions, so we thought this could be quite interesting. We felt that would give us an easier starting place, and more potential for clinical uptake. If you just needed to draw blood rather than do a tumor resection, it lowers the activation barrier.

You’ve started several companies. What have you learned about leading people to do their best work?

You make your job easy if you can hire really great people, who really believe in pushing forward new technologies and bringing things to the clinic. Those are the kinds of people that you have to find.

I think good leadership is about keeping the vision front and center, keeping people very engaged with what you’re trying to do, and doing that with a high level of transparency and integrity. It also requires making sure the team functions as a team, not a hierarchical structure. In a startup, everybody’s got to roll their sleeves up. If you can really get that dynamic going, where everybody is giving 100%, then great things come out the other end.

How do you approach a new challenge?

At this stage of my career, I don’t fear being wrong. We think something works a certain way. We put that into a paper. A reviewer says that it is totally wrong. I don’t have a problem with that. We take the feedback and try to improve the work.

What is advice you’ve found very impactful over your career?

“Don’t sweat the small stuff.” Your paper gets rejected? Don’t worry about it. Put it down for a few days. Then pick it back up, read the feedback and keep moving. An investor says, “No, we think your ideas are not very good and you’re not going to be successful.” Just do the next pitch and try harder. Life is just a collection of all these little things. Most of them just don’t mean much of anything, but you can’t get discouraged. I certainly did when I was getting going in my career. Every “no” was a deep personal insult to me.

It is part of the process, especially if you’re starting companies, trying to get investors in and trying to get new ideas out there. You’ll have a lot of people telling you “No,” or that you’re wrong. Stay very focused on the big picture, and don’t give up. Anybody who’s ever done anything important probably had a thousand opportunities to give up. But they didn’t.

What is your advice for communicating science to business investors?

You’ve got two minutes to really get people engaged, otherwise you’re not going to get anywhere. You have to find a way to very crisply describe what it is you’re doing, and then move right to why it’s important, and why there’s nobody else that can do it. It’s a one-two punch: get the science across, and then move very quickly to why they should care.

A decade ago, I used to do investor meetings with printed copies of a pitch deck. I’d be on my first slide trying to make my point, and investors would flip through it, and then just turn it upside down on the table. You could tell they were done with the meeting. They weren’t interested. I missed the opportunity to get them interested and engaged.

Do you have any book recommendations?

I read biographies mainly: Michelle Obama’s, Steve Jobs’s, Jennifer Doudna’s, etc. My favorite book is The Periodic Table by Primo Levi. It’s a chemistry book, but it goes into much, much more than that. It’s a wonderful piece of literature.
You worked in communications for a long time supporting biotechs; what inspired you to make the switch to funding IO programs?

I worked for close to 20 years running a communications agency for life-science companies – working with biotech, medical device and pharma companies to help them explain their science and technology to investors, partners and patients. We had the opportunity to work with groundbreaking companies like Gilead, Regeneron, Chiron, Human Genome Sciences, Genentech and exciting oncology companies like Sugen, Ariad, Medarex. I got hooked on science and biotech and the incredible progress being made in understanding disease and how to treat it.

At the same time, many of our employees and myself were dealing with cancer within our own families. There is great motivation in connecting promising cancer research with the common experiences we all have as cancer patients and families.

What makes you so passionate about making a difference?

The fact that science is making incredible progress building a deep understanding of cell biology, immunology and genetics and essentially how the human system works inspires me. We can now understand our genetic complexity and have the ability to engineer cells and genes to defeat cancer and other diseases. I am inspired by the humility and commitment I encounter every day in the researchers and clinicians we work with and I believe the work being done today will continue to bring hope and better medicine to us all. This is what makes me passionate about cancer cell and gene therapy – the idea that cancer can be cured in our lifetime.

You have changed careers. What is the work you’re currently leading?

As Chief Program Officer of the Alliance for Cancer Gene Therapy, I am responsible for programmatic initiatives, including leadership of the Academic Research Program and the Biotechnology Investment Program.

As Chief Program Officer of the Alliance for Cancer Gene Therapy, Barbara Lavery is responsible for programmatic initiatives, including leadership of the Academic Research Program and the Biotechnology Investment Program.
Tell us about the Alliance for Cancer Gene Therapy.

Alliance for Cancer Gene Therapy has been supporting and funding cancer cell and gene therapy for over 20 years, including the early work of Dr. Carl June and Dr. Michel Sadelain in developing CAR T cell therapy. Today our alliance of fellows and council members is a vital engine that is driving progress in cell and gene therapy breakthroughs in solid tumors.

ACGT continues to seed the most innovative research and scientists who believe in the power of cancer immunotherapy to bring cures to patients. If you point to a leading cancer cell and gene researcher, you’ll find ACGT’s support interwoven in the fabric of their scientific progress.

What is the best piece of career advice you received that you’d like to share?

Don’t be afraid to ask “dumb” questions and try not to be so intimidated by those who inspire you not to ask them a question. In my experience, they will not only answer you but they will often mentor you and share their expertise with generosity - especially, if they are women. My first boss was a fantastically talented Irish woman who took no prisoners and I am so grateful for her mentorship and friendship that set me up for life. Looking at my own path, I have continued to be curious and to seek out people and situations that provide opportunities to keep learning new stuff.

Is there anything else you would like to share with our readers about your work?

I would love readers to learn more about Alliance for Cancer Gene Therapy, and other organizations like ours, who do so much to support the most creative cancer researchers. Often non-profit funding is the first funding these investigators will receive and helps them make enough progress to then access NIH grants. Without science-driven philanthropy so many breakthroughs would not have gotten started and would have made much slower progress. If you have a corporate charitable program consider adding us to your list!

Do you have any book recommendations?

1) Eliot Pattison’s Inspector Shan Tao Yun series set in Tibet.
2) Eliot Pattison’s Bone Rattler series set in the 1700s in colonial America.

“I got hooked on science and biotech, and the incredible progress being made in understanding disease and how to treat it.”
What is the work you’re currently leading as CSO of Cytovia?

I lead the strategy of developing our iPSC NK platform and innovative gene-edited iNK product candidates as well as the preclinical development of our NK engagers. Cytovia has two platform technologies, iPSC-NK (iNK) and a proprietary Flex-NKTM NKp46 bispecific multifunctional NK engager antibody scaffold. We are developing gene-edited iNK/CAR-NK and NK engager therapies to fight against cancer, including solid tumors.

With the two platform technologies in hand, we are also developing combination therapies of iNK and NK engagers, either through conventional means or by pre-complexing the NK engagers to our iNK cells.

How is Cytovia's approach to IO different from other companies?

Most people understand that since many cancer patients have compromised immune systems, providing functional immune cells to these patients will greatly enhance the efficacy of immune engagers. But in addition to that, we also obtain data suggesting that our NK engagers can help recruit NK cells into tumors and reverse the NK dysfunction for better serial killing activity of these cells. This is because our NK engagers utilize NKp46, an activating receptor that expresses in all NK cells including tumor infiltrating NK cells, to engage NK cells.

How does this work contribute to tackling cancer through immunotherapy?

Our approach combines the advantages of iPSC, gene-editing, and multifunctional bi-specific antibody platforms to harness the power of NK cells to fight against cancer. NK cell therapy itself is naturally an allogeneic cancer therapy. It possesses ready-to-go antigen-independent cytotoxicity capability, and has an excellent safety profile. The iPSC-derived approach will eliminate the donor-to-donor variations and enable the full power of gene-editing. Gene-editing can create super NK cells with characteristics like improved persistence, resistance to suppressive tumor microenvironment, increased tumor infiltration, and better tumor recognition.

On top of that, combination of gene-edited iNK cells with bi-specific NK engagers can maximize the efficacy of both the bi-specific NK engagers and the edited iNK cells and provide optionality to patients depending on their disease status.

What made you passionate about entering the field?

As I witnessed some close friends suffer from and lose their battles to cancers, I am very keen to translate these cutting-edge technologies into disruptive therapies to benefit cancer patients and their families. CAR-T and
immune checkpoint therapies have achieved amazing efficacy results in some of the cancer patients. However, the constraints of autologous therapies, the T-cell associated toxicity, as well as the suppressive tumor environment to immune cells significantly limit the use of these therapies in the broader cancer patient population.

When Cytovia reached out to me back in mid-2020, I was fascinated by their platform technologies because combining the gene-editing with iNK has the potential to overcome many of the current challenges and bring IO cell therapy to the next level. In addition, the combination of NK engager and edited iNK cells may further bring out the best of both therapies and provide more optionality to patients.

What has surprised you about working in immuno-oncology?

Even though we have learned a lot about the immune system, it is very complicated and tightly regulated. While we are working on advancing our platform technologies and product candidates, we realized more and more that these immune cells are very sensitive to the environment, and there are many different subtypes of these cells.

Thoroughly understanding the biology of these immune cells is critical to make most effective therapies.

What would be your career advice for young women who are entering science careers?

A career in science is a long and challenging journey, especially in the biomedical field. But it is a very meaningful and highly rewarding career, if one persists. If this is your true calling, strong leaders and great mentors can really help along the way. Their visions, precious experiences, and unique approaches can help you to select your trajectories, enter the doors, go through the tough times, and extend collaborations. But of course, nothing will happen without one’s own hard work and resilience.

“Combining the gene-editing with iNK has the potential to overcome many of the current challenges and bring IO cell therapy to the next level.”

Is there anything else you would like to share with our readers about your work?

Cytovia’s leading franchise is targeting GPC3 to treat GPC3-expressing solid tumors such as hepatocellular carcinoma (HCC). GPC3 is a very safe target because it is highly expressed in HCC cells, but not expressed in normal adult tissues except placenta. Therefore, it is an ideal target for NK engager and CAR-NK.

We also have a CD38 franchise with both NK engager and CAR-NK product candidates to treat CD38 expressing liquid tumors such as multiple myeloma and cutaneous T-cell lymphoma. In both cases, it is perfect for us to combine the NK engagers with our edited super NK cells. Besides these two franchises, we are also developing an EGFR CAR-NK that targets both the mutant and wild type EGFR to fight against GBM via intracranial administration.
Elaine Long, PhD
Scientific Leader, Immuno-Oncology at GE Healthcare Pharmaceutical Diagnostics

Finding Career Fulfillment Working in Immune Diagnostics

Elaine Long, PhD is Scientific Leader for the Immuno-Oncology franchise at GE Healthcare Pharmaceutical Diagnostics. As part of her role, she partners with leading Immuno-Oncology experts and pharmaceutical companies developing immunotherapies, to help GE Healthcare develop the right diagnostic tools, including PET imaging agents and AI solutions, in order to address current unmet needs and better select and monitor immunotherapy patients.

Can you tell us what work you’re leading in immune diagnostics?

My team works at GE Healthcare Molecular Imaging for oncology, specifically for nuclear medicine diagnostics. That is whole-body imaging of patients, as opposed to in vitro diagnostics. My role is to speak to scientists, and clinicians in academia, pharmaceutical and biotech companies to understand what they are doing and relay that back to my team to make the right decisions about developing the right diagnostics in the right way to address the unmet needs.

Whole-body PET imaging has the advantages of being noninvasive, with no biopsies needed and being able to image over time. You get longitudinal analysis of patients, and very importantly for oncology, it is whole body. You overcome the limitations of getting information from small biopsies as opposed to a big picture for a patient, which is very important. We are interested in imaging various biomarkers to understand both the likelihood that a patient will benefit from various immunotherapies, and then also to understand early on whether those patients are responding to their treatment.

What are you looking for to determine if a patient is a good fit for a therapy?

To use an example, we are just about to start a clinical trial in patients and are looking at a biomarker for CD8+ T cells. That will inform whether, for example, they are likely to respond to immune checkpoint inhibitors because they have got CD8+ T cells in their tumors already, or whether they will benefit from treatments to generate CD8+ T cells or whether they will require other therapies such as CAR T cell therapies, etc.

What is the current group of technologies that folks are using for diagnostics?

For certain cancer types, patients are evaluated for expression of PD-L1, using immunohistochemistry staining of a tumor biopsy to understand if they are more likely to respond to immune checkpoint inhibitor therapy. It is the best available, however there are opportunities to improve. And we think that whole body PET imaging of CD8+ T cells will add value.

And how is treatment response currently assessed?

This is currently being evaluated using different types of RECIST criteria. Patients have a CT scan, and the size and volume of their tumors are measured at baseline and tracked on treatment. Response evaluation with RECIST often takes months. And some responding patients have an initial increase in the size of their tumors - immune cells infiltrate the tumors and proliferate, so on a CT scan it looks like the tumor has grown, when in fact the patient is responding to the immunotherapy.
We are developing whole body PET scanning with CD8 to look at T-cells very early on after patients receive their therapy to understand in perhaps one or two weeks, as opposed to months, whether a patient is responding. This could prevent patients receiving drugs that they are not benefiting from, which are both costly and can lead to immune-related toxicities.

You’re also using AI in your work. Can you tell us how it’s enabling better whole-body scanning?

We have a program at GE Healthcare that we have conducted and developed in partnership with Vanderbilt University in the US. It is a predictive tool using real world, baseline clinical data from patients before they start on treatment. It predicts both the likelihood of patients responding to their treatment, and the likelihood of them developing immune-related toxicities.

What data is this predictive tool pulling to make these predictions?

It uses their electronic health record data, before patients start any IO treatment, to be able to predict their likelihood of efficacy and toxicity. This dataset was trained purely using routinely acquired clinical data from over 3,300 patients receiving immune checkpoint inhibitors across all cancer types. We believe that this makes our models very scalable.

How did you transition from a career in research to one at GE?

My research career was going well at Oxford University; I was publishing, and I was mentoring and teaching there. I made knock-in and knockout mice, which involved working seven days a week for many months. You have to when you are growing and culturing embryonic stem cells to make animals. My experiments meant that I worked late nights and many weekends.

When I had young children, I chose to step away from the bench. I actually had a different career for a few years. I went into project management. I also learnt computer programming and did scientific consultancy work, so that I could manage my work around a young family. But my bedtime reading was immuno-oncology. When my children were a little bit older, I found I wanted to go back because my passion was immunology and oncology. I saw a job opportunity at GE Healthcare, and I thought it sounded perfect for my skill set and my experience.

What made you so passionate about your work?

I worked at Great Ormond Street Hospital for about 10 years. I worked on childhood diseases, first in immunodeficiency disease where children eventually got cancer and didn’t survive beyond their teens, and then I worked on childhood leukemia. Working in a hospital where children would come in with cancer and seeing the impact it had on them and their families, it makes me want to do better every day. The team I worked with at GOSH are developing game-changing cell and gene therapies that are now curing these previously incurable diseases.

Do you have a piece of career advice that’s always stuck with you?

I was in a meeting recently with someone. We ended up talking about science, and he said to me, “You’ve found your ikigai.” I didn’t know what that meant. But it’s a Japanese word that means the intersection of four things. What you’re good at; what you love; what you’re paid for; and what the world needs. And if you meet all of those in the center, that’s your ikigai. And I think as long as you’re doing that, it doesn’t feel like work.

I didn’t have any specific career goals. When I started, I just kept doing what I enjoyed. And that is what has brought me to where I am. For me, it is important to try and do what you are good at and what the world needs.

Do you have any book recommendations?

The Emperor of All Maladies by Siddhartha Mukherjee. It was an important book for me to understand why we are where we are now with our treatments that provide a standard of care, and it highlights that we have still got a lot to learn. I’d also recommend Neil Canavan’s A Cure Within to learn how IO evolved, written from the perspective of the researchers and clinicians who led the way.

To learn more, visit www.gehealthcare.com
What is the focus of the Maus Lab in immuno-oncology right now?

We’re interested in the biology of T cells and how we can optimize T cells to use as therapeutic agents for cancer. We know that T cells are incredibly powerful and incredibly potent. We’ve all seen incredible data in patients with leukemias, lymphomas or multiple myelomas, all of which are hematologic malignancies. We’re trying to improve responses in those diseases and extend beyond those diseases. We are trying to figure out what makes solid tumors different from liquid tumors and how we can engineer T cells to have that same level of impact in solid tumors.

What have you learned in focusing on the drivers of cancer, versus site of origin?

For us, our world revolves around the T cell. And so how do we use the T cell? And what areas are there of overlap and what areas are not? So for example, one thing we do is we sometimes lump pancreatic cancer and ovarian cancer together, in the sense that they have some of the same target expression that T cells can see. They’re in the same abdominal compartment. If we’re using mouse models, that ends up being similar. Even though in the human case, they are treated by different physicians and with different chemotherapies. But in that T cell engineering sense, to us, they behave somewhat similarly.

You led research that found a link between the interferon gamma (IFN-γ) pathway and CAR-T cell success in solid tumors. Can you tell us about that study?

We wanted to understand if and whether there were specific reasons for solid tumors being intrinsically resistant to T cells. Was that even a possibility? And it turns out that it was. What was very surprising is it had to do with this IFN-γ receptor signaling. When the T cell encounters a solid tumor, the T cell gets activated. One of the responses it has is spewing out IFN-γ. That’s actually necessary for the tumor to sense through the IFN-γ receptor for it to have a productive engagement with the T cell. If that IFN-γ receptor is not there, the T cell walks away thinking it’s done the job.
and finished with the solid tumor, but the solid tumor is not actually dead.

It turns out that there’s this whole building up of the engagement: the T cell recognizes the solid tumor, it makes IFN-γ. The solid tumor senses the IFN-γ through its receptor, and it upregulates adhesion molecules that will make it stick to the T cell longer. That stickiness and length of contact is important to actually enable the kill to happen. If that adhesion doesn’t stay around long enough or strong enough, the T cell can walk away a little bit too early, without actually finalizing the kill of the solid tumor.

What questions are left after learning this?

What we don’t know is how often that happens in the setting of patient care. We do know that with checkpoint blockade, loss of that pathway, IFN-γ receptor pathway, and its downstream molecules like JAK2, are actually a mechanism of resistance. We think this doesn’t apply just to CARs. It also applies to checkpoint blockade and other therapeutic areas where the T cell is the one you’re relying on to do the kill.

What would be the next step/response, after this research?

There are a couple of strategies. One is to use pharmacologics to change the biology of the solid tumor, so that it can be primed for the T cell or so that it becomes better able to engage the T cell when necessary. The other approach is to use what we call a genetic approach. In the lab, we can engineer the solid tumor to test various strategies. That’s very useful, and it’ll help us understand the best way to engineer a solid tumor is. But you cannot do that with patients.

What we’re focusing on instead is trying to figure out how to engineer the T cell to not need that feedback loop.

You also worked on reversible on/off-switch chimeric antigen receptors, controlled by lenalidomide. What were the implications of that work, particularly for toxicity and patient experience?

Right now when we put a CAR-T into a patient, biology takes over. That cell will grow and shrink and divide relatively autonomously. It would be nice to be able to have some form of control of how much contraction and how much expression there is of the CAR or of another amplifier, like a cytokine. That’s what we decided to do using lenalidomide, which is a small molecule drug. When you use a degron or degradation domain, the lenalidomide will target the protein for degradation. It’s very reversible. If you give the drug, the CAR gets degraded for the next 12 hours. But then if you don’t give another dose, they will come back up.

It gives you tight control over how much CAR is expressed, even though at the genetic level, or the DNA level or the cell level, it’s still there. But at the protein level, the active form of it can be tuned very carefully and very tightly.

What is the future potential for that research?

It could be used in the current CAR, so that you don’t have these wild swings in how much expansion and contraction there is. We could also potentially use it to engineer CARs that have like a second domain or a second gene that is a little riskier. For solid tumors in particular, you might want to add in a little more jet fuel into the CAR. But if you have no control over it, it’s a higher risk. To be able to tune the response very carefully is a platform tool that can be used to enable higher risk/higher reward.

Does that have any bearing of durability of response?

It’s possible; we didn’t test that directly. But there is nice work, such as from Dr Crystal Mackall’s lab for example. She used a small molecule, dasatinib, that basically turns the T cell off for a little bit. T cells like to have a “Go” signal, and then they like to relax.

They need to take some time off and rest. If you’re constantly pushing the T cell, it’ll become exhausted and sometimes it’ll die off. If you have these periods of rest, you can use something like dasatinib, which Dr Mackall showed. That will, of course, affect all T cells. If you just want to have this period of rest for the CAR T cell, theoretically we could do that with lenalidomide.

From your vantage point, where are we on this timeline?

I see us as at the end of the beginning. There’s clinical data, there are commercial products. Patients are getting this. We have a whole clinical service of patients who are getting CAR-T cells; that didn’t exist five years ago. We know that this can work on a clinical level. We know that it can work at a large-scale.

I think it needs to grow in two areas. One is that, right now, a lot of patients who could benefit from CAR-T are not getting them. It’s hard to know all the reasons why. Some of it has to do with our healthcare system and health insurance, but some of it is geography or the various other challenges in our system. So how do you make it more accessible? And second is that, right now, there are a limited number of diseases where CAR-Ts are effective. On the scientific side, we need to get to that proof of concept in more malignancies and in other diseases.
What are the main questions of cell therapy that are driving your work right now?

What we are trying to understand is how the cell therapies are working, and what the mechanisms of resistance are. We’re also trying to parse out what the common themes are across all our cell therapies. How does cell therapy work in lymphoma? How does it work in multiple myeloma? What are the similarities and differences? And importantly, how can we put that back into learnings applicable for cell therapies moving into solid tumors?

What can we learn about lymphoma and multiple myeloma that can feed into how we design our next-gen therapies? Cell therapy in lymphoma does provide long, durable benefit for patients, but we have a large proportion of our patients that are not achieving this benefit. And so everything that we’re focused on, not only with the combinations that we’re choosing, but also with the next-gen cell therapies that we’re developing, is about improving those response rates.

What is the scope of your team’s responsibilities?

Some of my team is devoted to doing clinical biomarker work. The biomarker work in those first-in-human studies is dedicated to determining that we’re treating the right patient population, and that the drug is safe, active and doing what we think it should in patients.

I also have another part of the team that does wet-lab translational research, because once a molecule is in the clinic, our understanding of how it works doesn’t stop there. There’s a lot of research that goes on to further our understanding of mechanism of action or follow up on interesting findings from our first-in-human studies, to help either generate data packages for those molecules to go into new indications/combination studies, or to help our developing pipeline.

Can you share a recent “A-ha” moment?

The importance of the endogenous immune system. Currently, we are focusing on what characteristics of cell therapy are associated with response. In our analysis, what we’re also coming to understand is that the patient and the patient’s immune system, both pre- and post-infusion, contributes to eliciting and maintaining their response. You cannot disconnect the patient and their endogenous immune system from the CAR T cell.

We see that even post-infusion patients treated with liso-cel, their endogenous T cells need to be functional. If we see signs of post-infusion exhaustion on the
patient’s own CAR-negative T cells, that typically is associated with a poor durable response to CAR T cells. The question then is, “What is the contribution of the endogenous immune system, and how does that contribute not only to the product you make, but also post-infusion in maintaining response?”

You’ve published work about using liso-cel in combinations to address issues like antitumor response and T cell exhaustion. What have you learned from that combination?

One piece of data that I can talk about, that we published at SITC last year, was in CLL from our liso-cel TRANSCEND 017004 study with liso-cel. In CLL the patient’s T cells in general are dysfunctional and this has been a huge barrier for CAR T cells in CLL. As part of our TRANSCEND 004 study we have a liso-cel combination arm with ibrutinib.

Ibrutinib notoriously has a lot of off-target kinase activity. One of ibrutinib’s off-target kinases is ITK in T cells, which is involved in T cell signaling. We had done some preclinical work to understand the direct impact of ibrutinib on CAR T cells. We expected to see a direct modulation of CAR T cell proliferation, and then also a change in their phenotype and reduced exhaustion in patients.

“Science is not a one-person show. It’s a collaboration.”

What did you see in those cells after the combo was used?

In the clinical trial, we took CAR T cells at various time points – peak CAR T cell proliferation, one month post-infusion, and two months post-infusion. We sorted out the CAR T cells and we did gene expression analysis.

Interestingly, what we saw there was exactly what we expected. We saw at one month and at two months, reduced exhaustion signatures in CAR T cells from patients treated with the combination and this was associated with improved progression free survival. This was some of the first evidence we generated that you could improve CAR T function in patients with combination treatment.

What drives your passion for translational science?

I love translational research, because it’s so close to patients. What keeps you going is getting that therapy into a patient, whether it’s a new therapy, or existing therapies for new indications or with combinations. When you are lucky enough to see patients are responding, it’s so rewarding.

We’re dealing with very ill patients, so if we’re able to contribute in any way to helping them or giving them some benefit, that’s a huge driver. We’re so invested in that. Sometimes it can take a while and there’s many different challenges. But the fact that at the end of that work, you’re potentially helping patients, there’s nothing better.

Do you have a piece of advice that’s been impactful to your career?

Make sure that you are following the data, and making decisions based on the data. As scientists when we’re interpreting the data, sometimes we only look for results we want to see.

It’s important to look at the results from all angles and understand when, “This isn’t telling me what I thought it would,” and to start over, or ask a question in a different way. You’re going to learn so much more because of that.

The other piece of advice is to always collaborate. Science is not a one-person show. It’s a collaboration. Especially moving a therapy forward, it’s not just me doing it. I’m a small cog in a large machine of wonderful scientists. You benefit from open and honest communication and collaboration. Many minds are better than one in dealing with the challenges we’re facing and trying to solve for. So collaborating well and following the data will help you in your career in my opinion.

How can we support women across all ranks in science careers?

We have to ensure that we are looking to provide opportunities. I’m so fortunate that in my current role, I work and partner with a lot of wonderful women scientists across all ranks in our company. And if you’re looking to be a leader, it’s about both seizing those opportunities for advancement presented to you, but also supporting each other in the process.

Do you have any book recommendations?

I really enjoy learning about English history, especially around the time of Henry the VIII – I really enjoyed the fiction about Cromwell in “Wolf Hall” by Hilary Mantel but also have read many non-fiction accounts about the period, in particular some books from Antonia Frasier called “The Weaker Vessel” about the lives of women in the seventeenth century at all levels of society and also her book on “The Wives of Henry the VIII.”
What is Senti Bio and what is it trying to achieve in IO?

Senti Bio is a gene circuit company. What’s unique about Senti is that the gene circuits we put into cells enable them to respond to stimuli. Simply put, the cell does different things depending on its environment and what signal it’s seeing.

We are working on our internal pipeline, where we put these gene circuits into allogeneic natural killer (NK) cells to develop products for oncology. We are also partnering with other companies to use our gene circuits to address non-oncology indications, like genetic disorders, neurology, etc.

Can you walk us through how gene circuit technology works?

It’s still relatively novel. It’s a feedback loop. To give you an example. I’ll walk through one of our lead products, SENTI-202. We use a logic gate. When our bivalent CAR sees either FLT3 or CD33, or both, which are very commonly expressed in AML blasts, it triggers a KILL signal. The very cool thing about what we do is we also have a NOT gate associated with a protective endomucin protein. It’s found on healthy bone marrow cells, but not on AML cells. So even if the healthy bone marrow cells have FLT3 or CD33, recognizing endomucin overrides the KILL signal. If it works, this changes the approach in general in cancer. Usually, the aim is to find a clean target so that you can affect the cancer cells, but not the normal cells. But not all cancers are like that. There are a few which have clean targets, but most cancers actually have pretty dirty targets. So this way, the gene circuits clean up the target using engineering.

The other example is the regulator dial. You have a payload like IL-12. You put the IL-12 under control of a small molecule, which drives its transcription. It gets integrated into the cell. When the small molecule is not there, it’s not expressed. When it is – and we use only FDA-approved small molecules to do this – then it is expressed.

With that, you have tight On/Off control, as well as the ability to control how much IL-12 comes out depending on the type of small molecule you use. You can imagine a situation where you have these NK cells, with these regulated dial-controlled IL-12. You can regulate how much IL-12 the cells express.

What does a logic gate change allow you to do in cell therapy?

First, it enables us to use cell therapy for cancers which traditionally have not had that one clean target. AML is a great example. It extends cell therapy into areas where traditionally it’s not been able to penetrate. If you look at our pipeline, it is AML and solid tumors. With AML, you don’t have a CD19 like with B-cell cancers. That’s where we come in and say, “The target is dirty but we can clean it up.”

Second, it’s being able to increase the potential benefit and decrease the potential risk. If you look at NK cells, they potentially have a much higher benefit to risk compared to a T cell, because inherently they don’t go in and divide.
like crazy, so they are less likely to cause side effects like cytokine release syndrome or CRS, like T cells. Then we come in with this engineering to further increase the benefits and decrease the risk. That selectivity of target selection might mean you can push the dose or the frequency. We’re enhancing an NK cell’s normal ability to recognize a normal cell from a cancer cell.

What are the challenges as a CMDO when working in a relatively novel space?

I’ve been doing oncology drug development for about 16 years. The big difference for a cell therapy CMO is pretty much 80% of my time is spent figuring out the manufacturing and the technical operations of the research. These are living drugs; there is so much that goes into it that has an impact on the clinic.

The other parts of my role that comes under the Chief Development Officer portion is working with the research directors to bring novel products into the clinic and ensuring the benefit continues to be increased while the risk continues to be decreased as the gene circuits are designed for clinical use.

A CMO role, in my opinion, anyway, is one of the folks at a company who needs to know a little bit of everything that’s going on in the company. So, you can ensure the therapy is safely evaluated in patients and has the potential desired effect on the disease. Which gene circuits? What is the release criteria? What is the testing needed for donors of allogeneic products? As a CMO, you end up touching almost every part of the organization.

What is the value of an allogeneic NK cell product versus an allogeneic T cell product?

My first foray into cell therapy was actually in a T cell company, but I’m a true believer in NK cells. I do believe that the advantages of NK cells override the advantages of T cells. It’s all about biology. Some of the advantages of NK cells are that they do not explosively divide. There isn’t an outpouring of cytokine. So if you think of an accessible cell therapy that can be given in a clinic in Sacramento, for example versus in a tertiary care center like UCSF, I think it’s likely to be something like an NK-based therapy. The flip side is that if it is not explosively dividing, it isn’t able to go in and clean up the bulky diseases and the heavy tumor burden. But there is a way to overcome it. Because it’s safer, you can give multiple doses and multiple cycles.

The other thing about NK cells is that they’re not as long-lived as T cells. As far as we know, there is no true memory NK cell. The advantage of not being long-lived is you don’t have to worry about late side effects. We overcome potential cell persistence in a few ways. We have something called a calibrated release IL-15, which we use across our pipeline. IL-15 is very important for NK cells to increase their persistence and their cytotoxicity. Some companies fit it into the membrane, or express it as a secreted form. We do both: the IL-15 is pinned to the membrane using a linker, which is susceptible to endogenous proteases; you get both autocrine and paracrine. Because as the NK cells get activated, they release proteases, which clip the IL-15. That goes out into the surrounding environment. But it’s also present in a membrane-bound fashion to preferentially make the NK cells live longer. You do need something like that for the cells to have the cytokine support to make it past manufacturing, go in there for a few weeks, and expect it to stay in the patient to do its job of clearing out the cancer cells.

What is a piece of career advice that’s been impactful for you?

When I first moved to industry, I was told by a mentor, “When you start your first role, you feel like you have so much certainty that this is the be-all-end-all.” But when you’ve gone through a few companies, you start realizing, “This is the next 3-5 years,” and that there will be another job, and another; and that as long as you are growing, that’s great.

The advice this mentor gave me was about how to evaluate a company you’re looking to join: Pennies, People and Product. “Pennies” is obviously how much you’re going to make. “Product” is the science: if the mission statement grabs you, if you’re excited to work on this. And “People” are these people you’ll want to spend time with?

It’s important to recognize that at different stages in your career, a different P is more important. I’m at the stage now where for me, it’s more about the people. No matter how exciting the science is, I don’t feel the need to spend time with people that I don’t want to spend time with. When I was younger, it was almost all about product. That is something that I find very useful to evaluate new opportunities. And, of course, once in a while, if you are lucky, there is an opportunity like Senti where you don’t have to choose and that is a good and rare thing!

How can we be better at supporting women, from young women entering the workforce to those rising in the ranks, and in science careers?

We have to make sure that the expectation is that it’s okay to make mistakes, especially for women. Society as a whole is more forgiving of men than it is for women to make mistakes. So especially for those of us in leadership roles, where we can do a better job is to say, “It’s okay to make mistakes. It’s natural. What’s important is how you react to that and how you move on from it.”
Isabelle Rivière, PhD, was at the beginning of the cell therapy manufacturing journey, and created many of the SOPs that serve as the backbone for the industry. Dr Rivière shares the beginnings of her journey, as well as her thoughts on how cell therapy manufacturing must evolve to meet the next set of demands. She is the Director of the Cell Therapy and Cell Engineering Laboratory at Memorial Sloan Kettering Cancer Center.

You were recruited to Memorial Sloan Kettering in the late 1990s to set up one of the first clinical-grade gene transfer facilities in the country. Can you tell us that backstory?

This is a field that we pioneered. We were lucky at Sloan Kettering to have some visionary scientists, like Dr Michel Sadelain, and the leadership at the time. Before we had even conceptualized cell therapies like CAR-T cells as they exist today, they had the vision that such developments would occur in one form or another. They decided to build a GMP facility by 1998 which became operational in the early 2000s.

We were just starting to study CD19 targeted CAR T cells in vivo and Dr Sadelain developed the first mouse model of systemic disseminated leukemia. I started to meet with various experts, particularly those people who were manipulating bone marrow for bone marrow transplantation. At the time, we drew a lot of the technologies that we used to manipulate T cells from the stem cell laboratory, while a few laboratories were starting to produce vectors and cell therapy products.

What were the first steps when you started?

When I got the keys of the facility in 1998, we only had a few pieces of equipment and one technician. We didn’t yet have the proof of concept of CAR-T cells being active in animal models. We were building the plane as we were flying it. Overtime, I assembled a multi-functional team encompassing quality assurance, analytics and quality control, facility operations and QA documentation.

I was lucky to also have met Dr Mark Bonyhadi who was involved in a cell therapy company that was already developing a T cell therapy based on the same types of reagents and manufacturing platform that we continue to use today, including the activation beads that are coated with anti-CD3, anti-CD28 antibodies. We started to work with these reagents and took advantage of this technology to subsequently genetically modify the T cells with viral vectors.

My expertise was in the design of viral vectors for the genetic modification of cells of the hematopoietic system. Over time, we learned how to integrate all these different functions and technologies to develop a manufacturing process with bioreactors and various other unit operations.

How soon after the facility was set up did you have your first patient?

We did treat our first patient in 2009, a patient with chronic lymphocytic leukemia. In 2010, we treated our first adult patient with acute lymphoblastic leukemia. In the first four patients with acute lymphoblastic leukemia, we observed complete responses. We couldn’t believe the magnitude of the clinical response at first. We thought that the technician had forgotten to add the antibodies in the experiment and
that therefore, we had missed the detection of the tumor cells. Upon repeating the experiment, we realized that this was true and that all the tumor cells had disappeared from the bone marrow 2-3 weeks after infusion of the CD19-positive CAR T cells.

In 2018, you said that often the impact of the quality of the manufacturing process is underestimated in cell therapies. What is your view on this now?

Since the approval by the FDA of the first CAR-T cell products, I think that there is more interest, more funding, and more appetite for developing and improving manufacturing platforms. Nevertheless, it is still challenging to find public funding for innovation in manufacturing especially in the academic setting. Now there are consortia – encompassing public, industry, foundations and academic organizations – that are addressing this issue. But it is taking time for this to be elevated to a significant amount of initiative from the various sectors. So I think there’s still work to do.

Why is it important to put this emphasis on manufacturing?

The fitness and antitumor properties of the cells are affected by the manufacturing process. Inadequate manufacturing can result in an inactive cell product or a more or less potent product. Scientists and engineers have realized that it is very important to perform in-line and on-line monitoring to assess in real time the characteristics and the critical quality attributes of the cells. You want to be able to abort runs very early if you know that they’re not going to be fruitful. Or even not run them at all, in the case of autologous cell therapies, if you determine from the initial apheresis sample that this is not going to be a successful run. It is also important to automate the manufacturing platforms in order to reduce human errors and to decrease the cost.

Do we have the capability now to judge early on in the manufacturing process if a cell therapy won’t be viable?

There are now more criteria that allow scientists to predict manufacturing success. These criteria include characterizing the number of cells and their proliferation at various steps, the types of cell subsets, their proportion and phenotype in terms of memory and effectors for example. Multivariate analysis of cell characteristics (e.g. metabolites, multiomics) can now be performed and will hopefully help determine in real time if the products can be successfully manufactured. Knowing what type of chemo patients have received, which may favor or hinder the cells’ ability to be manufactured is also important. The incorporation of these parameters in the manufacturing workflow is still work in progress.

It is really important to collect these parameters prospectively and to analyze them in conjunction with clinical characteristics and outcomes. This requires data mining and potentially utilizing AI technologies to mine the data sets at a significant scale. In academia, we can collect the data in our manufacturing batch records, but we have limited ability to mine the data because we’re lacking electronic documentation to record the manufacturing. These are significant investments for academic centers as these electronic records have to be customized to the academic center and manufacturing process.

What could be done to lower the cost of cell therapies?

Reducing the time the cells are in culture can reduce the need for manpower and reagents. That’s something that we are working towards. Some academic centers and industry are already working with these shorter protocols, culturing the cells for either a day or two. The cells coming out of these short processes seem to be quite potent.

Automation is also a goal. We have started to investigate some platforms to move into that direction. The collaboration models between academia and tool developers of automation is not straightforward. Automation platforms can be expensive. We need to establish the equivalency of the automated process with our current manufacturing process. If you don’t know that it’s going to be successful, you generally want to try it for free, which not all tool providers are willing to take the chance of doing with an academic center.

What do you see as some of the potential challenges in the process of automating manufacturing?

It’s great to have an automated process lasting only one or two days, but right now we don’t have the tools to perform quality control testing to release the cells within that time frame. You currently need more cells for your QC and release testing than for the cell dose given to the patient. In my view, this is currently the limiting step. You need to develop analytical methods so that quality control uses a small amount of product while the product is generated over one or two days.

Right now you can have a shorter, automated process that can happen in one or two days, but for your QC testing, you need to grow the cells longer to complete the release testing, because you require a number of cells that exceeds the cell dose that you will give to the patient. We need to work on those issues in parallel. Tool developers are working on closing those gaps but it’s not yet ready for primetime.
Tell us about the work you lead at CRI.

I lead our immuno-oncology landscape analysis efforts and publication strategy. Our team provides the IO community with updates on the immuno-oncology drug development landscape with the goal of informing CRI’s clinical strategy, business development decisions and start-up investments, and fosters effective relationships with industry, clinical and academic partners.

Together with the rest of the Clinical Accelerator team, I also lead CRI’s clinical activities. We have created a unique model of nonprofit-academia-industry collaboration that allows us to bring forward innovative clinical trials that no one partner alone could carry out. We focus on the most pressing unmet medical needs in IO and address them by collaborating with the scientific leaders, pharma, biotechs, and other nonprofits in the field. We put great emphasis on the correlative assays in our clinical studies, making sure we learn from each patient and glean crucial biological insights which, in turn, we apply on subsequent studies.

What does the Clinical Accelerator contribute to our greater understanding of immunotherapy?

We support basic, translational, and clinical research with the mission to make cancer immunotherapy effective for all patients. There is still a lot that we don’t understand about why immunotherapy works in some patients and not in others. In order to move the field forward we need to design trials that test smart combinations of drugs, and we need to put a lot of thought on what correlative assays can be incorporated in these trials so that we learn the most from each patient.

How can we design trials that test “smart combinations” of IO drugs?

We need to build computational infrastructure that allows the community of researchers to compare correlative data from these trials to get solid mechanistic insights into the observed response/lack of response. We also need to take these learnings back to the bench and continue supporting research at the preclinical and basic discovery levels. As a leader in the field of immunology and cancer immunotherapy, CRI does all these things.
What made you passionate about entering the field?

I wanted to contribute to the understanding of heterogeneity among oncology patients and to finding the best treatment for each of them. I also wanted to work close to innovation and surround myself with great minds that keep moving the field forward. I never stop learning on this job, and that really energizes me.

What would be your career advice for young women who are entering science careers?

It sounds trite but I really think it is important that you believe in yourself. Women in STEM have, almost by default, a very strong inner critic. This keeps us growing, but my advice is to not let it go unleashed: as you strive for excellence, give yourself the space and time required to grow. Enjoy each stage of your career, find mentors along the way that inspire you and surround yourself with supportive colleagues, family, and friends.

Is there anything else you would like to share with our readers about your work?

The Cancer Research Institute provides a variety of funding opportunities for scientists and clinicians in various fields of basic and translational cancer immunology at different stages in their careers, from postdocs to tenured academics.

We collaborate with academic institutions, pharma and biotech companies, as well as with other non-profit organizations in different clinical and non-clinical initiatives. We also provide educational resources to patients and caregivers helping them navigate the world of immunotherapy clinical care.

Do you have any book recommendations?

*Bad Handwriting*, by Sara Mesa and *Why Fish Don’t Exist: A Story of Loss, Love, and the Hidden Order of Life*, by Lulu Miller

“I wanted to contribute to the understanding of heterogeneity among oncology patients and to finding the best treatment for each of them.”
Barbra Sasu, PhD, is the Chief Scientific Officer of Allogene. She joined Allogene as Chief Scientific Officer in April 2018 when the company acquired the allogeneic cell therapy assets from Pfizer.

What was it about Allogene’s mission or technology that drew you to taking this role initially?

It’s because of the transformative nature of CAR T. I ran the CAR T programs at Pfizer, before Pfizer made the decision to outlicense that technology. When I first started working on CAR T, I had to build up the team and build up the pipeline. I felt very connected to that, so when Pfizer decided to outlicense it, I wanted to go with it, rather than stay to lead the rest of the portfolio. I wanted to be one of the people helping to validate that technology.

What is your vision for allogeneic CAR T cell therapy?

We envisage the future where everybody who qualifies for CAR T therapy gets it. The vision is that you’re not going to the one specialty center in your state; you’re going to the hospital that’s down the road. It’s very hard with an autologous cell therapy, to treat all the people who need therapy. Firstly, because you need very specialized centers to do that whole complex process. And because of the timings involved, the complexities of shipping products back and forth, while you’re waiting for your cell therapy, you get sicker. A lot of patients don’t manage to have a cell therapy product made because of the health of their cells. And if you can’t make it, there’s no treatment for that patient.

What is the scope of your responsibility as CSO of Allogene?

I lead the preclinical pipeline. A lot of my day-to-day is figuring out how to balance resources across programs, so that we do everything we need to do to support the programs that are in the clinic, or going into the clinic very soon, and building that deep pipeline that will lead to long-term success of the company. I work heavily with the translational group so that when we get data back from the clinic, we look at that data and ask, “How does that measure up to what we saw preclinically?” and “Can the learnings from that help us design a next-generation product?” etc.

Allogene just released exciting data from its ongoing programs. What was the key takeaway?

I’ll start with the data from the late-term CD19 and BCMA programs. What we showed was durability of response. Other allogeneic CAR Ts have shown that they can get initial response rates, but maybe the window engraftment is short or the responses are less durable. We showed that for most of the patients who showed an initial response a year ago, if they got past about six months, they have a high probability of staying in response.

What are some of the other learnings and their implications?

We tried less lymphodepletion upfront and then a second cell dose with more lymphodepletion. We tried hitting harder up front. We tried different doses of cells and lymphodepletion. Through that, we built a good understanding of a dose response relationship between how much ALLO-647 we give, how much lymphodepletion
Beta 2 microglobulin (B2M), which stops the peptide from immune cells, as well as attacking them. Dagger technology. Then the next component is masking a specific activity to attack alloreactive cells. That's the foundation of our platform was ALLO-647, which takes that concept, extends the half-life and only affects the immune system. The next level on top of that is having transiently because it gets you very deep, lymphodepletion-wise. But they're small molecule-based with a short half-life. As soon as you take them away, your cells start to rebound immediately. And if you give too much lymphodepletion, you get much broader toxicities.

Part of the success is due to the fact that CD70 is a good target. CD70 also brings unique biology: as well as killing CD70+ tumor cells, it kills alloreactive cells. It kills the cells that are trying to reject it. That is the potential basis for a new platform of ours, Dagger. I've been very excited to see the CD70 data mature. We sat quietly on it for a while, because we needed to understand it before we talked about it. Now we are finally ready to talk about it.

You also shared data on your first solid tumor program. What did you learn about CAR T in solid tumors?

We have shown that in a solid tumor with an allogeneic CAR T, we can show responses. There's been a lot of dogma over the years that CAR T doesn't work in solid tumors. I understand why people tend to under-lymphodeplete in solid tumors because it's not part of their normal regimen. Doing that kind of lymphodepletion is hard enough, especially if you are testing a CAR about which you're worried about safety. That's why it was important to us that we started with CD70. We felt we understood its safety profile. We knew what tissues expressed CD70. It allowed us to explore lymphodepletion.

Many of the other allogeneic CAR T players are looking at enhanced lymphodepletion – essentially they give a lot more lymphodepletion upfront. That actually works well transiently because it gets you very deep, lymphodepletion-wise. But they're small molecule-based with a short half-life. As soon as you take them away, your cells start to rebound immediately. And if you give too much lymphodepletion, you get much broader toxicities.

The foundation of our platform was ALLO-647, which takes that concept, extends the half-life and only affects the immune system. The next level on top of that is having a specific activity to attack alloreactive cells. That’s the Dagger technology. Then the next component is masking from immune cells, as well as attacking them.

You're also leading work in addressing cell rejection, specifically by knocking out two transcriptional regulators. What was the problem you were trying to solve?

With that base and knowledge, what did you pursue to avoid cell rejection?

What others have done is knocked out or knocked down Beta 2 microglobulin (B2M), which stops the peptide from immune cells, as well as attacking them. We also knocked down two transcription regulators NLRC5 and RFX5. NLRC5 is a transcription factor that controls class I; RFX5 is a transcription factor that controls both class I and II. That means you’re also avoiding CD4-mediated rejection, as well as CD8-mediated rejection. With this approach, you get a lot less T cell rejection, but you don’t get NK cell rejection.

Do you have a piece of advice that has been impactful for your career?

When I worked at Amgen, one of my mentors there, Dr Glenn Begley, used to tell me to pretend to have 20% more confidence than you may feel because then I will say I feel that women younger in their career often hang back to figure out if they’re ready. They wait for encouragement. They don’t necessarily step up for new opportunities, but wait to be selected. And sometimes people believe you are exactly what you say you are. So if you say “Do you think I’m ready for this?” they’ll think, “They’re not ready for this.”

You have to have faith in yourself. You have to give yourself permission to believe in yourself. Many times it didn’t even occur to me to apply for positions, and then I would see somebody else do it and think, “Actually, I’m more qualified than that person.” But maybe that person asked for the opportunity, or believed in themselves a little bit more. So 20% more confidence than you may feel because then perhaps you’ll get the balance right.

How do you think we can better support women, from young women entering the field to people that are rising the ranks, in their science careers?

We must open the door to communication more and give people permission to have outside interests and a family and feel that that is not career-limiting. Early on in my career, I would never talk about my children, because I felt maybe it was a bit of a target on my back. At this point in my career, I often have discussions and talk about the benefits of having two sides to my life. My kids know that sometimes I’m going to be sitting in a room and I just have to concentrate. That’s a good lesson for them to learn: if you’re doing something that’s important, you have to invest in it. Having an outside life doesn’t make you any less focused or any less dependable. In fact, that’s where you get a lot of your energy from.

Do you have any book recommendations?

The Peripheral by William Gibson.
What is 3T Biosciences?

3T Biosciences spun out of research I and my co-founder, Marvin Gee, did when we were at Stanford in Dr Christopher Garcia’s lab. This work was focused on trying to identify targets of T-cell receptors. It was at a time when immunotherapy was seeing transformational results in the clinic. The question came up, “If we have T cells that we know are producing clinical responses, what are the targets that are associated with those?” We wanted to know if we could map those targets from the T cell’s perspective unbiasedly. From that, we were able to develop a technology where we could take the T-cell receptors (TCRs), find these targets, and then develop therapeutics around that. We spun the company out and are working to translate these discoveries into medicines.

What were the early days like in building the company?

We spun 3T out at the end of 2017. The first few years were dedicated toward bringing the technology out of academia, because it was a platform technology. It took us two years to screen 20 TCRs; we’re now doing more than 200 TCRs a month and identifying targets from them.

We spent the first few years industrializing the platform, scaling it, building the team, having the initial pipeline of targets and proof of concept, to get us to the point where we could pitch raise our Series A with the opportunity to take 3T to the next stage and to truly develop these and translate them into patients.

Tell us about the focus on T-cell engagers?

We’re seeing that they have the ability to transform “cold” tumors into hot tumors, meaning that we’re seeing clinical responses when you’re targeting both a peptide HLA and T cells. This class of target and these types of molecules in particular, have huge promise, not just for finding the right targets and opening up this space of novel targets, but also for changing the immune environment.

The question has always been, “How can we broaden this work and find more targets?” That’s where we started. And then since the raise that we had last year, we’re translating those initial discoveries into the clinic.

What is 3T trying to achieve in immuno-oncology?

Our mission has always been to develop next-generation and transformative therapeutics, initially in solid tumors. However, we know T cells have a broad range of applications, not just in oncology, but also in autoimmunity, and other immune-related diseases. We can take this unbiased technology and develop therapeutics for these new classes of targets that we’re just seeing phenomenal responses toward in a number of different types of therapeutic settings. I’ve always been driven by being able to make an impact on patients.

You’re working to identify immunogenic targets that are generalizable for multiple tumor indications. Can you explain what that means, and how it could work?

If you’re a patient who has received checkpoint inhibitor therapy, and you’ve responded, we’re able to identify the T
cells that are mediators of those responses and identify what those targets are. T cells can actually recognize endogenous targets. That means that they aren’t specific to the patient’s tumor mutations. These are cancer testis antigens, etc. These are actually expressed in multiple tumor indications. The hard part has been finding out what the epitopes are. What is actually important about those proteins that can get them presented to the immune system?

3T’s method allows us to identify what the important immunogenic epitopes are, and then make that broadly applicable, because those antigens are expressed in other patient indications. Obviously, there is huge diversity amongst our immune systems, and therefore vastly different responses, especially after treatment. What we’re hoping to do is to provide patients with an optimal solution for going after the targets that happen to be there, but that their immune system doesn’t have the capabilities natively to respond to.

How is 3T addressing challenges like finding patient samples with the right types of data?

We’ve had partnerships with the Parker Institute for Cancer Immunotherapy, working with a lot of their clinicians on some of their patient trials. They have a tremendous amount of patient response data, with serial time points. With our technology, we’re able to query each of those to identify the key mediators of response.

Can you contextualize how novel this work is?

3T’s approach at both identification as well as designing the therapeutic is differentiated from the field. We go from the immune response to identify the targets. What we have done recently is in-licensed technology from Stanford, where we’ve developed therapeutic libraries that are structurally based, specifically targeted towards peptide HLA molecules. We’ve already talked about one of the biggest challenges in the field, which is the novel targets. Another big challenge is to improve clinical response by making specific, safe and effective therapeutics.

One of the challenges with peptide HLA targets is that it’s a very small difference between a target and a potential off-target. Our platform can screen any type of pHLA targeting molecule and identify how specific it is for that target. And then on top of that, we’ve combined with the technology of a structurally designed library to identify specific molecules targeting these. If you pair the two together, you have a rapid platform that can both identify targets and screen for cross reactivity, pairing with a structurally informed platform that can then identify specific molecules to target them.

What was the experience of transitioning work from the lab into a full-fledged company?

I was always driven by the science and by the technology that we were developing to understand TCRs and how they target molecules. I felt that if we could understand their recognition properties, we could tune them. Being within the Stanford environment was phenomenal, specifically being in Chris’s lab because he had spun technology out from his lab previously.

At the time, we were seeing tremendous needs in the field for novel targets, and better-designed therapeutics targeting peptide HLA. We had this platform that we had shown could address some of those gaps in the field. There weren’t a lot of other technologies out there to directly assess this. It was a risk to say this actually meets the need, and ask, “Can this technology be translated, scaled and further developed?” And that’s where we are now, developing it and bringing it into the clinic.

What have you learned since being a founder, about the business side of science?

One of the areas that I’ve learned a lot, from the science and tech side, is staying focused. Especially when you’re starting out with a platform technology, there will be interest in many different potential applications. You may want to pursue all those avenues, but when you’re in a company, you have to stay focused on: How do we make sure this translates to patients or to the next value inflection point? Being able to hone that focus is a skill, while also leaving open opportunities for innovation.

Is there a piece of career advice you find particularly impactful?

Get comfortable being uncomfortable. Because no matter what, you’re going to be in situations where you’ve never been; you’re going to be doing things you’ve never experienced. But as soon as you’re able to tackle those different situations, it becomes so much easier the next time. That’s how you grow.

And reach out to people. Something else I’ve always said is how surprised and grateful I am by how open people are to help you or to discuss a problem. When I was younger, I was very hesitant to “impose” on someone’s time. But reaching out to people has had a tremendous effect, not just on accelerating my company but for me professionally. People are open to discussing their experience, or helping you to tackle a problem, if you reach out to them.

Do you have any book recommendations?

I recently read Why We Sleep by Matthew Walker. It’s deep science translated into a great, informative read. Right now, I’m reading Thinking in Bets by Annie Duke. It’s about decision-making in the absence of a lot of input.
Tell us about your early career as a hematologist oncologist.

I have been in life sciences and specifically BMS for close to 10 years. I am a hematologist and oncologist by training. I started my career working as an academic bone marrow transplant physician and did so for five and a half years.

What inspired you to change the focus of your career?

There is great satisfaction in a career where you’re seeing patients and helping and treating them, but the drive to go into life sciences and specifically in oncology drug development was twofold. The first was the impact on patients. Working to develop new therapies that could bring hope to many patients with cancer is gratifying. The second was to be part of drug development, be at the forefront of innovation, and increase my impact on science and patients.

What is your scope of responsibility at BMS in cell therapy development?

I’m the development lead for Breyanzi, the CD19 CAR T at BMS. The responsibility is to lead the strategy from having a proof of concept that works for patients with a certain CD19 malignancy, develop and conduct registrational clinical trials to establish Breyanzi risk-benefit for patients with heme malignancies for health authority approval, and then deliver to patients. I lead a matrix team that helps execute this.

How does BMS's history with Breyanzi and Abecma impact your team’s role in expanding Breyanzi’s use easier?

The database. At BMS, we’re fortunate to be the only company with two approved CAR-T cell products against two targets in different indications. As a result of having two marketed CAR T products, we’ve treated many patients, and we have the largest database of translational work and clinical data, with over 2,000 patients.

We’re continuously tapping into that, looking at how we can understand the patient characteristics that would benefit them, and how we overcome mechanisms of resistance or the tumor microenvironment. We have more real world and manufacturing data which affords us the opportunity to apply learnings and build the future of next generation cell therapies.

We are also using the database to understand how we can improve scaling our manufacturing appropriately to meet the demands of patients. Our commercial launches
and research in CAR T have provided valuable lessons on the individualized nature of autologous cell therapy and introduces variability in manufacturing. Scaling appropriately for manufacturing capacity is paramount to ensuring we meet the patient demand. Cell therapy is innovative and an evolving field and it’s imperative we work closely with regulators and the healthcare authorities on how to develop cell therapies in a safe, accessible manner.

**What are the challenges for your role in expanding use of Breyanzi?**

The challenge is scaling up globally, and not only to meet the demands, but also improving the turnaround time of manufacturing the product for patients. We’re also focused on decreasing the cost and increasing our supply in a streamlined manner. This is coupled with researching off-the-shelf solutions, improving CAR T functionality, and expanding treatment in solid tumors.

We continue to explore several tracks to maximize the potential of cell therapy, with the ultimate goal of helping more patients and additional cancer types. In large B cell lymphoma in the United States, Breyanzi is approved in second, third or later lines of treatment, but we are investigating other potential indications to determine if it could be useful for additional patient populations with heme malignancies.

**What is your favorite part about your current role?**

I love getting to interact with intelligent people of varied expertise here at BMS that share the same vision and are dedicated to bringing innovative treatment for patients. We can provide a tremendous impact for patients. Being in the life sciences field and specifically at BMS, we are at the forefront of innovations. It’s a challenging role to keep advancing and raising the bar for our patients. That’s what makes you get up and go to work every day.

**Is there a piece of advice you can offer women going into life sciences?**

First, don’t be afraid of challenges or change. For me, it wasn’t a very common path to go from a medical doctor seeing patients to life sciences. But you can’t be afraid of challenges or change; you have to embrace them and this leads to growth both professionally and personally.

Second, it’s important to be driven by your guiding light. For me, that has been scientific curiosity and making an impact in the medical field.

And third, as people think about career progression, and setting yourself up for your “next job,” my advice is to do your current job very well. I try to absorb all that I can in what I’m doing day-to-day. Provide the best input I can, and contribute what I can, without being too overwhelmed with the future. That will all come. Being good at something requires some effort. But being great at something requires lots of focused effort.

And fourth, be humble and cultivate relationships.

**How do you think we can better support women in science careers?**

Mentoring and sponsorship. While rates have improved, women are still underrepresented in the highest level of the scientific field. In the past, I have benefited from mentoring, both from men and women. Because of that, I strive to provide mentoring back. I am keen to give back to the scientific community and strive to dedicate time to mentoring. It is fantastic that BMS has STEM initiatives where we’re supporting young women and students of color. I see it as an obligation for us to pull others up, through coaching, mentoring, providing tips, etc. I also recommend having mentors, women mentors and sponsors around you with different viewpoints whom you can go to for questions that arise in various subjects and fields.

Additionally, what continues to come up for everyone, but especially for women, is the work-life balance. It is beneficial to surround yourself with mentors and women mentors who are accessible, supportive of all stages of your career and who balance scientific and personal lives. What’s helped me in the past is anticipating that it will be difficult to balance the two. Luckily, the work environment has evolved to offer the flexibility to have both, but delegating and seeking support is key. Sometimes you have to step back from your career, or lean in, and that’s okay. Follow your heart and create that network of support and allies to help you outside of work as well as inside of work. Understand that you can have it all, but it may not be at the same time.

**Do you have any book recommendations?**

*My Life in Full*, by Indra Nooyi, the former CEO of PepsiCo. She speaks quite bluntly about leadership challenges, including as a female leader. That’s a great source of inspiration.
Book Recommendations

Stacey Adam, PhD
Foundation for the National Institutes of Health

Kelly Clark
Merck

Michelle Obama
The Light We Carry

Trevor Noah
Born a Crime

Shana Kelley, PhD
CTRL Therapeutics

Laura Johnson, PhD
Verismo Therapeutics

Elaine Long, PhD
GE Healthcare Pharmaceutical Diagnostics

Barbara Lavery
Alliance for Cancer Gene Therapy

Primo Levi
The Periodic Table

Projekt Hail Mary

This Naked Mind
Control Alcohol

The Emperor of All Maladies

A Cure Within

The Skull Mantra

Bone Rattler
Book Recommendations

Leanne Peiser, PhD
BMS

Barbra Sasu, PhD
Allogene

Ana Rosa Sáez Ibáñez, PhD
Cancer Research Institute

Shivani Srivastava, MD
BMS

Leah Sibener, PhD
3T Biosciences

The Six Wives of Henry VIII
Antonia Fraser

Hilary Mantel
Wolf Hall

William Gibson
Periphery

Indra Nooyi
My Life In Full

Why We Sleep
Matthew Walker

Thinking in Bets
Annie Duke

Why Fish Don’t Exist
Lulu Miller

Hidden Order
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