Dr Rachel Haurwitz on using CRISPR editing in creating allogeneic products for solid and hematologic tumors.

Dr Timothy Chan shares how he is combining exciting new genomics work with cancer treatments.

Dr Suzanne Topalian discusses next-generation strategies for anti-PD1 therapeutics.

A patient’s journey to getting into a clinical trial, new biomarker development and validation, creating in-house translational capabilities, and more.
Welcome to the IO360° Winter 2021 newsletter, highlighting leaders who are pushing immuno-oncology into new directions.

The interviews in this issue are:

Karen Peterson, patient advocate, on taking her cancer diagnosis and treatment into her own hands and her path to finding the immunotherapy trial that saved her life.

Rachel Haurwitz, PhD, Caribou Biosciences, on using CRISPR editing in creating allogeneic products for solid and hematologic tumors.

Timothy Chan, MD, PhD, Cleveland Clinic, on how he has developed the Center for Immunotherapy and Precision Immuno-Oncology at the Cleveland Clinic, marrying exciting new genomics work with cancer treatments.

Suzanne Topalian, MD, Johns Hopkins, on her work in melanoma and how her research in anti-PD1 therapies is moving into new indications and new combinations.

Christine Ward, PhD, Takeda, on her work at Takeda in developing an Oncology Precision & Translational Medicine organization for the Oncology Therapeutic Area Unit.

Genevive Hernandez-Pantua, PhD, IGM Biosciences, on identifying new biomarkers across the organization’s pipeline and her work as the Clinical Development Lead of IGM’s COVID-19 program.

The IO360° Newsletter is the official publication of the Immuno-Oncology 360° conference, which convenes key stakeholders spanning the science and business communities to report on the latest data impacting immuno-oncology to fight a wider range of cancers.

Enjoy reading.
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How did you identify and access clinical trials as an option for your care?

I had heard about clinical trials in depth for the very first time around 2016, when I snuck into a researcher’s office, just wanting to have a conversation with him in regards to clinical trials. I can remember, they didn’t call security, they said, “Let her look around; we’ll have a conversation.” This was before my diagnosis, which happened a couple of months later.

I can remember him saying to me, “You’re asking these questions. And I think you should take these questions back to your oncologist. Because where do you think we get our participants from?” Because I was asking, “Why aren’t more black women in clinical trials? And why can’t you cure triple-negative breast cancers?” etc, etc.

And he said, “These are questions that you should ask your doctor.” So this leader in the community implanted in my head that if you wanted to enter a clinical trial or learn more, your doctor is going to have to make that introduction. And so I knew right then and there to hold onto this information, which happened a couple of months later.

I just did hard research, like 10-12 hours a day, looking for peers. I didn’t care what color you were, I didn’t care what zip code you came from. If there was an article about you and you were in a clinical trial, I read about you. I wanted to hear from peers who had gone before me, who have gone into clinical trials, how they did it, how people got onto immunotherapy. And I needed to get the information from the researchers about what research they were doing and how they were doing it, and then what tests that I needed to do.

It was a sequence of events that had to happen; I had to work really hard. Things sometimes wouldn’t work.

I would call around to trial sites, and someone wouldn’t talk to me or that the number would be wrong, or they wouldn’t get back to me. I had to build an action plan. I was pulling information from everywhere. Eventually, I got to doctors and researchers who said, “You want to make an informed decision? Here’s how we can help you to.”

And thank goodness for the doctors and researchers that I contacted from looking at news reports, and reading white papers, and reading science magazines, gathering that information and talking to these researchers who had actually done this and published work, and then taking action. The goal was to stay alive.

The goal was to make an informed decision. The goal was to access quality care. And in order to do that, there were certain steps I had to take. Eventually it came down to the science: was I the right person for a clinical trial? Did my tumor’s genomic makeup or biomarkers indicate that this would work for me?

Are you still on the trial?

No, I moved on and graduated. I was on the trial from July 30, 2017. By 2018, they couldn’t see any cancer anymore, and I kept taking scan after scan; I was still on treatment. And by 2019, the realization came to me that I had done all I could do with this drug on this trial. My scans were showing nothing was happening. It was very quiet for over a year or more. And my thought was that if God forbid, anything happened, and I regressed on the drug that I was on, it would be taken off the table.

I had done as well as I could’ve. The principal investigator agreed that at that point, I had had a complete response. Remember, I was in a trial voluntarily, so I had the ability to stop at any time. So he took me off the drug, and we waited to see what could happen. Fortunately, I stayed the same; so in 2020, I was deemed a complete responder, with no evidence of disease.
From your experience, and from talking to other patients of color, what is top of mind to stress the importance to any clinical researchers reading this?

It’s all about trust. And I know people go “Oh my goodness, trust,” but from a patient of color with advanced cancer, who was trying to navigate a cancer diagnosis, fear is a real thing. Trust is a real thing. And it’s not a 30-second soundbite. You can understand historically why a person of color would not trust the system. That there have been instances of medical atrocities. We understand currently why that is the case. It can’t be dismissed. You then have to actually acknowledge that and say, “How can we build trust and break down some of the myths and acknowledge some of historical and current atrocities that are happening and move forward from there?

Because when you mistrust somebody, and you’re in fear of what could possibly happen, you can’t really move forward. The needle can’t move forward. You can’t make an informed decision. You don’t want to get educated. You don’t want to hear the information. You don’t want to see what your possibilities are, because the foundation isn’t there.

How much of the knowledge you amassed – knowing about needing the right biomarkers, or the risks of regressing on a drug, for example – was because of your own research versus being told in the trial?

I think I learned probably 90% of this on my own, and maybe like 10% of it from the trial. And so that’s the reason why it’s important for Karen’s Club to exist, because it’s important to relay the information to the community. I often tell people, I just didn’t roll over, look at my watch and say, “Today is the day that I’m going to enter a clinical trial.” There was a lot of science, a lot of research, and a lot of informed choices that had to be made in order to do it. A clinical trial is not for everyone. I was adamant about making an informed choice. Every conversation I had, it always came back to the fact that I’m here in front of you today, and I’m speaking with you, because I’m trying to make an informed choice.

I never wanted to get off track. And that’s really the key. The key is trying to decide whether or not if you’re having a conversation with a medical professional, is it an informed conversation? Is this conversation helping you get where you need to be, at whatever goal that is?

Everybody has different goals. But universally, everyone wants to be able to have a conversation and make an informed choice. And you can’t do that if you don’t understand what’s going on. I had to feel comfortable having a conversation and making an informed choice. But I had to do my due diligence as a patient; I had to be educated enough to be able to have a conversation and feel comfortable with the doctor. So I’m trying to provide a cheat sheet for other people, so they don’t have to do what I had to do.

Can you describe the origin of Karen’s Club?

Karen’s Club started as a challenge. When the COVID-19 pandemic first started, most of my in-person advocacy work had dried up, when a senior program manager at Robin Hood/Blue Ridge Labs, a non-profit, told me about a unique fellowship opportunity. I applied perhaps 48 hours before the closing deadline, and I was accepted. During one of the fellowship’s check-ins the same manager said to me, “Karen, you said that you’ve always wanted to start a nonprofit, here’s an opportunity to do so”. I was passionate about clinical trials; clinical trials saved my life, and so it was the question of, “How can I be in the position of effectively helping my community and paying it forward?” I found a partner who believed in my platform, Nava Friedman. She said, “I believe in what you’re doing. Let’s try and do this together.” So in May of 2021, Karen’s Club was born. We started doing the hard work of supporting patients of color with advanced cancer, helping to educate them and inform them about clinical trials.

What is Karen’s Club’s mission?

Karen’s club supports patients of color with advanced cancer, thinking about clinical trials, by giving them a one-on-one consultation for free. That consultation is with a patient advisor of color who actually can speak to a clinical trial because they actually have clinical trial experience. They’ve actually gone through a clinical trial.

And I know this is important, because during one of my recent consultations, there was a woman – very educated, African-American woman, graduated from college, young, with two children – who had been diagnosed with late stage cancer. One of the very first things she said to me during the consultation was, “Am I going to be the guinea pig? I’ve been offered a clinical trial.” Trust is a huge issue, so we definitely try to support patients of color, with education and information to address those feelings, because they are valid. In addition to that, we bridge the gap between patients and researchers by providing educational webinars.

We have wonderful partnerships with doctors, oncologists and expert advocates and are able to bring them in, call them to the carpet and ask them questions in a non-intimidating forum in the community that is underserved. With the forum, here you have a top researcher that’s actually doing the work who is willing to take any and all questions in regards to clinical trials. You can talk about benefits; you can talk about risk, and dispel myths.

It’s important to be able to have that information come from the doctor, oncologist or researcher because it lends credibility, and educates and informs the patient so that they can make an informed decision, have a conversation with their medical provider and take action if they want to be part of a clinical trial.
Pushing CRISPR to the Next Phase of Cancer Therapeutics, with Dr Rachel Haurwitz

Rachel Haurwitz, PhD, is a co-founder of Caribou Biosciences and has been its President and Chief Executive Officer and a director since the company’s inception in 2011. She is an inventor on patents and patent applications covering multiple CRISPR-based technologies.

What is the application of CRISPR for cancer treatment that Caribou is trying to pursue?

Caribou is advancing the development of allogeneic CAR-T cell therapies for hematologic malignancies and allogeneic CAR-NK cell therapies for solid tumors. We believe the key to developing successful allogeneic cell therapies is persistence, and we are using our proprietary technologies to enhance persistence by preventing rejection or rapid exhaustion of our cell therapies.

Can you tell me about the development of chRDNAs and how much more specific they’re able to make genome editing?

Caribou’s proprietary, next-generation CRISPR technology is called the chRDNA (pronounced like “chardonnay”) technology. It stands for “CRISPR hybrid RNA-DNA” and it describes the guides we have invented here at Caribou that contain both DNA and RNA. chRDNA guides yield genome edits that are orders of magnitude more specific (fewer off-target edits) than first generation CRISPR-Cas9 (using all-RNA guides).

The Cas12a protein guided by chRDNA guides can carry out very efficient multiplex editing including multiple gene insertions into the same cell.

What were the challenges in developing an allogeneic oncology product?

Although allogeneic cell therapy is positioned to unlock the broader potential of engineered immune cells as a leading therapeutic modality, allogeneic cell therapies emerging in the clinic today have yet to achieve the same rates and durability of response as autologous therapies. We believe there are multiple key elements to successfully developing an allogeneic CAR-T cell therapy. One key element is safety.

Caribou uses healthy donor T cells, not a patient’s own T cells, to make each batch of product. Therefore, we have to use genome editing to remove the T cell receptor (TCR) in order to prevent the risk of graft-versus-host disease (GvHD). A second key element is targeting. We use our chRDNA technology to site-specifically insert a CAR into the T cell genome in order to direct the T cells to a tumor-specific antigen. Another key element is persistence.

Allogeneic CAR-T cells are foreign to the patient’s immune system and are therefore rapidly rejected. This is quite different from autologous, or patient-specific, CAR-T cells which can persist for years after the delivery of only a single dose.

At Caribou, we use our genome editing to enhance persistence in different ways in our programs. For example, in our lead program (CB-010), we knock out PD-1 from the CAR-T cell to prevent rapid CAR-T cell exhaustion, and in our second program (CB-011), we immune cloak the CAR-T cells to blunt CAR-T cell rejection. We plan to apply the experience from these programs toward the future development of additional allogeneic CAR-T and CAR-NK programs.

Are there hurdles utilizing CRISPR, as a newer technology, for commercial applications?

New technologies may encounter manufacturing challenges as products approach commercialization. Currently, we rely on CMOs for the manufacture of our product candidates for clinical use, and most of these CMOs have demonstrated capability in preparation of materials for commercialization. We conduct our own process development internally prior to transferring our methodologies to the CMO that manufactures our cGMP cell products. While we are seeing an expansion in manufacturing capabilities and capacity for cellular therapies, we may build our own manufacturing facility in the future to provide us greater flexibility and control over our clinical and/or commercial manufacturing needs.
Can you tell us about the ANTLER study?

The ANTLER study is a phase 1 clinical trial to evaluate CB-010, Caribou’s allogeneic, anti-CD19 CAR-T cell therapy, in patients with relapsed or refractory B cell non-Hodgkin lymphoma. We announced in July of this year that we had dosed the first patient in this study, and we expect to share initial data from this trial next year.

To the best of our knowledge, CB-010 is the first allogeneic CAR-T in the clinic with a PD-1 knockout. We believe that removing PD-1 from the CAR-T genome will prevent rapid CAR-T exhaustion, thereby keeping the CAR-T cells in an active, antitumor state for a longer period of time.

Your most developed product is CB-010; on the Caribou website, it describes the specific edits made to that product. What was the process of picking those things to edit/change, to optimize its potential?

We believe enhancing the persistence of our cell therapy product candidates is the key to unlocking the broader potential of off-the-shelf cell therapies. There are multiple ways to enhance persistence, and we are evaluating two different strategies in our first two programs. As described in more detail above, we are removing PD-1 from CB-010 in order to prevent premature CAR-T exhaustion.

We understand from the literature that the PD-1/PD-L1 axis is important in NHL and the majority of NHL tumors are PD-L1 positive, so we felt that NHL is an appropriate disease setting in which to evaluate the safety and efficacy of a PD-1 knockout. CB-011, Caribou’s preclinical allogeneic CAR-T for multiple myeloma, is on track for an IND filing next year.

In CB-011, we enhance persistence by a different method: we immune cloak the cells to prevent their rapid rejection by the patient’s immune system.

How does Caribou hope to make progress in solid tumors using NKs?

Natural killer (NK) cells are emerging as an increasingly important cell type for therapeutic development, as they play an important role in ridding the body of cancer as well as viruses. Solid tumors are particularly challenging to treat, and CAR-T cells have largely underperformed in the solid tumor setting.

In contrast, NK cells inherently target both primary solid tumors and metastases. This is a promising approach and we are developing CAR-NK therapies for the treatment of multiple solid tumor types.

We are able to differentiate NK cells from induced pluripotent stem cells (iPSCs) that we first edit in multiple ways to address targeting, trafficking, proliferation, and overcoming the immunosuppressive tumor microenvironment.

What are the North Stars guiding your work, and where do you hope to see CRISPR technology, or Caribou, in the next 3-5 years?

Caribou’s mission is to develop innovative, transformative therapies for patients with devastating disease through novel genome editing. Over the next 3-5 years, I hope to see Caribou advance multiple additional programs into the clinic and I hope that those programs demonstrate promising safety and efficacy data in patients with unmet medical need. CRISPR technology holds tremendous potential for patients.

Especially coming into the role of CEO at a young age, and from the lab, how did you develop your leadership style and your approach to leading a company?

By learning; I have been on a steep learning curve for the past decade, and I expect to be a lifelong learner over the course of my career. People are the most important part of a company. I have learned so much from the many talented people with whom I have worked at Caribou over the years, and I’m grateful to the many fantastic people who are my colleagues today.

It’s inspiring to be on a collective mission to deliver promising therapies to patients who need new approaches.

We believe the key to developing successful allogeneic cell therapies is persistence.

We are using our proprietary technologies to enhance persistence by preventing rejection or rapid exhaustion of our cell therapies.
What is your work at the Cleveland Clinic?

I arrived here to take on the role of Chair of the Center for Immunotherapy and Precision Immuno-Oncology. My role is to develop programs that allow us to build a cadre of immuno-oncology investigators on the basic side, and also to build immunotherapy translational groups for therapeutic development leading into early phase trials. That spans strategies from vaccines to cell therapy approaches. I have a few other roles here: I’m the Director of the Immuno-oncology program, which is one of the components of the Case Comprehensive Cancer Center, and I also co-direct the National Center for Regenerative Medicine, which is the big cell therapy institute in Cleveland.

You’re a leader in using genomics for precision medicine and immunotherapy. Can you describe your interest in that?

There is a lot of momentum in science behind understanding cancers and understanding why different patients benefit from one type of treatment or the other. I work in the space of using genetics and molecular markers to understand why certain tumors behave the way they do, and why certain tumors respond to certain drugs and why others are resistant. This is a way for practitioners, scientists and doctors in the field to match patients with the best drugs that they’re likely to respond to. And you see a lot of things coming out: a lot of new types of molecules and new types of drugs that take advantage of targeting specific mutations and specific processes that go awry. Profiling tumors has been able to not only allow folks to match drugs with tumor type, but also reveal new targets as well.

What is the technology that has enabled this more advanced screening of the genome?

The technology was developed about 15 years ago, and it’s becoming better and better. Around 2005 or so, there started to be a big increase in the ability for us to sequence DNA. And this was really termed the next-generation sequencing revolution. Before, this type of work was very painstaking and slow. Now the platforms are getting faster and better.

And so, with improving technology driving this, and the ability to sequence faster and cheaper, we are now able to make deep genomic analysis part of clinical practice.. The other consideration, which is equally as important, is our increased understanding of why we need to sequence: the understanding that there are genes and processes that are driving the cancers and that there are genes you can target that allow you to kill tumor cells and not normal cells.

These principles combined together to set up what we have now: the ability to identify certain changes that we know about, married to a technological revolution that is accelerating our ability to be able to sequence patients and tumors in the clinic.

A little over 10 years ago the technology was there, and folks believed in it, but there were relatively few markers. Insurance really didn’t reimburse. People asked “Is this really actionable?” Nowadays the knowledge has caught up and the technology has continued to improve, so that this is really part of the standard of care. Our own work that discovered that tumor mutation burden and DNA repair pathway mutations like MSI identify cancers that will respond to immune checkpoint therapy has opened up this field. It led to the first tumor agnostic FDA approvals for any cancer therapy.

Is all of this within the center itself: leveraging insights from sequencing into developing molecules or identifying pathways and targets?

Yes; I spent almost 15 years at Memorial Sloan Kettering Cancer Center before coming to the Cleveland Clinic about a year and a half ago. My job here is relatively similar to what I was doing there, just on a much larger scale.
We are developing technologies, research and programs here, in the cancer center, to make best use of this type of information.

We recently launched a big program to broadly sequence the whole exome – all of the important coding areas of the cancer genome – on every patient with a solid tumor that needs sequencing. We are really the first in the country to do this. And the idea is to be able to comprehensively identify the markers and the processes in the genome that go awry, with the purpose of being able to assign the best treatments for these patients.

Many times, cancer patients have already exhausted first-line therapy or second-line therapy, and there’s not much left. you have to really look deeply and we hope our program will help patients extend hope. And with the whole exome sequencing, we can identify different trials going on that, potentially, will work best with them, given our knowledge of the biology and the type of mutations in the context of basket trials.

You’ve spoken about how true precision immuno-oncology could create, in effect, N of 1 trials for patients. How do you think genome sequencing could change the future of clinical trials?

N of 1 trials are a different paradigm; it’s precision oncology taken to the extreme. Basket trials are about organizing alterations into distinct baskets. Each individual tumor is different from another patient’s tumor, but often they actually have similar processes; it’s just that you have to match them.

Typically, how clinical trials are done in oncology is that you run these big trials that are for one disease site. For example, you run a big trial for colon cancer. And you use a process that’s slow and cumbersome, and takes several years. And if you have a certain drug that targets a certain pathway, let’s say, like a BRAF.

And you know that BRAF is actually mutated in 20 different types of cancers. Are you going to individually set up 20 different trials? Maybe not. It might be a more efficient way to set up a basket trial, where you put a smaller number of patients together, all with the same genotype, and you look for a signal.

Because if your hypothesis is that that mutation actually is responsible for allowing that patient to respond to your new drug that targets that mutation, then this may be a quicker, more efficient way to be able to identify where there’s a signal.

It is not a guarantee that every tumor type is going to behave the same. But again, that’s a quick way for you to sort that out and save the time and money of putting together big trials that may cost a lot more and may not yield the same information.

You mentioned the next generation of precision oncology. What is the hope for future applications of the work you’re leading right now?

What I’m talking about is very systematically being used in the clinic now. And as we move forward, our work, and the work of many others, is expanding on what we know about what makes tumors sensitive or resistant to immunotherapy.

Resistance is very important to understand, because those are our next targets and we’re looking at ways to deal with those genes that may be causing resistance. Right now, immunotherapies alone can definitely be improved. Most patients don’t respond, but new combinations are being put together where in many tumor types, the majority of patients will respond. We’re actually getting most patients to respond now in some tumor types, with these types of combinations, which would have been unheard of only a few years ago. This process of discovery, then testing, and so forth, continues. We’re not curing everybody, yet, and there’s a lot of nuances to how cancers can get around therapies. We’re using comprehensive profiling. We’re using basket trials to give access to patients more quickly and to potentially life saving therapies.

Another exciting program revolves around mutations: we’re working on making treatments and vaccines against these mutations. This is something that is actually coming into vogue, especially with RNA vaccines and the COVID vaccination efforts around the world. The COVID vaccines came onto the scene so quickly because there were years of development in the cancer space before then. There is a lot of excitement around vaccines, because of the fundamental ability to target certain mutations.

You could imagine that you have a patient with cancer who takes a drug and the tumor becomes resistant, because that’s what tumors do. If you can use a vaccine with the initial therapy, one could imagine the ability to prevent the genetic mutations that we know are going to cause resistance. You could prime the immune system to fight off resistance.

Are there any other research topics you’re working on that you can share with us?

We’re working on understudied tumors, especially pediatric tumors. These are tumors that big companies sometimes don’t focus so much on because there’s not a huge market share. We have a project here making immunotherapies for Ewing’s sarcoma and different pediatric sarcomas. And to me, that’s very exciting because progress in children’s cancers can sometimes go very slow, because they’re not as common as, say, breast cancer or prostate cancer. But we’re excited about that. I’m putting in resources to try to develop vaccines and different immunotherapies for some of these rare tumors because there’s such a medical need for them.
Can you describe the work you’re leading at Johns Hopkins in your lab?

I’ve been involved in the development of immune checkpoint blockers for cancer therapy. I have been at Hopkins for the past 15 years and really started this work in earnest as soon as I arrived in 2006. 2006 was an important year because it was the year that the very first patient was treated with an anti-PD-1 drug of any kind. And this happened to be nivolumab in a first-in-human trial. I was involved in that study, and things evolved from there. It’s been a very exciting trajectory.

We found out from our very earliest studies that patients with advanced cancers could respond to anti-PD-1 as a single drug. These were patients who had not responded to other forms of therapy available at the time, and really had run out of options. It was remarkable to see that at least in a subset of these patients, their tumors did regress. And I think one of the earliest observations that was very exciting to us was that advanced lung cancer could respond to anti-PD-1.

This really opened the doors to many opportunities for clinical testing in other common cancers, which before then had not responded to different kinds of cancer immunotherapies. I think it was really this observation in lung cancer that then catapulted this entire field into the mainstream of oncology.

How has your work with nivolumab evolved, in terms of applications and understanding, over the course of the last 15 years?

Our first objective was to find out which cancer types might respond to anti-PD-1, and the list continues to grow. To my knowledge, right now, there are 20 different types of cancers that respond to either anti-PD-1 or anti-PD-L1 drugs, and seven drugs in class are now approved by the US Food and Drug Administration. There’s a lot of research going on, and there have been thousands of trials in that 15-year span. The activity spectrum turned out to be broader than we had originally imagined.

Nevertheless, there are many patients whose tumors do not respond to this therapy. So the next objective was to figure out what we could use as markers of response or resistance to anti-PD-1. The first attempt we made to find a biomarker was to stain pre-treatment tumor specimens for expression of the ligand PD-L1. We reported the first results in that area in 2012, showing that tumors that expressed PD-L1 were more likely to respond to anti-PD-1 therapy.

After that, the field jumped in and did additional studies, which confirmed that in some cancer types – but not across the board – PD-L1 expression as detected in pre-treatment tumor biopsies may identify a group of patients who are more likely to respond than other patients. Since then, we have continued to look for biomarkers. There are two other markers that are currently FDA approved for anti-PD-1 or -PD-L1 drug use. One is microsatellite instability (MSI) and the other is tumor mutational burden (TMB). They’re both related to each other. MSI generates a subset of all TMB high tumors. It’s one mechanism that generates a high tumor mutational burden.

And so, it turns out that tumors that have more complex arrays of DNA mutations are generally more likely to respond to anti-PD-1, probably because those mutations lead to the translation of proteins that are abnormal and are sensed by the immune system. But the work for biomarkers that are even more predictive and more sensitive continues. This is a huge area of research today. It’s something that’s going on in my lab here at Hopkins.

How did you get involved in melanoma research?

My clinical specialty is melanoma but I came to that through immunotherapy research. After I finished my surgical residency, I did a fellowship at the National Cancer Institute in Steve Rosenberg’s group. It was a very exciting time in the mid-to-late 1980s. We were discovering interactions between the immune system and cancer, and testing new treatments in the clinic.
It became obvious early on, even though we were enrolling patients with a variety of different kinds of cancers in these immunotherapy trials in the 1980s, that it was the patients with melanoma who were most likely to show some kind of response. Even though it was a very small proportion of those patients, this was what grabbed our attention.

Gradually immunotherapy research in the 1980s and 1990s came to focus mostly on melanoma, and also on kidney cancer, which it turns out is also very well-seen by the human immune system. That’s how I came to know a lot about melanoma and eventually specialized in that disease clinically.

What is the latest on your work with melanoma?

Melanoma has always been a good model to test new immunotherapies. Where we are today is that melanomas have a high response rate to immunotherapy -- to anti-PD-1 therapy and also to some of the new combination therapies that are being tested.

However, about 50% of patients are not helped by this approach. There’s still a lot of work to do. But for studies looking into biomarkers, a disease like melanoma gives us a group of responders, which is fairly large, as well as a group of non-responders, enabling comparisons.

The story now for melanoma is the development of combination therapies that are going to be more effective than anti-PD-1 alone. There is a lot of exciting work that was reported at the AACR and ASCO meetings this year about new treatment combinations that may actually be helping patients who have not seen a response to anti-PD-1 alone, but who may respond to a new drug combination.

What is the latest data about biomarkers that’s influencing your work?

There is an important theme now: generic biomarkers that cross the boundaries of anatomic site of cancer origin. The first biomarker that was FDA-approved that did that was MSI. Microsatellite instability is a genetic feature that can be present in any kind of cancer. And if it is present, those tumors have a high response rate to anti-PD-1. We think it’s because MSI-high tumors are hyper-mutated, so they contain many abnormal proteins. Those proteins are seen as foreign by the immune system.

The TMB-high approval for anti-PD-1 also crosses all tumor types. These are universal markers, without regard for tissue of origin. That has been a very exciting advance. And going back to melanoma, people have hypothesized that one reason why melanoma has been responsive to many immunotherapies over the years, such as interleukin-2, et cetera, is because melanomas tend to be highly mutated.

What are the goals or targets on the horizon that you’ll be discussing at the IO360° conference?

At the IO360° conference in 2022, I’m going to be talking about neoadjuvant immunotherapy, which is pre-surgical immunotherapy. This is a huge area of focus for us now. The idea there is that we’ve learned a lot in the past 15 years about treating advanced cancers of many different kinds with anti-PD-1 or anti-PD-L1. We are learning about more effective treatment combinations. We’ve even learned about some biomarkers that are useful. We’ve also learned that these drugs are relatively safe. That supported the notion that maybe it would be safe to treat patients with earlier stages of cancer.

It’s all about risk and benefit. But once we had a pretty good idea about the risks and the potential benefits, we started to ask if we could move this treatment earlier in the course of cancer and would it prevent tumors from advancing to Stage IV, which is difficult to treat?

Going back to melanoma, this was the first tumor type where adjuvant (post-surgical) anti-PD-1 therapy became FDA-approved. After that, we asked the question, “Could we give this therapy before surgery to patients who are candidates for surgery, but at high risk for relapse because of certain properties of their cancer?” That’s what we’ve done.

A group of investigators here at Hopkins that I work with published the very first report of anti-PD-1 neoadjuvant therapy, in lung cancer. This was a paper from Patrick Forde and colleagues in the New England Journal of Medicine in 2018. The same approach is being used in melanoma by Christian Blank and colleagues, and others who have published on this, and now in many other cancer types.

We recently reported on neoadjuvant anti-PD-1 therapy in two additional cancer types – Merkel cell carcinoma (Journal of Clinical Oncology, 2020) and head and neck cancer (Journal for ImmunoTherapy of Cancer, 2021) – from the CheckMate 358 clinical trial. Those two studies are a good contrast to each other. Neoadjuvant anti-PD-1 worked very well in Merkel cell carcinoma. Almost 50% of the patients had a complete microscopic disappearance of tumor in pathology specimens after only four weeks of anti-PD-1.

That was very exciting. But then we found that head and neck cancer is relatively resistant to this approach. There, we need to find something that’s going to be more effective, and very likely, it’s going to require a combination treatment approach before surgery. So, while there have been some promising advances, we need to continue to build on this.

Dr Topalian receives research grants from Bristol-Myers Squibb, and has intellectual property through Johns Hopkins University related to the MSI biomarker; her spouse has intellectual property related to LAG-3.
What is the focus of Takeda in regards to oncology and immunotherapy?

Our North Star for oncology is that we aspire to cure cancer. So it’s a vision; obviously we have a ways to go to get there. But it trickles down into our mission to bring our treatments to patients as quickly as possible, and with as much data as possible, so that physicians can make informed treatment decisions for our patients.

The team that I’m building here at Takeda is really going to be central to that, because cancer drug development moves very quickly. You’re able to pivot and accelerate development programs based on understanding response in certain populations. So it’s really an important and integral part of what we do.

And in terms of our pipeline at Takeda over the past couple years, most outside companies and observers recognize Takeda as the Velcade company. We have a proteasome inhibitor for hematologic malignancies. We just recently had approved a small molecule drug for non-small cell lung cancer called mobocertinib, which targets a very specific mutation called EGFR Exon 20.

We have molecules in the proteasome inhibitor space; we have molecules that target specific mutations in lung cancer, so mobocertinib and brigatinib. Brigatinib targets ALK. And then over the past couple of years, we’ve really made a conscious effort to go down that immuno-oncology space. We have a number of programs that target the interferon pathway, as well as cell therapy now. We have an exciting collaboration with MD Anderson around CAR NKs that we’re very, very excited about.

Can you describe Takeda’s approaches to immunotherapy, turning tumors cold-to-hot and redirected immunity, in its pipeline?

With redirected immunity, we consider cell therapy and T cell engagers as parts of that bucket. That’s really our cell therapy/T cell engagers pipeline. It’s a little bit earlier, so we still need to see what the potential is in the clinic.

And then for what we call cold/hot, it’s about turning cold tumors warm. That’s where we have a lot of the interferon programs; we have a program called TAK-573, which is an exciting attenukine that delivers interferon into CD38-positive cells. That is very exciting. We have a STING agonist, also in this interferon space, as well as other programs. We think about it very mechanistically. But the two development paths are intertwined in terms of moving as quickly as possible, but the redirected immunity is a little earlier in the pipeline.

What can you tell us about building an Oncology Precision & Translational Medicine organization within Takeda?

I joined Takeda about a year ago; before that, the translational capabilities were very dispersed across the organization. And given the importance of precision and translational medicine to oncology, we needed to build a function to do this.

It’s basically a one-stop shop for everything translational in my organization, from the people that come up with the early translational strategies; to the colleagues that make and work in our clinical trials to implement the translational strategies, to really understand which patients are responding and how our drugs are working; to the group that does companion diagnostics. We’re building a team to do a lot of the assays and to help with the outsourcing of the assays. It’s a new model for Takeda. It existed in different parts around Takeda. But given the speed that oncology moves, we felt it was important to pull it all together in one organization.

Why is it crucial to have an in-house translational capability?

Translational is an indispensable part of oncology drug development. There are numerous examples of many companies taking the quick all-comers approach, where you just move your molecule as fast as possible.
The new way of doing this, the new model that most companies have embraced, is really taking a translational mindset. And to me, that is taking data from patients, very early on, to inform decisions.

That means you’re studying your target pathway in patients to understand which disease indications your drug might work best in. That means the way you run your Phase I one studies that you’re not just making decisions about your drug just based on safety, and early efficacy, but you’re looking at that pharmacodynamic relationship and the PK/PD relationship. That means using that information to pick your dose; while you’re in your studies of efficacy, you’re always continually looking at who’s responding better, and you’re developing those hypotheses and testing them in the clinic.

So it takes an incredibly strong partnership with clinical development. And in my experience, the best partnerships internally at a drug company are where the translational scientists and the clinical development/clinical science team are partnering, integrated in this same mindset, to bring the drugs as quickly as possible, but to study it very robustly while in the clinic.

What do you see as the biggest hurdle in getting a stronger response to immunotherapy and precision medicine?

There’s a couple of barriers. When I was discussing our pipeline, we have molecules that target EGFR Exon 20. It’s a very specific mutation. And either you have it or you don’t. There are different flavors of it, but we know how to look for them, especially now that we can do sequencing and see different levels of mutations. You can see different levels of the mutations, and not just the one point mutation. You can look at the whole gene and sequence it. The challenge with IO is that some of these biomarkers are what we call “continuous variables.” Rather than, “I have the mutation, I’m going to respond,” and “If I don’t have the mutation, I won’t respond,” it’s a continuum. As the marker of interest increases, you tend to see this increase in response. But how do you define that cutoff, because it’s not a binary readout?

That’s a challenge, particularly with immuno oncology. And if you look at the PD-1 space, you’ll see this with the PD-L1 story. You see it with tumor mutational burden as a biomarker. That was studied for a while and seemed to have some promise. It was the same thing: how do you define the cutoff to balance those that are responding and not responding? That’s a challenge.

The other thing is that you often need tumor samples to be able to study these pathways appropriately. Not all patients are able to give a tumor sample or there could be a risk associated with collecting a tumor sample. That is the case of a non-small cell lung cancer patient: we have to do an endoscopy or a guided CT to get a sample. There’s a risk associated with that. So we always have to balance the safety of the patient with the objectives.

And this is why the peripheral markers and the technologies that are emerging around liquid biopsy and understanding what that fingerprint of the tumor is, in blood, becomes so critically important. I don’t think we’re there yet in terms of the blood providing everything we need to tell us about a tumor that might be in the lung or the kidney or in the colon. But the technology is really promising. And we have our fingers on the pulse of it.

What are the watershed moments, in terms of technology or knowledge, that have shifted your understanding of cancer, how tumor cells act, how drugs act, etc?

In terms of watershed moments, that for me was in the work that I did on the checkpoint inhibitors on an anti-PD-1. It showed that there is not a one-size-fits-all approach. Cancer is very smart. We’ve been used to classifying cancers by where they are in the body – lung cancer, brain cancer, colon cancer – we need to think differently about cancer. Even lung cancer is probably hundreds of different submolecular phenotypes. I personally think we need to think more holistically about these phenotypes and follow the phenotypes across tumors of different origin.

Something that has been an exciting moment is now a number of companies have gotten drugs approved based on a particular mutation. There’s something called NTRK, which is a mutation present across multiple tumor types. And there’s a drug called larotrectinib, approved for the mutation across tumor types. There’s an example from Merck as well, where TMB and MSI – microsatellite instability – are now approved across tumor types. Those kinds of approaches are what’s going to be so important to helping us crack the nut of cancer more broadly. We need to stop thinking of cancer as “tumor of origin,” but more as a molecular phenotype.

Do you have a molecule or pathway in your portfolio right now that you’re particularly excited to see the potential in?

I am so inspired by the interferon pathway, and being able to activate the interferon pathway in a tumor to help kill cancer. Here at Takeda, we have three different programs that “tickle” the interferon pathway and activate it. We have the TAK-573 program, which is a very exciting program from our perspective. It delivers interferon alpha into the CD38-positive cells.

This SUMOylation inhibitor is called TAK-981. That is very interesting: you block this post-translational modification and you see activation of interferon pathways. Then we’ve got STING agonists as well that we’re very, very excited about. For me at the conference, I’m really excited to come see what other companies are doing around the interferon pathway, not just from the drugs themselves, but how we can understand the patient that should respond to these inhibitors. ●
Can you describe how you work across teams and throughout the pipeline?

As the clinical biomarkers lead, my main responsibility is to develop and execute the biomarker strategies of our clinical programs. Bottomline, I provide scientific leadership and oversight to help understand why our investigational candidates may or may not work in patients and how they can be improved. But this work doesn’t happen in a vacuum. It relies on having a strong understanding of the research that has been conducted to date and contributing to the design of new experiments and review of data.

In this regard, it’s crucial to have early engagement with our preclinical teams. I see my role, as well as the role of our clinical biomarkers group, to be the scientific bridge between our company’s Clinical and Research organizations. We maintain our collaborations for molecules that are already in the clinic, in order to follow-up on and initiate reverse translation efforts to further elucidate the activity of our drugs.

With respect to how our clinical studies are conducted, I work closely with clinical science, clinical operations, and sample operations to ensure appropriate collection and testing of biomarker samples. Finally, as a core member of Clinical and Development teams, I bring forward our biomarker learnings to inform further clinical development of our drugs and new molecules in the pipeline.

What are the big challenges in your work identifying and validating biomarkers?

Despite our vast collective knowledge of the immune system, the understanding of the dominant drivers of cancer immunity is still evolving. Therefore, a key challenge of biomarker research is looking at the immune system as a whole and not focusing on only one aspect of an anti-tumor immune response.

It’s equally important to think about practical considerations, for example “How do you translate hypotheses from preclinical learnings into a strategy that can be implemented in the clinic? What clinically translatable assays are feasible? What samples can be collected?”

Of course, evaluation of tumor tissue would be ideal because that’s where the action is happening, but it’s not always possible. In this case, we may begin to explore the utility of blood-based biomarkers and the question is whether changes that occur in the periphery are reflective of what happens in the tumor and are correlated with antitumor efficacy.

It is worth noting that, when we look at publications or reports of biomarker correlations with activity in anti-cancer therapies, many of these are based on retrospective analyses or looking at changes that happen after treatment. While these analyses may help us confirm target engagement or help describe mechanism of action, they may not necessarily identify predictive markers.

Ultimately, cancer immunotherapy drugs are only as good as a patient’s immune system. Therefore, in order to identify truly predictive biomarkers, we need to understand how to best characterize the basal immune status of a patient. Hopefully in the future, we can make enough generalizations that a therapy or a biomarker can be applicable to the general population, but to achieve that goal, we need to first understand biomarker responses at the individual patient level.

Can you describe being the Clinical Development Lead for IGM’s COVID-19 program?

What initially drew me to the field of immunology was working on vaccine development for tropical diseases while I was in the Philippines. As the clinical development lead for our COVID-19 program presented an exciting opportunity to marry the clinical research experience I’ve gained through immuno-oncology with my original interest in infectious disease, as well as my desire to help with the pandemic.
Our company, IGM Biosciences, specializes in the development of engineered IgM antibody therapies. We utilize IgG antibodies that we know are active and graft them into an IgM. This means that we can take molecules that have two binding sites and turn them into drug candidates with 10 binding sites. While oncology is our first therapeutic area, we believe the IgM platform can be beneficial in a wide range of therapeutic areas, including viral/infectious diseases.

We have developed a potent, multivalent antibody for COVID-19 that can potentially have an impact in both treatment and prophylactic settings. By utilizing an intranasal approach, sites that serve as points for viral entry and replication can be targeted. The COVID-19 landscape, including the regulatory environment, is evolving very quickly. My task as the clinical lead is to oversee the development of study designs and strategy for our indications of interest. Our team needs to keep abreast of developments within the COVID-19 landscape and identify opportunities to push our program forward.

Is there a specific example of something still unknown, biomarker-wise, that would be useful in your work?

Bispecific T cell engagers (TCE) form one pillar of IGM Bio’s immuno-oncology programs. This synthetic immunity approach relies on having a “good” T cell response, however there still is no consensus on what the definition of a “good” T cell is.

This poses a significant challenge in terms of biomarker development and biomarker testing because there are many different measures of T cell characteristics – for example, flow cytometry-based phenotyping with cell surface or intracellular markers, multiplex imaging, gene expression, repertoire sequencing, or functional assays like cytokine production or cytotoxic activity. Within each assay category there are different specificities, sensitivities, and cutoffs, which can then affect the relationships or correlations with antitumor activity that can be identified.

Instead of a single universal biomarker, a combination of markers obtained through a systems-based approach is likely to be most informative. A comprehensive blueprint or atlas of tumor-immune interactions and immune states would be extremely useful.

Has there been any new knowledge about T cell activation or activity that carries into your work?

With T cell responses, the general thinking is that more is more – you try to hit T cells as strongly as possible for as long as possible, because you want to have them exert their effector function immediately and very strongly. There are literature showing that this may not always be the best objective as it could mean sacrificing long-term gain for short-term effects.

There are a couple of recent publications by Crystal Mackall and her group regarding tonic signaling; this was also work that she presented at the IO360 2020 event. What they found was that CAR-T cells that are under constant stimulation become exhausted as evidenced by defective IL-2 production and other transcriptional changes. If the CAR-T cells are rested through transient downregulation of the CAR receptor, the T cell dysfunction is reversed and anti-tumor activity is restored.

These findings tie into how we can think about our bispecific T cell engagers and other cancer immuno-therapeutics. We want to make sure that we balance the positive effects of T cell stimulation with other downstream effects that may lead not just to unresponsiveness of T cells, but also some potential acute safety effects due to overstimulation.

Can you describe some of your work in biomarkers in regards to combinations?

Here, I’m going to draw on some of my experience when I was at Genentech. During the early days of cancer immunotherapy, the general approaches to induce a good anti-tumor immune response focused on increasing T cell priming, reactivation, or expansion. But ultimately, having activated T cells that are just circling around isn’t enough.

To be effective, T cells have to infiltrate tumor tissue. As a postdoc, I then investigated the interplay between cancer immunotherapy and vasculature. Using a mouse melanoma model, I showed that adoptive T cell immunotherapy combined with antibodies that inhibit angiogenesis leads to greater antitumor activity through increased migration of T cells into tumor.

In the Oncology Biomarkers Group, I then worked on Phase 1b combinations with the anti-PD1 checkpoint inhibitor, atezolizumab, including one with the anti-VEGF antibody, bevacizumab. The function of the latter is to inhibit angiogenesis and choke off tumors; it can also normalize the vasculature, leading to greater penetration of drugs and cells into tumors. The combination of atezolizumab and bevacizumab resulted in enhanced efficacy in renal cell carcinoma.

Our biomarker analyses for the study included gene expression profiling, flow cytometry-based detection of tumor-specific T cells via panels of peptide-MHC multimers, and TCR sequencing. Through these, we showed that the combination augmented anti-tumor T cell effector function as well as the frequency of intra-tumoral tumor-specific T cells. This is a powerful example of how two drugs with different, but complementary mechanisms can elicit effective antitumor immunotherapy and I’m honored to have contributed to it.
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