Can you tell us about the work you are leading?

I lead the early clinical development group at BMS focused on hematology, oncology and cell therapy. I came into this role following the BMS acquisition of Celgene where I held a similar position for 10 years until we were acquired by BMS late last year. Our pipeline is quite broad in terms of small molecules, antibodies, complex biologics, including bispecific T-cell engagers, and cell therapy. Currently, BMS has one of the largest cell therapy franchises in the industry. This includes two CAR-T cell products that are currently undergoing regulatory review for potential approval including a CD19 CAR-T cell product and a BCMA CAR-T cell product. I’ve been leading the development of the latter BCMA CAR-T product from the inception of our partnership on this program with bluebird bio.

I started working on CAR-T cells at the dawn of the field of cell therapy when I was at a small California biotech company called Cell Genesys in the mid-1990s through early 2000s. A little known fact is that we launched the first CAR-T trial in the field, in collaboration with the NIH, in discordant HIV infected twin pairs rather than cancer and then embarked on the first clinical trial of a CAR-T cell targeting solid tumors, which didn’t work so well. As the field advanced, we gained a better understanding of how to engineer these CAR-T cells for enhanced activity and learned that we needed to give lympho depleting chemotherapy before infusing the CAR-T cells to drive their expansion and anti-tumor responses. Those insights set the stage for the current state where there are now two approved CAR-T cell therapies, with potentially more to come. It’s been fun to be a part of this history from the early days when we only had hints of efficacy and focused on figuring out how to iterate to improve on the promise of CAR-T cells, through to where we are today where we are witnessing breakthrough innovations for the whole field of immuno-oncology.

What are next steps in your research?

We have many assets in early phase clinical trials for which we’re working to generate the informative safety, efficacy, pharmacodynamic and mechanistic data to provide proof-of-concept for these various modalities and set them up for success in late stage clinical development.

In addition to internal discovery research, we’re always looking for new innovations through partnering with biotech companies. Just in the last few weeks we announced two new partnerships, one with Dragonfly to access their next-generation IL-12 asset and one with Forbius to access their TGF-beta inhibitor. No single company can tackle all scientific innovation. You need to have internal discovery and translational research supplemented by partnering external innovations.

Looking forward, where do you see the field of cell therapy and IO going in the future?

For cell therapy, we have seen great success in hematologic cancers. The first wave of CAR-T approvals targeted CD19 on B-cell malignancies, including lymphoma and acute lymphoblastic leukemia. The next wave of CAR-T cells are targeting BCMA which is expressed on multiple myeloma. The activity of CAR-T cells in leukemia, lymphoma and myeloma has been truly transformational.

Beyond blood cancers, the open question is how do we bring the power of cell therapies to solid tumors? These are the common cancer killers but present increased complexity. T-cells need to be engineered against targets that are expressed in the cancer cells but not in essential normal tissues, which are not so simple to find. They need to effectively traffic to those solid tumors and overcome the immune inhibitory microenvironment of these tumors.

Kristen Hege, MD
SVP, Early Clinical Development, Hematology/Oncology & Cell Therapy at BMS

How Far Cell Therapy Has Come, Where It Needs to Go and Improving Diversity of All Kinds

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Many groups are trying to tackle each of these hurdles in innovative ways in order to bring the power of cell therapies to solid tumors.

In the field of IO, next steps are trying to understand the best way to use the immune system to kill cancer and how to get over the immune inhibitory microenvironment of solid tumors. The more we understand about what is shutting down the immune signal, the more we can scientifically optimize our strategies to combat it. This includes prioritizing targets to focus on and combination strategies for specific subsets of cancer. Every cancer has its own unique way of avoiding recognition by the immune system and therefore treatment to get around these roadblocks needs to be individualized.

Could you expand on what challenges you expect in those innovations?

The challenges center on our incomplete understanding of the specific mechanisms that are driving resistance to immune therapies patient-to-patient and tumor-to-tumor. The tumor microenvironment factors are very complex and we need to sort out what’s a real driver of resistance and what’s more of a passenger. We have enough therapeutic modalities and enough deep scientific capabilities that I am confident that we will ultimately discover how to unleash the power of T cell therapies against solid tumors but there are clearly still problems to solve. There is no shortage of good ideas of how to do that and part of the challenge is prioritizing these efforts because there are only so many things you can advance into the clinic.

How do you prioritize?

We try to prioritize next-gen therapies based on data and science: generate sound hypotheses, test them and use the results to apply a filter for what moves forward into the clinic. We next try to generate compelling and deeply scientific data in those early human trials and apply disciplined gates to determine what products to advance to late development. There is a strong need for collaboration between translational scientists, clinical scientists and physician scientists to optimize this critical early phase of drug development. At Celgene, early clinical development was embedded in the discovery research organization. That organizational structure in now being implemented at BMS as well to make sure that we apply deeply aligned scientific and medical thinking to determine which targets to prioritize, which assets to move forward to the clinic and what clinical and translational data to generate in our first-in-human trials to best inform what therapies to advance, how to advance them, what combinations to develop and which subset of tumors might be most sensitive to the modalities we’re testing.

What has surprised you about working in IO?

Having started working in IO in the early days when nothing was really working, the breakthrough success of CAR-T cells has surprised me. We’ve gone from being unable to generate excitement or raise money to fund research in this new field in the early biotech days to today where there has been an explosion of new companies and research focus. As a result, we now have breakthrough therapies that lead to deep and durable remissions following a single infusion of a CAR-T therapy in multiple blood cancers. Being able to experience such a transformational event in my lifetime – working on first gen CAR-T products that didn’t work to next gen CAR-T products that elicit deep and durable responses– is powerful. That’s been one of the biggest positive surprises of my career.

The other positive surprise is how important T-cell checkpoints are in the fight against cancer. I was also working in that field 20 years ago, before anyone believed that blocking molecules on the surface of a T-cell could have meaningful activity in cancer. Then, the CTLA-4 and PD-1 blocking antibodies came along and they really worked, and in solid tumors no less. Who knew that blocking these brakes on T-cells would unleash such powerful tumor-specific immune responses? If you asked people 20 years ago if that might work they would have uniformly said, “No way.”

One of the challenges is that more than 20 years has gone by since the first human trials with T-cell checkpoint inhibitors and engineered CAR-T cells and there is still a lot of room for improvement. We don’t yet have a cell therapy approved for a solid tumor indication and there are still patients who do not respond to the current generation of T-cell checkpoint therapies. There is still a lot to do.

What are your thoughts on encouraging women to enter STEM?

I’m a big proponent of encouraging women and underrepresented minorities to enter STEM careers, helping them advance in their careers and increase their representation in leadership roles in academia and industry.

I’m based in San Francisco and we’ve kicked off a number of local initiatives sponsored by BMS to support STEM education for both female students and students of color starting in elementary school and continuing through high school, college and graduate school, to make it easier for both women and underserved minorities to pursue and
succeed in STEM careers. We’ve all been motivated by recent events to do more and we appreciate that you have to start early if you want the future to look different.

**What are your thoughts on increasing diverse representation in higher levels of leadership positions?**

I got very involved in these diversity initiatives at Celgene over the last five years. In 2015, Celgene sent me to an Executive MBA program. I thought I would learn about finance and business strategy (which I did), but the subject matter that grabbed me most was the topic of diversity in corporate leadership and the still striking imbalance observed across all industries. I came back from that program more focused on tackling issues of gender and racial diversity at my own company and we made quite a bit of progress over the next 5 years, mostly by engaging senior leadership to focus on the topic, establishing metrics to measure our progress, and making issues of diversity and inclusion front and center in many of our leadership team conversations. We really need to be more focused on thinking about this topic at every step in the hiring, promotion and retention process to tackle the progressive loss of diversity that is still present across our industry as you go up the ranks of corporate and academic leadership.

First, you need to actively think about and discuss diversity because of unconscious bias. You need to bring it to the forefront of your conversations so that every time you’re involved in a promotions committee, you’re actively thinking about the gender and racial balance. When you’re hiring, you need to make a better effort to reach outside your normal networks, which tend to be filled with people just like you, to identify qualified candidates from other diverse pools. It is amazing how quickly things can change if you just give the topic some mind space.

Now that I am a part of BMS, I am reassured that BMS is quite attuned to the topic of diversity and committed to hiring and promoting a more diverse talent pool as well as tackling racial disparities in healthcare overall. I find that it’s not that people in leadership positions don’t care about diversity and inclusion, but that there are so many things to care about in your day-to-day life that you need to prioritize and actively discuss diversity issues to promote real change. Once you focus on the topic, especially at the senior leadership team level, it’s impressive how quickly change happens.

**Is there anything else that you wanted to highlight?**

I come from a family with very strong female role models. My grandmother attended graduate school in economics and was a founding board member of Planned Parenthood. My mother was one of four women in her medical school class at the University of Pennsylvania. When I entered medical school, I reflected on what felt like great generational progress. While 2% of her class at Penn were women, 35 years later, 50% of my class at UCSF was made up of women. Now I look back at where things stand from today’s vantage and wonder if the progress has stalled. I have two daughters, one of whom just started at Harvard medical school. I think about how relatively little incremental progress has been made during my lifetime in gaining both gender and racial balance in executive leadership positions. One still sees a gap in terms of women and underrepresented racial groups at these highest levels, whether it’s in academia as cancer center directors or department chairs, or in industry as executives and CEOs. Unfortunately, we haven’t made as much progress in my lifetime as I would have hoped. As a result, I find myself spending more time thinking, what can we all do now so that our children’s generation can be part of a world with greater leadership opportunities for both women and underserved minorities?