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PEOPLE & IDEAS

Esther Obeng: It's exciting to tackle questions that don't yet have answers

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Esther Obeng is an attending physician and associate professor at Emory University School of Medicine, where she leads a research group focused on myelodysplastic syndromes (MDS). Esther's team is investigating how normal hematopoietic stem cells develop into cancerous cells, as well as developing targeted therapies for MDS patients. We recently spoke to Esther about her move from St. Jude Children's Research Hospital to Emory, how her patients inform her research, as well as the joys and struggles of having running as a hobby.

Please tell us a little about yourself and how you first became interested in science (i.e., where did you grow up? What was your first experience of science?).

My father was an electrical engineer who came to study in the United States right as computer engineers were being recruited to develop personal computers. He embodied the idea of a life-long learner, applying his skills to a developing field and eventually going back to school for his PhD when his company began to downsize. I saw how hard he worked on his dissertation research and told him I would never get a PhD. I was grateful, however, when he helped me find a research lab on his campus where I would be able to fulfill a certain portion of the volunteer hours required for me to graduate from high school. Dr. Perry studied sudden infant death syndrome, and Allison was the investigator in his group charged with showing me the ropes. I don't recall how many hours I was supposed to be there, just that I loved every minute of it and went to the lab for as long as they could stand me. Allison was a skilled and compassionate teacher. Working with her exposed me to new and exciting techniques that I didn't see in my public high school and showed me how exciting it can be to tackle a question that doesn't yet have an answer. After that summer, I knew I needed to be a scientist.

Tell us about your career trajectory, and what made you decide to pursue being an MD PhD.

The earliest I can recall telling someone I wanted to be a physician was in my seventh grade science class. My teacher asked, and that was my answer. Sometime after that, I decided I wanted to be a pediatrician. Something about the fact that children don't usually make the choices that cause them to become ill drove me to want to improve the quality of life and survival of children with catastrophic diseases. It was not until my senior year in high school that I was exposed to the Perry Lab and began to understand that it was the application of basic science findings that fed the medical breakthroughs that were developing around me, such as immunotherapy as a less toxic approach to treat cancers and the use of all-trans retinoic acid to cure a leukemia that had been universally fatal. There are no physicians in my immediate family, so I was unsure how to combine a desire to care for sick children with basic and translational research until some friends of mine showed me the University of Miami MD/PhD program. I was able to get an interview late in the year and remember the director, Dr. Bookman, being very frank about not doing this to get extra letters after my name. It was a tough program, but I learn from doing and took away valuable lessons from every patient we saw at our busy county hospital, the VA, and our level 1 trauma center. I also had an incredible PhD advisor, Dr. Lawrence Boise, who took someone who did physical chemistry research during undergrad and never held a pipette and taught her how to apply an understanding of the extrinsic and intrinsic apoptotic pathways to the question of why proteosome inhibitors were so effective in multiple myeloma.

Esther Obeng.

How did you first become interested in studying hematologic malignancies, and specifically myelodysplastic syndromes (MDS)? Did your clinical work influence your research, or vice versa?

I first became interested in the study of hematologic malignancies as a graduate

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student in the Department of Microbiology and Immunology. It was remarkable how much information one could learn about a patient's disease from their blood or bone marrow and that one could also use that material to ask new questions about disease pathogenesis or new therapeutic targets. The latter was top of mind when I took care of a patient with bone marrow failure as a first-year fellow in pediatric hematology/oncology. I followed this patient, JM, from a diagnosis that shocked her entire family, through red blood cell transfusions that increased from monthly to weekly as she failed to respond to immunosuppressive therapy, and ultimately through a matched unrelated bone marrow transplant. JM was an amazing patient. She asked deep, thoughtful questions about her treatment and learned to walk again with pure resolve and determination after a very serious infectious complication, caused by her lack of white blood cells, that would have left many people wheelchair bound. I learned so much about our current standard of care as we did all we could to cure her. Sadly, she developed a serious posttransplant complication and passed away in the intensive care unit, surrounded by her family and the army of providers that had come to know and love her over that year. At her funeral, her mother told our team she knew we did everything we could to cure her and that she only wished we knew more. I agreed, and to me, the "more" was a better understanding of how acquired somatic mutations affect blood stem cell function, increase one's risk of leukemic transformation, and provide new therapeutic targets that I hope will be less toxic and make fewer patients need a bone marrow transplant. At the time, I was very fortunate that the "only" lab where I could learn to tackle these questions was with Dr. Benjamin Ebert.

What are you currently working on, and what projects are you most excited about?

My interest in understanding how somatic mutations affect leukemia development has taken the lab toward the impact of clonal hematopoiesis of indeterminate potential (CHIP) in pediatric cancer survivors and patients with sickle cell disease. In collaboration with Dr. Xiaotu Ma in the Department of Computational Biology, we have developed a panel to screen for CHIP in pediatric patients and healthy adult bone marrow donors. At the time, the field did not think CHIP occurred in individuals younger than 50, but we have found that healthy adult bone marrow donors (older than 30) can have CHIP clones and pass them on to pediatric bone marrow transplant recipients. We have sequenced thousands of samples and are starting to work on determining how these mutations may influence the development of some of the complications of bone marrow transplant, including graft-versus-host disease and cardiovascular disease. We are also using a mouse model of the most common CHIP gene that was developed by Dr. Jennifer Trowbridge to gain insights into how a mutation in a blood-forming stem cell can affect T cell function and promote either graft-versus-host disease or graft-vs-leukemia.

Please tell us about some work in your field that you are currently interested in.

This is an exciting time for the stem cell biology and immunotherapy fields. We finally have the tools, both at the bench and computationally, to dissect how mutations in blood-forming stem cells can lead to leukemia development and to identify new therapeutic targets. Long-read and single-cell RNA sequencing are informing our understanding of how cancer cells evade the immune system or alter the bone marrow microenvironment. We are also using these approaches to understand the interplay between germline and somatic mutations in diseases such as sickle cell disease and RUNX1 familial platelet disorder.

How do you juggle being both an active clinician and also leading your own lab?

It helps to have great mentors. The Chairs of the Hematology and Bone Marrow Transplantation and Cellular Therapy Departments have been great role models for me. Both run highly productive research labs in addition to leading clinical departments that are offering new immunotherapy and gene therapy treatments. They are incredible physicians who always keep our patients at the forefront of what they do while also embracing new technologies and using them to address challenging questions in the field. Instead of juggling, it really is more about having balance between having enough clinical time to be up to date on the current treatment regimens and mentoring and collaborating with strong scientists in the lab to ask how one can improve the things that are missing. The Chief of the Division of Experimental Hematology has also been an inspiring role model. In addition to seminal discoveries in leukemia pathogenesis he has also led several studies that moved targeted theraies from the preclinical to the clinical stage.

Tell us a little about how being a clinician influences your research, and what the benefits are to having clinicians as part of research teams.

I am very fortunate to be in an environment with patient-centered care and patient-driven research. It is truly a privilege to work at an academic medical center where patients receive the most current and effective treatments we know to offer, and many of these patients and their families are also willing to participate in clinical trials to help us identify less toxic and more effective treatments for the patients that will come after them. Because we work as a team, the patients I care for in the clinic have helped inform the questions we are asking in the lab about CHIP, and it is my hope that our findings will inform future studies to improve the immediate and long-term care of patients with hematologic malignancies and blood disorders.

You are about to move institutions; this must be exciting and a bit daunting at the same time! What are you looking forward to most at your new institute? And do you have any advice for early career researchers who are thinking about relocating or moving for their jobs?

Indeed! St. Jude has been a great place to become established. I will miss the fact that people were often confused about which department held my primary appointment because I have been mentored and supported by leaders in several departments and divisions. Even though I never wanted to be anything other than a pediatrician, I seem to have a predilection for studying adult diseases since my research has gone from multiple myeloma to MDS, both diseases that affect older individuals. While children are not just little adults, there are questions and studies that are raised much faster in adults, such as the use of next-

generation sequencing to inform leukemia diagnosis and prognosis, that inform what we should be looking for in children. I found this to be true as I started thinking about how clonal hematopoiesis may affect pediatric bone marrow transplant recipients and cancer survivors. So, I am really looking forward to being part of an institution that serves the clinical and translational research needs of both pediatric and adult populations. My new adult colleagues have been welcoming and eager to collaborate.

What do you most enjoy about your work and role as a group leader?

The people. The members of my lab come from all over the world and bring a variety of training backgrounds to their work. Together we are "mission driven," combining our different skill sets to ask novel questions and identify new approaches. Hiring a career immunologist to help us study a mouse model of CHIP helped relieve me of my "myeloid bias" toward the way this particular mutation caused disease and led us to explore how blood stem cell mutations can affect the immune system. I have also been impressed at how quickly the people in my lab have learned about the complex computational approaches needed to study the other main focus of my lab—how mutations in RNA splicing factors transform blood-forming stem cells. I have a group that is collaborative both internally and with other labs, which has led to many fruitful collaborations.

While not in the lab, how do you like to spend your time, or alternatively, how would you like to spend your time?

I enjoy the arts and wish I was a better runner. I have a great group of colleagues who are always up for going to see a show at the Orpheum or smaller venues around the city. It can be painful at times (for my legs and my ego), but many members of my former COVID bubble are avid runners. I am only at the 5K stage, but seeing them run half-marathons reminds me that there is more to do.