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Benjamin Ebert wins the 2021 ASCI/Stanley J. Korsmeyer Award

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News

Benjamin L. Ebert has been honored by the American Society for Clinical Investigation (ASCI) with the Stanley J. Korsmeyer Award, an annual prize in recognition of outstanding scientific contributions and excellence in mentorship (Figure 1). Dr. Ebert, Chair of Medical Oncology at the Dana-Farber Cancer Institute and Professor of Medicine at Harvard Medical School, and his team discovered the mechanism of action underlying the therapeutic benefits of lenalidomide, used to treat multiple myeloma and myelodysplastic syndromes. His laboratory has also made seminal contributions to our understanding of clonal hematopoiesis of indeterminate potential (CHIP), which not only increases the risk of hematological malignancies but also is associated with cardiovascular disease risk. Dr. Ebert recently spoke to the JCI about his research career and key discoveries made to date. JCI: Were you always interested in a career in medicine? Ebert: It was certainly always in my mind, because family members have pursued careers in academic medicine, but I became most interested in a career as a physician-scientist in college, when I spent time working in a lab during the summers. I worked with Daryl Granner, who at the time was the head of the MD/PhD program at Vanderbilt, and started to see the careers of people who combine medicine and basic science. As a college senior, I applied to MD/PhD programs and […]

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Figure 1. Benjamin L. Ebert is the recipient of the 2021 ASCI/Stanley J. Korsmeyer Award.

JCI: Were you always interested in a career in medicine?

Ebert: It was certainly always in my mind, because family members have pursued careers in academic medicine, but I became most interested in a career as a physician-scientist in college, when I spent time working in a lab during the summers. I worked with Daryl Granner, who at the time was the head of the MD/PhD program at Vanderbilt, and started to see the careers of people who combine medicine and basic science. As a college senior, I applied to MD/PhD programs and for one scholarship that I had absolutely no expectation of receiving. When that [Rhodes scholarship] came through, I went to Oxford without a clear idea of what I was going do when I arrived, having initially enrolled to do a second BA in biochemistry. I eventually decided to do research instead and found my way to the lab of Peter Ratcliffe. I absolutely loved working with him. It was early days in his lab, and I was one of his first graduate students. We were working on how erythropoietin is regulated by hypoxia, just at the time it was becoming clear that this mechanism of sensing oxygen and regulating transcription was not limited to erythropoietin but probably regulating many physiological processes. It was not my initial plan to complete my PhD at Oxford, but I found myself in such a wonderful scientific environment, and Peter was an extraordinary mentor — a focused, rigorous scientist who thinks and writes with great precision.

JCI: What sparked your interest in a hematology and oncology fellowship?

Ebert: Throughout my training, I had hematologists as role models and mentors. At Oxford, we were focused on the regulation of erythropoietin, the hormone that promotes red blood cell production. While Peter Ratcliffe and other scientists in the lab were nephrologists, Doug Higgs and Sir David Weatherall were hematologists and important role models for me. In medical school, I worked with Frank Bunn, who made seminal discoveries as a hematologist. I always found hematology to be incredibly interesting clinically, and I found many role models among hematologists who had brilliant scientific careers.

JCI: Can you tell us about your early discoveries from studying the 5q deletion in myelodysplastic syndrome (MDS)?

Ebert: I worked with Todd Golub as a postdoc in the early days of genomics, and I was eager to learn and apply the new technologies to a disease that was still very poorly understood. My focus was on understanding MDS with deletions of chromosome 5q, a molecular subtype of MDS that had a very specific clinical phenotype, indicating that this molecular abnormality must have a distinct biological basis that could hopefully be deciphered in the lab. Most of my postdoc work was focused on identifying a critical gene for the phenotype of del(5q) MDS. But an extremely exciting discovery published during the course of my postdoc was that patients with del(5q) MDS had a marked response to a new drug, lenalidomide. The basis for the activity of lenalidomide in del(5q) MDS and in myeloma was not known. I became extremely eager to understand why the drug had such a phenomenal clinical activity, so when I started my own lab, one of the projects was to try to understand how lenalidomide works.

JCI: Lenalidomide has quite a unique mechanism of action. How did you uncover how it works?

Ebert: It was such a fun journey. First, we wanted to understand what lenalidomide binds. We made a derivative of lenalidomide that we could pull down, and identified by mass spectrometry a protein called cereblon (CRBN). While we were doing that work, a group in Japan, led by Hiroshi Handa, conducted similar studies with thalidomide, and they published that thalidomide binds CRBN. CRBN is a substrate receptor for a ubiquitin ligase, so at that stage we thought that lenalidomide was probably an inhibitor of the ubiquitin ligase, as most drugs act as inhibitors. We did proteomic studies to try to see what

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proteins might accumulate in the presence of lenalidomide. We couldn't find any proteins with increased expression following lenalidomide treatment, but the levels of a handful of proteins decreased rapidly following the addition of the drug. This was the opposite of what we expected, so I initially thought the samples had somehow been switched!

The next series of experiments validated that a couple of transcription factors, Ikaros family zinc finger protein 1, or IKZF1, and IKZF3, were very rapidly degraded after treatment with the drug. We were then able to show that these proteins had increased affinity for CRBN, the ubiquitin ligase substrate adaptor, in the presence of lenalidomide, and that these proteins were subsequently ubiquitinated and degraded. Lenalidomide was acting like a molecular glue, increasing the affinity of substrate proteins for the ubiquitin ligase only in the presence of the drug, resulting in ubiquitination and degradation. Degradation of IKZF1 and IKZF3 results in the killing of multiple myeloma cells, providing a molecular basis for the activity of lenalidomide, thalidomide, and pomalidomide in this disease.

After we worked out the mechanism of action of lenalidomide in myeloma, we examined its activity in del(5q) MDS. In this case, lenalidomide promotes the degradation of another protein, casein kinase 1 α, which leads to selective killing of del(5q) MDS cells.

JCI: Your laboratory recently published two highly innovative studies with other drugs that promote ubiquitination. Can you tell us about this work?

Ebert: We were so fascinated by the ability of a small molecule to recruit substrates to a ubiquitin ligase and wondered whether this activity was entirely unique to lenalidomide and CRBN, or whether we could find additional examples, making it a more generalizable phenomenon. We used a few different approaches to identify other small molecules that might act as molecular glues to induce targeted protein degradation, working with our close collaborators, Nico Thomä and Eric Fischer.

One set of studies started with a bioinformatic approach of looking for molecules that kill cells in a manner that correlates with the expression of ubiquitin ligase components. That work led to the identification of a small molecule called CR8, which is a CDK inhibitor. We found that CR8 killed cells in a manner that was dependent on an adaptor protein for a ubiquitin ligase known as DDB1. With the Thomä lab, we found that CR8 was acting like a molecular glue, but not between a substrate receptor and a substrate. Instead, CR8 is a molecular glue between a core component of the ubiquitin ligase, the DDB1 adaptor protein, and CDK12, which is not normally part of a ubiquitin ligase. In the presence of CR8, CDK12 acts as an adaptor protein, and its partner cyclin K is ubiquitinated and degraded. This provided another new mechanism of drug-induced protein degradation.

In another study, we explored the activity of a molecule developed by Boehringer Ingelheim targeting BCL6, which is a major oncoprotein for lymphomas. Boehringer Ingelheim had the foresight to recognize that one of their BCL6 inhibitors also induced BCL6 degradation. While they didn't know the mechanism, they published that finding and the molecule, enabling others, like us, to investigate how the molecule induces protein degradation. In proteomic studies, we found that when the drug was added, BCL6 was very specifically degraded. The drug also caused foci of BCL6 to form within a cell prior to degradation. When the drug was added to recombinant protein in vitro, the protein would precipitate. Our close colleague, Eric Fischer, at the Dana-Farber, performed structural studies demonstrating that the drug induced BCL6 to form polymers in vitro. His lab solved a cryo-EM structure, showing that the molecule was acting like a molecular glue, not between the ubiquitin ligase and a protein, but between a protein and itself. It was basically gluing dimers of BCL6 together to create a polymer that would come out of solution. We then identified the ubiquitin ligase that degrades the polymerized BCL6.

JCI: What initially drove your interest in studying clonal hematopoiesis?

Ebert: The lab's foundation is the investigation of MDS and myeloid malignancies. This led to studies of lenalidomide, due to its therapeutic efficacy in MDS, and also studies of MDS biology and genetics. In some cases, MDS can be a relatively indolent disease, but in some cases, it can be very aggressive. One of the more indolent forms is del(5q) MDS, which I started working on from the beginning of my postdoc. One of the reasons it is relatively indolent is that it looks like del(5q) can be the initiating lesion all by itself, leading to a clonal expansion of cells, dysplastic cells, and a clinical phenotype, but not an aggressive cancer. As we learned that patients with MDS or leukemia generally have multiple mutations that drive the cancer, we wondered what the prevalence might be of clonal populations of cells that bear initiating mutations, but not the full complement of mutations that lead to malignancy. There was good evidence that such a clonal process exists, based on studies of skewed X chromosome inactivation in females, as with increased age, but the genetics had not been characterized.

The field was really broken open for us by the advent of very large-scale exome sequencing. In collaborations with the Broad Institute, initially with David Altshuler, we were able to analyze data from about 17,000 exomes from peripheral blood that were generated for the study of germline predisposition to various diseases. We identified populations of blood cells with initiating somatic mutations that lead to myeloid malignancy in a much larger fraction of the population than we expected. In over 10% of people by the age of 70, we detected a large population of cells with a somatic mutation that is found in myeloid malignancies. The median size of the clones we identified was approximately 20% of that of all peripheral blood cells.

Clonal hematopoiesis is associated with an increased risk of developing a blood cancer. That finding was not too surprising; it is similar to how a polyp increases the risk of progressing to colon cancer. What has been much more surprising is that those mutant blood cells behave abnormally. In particular, the mutant cells activate inflammatory pathways more easily. In human genetic studies, we see a strong association between clonal hematopoiesis and nonmalignant disorders, including cardiovascular disease. One of the really fascinating aspects of clonal hematopoiesis is understanding how mutant blood cells in a premalignant state can lead to both malignant and nonmalignant consequences. What we don't know yet, and hopefully will learn, is how the diagnosis of clonal hematopoiesis might

change clinical management — but that's an area of really active investigation now.

JCI: Your laboratory has been remarkably productive, and many of your trainees have gone on to their own successful careers. How do you approach mentorship?

Ebert: I have certainly been the beneficiary of phenomenal mentorship from Peter Ratcliffe, Frank Bunn, Todd Golub, and many others. I am absolutely convinced of the value of mentorship, particularly the impact of guidance at critical moments and the importance of role models. I watched their mentorship style closely as I was training, and being a good mentor has been at the very top of my professional priorities. I have been incredibly fortunate to have extraordinary trainees in my lab. I have always found that the most rewarding aspect of my job has been to help early-stage investigators develop as scientists and as physician-scientists. Watching former trainees start their own independent labs and flourish has been something I've enjoyed as much as anything in my career.

JCI: What does winning the Korsmeyer Award mean to you?

Ebert: This is an extremely special award, and I feel very humbled to receive it. I did not know Stan Korsmeyer personally, but he is legendary at the Dana-Farber, as a mentor and as a scientist. He had such a profound influence on the entire institution through his leadership, and his former mentees are among the current leaders at the Dana-Farber. For many, he has been the premier role model of a physician-scientist and mentor.

The ASCI has been very dear to me and played an important part in my career in recent years. At the annual meeting, I have always particularly enjoyed hearing talks by Korsmeyer Award recipients, both because of the amazing scientific discoveries they have made and because of the stories of their careers. One of the great aspects of the ASCI in general is the opportunity to get to know physician-scientists from diverse backgrounds who combine medicine and basic research in such interesting and creative ways.

Sarah Jackson