

Jacques Miller:

How did you come to study the thymus, considering it was thought to be an organ with no purpose at the time?

The thymus is involved in leukemia in mice, and I wanted to study leukemia in mice. As a result of these studies, I found that mice born without a thymus do not reject foreign skin, and this means that the immune system has not developed properly. So, it looked to me as if the thymus was essential for the development of immunity.

How do B and T cells work together?

B cells need the help of T cells to produce very strong antibodies. Without T cells, the B cells cannot, in many cases, produce the correct antibody. T cells secrete factors which act on B cells and also [B and T cells] contact each other and put out molecules that strengthen the bond between the T and B cells. As a result of this strengthening, and as a result of the factors produced by T cells (which are called interleukins), the B cells can now switch on their antibody-producing capacities.

Max D Cooper:

Dr. Cooper, you trained as a pediatrician. Why did you turn to the chicken to study the immune system?

At the time, it wasn't clear whether the thymus could do everything or not. At least some of our children with immune deficiency diseases didn't have a good thymus or thymus-dependent lymphocyte development, but they did make antibodies; they had humoral immunity that seemed to work without the thymus.

The chicken was a model because it has a thymus and an organ called the bursa of Fabricius that is needed for normal antibody production. We thought that it might be clear what the thymus and bursa were doing if we eliminate cells that had developed before chicks hatched and then remove the bursa or thymus at that time and see what immune system capabilities they would develop afterward. That was a starting point that let us realize that there were two lineages, one thymus-dependent T-cells and the other bursa-dependent B-cells.

How did other scientists respond to your work with irradiated chickens?

There were two kinds of responses. One response was from other pediatricians who had found children born without a thymus who had lots of antibody-producing plasma cells, clearly showing that the thymus wasn't essential for development of the B lineage in us humans as well. Other scientists thought it was a stretch to extrapolate data from chickens to humans. Clinicians were much more responsive to the two-lineage hypothesis. They could see how it could affect their diagnosis and treatment of immune deficiency diseases – inherited ones in particular – and also malignancies, whether they affected the T lineage or the B cell lineage.

H. Michael Shepard:

How did you decide that the oncogene HER2 was a promising target for a breast cancer drug?

As we studied the interaction between tumor cells and the immune system, we discovered that highly expressed tyrosine kinase oncogenes made tumor cells resistant to what's called the innate immune system - in particular macrophages. The question was: if you could downregulate the HER2 oncogene in tumor cells, could we make them again sensitive to killing by macrophages and the innate immune system? We were very surprised and excited that when we put one of our antibodies on tumors cells that overexpress HER2, [the tumor cells] did become sensitive again to immune cell killing. After that, we thought that we had a tiger by the tail and we never gave up working together, especially with Dennis Slamon, to get the drug out to patients.

It was a non-orthodox idea that an antibody could fight a solid tumor. Did you receive resistance to this idea as you were pursuing this science?

The team working with me at Genentech did run into a theoretical difficulty that arises from the fact that solid tumors have a great amount of pressure that accumulates inside of them. There's actually an outward flow of fluid from a tumor, in many cases. Because of this, some scientists thought that trying to get an antibody into a tumor would be very much like getting a fish to swim upstream against a very strong current.

For this reason, [Genentech] was very careful. What they did do to help us was set aside \$3 million for our research group to make FDA approved mouse antibodies to show that the antibody (which was radiolabeled) could accumulate in the tumor.

Dennis J Slamon:

It was a non-orthodox idea that an antibody could fight a solid tumor. Did you receive resistance to this idea as you were pursuing this line of research?

I think it wasn't so much that it was not orthodox, but I could say that it probably wasn't enormously popular, mostly because there had been a couple of other attempts to generate antibodies directed against cancer antigens, and clinical trials for those antibodies had not been proved successful. There was some prejudice in the industry that this kind of approach would not be positive. I think it was in large part [Shepard's] tenacity within the company that kept the program alive and kept the scientists who were excited about the data that was being generated involved even though there wasn't uniform enthusiasm at the time of the initial work.

Could you comment on how patients responded? You have emphasized how important their willingness to participate in those trials was to the development of this successful therapy.

We started at doses that were incredibly low to make sure there were no side effects to the drug. The [participants] in the first group were told in the informed consent process that while this may not benefit them, we would learn [from these early trials] and be able to move forward with the next doses. Without exception, they agreed to enter the clinical program, knowing fully well that it may not benefit

them, but benefit the next group. As I've said in the past, they are not research subjects; they are colleagues in every sense of the word. They played a very big role in the whole story.

Seth Berkley:

Gavi was created as a private-public partnership. It utilizes economies of scale to reduce the cost of vaccines. Can you tell us about how Gavi came up with this model and how well is it working?

Vaccines, of course, are some of the most powerful tools in our armamentarium and are, in fact, the most cost-effective interventions. New and powerful vaccines were coming out of science, but they weren't getting to the places that need them the most: the absolute poorest countries. The reason is that people [in those countries] didn't have hard currency and manufacturing was being done in low volume, high-cost settings. The idea was, could we come together and begin to purchase vaccines for these countries? We ended up putting together 73 countries as the Gavi countries based upon their economics – that is low-income countries – and were able to buy products for them. In doing that, companies have stepped up their volumes dramatically increasing them. That, of course, reduces the cost of those products, which ultimately makes them affordable.

Can you talk about innovative ways to get these vaccines out to the people who need them?

Vaccines don't deliver themselves, so it's critical that you have a strong and resilient health system and many of the countries that we work with do not. What we try to do is help build strong systems working with countries and focusing on where coverage is low. But we also try to work with the private sector to bring new tools and technologies forward.

We worked with a small American company to test using drone deliveries in Rwanda. We started by using it for blood transfusions because women were dying because they couldn't get blood. We centralized the blood bank. Wastage went to zero, and within 20 minutes, anywhere in Rwanda, you could get blood delivered by drone. That procedure now, with a company called Zipline, has been moved to Ghana where they're supplying most of the country with a full range of health interventions. They're able to deliver a full range of products to 2000 clinics.