Immune System Research Underlies Lasker Awards

Scientists who identified B and T cells, as well as those who developed trastuzumab, capture coveted prizes

The Albert and Mary Lasker Foundation bestowed two of its prestigious awards on five scientists for their ground-breaking immune system-related research—work that led to the identification of B and T lymphocytes, as well as the development of trastuzumab (Herceptin; Genentech) to treat HER2-positive breast cancer. Among the most coveted biomedical research prizes in the United States, the awards each carry a $250,000 honorarium. The honorees received their awards at a ceremony on September 20.

Max D. Cooper, MD, of the Emory University School of Medicine in Atlanta, GA, and Jacques Miller, PhD, of the Walter and Eliza Hall Institute of Medical Research in Parkville, Australia, received the 2019 Albert Lasker Basic Medical Research Award for identifying the two classes of lymphocytes, which the Lasker Foundation called an “achievement that provided the organizing principle of the adaptive immune system.”

Three other scientists—H. Michael Shepard, PhD, formerly of Genentech; Dennis J. Slamon, MD, of the University of California, Los Angeles; and Axel Ullrich, PhD, of the Max Planck Institute of Biochemistry in Martinsried, Germany—shared the 2019 Lasker–DeBakey Clinical Medical Research Award for developing the first mAb to block a cancer-causing protein and turning it into a life-saving therapy.

LYMPHOCYTE SUBTYPES IDENTIFIED

Miller’s tale began in the early 1960s, when he was studying lymphocytic leukemia in mice. Earlier research had indicated that a newly discovered virus, when introduced at birth, caused the cancer. Other experiments had suggested that the virus homed in on the thymus, so he removed the organ from newborn mice and injected them with the virus. They soon developed diarrhea and became deficient in lymphocytes, Miller recalled, and unlike animals with a thymus, they failed to reject skin transplanted from unrelated mice or respond to bacterial infection. “The white blood cells that should’ve been there weren’t there,” he said.

Miller theorized that thymus cells might circulate throughout the body and attack “foreigners.” To test the idea, he replaced the thymuses in newborn mice with ones from other animals. Again, he transplanted skin from other mice. This time, the animals mounted an immune response—unless the tissue came from the same strain of mouse as the transplanted thymus, in which case the animals tolerated it.

Cooper, a pediatrician, built on Miller’s work. He wondered why some children with immune-deficiency diseases didn’t produce enough lymphocytes but still made antibodies. “It wasn’t clear whether the thymus could do everything or not,” he explained.

To probe the question, Cooper turned to the chicken because it has a thymus and an organ called the bursa of Fabricius. He explained.

FURTHER PROGRESS IN BREAST CANCER

Other researchers had established that the bursa was critical for the normal development of antibodies. Thus, when he removed the bursa from chicks before they hatched, “it wiped out plasma cells and antibody production entirely, although the thymus and its dependent system was still intact,” he noted. “It led us to realize that there were two lineages: one, thymus-dependent T cells; the other, bursa-dependent B cells.”

MONOCLONAL ANTIBODIES TAMPER DOWN HER2

In 1985, Ullrich and his Genentech colleagues uncovered a gene with a sequence resembling that of human EGFR, or HER1, and the chicken oncogene v-erbB, which they named HER2. Slamon, who had been collecting breast cancer tissue, combed through samples with Ullrich, noting that nearly 30% of 189 breast tumors had multiple copies of HER2. Comparing their findings with medical records, they discovered that women with multiple copies of the gene had a worse prognosis than those with a single copy. “That told us that there was smoke there,” said Slamon, “but would there be fire?”

In the lab, Ullrich engineered cells from mice to overexpress HER2. In culture, the cells exhibited uncontrolled proliferation. Further, when the cells were injected into the animals, they indeed caused tumor formation.

Meanwhile, Shepard was studying how cancer cells avoided the killing power of the immune system and TNFα. HER2, he and Ullrich found, not only aided cancer cells in developing resistance to TNFα, but also allowed the unchecked proliferation of the aberrant cells.

Blocking HER2 signaling, the scientists reasoned, might rein in the proliferation of cancer cells—and resensitize them to TNFα. They developed a humanized mAb, later called trastuzumab, that blocked the growth of HER2-overexpressing cells in cell lines without sending the immune system into overdrive. “After that, we thought that we had a tiger by the tail,” reflected Shepard. “We never gave up working together, especially with Dennis Slamon, to get the drug out to patients.”

Doing that proved challenging, “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 proved successful,” explained Slamon. However, “just looking at the data continuing to be positive was impetus enough for us to keep pushing.”

Patient responses also drove the researchers to bring trastuzumab into the clinic. They didn’t shy away from participating in clinical trials, Slamon said, and understood that the knowledge generated by the trials could help others. “That was a significant part of the story,” he noted. –Suzanne Rose

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