**Trio Wins Nobel Prize for Immunology Research**

The Nobel Assembly announced in early October that it will bestow the 2011 Prize in Physiology or Medicine upon 3 renowned immunology researchers: Ralph M. Steinman, MD; Jules A. Hoffmann, PhD; and Bruce A. Beutler, MD.

“Their work had a profound impact on helping us understand how immune responses are generated," says Louis M. Weiner, MD, director of the Georgetown Lombardi Comprehensive Cancer Center. "It revolutionized cancer immunology and immunology in general."

In 1973, Steinman discovered a type of immune cell that he dubbed the dendritic cell. At the time, "the idea that these cells would be clinically useful wasn't on anyone's mind," says Sarah Schlesinger, MD, an immunologist at Rockefeller University who worked with Steinman. But Steinman found that mature dendritic cells process and present antigens, allowing the immune system to decide whether an invader might be harmful. If so, the dendritic cells activate T cells, immune cells that help the body mount a defense.

But what, precisely, tripped the body’s alarm system in the first place remained unclear until 1996, when Hoffman discovered that fruit flies with mutated versions of the protein Toll died when infected with bacteria or fungi. Two years later, Beutler showed that mice with a mutation in an immune cell surface protein similar to Toll could survive infection with endotoxin, which usually kills mice and can cause septic shock in humans. As several more Toll-like receptors (TLR) were identified, scientists realized that triggering these TLRs spurred the innate immune response by promoting the maturation of antigen presenting cells.

In the last 15 years, an entire field of advanced prostate cancer—may enhance dendritic cell function. Other cancer vaccines are under study. Clinical trials have also demonstrated the feasibility of TLR agonists, although none has garnered approval for treating cancer to date.

Steinman, a professor of immunology at Rockefeller University, died of pancreatic cancer just days before the October 3 award announcement. His survivors will receive half of the $1.5-million prize. Hoffman, a former director of the Institute for Molecular Cell Biology in Strasbourg, France, and Beutler, a researcher at the University of Texas Southwestern Medical Center in Dallas, will share the other half. Recipients will receive their prizes on December 10 in Stockholm.

**Mighty Mouse Resource**

The National Institutes of Health will dole out $110 million to begin the second phase of the Knockout Mouse Project (KOMP), which will generate about 5,000 strains of adult mice from knockout mouse embryonic stem cells. Over the next 5 years, researchers will document the appearance, behavior, and other characteristics of the mice to reveal how traits are affected by deleting a given gene. Each mouse will undergo the same analyses so that results can be compared for all of the tested mice.
KOMP will enable researchers to establish the traits associated with the function of every protein-coding gene. Such information will aid in the discovery of the genetic causes of human cancers and other diseases, as well as efforts to identify new drug targets. The data will be placed in a public database, allowing researchers to explore gene function without having to generate their own lines of knockout mice, an often expensive and inefficient approach. For more information, go to www.komp.org.

BATTLES IN THE WAR ON CANCER: MAKING ANTIBODIES

Since antibodies were first described in the late 1800s, scientists have wondered whether these proteins might be manufactured or manipulated to attack cancer cells. However, propagating cells that could churn out a specific antibody remained a stumbling block until 1975, when immunologists Georges J.F. Köhler and César Milstein fused a mouse myeloma cell and a B cell, forming a hybridoma. This cell pumped out antibodies that were identical clones.

But researchers met with little success in using monoclonal antibodies (mAb) to treat human cancer because tumor-specific antigens hadn’t been identified in humans. “In the mid-1980s, the field was dead in the water,” recalls Lee M. Nadler, MD, who joined Dana-Farber Cancer Institute (DFCI) in 1977.

Nadler and his team immunized mice with cells from a patient with Burkitt’s lymphoma, and in 1979 created a hybridoma that produced a mAb that only reacted with the patient’s normal and cancerous B cells. Because it was the first B-cell–specific antigen ever discovered, they named the antigen B1. (Nadler, now senior vice president of Experimental Medicine at DFCI and dean for Clinical and Translational Research at Harvard, renamed it CD20 in 1985.)

In 1997, Nadler also treated a patient with a mAb for the first time in the world. After the advent of recombinant DNA tools, in 1991 IDEC Pharmaceuticals began to develop a mAb that latched on to the CD20 antigen, which sticks out of the surface of B cells, to treat non-Hodgkin lymphoma. Known as rituximab (Rituxan; Biogen Idec), the mAb drug induced apoptosis, activated complement, and recruited macrophages and other effector cells to slay tumor cells.

In clinical trials conducted at Stanford, M.D. Anderson Cancer Center, and other institutions, more than 40% of patients responded to rituximab alone. Because it was combined with a standard chemotherapy, patients lived significantly longer. “It did just what we engineered it to do,” says Antonio Grillo-López, MD, who was chief medical officer at IDEC Pharmaceuticals from 1992 to 2001.

Approved in 1997, rituximab was the first mAb approved to treat cancer. Today, more than a dozen such agents, including the breast cancer drug trastuzumab (Herceptin; Genentech), have been approved.

This article is the fourth in a 5-part series commemorating the passage of the National Cancer Act in 1971.

For more news on cancer research, visit Cancer Discovery online at www.AACR.org/CDnews.