

Immunology in the limelight

With the announcement of the Nobel Prize in physiology or medicine, immunology research is once again in the limelight.

In talks in the 1970s, Niels Jerne and Jan Klein predicted the end of immunology research because all fundamental questions would soon be resolved and there would be nothing of interest left to investigate. Decades later, immunology research is still going strong. The fact that on 3 October 2011, the Nobel Assembly at the Karolinska Institute in Sweden awarded the Nobel Prize in physiology or medicine to another three eminent immunologists attests to this.

Jules Hoffmann, of the University of Strasbourg in France, and Bruce Beutler, formerly of the Scripps Research Institute in San Diego, were awarded one half of the \$1.45 million prize for their discoveries about the activation of innate immunity. In their original 1996 *Cell* paper (<http://www.cell.com/retrieve/pii/S0092867400801725>), Hoffmann and Bruno Lemaitre reported that the *Drosophila Toll* gene, previously associated only with a developmental role, is also important for the innate immune response to fungal and Gram-positive bacteria.

Since that landmark paper, the Hoffmann group has continued to work on the molecular and cellular aspects of the innate immune response of *Drosophila*. More recently, the group has also started working on the mosquito *Anopheles*, the vector for the malaria parasite.

Since the early 1890s it has been known that substances that induce a biological effect at extremely low concentrations often function by interacting with specific, high-affinity receptors. In mammals, therefore, the existence of an 'endotoxin receptor' was predicted after the chemical characterization of lipopolysaccharide, a well-known inducer of the inflammatory response and septic shock. However, it was not until Beutler's landmark 1998 paper in *Science* (<http://www.sciencemag.org/content/282/5396/2085.long>) that the lipopolysaccharide-sensing receptor was identified. This receptor, now called Toll-like receptor 4, looked similar to Hoffmann's Toll. Thus, the field of innate immunity experienced what could be called a renaissance. Because many other microbial components induce effects similar to those of lipopolysaccharide in the mammalian system, it was assumed that a family of receptors existed; this paved the way for the discovery of more than nine other Toll-like receptors in the past two decades. More recently, many other pattern-recognition receptors, such as RIG-I and Mda5, have been identified.

Notably, Beutler also isolated mouse tumor necrosis factor and discovered its inflammatory properties, along with inventing recombinant inhibitors for tumor necrosis factor. Those inhibitors are now used for the treatment of inflammatory diseases. Now at the University of Texas Southwestern Medical Center, Beutler has in recent years been doing pioneering work using *N*-ethyl-*N*-nitrosourea-induced mutagenesis to isolate additional molecules involved in the innate immune response.

The other half of the Nobel prize in physiology or medicine was awarded to Ralph Steinman, of the Rockefeller University in New York, for his discovery in 1973 of dendritic cells, published in the *Journal of Experimental Medicine* (<http://www.ncbi.nlm.nih.gov/pmc/articles/>

PMC2139237/?tool=pubmed). Tragically, Steinman never heard the news, as he died after a long battle with pancreatic cancer a few days before the Nobel Prize was announced (an obituary by Carl Nathan is on p 1129 in this issue of *Nature Immunology*). Fortunately, the Nobel Assembly reaffirmed the prize despite its rules against posthumous awards.

Despite much resistance by many in the community to accept the existence of dendritic cells, Steinman continued to collect data over the years that would eventually silence his critics. By the 1990s it had become dogma that dendritic cells trigger the adaptive immune response and are pivotal in determining activation versus tolerance of the immune system.

The effect of these three immunologists cannot be underestimated. The identification of dendritic cells and innate immune receptors has paved the way for the development of better vaccines and adjuvants, as well as for new treatments for asthma and autoimmune diseases such as rheumatoid arthritis, type I diabetes and multiple sclerosis. In addition, the work of the three Nobel laureates may lead to better immunotherapy to fight cancer. Indeed, Steinman tried three different dendritic cell therapies to treat his cancer. Although it is difficult to say if the therapies he used extended his life, he did live several years beyond his initial prognosis.

With the renaissance of innate immunity, and indeed of other areas of immune research, the field of immunology seems far from over. Big questions that remain include how the immune system controls the balance between responding to exogenous antigens and tolerance to self, and, along the same lines, what triggers the immune system to attack self and cause autoimmunity. Can the immune system be harnessed to be protective against diseases such as human immunodeficiency virus or cancer? How is allergy triggered? Newer questions have also arisen, such as how the microbiome influences the immune response both locally and systemically. These are of course but a few examples of active and interesting research being conducted by immunologists. Many new techniques, such as systems biology, will surely help delineate some of these questions in the near future.

Hoffmann, Beutler and Steinman now join 23 other Nobel laureates in immunology (and other closely related fields), including Eli Metchnikoff, MacFarlane Burnet and César Milstein, as elegantly described in the commentary "The Glittering Prizes" by Peter Doherty in *Nature Immunology* (<http://www.nature.com/ni/journal/v11/n10/full/ni1010-875.html>). *Nature Immunology* is confident that the field of immunology research is so fertile, and we look forward to many more Nobel laureates in the future. However, it must be noted that the Nobel prize, like all awards, can be given to three people at a time only across many disciplines. Many scientists past and present have contributed greatly to this field, and *Nature Immunology* also salutes those unsung heroes.

