Jürg Tschopp

(1951–2011)

Immunologist whose discoveries transformed patients' lives.

Jürg Tschopp stood apart from most of his colleagues in immunology in that his discoveries in fundamental research brought striking and almost immediate benefits to patients suffering from painful, debilitating diseases. Of his numerous findings, one led to a treatment for the autoimmune disorder systemic lupus erythematosus, and another brought dramatic relief to patients with gout.

Tschopp, who died on 22 March aged 59, trained as a biophysicist and obtained a PhD from the University of Basel in Switzerland in 1979. Yet it was immunological questions that captured his attention. He did postdoctoral work with molecular immunologist Hans Müller-Eberhard at the Scripps Clinic in La Jolla, California, before joining the Department of Biochemistry at the University of Lausanne in Switzerland in 1982.

An early milestone in his career was the characterization of the final step in a signalling pathway called the complement cascade. This is a crucial component of the innate immune response, which protects animals from an infection through a generic mechanism, rather than on the basis of previous 'remembered' encounters with an infectious agent.

In the early 1980s, immunologists knew that one protein involved in the complement cascade, C9, could kill bacteria, but how it worked was a mystery. Tschopp showed that C9 essentially drills holes in the cell wall of a bacterium by assembling into a pore within its cell membrane. Vital macromolecules leak out through the pore, and the bacterium quickly dies.

Subsequently, Tschopp found that a class of white blood cells called T cells destroy tumour cells or those harbouring viruses using a similar mechanism. In this case, these T cells release perforin, a channel-forming protein that inserts itself into the membrane of the target cell, allowing an enzyme called granzyme to enter the cell and destroy it.

Tschopp relished turning up clues in the detective stories unfolding in his laboratory. To his and everyone else's surprise, T cells in mice lacking the gene encoding perforin could still destroy target cells. The back-up pathway turned out to involve a membrane protein called the Fas ligand. When this protein binds to its receptor protein Fas on target cells, a molecular cascade begins that activates a cell-destroying enzyme similar to granzyme.

It was Tschopp's later discoveries that had a direct impact on patients. Along with other groups, he identified BLyS as a ligand for a receptor that drives the proliferation of B cells — a type of white blood cell that produces antibodies. These antibodies are proteins that recognize and neutralize certain types of infecting agents as part of a longer-term defence strategy.

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Tschopp's discovery catalysed the development of a compound called Benlysta (belimumab) by the pharmaceutical company Human Genome Sciences in Rockville, Maryland. Benlysta neutralizes the BLyS ligand, and so can treat immune disorders in which B cells produce antibodies against the body's own healthy cells. Benlysta received approval from the US Food and Drug Administration just last month as a treatment for the chronic autoimmune disorder systemic lupus erythematosus. It is the first new lupus drug in more than 50 years.

About ten years ago, while working on BLyS, Tschopp mentioned to me over dinner that he wished to devote the rest of his career to discoveries that made a difference to patients' lives. Soon after, he began his quest to characterize the inflammasome signalling complex.

The inflammasome complex is a protein pathway that starts the production of two cytokine proteins that orchestrate the inflammatory response. In a scientific tour de force, Tschopp's laboratory showed that the tender, swollen joints and excruciating pain associated with gout are caused by uric-acid crystals activating the inflammasome. Based on these findings, Tschopp persuaded the clinical-rheumatology group at the University of Lausanne to conduct human trials on blockers of one of the cytokines for the treatment of gout. The results were stunning. Patients enjoyed almost immediate, dramatic and prolonged relief.

This success thrilled Tschopp. He took particular pleasure in showing the clinical data at meetings to support the claim that basic research yields significant clinical achievements. For the inflammasome discovery and other advances, he was showered with accolades and prizes, including the Louis-Jeantet Prize in 2008 and the Novartis Prize in Clinical Immunology in 2010.

Jürg was a formidable athlete and competed in the decathlon in his youth — a competition consisting of ten events ranging from long jump to discus. Throughout his life, he maintained a vigorous outdoor lifestyle, skiing and playing tennis with his family and jogging with his precious dogs. Tragically, he died while hiking in his beloved Swiss mountains.

He once told me of how he had swum in a lake with his retriever, realizing too late that his wallet had been in his pocket and had fallen out. Suddenly he spotted his dog running furiously towards him, wallet in mouth! The story is fitting because Jürg had an uncanny ability to dive into the murky waters of complex scientific issues and emerge, faster than the rest of us, with the answer.

As we mourn Jürg's unexpected death, we can take solace that his work will live on and benefit many patients. ■

Vishva Dixit *is vice-president of research at Genentech, South San Francisco, California 94080, USA.*
e-mail: dixit.vishva@gene.com