Jürg Tschopp 1951–2011

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The scientific community mourns the loss of Jürg Tschopp, who died recently while doing what he loved most, practicing sports in his beloved Swiss Alps. Jürg loved to escape to the rarefied air of the high peaks of the Valais to be with his family after busy periods of work or travel.

Jürg was from Basel, Switzerland. An outstanding athlete in his youth, ranked nationally in the decathlon, he never lost his athleticism and competitive spirit, as anyone who ever went skiing, running or hiking with him soon noticed. After obtaining his PhD in biophysics with Professor Jürgen Engel at the Biocentre of the University of Basel, Jürg moved to the Scripps Research Institute as a postdoctoral fellow with Hans Mueller-Eberhard, where he discovered that complement pores are formed by C9 multimers.

This understanding of the complement system led him to study other lytic pathways upon his return to Switzerland at the University of Lausanne. He characterized cytoplasmic granules within cytolytic T cells (CTLs) and discovered perforin, the primary lytic protein, as well as a family of proteases known as granzymes. Jürg's interest in studying the function of perforin *in vivo* led him to create perforin-deficient mice, which in 1995 was a remarkable endeavor. Analysis of these mice revealed a second lytic pathway used by CTLs that was dependent on the then recently identified death-inducing ligand, FasL, and its receptor Fas (CD95, APO-1). This discovery turned Jürg's interest toward the TNF family of ligands and the mechanisms of apoptosis. For these projects, Jürg combined his talent in the study of molecular mechanisms with his everlasting keen interest in bioinformatics. This began his most prodigious period of research, which included the discovery of viral and mammalian forms of the caspase-8-related protein FLIP, the physiological regulators of caspase-8 and therefore death receptor–mediated apoptosis. He aptly demonstrated that c-FLIP not only inhibits Fas-induced cell death but also activates nonapoptotic signaling pathways, proposing that caspase-8 might be involved in cell growth as well as cell death processes; genetic studies confirmed this paradigm shift. He was also the first to implicate the kinase RIP1 as an important component of the caspase-independent cell death program, known today as necroptosis, and to provide both a model and supportive evidence to unravel the long-standing molecular mystery of how TNF-TNFR1 signaling can induce either NF-κB activation or cell death.

Using a bioinformatics approach, Jürg discovered several additional members of the TNF and TNFR ligand and receptor families, including the APRIL, BAFF and TRAIL receptors. BAFF is now recognized as an essential survival and differentiation factor for peripheral B cells and is being targeted in several ongoing clinical trials for the treatment of autoimmune diseases. Importantly, the numerous cell death regulators identified in Jürg's laboratory eventually provided impetus for the formation of three biotechnology companies.

One of Jürg's most striking traits was his constant attraction to unexplored fields of biology. At the summit of his productivity in his studies of the TNF and TNFR families and cell death regulation, he was already developing a future research focus by designing a theoretical model, based entirely on the prediction of protein-protein interactions, proposing that caspase-1 activates pro-interleukin-1β in a molecular complex termed the "inflammasome." Since then, he dedicated most of his thoughts and efforts to tackling this idea, which, after minor adjustments, his group described in 2002. The description of the inflammasome was undoubtedly the crowning achievement of Jürg's career. This molecular machine consists of numerous intracellular sensors, known collectively as NLRPs—NACHT, LRR and PYD domain–containing proteins—that, when activated, associate with the adaptor ASC and with caspase-1 to convert the interleukin-1β precursor into a proinflammatory cytokine. This elegant pathway suggested that autoimmune symptoms in people with genetic mutations of *NLRP3* could be due to overproduction of interleukin-1β. Fortunately, an interleukin-1β receptor antagonist, Anakinra, was available for testing and resulted in rapid and spectacular improvement of patient's symptoms. This drug, and other antagonists of interleukin-1β and its receptor, are now being used or tested to treat numerous inflammatory pathologies, ranging from gout to type 2 diabetes. This new therapeutic strategy is perhaps the most appropriate valediction of Jürg Tschopp's legacy.

One of Jürg's trademark skills was reducing complex questions to models so simple that they could only be right or wrong and therefore be experimentally validated or discarded. He would joke that the half-life of models in his laboratory was about two weeks. Perhaps most endearing was Jürg's collegial nature, his generosity not only with reagents but also with his creative mind. He was very willing to help other scientists, particularly young students and postdoctoral fellows, improve their work, and he possessed the rare attribute of genuinely enjoying great scientific discoveries made by others, even his competitors. Therefore, one of the highest plaudits for Jürg was that even his fiercest scientific rivals would all readily acknowledge that he was a "great bloke" and not just a great scientist.

Jürg Tschopp was a consummate scientist, a deep thinker on a broad array of issues, and a great humanitarian. In essence, he was a highly civilized man, something that has always been distinguished by its rarity. We will remember him as a daredevil skier ever ready to be challenged by a new double black diamond or, even better, an off-piste run—an attribute that was also clearly evident in his scientific endeavors, where he was always ready to tackle new areas of research and difficult problems.

The scientific community has lost a wonderful mind. Jürg's outstanding contributions, friendship, mentorship and collaborative spirit will be sorely missed. Our thoughts and condolences go to Jürg's wife Erna and his family.

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