REMEMBRANCE

Death of a Titan

Marius Sudol and Michael B. Yaffe

When Tony Pawson passed away this summer, the cell signaling community lost a great scientist. His outgoing nature and inquisitiveness and excitement about science influenced many members of the field. Researchers who knew Tony offer fond remembrances here to commemorate his impact on our understanding the molecular mechanisms governing signal transduction and on many individual careers.

Tony Pawson, a pioneer in the area of cell signaling and modular protein domains, passed away unexpectedly on August 7th of this year. He was only 60.

Tony’s discovery of the first modular protein domain, which he named SH2 (Src homology 2), emerged from his insertional mutagenesis studies on Fujinama sarcoma virus and revolutionized our understanding of signal transduction processes. The SH2 domain turned out to be an independent, structured functional unit that mediates specific protein-protein interactions in a phosphotyrosine-dependent manner. Before the late 1980s, a protein-protein interaction was frequently explained as involving large, convoluted, and complementary surfaces, in keeping with the “lock and key” hypothesis of Emil Fischer. Tony’s paradigm-shifting discovery revealed that only a snippet of a protein kinase, which was shared evolutionarily with other protein kinases, rather than a large surface, is sufficient for one protein to form a complex with another partner molecule. Subsequent work by Tony and others led to the discovery of additional protein “modules,” many of which do not require phosphorylation to mediate protein-protein interactions, and many of which are also found in proteins that are not kinases. Moreover, these snippets, now known as modular protein domains, act in a reiterated and combinatorial fashion, somewhat reminiscent of “Lego” blocks. Modular protein domains are indeed basic units of the canonical code of cellular signaling.

Tony was a gregarious and highly interactive scientist. He influenced many researchers worldwide not only by his high-impact published research but also through dynamic lectures and highly insightful review articles. He especially loved personal interactions with other scientists, both young and old, and was a constant fixture at the poster sessions of scientific meetings, where he would ask the most insightful and probing questions and freely dispense some of the most extraordinarily useful scientific and career advice to postdocs and students. His enthusiasm for science was infectious. His death was a shock to the research community, and, in the past three months, several obituaries were published by his close colleagues and collaborators. We decided to honor his memory by gathering words and short vignettes from researchers who knew him. We present them here in alphabetical order of contributors:

Gary Bader, University of Toronto

“Tony had an amazing mind, as was clear to anyone who discussed science with him. The first time I met him in 1998, he went up to his whiteboard and passionately explained how complex cell signaling was and how we desperately needed to capture it all in the computer. Interestingly, while he was explaining protein interaction networks, he noted which scientist worked on which proteins and sometimes would skip to a distant protein worked on by the same person. I realized he supplemented the protein interaction network knowledge with a vast social network of scientists. Amazingly, he surfed between these networks with ease. I will miss his energy and insight.”

David Baltimore, California Institute of Technology

“I admired him and would never miss a talk by him because there was always something new and surprising. We talked about fly fishing, something I enjoy and he was born to. His death was a huge shock—there was so much more he had to contribute to our science.”

Sydney Brenner, Agency for Science, Technology and Research, A*STAR, Singapore

“Tony Pawson will be remembered for bringing reason into the jungle of signal transduction by his discovery of the interaction of the SH2 domain of proteins with a phosphorylated tyrosine on a partner. In the ’90s, when I was organizing a new research institute in California, he was the first on my list of four talented young scientists I wanted to recruit. On my many visits to Toronto since then, I always made a point of seeing him to discuss the ramifications of protein interactions—the ’strong force’ of molecular biology. I shall miss him.”

David Brindley, University of Alberta, Edmonton

“I feel privileged to have known and followed the work of Tony Pawson. Tony made a great contribution to the understanding of cell signaling...
and the role of conservative domains in signaling proteins. We were very pleased that Tony accepted an honorary doctorate in recognition of his outstanding work from the University of Alberta. Moreover, Tony was a very personable and compassionate person. He will be greatly missed.”

Lew Cantley, Weill Cornell Medical College

“Tony’s passing has heavily saddened me. We have been friends for more than 20 years and published a few papers together. At scientific meetings, I always sought Tony out and caught up on his latest ideas, which were always exciting and on the cutting edge. However, my fondest memories are of the time, in the summer of 1995, that he invited my extended family for afternoon tea at his family estate near Winchester. Tony’s parents were charming in the most British way, and the discussion, of course, wandered to trout fishing and soccer and inside political gossip. It was a beautiful summer day. We sat in the garden and had smoked trout, cucumber sandwiches, and Pimm’s. We visited the ~500-year-old family chapel at the top of the knoll. My daughters played with his son and still talk about the experience.”

David Foster, Hunter College of the City University of New York

“I met Tony when I was a postdoc in the Hanafusa lab at The Rockefeller University working on the Fps oncogene. Tony’s lab was one of very few labs also working on Fps—like Src, a nonreceptor tyrosine kinase. I remember well Tony showing up at my poster at the 1983 Cold Spring Harbor meeting on RNA tumor viruses that was being crowded out by those trying to see the flanking posters on Src. His arrival at my poster was of great comfort—finally, someone who believed that what I was working on was of relevance. Of course, Tony was also sensitive to the scant attention that Fps received relative to Src, but used it to his advantage and famously identified two regions of homology between the two tyrosine kinases—Src homology regions 1 and 2 (SH1 and SH2). The SH2 domain turned out to be one of the most significant breakthroughs in intracellular signaling and cancer. I like to think that, although Fps never proved to be of high significance in cancer, without Tony’s involvement with Fps, the roadmap to understanding of the phosphotyrosine-SH2 interaction would have been seriously compromised. In the end, Fps really was relevant.”

Giulio Superti-Furga, Research Center for Molecular Medicine, Vienna

“The first time I met Tony Pawson, he was visiting the EMBL in 1992 and I was a postdoc in Giulio Dractta’s lab and working on Src regulation in collaboration with Sara Courtneidge. To start the conversation in a chance meeting in the elevator, I asked him what residue I should mutate in the SH2 domain of Src to abolish ligand binding. The answer was available in the literature, and he could have easily referred to that. Instead, he started a wonderful scientific dialogue that lasted 20 years, pulling me up at a higher and more intense intellectual level and welcoming me in a mentorship, based on scientific rigor and honesty that gripped me and has been inspiring me ever since.”

Mario Gimona, Paracelsus Medical University, Salzburg

“To me, Tony has been (before I met him in person) and remained after having had the privilege of talking to him—The Master and Commander of the Modular World.”

Anne-Claude Gingras, University of Toronto

“What I will remember the most about Tony is his contagious enthusiasm for science and discovery. It was not unusual for him to literally run down to my office to show me a new cool piece of data that his lab members had just obtained. He knew just what results had the potential to lead to groundbreaking discoveries and was able to rapidly organize follow-up experiments. His passion as he was describing this new mass spec result or this cool new phenotype was amazing, and after a few minutes of talking to him, I myself felt so energized that I would often reply: ‘Oh wow, this is so neat! Can I do anything to help?’ Not only was Tony not afraid to embrace new technology, he thrived in trying new things. In the past few years, he was almost equally excited by being able to develop quantitative proteomics to monitor signaling complex composition and by the protein engineering he was doing with Shohei Koide to rewrite pathways. This love of the unknown, together with a keen appreciation of what was possible and what was not, greatly contributed to his role as a pioneer, not only in signal transduction, but in systems biology, and, more recently, in proteomics. As a starting researcher at the Lunenfeld-Tanenbaum, I could not help but aspire to emulate this, and, indeed, I have seen myself widening my horizons because of his influence. I do owe him a lot.”

Wan Jin Hong, Institute of Molecular and Cellular Biology, Singapore

“Tony had a long-term association with Singapore. As a member of the Scientific Advisory Board of the Institute of Molecular and Cell Biology (IMCB), he helped IMCB to develop a highly competitive program in cell signaling. He also nurtured young IMCB scientists by hosting them in his vibrant lab in Toronto. In the past 6 years, he was playing a prominent role as a member of the Biomedical Sciences International Advisory Council (IAC) of the Agency for Science, Technology, and Research, which oversees the entire landscape of biomedical sciences in Singapore. At a personal level, I enjoyed very much chats with him over coffee, lunch, or dinner and truly respected him as a humble individual, despite being such an accomplished scientist. He and his contributions will be remembered forever.”

Stefan Knapp, University of Oxford

“In 2007, I met Tony at a meeting in Basel. After drinking coffee, he talked about FES/FPS kinase and
the discovery of the SH2 domain as a regulatory module in tyrosine kinases. Tony finished his story telling me, ‘You know, what has been bothering me all these years since the discovery of the SH2 domain is that we have never been able to show how it works activating tyrosine kinases.’ Indeed, all structural information on SH2 domain kinase interactions that have been published to this point showed that the SH2 domain locked cytoplasmic tyrosine kinases tightly in an inactive state, rather than stimulating catalytic activity, as suggested by Tony’s biochemical data on FES/FPS. When I returned to Oxford, we set out crystallizing the SH2-kinase domain of FES, and we had been incredibly lucky to find one construct among many tested that expressed active protein and readily yielded crystals. The structure revealed an active conformation of FES where the SH2 domain stabilized helix alphaC, as predicted by Tony more than 20 years earlier. Tony was enthusiastic about these data and after an uncountable number of (late night) Skype sessions and telephone calls, we finished the paper, which was published in September 2008 in Cell. It was an incredibly stimulating experience working with Tony on this and many other projects, which significantly influence research in my laboratory.”

Wendell Lim, University of California, San Francisco

“It is hard to emphasize how strong an influence Tony had on my work, even though I never directly trained with him. As a young postdoc, trained in mechanistic biochemistry, I had always found signal transduction pathways byzantine and overly complex to wrap my head around. Tony’s discovery of modular protein domains and the concept that complex signaling proteins and networks were constructed from modules with simple elemental functions was an epiphany for me. For the first time, I saw hope of truly understanding how cellular decision-making systems might work, and perhaps more importantly, a plausible mechanism for how they might have evolved.”

Helen McNeill, University of Toronto

“Like everyone else, I can say that he was infectious and enthusiastic about his science, that he inspired his students and postdocs and other lab heads with his excitement about the possibilities of science. He always helped if I asked for ideas or reagents or collaborations.”

Robert Rottapel, University of Toronto

“The essential magic of Tony was that though he had traveled the world, written many articles, had given uncountable keynote addresses and won many prizes, he never tired from the basic joy of scientific discovery. He was like a kid in a sandbox or a child on the beach fascinated with each new seashell that he uncovered. He rejoiced in his own discoveries and also in the discoveries of others. It was that enthusiasm that was infectious and why he was loved. Many scientists, even great ones, often tire of the grind associated with doing science as they age. Tony was, on the contrary, an example of how to traverse one’s career, holding dear the central human principle that it is the unexplainable simple joy of discovery, of pushing back on the shadows of the unknown, that animates what we as scientists have always done and hopefully will always do.”

Ivan Sadowski, University of British Columbia, Vancouver

“As a young impressionable graduate student, it was Tony’s unwavering enthusiasm for science that initially attracted me to his research group, and this enthusiasm for even the smallest new result was also a source of inspiration and encouragement throughout my tenure in his laboratory. One important skill that Tony provided was the capability to recognize that the simplest hypothesis is often correct. I recall one conversation we had regarding protein tyrosine kinases and what the critical substrates might be for signaling, where at one point Tony mentioned that maybe the most important substrate for v-fps is itself. I think in combination with our early observations that SH2 must be directing interaction with other proteins in the cell, this inkling of an idea eventually contributed to elucidation of how tyrosine kinases transmit signals to downstream pathways. I consider myself fortunate to have known him as a mentor and friend, and am very proud to have trained in his laboratory.”

Clark Wells, Indiana University School of Medicine

“When we were writing manuscripts, Tony recalled a story of when he was a child and his father, who wrote the sports column for the newspaper [The London Observer] would spend all day away writing. Tony asked his father why he was gone all day only to write a paragraph, and his father said that anyone could write five pages, but it took work to write a good paragraph. I think it is something Tony thought about often, since he told me the story multiple times. And all paragraphs in Tony’s influential review articles on modular domains and signaling are indeed impeccable, if not perfect.”

Many of us who knew Tony well, including the authors of this piece and those who were privileged to work and socialize with him, remember Tony as a brilliant researcher with an insatiable hunger for knowledge. In Gladwellian prose, Tony was a fine “maven,” whose seminal discovery of a protein module was a “tipping point” that allowed an unprecedented insight into the molecular machinery of life.

10.1126/scisignal.2004914

Citation: M. Sudol, M. B. Yaffe, Death of a titan. Sci. Signal. 6, eg6 (2013).
Death of a Titan
Marius Sudol and Michael B. Yaffe

Sci. Signal. 6 (306), eg6.
DOI: 10.1126/scisignal.2004914