Professor Chris Marshall, 1949-2015

Chris Marshall was born and grew up in Coventry, UK. At school he excelled in Chemistry and won a scholarship to Cambridge where he earned a B.A. in Natural Sciences. He was the first person in his family to go to university. He then moved to the laboratory of Sir Henry Harris in Oxford switching his interests from the chemistry of molecules to the chemistry of cells, and investigating how proteins are synthesized in cells Chris earned a DPhil in cell biology in 1973.

Chris then spent five years at the Imperial Cancer Research Fund (now The Francis Crick Institute) in London studying the mechanisms of carcinogenesis. His career then took him to the Sidney Farber Cancer Institute in Boston where he spent two years, but his time in Boston was cut short when in 1980 Robin Weiss, the recently appointed Chief Executive of the Institute of Cancer Research (ICR), invited Chris to return to London to join their faculty. Chris would spend the next 35 years, the majority of his working career, at the ICR. Shortly after Chris’ arrival, Robin also recruited Alan Hall. Chris and Alan were like chalk and cheese, but they complemented each other wonderfully both in approach and temperament, and by recruiting these two exceptional scientists, Robin forged, perhaps by accident or perhaps design, one of the most extraordinarily effective collaborations in modern cancer cell biology.

During his time in Boston, Chris was inspired by Bob Weinberg and colleagues who showed that DNA from cancer cells could transform normal cells. Analysis of the transforming DNA could then reveal “oncogenes”, the drivers of human cancer. Chris and Alan set out to become oncogene hunters, but this was technically challenging work fraught with difficulties, and after a year without progress they decided to run the experiment another 20 times and if it did not work, they would give up and do something else. Chris was fond of citing Pasteur “luck favours the prepared mind” and luck certainly favoured theirs, because in 1982 and 1983, Chris, Alan and Robin reported a “new transforming entity” that turned out to be neuroblastoma (N)RAS, the third member of the RAS protein family after HRAS and KRAS and fittingly, Chris called his laboratory The Oncogene Team and would not change that name for the rest of his career.

A new field had been born and it attracted some of the brightest minds. The competition was intense and the field progressed rapidly. It was proven that RAS genes were mutated in cancer and that the mutant genes could transform cells, whereas the wild-type genes could not. With Hans Bos, Chris discovered NRAS mutations in acute myeloid leukaemia and with Karen Vousden he demonstrated that carcinogens could induce codon 12 and codon 61 mutations in HRAS, connecting cell transformation by RAS genes to agents that were known to drive cancer. Hans and Karen would both become Chris’ life-long friends. It was shown that RAS was a guanine nucleotide binding protein that cycled between GTP (active) and GDP (inactive) bound forms (hence G-protein), providing a relatively simple way to measure its activity and allowing confirmation that the mutant protein was constitutively active, whereas the wild-type protein was activated by agents that stimulated cell growth. Thus, RAS was an oncogene that could drive cancer, but how?

In 1982, Ed Scolnick reported that HRAS was covalently bound to lipids that targeted it to the plasma membrane. Shortly afterwards Dough Lowy reported that a cysteine amino acid from the C-terminus (C186) was essential for this modification and for RAS function. Chris and Tony McGee established that this lipid modification was dynamic and with John Hancock, Chris performed heroic biochemical studies to reveal a complex series of modifications at the C-terminus of RAS, involving C186 being modified via farnesylation, removal of the last 3 amino acids in the protein and methylation of the carboxy moiety on the newly exposed C186. This provided the first signal for RAS membrane targeting, but they discovered that two signals were needed; in HRAS, NRAS and in the 4A form of KRAS this was provided by palmitoylation of additional nearby cysteines (two for HRAS, one each for NRAS and KRAS4A), whereas in the 4B form of KRAS it was provided by six consecutive lysine amino acids that provided a basic patch that interacted with the acidic head groups of the membrane phospho-lipids. Although we still do not fully understand the underlying biology, Chris’ discovery led to the realization that the RAS isoforms occupy distinct sub-domains of the membrane and this allows them to regulate different signalling functions within the cell.

As the 1990s progressed, various cell signalling events were discovered. Of particular note, the protein kinase ERK and RAS were shown to be activated by the same stimuli in cells, but were these events linked? Working again with Hans Bos, and also with Philip Cohen, Dario Alessi and Alan Ashworth, Chris showed that ERK was activated by RAS and the protein kinase CRAF; and that ERK activation was dependent on both of these “proto-oncogenes”. They showed that CRAF phosphorylated and activated MEK; MEK activates ERK; ERK phosphorylates substrates to control cell functions. In 1994, Chris reported...
that neuronal cells could be induced to proliferate or differentiate depending on the duration of activity of the pathway, establishing that this was a versatile pathway that could control fundamentally distinct cell fates.

It was known that CRAF activated MEK by direct phosphorylation, and that MEK activated ERK by direct phosphorylation, but how did RAS, a guanine nucleotide-binding protein activate CRAF? The vital clue to this question came from a yeast two-hybrid screen by Jonathan Cooper and rapidly confirmed by many others who demonstrated that CRAF bound to active, but not inactive RAS. Quick to understand the significance of this, Chris posited that the role of RAS was to bring CRAF to the plasma membrane for activation, and to prove this he attached the membrane localisation signal from HRAS onto CRAF, and showed that this was sufficient to take CRAF to the plasma membrane, and also to activate it.

I joined Chris’ lab shortly after this discovery. Operating in a busy field, we confirmed Debbie Morrison’s earlier work showing that RAS and the protein SRC cooperated to activate CRAF, allowing us to propose that RAS took CRAF to the membrane where it was phosphorylated and activated by SRC. Over the next few years we contributed to what became an increasingly complex model of CRAF regulation, and in 1997, we published a small paper reporting that BRAF, a protein closely related to CRAF, did not need SRC and was activated by RAS alone.

We had found that BRAF was primed for activation, whereas CRAF was dependent on more events, but the true significance of this result only emerged 5 years later, when Mike Stratton and his colleagues started resequencing tumour genomes. They had realised that the release of the first draft of the human genome in 2001 provided an opportunity to define the genomic landscape of human cancers. Chris, still an oncogene hunter at heart, suggested an excellent start point for this massive project was the RAS-ERK pathway. He argued cogently that RAS mutations could be expected to become more frequent in cancer than in normal tissues. Mike was quick to understand the significance of this, and soon we found that at least the BRAF and CRAF kinases were the most frequently mutated oncoproteins in human cancers, and that the RAS-ERK pathway was the major driver of cancer cell migration and invasion. The BRAF field exploded and less than 10 years later, in 2011 the first BRAF drug was approved for use in melanoma patients. The groundwork laid down by Chris over his previous 30 years contributed to this enormous achievement and is something that he could rightly be proud of.

Chris generously allowed me to take forward the RAF kinase work, and he returned to his first scientific love and continued to advance our understanding of the biology of RAS over the last 10 years of his life. He demonstrated a key role in angiogenesis and showed that it signalled through a related G-protein called RAL, but his major contribution during this time was to produce a wonderfully elegant body of work revealing how G-protein RHO signalling in RAS and BRAF mutant cells regulated cancer cell migration and invasion. He found that cancer cells could invade biological matrices in two modes, which he called amoeboid and elongated. Importantly, he showed that the cells could shift between these modes, allowing them to adapt to the tumour microenvironment and to anti-cancer drugs. He worked out the underlying biochemical mechanisms and revealed the clinical significance of this for patients. The important work that Chris started in this area will continue as the people he trained take forward their own studies.

Chris was an inspiring scientist and it was a privilege to know him and work with him. He was extraordinarily intelligent and loved a good scientific discussion, but had an infuriating habit of being right more often than not. He was always delighted to talk to young people and supported many of us through our careers. He was loyal, generous in spirit and liberal with his time. He trained us, helped and guided us and continued to do so long after we left his lab. He had an acerbic wit that he could use to incapacitate you with laughter; or to point out the weaknesses in your science. It was a powerful weapon and he used it sparingly. Chris felt tremendous loss and sadness at the sudden death of Alan Hall in May 2015 and we now feel that same massive loss and sadness at Chris’ passing. In a short time we have lost two giants who still had much to give and we miss their scientific insights, their vision and their rigor.

This year Chris received the Centenary Award from the Biochemical Society, and was due to receive the medal at the 78th Harden in Winchester in September. He did not make it, but his second wife Lesley and his eldest son Joe honoured us by attending the conference to receive the medal on his behalf.

Outside the lab, Chris was a talented cyclist who excelled on the hills, and although a lover of fine food and wines, he still appreciated the pleasure to be had from a simple dinner of egg and chips. He was a family man who was proud of his three children and four grandchildren. Chris is missed by his family, his many friends and colleagues, and his cycling buddies.

In the pub, he once smiled mischievously and said “Our lives are pretty meaningless and nobody will remember us once we are gone, so let’s have some fun”, then drank his pint. He was wrong. His life was full of meaning and we remember him and what he achieved. If we see further than he saw, it is because we are standing on his gigantic shoulders.

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The Centenary Award is awarded annually to a biochemist of distinction from any part of the world. In 2011, to celebrate its first 100 years, the Biochemical Society introduced this award to replace the Jubilee Lecture. Previous recipients of the Centenary award include Nahum Sonenberg, David Baker and G Marius Clore. Professor Marshall was due to give his lecture at the 78th Harden Conference entitled ‘Protein Kinases in Health and Disease’, 15–18 September 2015, Norton Park Hotel, Winchester. The author, Richard Marais, a colleague and friend of Professor Marshall presented a talk on his life and work in the slot in which Professor Marshall was due to speak, after which Dr Steven Ley presented the medal to Professor Marshall’s son, Joe and wife, Lesley, who attended the lecture.