Yasutomi Nishizuka

1932–2004

Yasutomi Nishizuka, ex-President and Professor Emeritus of Kobe University, died suddenly in Kobe on November 4, 2004. Nishizuka was born in Ashiya City (Hyogo Prefecture, Japan) on July 12, 1932 and was made famous by his discovery of protein kinase C. He will be sadly missed by all who knew him.

Nishizuka obtained his MD (1957) and PhD (1962) from Kyoto University, and — except for a year at Rockefeller University with Nobel laureate Fritz Lipmann — remained there until 1969. His work during that period included studies on the biosynthesis of nicotinamide adenine dinucleotide (NAD), the involvement of GTP in ribosomal protein translation and ADP-ribosylation by diphtheria toxin. In 1969 he became professor and head of the Department of Biochemistry at Kobe University, where he established an outstanding research group focused on the roles of protein kinases in signal transduction.

When he and his colleagues identified a novel protein kinase that required membrane phospholipids and Ca^{2+} ions, and dubbed it protein kinase C (PKC; Takai *et al.* *J. Biol. Chem.* **252**, 7603–7609; 1977 and Takai *et al.* *J. Biol. Chem.* **254**, 3692–3695; 1979), this was the start of a sequence of remarkable results. They found that ‘contaminants’ in the initial phospholipid samples were needed for PKC activation: a ‘trace’ of unsaturated 1,2-diacylglycerol was the key. This evoked a most improbable insight: the activating diacylglycerol — to most of us, a common and fairly boring lipid — might be a novel second messenger generated by receptor-stimulated phosphoinositide hydrolysis (Takai, Y. *et al.* *Biochem. Biophys. Res. Commun.* **91**, 1218–1224; 1979).

To validate this extraordinary idea, they showed that treating platelets with a combination of a Ca^{2+} ionophore and a membrane-permeant short-chain diacylglycerol mimicked stimulation by the aggregating agent thrombin. This yielded a remarkable conceptual synthesis that pre-dated recognition of the Ca^{2+} -mobilizing ability of inositol 1,4,5-trisphosphate — that simultaneously generated diacylglycerol and Ca^{2+} signals might stimulate cells synergistically (Kaibuchi, K. *et al.* *Cell Calcium* **3**, 323–335; 1982, from which the figure comes).

With Monique Castagna, Nishizuka and his colleagues then discovered that PKC is the biological target of tumour-promoting phorbol esters (Castagna, M. *et al.* *J. Biol. Chem.* **257**, 7847–7851; 1982). This discovery both fixed PKC at the heart of normal and pathological cell control and provided convenient tools for manipulating PKC activity in intact cells.

These papers provided the base from which an enormous amount of work on the complex PKC family has grown, much of it from Nishizuka's group, that still continues apace. Nishizuka was also a cogent and prolific review writer. One of his reviews was the most-cited publication of the 1980s (Nishizuka, Y. *Nature* **308**, 693–698; 1984), and there is no more telling comment on his influence than the fact that his papers have amassed more than 40,000 citations to date.

It was always a delight when arriving at a meeting to find that Yasu was going to be there, especially during the heady days of the early 1980s during which the lineaments of phospholipase C-based signalling were finally becoming clearer. He always brought some scientific surprise, and contributed to every discussion with rigour and good humour. And if the meeting was in Japan, he took great pride in ensuring that his visitors got the best — whether it was stunning autumn foliage in Kyoto or his favourite noodle restaurant.

In 1975, one month after the catastrophic Kobe earthquake, Nishizuka assumed the presidency of the University of Kobe, which he held until 2001. When asked about the impact of the earthquake on research in Kobe, his response was characteristically optimistic — that it would have little effect on ‘creative’ science.

Nishizuka received many honours, including the Order of Culture (Japan, 1988); The Gairdner Foundation International

Award (1988); The Kyoto Prize (1992); the Albert Lasker Basic Medical Research Award (1989); the Wolf Prize in Medicine (1995); and The Schering Prize (1995). He was elected a foreign member of many academies, including the National Academy of Sciences of the USA (1988) and the UK Royal Society (1990). He was often mentioned as a possible future Nobel laureate.

The Kobe earthquake heavily damaged Nishizuka's house in Ashiya City, and it was rebuilt to a design of his younger daughter Tsukiko Hanibuchi. It was here that his family carried out his funeral ceremony on November 6 and 7.

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