Obituary

Remembering Michael S Neuberger (1953–2013)

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Michael Neuberger died in Cambridge on 26 October 2013, surrounded by his loving wife Gill and children, Saskia, Lydia, Thomas and Benjamin. He now rests in peace next to their house in Suffolk. A particularly aggressive myeloma ended most prematurely a life full of science, human relationships, fatherhood, *joie de vivre*, understatement and humour. ‘Shut up, you fat face’ Michael said once as he picked up the phone, thinking it was Franco Calabi playing yet another game. We realized it was not Franco when Michael turned purple and said ‘Oh, good afternoon Sir’ (it turned out he was talking to the Director General of the MRC). After a few minutes of total embarrassment, we started laughing, only to resume our discussion about antibodies.

Michael was a gentle and generous person, an outstanding scientist and mentor. After his PhD in Biochemistry with Brian Hartley in London, Michael went to work with Klaus Rajewski in Köln, on César Milstein’s recommendation that he should learn some immunology before joining the LMB in Cambridge. Here, Michael spent his brilliant career, soon becoming one of its pillars, as Joint Head of the PNAC Division and Deputy Director. His contribution to immunology and biotechnology research is legendary, his work always rooted in his profound interest in basic science. Moreover, his ground-breaking contributions on antibody expression and diversification have implications that go far beyond immunology, impacting cancer, virus biology and DNA stability.

Michael’s pioneering work on antibody engineering was an important part of what is often called the ‘antibody revolution’. In a landmark paper in 1984, the Fc portion of an antibody was substituted by an active enzyme moiety—as he put it ‘the introduction into lymphocytes of immunoglobulin-gene DNA that has been manipulated *in vitro* allows the production of novel antibodies’ (Neuberger *et al*, 1984). This simple yet powerful idea paved the way to derive the first chimaeric mouse–human (with Terry Rabbitts) and humanized (with Greg Winter) antibodies, and subsequently for inserting a human Ig locus into lymphocytes of transgenic mice and for redirecting antibodies to novel intracellular compartments. These experiments were made possible by the vectors that Michael engineered to study Ig transcription, an endeavour that led to discovering the IgH enhancer (Neuberger, 1983).

While these advances sparked a revolution in biomedical research, industry and society, Michael considered them with great understatement a ‘divertissement’, satisfied to show the proof-of-concept. His lifetime ambition was to solve the antibody ‘GOD problem’ (generation of diversity). When Michael entered the field, at the beginning of the 1980s, the discovery of VDJ joining by Susumu Tonegawa and colleagues had relegated somatic mutation, one of the first theories put up to address GOD, somewhat to the back seat. In their classic *Nature* paper, Brenner and Milstein wrote ‘We cannot propose a definitive test of this theory apart from the

Michael Neuberger (right) and César Milstein in the LMB library, 1998. With permission - Visual Aids LMB, MRC.

direct demonstration of a cleaving enzyme and a mutagenic polymerase in precursor cells, which may not be easy to do' (Brenner and Milstein, 1966). Indeed, it was over 30 years later that Michael demonstrated the mechanism responsible. By the end of the 90s, Michael's, César's and other labs had characterized many features of somatic mutation and the quest for the mechanism was heating up worldwide when, while studying class switch recombination, Tasuku Honjo and colleagues identified AID, proposing an RNA editing mechanism. This was, at first, an anticlimax for the Cambridge dream team. Yet, Michael was convinced that the new enzyme had to act on DNA and was directly responsible for the mutations at G:C pairs. In a remarkable *tour de force*, he demonstrated deamination of cytosine bases on DNA by AID as the mechanism of somatic mutation (Petersen-Mahrt *et al.*, 2002), as well as gene conversion (Harris *et al.*, 2002) and class switching (Rada *et al.*, 2002). The discovery of DNA deamination by AID provided the unifying missing piece of the GOD jigsaw and allowed many testable predictions to be made (Di Noia and Neuberger, 2002). Although there was no precedent for any physiological programme in vertebrates that depended on targeted deamination of DNA, invoking such a mechanism of AID action immediately suggested explanations for several previously unconnected observations. In Michael's words, the 'DNA deamination model then simply fell out on us', underlining that it was the result of a 'resurgence of hypothesis driven research', something that he felt intellectually and aesthetically particularly gratified by.

Sharp, always quick to get to the core of questions and pervaded by natural empathy, Michael has been an ideal mentor for flocks of students and colleagues, whose only problem was to cope with his quick-fire thinking and even

faster talking (and mumbling). But what a joy when one guessed right! And what a joy to see the Milstein–Neuberger–Winter trio share their different styles and accents to satisfy their thirst for knowledge and together drive the antibody revolution.

Among the many awards and recognitions in Michael's much too short life, he enjoyed the rare privilege of sharing the membership of the Royal Society with his father, a distinguished glycoprotein biochemist. An EMBO member and a Fellow of Trinity College, where he was Director of Studies in Natural Sciences, Michael was recently elected as a foreign associate of the US National Academy of Sciences. A lover of music, when asked about his piano lessons, he generally smiled, quoting his teacher telling him '*Michael, you might consider taking up another instrument*'.

He worked throughout his illness, saying that he found it convenient to have the hospital so close to the lab, so that he could shuttle between the two. In the last few months, he felt like Moses, having brought the people across the sea to the new LMB building but not being able to get there himself.

In 1967 Niels Jerne wrote 'as this younger generation of professionals is pressing rapidly towards the definitive solution of the antibody problem, we older amateurs had perhaps better sit back, waiting for the END'. Michael did provide the end of the scientific story of somatic mutation.

'Now I imagine Michael knocking at the Heaven's door, apologising for being early' said a friend, summarizing his sweet and natural kindness well. Far, far too early.

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