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Professor Michael Neuberger: Biochemist behind life-saving work on the immune system

He was seen as an outstanding mentor, with his sharp intellect and ability to get to the core issue

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Professor Michael Neuberger was pivotal to the great advances in biomedical research, with his unravelling of the mysteries of human antibodies. A Fellow of Trinity College, Cambridge where he was a director of studies in Natural Sciences, he was also deputy director of Cambridge's Medical Research Council Laboratory of Molecular Biology (LMB).

With the demand for a new class of drugs to fight diseases, such as cancer, as well as immune disorders such as rheumatoid arthritis, the bio-tech industries have shown rapid growth.

Over 25 years, Neuberger made significant discoveries in the molecular mechanisms of antibody gene expression and diversification, as well as important contributions to the major technologies underpinning antibody engineering. This helped spark a

multibillion-pound world bio-technology industry revolution within the pharmaceutical industry. Seventeen of the top 20 companies now having R&D and manufacturing and sales sites in the UK.

Widely viewed as an exceptional scientist, Neuberger discovered key aspects of how the production of antibodies is controlled in lymphocytes – the antibody-producing cells. He contributed to the antibody revolution initiated by the discovery in the 1970s, by César Milstein and George Köhler, of monoclonal antibodies. He also contributed towards the engineering of therapeutic antibodies, as pioneered by Greg Winter. The work by Milstein and others had made clear that mutation of antibody

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genes was at the core of the creation of diversity, but it was Neuberger who finally identified a protein called AID, required for the mutation process. With a series of elegant experiments using genetics and biochemistry, he demonstrated that this was indeed the case.

Recognition of pathogens by the immune system is the first step in promoting immunity. The ability to vary – mutate – their molecular components at speed is the main trick that pathogens – bugs and viruses – exploit to evade host attempts to neutralise or destroy them. Antibiotic resistance and the seasonal changes in flu strains are examples of this. The immune system responds by going to enormous lengths to create diverse pathogen recognition receptors.

Neuberger’s research revealed a key molecular process, known as DNA deamination, that promotes immunity to pathogens through the mutagenesis of antibodies – protein molecules in the body fluids which confer immunity and are elicited by vaccination – and through intracellular proteins which prevent viruses and parasites from multiplying in cells. In the case of antibodies, this mechanism involves programmed mutation of the tiny region of the genome containing the genes that produce the antibody proteins, by removing a chemical part in one of the four building blocks of DNA, the cytosine base. The cells’ own repair and maintenance tools then propagate the mutations in the DNA and allow lymphocytes to evolve their antibodies, to catch up with the changes in viruses and other pathogens.

The efficacy of antibodies depends on the ability to rapidly adapt the recognition part of the molecule, to improve the binding to pathogens. (This is a kind of fast Darwinian evolution by mutation and selection within the immune system known as somatic hyper-mutation). But it also depends on the flexibility to swap the effector part of the molecule to couple pathogen recognition to alternative neutralising pathways. This process is known as isotype class switching.

These are the two mechanisms that are triggered by the “deamination” or chemical modification of cytosines in antibody genes. Deamination of cytosines in the genetic code of viruses cripples their ability to infect other cells and prevents their spread. The versatility of antibodies and their biological activity is the basis for their increasing and extensive use as therapeutic drugs.

Born in London in 1953, Michael Samuel Neuberger was the youngest of four sons of the distinguished biochemist Albert Neuberger and former PhD supervisor of Frederick Sanger, a biochemist who was twice the

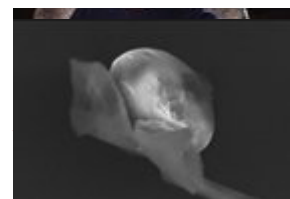


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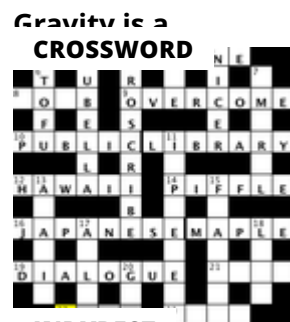


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recipient of the Nobel prize for Chemistry. When Hitler gained power in 1933, Albert moved to Britain and worked at St Mary's Hospital, London University, where he became a professor of chemical pathology. He later was the first to successfully prove the existence of glycoproteins – substances that perform an important role in the interactions between living cells. He was elected a Fellow of the Royal Society in 1951. Father and son enjoyed the rare distinction of both being fellows upon Michael's election in 1993.

Samuel's three siblings, all Oxbridge graduates, went on to excel in different fields. James is now an associate medical director for NHS Blood and Transplant and professor of medicine at the University of Birmingham; Anthony is a professor of finance at City University and is married to Rabbi Julia Neuberger. David Lord Neuberger of Abbotsbury, is president of the Supreme Court. A younger sister, Janet, who was born with Down's syndrome, died in her late twenties.

In the 1960s, Michael followed his brothers to Westminster School, where he excelled and progressed to Trinity College, Cambridge with a scholarship to read Natural Sciences. Upon graduation with a First, he undertook/commenced a PhD in biochemistry with Brian Hartley at Imperial College, London. In 1977, his PhD dissertation on enzymes in the bacterium *Klebsiella aerogenes* won him a research fellowship at Trinity and, after a year of post-doctoral work at Imperial and at the University of Cologne on a European Molecular Biology Organisation fellowship (studying immunology under Klaus Rajewsky), he joined Milstein at the LMB.

In 2002, Neuberger was appointed professor of Molecular Immunology. He received many awards including the Novartis Medal (Biochemical Society), the William Bate Hardy prize, the Royal Society's GlaxoSmithKline Medal and the Dannie-Heineman prize. In May, he was elected Foreign Associate of the US National Academy of Sciences. He published over 150 manuscripts and was a Trustee of the Isaac Newton Trust.

In addition to his relaxed teaching style and scientific accomplishments, Neuberger was regarded as an outstanding mentor and was revered for his sharp intellect and his ability to get to the core of the question; he produced scores of young researchers both at the LMB, around the UK and abroad. Long-standing colleague Cristina Rada said, "The success of his influence was due to his unassuming and warm personality and his passion for learning, and he enjoyed talking about science."



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A generous and humorous man, Neuberger enjoyed music, walking, skiing and running, but ultimately spending time with his close-knot family. Though intensely proud of his Jewish heritage, he was not an overtly religious man.





Diagnosed last February with multiple myeloma, a disease of the cells that produce antibodies, Neuberger continued working until a fortnight before his death at 59. The irony of his disease was not lost on him.

Martin Childs

Michael Neuberger, born London 2 November 1953; married 1991 Gill (one son, two daughters); died Cambridge 26 October 2013.



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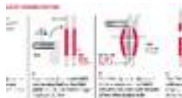
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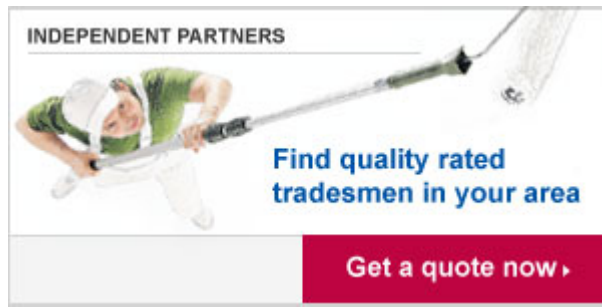
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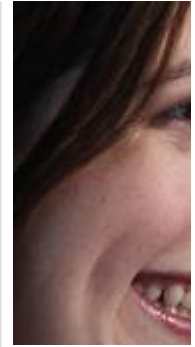
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