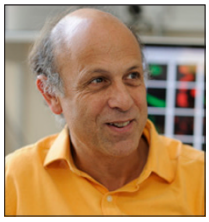

Michael S. Neuberger 1953–2013

Cristina Rada

Michael Samuel Neuberger, one of the most brilliant molecular immunologists of his generation, died on 26 October 2013, just short of his 60th birthday. At the time of his death he was probably most widely known for delineating the role of DNA deamination in immunity through his pioneering work that explained how cytosine deamination drives the somatic hypermutation and class-switch recombination of antibody-encoding genes. Following the identification of activation-induced cytidine deaminase (AID) by Honjo and Durandy as the protein essential for both of those processes, Michael produced a series of seminal papers during 2002 that laid bare the mechanism that had perplexed immunologists for 30 years. The now-textbook scheme describes how by deaminating deoxycytidine in the variable domains of rearranged immunoglobulin-encoding genes, AID creates uracil residues and thus, on its own or through the action of uracil DNA glycosylase, triggers the mutagenic cascade that drives affinity maturation. This insightful model also provided an explanation for how AID induces class-switch recombination by focusing deamination on both strands in the switch repeat sequences, which leads to recombination-inducing double-strand breaks. Michael found it intellectually pleasing that the answer to the puzzle of antibody diversification had such an elegant and logical simplicity. His work spawned a new field studying programmed deamination both by AID and its relatives, the APOBEC proteins, that has had ramifications for processes as diverse as the restriction of viral replication and the generation of the highly clustered mutations ('kataegis') seen in some cancers, all areas in which he led and left his mark.

Michael's earlier work has arguably had an even broader and more practical impact. He was the first person to be able to ectopically express immunoglobulin-encoding genes in lymphocytes, work that resulted in the identification of the key enhancer elements that control expression of immunoglobulin light chains. This technology was also instrumental in the invention of CDR (complementarity-determining region) grafting, in collaboration with Greg Winter, and later led to the generation of mice that produce wholly human transgene-encoded antibodies and the foundation of a now multi-billion-dollar industry.

Michael was born 2 November 1953 into an academically gifted family. His father, Albert Neuberger, was a noted biochemist who founded the modern field of glycobiology and who, coincidentally, supervised Fred Sanger's Ph.D. In 1974, after graduating with a First class Honors degree in Natural Sciences from Trinity College, Cambridge, Michael joined Brian Hartley as he moved from the Laboratory of Molecular Biology to head the Department of Biochemistry at Imperial College in London. There he joined Greg Winter as a fellow graduate student, the start of an amicable competition and lasting friendship. Michael's Ph.D. work on characterizing gene amplifications in bacteria won him a research fellowship back at Trinity College and the freedom to start research in any laboratory that would host him. He sought advice from Sydney Brenner, who suggested approaching César Milstein and—if he could get more 'yes' than 'no' responses during the conversation—joining César's subdivision of protein chemistry at the Laboratory of Molecular Biology to study antibodies. 'Yes' responses prevailed, but César recommended that he first go and learn some immunology, so Michael joined Klaus Rajewsky's laboratory in Cologne for 18 months before returning to Cambridge and the Laboratory of Molecular Biology, where he remained for the rest of his career, becoming head of the Protein and Nucleic Acid Division and deputy director. He was elected to the Royal Society before the age of 40, a source of particular pride for his father and a very rare concurrence of father and son as Fellows. Only this year, he was elected a Foreign Associate of the United Stated National Academy of Sciences, a rare honor for a non-US citizen.

Michael's influence extends well beyond his towering scientific contributions. He was a devoted teacher of undergraduates at Trinity and an exemplary but exacting mentor to his graduate students and postdoctoral fellows in his laboratory and to junior group leaders at the Laboratory of Molecular Biology, always ready with good counsel and sharp questioning. His graduate students and postdoctoral fellows will remember vividly the final stages of writing papers with Michael, which involved sitting in his tiny office perched on a wooden stool, seemingly hovering far above the action, as Michael tapped furiously with one finger (the thumb of his other hand operating the 'shift' key), muttering "Don't say anything!" as sentences were honed to perfection. As Julian Sale, a former student, recalls, "In those times you entered part of his mind. It was not always a comfortable place to be, endlessly challenging but always stimulating and fascinating." He left an indelible mark on his numerous scientific 'offspring' who have gone on to establish their own groups and all of whom try to emulate the 'Neuberger school' of absolute rigor and precision of thought. Michael was the embodiment of Max Perutz's aphorism "Good science needs no rhetoric, only clarity."

The irony that his illness, myeloma, was caused by a tumor that secreted immunoglobulin-κ light chain was not lost on him. He carried on, as ever supported by his remarkable family: Gill, an Australian doctor, whom he married in 1991, and his four children, Saskia and Lydia, both at university, and Thomas and Benjamin, still at school. He will be sorely missed by all those whose lives, careers and science he touched.

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