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Rajewsky, K.

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Michael S. Neuberger 1953-2013

Klaus Rajewsky[1]

[1] Max-Delbrück-Center for Molecular Medicine, 13125 Berlin, Germany

Michael Neuberger's untimely death on October 26 last year was a shock for his friends and the scientific community. The many obituaries written about him by friends and colleagues testify to his unique, overarching stature as a scientist, colleague, and human companion. I am writing this retrospective mourning a personal friend and irreplaceable loss.

Michael's father, Albert Neuberger, came from a Jewish family in southern Germany, where he got his education as a biochemist but lost his position shortly after Hitler came to power, and emigrated to the United Kingdom, which became his home country. He pursued a highly successful academic career in Cambridge and London, and became one of the leading biochemists in the country and an elected Fellow of the Royal Society. He and his wife Lilian née Dreyfus had four sons, who all pursued distinguished careers in higher education. Michael, the youngest, studied Natural Sciences at Cambridge and then did his PhD work in Brian Hartley's laboratory at Imperial College in London, on gene duplication in bacteria. On the basis of this work, he was elected to a Research Fellowship at Trinity College, Cambridge, and it was there that Michael sought advice from Sidney Brenner at the Medical Research Council laboratory of Molecular Biology (LMB) about how to pursue his interest in the emerging area of molecular immunology. Sidney referred him to César Milstein (whose mentor at the LMB had been Fred Sanger, a former PhD student of Albert Neuberger), who had developed, with Georges Köhler, the hybridoma technique for the production of monoclonal antibodies, a Nobel-winning achievement. To my personal good luck, César advised Michael to first do a postdoc in my laboratory in Cologne, Germany, to learn some immunology.

Thus, one day in 1979, Michael appeared in my office at the Genetics Institute to explore the situation. We had just learned, with César's help, to produce monoclonal antibodies, and had begun to use the hybridoma technique for various purposes, among them the dissection of the antibody response itself. After having spent a day of discussions in the laboratory, Michael decided to join ongoing efforts to isolate somatic cell variants by fluorescence-activated cell sorting (FACS), with the help of monoclonal antibodies recognizing different epitopes on a given target cell-surface molecule. His molecule of choice was surface Ig on hybridoma cells, where he planned to isolate variants that had selectively lost a variable region determinant (as recognized by an "anti-idiotypic" monoclonal antibody), and thus to study somatic antibody diversification, the subject that would occupy him until the end of his life.

It was clear from the first minute that Michael was an exceptional, almost frighteningly clever young scientist. Bare of any real knowledge of immunology, he produced an EMBO long-term fellowship application in a single morning in the institute's library, to be sent off—essentially unmodified—in the afternoon of the same day, and granted shortly thereafter. The eighteen months he spent with us were most enjoyable, entertaining, and productive, although the hybridoma cells turned out to be unsuitable for the study of antibody somatic hypermutation (SHM). Thus, when Michael returned to the LMB in Cambridge, he had familiarized himself with immunology and published two interesting papers on families of monoclonal antibodies sharing identical V regions although differing in antibody class, but SHM remained to be resolved. The future looked bright, however, with him and César Milstein working at the LMB side-by-side.

Using the antibody system to study the control of gene expression at a molecular level, Michael discovered and characterized enhancer elements in the Ig gene loci and developed, together with his office neighbor Greg Winter and others, the first tools for the expression and engineering of recombinant and humanized antibodies. He thus became one of the founders of this vast field of present-day "translational" research. However, his main interest remained the control of the antibody response. Although he contributed in highly original and major ways to such issues as the mechanisms of B-cell activation by antigen and of immunological tolerance, his real passion continued to be the problem of the somatic diversification of antibody specificity. And it is here that his scientific genius struck most dramatically.

Following the generation of the primary antibody repertoire by Ig gene rearrangements, antibodies are further diversified by SHM and class-switch recombination (CSR), a process by which antibodies acquire distinct effector functions. A third diversification mechanism was discovered during those years, namely the modification of expressed variable region genes in chickens, through gene conversion mediated by upstream pseudogenes. Work on these issues was carried out in many laboratories around the world, including the compilation of large sets of DNA sequences, from which salient features of the SHM process became apparent. Michael and the LMB group were involved at all levels and repeatedly came up with conceptually new insights. Thus, during a time in which analyses of the role of error-prone DNA polymerases in SHM were in the center of interest, along the lines of the 1966 Brenner-Milstein model of SHM, Neuberger and colleagues interpreted differences in the targeting of C:G versus A:T base pairs in certain cell lines and upon ablation of a mismatch repair-sensing enzyme as a reflection of two distinct stages of SHM, with the targeting of C:G pairs (and C:G-based mutational hot spots) at its initiation. Further, working on Ig gene conversion, they produced genetic evidence that the gene conversion process could be converted into SHM by ablation of components of the homologous recombination machinery. And finally, they came up with the notion that SHM and CSR, although seemingly distinct processes, may be mechanistically related.

Thus, when in a landmark discovery Activation Induced Cytidine Deaminase (AID) was identified by Tasuku Honjo's group in 1999 and subsequently shown to control both SHM and CSR in mice and humans (and later, also gene conversion in chickens), Michael's mind was set to interpret AID function not in the context of its homology to APOBEC1, an RNA-editing enzyme, but in the frame of the idea of an initial targeting of C:G base pairs in DNA. To quote him (1), "It was an interleaving of the discovery of AID with previous information about antibody mutation spectra that led [me] to the formulation of the DNA deamination model of antibody diversification" (1). In the by now famous paper describing the new model (2), Neuberger and colleagues presented evidence in bacteria that AID could indeed function as a DNA mutator through C→U conversion. In a flurry of subsequent papers from Neuberger and colleagues and several other groups, the DNA deamination model received further support from biochemical and genetic experiments, including analyses in chicken, mouse, and human B cells, and is now widely accepted in the community.

For Michael, these times of scientific synthesis, with a unifying mechanism of postrearrangement antibody diversification emerging, must have been deeply satisfying. In the spring of 2002, he contacted me at the Center for Blood Research at Harvard Medical School and, in an unusual initiative, offered to give a seminar. This memorable event took place on July 30 at 9:30 AM in our packed small lecture hall, a few weeks after his paper on the deamination model (2) had appeared. Since then, it has become apparent that DNA deamination by APOBEC family members plays a critical role beyond the immune system, in processes such as intracellular defense against viruses and acquisition of mutations in cancerogenesis. Michael contributed substantially to this new field of research. In a paper typical for him in its elegance, published a few months before his death, he and his

colleagues showed that in a yeast model system APOBEC proteins can generate large stretches of clustered mutations similar to the “kataegis” seen in many cancers (3).

Michael stayed at the LMB, where he became head of the Protein and Nucleic Acid Division and deputy director. He always worked with only a small group of people. He received many awards and honors, prominently among them his election to the Royal Society at young age, and in 2013, the National Academy of Sciences of the USA as a Foreign Associate. He was a brilliant scientist of the highest caliber and an inspiring, caring academic teacher, colleague, and friend, with a genuine interest in other people’s work and lives, always being encouraging, full of energy, and ready to help. Deeply attached to his family and homes in Cambridge and East Anglia, he loved to travel because of his insatiable curiosity about the world. He spoke affectionately and with great respect about collaborators and colleagues, notably also the young group leaders he mentored at the LMB, and he has left his mark on generations of young scientists. Meeting him was like continuing an uninterrupted dialogue, about science, books, history, and whatever else was on one’s mind. I still cannot believe that this dialogue has now ended.

Author contributions

K.R. wrote the paper.

Corresponding Author

[1] E-mail: klaus.rajewsky@mdc-berlin.de

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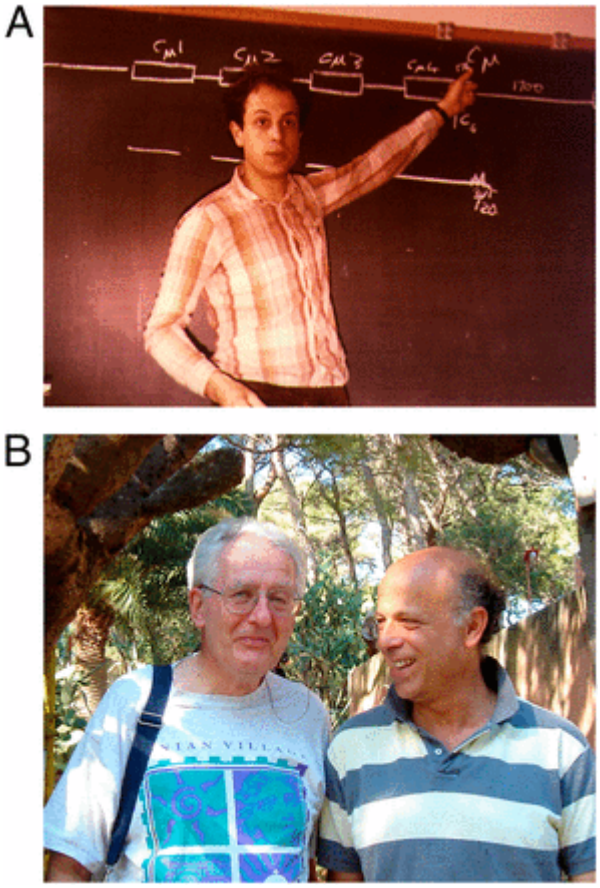

Fig.1: Michael Neuberger at the Genetics Institute in Cologne, 1981 (*A*), and together with the author at a FEBS course on immunology in Croatia in 2007 (*B*). Michael had been teaching and inspiring young scientists at this biannual summer school for decades.