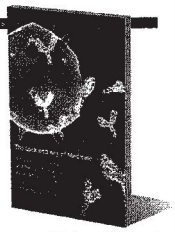
IMMUNOLOGY

The quest for a magic bullet

Widely used in science and medicine today, monoclonal antibodies got off to a rocky start

By **Sudhakaran Prabakaran**



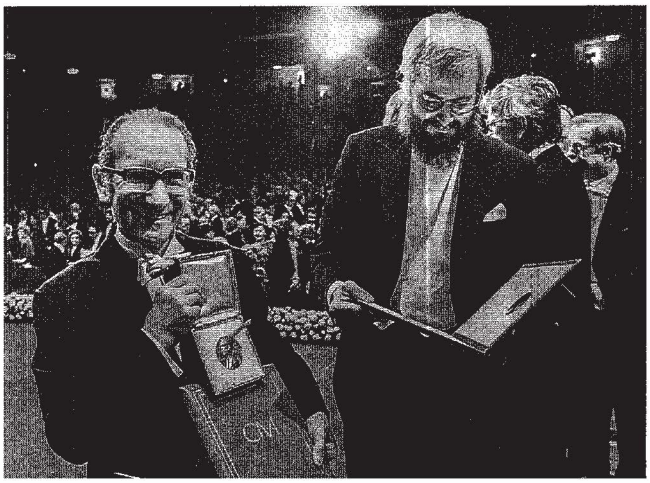
The Lock and Key of Medicine
Monoclonal Antibodies and the Transformation of Healthcare
Lara V. Marks
Yale University Press, 2015.
344 pp.

On a cold January evening in 1975, postdoctoral fellow Georges Köhler brought his wife to the lab to keep him company as he checked on his latest experiment. Far from the uneventful evening he anticipated, what he observed that night would transform the world of drug development and disease treatment. "I looked down at the first two plates. I saw these halos.... It was the best result I could think of," he recalls. The halos were evidence that the cells in the petri dish were secreting highly specific antibodies. Dubbed "monoclonal antibodies," or Mabs, they would have a radical influence on both science and medicine in the years that followed.

In her book, *The Lock and Key of Medicine,* Lara Marks presents a compelling, well-researched account of the discovery of Mabs and the development of Mab-based treatments and therapies. The book also narrates the challenges faced by César Milstein (Köhler's postdoctoral adviser) and his collaborators, from patenting their findings to raising money for further testing and scaling up production. It is an excellent account of all the impediments the researchers faced in bringing Mabs from the bench to the market. Personal stories of the major players involved are skillfully interwoven with the narrative, bringing a human face to the drug discovery process.

In the early 1970s, Köhler and Milstein were studying the variable regions of antibodies—the proteins that recognize foreign molecules and tag them for destruction—with the hope of understanding how diverse populations of antibodies are generated by the mammalian immune system. In the course of their studies, they developed a technique that enabled the mass production of antibodies designed to recognize a specific antigen. The technique involved fusing a myeloma cell with an antibody-producing B cell taken from the spleen of an immunized mouse. The B cell provided the immunological specificity, whereas the myeloma lent immortality to the construct.

These hybrid cells, or hybridomas as they were later called, became a vehicle for thousands of other biomedical inventions. However, the initial reception to this breakthrough was lukewarm. When they tried to publish their results, the editors at *Nature* reportedly requested that the article be shortened and did not feature it prominently in the journal, and their patent application was rejected.



César Milstein (left), Georges Köhler (right), and Niels Jerne (not pictured) were awarded the Nobel Prize in 1984 for their work on monoclonal antibodies.

Milstein sent samples and protocols of his newly created antibody-secreting cell lines to other research institutions and even trained scientists to generate their own hybridomas. One such scientist who benefited from this goodwill was Hilary Koprowski, director of the Wistar Institute in Philadelphia. The first patents for monoclonal antibodies were granted to Koprowski and his colleagues in October 1979 (for Mabs targeting influenza antigens) and April 1980 (for Mabs targeting tumor antigens). The "Wistar patents" proved controversial in the scientific community, because the antibodies had been created using the cell lines originally supplied by Milstein.

In the years that followed, there was an explosion in Mab research. Some were generated to identify different types of white blood cells, and several proved to be important in investigating HIV/AIDS. The first medical application of this technology used Mabs to purify interferons, signaling proteins that are released by cells in response to the presence of pathogens.

Mabs were soon being used to identify blood group types, an application that radically improved the accuracy and cost of blood typing. This now-routine test has since saved millions of lives.

After these initial success stories, many clinicians and founders of biotech companies began to believe that Mabs were "magic bullets" for diagnosing and curing diseases. In 1979, Koprowski cofounded Centocor, one of the original companies that exploited Mabs to diagnose cancer, cardiovascular disorders, and liver problems. The fortunes of Centocor ebbed and flowed during the 1980s and 1990s. It was acquired by Johnson & Johnson in 1999 and is known today as Janssen Biotech. It is one of the few original companies still in existence today.

In 1995, edrecolomab (Panorex)—a Mab developed in mice—was licensed by German authorities as an adjuvant therapy for postoperative colorectal cancer. It was the first Mab-based cancer therapeutic to proceed to market. In 1997, rituximab (Rituxan), a chimeric (part human and part mouse) Mab, was authorized by the FDA to treat B cell lymphoma. It was later found to be beneficial in the treatment of rheumatoid arthritis as well.

By 2012, there were more than 30 Mab drugs on the market, generating more than $50 billion in revenue (10 of which generated profits exceeding $1 billion each). The number of Mab-based therapies (and their market share) will likely increase with time.

Marks has done great justice to the topic, although the book would have been strengthened by the inclusion of additional illustrations and a broader discussion of the impact of Mabs on basic science. This book is in many ways a tribute to Köhler and Milstein, which makes the timing of its publication (just over 40 years since that fateful January evening) all the more appropriate.

The reviewer is at Science Signaling, AAAS, Washington, DC 20005, USA. E-mail: sprabaka@aaas.org

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