Magic bullets to blockbusters

Marian Turner delves into a history of the rapid rise of monoclonal antibodies.

In 2003, freshly graduated from university, I made a monoclonal antibody. After weeks of waiting for the mice that I had immunized with *Acanthamoeba* parasites to mount a robust immune response, I fused some of their spleen cells to cells derived from a mouse myeloma cancer. The aim: to generate immortal hybridoma cells, from which I could purify an endless stream of specific antibodies that bound to the parasites.

The protocol I used was a barely refined version of one described by biologists César Milstein and Gorges Köhler in the United Kingdom almost three decades before. Hybridoma technology spawned the broad-reaching field of monoclonal antibodies, which is celebrated by historian of medicine Lara Marks in *The Lock and Key of Medicine*. Essential reagents in any cell-biology laboratory, monoclonal antibodies are now also common in medicine, from pregnancy testing to blood typing and disease diagnostics.

Marks begins by summarizing scientists' early attempts to understand protective immunity and vaccination. The term magic bullets, coined by German physician Paul Ehrlich (who died 100 years ago next month) in his 1897 description of antibodies, is held up as an early beacon of researchers' hopes for antibodies in medicine. As Marks shows, the hypotheses of pioneering scientists, amazingly, have often only just missed the mark. Ehrlich's description of a cell producing 'side chains' that break off as antibodies in response to encountering foreign substances is remarkably close to our current knowledge of surface immunoglobulins and secreted antibodies. The book's early chapters also chronicle how physicians of the 1920s and 1930s developed serum-based therapies decades before anyone understood the basic mechanisms of antibody action.

There were high hopes for the revenue potential of monoclonal antibodies, but not everyone was convinced at first. Marks describes how the National Research and Development Corporation in the United Kingdom initially failed to see the practical applications. As a result, the original hybridoma technology was not patented. In 1979 and 1980, US scientists won patents for essentially equivalent technology using myeloma cells provided by Milstein — a development that left many in Britain chagrined, including then-prime minister Margaret Thatcher.

Such early hiccups were soon replaced

The fundamental protocol for making monoclonal antibodies has changed little in 40 years.

by focused commercialization, leading to an exponential rise in patents and several intellectual-property battles. Although some scientists have found this unpalatable, antibody-related royalties have been ploughed back into medical research — by 2012, the UK Medical Research Council's patents alone had earned £486 million (US\$770 million).

The possible ways of modifying antibodies have surged in the 40 years since Milstein and Köhler published their hybridoma protocol. Marks discusses the generation of antibody fragments, chimaeric antibodies and 'humanized' antibodies — products from non-human cells that have been modified to reduce unwanted immune responses. The unfolding antibody story paralleled advances in recombinant-DNA technology and transgenic animal models, which made such alterations possible. Yet it is mind-boggling that the first humanized antibodies were made before the advent of DNA-amplification technology.

The Lock and Key of Medicine: Monoclonal Antibodies and the Transformation of Healthcare
LARA V. MARKS
Yale Univ. Press: 2015.

'Humanized' also describes what Marks has done for the antibody story. *The Lock and Key of Medicine* presents rich details of who at which institute collaborated with whom on which scientific advance or commercialization process, and when. The meticulous accounts sometimes blur, but they convey a deep sense of the cumulative thought and effort embodied in today's antibody technologies, and remind us that interdisciplinary and international collaborations are not new. Readers in the field will appreciate the attention paid to defining episodes, such as the HLDA workshops starting in 1982, which resulted in classification and verification systems that brought coherence to the expanding catalogue of monoclonal antibodies.

In the closing chapters, Marks describes some of the monoclonals that have become blockbuster drugs: rituximab, infliximab and trastuzumab. The stories of these antibodies reflect how serendipitous clinical outcomes, such as cancer drugs successfully treating arthritis, have led to deeper understanding of the biology of both classes of disease.

There are some surprising gaps. There is no mention of the catastrophic 2006 phase I clinical trial of the monoclonal antibody TGN1412, manufactured by TeGenero to treat cancer and autoimmune diseases. The drug induced multiple organ failure in six healthy volunteers, caused by an unanticipated extreme immune reaction called a cytokine storm. The episode led to a revision of European guidelines for first-in-human trials. Also missing is a discussion of monoclonal antibodies that block the immune regulatory proteins PD-1 or CTLA-4, which are arguably the hottest up-and-coming agents in cancer therapy today, or of the use of HIV-specific monoclonal antibodies for treatment and vaccine design.

But it is a fast-paced field. The history of monoclonal antibodies ricochets between basic science, the clinic and the commercial world, and *The Lock and Key of Medicine* documents how lessons from one sphere have repeatedly led to advances in another. Marks concludes by pointing out that monoclonal antibodies have received less fanfare than their biotechnological peers, genetic engineering and stem cells. Her thorough telling of this rich history goes some way towards restoring the balance. ■

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