MONOCLONAL ANTIBODIES: THE INTERSECTION OF MEDICINE AND TECHNOLOGY

Michelle Ovanesian*

CITE AS: 1 GEO. L. TECH. REV. 220 (2017)

https://perma.cc/5EJX-N6UW

INTRODUCTION..................................................................................................................220

DISCUSSION ......................................................................................................................222
Antibodies defined.................................................................................................................222
Polyclonal versus monoclonal antibodies.............................................................................223
Monoclonal antibodies as therapeutics................................................................................224

CONCLUSION ....................................................................................................................227

I. INTRODUCTION

Biologics, such as the arthritis drug Humira, are therapeutics and diagnostics derived from living systems—as opposed to non-biologic drugs derived from chemical synthesis—and are often state-of-the-art treatment for many diseases.¹ Today, biologics account for at least one-third of all drug approvals, and the majority of biologics research and development is in monoclonal antibodies (mAbs).² Thirty years after they were first developed, biologics are treating or will soon treat the most costly and challenging diseases.³ One such disease is Alzheimer’s. Alzheimer’s disease is the most common form of dementia, and it currently affects more than five million Americans and costs the health care system more than $200 billion per year.⁴ As baby boomers age, estimates suggest that more than thirteen million Americans will suffer from the disease, with a cost of $1.1 trillion to the

---


² Defined below.

³ PhRMA, supra note 1, at 2-5.

health care system. A new drug that delays the onset of Alzheimer’s disease by just five years could save $367 billion in annual health care costs by 2050. In September 2016, favorable clinical trial results were published for a mAb called aducanumab, which may become the gold standard biologic treatment for Alzheimer’s.

However, a majority of future Alzheimer’s patients probably will not be able to afford the gold standard treatment—the average daily cost of a biologic is at least twenty-two times that of a non-biologic—and a biosimilar, a generic version of a biologic, may not yet have been approved for market entry. As with non-biologic generic drugs, a special approval process is in place to ensure the safety and efficacy of biosimilars. The public stands to benefit from a competitive biosimilars market; however, due to a recent court decision, biosimilars could be prevented from entering the market, even if they are approved as safe and effective. Nonetheless, biologics continue to offer great hope for patients, and they promise substantial revenues for the pharmaceutical industry. Several biologics already have sales of over $1 billion annually—for example, Humira had sales of $11 billion in 2013.

---

5 Id.
6 Id.
7 Note that drugs ending in “mab” involve or are a mAb.
8 Jeff Sevigny, The Antibody Aducanumab Reduces Ab plaques in Alzheimer’s Disease, 537 NATURE 50-56 (2016).
11 Momenta Pharmaceuticals, Inc. v. Teva Pharmaceuticals USA Inc., 809 F.3d 610 (Fed. Cir. 2015). Prior to marketing but after approval, batch-to-batch testing of biosimilars is required. Because biosimilars are complex, special analytical methods are used to compare batches of biosimilars. Often, these analytical methods are patented by the pioneer biologic developer and cannot be designed around. While a safe harbor from infringement liability exists for certain pre- and post-approval activities, Momenta II did not explicitly extend the safe harbor to analytical methods that have no non-infringing alternatives.
Because mAbs likely will continue to comprise a major portion of biologics on the market, they are an important part of the future of medicine and illustrate the intersection between health and technology.

II. DISCUSSION

This technology explainer addresses mAbs in detail. First, antibodies in general—what they are and how they are produced and work in the human body—will be discussed. Next, the difference between monoclonal and polyclonal antibodies will be established. Finally, the development of monoclonal antibodies in the pharmaceutical industry will be probed.

A. Antibodies Defined

Antibodies are large Y-shaped proteins that are produced in response to an invasion by a “pathogen” or foreign agent, such as a virus. They are created exclusively by a special type of cell formed in the bone marrow called B cells. When a pathogen enters the body, it encounters B cells because they are constantly circulating in the bloodstream looking for pathogens. Upon encountering a pathogen, B cells become activated and secrete antibodies which can selectively target the pathogen that was just encountered. As an analogy, when a person is missing in the woods and police (B cells) encounter an item that belonged to and smells like the missing person, they present that item to a trained dog (antibodies). The trained dog is on alert to the smell from then on and homes in on anything that smells like the item.

Once antibodies are created, a pathogen is handled by antibodies in two ways: 1) the pathogen is tagged for attack; or, 2) the pathogen is directly inactivated. When an antibody binds to an invading pathogen, the pathogen is then “marked.” Various types of cells and proteins are then recruited to kill the pathogen. Inactivation of the pathogen occurs when an antibody binds to and covers up an area on a pathogen that is crucial for its ability to spread.

14 Id.
15 Id.
16 Bruce Alberts et al., supra note 13.
17 Id.
18 Id.
B. Polyclonal Versus Monoclonal Antibodies

If you think of antibodies as your body’s arsenal against attack by diseases, the right weapon for the right job is important. In the same way that gun manufacturers make anti-tank and anti-aircraft guns, your body has specific B cells that make billions of specialized forms of antibodies to fight off a single pathogen. These billions of different forms of antibodies are referred to as “polyclonal antibodies.” Just as the anti-tank guns can be separated from the rest of the weapons, one form of antibodies can be isolated from the other forms and be used for study. These antibodies are referred to as “monoclonal antibodies.”

Monoclonal antibodies are used in therapeutics because, as will be discussed in detail below, they can be developed in large volumes and in identical, consistent, and pure batches. Additionally, they can be made to bind to a desired target with high specificity. Whereas polyclonal antibodies represent an arsenal of different weapons—some of which may work and some of which may not—monoclonal antibodies are more like combat drones because they are developed to attack only a particular region on a particular target. For example, with colon cancer, cancer cells overproduce a certain protein on their membranes. This protein exhibits minor differences from the protein found on healthy cells. In order to target the cancer cells and not the healthy cells, the minor differences between the two proteins need to be exploited. Monoclonal antibodies can be used to discriminate between the two proteins and target only the protein found on the membranes of cancer cells. Monoclonal antibodies also tend to be of higher affinity. Affinity refers to

---

19 Id.
20 Id.
22 SIGMA-ALDRICH, supra note 21.
24 Id.
25 Id.
the strength of binding between the pathogen and the antibody. An antibody of higher affinity is more effective because the antibody and pathogen come together like a lock and key that will not separate. Finally, compared to polyclonal antibodies, monoclonal antibodies are less likely to “cross-react,” or attack objects other than the desired target.

C. Monoclonal Antibodies as Therapeutics

Monoclonal antibody development for therapeutics involves the following critical steps: 1) target selection and validation; 2) determination of monoclonal antibody candidates; and 3) optimization of candidates. Each of the steps will be described below.

1. Target Selection and Validation

Target selection refers to the process of choosing a protein or peptide that can serve as a point of attack. In the case of Alzheimer’s, the target is a peptide called amyloid beta. Selection of a target involves searching a myriad of sources, such as genetic databases, patents, and publications, in order to identify a target that is reliably linked to the disease for which a therapeutic is desired. When choosing a target, a researcher must consider whether the target is homogenous, found in abundance, accessible, and either absent or in limited quantity on or in healthy cells. Homogeneity is important in a target because it allows researchers to focus on developing a single, highly specific type of monoclonal antibody. If a target comes in form A and form B, a mixture of monoclonal antibodies to target form A and form B would have to be developed, which would increase the complexity and cost of the process, while reducing the efficacy. Abundance is also essential so that a target is easier to attack, just like a group in a crowd is more easily

---

27 Id.  
28 Id.  
29 Heather H. Shih, *Discovery Process for Antibody-Based Therapeutics*, in *DEVELOPMENT OF ANTIBODY-BASED THERAPEUTICS* 9, 9-32 (Mohammad A. Tabrizi et al. eds., 2012).  
30 Id. at 10-13.  
33 Shih, *supra* note 29.  
34 Id.
targeted than a single individual in a crowd. Finally, accessibility is necessary so that a target can be reached. A target is deemed to be easily accessible when it is on the cell surface or is freely circulating in the body’s various vessels.

Target validation is the process of collecting evidence to confirm that the selected target is responsible for or an essential part of the disease sought to be treated. One experiment commonly used to confirm target selection involves using “knockout” (KO) cell lines and animals. Cell lines are cells that have been taken from a living organism but have been modified. The cells have been modified by using genes or viruses so that they are immortal and can be used in the laboratory over and over again without continually having to take a sample from a living organism. In a KO cell line or mouse, a gene responsible for the production of a certain protein or peptide—such as the gene that is responsible for the production of amyloid beta—has been deleted or “knocked out” in order to determine whether, without the gene, the disease still develops. If the disease does not develop without the gene, then the gene target is considered validated.

2. Determination of Monoclonal Antibody Candidates

Monoclonal antibody candidates are developed using hybridoma technology. Hybridoma technology involves: 1) immunizing an animal against the selected target, and using the animal’s B cells to form hybridoma cells; and 2) collecting and screening the resulting antibodies.

---

35 Id.
36 Id.
37 Id. at 13-14.
38 Fan, supra note 32.
40 Id.
42 Id.; Greenfield, supra note 21, at 202.
Immunization of the animal against the selected protein or peptide target—amyloid beta in the case of Alzheimer’s—involves transforming the target into a vaccine and administering the vaccine to animals. Following the initial vaccination, the animals receive additional vaccinations every two to three weeks until sufficient antibody quantities are reached. When sufficient antibody quantities have been obtained, the animals are euthanized and their spleens are removed. While B cells are produced in the bone marrow, they migrate to the spleen and lymph nodes in order to produce antibodies. Upon removal, the spleen is separated into its component cells, some of which are B cells. Then, the B cells are isolated and immortalized by fusion with an immortalized cell. The resulting immortalized B cell is referred to as a hybridoma cell. Immortalization is necessary because B cells survive for only limited periods of time outside the body.

The resulting hybridoma cells are separated and screened in order to select for the cells that produce antibodies against the target. The cells that have been identified, which are polyclonal populations, are then repeatedly diluted in a process called dilution cloning. Dilution cloning involves a series of increasing dilutions on a plate with wells. The result is many wells each containing one cell. The individual cells then are allowed to divide, leading to the production of millions of identical copies of each cell. The antibodies that are produced from the cell copies are tested for various attributes, such as specificity, affinity, and cross-reactivity. Various methods are used to test for the desired characteristics, and those that possess the desired characteristics are chosen to move forward in the process of developing a therapeutic.

3. Candidate Optimization


45 Greenfield, supra note 21, at 207.
46 Id., at 216.
47 Id., at 218.
48 Id., at 219-220.
49 Id., at 208.
51 Id.
52 Id.
53 Id.
After a monoclonal antibody candidate with the desired characteristics has been selected, the candidate is optimized. A common optimization technique is humanization, which is the process of replacing certain parts on a non-human antibody with human ones (or vice versa) without compromising the characteristics of the antibody. Antibodies are humanized so that the human body does not think that the antibodies are pathogens. Today, researchers employ a variety of methods to humanize antibodies. One such method is known as “grafting,” which essentially comprises cutting and pasting essential parts from the non-human antibody onto the backbone of a human antibody. Once an antibody has been optimized, it is validated using pre-clinical studies in cell lines and animals. Pre-clinical studies are a predicate to clinical studies in humans and involve a battery of repeated experiments occurring over a period of several years in order to demonstrate that the antibody would be an effective therapeutic in humans.

CONCLUSION

Biologics will comprise a substantial part of the state-of-the-art and most effective drugs of the future. Because monoclonal antibodies likely will continue to account for the majority of pharmaceutical research and development in the area of biologics, these antibodies were discussed in detail. As evidenced from the discussion, the production of monoclonal antibodies is a complex and lengthy process. The complexity of producing monoclonal antibodies, and biologics in general, is part of the reason that their cost is so high. Competition from biosimilars will be necessary to drive down the cost of biologics, just as competition from generic drugs has helped to decrease the cost of pioneer chemical therapeutics. Accordingly, biosimilars will likely have an important role in the future face of American healthcare.

54 Fan, supra note 32; Shih, supra note 29, at 20-21.
55 Fan, supra note 32.
56 Id.
58 Id., at 1619-27.
59 Id., at 1623-25.