Biotechnology Advances 34 (2016) 1149–1158

Contents lists available at ScienceDirect

Biotechnology Advances

journal homepage: www.elsevier.com/locate/biotechadv

Research review paper

Therapeutic monoclonal antibodies and derivatives: Historical perspectives and future directions

Kyla R. Rodgers [a], Richard C. Chou [a,b,*]

[a] Department of Medicine, Geisel School of Medicine at Dartmouth, Lebanon, NH 03756, United States
[b] Section of Rheumatology, Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756, United States

ARTICLE INFO

Article history:
Received 27 May 2016
Received in revised form 21 July 2016
Accepted 22 July 2016
Available online 25 July 2016

Keywords:
Biologics
Monoclonal antibodies
Fusion proteins
Immunotherapy
Clinical immunology

ABSTRACT

Biologics, both monoclonal antibodies (mAbs) and fusion proteins, have revolutionized the practice of medicine. This year marks the 30th anniversary of the Food and Drug Administration approval of the first mAb for human use. In this review, we examine the biotechnological breakthroughs that spurred the explosive development of the biopharmaceutical mAb industry, as well as how critical lessons learned about human immunology informed the development of improved biologics. We also discuss the most common mechanisms of action of currently approved biologics and the indications for which they have been approved to date.

© 2016 Elsevier Inc. All rights reserved.

Contents

1. Introduction . . . 1149
2. History of biologics . . . 1150
   2.1. Foundational technology and first-generation biologics . . . 1150
   2.2. Second-generation biologics. . . . 1150
   2.3. Third-generation biologics . . . 1152
   2.4. Modified biologics . . . 1154
3. Functional diversity of biologics . . . 1154
   3.1. Cytotoxicity . . . 1154
   3.2. Modulation of cellular activation/interaction . . . 1154
   3.3. Prevention of growth and proliferation . . . 1155
   3.4. Modulation of immune signaling . . . 1155
   3.5. Neutralization of foreign entities. . . . 1155
4. Indications for biologics . . . 1156
5. Future of therapeutic biologics . . . 1156
6. Conclusions . . . 1156
Funding. . . . 1157
References . . . 1157

1. Introduction

This year marks the 30th anniversary of the Food and Drug Administration (FDA) approval of the first monoclonal antibody (mAb) for clinical use. Biologics have revolutionized the pharmaceutical industry and the practice of medicine, providing new hope for patients for whom traditional therapies have failed or treatment options did not

Abbreviations: mAb, monoclonal antibody; HAMA, human anti-mouse antibody; HACA, human anti-chimeric antibody; HAHA, human anti-humanized antibody; ADC, antibody-drug conjugates.

* Corresponding author at: Department of Medicine, Geisel School of Medicine at Dartmouth, One Medical Center Drive, Lebanon, NH 03756, United States.
E-mail address: Richard.c.chou@dartmouth.edu (R.C. Chou).

http://dx.doi.org/10.1016/j.biotechadv.2016.07.004
0734-9750/© 2016 Elsevier Inc. All rights reserved.

previously exist. Although the use of biologics has become a standard and well-characterized part of clinical practice, their development has traveled a long and tortuous road. Each phase of development has been met with new challenges, yet they have catalyzed some of the most prolific and exciting advances in biotechnology. In this review, we will describe how advances in biotechnology and important lessons learned from clinical practice shaped the development of biologics.

2. History of biologics

2.1. Foundational technology and first-generation biologics

Two technologies were paramount in the development of biologics: plasmid engineering and hybridoma technology. In 1973, Cohen and collaborators reported that plasmids constructed in vitro could be introduced into *E. coli* to express genes for antibiotic resistance (Cohen et al., 1973). Cohen et al. mused that this discovery could be used to express specific sequences in bacterial plasmids. *E. coli* was soon harnessed to produce the first recombinant therapeutic agent that was later approved by the FDA for clinical use: human insulin (Chance et al., 1981; Goeddel et al., 1979; Tibaldi, 2012). The ability to express human proteins in bacterial plasmids was a critical step for both basic science and the development of new therapeutics and was later used to overcome challenges in protein engineering.

Another critical advance was the development of hybridoma technology. A major technical challenge in the early 1970s was the production of mAbs of pre-defined specificity. In 1975, Köhler and Milstein established a cell line of fused murine myeloma cells and murine splenocytes from an immunized donor, which secreted anti-sheep red blood cell antibodies (Köhler and Milstein, 1975). The myelomas harbor a mutation in the gene for hypoxanthine-guanine phosphoribosyltransferase, an enzyme required for the nucleotide salvage pathway (Ribatti, 2014). Köhler and Milstein took advantage of this deficiency as a selection marker for successful hybridomas (Köhler and Milstein, 1975, 1976). If myelomas successfully fused with antibody-producing B-cells from the mouse spleen, they would survive in hypoxanthine-aminopterin-thymidine medium, which blocks de novo nucleotide synthesis (Ribatti, 2014). The survival of hybridomas depends on the functional salvage pathway provided by splenocytes, whereas unfused myeloma cells perish due to their inability to produce nucleotides; unfused B-cells survive only short-term in culture (Ribatti, 2014). This system became the foundation of modern monoclonal antibody production and led to FDA approval of the first therapeutic mAb after only a decade: a murine anti-CD3 mAb called muromonab-CD3 (OKT-3) for preventing acute kidney transplant rejection (Brekke and Sandlie, 2003).

Although antibody-based therapy was anticipated to revolutionize medicine, its premiere fell short of expectations. First-generation mAbs were fully murine in origin (Fig. 1A), which was problematic for two major reasons: 1) human complement and Fc receptors do not bind well to the Fc region of murine immunoglobulins (Bruhns, 2012), resulting in a failure to direct human immune components to the target intended for elimination; and 2) patients develop human anti-mouse antibodies (HAMAs) (Clark, 2000), leading to rapid clearance of murine antibodies and truncating their therapeutic window. Although problematic for drugs meant to be long-acting, the high clearance rate of murine mAbs is beneficial for agents designed for short-term action, such as radioisotope-antibody conjugates utilized in the diagnosis of tumors (e.g., ^{111}In-cabromab pendetide). However, HAMAs can cause a dramatic, widespread immune response that may be fatal (Clark, 2000; Hwang and Foote, 2005). As a result of these complications, most first-generation therapeutic mAbs have been withdrawn; currently, only one unconjugated murine mAb maintains FDA approval (muromonab-CD3; Table 1). The shortcomings of first-generation biologics highlighted the importance of making mAbs less immunogenic, teeing off the race to make mAbs more human in origin.

2.2. Second-generation biologics

Second-generation mAbs are characterized by their partial human origin; the two major classes are chimeric (Fig. 1B) and humanized (Fig. 1C) mAbs. The enhanced complexity of these molecules required an equally elaborate advance in biotechnology, combining genetic engineering and hybridoma techniques. In 1984, Morrison et al. joined the exon for the heavy chain variable region of an anti-phosphocholine antibody gene with those for human IgG1 or IgG2 heavy chain constant (Fc) regions (Morrison et al., 1984). They used this construct to produce chimeric anti-phosphocholine antibodies bearing human Fc regions and murine variable regions in a well-characterized mouse myeloma (Morrison et al., 1984). Nearly simultaneously, Boulianne and colleagues reported a similar technique to create chimeric IgM antibodies (Boulianne et al., 1984). Just a decade later, the first chimeric therapeutic mAb, abciximab, received FDA approval for peri-surgical prevention of thrombosis for coronary artery interventions (Lefkovits and Topol, 1995); there are currently eight unconjugated chimeric mAbs and one chimeric biosimilar (discussed later) that are FDA approved for clinical use (Table 1). Although chimeric mAbs are approximately 75% human in origin and markedly less immunogenic than murine mAbs, their administration nevertheless induces human anti-chimeric antibodies (Clark, 2000; Lee et al., 2010).

In 1986, Jones et al. reported that the hypervariable, complementarity-determining region (CDR), which determines antigen specificity, could be replaced using the same genetic engineering strategy as that used for chimeric antibodies (Jones et al., 1986). They replaced the CDR of a human myeloma protein with that of a murine antibody against hapten NP-cap, resulting in a product that maintained the antigen specificity of the murine component but was approximately 95%

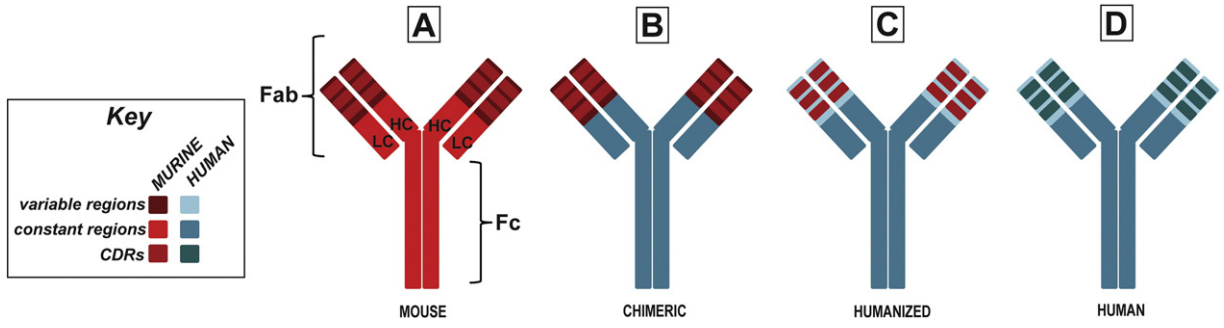

Fig. 1. The evolution of monoclonal antibodies. A) The initial wave of FDA approved monoclonal antibodies were produced by murine hybridomas, and were fully murine in origin. Advances in recombinant DNA technology allowed for the creation of B) chimeric antibodies, which consisted of murine variable regions and human constant regions and C) humanized antibodies, which replaced hypervariable regions of human antibodies with their murine counterparts. The advent of transgenic and phage display technologies allowed for the creation of D) fully human antibodies. Abbreviations: CDR: complementarity determining region; Fab: fragment, antigen-binding; Fc: fragment, crystallizable; HC: heavy chain; LC: light chain.

Download English Version:

https://daneshyari.com/en/article/4752565

Download Persian Version:

https://daneshyari.com/article/4752565

Daneshyari.com