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Recent Advances in Biotherapeutics Drug Discovery and Development

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1. Introduction

Biotherapeutics drugs, such as antibodies, Fc-like fusion proteins, and therapeutic replacement enzymes, constitute the most rapidly growing drug class, and have become a major clinical success of human therapeutics over the past decade. These therapeutics of large-molecule have revolutionized the treatment of a variety of diseases in areas such as oncology, inflammatory and autoimmune diseases, hemophilia, cardiovascular disease, infectious diseases, and rare genetic diseases. In comparison with small-molecule therapeutics, biotherapeutics have a higher approval success rate and a similar development phase length. Physician and patients have accepted biotherapeutics drugs even though most of these products are administrated via injection. Many new biotherapeutics candidates are filling the pre-clinical and clinical pipelines of major Biopharmaceutical companies. The aim of this chapter is to provide a review on recent advances in Biotherapeutics drug discovery and development. Action mechanisms, tools for biotherapeutics generation, design processes, issues like safety and side effects, will be described. In addition, pharmacoeconomics and strategies to provide affordable biotherapeutics drugs will be discussed.

2. An overview of biotherapeutics drug discovery and development

Since the first recombinant-DNA-derived drug human insulin was approved for Eli Lilly by the UK and the US regulators in 1982, more than 170 biotherapeutics products have been launched to benefit quality of life of millions of patients worldwide. These biotherapeutics drugs compose of various types of biological molecular entities, and have revolutionized the treatment of a variety of human diseases ranging from cancer and autoimmune diseases to rare genetic disorders over the past three decades.

Biotherapeutics drugs can be generally classified into three big groups (Table I), based on their physiological properties and mode of actions. The first group is peptides and small protein therapeutics which include growth factors, hormones, and cytokines. This category has been traditionally a major engine for the growth of biotherapeutics drugs, exemplified

by insulins, epoetin alpha (Epogen, Aranesp), and granulocyte colony-stimulating factor (Neupogen, Neulasta).

Drug Classes	Examples
1) Peptides and small therapeutic proteins	
A. Growth factors	erythropietins, granulocyte colony-stimulating factors
B. Hormones	insulin, human growth hormone, glucagon-like peptide analogs
C. Cytokines	Interferon-α, β,γ, Interleukins (Neumega, anakinra)
2) Non-immune proteins	
A. Therapeutic replacement enzymes	Naglazyme, Myozyme, Elaprase
B. Blood factors	Factor VIII; factor VIIa, factor IX
C. Anticoagulants	Tissue plasminogen activator, recombinant hirudin, activated protein C
3) Therapeutic antibodies and Fc-like fusion proteins	
A. Therapeutic antibodies	rituximab, adalimumab, cetuximab, trastuzumab
B. Fc-Fusion proteins	etanercept, CD2-Fc, abatacept, Nplate

Table 1. Drug classes of Biotherapeutics drugs

The second group is non-immune therapeutic proteins which include therapeutic replacement enzymes, blood factors, and anticoagulants. This category typically includes recombinant proteins used for treatment of rare genetic disorders, i.e. Naglazyme for Maroteaux-Lamy syndrome, Myozyme for Prompe disease, and Elaprase for Hunter syndrome. Though relatively small, this is a rapidly growing sector of Biotherapeutics drugs.

The third group is therapeutic antibodies and Fc-like fusion proteins. This category ranks the most rapidly growing group of biotherapeutics drugs, propelled by the success of the "big 6": Enbrel, Remicade, and Humira for autoimmune diseases; Rituxan, Herceptin, and Avastin for treatment of several types of cancers. By 2010, at least 11 products from this group have reached global sales of exceeding 1 billion US dollars.

Over the past 10 years, biotherapeutics drugs have become the fastest growing class of therapeutic agents. The total sales of biotherapeutic drug in the US alone reached close to $50 billion in 2010 (Aggarwal 2010). Novel biotherapeutics molecules, i.e. monoclonal antibodies and fusion proteins especially, have been entering clinical study at a rate of over 40 per year since 2007 (Reichert 2011). Hundreds of antibodies and fusion proteins are undergoing clinical evaluation. By the end of 2010, over 30 of this kind of drug candidates

were in Phase2/3 or Phase 3 clinical studies, representing a substantial proportion of the late stage therapeutics pipeline. In addition, biotherapeutics drugs have a significantly higher likelihood of being a first-in-class therapy compared with small molecule drugs, considering their novelty and quality. The pharmaceutical and biotechnology industry has therefore been investing increasingly substantial resources in the discovery and development of biotherapeutics products.

Clearly, the process of the discovery and development of a biotherapeutics drug poses challenges that are different from those set by a traditional small molecule drug. In general, biotherapeutics drugs are designer drugs whose mode of action in an underlying disease pathophysiology is usually better understood than those targeted by small-molecule drugs. The data derived from relevant models can support a more rational clinical development program, facilitating better predictions of dosing, efficacy and safety profiles in comparison with small molecule therapeutics. Biotherapeutics drugs therefore have a higher approval success rate, though a similar development phase length, compared with those of small molecule drugs (Reichert 2010). However, as proteins or peptides produced from living cells, biotherapeutics agents require more complicated manufacturing and characterization process to minimize product variation among bath-to-batch. They must be well characterized with regards to potency, identity, quality, purity, and stability.

Advancements in biotherapeutics engineering technologies, and a deeper understanding of mechanism for biotherapeutics action, their safety and side effects in human, have been in action in producing a new generation of biotherapeutics drugs. Experience gained through current biotherapeutics has helped guide future development process via strength building, limitation overcoming, and opportunity seizing. Details of these scientific and technologic knowledges are reviewed in the following sections. By examining the cost issue associated with biotherapeutics drugs, insights into the strategies for affordable biotherapeutics drugs are also discussed.

3. Mechanisms for biotherapeutics action

Diverse mechanisms have been employed by biotherapeutics drugs to achieve therapeutic efficacy and disease modulation. These include direct enzyme replacement, stimulation of biological signal responses, enzymes inhibition, effector functions, Toxin conjugation, cytokine and growth factor blockade.

A. Direct enzyme replacement

Insulin for diabetes control is considered to be the oldest example for enzyme replacement therapy since its breakthrough discovery more than 80 years ago (Hirsch 2005). The development of recombinant insulin in early 1980 eliminates side effects posted by bovine and porcine extracted products. Since then, new generations of insulin analogues such as rapidly-acting analogues and long-acting analogues have been produced. A more recent example for enzyme replacement drugs is the treatment of rare disease disorders such as Lysosomal storage disorders. Gaucher disease and Prompe disease are caused by the lack or dysfunction of an enzyme in the lysosome. Imiglucerase (Genzyme), a recombinant version of glucocerebrosidase, can rescue the deficiency of the disease when this replacement drug is injected regularly throughout patients' lives. After the medical and commercial success in Gaucher disease, a number of enzyme replacement therapies have been approved for several different diseases. Agalsidase β (Genzyme) and agalsidase α (Shire) are for Farbry

disease; Laronidase (BioMarin/Genzyme) for Hurler-Schcic syndrome; Idursulphase (Shire) for Hunters Syndrome; Alglucosidase α (Genzyme) for Pompe disease; galsuphase (BioMarin) for Maroteaux-Lamy syndrome. All these products are in orphan diseases group. Recombinant Factor VIII, VIIa, and IX play an important role in blood clotting and are used for people who are genetically deficient (Hemophilia A & B) or have undergone blood loss during a surgery or trauma.

B. Effector functions

The Fc portion of an antibody, composed of the hinge and constant domains, can communicates with the immune system once the antibody binds its target. The communication is through effector functions which include antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC). ADCC and ADCP are through the interaction between Fc and FcγR receptors expressed on a variety of immune cells such as natural killer cells, monocytes, neutrophils and macrophages. CDC is mediated via the interaction of Fc with complement proteins such as C1q. Several antibody therapeutics, including rituximab, adalimumab, cetuximab, trastuzumab and alemtuzumab support ADCC and CDC in vitro, which might also contribute to the therapeutic efficacy in clinical setting such as the destruction of tumor cells or viral infected cells.

C. Cytokine and growth factor blockage.

Tumor necrosis factor (TNF) antagonists, such as therapeutic antibody infliximab, adalimumab, golimumab, certolizumab, and Fc fusion protein etanercept, are presently the most successful class of biotherapeutics drugs for inflammatory diseases. One major mode of action for these antagonists are blocking either soluble TNF or membrane associated factor. Other biotherapeutics drugs with a similar mechanism include canakinumab (Anti-IL-1β antibody) for the treatment of cryopyrin-associated periodic syndrome and ustekinumab (anti-IL-12/IL-23 antibody) for the treatment of psoriasis.

D. Receptor blockage and modulation

Therapeutics antibody can target receptors to block ligand-receptor interaction, which also down-regulate surface expression of the targeted receptor. These antibodies include tocillizumab (targeting IL-6 receptor), efalizumab (targeting αL integrin [CD11a/LFA1]), and natalizumab (targeting α4 subunit of α4β1 & α4β7 integrin). However, targeting surface receptors can potentially result in antigen-induced clearance of therapeutic antibody and decrease its serum half-life. This mechanism can also theoretically have a greater risk for triggering immunogenic response, as antigen-dependent internalization can increase MHC class II antigen processing.

E. Toxin conjugation

To enhance monoclonal antibody utility in the clinical treatment of cancer, cytotoxic drugs such as doxorubicin, calicheamicin, auristatins, and maytansinoids, have been conjugated with monoclonal antibodies (Senter 2009). Targeted site-specific and intracellular delivery of toxins into tumor cells elicits potent antitumor activity in both preclinical and clinical studies. Currently there are one approved antibody conjugated molecule (Gemtuzumab ozogamicin, Mylotarg) and several in late-stage clinical trials (Trastuzumab-DM1, Inotuzumab Ozogamicin).

F. Stimulation of biological signal responses

Romiplotim, a peptide –Fc fusion protein of thrombopoietin analogue, activates Tie2 receptor for the platelet regeneration to treat chronic idiopathic thrombocytopenic purpura. Exenatide mimics a natural peptide (Glucagon-like peptide 1) but is resistant to degradation by protease DPP4 for diabetes control. Erythropietins trigger red blood cell regeneration for anemia. Granulocyte colony-stimulating factors set off white blood cells regeneration for neutropenia; Neumega (recombinant IL-11 receptor agonist) stimulates biological signaling response for chemotherapy-induced thrombocytopenia.

G. Enzymes inhibition

Ecallantide (Dyax), a Kunitz domain-based scaffold, targets human plasma kallikrein for the treatment of attacks of hereditary angioedema. Recombinant hirudin is an inhibitor of thrombin, and activated protein C also has anti-thrombic activity.

4. Tools for biotherapeutics generation

The success of biotherapeutics drugs is attributed to the great technology and tool development for biotherapeutics generation over the past three decades. Various selection technologies, multiple protein engineering platforms, a profusion of biotherapeutics formats and scaffolds, new production systems, and new methods for increasing stability and aggregation resistance, have blossomed into a next wave of therapeutic candidates. The following is a summary of early tools and recent developments.

A. Hybridomas

Mouse hybridomas generated from the stable fusion of immortalized myeloma cells with B cell from immunized mice is the first developed and most widely used technology for the generation of monoclonal antibodies (Kohler and Milstein 1975). This technology has a ubiquitous use and a broad success in drug discovery research. However due to mouse antibodies' high immunogenicity in humans, the weak interaction with human complement and FcγRs, and short half-life with no binding to human salvage receptor FcRn, they have a very low clinical success rate. These limitations have been largely overcome by chimerization and humanization in the current era of antibody therapeutics.

B. Chimerization and humanization

Chimerization of an antibody is joining the variable domains of a mouse monoclonal antibody to the constant domains of a human antibody (Boulianne et al. 1984; Morrison et al. 1984). This tool utilizes a detailed understanding of the structure and function of immunoglobulin domains as well as the determinants of antigen binding. The humanization strategies involve transferring the complementary-determining regions (CDRs, the antigen-binding loops) from a mouse antibody to a human IgGs, and additional mutagenesis of one or more framework-region residues back to the parent mouse antibody.

C. Human antibodies from transgenic mice

A growing number of antibodies entering clinical trials and the market are completely human. Some of them are derived from transgenic mice that express human immunoglobulin genes (Lonberg 2005). Mice that are transgenic for human immunoglobulin genes and have disrupted mouse immunoglobulin heavy-chain and Igκ light-chain can be

immunized with target-antigens to produce human antibodies. B cells that express specific human antibodies can be cloned for hybridomas, similar to the generation of mouse monoclonal antibodies. The binding affinity of these transgenic-mouse-generated antibodies is often high, likely due to the in vivo affinity maturation process and therefore obviating the in vitro affinity optimization steps. Human IgG1 output from transgenic mice and the direct use of hybridomas cell lines for human antibody production can allow early screening for biological function and for pre-clinical development. One challenge to use transgenic mice is to derive antibodies that are crossreactive with mouse antigens. It is often desirable to evaluate biological function of the species-crossreactive antibodies in animal models of disease. In transgenic mice, self-reactive antibody-producing cells are selected against by the processes of immune tolerance induction.

D. Human antibodies from phage-display libraries

Phages encoding a single-chain V-domain antibody fragment(scFv) on their surface and selective recovery of phage on the basis of antigen binding were first reported by McCafferty et al (McCafferty et al. 1990). Diverse human immunoglobulin-heavy-chain V (VH) gene segments and light-chain V (VL) gene segments were prepared from peripheral-blood lymphocytes of non-immunized donors by PCR, and scFvs genes were made by randomly combining VH and VL gene segments using PCR. The combinatorial library (up to ~10^{11} genes) can be cloned for display on the surface of phage and used to identify scFvs that bind target antigens. Further progress in phage-display technology has included display of Fabs and high-throughput screening methods adapted from small-molecule drug discovery. A particular strength of phage-display libraries, in contrast to hybridomas technology, is the direct selection for specific binding properties, such as species crossreactivities. In addition, phage-display technology has a capability to provide very large collections of antibodies, which allows the identification of high potency antibodies or with rare combinations of properties.

E. Glycoengineering

Glycoengineering is changing protein-associated carbohydrate to alter pharmacokinetic property or biological function of therapeutic proteins, because of the ability to manipulate DNA sequences. Glycoengineering can increase molecular stability, solubility, serum half-life, in vivo biological activity, and reduce immunogenicity. One well known example of this technology is the discovery of darbepoetin alfa, a hyperglycosylated analogue of erythropoietin that contains two additional N-linked carbohydrates (Elliott et al. 2003). The introduction of new N-linked glycosylation consensus sequences into desirable position in the peptide backbone can increase sialic acid containing carbohydrate, thereby increasing serum half-life. Another aspect of glycoengineering is generating various glycoforms of a glycoprotein. An engineered CHO cells with overexpressing galactosyltransferease and sialyltransferase can maximize sialic acid content of recombinant glycoproteins produced (Weikert et al. 1999). A fucosyl-transferase knock-out cell line produce antibody protein with fucose-free glycan attached at Asn 297 in the IgG-Fc region, which possess a significantly increased ADCC activity (Niwa et al. 2004; Shields et al. 2002). Another glycoengineering approach involves in vitro treatment of a purified glycoprotein with glycosidases or glycotransferases. Cerezyme, the recombinant glucocerebrosidase, has been treated with neuraminidase, β-galactosidase and β-hexosaminidase, to trim outer

oligosaccharide to expose core mannose residues underneath for macrophage targeting (Brady and Barton 1994; Hoppe 2000).

F. Multispecific antibodies

Bispecific antibodies that are capable of strong and specific binding with two different antigens have been on the scene for decades. They can target two or more disease mechanisms as a single agent and provide a unique alternative to combination therapies. More importantly, bispecific antibodies can achieve some therapeutic strategies that are not feasible with conventional monospecific monoclonal antibody combination. For instance, by targeting both immune effector cells surface molecules and tumor cell surface markers, bispecific antibodies could preferentially recruit activating effector cells to kill tumor cells (Chames and Baty 2009). Bispecific antibodies have been used for the site-specific targeting insulin and transferring receptors on the blood-brain barrier (BBB) as transporter and anti-amyloid-β targeting binding across BBB is significantly increased (Boado et al. 2010). Bispecific antibodies can be generated via several approaches, including cell fusion-based quadromas and triomas(Nisonoff and Rivers 1961), chemical cross-linking-based approach (Graziano and Guptill 2004), and recombinant technology-based approaches, such as using Ig hetero-oligomerization domain(Muller et al. 1998; Ridgway et al. 1996), non-Ig hetero-oligomerization domains, scFv-based bispecific, and single variable domain-based bispecific (Holt et al. 2003), dual-variable domain immunoglobulin(Wu et al. 2007).

G. Intrabodies

Intrabodies are antibodies that are designed to be expressed intracellularly against different target antigens present in cytosol, nucleus, endoplasmic reticulum, mitochondria, peroxisomes, and plasma membrane (Lo 2008; Williams and Zhu 2006). Though Introbodies have the potential of interfering with intracellular biosynthetic pathways, the major obstacle of Intrabodies is the absence of efficient in vivo delivery method to live target cells(Stocks 2006). Current attempts are using recombinant adenovirus and vaccinia virus vetors or immunoliposomes (Williams and Zhu 2006).

H. Protein engineering,

Molecular biology techniques such as site-directed mutagenesis and error-prone PCR have been routinely used for biotherapeutics generation. Computational modeling and structure-based drug design with three-dimentional structural information are widely applied to protein engineering. Screening technologies such Peptide Phage-display Libraries, "Peptides on Plasmids" libraries, Ribosome display, mRNA display, CIS display, and DNA display, have also been utilized for biotherapeutics lead generation (McGregor 2008).

5. Design processes for biotherapeutics

Biotherapeutics-based drug development is driven by unmet medical needs. Designing a successful biotherapeutics requires understanding of several critical areas.
First is the understanding of disease biology. Human diseases are complex and heterogeneous that multiple redundant and distinct mechanisms determine the final disease outcome and contribute to multifaceted, distinct disease symptoms (acute versus chronicle) and pathologies. It is important to evaluate if there are good preclinical models and

understand the limitation of the predictive power of these animal models. Translational medicine helps define good biomarkers for disease progress and designing clinical trials with appropriate end points that reflect the role of the specific targeted mechanism in a complex disease.

Second is the understanding of target biology. It is critical to determine which target should be chosen in a defined mechanism. Targeting either soluble ligands or surface receptors, serving as agonist or antagonist, need to be determined. An overall target biology within the context of the disease (specific aspects of the disease that are driven by the target) need to be understood. Typically drug targets can be classified into three groups. The first group is so-called "clinically validated targets" because of their proof-of-activity shown in humans. This validated approach has a high probability of success, but the competition is crowded and freedom to operation is decreased. The second group is experimentally- validated targets, whose importance for disease mechanisms have been demonstrated by a vast literature. Most cytokines and associated receptors for immunological disorders and tyrosine kinases receptors in oncology fall into this category, as the mechanisms driving these disorders are reasonably well known. The third group of targets is those new or less well studied target proteins that might be involved in pathogenic disorders. More extensive and careful validation is required. They are with a greater potential for new therapeutic breakthroughs, but carrying out a greater risk of development failures.

Lastly is the advancement of biotherapeutic technologies. We need to understand affinity and potency, specificity and cross-reactivity, physicochemical properties, immunogenicity, expression and purification, solubility and stability, pharmacokinetics and pharmacodynamics, and formulability and manufacturability. In short, we need to know what features a good biotherapeutic protein must possess by incorporation of lessons learned over the years, as well as identify key issues critical for technology advancement.

6. Safety and side effects of biotherapeutics

Administration of biotherapeutics carries the risk of immune response and numerous adverse effects that are related to their specific targets and organ-specific adverse events (Giezen et al. 2008; Hansel et al. 2010). The following discuss a range of adverse effects encountered with biotherapeutics, some of which have been fatal, and strategies to minimize these events. These events include those documented for licensed biotherapeutics as well as examples of side effects found during exploratory clinical studies. Some of the severe adverse effects are not anticipated from currently available preclinical screening tools and animal models. These lessons can provide new strategies and guidelines needed for the development of safer and more efficacious biotherapeutics.

A. Acute Immune reactions

Biotherapeutics can induce acute infusion reactions either due to their mechanism of action and/or their foreign nature of the molecule and/or co-purified impurities that result in acute reactions either via innate immunity or due to the reaction with pre-existing, or induced IgE antibodies. Clinical magnification can range from local skin reactions at the injection site through acute anaphylaxis and systemic inflammatory response syndrome. For rituximab (Coiffier et al, 2002), first dose infusion reactions combine serum sickness, tumor lysis syndrome and cytokine release syndrome, primarily as a result of its mechanism of action. These initial reactions can be minimized by appropriate hydration and

premedication, and cautious incremental increases in the rate of infusion. Acute anaphylactic and anaphylactoid reactions are commonly described for cetuximab which has been attributed to pre-existing IgE antibodies against galactose-α1,3-galactose which is expressed on the cetuximab molecule (Chung et al. 2008).

B. Immunogenicity

The development of immunogenicity, or anti-drug antibodies, has important clinical ramifications. The development of immunogenicity could lead to a number of important clinical implications, including alternation in PK and loss of efficacy through neutralization, an increase in adverse events associated with drug-antibody interactions, and, dependent upon the nature of the biotherapeutic, the potential for cross reactivity of antibodies with endogenous ligands. As such, the assessment of immunogenicity and the assessment of ADA's clinical implications is a crucial part of biotherapeutics development. The development and appropriate validation of anti-drug antibody assays is a fundamental necessity in understanding ADA. Interference by a parent drug and existing antibodies must be evaluated. In addition, a comprehensive assessment of the clinical implications of the ADA must be assessed in the clinical setting to evaluate both safety and efficacy, as well as any reasonable cross-reactive effect.

C. Infections

A well documented side effect of biotherapeutics is infection, which is generally due to removal of the therapeutic targets that have a protective function in the normal immune system. An increased risk of tuberculosis infection has been associated with TNFα-specific biotherapeutics (Schneeweiss et al. 2007). Progressive multifocal leukoencephalopathy (PML) is a rapidly progressive demyelinating disease that is due to reactivation of the infection in the central nervous system with the polyoma virus John Cunningham virus (JCV), though most healthy people are seropositive for JCV. The risk of PML is about 1 in 1,000 multiple sclerosis patients treated with natalizamab (Yousry et al. 2006). A number of PML cases are found for rituximab (Carson et al. 2009) and efaliziumab (Molloy and Calabrese 2009).

D. Autoimmune diseases

Biotherapeutics such as monoclonal antibodies have the capacity through their immunomodulatory actions to cause various autoimmune conditions (Mongey and Hess 2008), such as Lupus-like syndromes and drug-related lupus, Thyroid disease, and autoimmune colitis. For instance, the treatment of TNFα specific monoclonal antibodies has been found associated with the development of anti-nuclear antibodies and anti-bodies to double-stranded DNA as well as with lupus-like syndromes (Mongey and Hess 2008). When used in multiple sclerosis, anti-CD52 immunosuppressive monoclonal antibody alemtuzumab was found to cause antibody-mediated thyroid autoimmunity in almost 25% of study patients (Coles et al. 1999).

Other agents have observed autoimmune events as a result of their direct mechanism of action. Anti-Cytotoxic T-lymphocyte-antigen 4 (CTLA4) specific monoclonal antibodies such as ipilimumab and tremelimumab increase T-cell stimulation and has been shown antitumor activity (Maker et al. 2005), but also cause an autoimmune enterocolitis and other immune-related adverse events such as rash and hepatitis (Peggs et al. 2006).

E. Cancer

Some antibody therapeutics such as infliximab and ustekinumab (Rennard et al. 2007; Weiss et al. 2007) have even been found inducing tumorigenicity in auto-immune patients.

F. Platelet and thrombotic disorders

Drug-induced immune thrombocytopaenia is a decrease in the number of circulatory platelets in the blood caused by medications such as biotherapeutics (Aster and Bougie 2007). An acute severe, self-limiting thrombocytopaenia has been found with the treatment of infliximab (TNFα-specific), efalizumab [CD11a-specific; (Tamhane and Gurm 2008)] and rituximab (CD20-specific), but the mechanisms of action remain unknown.

G. Dermatitis

The EGFR-specific antibodies such cetuximab and panitumumab can commonly cause a skin rash on the face and upper torso (Perez-Soler and Saltz 2005). The dermatitis is thought to be part of the pharmacodynamic action of these agents, because EGFR is widely expressed on epithelial cells (Bianchini et al. 2008).

H. Cardiotoxicity

Trastuzumab, a humanized monoclonal antibody targeting HER2, has been used to treat HER2-positive metastatic breast cancer (Hudis 2007). However in the trials, cardiotoxicity as an unexpected adverse event was discovered (Force and Kerkela 2008). This cardiac dysfunction caused by trastuzumab is target-related, because blocking HER2 signaling causes mitochondrial outer membrane permeabilization and eventually apoptosis of cardiac muscle cells with impaired contractility and ventricular function (Kuramochi et al. 2006).

I. Cytokine storm

Cytokine storm is an uncontrolled hypercytokinaemia that causes multiple organ damage. It is a prominent side effect with CD3 specific [muromonab; (Plevy et al. 2007)], CD52 specific [alemtuzumab; (Wing et al. 1996; Wing et al. 1995)] and CD20 specific [rituximab; (Winkler et al. 1999)]. A fully humanized monoclonal antibody TGN1412 triggered an immediate and severe cytokine storm when given to six healthy male volunteers (Suntharalingam et al. 2006).

7. Pharmacoeconomics and strategies to provide affordable biotherapeutics drugs

Biotherapeutics are distinctive from traditional small molecule pharmaceuticals in terms of administration mode, relatively high prices, and significant disease modification. The high development cost and high financial risk are associated with the complex process of biotherapeutics drug discovery and development as seen in the previous sections. However the new and effective biotherapeutics drugs present society a fundamental question about how to make these promising drugs more affordable. One example is Orphan drugs whose prices are often substantially higher than those of other drugs, and might occur at the expense of common diseases if more orphan drugs are approved (Tambuyzer 2010). In UK, due to the high treatment cost relative to patient benefit, National Institute of Clinical Excellence did not approve reimbursement for several cancer drugs including monoclonal antibody Avastin (Raftery 2009). In US, some health plans require more than 30% co-insurance and some biotherapeutics can cost as high as $100,000, the financial burden on

patients is significant. A concern has been raised for society how to pay for these innovative drugs (Zhong 2010).

Pharmacoeconomic evaluation and value-based analysis, which serve to guide optimal healthcare resource allocation, have been used for new drug reimbursement and coverage (Cohen and Wilson 2009; Neumann 2009). But the direct application of these evaluation in health policy recommendation and formulation remains highly debated (Neumann and Weinstein 2010). It has been argued that weeding out inefficiencies may be more effective in controlling cost than denying reimbursement. From research and development standpoints, decreasing costs and increasing success rate for the drug approval is a critical part of achieving this mission.

Clinical testing in human for new biotherapeutics drugs entails a large sum of financial investment. Though biotherapeutics have higher probabilities of clinical success, they have a higher attrition rate in phase III trials than small-molecule drugs (Grabowski 2008), indicating that the failure results are known only after high development cost have been incurred. Improving trial designs with biomarker identification and proper patient selection is the key to decreasing trial attrition rate. One good example is the EGFR-targeted therapy of colorectal cancer. Even though EGFR is widely overexpressed in tumor cells from most of patients, only those with a wild type KRAS phenotype will benefit from EGFR-specific cetuximab or panitumumab treatment (Walther et al. 2009).

Besides increasing productivity, lowering production and processing cost is another important factor to provide affordable biotherapeutics treatments. Recent breakthroughs in production yields of mammalian cells, shortening production time, and improving purification and formulation for antibody production, are critical features for cost reduction. In addition, non-mammalian production systems such as engineered yeast and plant cells are being used for biotherapeutics production, which could be a substantial saving for the removal of costly viral inactivation validations step.

Increasing expenditures and the high prices of biotherapeutics have highlighted the need of lower-cost generic substitutes for off-patent biotherapeutics drugs, usually called biosimilars (Ledford 2010).

Biosimilars terminology stems from the inherent variability in the production of complex proteins in a living organism. As such, the innovator, or reference product has a range of critical quality attributes that affect the overall properties of the molecule. These attributes range from the fundamental amino acid sequence, through complex glycosylation. Given the complexity of these molecules, the determination of biosimilarity is a broad assessment of similarity, encompassing advanced analytical techniques, and nonclinical and clinical assessments. It is the confluence of these data that allow for the assessment of biosmilarity. Typically, the biosimilar process begins with the reverse engineering of the reference innovator product. While the amino acid sequence may be published, variability must be confirmed. Additionally, post-translational modification, such as glycosylation profile must be determined analytically as these are dependent upon the cell line, fermentation conditions and purification process. The glycoforms on the protein often contribute not only to their pharmacokinetics, but their inherent activity. Once the critical quality attributes are determined, cell line development is used to determine an appropriate cell line and subclone to produce a molecule within the desired attribute framework. While molecule dependent, it is likely that some nonclinical and clinical work will be necessary to demonstrate biosimilarity. Clinical experience may be required to ensure the safety and efficacy of the biosimilar. The level of clinical experience may range from human bioequivalence up

through and including non-inferiority/equivalence studies based upon efficacy. Additionally, the post market surveillance of biosimilars will be important in understanding their long term safety profile relative to the innovator molecule.

The regulatory requirements for biosimilar approval should be sufficiently high to ensure that patient safety and efficacy are assured so that these important treatments can be used with confidence.

At this point in time, at least 12 biosimilar products, encompassing human growth hormone, erythropoietin, and granulocyte colony-stimulating factors, have been authorized for marketing. Some complex biotherapeutics such as antibody of rituximab are approved locally in India, China, and South Korea. The US Food and Drug Administration has been developing guidelines that will expand the development of biosimilars since it received the authority to approve biosimilars as part of President Barack Obama's health-care reforms. The introduction of biosimilars will make a number of biotherapeutics drugs significantly affordable when their patents expire. The EMEA has published biosimilar guidelines, as have other countries. Additionally, the World Health Organization (WHO) has developed a position paper on the development of biosimilars.

8. Conclusions and perspectives

Tremendous progress has been made in the research and development of biotherapeutics drugs. Much has been learnt from the scientific and clinical experiences of these biological molecules. New technologies and new discoveries are always emerging, yet many challenges remain. Identifying and validating new targets, addressing oral delivery of biotherapeutics drugs, and improving phase III success rate, are a few to be named. The advent of age of biosimilars will surely make biotherapeutics drugs more accessible and economical. The key is striking a balance between the incentives for cost saving and rewarding innovation.

9. Acknowledgement

This book chapter is dedicated to the centenary of the late Prof. Haoran Jian (1911-2011) (by X.Z.).

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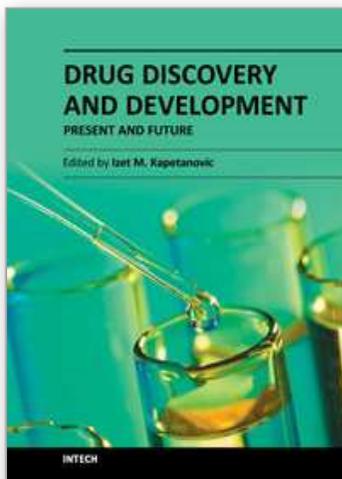
Drug Discovery and Development - Present and Future

Edited by Dr. Izet Kapetanović

Drug discovery and development process aims to make available medications that are safe and effective in improving the length and quality of life and relieving pain and suffering. However, the process is very complex, time consuming, resource intensive, requiring multi-disciplinary expertise and innovative approaches. There is a growing urgency to identify and develop more effective, efficient, and expedient ways to bring safe and effective products to the market. The drug discovery and development process relies on the utilization of relevant and robust tools, methods, models, and validated biomarkers that are predictive of clinical effects in terms of diagnosis, prevention, therapy, and prognosis. There is a growing emphasis on translational research, a bidirectional bench to the bedside approach, in an effort to improve the process efficiency and the need for further innovations. The authors in the book discuss the current and evolving state of drug discovery and development.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Xiaotian Zhong, Peter Neumann, Michael Corbo and Evan Loh (2011). Recent Advances in Biotherapeutics Drug Discovery and Development, Drug Discovery and Development - Present and Future, Dr. Izet Kapetanović (Ed.), ISBN: 978-953-307-615-7, InTech, Available from: http://www.intechopen.com/books/drug-discovery-and-development-present-and-future/recent-advances-in-biotherapeutics-drug-discovery-and-development

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