Chapter 9
Pharmaceutical Biotechnology: The Role of Biotechnology in the Drug Discovery and Development

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Abstract Biotechnology has made a great impact on the drug discovery and development process and improved human health and well-being in an unprecedented manner. It happened due to better understanding of the pathological signaling pathways, which allowed identification of the potential drug targets. Besides, advancements in cell and molecular biology techniques made the researchers able to screen the drugs in a timely manner and to gather mechanism of action and the toxicity of the drugs more efficiently. This decreased the failure rate of the drugs and improved therapeutic outcomes. This chapter provides a brief overview of the overall processes involved in drug discovery and development. Thus, our aim here is to provide readers a perspective on how biotechnology is increasingly becoming a reliable tool in the drug industry with a significant role in rational drug design.

Keywords Drug development · Biotechnology · Clinical research · Target validation · Preclinical research

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M. Anwar et al. (eds.), *Fundamentals and Advances in Medical Biotechnology*,
https://doi.org/10.1007/978-3-030-98554-7_9

9.1 Drugs: Definition, Types, Properties, and Classification

In recent years, pharmaceutical biotechnology has emerged as a rapidly growing field due to its vast applications in the discovery and development of drugs [1–4]. The current trends in the market suggest that biotechnology-based therapeutics are surging up with the discovery of novel nucleic acid products and vaccines to target the disease progression and immune system of the patient [5]. Clinical drug discovery requires a robust understanding of the principles underlying health and diseases. It also requires sound understanding of the role of the molecular signaling mechanisms governing the functions of related biomolecules in pathology [2, 3]. Biotechnology also plays an important role in enhancing biomolecule synthesis and purification, determining the product shelf life, stability, toxicity, and immunogenicity studies of the drug molecule [6]. It is actively participating in developing novel drug delivery systems including liposome and nano-technology based therapeutics in the patients [3, 6, 7].

9.1.1 The Critical Steps Involved in Drug Discovery

There are multiple yet sequential steps involved in the drug discovery process [5, 8]. The process begins with the identification of the drug targets and often concludes at the build of the sound preclinical data with the opportunity to file an Investigational New Drug (IND) application to the US Food and Drug Administration (FDA). The processes involved between the target identification and preclinical discovery such as assay and reagent development, hit-to-lead generation, lead optimization, extensive lead characterization, and clinical candidate selection require robust collaborative efforts and availability of enough resources to carry forward the project [4]. As the process moves from one step to another, failure rates are also decreased gradually [5]. The pharmaceutical and biotechnology companies are always trying to bring up the discovery portfolio with large number of early projects to build pipelines. This enables the companies to end up with mature projects, which will help them to thrive [5, 8]. Even after spending huge amount of money and spending time and efforts on multi-layered projects, still the process of discovery is always remaining at high risk of failure. More importantly, if the steps at the beginning of the process are not planned properly and if there would be any caveat remained in applying any criteria, the entire process will show up in highly expensive preclinical and clinical phases [9]. This will add up the cost of the final product tremendously. Here, the valid questions to ask are how to make the entire process less risky to increase the success rate? If we will be able to accurately find the answer of these questions, we hope that we will be able to shed down huge cost associated with the entire drug development process [10]. Ultimately, this will not only bring medicines fast in the market but will also put less economic burden on the patients. What will be the starting point in the pharmaceutical company to initiate the effective drug

discovery process? There may be multiple starting points such as by bringing clarity in the entire research and development culture of the company in terms of well-defined specific goal and enhanced collaborations, utilizing specific and up to date technologies, changing corporate culture and make use of the availability of alternative drug discovery and developments tools [5]. More importantly, recent advances in the drug discovery show the utilization of advanced drug discovery technologies often easier to implement and better as a starting point. Indeed, latest technological advancements have proven the above points by accelerating the entire drug discovery process [9].

Biotechnology has emerged as a major platform and a niche in the discovery and development of drugs. For example, it did not only provide ability to decipher the complexities of pathologies but simultaneously bring novel treatments and vaccines to the clinic [11]. On the other side, gene therapy is ready to treat the previously called untreatable genetic diseases. Thus, at this point of time with the advancement and expansion of biotechnology in drug discovery, we are more hopeful than before. How biotechnology led to the paradigm shift in drug discovery and development? This is being owed due to the simultaneous advancement of molecular and cell biology sciences [11]. This enables us rapid and reliable testing of new molecules using in vitro models compared to time consuming work at organ or whole animal level. Thus, an early part of the drug discovery process heavily relies on discovering and developing of the molecular drug targets using purified recombinant proteins as well as genetically modified cell lines. And this brings the era of high throughput drug screening where large number of molecules are screened in short period of time with even limited budget [11]. This entire drug development process would even be impossible to imagine if there was no improvement of the understanding of the molecular basis of the disease process through the developments of newer biotechnology tools [12].

9.2 Drug Metabolism, Efficacy, and Drug Interactions

Here, we briefly summarized the sequential steps involved in the entire drug discovery process.

The first step in the path of drug discovery is target selection. Although it appears as step one, it is a multi-layered process, which requires a multidisciplinary work and collaborations. Here, the focus is to identify targets against which to develop the small molecules for the interventions [13]. Therefore, the overall aim in this step is to find out the potential modulator which affects the underlying cellular and biochemical disease pathways operating the disease processes. This is followed by the second step, the lead discovery. During the lead discovery process the entire focus is geared towards identification of a collection of small organic molecules which inhibit the selected drugs targets. These small molecule inhibitors are called “hits.” Later, these “hits” are further modified chemically to enhance and improve their potency and selectivity towards the identified molecular target [13]. The premise of

this final modification is to further narrow down selectivity of the compounds to a few where the structure–activity relationships may be promiscuous and defined. This will further enhance a degree of in vivo activity of the lead compounds. Following the chemical modifications, these lead molecules enter the next phase called lead optimization [9]. This is the longest and most resource intensive phase. Here the sequential steps of chemical synthesis of analogues will be done, which will be followed by their biological testing to further optimize the lead molecule in terms of their selectivity, potency metabolic and pharmacokinetic behavior, bioavailability, and finally activity in relevant in vivo animal models of disease [9, 13]. At this point there is a great opportunity to investigate and to minimize any anticipated toxicology. After this intensive phase, the molecule is ready for preclinical pharmacology and followed by clinical testing. Due to multifaceted and prolonged steps involved, the drug development process takes several years to complete. It demands a serious investigation to establish the safety profile of the compound, along with the optimization of the drug dose to be used and finally its efficacy in treating the disease [12].

9.3 Advantages of Sustained Release Technology in Drugs

Despite the plethora of scientific and technological progress, the entire process of drug discovery and drug development still demonstrates a high degree of uncertainty and the process is typically based on serendipity [4]. This leads to most of the time high rates of failure at clinical level. Therefore, there is an urgent requirement to make an entire process foreseeable. In this regard, the role of biotechnology in the drug industry is booming [2]. For instance, the Human Genome Project had a breakthrough role in changing the fate of entire drug discovery process and the ways new medicines are discovered and thus set up the foundation of the biotechnology era in bringing the new medicine at fast pace. The significant contribution of this project is perceived in a way that it will transform pharmaceutical research and drug discovery processes and improve the lives of the patients [2, 5].

9.4 Molecular Complexes and Their Stability

9.4.1 Traditional Small Molecule Drug Development

Here, biotechnology as a tool allows the researchers to focus the drug discovery process particularly on a single molecular therapeutic target. For example, the tools and techniques allowed in this regard are molecular biology, biophysical and biochemical methods. These methods are utilized to identify specific drug targets along with target validation, target protein expression, and generation of specific drug

screening assays. Although recombinant technology has its own niche in the drug discovery process, it is important to mention here that it is not involved in the synthesis of the leads and development of the candidate compound [2, 14].

9.4.2 Protein Therapeutics Development

In this process, which may include not only the traditional small molecule, but also the important role of recombinant technology in the expression or synthesis of protein medicine. In this regard the notable example of protein therapeutics is antibodies, which will be discussed further at length in this chapter [2, 14].

9.5 Evaluation of Toxicity of a Drug, Approval of New Drugs, Clinical Trials, and Post marketing Surveillance (PMS)

Before the development of the concept of drug target, most of the pharmaceutical research used to be specifically focused on the identification of pharmacological effects of the potential therapeutics [5]. Moreover, the activity of a given therapeutics was described as targeting a disease. Later, to search the specific therapeutics to treat the disease and simultaneously increasing the success at drug development level, the term "target" was coined. So, what is a target? The term, target, is a recently evolved concept, which describes a specific protein or a molecular entity [2, 5]. More precisely, it is a molecular or a cellular or even a biochemical unit which can be affected or regulated by a specific action of the therapeutics. As per the present rough estimate, the number of targets affected by the drugs in the clinic is between 120 and 500 [5]. Interestingly, if we talk about the most successful drugs in the market, the estimated number of targets is 43.4 [5, 14, 15]. On the other side, there are about 7% drugs in the clinical practice with no known targets [5, 14]. As we explained above, targets are molecular entities which make them specific candidate to be regulated by the medications during diseases. Biotechnology has played a significant role to understand the precise role of these targets both in homeostasis and in pathology. Intriguingly, studies show that during inflammatory conditions, where multiple pathologies share the common underlying disease mechanism, targeting that common molecular entity could result in beneficial outcomes [16]. Thus, once we know the specific target in disease condition, we may predict both efficacy and specificity of the potential therapeutics. We may even predict the adverse effects and the toxicity profile of the medications. In this way disease could be managed without serious adverse outcomes [15, 16].

9.5.1 The Role of Genomics and Proteomics in Identification of Targets

Mapping of the human genome followed by the development of proteomics flooded the information of the role of genes and proteins in health and diseases. Both genomic and proteomic studies also provided the precise targets of the drugs, which were hidden previously. Besides, development of latest scientific tools and techniques due to the advancement of biotechnology also enhanced the discovery of target genes [15]. However, this also poses a change to researchers to validate the so many drug targets, which are available to consider. Advancement of the research provides us a good estimate of the "druggable genome" and suggests the number of the genes as drug targets or "druggable genes" are somewhere around 5000 [17, 18]. Besides, the number of diseases modifying genes are estimated about 3000 [17, 18], and estimate of overlapping between above two groups is somewhere between 600 and 1500 [17]. Please note that the above estimate is excluding the recombinant protein drugs and the soluble, extracellular targets for antibodies, used as the therapeutics [5].

9.5.2 Proteins as Potential Drug Targets

In human proteome we may find a family of proteins such as protease, G-protein coupled receptors, and family of kinases [19]. Medication are available clinically to target currently 130 families of proteins, in which about half of the drugs target six gene families [18]. These six gene families are G-protein coupled receptors, zinc metallo-peptidases, nuclear hormone receptors, serine/threonine and tyrosine protein, serine proteases, and phosphodiesterases [18, 19]. On the one hand it may look tempting that evaluation helped us in that aspect, however, realistically it brings complexities due to the reason that homology would remain very high particularly at the conserved domains of the active sites [5]. Besides, there is a tendency that a drug molecule, which is a member of one target family may be able to bind and inhibit the related molecules. Thus, it is understandable how much time and effort are required to develop very specific therapeutics. Besides constraints in targeting the family of proteins, it brings its own advantages on the other side. For example, chemical libraries can be developed with leads variants for protein families [20]. This will increase a significant propensity of a "hit" with another member of the family during high throughput screening [21]. Further, inadvertent or chance cross-target most of the times may turn out to be advantageous [20]. This can be conceptualized with the help of example such as imatinib mesylate (Gleevec), which is a tyrosine kinase inhibitor [5, 22]. It is initially developed as a drug to target bcr-abl. However, it was revealed that it targets and inhibits four distinct families of kinase such as bcr-abl, c-kit, the two PDGF receptors, and ARG kinase [5, 23]. The drug's action on these other kinases may appear as off-target action, however, the

prevailing understanding of the mechanism of action of the therapeutics suggests that all the afore mentioned targets are required for the inclusive efficacy of the medication [24]. In another example, an antibody abciximab (ReoPro), which is in clinic, targets a glycoprotein IIb/IIIa (GP IIb/IIIa) [25]. Later studies show that it may also bind to the vitronectin receptors avb3 and the Mac-1 receptors [5]. Studies suggest that those off-targets are clinically important and beneficial [26]. These observations demand a very careful pharmacological analysis of the medications to delineate their mechanism of actions [15]. It is worth to mention here, these further clinical assessments should not remain to be restricted at only developmental stage of the drug, rather it would be useful if it may be applied to the approved medications as well [15].

9.6 Drug Delivery Systems: Introduction and Types, Targeted Drug Delivery, Vehicles for Targeted Drug Delivery

Both the academic researchers and physician scientist are heavily involved at early stage of the drug development as well as on the clinical trials [27]. Besides, they are involved in the optimization of the treatment schemes following drugs approval [27, 28]. These clinical studies revealed how the drugs work in human body and provide relevant information about the possible targeting of the pathology particularly in disease sub-set responder and non-responders. Therefore, these data set not only provide a novel mechanism of action of the drug in question, but also provides feedback on medical need in the patients who failed to show response to the drugs [29]. Therefore, not only non-responder class but even partial responders may emerge as novel subpopulation which requires a new drug with a different mechanism of action to treat. It is important to mention here that to diagnose a disease using a conventional single approach may not be enough in the above set of population [28]. This requires novel ways to get deeper knowledge of pathology due to the involvement of multiple molecules. In this regard gene array and other advanced biotechnology tools are warranted to accurately characterize the sub-set of patients and later to identify the novel targets to treat the disease. For instance, the use of novel anti-TNF class of drug therapies is currently under active investigation to treat rheumatoid arthritis in patients [28, 29].

9.6.1 The Role of a Target Product Profile in Drug Discovery Process

The target product profile is the exact expectations of the drug candidate in the process of the development [30]. If we talk about the small molecules, this profile includes the anticipated clinical indications, the proposed mechanism of action of the drug, the drug target, drug specificity, affinity, in vitro and in vivo potency, pharmacokinetic profile, biopharmaceutics characteristics such as drug absorption, distribution, metabolism and elimination [5]. Besides, chemical accessibility, safety profile of the drug, and biomarker requirements are also being considered for the target product profiling [30]. For the therapeutic antibodies, the criteria include suggested clinical indications, the target of the antibody, the mechanism of the action of the antibody, epitope affinity, specificity, constant region isotype, expression rate in mammalian cells, effector functions, specificity in formulations, unwanted effects, pharmacokinetic and biomarker requirements [31].

It is necessary to mention here that biomarkers are important to decrease the risk in drug discovery projects [9]. It is worth remembering that when two discovery projects are competing for scarce resources, the one with predefined knowledge of biomarkers should be preferred [5] because it has a better chance of being successful [9]. The next logical question arises who provide the input of biomarkers? The answers include pharmacologists, molecular and cell biologists, regulatory scientists, and clinicians. Next to the biomarkers, is the implementation of plan of how and when each of the profile parameters is assessed. It is imperative to understand here that the problems in pharmacokinetic parameters of the drug such as absorption, distribution, metabolism, and elimination (ADME) are used to contribute about 40% of the clinical drug failure. However, early implementation of in vitro and in vivo tests reduced this failure rate to about only 10% [31]. Besides, the biochemical and cellular assays, reagents, surrogate antibodies, reference compounds, and animal models are cornerstone requirements of the successful target product profile. Therefore, target product profiles develop and thus evolve throughout the life of a discovery project [31]. However, the following three points are significant [5, 32]:

1. If require any changes to the target profile, it only occurs according to the thorough review of the up to date scientific data.
2. When progress from one project transitions to another, the target product profile is the only reliable standard to follow for approval. Since organizations vary within their own criteria of defining target profile, thus, transition criteria will be solely based on the specific target product profile.
3. Each specific component of the discovery project such as chemistry or antibody technology, proof-of-concept research, ADME assays, etc. should be at the appropriate pace relative to each other. For example, if one activity of the project is going on at a faster rate than others, required tests may not be feasible, and thus proof-of-concept test may be conducted too late. This will be very difficult

to continue the project due to the lack of scientific foundations. Therefore, it is required an appropriate and balanced resourcing to manage all arms of the projects including a sound planning and collaboration. Thus, it is difficult to conceive an idea of successful drug discovery project without a target product profile, with the notion that all the concerned departments and relevant people are determined to work as unit [5, 32].

9.7 Advantages of Targeted Drug Delivery System

Initial discovery of the potential drug targets differs substantially from one another in terms of validation [13, 20]. The academic pharmaceutical or biotechnology researchers contribute immensely in the investigation of the biology of a target [20]. Following the target identification including from the genome database require complete validation to its role in normal physiology, and the intended target disease, before moving forward towards expensive drug discovery cycle [33]. The pharmaceutical and biotechnology fields have generated novel platforms and technologies that provide additional key information helpful to take decision regarding the forward move of the target. It is clearly defined that thorough target validation is of utmost necessity to prevent high rate of failure of the discovery [33]. However, already validated and researched drug targets most of the time may need very minimal process of validations and thus save time as well as money [13]. However, as general rule in the process in industry researchers are always inclined to confirm published reports on drug target validation because of the developments and validation of reagents and assays in the laboratory [33]. Once the targets become validated, it would signal to move on to the in vivo pharmacology and biomarker development phase of discovery cycles [34]. One of the important reasons of these studies is the fulfillment of the regulatory requirements, which ask specifically about the thorough understanding of the mechanisms of drug actions before moving forward to clinical studies [35]. This phase of the discovery also elaborates the unwanted effects of the drugs including the toxicological effects [33].

As suggested by Jurgen Drews [36], former president, Global Research of the Roche Group, the target validation is not a onetime process, rather it is continuous process throughout life cycle of the project [5]. He laid out the following four-point criteria of the target validation [5, 33, 35, 36].

1. The manipulation of a potential target by genetic or pharmacological means should consistently lead to phenotypic changes that are consistent with the desired therapeutic effect.
2. The observed effect should be dose-dependent (this is approachable once early drug leads with enough specificity are available). Alternatively, conditional knockout (see below) could be used.

3. The desired phenotypic changes must be inducible in at least one relevant animal model. If possible, several animal models should be used, all of which reflect at least some important aspects of the human pathogenesis of the respective disease.
4. The specific mechanism of action of the new therapeutic agent and any possible off-target activities should be known. This would allow for appropriate benefit and risk assessment.

9.8 Genomics in Drug Discovery

One of the most promising tools emerged in recent years is the use of the gene-deleted or gene knockout mice model in target validations [14, 37]. Upon deletion of the target gene in the mice and if the mice will be viable, this technology will completely block the biological effects of the target in mice [34]. Gene knockout technology will also provide any causative role of the target on the development of disease, if any, in the mouse model [38]. These mice will provide the overall role of the target on the physiological outcomes [37]. This will ultimately provide the relevant data on the biological functions of the target [14, 34].

Studies also show the role of the knockout mice model in the investigation and identification of "druggable" genome [38]. Although this is still in infancy but has tremendous potential to provide information on novel druggable targets. Besides, these knockout models serve as a valuable tool to identify prophylactic intervention, where the gene is already deleted before the induction of the disease [14, 38]. Next to the whole-body knockout, research has shifted heavily in conditional knockouts where they are deleting the gene only in specific tissue or organ in the mouse body [39]. For example, the endothelial specific knockout mouse models are catalyst in the identification of drug targets to prevent and treat vascular inflammatory diseases such as sepsis, acute respiratory distress syndrome, and atherosclerosis [38, 40]. Thus, these conditional knockout mouse models are more relevant for therapeutic interventions [41]. The disease can be induced in the adult mouse with the gene in the "on" state, and the gene is later turned "off" by a generic agent that triggers a genetic switch. These models are providing clinically relevant data with high precision and reproducibility. They also helped to lower the cost of the drug research by decreasing overall time of the target validation [41].

In vivo research will further complement in vitro cell culture research using primary or modified cell lines [42]. So, while the researcher will be waiting to get the genetic knockout mice, the basic premise of the research would have been done on cell lines. This will further validate later the mouse models [43]. This will provide a robust data sets and complete function of the drugs targets under in vitro and in vivo environment. In vitro target identification technology will also enhance the development of novel biochemical assays to screen the novel drug molecules in short span of time. This will provide quick guide on the biology of the targets including their mechanism and side effect profile [42].

In recent years the small-interfering ribonucleic acid (siRNA) technology has emerged as a powerful tool for target identifications and validation both in vivo and in vitro. siRNA technology is employed to deplete the genes in animal models and cell lines [44]. Unlike gene deletion technology, which is irreversible, the siRNA technology deletes gene in a reversible manner [40]. This technology is deeply immersed in the laboratories both in academic and industry research focusing on the drug discovery [40]. High number of peer reviewed published articles are coming up regularly and further validating the potential role of this technology in biotechnology and drug research [44].

9.8.1 The Role of Academic Research in the Drug Target Identification and Validation

Academic researchers are actively involved in drug discovery research and utilizing heavily both in vivo and in vitro models [40, 45]. Their research provides insights on the role of the targets in health and diseases [46]. Academic scientists are meticulously involved to understand the signaling pathways that regulate the targets in the molecular and cellular environments [45]. Researchers investigate both upstream and downstream signaling, which will be very helpful in understanding the molecular circuitry of the drug targets [46]. This will be further helpful in the prediction of adverse profile of the target. Thus, a close networking between academic and industry scientists is required to fully yield the potential of their work and decreasing the time and cost of the drug discovery [45, 46].

9.8.2 Potential Role of Technologies in the Process of Target Identification in Drug Discovery Process

Statistics show that drug discovery failure rate is high and only less than 1% of projects yield the compounds for further clinical development [47]. Data show that only 10% of those 1% compounds will end up to be approved by the FDA to treat diseases in the clinical setting [48]. This gives a picture that there is very high risk of failure compared to success in drug discovery process [47]. Recent industry trends further show that the success rate is higher in protein-based therapeutics including antibodies-based discoveries as compared to small molecule inhibitors [47]. This data guides the companies to invest in balance way to enhance their success in the process. It also brings into attention that companies should also invest to build up their technology and expertise to be involved in wide range of the projects [47, 49].

9.8.3 Antibodies vs. Small Molecule Inhibitors as Therapeutic Agents

The therapeutic antibodies are emerging class of drugs and hold a great promise in the management of variety of diseases [50]. As of December 2019, 79 therapeutic monoclonal antibodies have been approved by the US FDA, but there is still significant growth potential [51]. Antibody-based therapeutics provide predictable responses, faster delivery due to the intravenous route of injection, and require short period of time to validate the target. On the other side, small molecules possess their own line of advantages including oral delivery due to better bioavailability; however, less efficacious compared to therapeutic antibodies [51]. Regarding the discovery risk, antibodies developments have a lesser risk of failure compared to small molecule drugs due to differences in their specificity and the structure and binding to their unique epitopes. For example, antibodies interact with their larger region of the target molecule surface, thus providing a higher rate of selectivity and affinity. Small molecule drugs often displayed more conserved binding to their target sites and thus less advantageous compared to antibody therapeutics. Due to the profound specificity and inability to cross plasma membranes, antibodies have minimum "off-target" effects and thus less toxicity. This brings another advantage of them over the small molecule drugs [51].

9.8.4 Example of Antibody Therapeutics

Although antibodies as therapeutics gained clinical popularity and approval in recent years, the foundation was laid down more than a century ago when Behring and Kitasato received the Nobel Prize for passive immunotherapy [52, 53]. Later, in their ground-breaking work, Milstein and colleagues after isolating monoclonal antibodies provided the cue that a paradigm shift in the medicine would soon be going to be witnessed [54, 55]. Since then with advancement of the technology allowed the development of initially murine and chimeric, and followed by humanized antibodies, and now we are having fully human antibodies are actively involved in diagnosis and treatment of the previously thought treatable diseases. Today, more than 80 antibodies are approved by the FDA as potential therapeutics for the treatment and the management of cancers, rheumatoid arthritis as well as for the prevention of transplant rejection [50, 54].

As the understanding of the antibody-based therapy grew, it was recognized that mouse and mouse-sequence-containing antibodies are not efficacious due to identification of them by the human immune system as foreign. Later, recombinant human antibodies are generated and gained popularity clinically and were also better accepted by the human system. These antibodies were developed by employing advanced molecular and cell biology techniques such as phage display [55] and transgenic mice with a human immune repertoire [54, 56].

One of the major breakthroughs happened when FDA approved Adalimumab (Humira), a fully human monoclonal antibody in 2002 and by the European Medicines Evaluation Agency (EMEA) in 2003 for management of rheumatoid arthritis in patients [57, 58]. Adalimumab was discovered using phage display technology [57, 59]. This antibody is an immunoglobulin G1 (IgG1), which contains highly selected heavy and light variable domains of human origin [59, 60]. Adalimumab has a high specificity and an affinity for TNF but not with other inflammatory cytokines, such as lymphotoxin. It exerts its pharmacological effects by blocking the interaction of TNF with p55 and p75 TNF receptors [57, 58].

9.8.5 Biomarkers

Good biomarkers play cardinal role in a drug discovery project in the company. These biomarkers are acting as connection between animal models and patients and are significant in assessing the impact of the drug molecule on the target [61, 62]. Recent literature shows that changes in a biomarker need to be measurable objectively such as by using gene array technique, enzyme-linked immunosorbent assay (ELISA), etc., in response to the drug intervention [5, 61].

By determining the effect on potentially known downstream biomarkers, we can determine if the drug is affecting the intended target or not [1]. Besides, biomarkers for other pathways help to assess the specificity of the effect [62]. It has been shown that when the therapeutic molecule has the required effect on the biomarkers, however the clinical assessment measures failed to show any effects, this observed discontinuity is either may be due to the dose of the drug or it could be due to inappropriate duration of the treatment [1, 5]. When the biomarkers indicate complete target inhibition, but the disease still does not respond, it is likely that the target is inappropriate for the disease [1, 5].

9.9 Summary

Drug discovery is always a risky process for companies. However, using proper approaches and strategies including latest available technologies, a company may energize its discovery research to maximize the success rate. To check on the failures, companies also require focusing on their available resources including regular training of the researchers on latest techniques, internal decision-making capabilities, choosing the appropriate projects and establishing the goals and improving project management and collaborative environments. Besides, industry-wide data collection on the overall success and failure, will help to set the priorities, and streamline the projects. This will provide the team with the direction where project will be moving and researchers will learn from successes and from the failures in a timely manner and will be able to take an informed decision.

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