**Biological Research and the Drug Development of Rare Genetic Disorders**

**Abstract**

There are many cases of rare genetic disorders in the United States. Millions of people in the United States are affected by approximately 7,000 rare diseases. Are researchers and their studies doing well on the knowledge of this? There actually is a lot of research on how the genetic disorders occur and how and what is being done to not exactly cure the disease, but to stabilize the rare occurrence. As mentioned, a lot of research has been done and is still going on. With that being said, drug discovery has grown rapidly. Examples of drug repurposing and some explanations on how it is done, is given. As well as the pros and the cons of the target-based screens are discussed. Reflection about biologics will be given, such that about recombinant and gene therapy, along with autologous transplant. The type of disease models used and the role biomarkers have in drug discovery will be taken in consideration.

**Introduction**

Research and drug discovery have risen very fast these last few years. The advancement of what is pharmacogenomics and in the rare disease diagnostics, have made a better understanding of these rare diseases (Sun, Zheng, & Simeonov, 2017). There are about 7,000 rare diseases in which they are identified and the way that they are caused. A long time before the ODA (Orphan Drug Act) was made, there were only ten drugs had been approved by the FDA(The Food and Drug Administration) (Sun, Zheng, & Simeonov, 2017). Compared to what has been discovered and made this day, it was very low. There is something referred to new molecular entity (NME) and BLA. These are the ways that a drug can be approved by. NME is a drug that has not been able to be marketed in the U.S. (Sun, Zheng, & Simeonov, 2017). A BLA is more on the information of the pharmacology, clinical and manufacturing processes of the specific biological product. If by any means this product doesn’t reach the compatibility of the FDA requirements, it is declined. If it does meet with the FDA compatibility, it is accepted and a license is then issued and the company can then market the product. The number of NMEs and BLAs have increased over the years. For example, in 2006 there were 5 and it increased to 21 in 2015. These were obviously just for the rare diseases (Sun, Zheng, & Simeonov, 2017 Figure 1b). The drugs that are used to treat what are known the rare diseases are called Orphan drugs. The Orphan drugs serve for the positive effects on the disorders. Some of the advantages of them are that they lower the cost and development of research, less generic competition, and shorter development. It’s said that more than 35% of the FDA drugs have helped with treating the rare diseases. One of the cons of this is that the cost of the treatment is high, notable to the fact that not many patients suffering from the same rare disease. The biggest reason that these diseases even occur is due to genetic mutations. The diversity of diseases makes a huge impact on how challenging it is to achieve good treatments.

**Recent Progress**

Drugs are the biggest impact for treatment, therefore; they have to have significant resources and it has to last ten to twelve years (Sun, Zheng, & Simeonov, 2017).

Drugs from small-molecule contain some advantages. They are super easy going through manufacture, oral admission, well-defined structures, and non-immunogenic profiles. The NMEs that were FDA approved, were orphan drugs and mainly small-molecule. That was through 2000 to 2008 where 22% of the NMEs were that (Sun, Zheng, & Simeonov, 2017). Drug discovery has been transformed throughout the years. What is now used is very well advanced, along with the development. Examples of the well development discovery is as listed: target identification, assay development, compound library, high throughput screening, screening data analysis and hit selection, hit confirmation, lead optimization, and preclinical drug development. A whole genome or exome sequence have helped with the discoveries of the cause of these rare diseases. The very first thing identified is a protein target, such as an enzyme. An assay is then made after the target is identified. The reason for this is to figure out the therapeutic therapy needed for the “candidate” (Sun, Zheng, & Simeonov, 2017). Then, small-molecule drug candidates are collected. Proceeding that, when the assay is well developed and is as best as can be, large sections of screening of the small-molecule is made from a automatic robot. This robot has been a great discovery making it high advanced and super efficient with time. Some kind of informative software is used after to load up into a database. With that information, it is then analyzed. The rest of the steps are to confirm, optimize, and the preclinical drug development. So, this process is for the diseases where the etiology is known. The only thing is that not all the etiologies are known for all rare diseases. It’s known that the genome has mutations and that’s why it is caused and that it’s a protein that mutates. There are still discoveries going on and as technology keeps advancing, there should be better research. Biologics is something very important for this kind of topic. Biologics include gene therapies, recombinant proteins, blood, tissues, cell, vaccine and blood. These are more complex than small-molecule without defined structures. It is believed that biologics are more effective for these that lack approved therapeutics (Sun, Zheng, & Simeonov, 2017). Enzyme replacement therapy, other recombinant human proteins, stem-cell based therapy, and gene therapy are examples of biologics. Stem-cell therapy is one really important biologic. It helps out with bone marrow transplants and it helps with long-term correction (Sun, Zheng, & Simeonov, 2017). There have been some issues that have occurred during this kind of therapy though because of the bone marrow transplant. The incidents such as failure of reconstitution, graft versus host disease, severe infection, and even death (Sun, Zheng, & Simeonov, 2017). They are trying better ways to make this method better. Gene therapy is used for the diseases that were caused by the gene mutation or the loss of a gene. What it does is that it delivers a normal and functioning gene as a nucleic acid polymer into the patient’s cells to the part where it has those missing genes. This is a process and it has it pros. Disease models are a big part and can help out with the finding the right of drug needed, the makeup of the rare disease, and even the assessment of the drug. The types of disease models used are: cell-based models, those who use IPSC(Induced pluripotent stem cell), and animal disease models. Biomarkers have huge impact on the clinical drug development. They are put in four types of categories such as the surrogate, pharmacodynamics, predictive, and prognostic biomarkers (Sun, Zheng, & Simeonov, 2017).Biomarkers really help out with drug information towards the therapy and the improvement of drug development in clinical studies. A surrogate measures drug efficiency and serve as end points in clinical trials (Sun, Zheng, & Simeonov, 2017, Table 3). A pharmacodynamic detects the activity of a drug on the targeted pathway (Sun, Zheng, & Simeonov, 2017,Table 3). A predictive reflects biology central to disease pathophysiology (Sun, Zheng, & Simeonov, 2017, Table 3). A prognostic links with disease activity but may be distal from the targeted pathway (Sun, Zheng, & Simeonov, 2017, Table 3). Biomarkers are really helpful and are needed for the clinical drug development.

**Discussion**

In conclusion to all of the information given, the biological research programs do what they can to grab all needed information. Yes, there are a lot of rare genetic diseases identified and what the causes of them are. On another note, not all are identified and not all of their etiologies are known. With that being said, right now the United States has some great advancements on its technologies and drugs development that there are many possible ways to not hinder out the possibilities of finding the new rare diseases. Of course there are still many and many unanswered questions, but with the advancement the U.S. has, there should be many more discoveries as well. Researchers and doctors are working alongside with their patients and helping them understand the cause of their diseases. Doctors have hope that they can discover life-saving therapies for the people suffering of rare genetic disorders.

**References**

Wei Sun, Wei Zheng, Anton Simenov; “American Journal of Medical Genetics”; “Drug discovery and development” 21 July 2017.