

The Development History of Huntington's Disease's Therapeutic Strategies: Events and Lessons Learned

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Abstract. Huntington's disease is a kind of fatal autosomal dominant neurodegenerative disorder. In terms of treatment approaches, the gene-silencing strategy was recognized as the most promising method to treat Huntington's disease. However, several recent high-profile clinical research have failed due to some reasons that were previously overlooked by researchers before. This review is written for the purpose of reviewing those failures and concluding their reasons, then illustrate possible directions of future treatment. In this review, three different kinds of failure reasons of three different pharmaceutical companies are concluded. Roche failed to distinguish the allele specificity, wrongly lowering both wild type Huntington's (HTT) protein and mutated HTT protein; Wave Life Science failed to keep the structure and the function of Antisense Oligonucleotide (ASO) drugs after they are delivered; and Novartis failed to promise the targeting precision of its small molecule drug. In the future, more precise and stable drugs will be the next direction of the development of treatment. The newly modified ASO drugs possess the hope to improve its stability after delivery, and the new generation drug CRISPR-Cas9 can be more precise with its deliverer Adeno-Associated Virus (AAV) virus.

Keywords: Huntington's disease, allele, Antisense Oligonucleotide, Brain Blood Barrier

1. Introduction

Huntington's disease is a devastating neurodegenerative disorder characterized by progressive motor dysfunction, cognitive decline, and psychiatric symptoms. The main source of Huntington's disease is the mutation of HTT gene [1]. The mutated HTT gene repeats CAG sequence, which is a kind of trinucleotide [2]. Within unaffected people, the CAG sequence will only be repeated around 6 ~ 35 times, while people with Huntington's disease can have more than 40 times of repeated CAG sequence, called trinucleotide repeat extension [3]. The HTT protein produced by the HTT gene is extremely essential for human neural systems. It assists neuronal migration, synaptogenesis, and the suppression of apoptosis in neural cells [4].

First, it undertakes the role of transporting a kind of neural factor named Brain-Derived Neural Factor (BDNF), which is a kind of extremely important factor [5]. About this BDNF, it plays an essential role in memory and anti-apoptosis. It binds to receptors in synaptic gaps, mainly TrkB receptors, and grows a new dendritic spine to enhance the connection between neurons [6]. Every patient has two HTT alleles, mostly a normal one with a mutated one. Different kinds of HTT genes

will produce different kinds of HTT proteins. In patients, mutant HTT protein with expanded polyglutamine tracts (mHTT) will be toxic. Excessive long mHTT protein could be very hydrophobic, so proteins cannot keep functional 3-dimensional structures. They will wind together, form oligomers, and finally become inclusion bodies. Massive oligomers will dissociate everywhere and combine with other proteins and interrupt normal function [7].

Patients who suffer Huntington's disease will perform three dominant symptoms: movement disorder, cognitive decline, and psychiatric symptoms [8]. Patients express involuntary dancing twitches, limbs and face twitch without control; they show significantly impaired processing speed, hard to remember new things; they usually show severe psychiatric issues like depression, anxiety and so on [9].

According to data, global pooled incidence is about 0.48/100,000 people, and the global pooled prevalence is about 4.88/100,000 people [10]. However, the pooled prevalence could be very different across different regions. For America and Europe, the pooled prevalence could be extremely high, some regions even could be more than 12/100,000 people. Asia has lower data, about 0.4~0.99/100,000 people. Africa is lower, about 0.25/100,000 people [11]. This circumstance is due to the difference in hereditary conditions. White people widely possess a kind of highly risky HTT genetic haploid named Haplogroups A1 and A2, but Asians and Africans possess a safer type named Haplogroups C. Plus, most of them possess a longer CAG repeat than Asians and Africans do [12].

In the past decades, numerous pharmaceutical companies endeavored to invent and produce powerful drugs to treat Huntington's disease. The most famous event is the collaboration of Roche and Ionis Pharmaceuticals [13]. Their first theory about Huntington's disease and the HTT gene is that all kinds of HTT genes are the source of Huntington's disease, thus, they decided to remove all HTT genes completely [14]. However, in the experiment, patients who received treatment deteriorated even faster than patients who haven't received treatment [15]. This failure reminds people of the importance of the normal HTT gene and leads to further research.

Furthermore, another instance, Novartis, has researched orally administered drugs to lower the level of mHTT protein [16]. However, in 2022, the experiments of Novartis' drug aroused severe peripheral neuropathy [17]. Those setbacks reflected the unprecedented challenges in central nervous system drugs development. In this article, the failure events of those drugs, the reasons why they cannot reach success, and the experiences and lessons people have to learn are discussed. By synthesizing those historical events, this article aims to provide valuable insights for future directions for the design of new HD therapeutic drugs.

In this article, the history of drugs for Huntington's disease, their failures, and the lessons that can be learnt from those products will be mainly discussed. Furthermore, some possible future directions will be constructed by this article.

2. Neglect of allele specificity

When Roche, a huge pharmaceutical company, started to make plans for treating Huntington's disease, a characteristic of Huntington's disease occurred. They didn't notice the problem that HTT has two alleles, which became a potential risk for future.

Commonly, if a drug has the purpose to silent or even cut off the target gene but keep the healthy gene, the drug has to take advantage of Single Nucleotide Polymorphism (SNP). SNP means that, among human beings, the majority of our nucleotides in DNA are the same, but some small points will be different due to some mutation [18]. SNP could be an essential biomarker that could be used to mark mutated gene parts of Huntington's disease. However, it holds some drawbacks, and the

most apparent one is that the generalizability of certain kinds of SNP could be limited. It is hard to develop several kinds of drugs with certain SNP kinds to cover the majority of those patients. If a patient has a specific kind of SNP, then the whole set of drugs need to be custom-tailored. That is both time and money consuming and not friendly to normal people in society. To avoid the problem, Roche decided to develop a kind of drug with 100% generalizability in order to fit every patient in the world. Thus, they decided to eliminate both healthy HTT mRNA and mHTT mRNA.

Roche operated an experiment first to test whether eliminating healthy HTT mRNA will be harmful to creatures. They used small rodents and non-human primates, lowered their HTT protein level under 50%, and didn't observe any obvious negative influence [19]. This initial result appeared encouraging, and it is regarded as a sign of success. However, this scene showed potential risk for future experiments.

Roche has developed a kind of drug named Tominerson, which is used to treat Huntington's disease. Tominerson is a kind of ASO, which is a kind of short DNA/RNA heterochain. The principle is, first, they are designed as a complementary shape of human HTT mRNA, so it aims to HTT mRNA and try to combine with them. Once they find and successfully combine with those mRNA, a kind of enzyme called RNase H1 will identify the combination and destroy it.

In January 2019, Roche initiated the trial named "GENERATION HD1" and recruited 899 participants with dominant Huntington's disease. The experiment operated 3 groups: patients in the experimental group 1 are treated with 120mg Tominerson, which is the drug developed by Roche for Huntington's disease, 8 weeks a time, so called q8w; patients in the experiment group 2 are treated with 120mg Tominerson 16 weeks a time, so called q16w; and patients in control groups are treated with placebo [20]. March 22nd, 2021, iDMC prohibited the whole experiment after they analyzed the data. They found that there was a growing speed of decomposition of patients' neural systems in the q8w group, even faster than that of patients in the control group [17]. Roche found that patients who received the drug suffered apparent speeding up of cerebral atrophy, even higher than that of patients in the control group [20].

This failure aroused widespread concern in the medical field, and people started to discuss the potential risk of encephalatrophy [21]. The science field was completely shocked by this result, "Whether the healthy HTT protein is necessary in the human brain" became a hotspot [22].

3. Obstacle of delivering, instability of structure

Another famous company that strived to research new drugs for Huntington's disease is Wave Life Science (later referred to as WLS). Their target is different from that of Roche. Instead, they decided to knock down any mutated [7] alleles and cure the disease permanently. Therefore, they used another kind of technology, SNP, as introduced before.

WLS found that about 2/3 of Huntington's patients carry certain disease-associated SNPs on their mutated alleles. Thus, they designed a drug with ASO to identify the specific SNPs. The drug will only identify and bind to mRNA sequence which contains the SNPs.

This kind of drug resolved the problem of targeting by taking advantage of SNP locating technique, making the whole process becoming more precise. It seems like the strategy has already resolved all problems that have occurred on Roche's result. However, the fact is, the drug WLS possesses limitations, too. The most apparent one of backwardness is the transportation problem, the drug cannot cross the brain blood barrier (BBB).

BBB is a natural shelter of the human brain. It is a complex neural blood vessel unit, and it is a kind of highly selective pellicle. It is formed by Brain Microvascular Endothelial Cells (BMEC), pericytes, astrocytes, and basement membrane [23]. It is not only a physical barrier, but also a

dynamic modifier. First, due to its tight construction, a vast majority of drugs and hydrophilic molecules cannot pass through. Second, it has plenty of transportation proteins to deliver necessities into or out of the brain. Third, it contains many kinds of enzymes, and those enzymes will degrade substances that attempt to pass the BBB [24]. Due to these characteristics, ASO drugs cannot go across the BBB due to three main reasons: firstly, its molecular mass is huge, about 7000 Da, far beyond the crossing limitation of BBB, which is 500 Da or less; secondly, in order to prevent ASO drugs from easily degraded inside cells, researchers use phosphorothioate regulation on their main chain. Because of this, ASO drugs are fully negatively charged and highly hydrophilic, which means they cannot go across the BBB because of its charge [25].

While the molecule amount of ASO is too large to go across the BBB, neither WLS's drugs nor Roche's drugs can be successfully delivered into the brain and work. To bypass the BBB, WLS figured out a new method, which is Intrathecal Injection, which means inject drugs into cerebrospinal fluid in the spinal cord cavity which is located at the lower back of patients. Then, the drugs will be delivered into the brain and via the circulation of cerebrospinal fluid [26].

However, because of the instability of ASO structure, drugs of WLS cannot keep highly efficient after entering the brain. Therefore, the therapeutic effect could be extremely weak. According to the data of an experiment operated by WLS, the level of mHTT protein in experimental groups only lowered less than 10%, and it did not have statistical significance compared with placebo group [27].

This failure aroused a problem, which is a popular hotspot in the biomedical field, that: How can drugs go across the BBB noninvasively without the loss of therapeutic effect? In the future, nearly every kind of medicine that works in the brain has to consider this problem carefully.

4. Drug size and off-target effect

Apart from ASO drugs, there is another totally different drug that exists in the world, which was unexpectedly discovered by Novartis, a pharmaceutical company in Switzerland.

Branaplam, an oral RNA Splicing Modulator that is originally developed for treating Spinal Muscular Atrophy (SMA), was accidentally found that it could be useful in treating Huntington's disease.

As an RNA Splicing Modulator, the principle of Branaplam is totally different from the two kinds of drug that are discussed before. First, Branaplam will combine with HTT pre-mRNA at a specific position, and this combination will change the 3D structure of this pre-mRNA. Thus, due to the change of structure, spliceosome, a large ribonucleoprotein complex responsible for pre-mRNA splicing in cells, will cut off the introns of pre-mRNA and sew up other exons, will be deceived [9]. It will misidentify an intron into an exon, so called pseudo exon, and keep it. After that, this pseudo exon will be spliced with other normal exons and become a part of mature mRNA [28]. Then, when the mRNA is being translated, the stop codon of the pseudo exon will stop the translation process, and this mRNA will be decomposed instead of being translated into protein [29].

Furthermore, Branaplam has a strong advantage: it could go across the BBB easily because it is small enough, electroneutral, and lipophilic [16]. This means Branaplam can be delivered into the brain without any invasive injections or even surgeries.

However, because of widespread peripheral neural injury in participants, the experiment of Novartis soon failed. After that, some research has proved why Branaplam will cause neural injury [30]. Branaplam is too small, so unavoidably, it will pose some slight, unpredictable effect on the whole transcriptome. It arouses severe Nucleolar Stress, which is a kind of upstream signal and will arouse strong p53 anticancer signals. Then, much more downstream apoptosis genes will be

expressed and a kind of protein named BBC3 will be translated. This protein is extremely toxic to the neural system. It will attack axons and dendrites, finally leading to severe decomposition of neural synapses [31].

5. Conclusion

In the past decade, those failures were not without value. They ended the era of oversimplified approaches of treating Huntington's disease, and compelled researchers to recognize the complexity of human brains.

Firstly, biological specificity becomes a definite red line of treatment. Human brains cannot stand the cost of losing wild-type HTT protein, which means any treatment in the future has to consider the allele specificity as an essential point.

Secondly, how to deliver drugs without disturbing its structure and weakening its pharmaceutical effect remains a critical challenge that deserves our consideration. A method can be found from the spinal cord to enter our brain, but we have to improve the structural stability of the ASO drug to keep its function after it enters the human brain.

Thirdly, the cost of escaping BBB via extremely small-molecule drugs might be considerably heavy. Small-molecule drugs require higher precision of targeting due to its characteristic of easy to be diffused to other places. If some specific drugs, especially those with the function of gene knocking down, are widely diffused to our other body parts, the result could be serious.

In the future, ASO drugs with better modification and the new generation drug CRISPR-Cas9 and AAV virus might be our next direction. Newly modified ASO drugs could be more efficient to keep structure function, and CRISPR-Cas9 could be more precise when it is locating target points. In the road of treating Huntington's disease, these failures provide us indispensable value to point out our correct direction of drug development.

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