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Short Communication

Current Opinion on Oligonucleotide Therapeutics for Allergy

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DESCRIPTION

In the previous article [1] we presented an overview of the state of oligonucleotide therapeutics development in Japan to the local research community as well as the international community of investors and researchers. In this communication we analyzed the state of research and development of oligonucleotide therapeutics for allergy. Oligonucleotide therapeutics has received attention as a new modality following small molecule and antibody drugs. Oligonucleotide therapeutics inhibit the translation of certain proteins from mRNA, regulate the expression of microRNA that are complementary to certain mRNAs [2], and involve decoys [3] that suppress transcription activities by targeting transcription factors. They also function as aptamers [4] that specifically attach to various proteins to inhibit intracellular signal transduction and as CpG oligos [5] that bind to Toll-Like Receptors (TLR) to generate innate immunity [6]. Splicing modulation is the mode of action of the antisense oligonucleotides used to treat Duchenne Muscular Dystrophy (DMD) patients [7]. Steroids, drug for allergies and asthma, are used in many cases as a symptomatic treatment for skeletal muscle symptoms in patients with DMD.

In addition, mRNA drug discovery in the field of oligonucleotide therapeutics is attracting attention. The idea of using mRNA as a drug has been around for a long time; however, it has been difficult to put it into practical use because of various problems, such as the extremely low stability of mRNA *in vivo*. However, due to the recent advances in RNA modification technology to improve RNA stability and Drug Delivery System (DDS) technologies, the practical application of mRNA drugs is progressing in the areas of allergy and COVID-19 vaccine [8,9]. Drug therapy by mRNA involves administering artificially produced mRNA to humans and producing treatment-related proteins from the mRNA in the human body to treat a disease. Since mRNA is administered, there is no need for viral vector-like gene therapies or concern that it will be incorporated into the patient's DNA.

Fifteen oligonucleotide therapeutics, including fomivirsen [4], pegaptanib [4], mipomersen [4], defibrotide [4], eteplirsen [4], nusinersen [10], inotersen [11], patisiran [12], volanesorsen [13], givosiran [14], golodirsen [15], viltolarsen [7], lumasiran [16], inclisiran [17], and casimersen [18], have been approved in various countries for a range of diseases. All these approved oligonucleotide therapeutics employ 20-mers or longer sequences with a molecular weight of approximately 6,000 Da. These approved oligonucleotide therapeutics have no use in the field of allergy and inflammation except CpG1018 as an adjuvant of hepatitis B virus vaccine. Oligonucleotide therapeutics for allergy and inflammation have been known as decoy targeting transcription factor, DNA agonist targeting TLR 7, 8 and 9, antisense oligonucleotide for enzyme and aptamer for cytokine. Oligonucleotide therapeutics for allergy and inflammation are under the development at the laboratory study level to the early clinical study.

The progress in domestically developed oligonucleotide therapeutics in Japan has been remarkable, although Japan started later than Europe and the United States. Thus, the innovative oligonucleotide and DDS products in Japan will contribute substantially to the field of oligonucleotide therapeutics and allergy treatment. For example, an ecosystem in the Fukuoka Bio community has brought seeds of technology that contribute to solving social issues to practical use at an early stage. Among them, Bonac Corporation established in 2010, developed oligonucleotide chemistry, including the research and development of the Bonac Nucleic Acids nkRNA and PnkRNA [19]. Although medical technologies have advanced, many intractable allergies remain unresolved by conventional medical treatment. Therefore, oligonucleotide therapeutics, an

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alternative type of drugs for allergy, will continue to be developed.

OLIGONUCLEOTIDE THERAPEUTICS FOR ALLERGY

The immune response is one of the essential mechanisms for the life support of the living organisms [20]. It has been clarified two major biological reaction pathways, the innate immunity and acquired immunity. The innate immunity is first activated and then the acquired immune is reacted by exposed antigens. The innate immunity is considered to initiate biological defense responses that recognizes and reacts with antigens such as viruses and bacteria in humans [21]. The cascades of immune responses are differed depending on the species, developmental stage, tissue/organ, and cell type [22]. Allergic diseases are thought to be a disorder of the homeostasis of the immune response system [23]. However, the mechanism of the cause and exacerbation of allergic diseases has not been completely elucidated.

The drugs used for allergic diseases are mainly small molecule drugs which are used symptomatically with inflammation. The oligonucleotide therapeutics has been expected as a new drug for allergies for more than 20 years since TLR 9 was identified as the initiating molecule of innate immunity. CpG oligo as oligonucleotide therapeutics for allergic disease is still under research and development level and has not reached the level of the approval [24]. From the current research and development status of oligonucleotide therapeutics, it can exert its effect on one kind of gene or protein. Because multiple factors are implicated in allergic diseases, the effectiveness of nucleic acid drugs as anti-allergic agents must be limited [25,26].

Recently, there was a report on a new type of oligonucleotide therapeutics to control inflammatory diseases that may be a breakthrough for treatment of the intractable inflammatory diseases [27]. Regnase-1 has RNA degrading enzyme activity and act as a brake on the immune response by degrading the inflammatory cytokine mRNA in various immune cells. Oligonucleotide therapeutics made from phosphorodiamidate morpholino group to show inhibition of the degradation of Regnase-1 was synthesized to present improvement of the symptoms in disease model mice for Acute Respiratory Distress Syndrome (ARDS), Idiopathic Pulmonary Fibrosis (IPF), and multiple sclerosis. Until now, oligonucleotide therapeutics has mainly suppressed protein expression by degrading mRNA and inhibiting translation. Increasing the amount of mRNA of Regnase-1 by changing the stem loop structure like this case was a highly novel approach. This oligonucleotide therapeutics, which suppresses the expression of multiple cytokines upstream, may be effective in treating inflammatory diseases and autoimmune diseases that are ineffective with conventional drugs. Regnase-1 was a new target for inflammatory diseases, which is different from anti-cytokine treatment and immunosuppressive drugs.

CONCLUSION

Effective treatments for ARDS and IPF are limited. For autoimmune diseases, immunosuppressive drugs and bio products are used and the treatment methods are rapidly advancing, but there are still patients who are refractory to these treatment methods. As seen in the Regnase-1 case, the development of new inflammation control methods by oligonucleotide therapeutics may be effective in various diseases associated with inflammation. In the future, oligonucleotide therapeutics may provide more advantages so that its application may supersede that of small molecule and antibody drugs for allergy.

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