Overview and Case Study of Antibody Oligonucleotide Conjugates (AOC)

AOC – Antibody Oligonucleotide Conjugates to Overcome Disease Difficulties

In the field of biomedical science, technological changes are common and constantly evolving. In recent years, antibody oligonucleotide conjugates (AOCs) have attracted considerable attention in the industry as an innovative and advanced biomedical method, and more and more domestic and foreign biopharmaceutical companies have participated in the research and application of AOCs. Because AOC combines the advantages of oligonucleotide technology and antibodies, it is considered to have the potential to provide precise targeted therapy and is expected to bring about a revolution in the biomedical field.

As the name implies, AOC is a type of oligonucleotide molecular complex formed by covalent conjugation between oligonucleotides and antibodies. It forms a therapy that can precisely target and regulate gene expression by chemically linking oligonucleotides with specific antibodies.

Strong Association between Oligonucleotides and Antibodies

Antibodies can provide targeted specificity, allowing AOC to accurately locate specific cells or tissues; Oligonucleotides provide multiple therapeutic mechanisms by interfering with gene expression to endow cells with functions or protein synthesis. That is to say, AOC is a drug that uses oligonucleotides to regulate the expression of specific genes. This type of drug intervenes in disease-related gene expression by targeting specific RNA or DNA targets. This combination can enhance drug efficacy, reduce side effects, and achieve the effect of treating or even curing stubborn diseases.

Common oligonucleotide drugs can be mainly divided into the following categories:

1. Antisense oligonucleotides (ASOs): By specifically binding to the target mRNA, they block its translation process, thereby inhibiting the production of disease-related proteins. ASOs can promote the degradation of specific mRNAs or alter splicing patterns to produce different forms of proteins.

2. Small interfering RNA (siRNA): guides the degradation of specific mRNA and blocks protein expression through the RNA interference (RNAi) pathway. SiRNA is a double stranded structure that can be recognized by intracellular RISC complexes, leading to the breakdown of complementary mRNA.

3. MicroRNAs (miRNAs) and their mimetics: miRNAs are a class of small non-coding RNA molecules that regulate gene expression by affecting mRNA stability and translation. miRNA mimetics and inhibitors can be used to mimic or inhibit the biological functions of specific miRNAs.

4. Aptamers: Single stranded nucleic acid molecules selected through in vitro chemical evolution techniques that can specifically bind to specific proteins or other molecules. Aptamers can inhibit the activity of target proteins or serve as recognition elements for specific molecules.

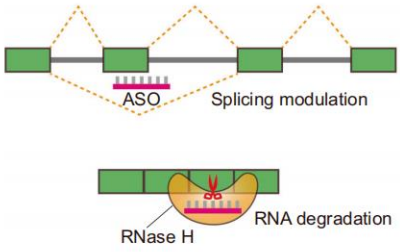


Fig1. Mechanism of Action of ASO Drug
Image source: Reference 1

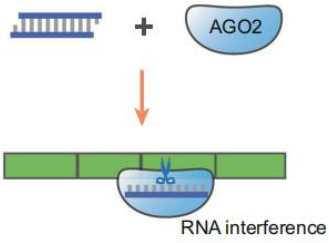


Fig2. Mechanism of Action of siRNA Drugs
Image source: Reference 1

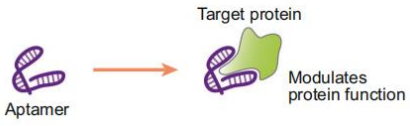


Fig3. Mechanism of Action of Aptamers
Image source: Reference 1

At present, the main companies developing AOC globally include Avidity Biosciences, Dyne Therapeutics, Tallac Therapeutics, Denali Therapeutics, and domestic company ChainGen Bio Ltd.. At present, the indications for AOC are mostly muscle diseases, central nervous system diseases, and tumors. The selected payloads include small interfering RNA, antisense oligonucleotides, etc. The drug with the fastest clinical progress at present is Avidity's AOC 1001, which obtained FDA breakthrough therapy certification in May this year and a global Phase 3 trial of AOC 1001 had been initiated.

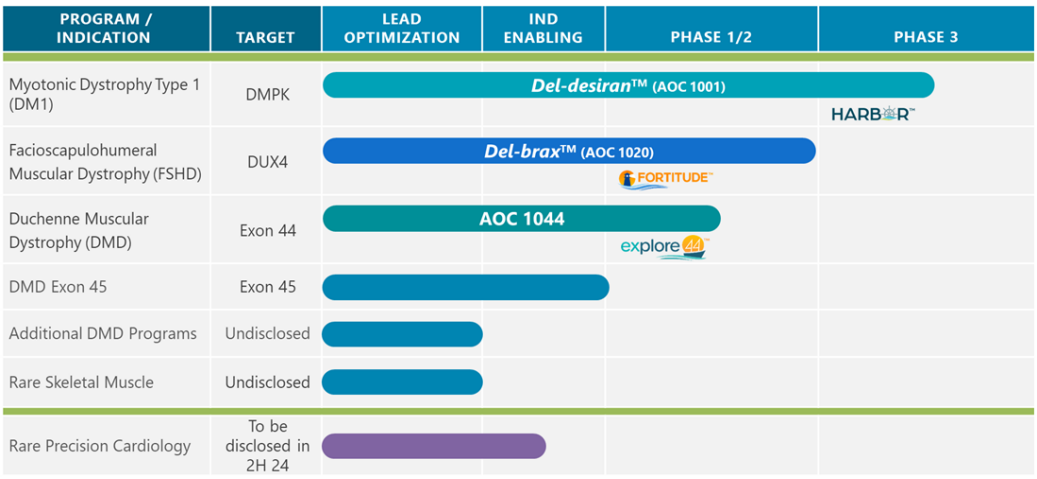


Fig4. Avidity Company's Pipeline under Development
Image source: Avidity official website

Advantages and Characteristics of AOC

Although AOC conjugation methods are similar to ADC, often using techniques such as cysteine, lysine, and site-specific conjugation, AOC has its own distinct characteristics and advantages compared to traditional therapies. For example, oligonucleotides have good hydrophilicity and can use fewer or no organic reagents during the conjugation process. Moreover, natural oligonucleotides carry a higher negative charge and can be purified using ion chromatography to remove unconjugated oligonucleotides, or to separate components with different OAR (oligonucleotide to antibody ratios) values. In addition, their ability to regulate gene expression opens up the potential for personalized medicine, with promising development prospects.

In the AOC conjugation process development service case shown in the figure below, reduced capillary electrophoresis (CE-SDS) was used to determine OAR values and residual oligonucleotides. Firstly, the prepared AOC sample needs to undergo denaturation reduction and alkylation, followed by CE-SDS analysis. The left figure shows the part of oligonucleotides, with a light chain and one oligonucleotide component conjugated to the light chain, and a heavy chain and one or two oligonucleotide components conjugated to the heavy chain, allowing for the confirmation of OAR values based on the proportion of each component. Furthermore, by using ion chromatography technology, unreacted oligonucleotides were removed and subjected to reduced CE-SDS detection again. It was found that the free oligonucleotides were basically eliminated, and the residual proportion of oligonucleotides was less than 1.0%.

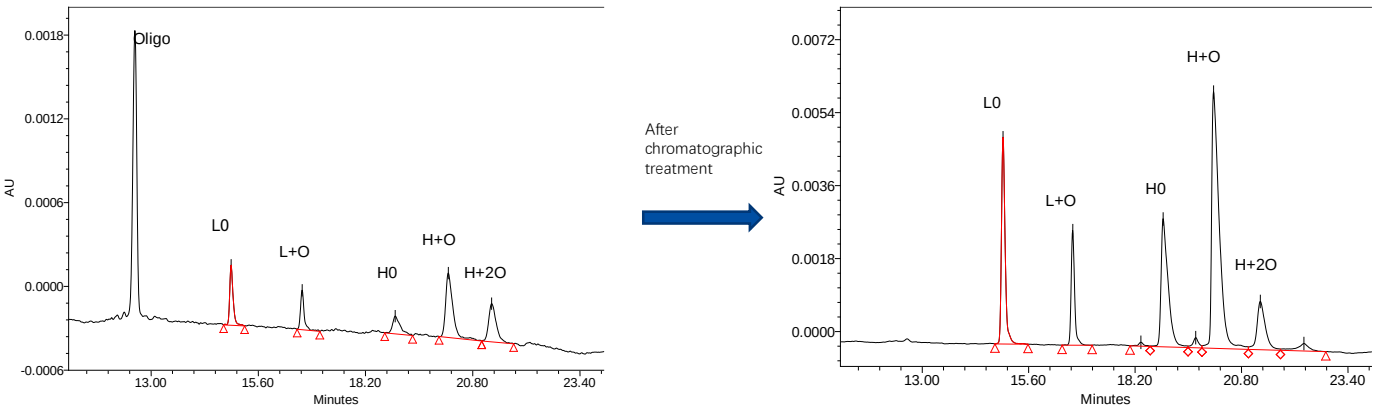


Fig5. A Case of AOC Conjugation Process Development

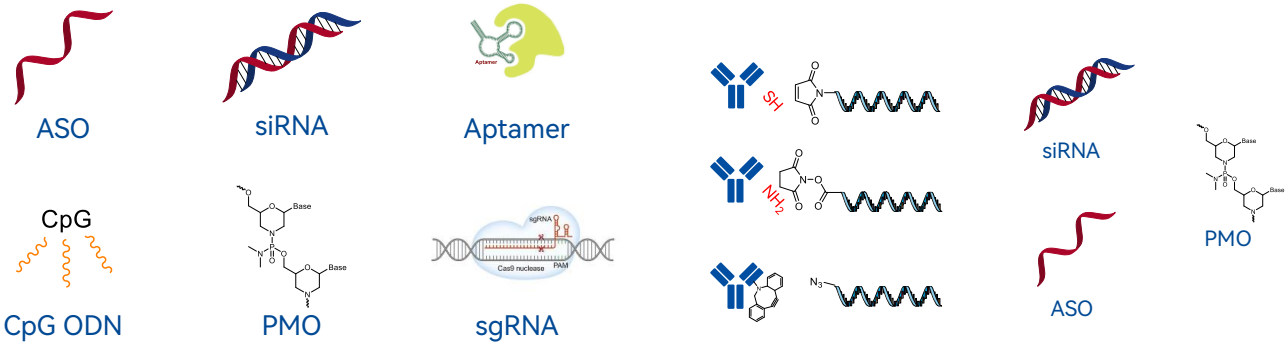
Summary

AOC combines the targeting ability of antibody drugs with the ability of oligonucleotide drugs to regulate gene expression, opening up a new avenue for treating diseases, especially in the fields of genetic diseases and tumors, showing great potential. Faced with the broad application prospects of AOC, new drug research and development institutions have put forward higher requirements and challenges for the development and manufacturing capacity of oligonucleotides and coupling technology processes.

With the completion of the construction and production of four R&D and manufacturing sites in Minhang(Shanghai), Fengxian(Shanghai), Waigaoqiao(Shanghai), and New Jersey(USA) in the past two years, Porton has the ability to provide end-to-end CDMO services for AOC drugs and has accumulated experience in multiple AOC Drug, Payload-Linker and Oligonucleotide one-stop R&D and manufacturing projects.

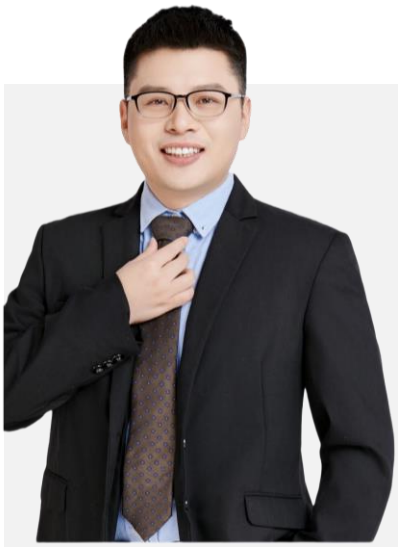
At present, the oligonucleotides development and manufacturing of Porton can cover various molecular types, including oligonucleotides and their derivatives, nucleic acid modifications, oligonucleotide conjugates, etc. At the same time, we can also accept customized development and manufacturing of monomers and GalNAc and its derivatives; and has oligonucleotide solid-phase synthesis technology platform, various purification, separation and post-treatment techniques, LNP and other formulation technologies, as well as comprehensive analysis, testing and quality research platform.

In addition to the oligonucleotide related services mentioned above, we have also accumulated rich project experience in AOC conjugation technology, covering various conjugation methods including traditional lysine and cysteine conjugation, enzyme catalyzed site-specific conjugation, and engineered cysteine modification. The payload types can include siRNA, PMO, ASO and other forms.



In summary, Porton can provide one-stop services from the development and manufacturing of oligonucleotides, to the development and manufacturing of AOC conjugation processes and drug products. It can provide comprehensive solutions for the whole process development, including CMC services from developability evaluation, process and formulation development, process scale-up and manufacturing, analysis and quality research to IND filing and clinical drug manufacturing. It can meet customers' various CMC needs at different project stages.

In the future, Porton will always adhere to the attitude of "compliance, professionalism, focus, and open collaboration", fully customer-centric, and continue to deepen its cultivation in the ADC drug field. We will persist in using new technologies and solutions, and work together with global new drug research and development institutions to "enabling the public's early access to good medicines".



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Mr. Xu Jun has nearly 20 years of experience in the development and CMC manufacturing of biologicsHe possesses rich experience in the development of monoclonal antibody purification and conjugation processes, QbD (Quality by Design) studies, and GMP scale-up manufacturing..

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Reference 1::

Kim, YK. RNA therapy: rich history, various applications and unlimited future prospects. Exp Mol Med 54, 455–465 (2022). https://doi.org/10.1038/s12276-022-00757-5