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The Role of OGNTs in the Personalized Medicine Revolution

Aihua Liu, Ph.D., Director, Bioanalysis; Min Meng, Ph.D., Executive CEO;
Laixin Wang, Ph.D., Executive Vice President

Small molecules and antibodies are two of the three most common drug discovery platform categories. The third is nucleic acids, and an emerging platform within that group is oligonucleotides (OGNTs). OGNTs hold tremendous promise in personalized medicine because of their potential to treat a vast range of diseases with a high level of individually tailored specificity. By interfering with the production of disease-related proteins, OGNT-based therapies are designed to attack diseases at their source, not at the level of symptoms.

OGNTs are short, synthesized single or double strands of DNA or RNA molecules that can bind to specific RNA or DNA molecules to modulate gene expression.[1] The prefix "oligo" is from the Greek word "oligos," meaning "few," referring to the fact that OGNTs only have anywhere from about 15 to at most about 100 nucleotides (typically far fewer). This is in comparison to perhaps a few thousand for RNA and up to 250 million nucleotide pairs for a DNA molecule.[2]

Broadly, due to their mechanisms of action, OGNTs offer the advantage of highly specific sequence targeting to drug developers. Since OGNTs can be specifically designed to selectively target any gene with minimal off-target effects — in theory, at least — they occupy a position of great importance in the rapidly expanding personalized medicine space.

From 2021 to 2022, this market grew from $1.9 to $2.2 trillion globally; by 2030, it is predicted to reach $5.7 trillion with a CAGR of 11.6%.[3] There are numerous drivers of this growth, including:

- Technological advances
- Growing public awareness
- Government initiatives
- Expanding genetic databases
- Use in new therapeutic areas
- Greater use in emerging nations/economies

What does all of this indicate? For the foreseeable future, we can expect a significant increase in the demand for — and use of — medicines that are based on the specific genetic sequencing of individuals. This means greater focus on this area by biopharmaceutical companies and contract research organizations (CROs), and an uptick in the number of personalized medicine trials.

How will OGNTs contribute to this growth?
Here, we explore three key factors:

1) Drugging the "undruggable"

2) Accelerating drug development

3) Driving technological advancements

While OGNT-based therapies are still in their infancy in the overall pharmaceutical industry, they have already shown promise in clinical trials for a variety of diseases, including genetic disorders, viral infections, and cancer, thus providing hope for many rare or incurable diseases.

1) Drugging the "Undruggable"

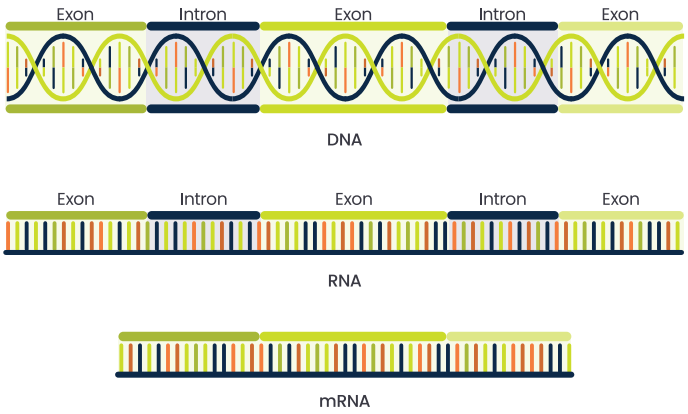
The drug candidate research on OGNTs began over 30 years ago, and the first marketing authorization for an OGNT-based therapy was Novartis' Vitravene (fomivirsen, ISIS 2922), which was approved by the FDA in 1998.[1] As of today, 18 OGNT-based drugs have been approved, with 15 having hit the market since 2016.[4]

Their functional properties are at the heart of the rise in the popularity of OGNT-based therapies. The ability of oligonucleotides to selectively target specific genes or proteins makes them a promising class of drugs for proteins that were previously "undruggable," as in the case of those that do not have hydrophobic pockets that accommodate small molecules.[5] OGNTs do not interfere with receptor sites like many drugs that target protein functioning; rather, most interact with their targets' RNA or DNA via Watson-Crick base pairing.

The categories of OGNTs can be broken down by specific modes of action, and the two most common are antisense oligonucleotides (ASOs) and small interfering RNA (siRNA). ASOs are single-stranded and there are three major classifications:

- **Gene-expression inhibitors** — these single strands of DNA/RNA act through RNAses (ribonucleases) that catalyze the degradation of mRNA strands
- **Splicing modulators** — these bind to pre-mRNA intron-exon junctions and inhibit splicing
- **Steric block of translation** — these single strands of DNA/RNA bind to mRNA and physically block its translation to protein

As for siRNAs, these are double-stranded RNA molecules that use microRNA (miRNA) machinery to cause RNA degradation or inhibit translation, thereby inhibiting gene expression.[1] Additional OGNT categories include aptamers, which are short single-stranded sequences that fold into functional three-dimensional shapes and bind to the specific target through adaptive fitting. Yet another category is CRISPR/Cas9 guide RNAs, which hold great promise for gene editing because of their ability to make extremely precise cuts and leave behind healthier DNA.[6,7]



RNA splicing - introns are removed by the spliceosome and exons are spliced back together. This process is inhibited by splicing modulators.

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The apparently favorable regulatory environment includes cases of priority review and fast track status, as well as accelerated approval.[8] This shortened clinical development schedule speeds time to market for new drugs and contributes to the positive expectations for this space.

2) Accelerating Drug Development

OGNTs have the potential to accelerate drug development and offer a faster, more efficient path to the clinic. Given the aforementioned degree of target specificity that is obtainable using OGNTs, they offer the benefit of fewer and more predictable "off-target" effects, reducing the need for extensive preclinical studies. Additionally, OGNTs have shown very good translational behaviors from preclinical to clinical studies. This accelerates drug development timelines and reduces costs, allowing for more efficient development of lead compounds with desirable pharmacological properties. Adding high-throughput screening for candidate identification to this process allows drug development efforts for OGNTs to be highly focused.

The rate at which OGNT-based therapies are being approved is also encouraging. The apparently favorable regulatory environment includes cases of priority review and fast track status, as well as accelerated approval.[8] This shortened clinical development schedule speeds time to market for new drugs and contributes to the positive expectations for this space.

In summary, OGNTs can accelerate drug development by reducing the need for extensive preclinical testing, enabling faster lead identification and optimization, and allowing for targeted drug development efforts that could be fast tracked by regulators. It seems highly likely that OGNTs will continue to have a significant impact on timelines and efficiency, and that the complex testing methods used by CROs to expedite drug development will likewise play a critical role going forward.

3) Driving Technological Advancements

Personalized medicines have had a significant impact on clinical research, changing the way clinical trials are designed, conducted, and analyzed. One of the main impacts of the rising demand for personalized medicines has been the development and use of quantification methods for OGNT-based therapeutics and biomarkers, which demand highly sophisticated instrumentation, software, and expertise.

Successful development depends on high-throughput bioanalytical methods that generate accurate bioavailability, metabolic stability, pharmacokinetic (PK), and toxicokinetic (TK) data. The traditional methods of liquid chromatography (LC) and ligand-binding assays (LBAs) — or even a hybrid approach (LBA/LC) — are not sufficient. There are several advanced methods, however, that may be suitable.[9,10]

One set of applicable methods includes LC with UV/fluorescence (LC-UV or LC-FLD), Tandem Mass Spectrometry (LC-MS/MS), and High-Resolution Accurate Mass Spectrometry (LC-HRAM). These are leading-edge methods for TK and PK studies, offering high specificity, throughput, selectivity, and reproducibility. These methods, however, carry high requirements for user expertise and monetary investment. Another useful method is the electrochemiluminescent hybridization ELISA (ECL-hybridization immunoassay) using MSD (Meso Scale Discovery) technology,

which offers high sensitivity, multiplexing capabilities, as well as low matrix effects and sample volume requirements. A third type of method is quantitative polymerase chain reaction (qPCR), the gold standard for gene expression. A qPCR approach with a stem-loop reverse transcription (RT) primer can sensitively quantify siRNAs. The downside, however, is that this method is frequently incapable of differentiating OGNTs from their metabolites, an issue shared with hybridization ELISA.

The inherent complexities in OGNT research demand extreme care, expertise, and investment in technology by CROs. The benefits of drug developers being able to perform these kinds of studies, though, far exceed the costs. This class of drugs is invaluable to society, and the capability of CROs to drive advancements that facilitate the growth of OGNT-based personalized medicines is paramount.

The Future of Personalized Medicine

There is little doubt that OGNTs will continue to play an increasingly important role in personalized medicines for a long time to come. They are highly specific and targeted, so they can be particularly useful for treating rare genetic diseases and other conditions that are caused by genetic mutations or dysregulated gene expression. OGNTs may also be used in personalized medicine for diagnostic purposes by detecting specific DNA or RNA sequences, providing a highly sensitive tool for a wide range of diseases.

Demand will continue to grow, and researchers will continue to develop new and innovative ways to target specific genes and proteins for therapeutic and diagnostic purposes. There are many OGNT drugs currently in research and clinical stages, and we expect OGNTs to remain at the forefront of the personalized medicine movement for the foreseeable future.

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