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NUCLEIC ACID INSIGHTS

CONTENT PILLAR

mRNA

New directions, new modalities

NUCLEIC ACID INSIGHTS

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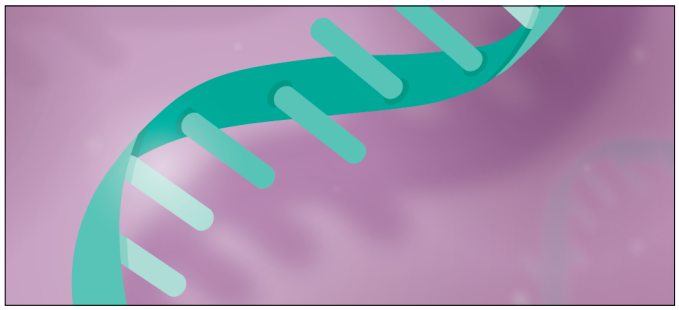

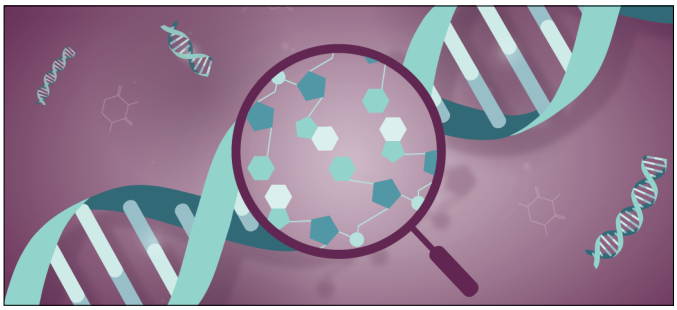

NUCLEIC ACID INSIGHTS

mRNA
NEW DIRECTIONS, NEW MODALITIES

SPOTLIGHT

Advancing nucleic acid therapeutics with circular RNA

INTERVIEW

"...the key realization is that optimizing each component individually...is necessary but not sufficient."

In this podcast episode, **Jokūbas Leikauskas**, Editor, BioInsights, speaks to **Trevor Hallam**, who served as Chief Scientific Officer of Sail Biomedicines until July 2025. The interview, recorded in June 2025, explores advances in RNA therapeutics, particularly circular RNA (circRNA or eRNA) technologies, and how they may help overcome current limitations in delivery, durability, and specificity for applications such as CAR-T cell therapies and autoimmune disease treatment.

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Q Firstly, can you tell me a bit about your career to date and what you are working on right now?

TH My career began many years ago, starting in England. My background is in biochemistry, including a PhD from the University of London.

I started getting enthusiastic about disruptive technologies when I joined the Physiological Laboratory at the University of Cambridge, and was fortunate to work with many remarkable people, including Tim Rink and Roger Tsien. Roger later went on to win

the Nobel Prize for his work in fluorescent technologies. That experience immediately opened my eyes to disruptive technologies and how they could be applied. At the time, there was very little funding in academic institutions in the UK, so a big part of the culture involved sitting around and thinking about what would make a 'killer experiment'. It taught me not only about disruptive technologies but also how to use them properly. Sometimes that does not lead to easy answers—it often highlights the key biological questions that need to be solved. Ultimately, that became my passion.

I then spent over a decade in large pharmaceutical companies in R&D, culminating in about nine years at AstraZeneca as Head of R&D at one of their Swedish sites following a merger. I also had the opportunity to head medical affairs, messaging, scientific liaisons, and call centers across the entire US commercial product base at the time. After that, AstraZeneca invited me to help develop a biologics strategy, which put me in front of many small companies with fascinating takes on what might be considered disruptive. A few of them excited me, and that experience ultimately shaped my future moves.

I have always had a passion for drug design, particularly involving disruptive technologies. I spent some time working with unnatural peptides, which has come full circle and proved useful in my current role at Sail Biomedicines. During that period, we had an approved drug, but our work also expanded into metabolic disease and cardiovascular indications.

In 2011, I moved into the antibody space by joining a company focusing on synthetic biology called Sutro Biopharma. They were using a technology that allowed proteins to be produced in just 10 hours, at any scale, like a conventional biologic—but with the added ability to incorporate conjugation sites, which was previously unknown. We applied that to antibody-drug conjugates (ADCs), as well as other targeted therapies, such as prodrug cytokines, conjugate vaccines, and bispecific antibodies. It was a truly disruptive approach.

That work advanced the entire ADC field into targeted therapeutics that were not only well-designed but also formulated as single molecules. This approach significantly enhanced the therapeutic window. With all that targeting expertise under my belt, RNA became the next area in my sights.

I was thrilled when I was invited to join Flagship Pioneering and Laronde as Chief Scientific Officer to explore how RNA technologies could be advanced, not just for vaccines, but as therapeutic moieties more broadly, which is what ultimately brought me to Sail Biomedicines.

Q What are the key limitations of current mRNA therapeutic approaches, as you see them?

TH The whole field of RNA therapeutics, at least gain-of-function RNA or translatable RNA in general, ultimately depends on delivery, which is still the biggest challenge. How do you deliver beyond the liver when these therapeutics are usually encapsulated in LNPs? Lipids are, of course, very efficiently metabolized by the liver, so the liver becomes a major sink as soon as you introduce these therapies.

The other critical aspect is dose efficiency. If you do not have very efficient delivery to the right cells or tissues, where you want the RNA to produce the encoded protein, then you will not see sufficient expression. As a result, you must increase the dose, and that leads to other challenges, such as tolerability. That is the big difference compared to vaccines, which use very small doses with long-lasting effects.

"Naturally, mRNA has evolved not to linger in the system… one of the big challenges is achieving durability, because now we want it to be stable and preserved."

Regarding therapies involving gain-of-function, the dosing scale is different, with tolerability issues coming to the forefront. There is also the challenge of repeat dosing, which has not typically been a strength of these first-generation RNA medicines.

Q How can utilizing circRNA help to address these challenges? What unique benefits does it offer versus other forms of RNA?

TH We have taken circRNA as the foundation for the modality we are developing at Sail Biomedicines. In its natural form circRNA is quite inert and typically does not translate. Therefore, we have also introduced internal ribosome entry sites (IRES), which are originally viral mechanisms that enable ribosomes to initiate translation on circRNA. In contrast, typical mRNA, whether modified or natural, has an open 5′ end, which provides a straightforward entry point for the ribosome to attach and begin producing protein. With circRNA, we hijacked these viral strategies to enable the ribosome to access what is, by nature, an 'endless' RNA circle. That is why we refer to our version as Endless RNA (eRNA)—it is engineered to support translation.

The promise here is greater stability and a longer duration of translation. However, it is not an endless translation, and in many ways, we do not want that. If you think about how proteins are made biologically, there is tight control. The step between DNA and protein, transcription, is highly regulated to turn genes on and off as needed and control protein production.

The other side of this is that mRNA is meant to be transient—it produces protein while it is present, and once transcription of that mRNA stops, protein production stops as well. Naturally, mRNA has evolved not to linger in the system. Therefore, one of the big challenges is achieving durability, because now we want it to be stable and preserved.

Furthermore, it is important to interrogate how you will use that durability. It is not always the case that more translation or longer translation is better. Modified RNAs perform very well—they are highly efficient and very fast. But there are important trials and tribulations depending on the use case. If the goal is simply to produce a large amount of protein very quickly, then either technology can be effective.

This gets into the nuance of how we apply these platforms. With conventional mRNA, it is essentially uncontrolled. The open 5′ end means that as soon as the mRNA is introduced into the system, protein production begins, and it happens fast and at high levels. However, it typically does not last long—maybe 24–48 hours of useful translation. In contrast, with eRNA, you can achieve similar or even greater amounts of protein but spread out over five to seven days of useful translation.

It is slightly less efficient because the ribosome must be recruited using this IRES mechanism, which is not as straightforward, quick, or efficient as an open 5′ end. If both methods ultimately produce the same total amount of protein, it becomes interesting to think about why that might matter.

For example, the CFTR protein in cystic fibrosis is a highly complex ion channel in the lung. From many published papers on natural CFTR expression, we know that its translation is slowed down at certain points. This happens to give sections of the protein time to fold properly before moving on to translate the rest of this rather long sequence. Proper folding is critical for functionality.

If translation happens too quickly, there may not be enough time for the protein to fold correctly, and, as a result, it may lose its function. With eRNA, we now have an opportunity to slow the process down a bit. Since the molecule is more durable, we can allow proteins more time to fold properly, which can lead to better function relative to the total amount of protein produced. Another way we can modify this is by adjusting translation efficiency itself. Since we know that eRNA has slightly less efficient initiation due to the IRES, we can play with that—using less efficient or more efficient IRES elements to fine-tune translation.

Regarding secreted biologics, whether it is a T cell engager, a bispecific antibody, or even a GLP-1 variant, the challenge with both traditional and modified mRNA is that when you have a wide-open mRNA, you get a large burst of protein production. That leads to a big spike in the plasma, which can cause toxicity issues. We are very familiar with that challenge in the GLP-1 space and the constant struggle to stay within the therapeutic window for weight loss without tipping over into nausea, which undermines the benefit. Controlling the peak plasma concentration (C_{max}) is a well-known issue for biologics.

Similarly, we can control this in mRNA-based protein production by dialing down the rate of initiation using the IRES mechanism. This lets us essentially program the translation to stay within the desired clinical plasma exposure range without toxicity.

Q Achieving extrahepatic and tissue-specific delivery is a perennial challenge for the mRNA therapeutic space. How is Sail Biomedicines approaching this challenge?

TH The first priority is avoiding the liver, because that is where most of the dose tends to end up, at least when using LNP-carried RNA.

Furthermore, if you can maintain plasma exposure, you have a real chance of getting the therapy to the target cells. Interestingly, the exposure does not have to be as long as we might think. There have been many different strategies—some aiming for nanoparticles to circulate for a week or two, others sufficing with just a day. Most unoptimized particles only last several hours before being cleared. The question becomes: what is the right hotspot?

We are tying all this together—the circulation and exposure—with strategies to improve uptake efficiency into specific cells and enhance specificity. Our approach uses ligands attached or conjugated to the outside of the LNP. These ligands are designed to recognize specific proteins expressed on target cell types or tissues. Once sufficient exposure with your base particle is established, adding this targeting ligand enables highly efficient endosomal uptake of the LNP into the intended cells. The efficiency is 100–1,000 times greater for a given plasma concentration compared to an LNP on its own.

One major advantage of targeting is the specificity—you can deliver the payload exactly where you want it. But just as important is the leftward shift in the dose-response curve. The amount of circulating LNP needed is now dramatically reduced. This is crucial

"Looking at the whole system, what we are talking about is a complex, systems-based approach."

because, as I mentioned earlier, we do not need the nanoparticle to circulate for too long due to tolerability problems. The same goes for large doses—higher doses lead to more accumulation in the liver, which then requires metabolic clearance, not to mention clearance of other components through the kidneys and other pathways.

All things considered, by combining lower dosing with highly efficient targeting, the tolerability is improved significantly. Additionally, when you combine that with the extended durability of eRNA, the advantages compound.

Looking at the whole system, what we are talking about is a complex, systems-based approach. It becomes a real challenge to tease apart the structure-activity relationships because there are so many interacting components, which is exactly why we are now leveraging machine learning to help navigate this complexity.

Q What other potentially promising approaches are you seeing to address issues surrounding delivery?

TH There are many advanced modalities, such as bispecific antibodies and even ADCs, which target CAR-T cells, particularly in the autoimmune disease space. If we take out a certain T cell population, we could reset an autoimmune disease. The big question, of course, is whether you can do it safely.

For example, Singh's paper, published in 2022, demonstrated that lentiviral CAR-T cell therapy could deplete B cells and reset the immune system, allowing progenitor B cells to grow back and effectively making patients symptom-free [1].

Many companies are exploring this from various angles, but what we are excited about is our ability to target T cells using LNPs. I have mentioned circulation and the efficiency of targeting, and now we can get those T cells to express a CAR that recognizes B cells and fully depletes them.

This technology is complex compared to lentiviral methods, where you have an integrated technology delivered in a single dose. In essence, the patient's cells are harvested, transformed *ex vivo* into CAR T cells, amplified, and then the patient undergoes fairly intense conditioning to accept those cells back.

In order to achieve all of that with just a simple IV injection, we need an IV-targeted LNP carrying extended RNA, where we can truly optimize CAR expression in circulating T cells, especially those in the spleen. Then, we want to drive sufficient expression so these CAR-T cells can target and fully deplete B cells, even after a very short dosing cycle, maybe one to three doses over just a few days.

If we can pull that off safely and effectively, it would open this entire space to patients receiving treatment in community centers instead of highly specialized clinical centers of excellence that currently handle these therapies.

There are already a few companies that have entered the clinic with similar approaches, showing this may be possible, although the efficiency gains required to make it stick remain significant.

Q Can you tell us more about your current pipeline and your biggest milestones to date?

THASAIL-0804 is our lead program, and it involves a CAR-T-encoded eRNA encapsulated in a targeted LNP. The RNA expresses an anti-human CD19 CAR, which, once expressed, can engage its antigen targets on B cells and deplete them.

The targeting ligands are particularly interesting because they facilitate efficient entry of the LNP carrying the RNA payload into both CD4 and CD8 T cells. Although most traditional approaches focus on CD8 T cells, CD4 T cells actually represent the largest population of T cells.

Since this is a transient modification of the total T cell population for just a few days, we thought this might be a promising way to 'up the horsepower' by targeting both CD4 and CD8 T cells. CD4 T cells are certainly capable of killing as well, and since they are more plentiful than CD8s, this approach broadens the potential impact.

Additionally, our early studies suggest this approach is very well tolerated: we have been able to produce several thousand CARs per cell and transfect upward of 80% or more of peripheral T cells *in vivo* using this targeted LNP method, which is phenomenal.

The combination of targeting a larger population of T cells—both CD4 and CD8—using a targeting ligand is very exciting, along with the way we assemble that conjugated ligand onto the nanoparticle. Many conjugation chemistries, often borrowed from the ADC field, are not as stable as you would want, but the chemistry we use ensures an irreversible association.

It is common to see some loss of targeting ligands from their payloads in ADCs, and unfortunately, some of those same chemistries are now being used with targeted LNPs, which is concerning. Losing the targeting ligand means losing dose efficiency.

We chose to use 'click chemistry'—a highly specific method of conjugation that does not come off. I think of this as more like spot welding—it is not going to spontaneously detach from the nanoparticle during circulation, which is key.

With this stable conjugation, the nanoparticle retains its ability to internalize once it finds the right cell. Combined with our targeted ligands for CD4 and CD8 T cells, and the extended RNA expression from our eRNA, we are seeing full depletion in CD34 humanized mice.

These are human CD34 cells derived from human umbilical cord blood, which are then engrafted into immunocompromised mice and left for 6 months so the human immune cells can colonize and develop fully, including all the progenitors in the bone marrow. After this 6-month setup, we administer our *in vivo* CAR-T therapy.

We observed that a sequence of doses of the targeted eRNA leads to complete depletion, not only in the peripheral blood but also in the spleen, lymph nodes, and, importantly, in the bone marrow, which is crucial for achieving an immune reset.

When we plot this on a log scale, we observe about a three-order-of-magnitude depletion—far below 1%, which on a linear scale would lose resolution. We are reaching around 0.1% or less of these populations, essentially hitting the noise level of the system. This

"Although most traditional approaches focus on CD8 T cells, CD4 T cells actually represent the largest population of T cells."

depletion occurs not only in peripheral cells but also in bone marrow progenitor B cells, pre-B cells, and mature B cells—we are reducing the population right down to the progenitors.

Longitudinally, as the cells begin to recover around days 8–10, the repopulating cells coming from bone marrow stem cells are predominantly progenitors. While this is not evidence of an immune reset, it strongly suggests that we are establishing a fresh population of progenitor cells, which is necessary for any meaningful reset in humans.

Another exciting aspect of this is the systems approach I mentioned earlier. The systems we design and control are just one side of the equation. The other key part is context—understanding the biology, the underlying pathophysiology of the disease, and how we fit into this system by using T cells.

T cells are naturally designed to seek out infected tissues, where they encounter foreign RNA from viruses and similar pathogens. Unlike many other cells, T cells are not shut down by some of the impurities that can be present in RNA generation processes carried over into therapies—they are quite hardy and resistant. Normal cells have mechanisms that prevent translation of potentially viral proteins, but T cells do not. Additionally, once T cells identify a target antigen, they amplify the signal by clonally expanding and activating. They are primed to turn on many downstream responses, proliferate, and attack the target. This clonal expansion is central—it is what gives T cells their diversity.

Once the T cells have recognized the antigen, they produce the CAR, engage with the target, get activated, and start to amplify. Then, when we come back with a second dose, usually around three days later, we see that this dose is taken up by an already expanded population of T cells. The impact is tremendous: there are many more CAR-T cells after the second dose, leading to full depletion of target cells. A third dose finalizes everything, especially in the bone marrow, though we believe two doses might be enough to achieve complete clearance and immune reset.

Furthermore, T cells expand dramatically, so you do not need a very high initial dose. You give the cells a 'taste', and then they do the rest themselves—activating and multiplying. This is a fascinating example of how the design of the therapy works together with natural T cell physiology and can impact the treatment of specific indications.

Delivering RNA over 2 or 3 days is ideal—it provides enough CAR expression on the first dose to activate a good number of T cells, preparing them for the second dose and onward. Fractionated dosing takes advantage of this cellular physiology, offering fantastic benefits with a transient treatment.

Q What will your own and your organisation's biggest priorities be in the coming few years?

TH We would like to apply these approaches across the entire therapeutic landscape, and double down on what works. That focus is crucial as this field matures. Many companies are pursuing similar goals, and I hope they all find a solution. It is also important that their solutions are diverse, because out of that variety comes a robust industry built on best practices.

One of the biggest learnings for me has been the value of playing to biology's evolved systems and understanding the context of the biological problem you are trying to solve, whether it is ensuring proper folding for complex proteins like CFTR or controlling C_{max} to

avoid toxicity with molecules like GLP-1, as well as using amplification and natural physiological processes.

This approach drives lower dosing, greater efficiency, and ultimately widens the therapeutic index. It also supports the possibility of repeat dosing, which is critical for autoimmune diseases or chronic conditions like cystic fibrosis, where sustained protein function is needed. Looking ahead, it is exciting to start exploring how orthogonal, or independent, we can make subsequent doses to further optimize treatment regimens.

One of the things from the oncology field, where I have spent the last 12 years, is the realization that there are many complex, multifunctional mechanisms that come into play. One of the things I have always been fascinated by in oncology, more recently, is the immuno-oncology field, where you are starting to see good therapies now being targeted at antibodies rather than a low-dose, sustained chemotherapy.

Eventually, we might bring gain-of-function or other aspects to bear with CAR-T cells, for example. You could take those and start putting additional payloads in there, such as bispecific antibodies and T-cell engagers, to amplify things further. Additionally, you could condition the tumor microenvironment to take cold tumors, which lack T cells, and make them warmer.

There are precedents already in the clinic, such as poking cytokines into tumors, innate stimulators of the immune system, and various other biologics. The ability to use the T cell as a vehicle to reach tissues or resident cells in tissues where LNPs cannot go is very exciting.

Q Finally, what are your hopes—and fears—for the future of the mRNA space as a whole as it moves in new directions, and into new disease areas?

TH There was massive optimism after the success of RNA vaccines, but the truth is, it is an incredibly complex therapeutic modality.

For us, the key realization is that optimizing each component individually—whether it is the eRNA sequence, the LNP chemistry, the ionizable lipids, the formulation, or the targeting ligand—is necessary but not sufficient. You also must consider the biological context: what is the pathophysiology of the disease you are aiming to correct?

This area is unique because mRNA delivery essentially bypasses natural transcriptional control, turning it 'all on' or 'off'. With our approach, we are trying to reintroduce durability and tunable exposure (C_{max}), impacting protein translation rates. That is crucial because it gives back some of the control lost by jumping straight to mRNA.

Now that we can program RNA therapeutics with precision, the critical next step is to program them in the context of the underlying physiology. I also hope that the field continues to attract strong funding and commitment. We are already seeing some attrition as people try numerous approaches that do not fully deliver. What is needed now is a broader approach—a deeper understanding of the niches and contexts where these therapies bring the real benefits. Through these approaches, I am confident RNA therapeutics will return to mainstream adoption. I am genuinely positive and excited about where this is headed and how the ecosystem evolves.

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BIOGRAPHY

Trevor Hallam PhD served as Chief Scientific Officer of Sail Biomedicines until July 2025. Prior to Sail, he served as President, Research and Chief Scientific Officer of Sutro Biopharma from 2010–2023, a clinical stage company focused on next-generation cancer therapeutics. At Sutro, Trevor was instrumental in transforming the company's early-stage cell-free protein synthesis technology into a uniquely rapid and precise multi-modality platform for complex biologics with proven manufacturing capability. Prior to joining Sutro, Trevor was Executive Vice President of R&D of publicly-traded Palatin Technologies, Inc., and led their early stage research and Phase 1 and 2 clinical development of multiple synthetic programs leading to the eventual approval of Vyleesi. Trevor held several senior management positions at AstraZeneca over 9 years, including as Head of Respiratory Research & Preclinical Development in Sweden, Head of Medical Affairs, USA, and latterly as Head of an emerging Biologics Strategy in the UK. He previously worked in the UK with Roche, Glaxo and SmithKline & French over 11 years. Trevor is a member of the Scientific Advisory Board for Sutro Biopharma. Trevor received a BSc (Hons) in Biochemistry from the University of Leeds, UK and a PhD in Biochemistry from Kings College, University of London, UK where he was sponsored by CIBA-Geigy (now Novartis), before moving to the University of Cambridge, UK where he conducted post-doctoral work with Drs Tim Rink, Roger Tsien, and numerous collaborators at The Physiological Laboratory.

Trevor Hallam, Chief Scientific Officer, Sail Biomedicines, Cambridge, MA, USA

AUTHORSHIP & CONFLICT OF INTEREST

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NUCLEIC ACID INSIGHTS

Oligotherapeutics
status quo and future outlook

Oligonucleotide therapeutics offer promising treatments for rare and genetic diseases, with 22 US FDA-approved drugs to date. This interactive infographic covers their types, leading developers in 2025, ongoing trials, key challenges, and includes expert insights from Christopher Serpell (Associate Professor of Drug Discovery, UCL), David W. Salzman (Gatehouse Bio), and Nizar Saad (Research Assistant Professor, Nationwide Children's Hospital).

Small strands, big impact

Oligonucleotides are **short DNA or RNA molecules**, typically **10-100 bases long**, and can be either **single- or double-stranded** [1].

In **nature**, oligonucleotides typically exist as **small RNA molecules** that regulate gene expression or as **fragments that result from the degradation** of larger nucleic acid molecules.

Oligonucleotides can **selectively target and modulate gene expression at the RNA level**. For this reason, they have emerged as **promising therapeutic agents** for treating a variety of genetic and rare diseases.

Fomivirsen (Vitravene), the first US FDA-approved oligonucleotide drug, was approved in 1998 for **cytomegalovirus retinitis in AIDS patients** [2]. As of September 2024, 22 nucleic acid drugs have been approved by the FDA and/or EMA [3].

The many faces of oligotherapeutics

There are several different types of oligotherapeutics, each with unique mechanisms of action: antisense oligonucleotides (ASOs), RNA interference (RNAi) agents, and aptamers.

ASOs

ASOs are short, single-stranded nucleic acid sequences (15-20 nucleotides) that bind to mRNA to block translation or modify splicing [4], enabling precise gene expression control.

RNAi

RNAi agents include double-stranded small interfering RNA (siRNA) (19-21 nucleotides) and single-stranded microRNA (21-25 nucleotides). siRNA binds perfectly to mRNA to trigger degradation, while synthetic microRNA suppresses translation or degrades mRNA, making both effective tools for gene silencing [4].

Aptamers

Aptamers are short synthetic single-stranded RNA or DNA strands (15-60 nucleotides) that bind targets with high specificity, often blocking protein-protein interactions [4].

Other types

Other types of oligotherapeutics include DNAzymes, CpG oligonucleotides, clustered regularly interspaced palindromic repeats, and decoys [4].

The oligotherapeutic hall of fame

7 **small interfering RNA (siRNA) therapies** have been approved. These drugs are mainly used to treat rare, genetic, and metabolic conditions such as hereditary transthyretin-mediated polyneuropathy and primary hyperoxaluria type 1 [3].

Among aptamer-based therapies, **Pegaptanib** (now withdrawn) and **Avacincaptad pegol** have been approved, with the latter used for treating geographic atrophy [3].

As of now, there are **13** **FDA and/or EMA-approved ASOs** which primarily target neuromuscular and rare genetic disorders, with Duchenne muscular dystrophy (DMD) being a notable example [3].

The leading companies in approved oligotherapeutics include

Ionis Pharmaceuticals **8** approved oligotherapeutics including collaborations with other companies

Alnylam Pharmaceuticals **4** approved oligotherapeutics

Sarepta Therapeutics **3** approved oligotherapeutics [3].

Status quo and future outlook

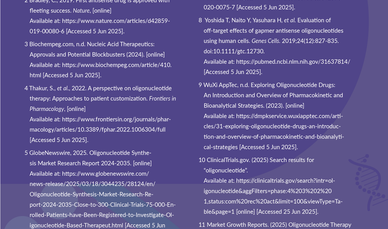
Oligotherapeutics is one of biotech's fastest-growing fields, with nearly 300 clinical trials underway worldwide, reflecting strong global momentum [5].

The broader oligonucleotide landscape includes approximately 2,170 therapies, although most remain in preclinical development [6]. Among these, RNAi and ASOs continue to dominate as the most widely pursued approaches.

Since the first oligonucleotide drug was approved >25 years ago, the field has expanded dramatically to address a range of diseases, from neurological and metabolic disorders to solid tumors and ocular conditions [6].

Of 149 active oligotherapeutic trials and 22 approved therapies, 43% are in Phase 1, 36% in Phase 2, while only 8% and 1% have reached Phases 3 and 4, respectively [10].

Most oligotherapeutic clinical trials are conducted in North America (61%), followed by Europe (23%) and the Asia-Pacific region (15%). A small fraction (1%) takes place in other regions like Argentina and South Africa [10].



Oligotherapeutics are primarily studied in oncology (29.5%), neurology (14.8%), and rare genetic diseases (11.4%). Other targets include infectious, cardiovascular, autoimmune, and respiratory diseases, with smaller shares in ophthalmology and musculoskeletal disorders [10].

Current industry leaders in the oligotherapeutic field include Ionis Pharmaceuticals, Alnylam Pharmaceuticals, Biogen, Dynavax Technologies, Merck, Viridian Therapeutics, Sarepta Therapeutics, GlaxoSmithKline, Pfizer, AstraZeneca, Novo Nordisk, and Gilead Sciences [11].

Hear experts discuss the major challenges that must be addressed to drive progress in the development of oligotherapeutics

Christopher Serpell
Associate Professor of Drug Discovery
UCL

Christopher discusses the challenges of effective tissue targeting beyond the liver and scalable, cost-efficient manufacturing of oligonucleotides.

David W. Salzman
Founder & CEO
Gatehouse Bio

David highlights the hurdle of identifying precise patient populations for oligonucleotide therapies, especially in complex diseases without clear genetic drivers.

Nizar Saad
Research Assistant Professor
Nationwide Children's Hospital

Nizar emphasizes the need to reduce immunogenicity and manufacturing costs through automation and efficiency to make oligonucleotide therapeutics more accessible to patients

Summary

Since the first FDA approval in 1998, 22 oligonucleotide drugs have been approved, targeting rare and genetic diseases. Key types include ASOs, RNAi agents, and aptamers. With nearly 300 clinical trials and 2,170 therapies in development, the field is rapidly expanding. However, challenges like tissue-specific delivery, off-target effects, and high manufacturing costs must be addressed to advance the field.

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