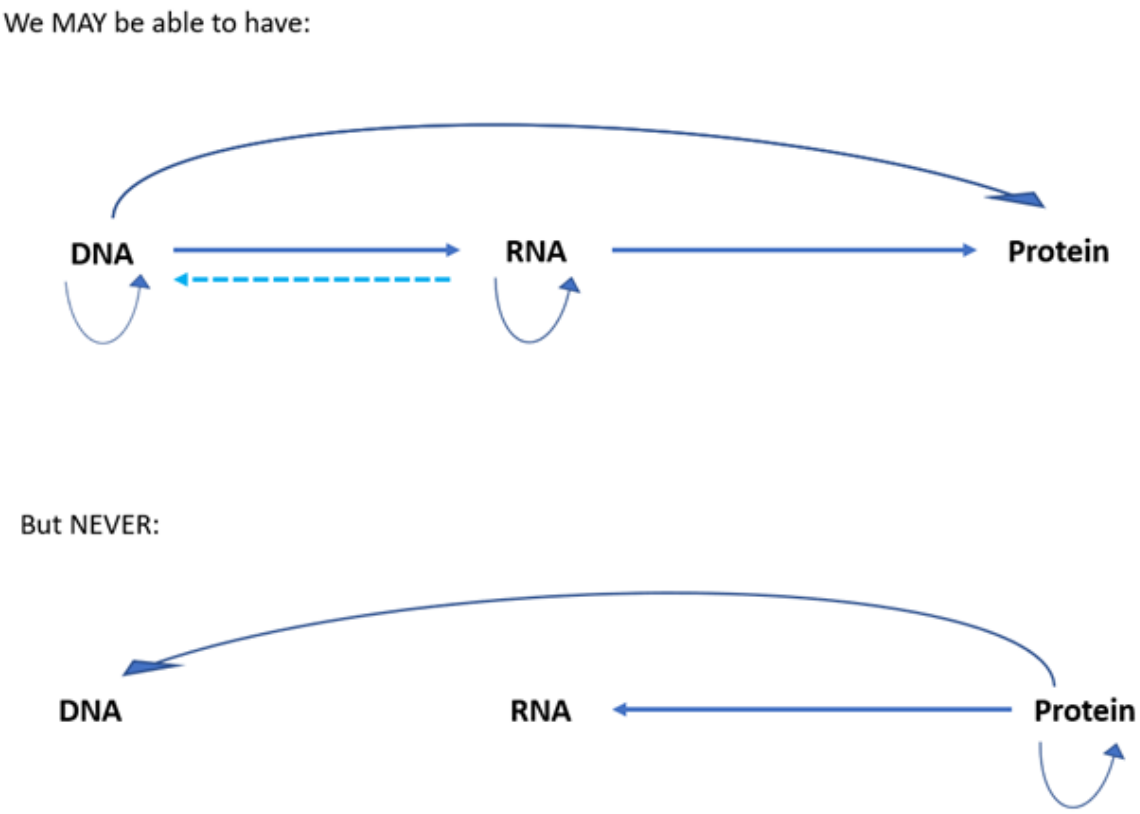
A Deep Dive into RNA Therapies

A PatSnap Report

patsnap

Future of RNA Therapeutics Post COVID

Ribonucleic Acid (RNA) therapeutics made their first major appearance during the pandemic years of 2019 to 2021 through the breakthrough of the messenger RNA (mRNA) vaccines. RNA is a type of nucleic acid which is crucial for our bodies to be able to produce new proteins. From the discovery of deoxyribonucleic acid (DNA) by Johann Friedrich Miescher in the 1860s, we now have a huge understanding of how vital nucleic acids are for coding new proteins and allowing our bodies to react to our environment appropriately. RNA is present in every living cell, just like DNA, however its main role is to transport the instructions for new proteins from the nucleus to the cytoplasm, where protein machinery can translate it. This was first discovered in 1957 when Francis Crick gave a talk about his Central Dogma Theory, explaining RNA's role within the protein synthesis process.



A recreation of the Central Dogma Theory, first spoken about by Francis Crick in 1957

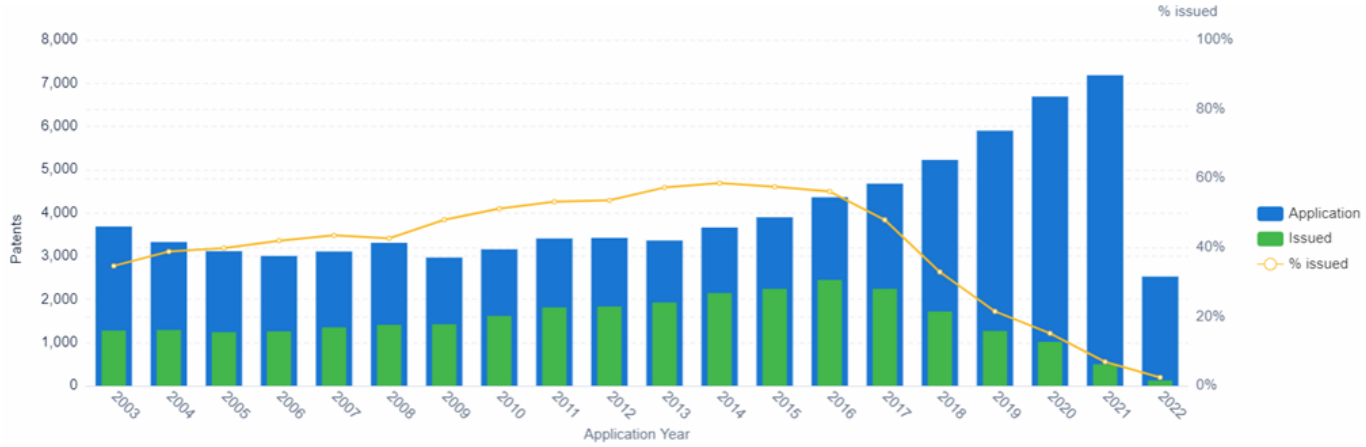
RNA comes in many forms, all of which have different roles within the cell. To name a few, mRNA, and small interfering RNA (siRNA) are some of the RNAs which are gaining a lot of interest within therapeutics. Even though the knowledge of RNA and its role has been around since the 1860s, it's not until the 1990s where this knowledge was applied to potential therapies. mRNA was the first type of RNA to be experimented with to produce a new drug. In 1990, a study involving injecting mice with mRNA led to the production of the protein which the mRNA coded for. This discovery laid the foundation for various types of RNA-based drugs that have been or are being developed today.

When we talk about RNA therapies, it mainly refers to the use of RNA-based molecules to treat or prevent diseases. During the COVID-19 pandemic, the mRNA vaccines demonstrated that RNA therapies are affective. The speed at which the mRNA vaccines were able to be rolled out after determining the structure of SARS-CoV-2, has proved that these technologies are effective. Furthermore, RNA biology has been driving heavy innovation in the development of CRISPR-Cas gene editing [see CRISPR report here], which in turn has spurred both research and drug development (R&D) in this field.

Here we will explore how RNA therapeutic technologies face against each other within the pharmaceutical industry. There will be a focus on two types of technology which are gaining a lot of interest – Antisense Oligonucleotides (ASOs) and RNA interference (RNAi). Both of these technologies have proven to be successful, despite their difference in mechanism. Exploring the different avenues of RNA therapeutics and how the key players are moving within them allows us to uncover how the industry will be shaped in the years to come.

Digging Deeper: RNA Therapeutics IP Analysis:

Intellectual Property (IP) within the pharmaceutical industry is crucial for the success of a company. Without it, researchers would struggle to explore, build upon, and improve medical innovations. IP rights create an opportunity for pharmaceutical companies to plan, commercialize, and protect their innovations. Of course, these same companies also struggle to create value through exploitation of IP rights while also trying to avoid reputational harm. Pharmaceutical companies face growing pressure to bring the value of R&D forward while adhereing to strict regulatory compliance and maintaining product quality. All the while, the generics industry is becoming more aggressive and consolidating their place in the market.



Application, Issue an Grant trend for RNA therapeutic industry, PatSnap Insights

As the graph above illustrates, RNA therapeutics continue to gain interest as the years go by. The U.S. Food and Drug Administration (FDA) approved the first antisense oligonucleotide (ASO) back in 1998 to treat cytomegalovirus retinitis, especially in patients with human immunodeficiency virus (HIV). From this approval, more developments were coming out of the industry, showing that the technology was bound to have a major impact on how difficult diseases were to be treated. In 2016, Nusinersen was approved and commercialized. It's used to target spinal muscular atrophy — and Eteplirsen — an ASO to treat Duchenne muscular dystrophy. From 2016 onwards, there's been an upward trend within RNA therapeutics with notoriously difficult diseases, such as SMA, RNA-based molecules have opened the door to developing a cure for these conditions. This may have led to the large jump from 3,900 patents applied for in 2015 to 4,350 patents in 2016. Despite the decrease in the issued percentage of patents post 2016, the increase in the number of applications per year is something to note. The increasing number of applications per year signifies that this industry is continuously growing, and it is not about to slow down. Pharmaceutical companies are competing to protect their RNA-based technology to reduce the chance of being overtaken by competition.

Technology Life Cycle (2009-2021), RNA therapeutics, PatSnap Insights.

Understanding how technology changes over time indicates what stage the technology is in and whether it's wise to invest in it or not. Above is the lifecycle from 2009 to 2021, showing how the RNA therapeutics industry has changed as time has gone on. Similar to the patent application graph on page two, 2015 - 2016 noted a sizable increase in the number of assignees and applications. The growing number of assignees within the industry shows that it's not dominated by a few giants. This offers hope to smaller companies looking to make their stamp in the industry. However, as the players within a given space increase, so too does the competition. This makes it harder to protect innovations. With IP being notoriously difficult to interpret, all companies in the RNA therapeutic space need to have their finger on the pulse around new innovations. Without this, projects are hard to finalize and get protection over, therefore leaving companies vulnerable. And without adequate protection, it's hard to monetize discoveries.

The 2020 to 2021 uptick in applications is a direct result of COVID-19. Due to the urgency of the pandemic, vaccine development timelines were accelerated. The structure and mechanism of SARS-CoV determined from the SARS outbreak in 2002-2004 allowed for the quick turnaround of the SARS-CoV-2 vaccines. It's known that coronaviruses encode a spike protein on their surface, which is vital to penetrate the host's cells. Antibodies were known to bind with the spike protein to neutralise the virus and prevent its entry into the host cells – this became the target of SARS-CoV-2. The years of research into mRNA technology, meant that clinical trials for mRNA vaccines (BioNTech, Pfizer vaccines) were rolled out at lightning speed. Additonally, governments worked to lift stringent restrictions, which promoted faster research and allowed clinical trials to begin sooner. These mRNA vaccines transported the mRNA code for the spike protein, leading to the immune response from the host. The peak in assignees and applications (so far) came out in the years 2020 to 2021 through the race of the COVID-19 vaccine. However, with the success of the vaccines, it showed the impact the technology has on diseases that were thought to be impossible to control. Now in 2022, it's just a matter of building on what we already know, increasing the developments and applications of the technology.

IP plays a huge role in the pharmaceutical industry to ensure a temporary monopoly for a period of market exclusivity, but once this time is over, it leaves the technology vulnerable. A patent cliff is where many of a company's successful patents expire, so their market share is lost. A patent comes with a 20 year protection whereby pharmaceutical companies must develop the drug in that time, however, due to the longevity of the drug development process, this can take up to 15 years. Many companies file secondary patents to extend the exclusivity of the investment. Despite this, once the patent has expired, other companies are free to develop generics of the branded drug — generic competition. These generic drugs that come out after a patent expiry, on average, can lead to an 80% market share loss and a 20 to 30% reduction in drug price, which has negative financial implications for the original company.

Antisense Oligonucleotides VS RNA Interference:

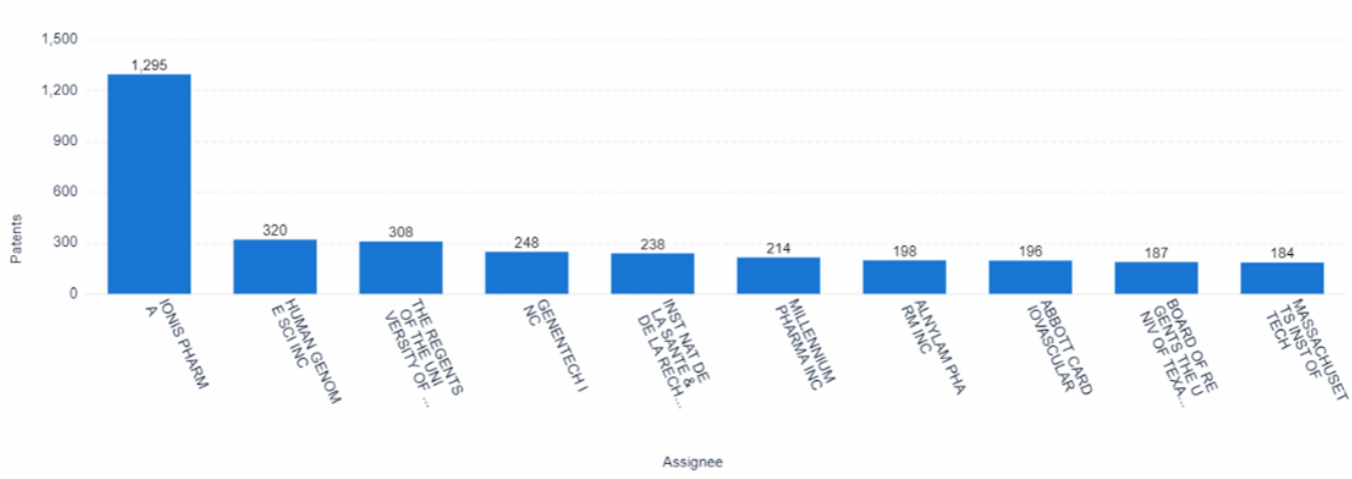
Within the RNA therapeutic scene, there are two main technologies companies are focusing on: Antisense Oligonucleotides (ASOs) and RNA interference (RNAi). These technologies have different mechanisms of action; however, they are both used to target difficult to treat diseases. Here, we discuss how each technology is fairing and the developments coming out of them. Initial commercialization of the mRNA vaccines (COVID-19 vaccines) meant growth opportunities were exposed for ASOs and short interfering RNA (siRNA)-based therapies – attracting biotechnology and pharmaceutical companies to invest in the industry but also their R&D.

1. Antisense Oligonucleotides (ASOs):

ASOs work as a single-stranded deoxyribonucleotide which is complementary to an mRNA target. Its aim is to downregulate a target which is usually achieved by the induction of RNase H endonuclease activity that cleaves DNA-RNA heteroduplex, leading to a significant reduction in the target gene translation.

Looking into key players in the ASO space:

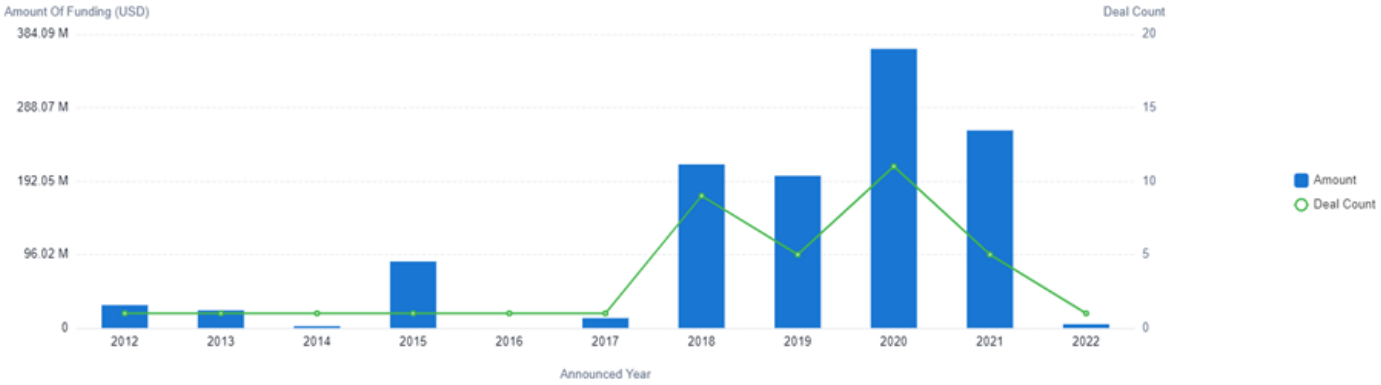
Ionis Pharmaceuticals was the first player in this space that was determined to find a radically different drug discovery technique. Thirty years ago, the company explored the use of using molecules, such as RNA, which had never been used for drug discovery. Within the ASO market, Ionis still maintains its hold over the technology, with many other companies far behind what they are doing.



Top Assignees, Antisense Oligonucleotide therapeutics, PatSnap Insights.

From the insight above, it seems that Ionis Pharmaceuticals is going to be hard to catch up with. The compapny has approximately 1,000 more patents within the space than any of its competitors, but this doesn't mean that it will be impossible for others to make a mark. Taking a deeper look into the money going into the industry, VC trends are interesting to see what is gaining traction for investors currently.

ASO Investment Trends:



VC investment (2012-2022), Antisense Oligonucleotide therapeutics, PatSnap Insights.

During the pandemic, not everyone was focused on developing the Coronavirus vaccine. The industry received a lot of funding during this time, with 2020 seeing the highest deal count with the highest funding level. Even though Ionis Pharmaceuticals dominate through their patent filings, throughout 2020 and 2021, they did not receive funding. In fact, many smaller companies were receiving substantial amounts to support their developments outside of coronavirus. For example, Oxfordshire (UK) based Pepgen raised $112.5 million (2021) to advance its new candidate (EDO51) to tackle Great Duchenne muscular dystrophy (DMD). Pepgen competed with Sarepta's approved therapy, Exondys 51, both targeting exon 51 to enable patients of DMD to produce functional dystrophin needed to strengthen their muscles.

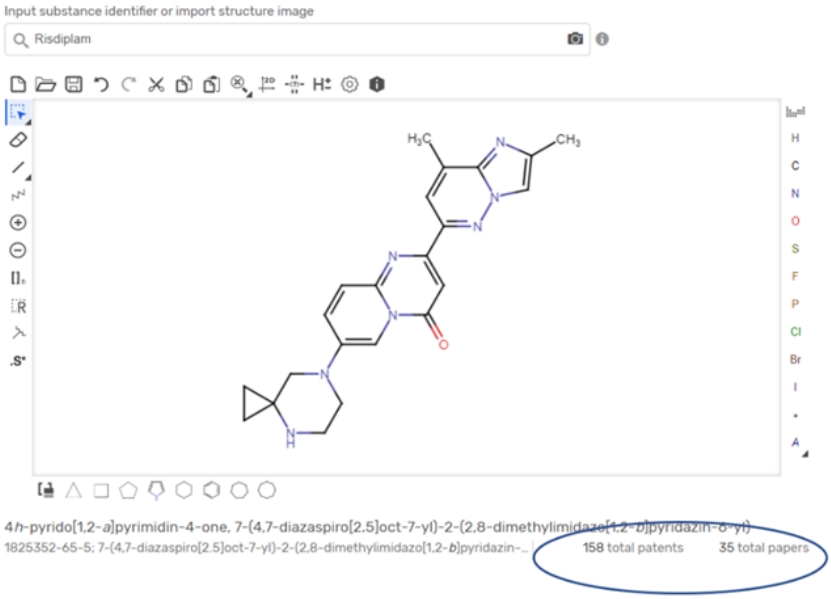
James McArther, Ph.D (CEO of Pepgen) states that "One of the fundamental challenges is that you have these great therapies, but they are not getting into the cells in sufficiently high concentrations to mediate a meaningful therapeutic benefit". Pepgen created a way to develop higher levels of oligonucleotides through its own cell-penetrating peptides. By late 2022, the company may be able to produce biopsy results showing if the drug works and potentially predict the efficacy of EDO51 in DMD patients either being in a wheelchair or walking.

To further demonstrate this, biotechnology company Vico Therapeutics secured Series A financing ($31 million) in 2020 to advance its therapies for rare central nervous system diseases. The Netherland-based startup focuses on the development of RNA modulating therapies and plans on using its funding to advance its Antisense Oligonucleotide lead platform into first-in-human clinical trials. "We see tremendous potential to advance the field and apply the breadth of our antisense oligonucleotide (AON) expertise to address severe neurological disorders. We are looking forward to accelerating the development of our platform technologies around AON technology and RNA-modulation/editing to bring best-in-class therapies to patients" stated Luc Dochez, Founder and Chairman of Vico Therapeutics.

These two examples demonstrate that not only are there so many areas in which ASOs are able to be successfully developed for, but also that smaller companies are not limited. Investors have their eyes on smaller and startup companies that have developed innovative ways to develop these therapeutics. If the data supports these therapeutics and shows them to be beneficial to patients, there's no stopping these smaller contenders from leaving their mark on the industry.

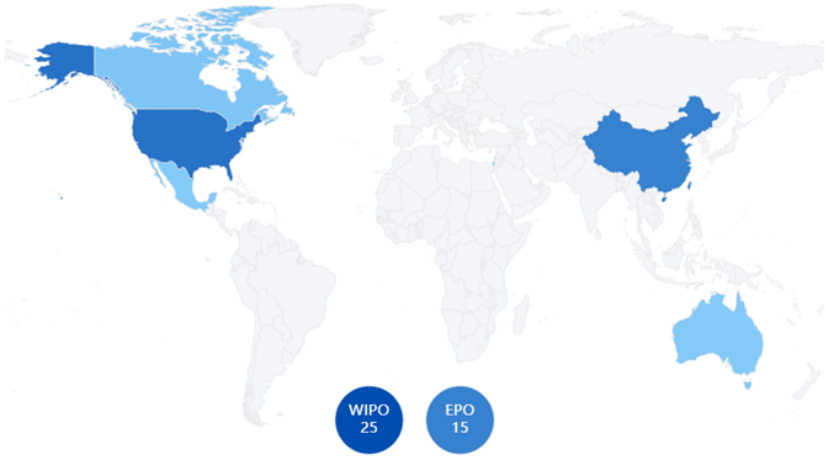
New ASO Drug Spotlight: Risdiplam:

2020 brought a new ASO drug to the market, Risdiplam. It's used in the treatment of Spinal Muscular Atrophy (SMA), and it is the first of its kind to be taken orally and given to patients from two months of age. Below is an example of PatSnap's Chemical platform, which aids in the drug development process through an IP lens. It shows the chemical structure of Risdiplam and how many patents and papers it's used in. Typically, this helps pharmaceutical companies understand how a process using Risdiplam could be protected through IP based on what has already been protected.



Structure of Risdiplam with the number of patents and papers higlighted, PatSnap Chemical.

Since this new drug was approved, there's a lot of talk about what doors this therapy could open for the rest of the world. ASOs have been developed for many neurological diseases currently, however, many of them are not practical for the patient in terms for administration. With SMA, other current treatments are administered through injections to the spine, for example. However, with Risdiplam, it's the first to be taken orally, making it easier for patients to have control over their treatment from home. Looking at the geographic locations of patent activity related to Risdiplam allows us to uncover the next places where developments to this type of drug could be coming from.



Top Countries - Patent Applications, Risdiplam, PatSnap Discovery

The map on page six shows where the geographic distribution for patents which mention Risdiplam. Since publication (Aug 2022), it has only been two years since the drug was approved. This shows that once an idea or solution is out in the public eye, it doesn't take long for others to jump onto the same boat. China isn't far behind the United States for this therapeutic, followed by Australia. Even though the patenting cycle is a lot slower within the pharmaceutical industry than for non-pharmaceutical industries, it demonstrates that competitors are not far behind.

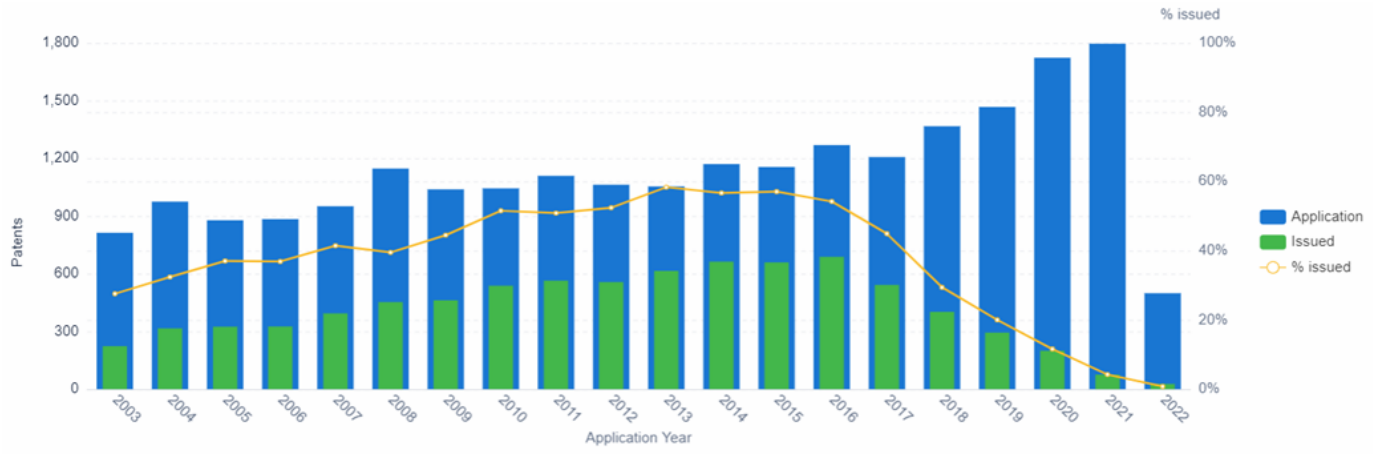
However, it also signifies that there are many different organizations working on therapies for SMA. With the success of Risdiplam, this technology is only going to improve. These diseases which were deemed to be untreatable, now have a chance to be improved and potentially treated. The high amount of activity only can lead to positive outcomes within this area.

2. RNA Interference (RNAi):

ASOs are great and the technology is producing strong candidates for certain diseases, however, it's not the only mechanism out there for RNA therapies. RNA interference (RNAi) is a mechanism where double stranded RNA (dsRNA) induces gene silencing by targeting its complimentary mRNA for degradation. Human diseases caused by the activity of one or a few genes should have the ability to have RNAi-based intervention. The RNAi mechanism can be triggered by two pathways – (1) through RNA-based strategies where synthetic small interfering RNA (siRNA) are delivered to target cells via carriers or (2) DNA-based strategies which siRNA effectors are produced by intracellular processing of RNA hairpin transcripts. Understanding the biology of RNAi has led to extensive applications in research and therefore applications for the treatment of disease

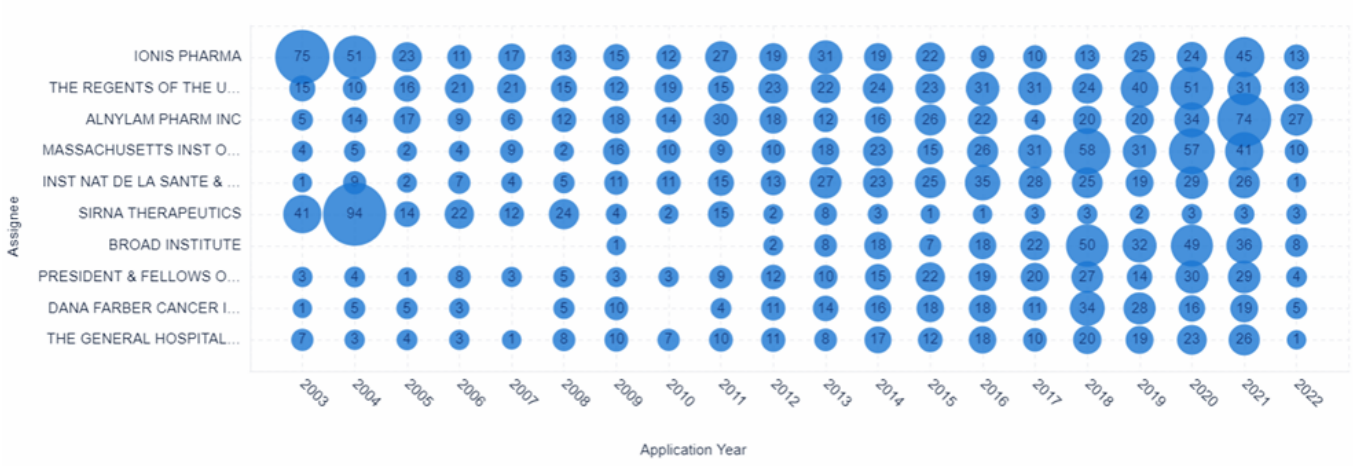
RNAi Patent Landscape:

Within the RNAi space, to understand how the market is changing, IP is a strong indication of the level of development within this technology. Below, we explore what's going on within the industry and what we recommend paying attention to.



Application and Issue Trend, RNAi therapeutics, PatSnap Insights.

The general theme within RNAi, is that throughout the years there are more applications within the technology space. However, there has been drastic decrease in the percentage of applications being issued. To explain how this happens it must be understood how technologies can peak within the IP space. As a technology gains more interest, it leads to a peak in the ability to find a novel outcome. This is because once the technology has been discovered and protected, the probability of finding novel aspects to it decreases. This explains the decrease in issued patents, in the graph above. For example, in 2013 there was a peak in novel discoveries within RNAi due to the high 58.05% issue rate. Since then, there has been a decrease in the percentage of applications granted. As time goes on, it's harder to develop novel applications to RNAi technology. Due to the process already being protected, other assignees must dig deep to have a chance at their technology being protected within this space. Even though RNAi is a huge area of interest for pharmaceutical companies currently, it's becoming harder to find and protect their investments.



Application Trend of Top Assignees, RNAi Therapeutics, PatSnap Insights.

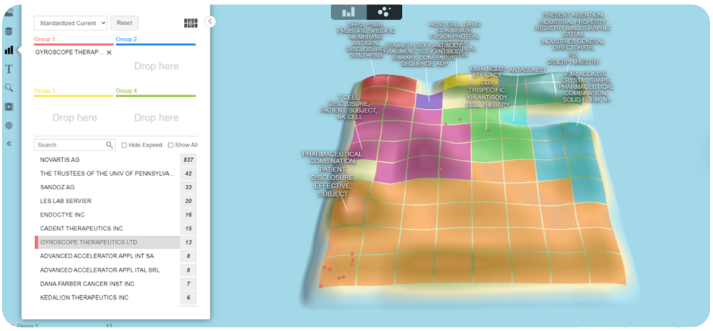
Big Pharma is making big moves — including choosing to partner with smaller companies is due to challenges related to patent cliffs.

Patent cliffs refer to the potential decline in revenues due to patent expiry of one or more of a company's leading products. By 2025, big pharmaceutical companies need to be aware that a lot of their internal pipeline may not overcome the gap possibly created by the fall of revenues after patent expiry. This means that pharmaceutical companies need to ensure that products in the pipeline will generate revenue to cover the loss of these vital patents. A lot of these companies are now heavily reliant on external innovation. Therefore, mid-sized biopharma companies have some more bargaining power due to the innovation deficit and access to capital. Big Pharma companies are in need to fill their pipelines with the patent cliff in the near-distant-future, so it is predicted a lot of deals will occur in 2022 and 2023. It can be seen from Alnylam Pharmaceuticals, Inc., a mid-sized pharmaceutical company based in the U.S., has the highest number of patent applications, storming ahead of the giant, Ionis Pharmaceuticals in recent years. This further shows that mid-sized pharma companies are starting to gain a bigger presence through their industry, which has us wondering: will this lead to more mid-sized partnerships forming in the coming years?

Partnerships within RNA Technology:

With this, there is a shift within the Big Pharma mindset. Through the pandemic years, collaboration across pharmaceutical companies increased — an exciting aspect of this is that this collaboration is between Big Pharma and mid-sized companies. For example, the partnership between Pfizer/BioNTech leading to the mRNA vaccine for COVID-19. In addition, merger & acquisitions (M&A) are increasing within this industry; however, the value of these deals is decreasing. For example, in 2021 there were 90 M&As compared to 70 in 2019. However, 2021 saw the value of these deals be at $108 billion, compared to $261 billion in 2019 – causing a 60% decrease in value.

To highlight this, 2019 saw Novartis Ag acquire The Medicines Company for $7.45 billion. The Medicines Company, based in New Jersey, U.S., develops medicines for critical care patients. The acquisition by Novartis Ag is all part of their M&A strategy — to build pipeline depth in a key therapeutic area – as The Medicines Company had just released data from three Phase III trials for its new drug, inclisiran (an siRNA, a type of RNAi), involving 3,600 high-risk patients with atherosclerosis cardiovascular disease and familial hypercholesterolemia. Novartis saw this as a near-term product launch in 2021 which would contribute to Group sales. Just two years later, Novartis Ag went and acquired U.K.-based Gyroscope Therapeutics for $1.49 billion in 2021. This acquisition also fits in with Novartis' strategy to build pipeline in a key area as Gyroscope Therapeutics focus on gene therapies for diseases of the eye. The company's lead candidate, AAV2-based GT005, (see AAV report here) is a one-time gene therapy for Geographic atrophy (GA) and is being evaluated in many clinical trials. This example highlights how large pharmaceutical companies are developing their M&A strategy; however, the recent deals have had a significant decrease in value.



Landscape of Gyroscope Therapeutic's patent portfolio and the areas which it sits, PatSnap Landscape

Above shows areas in which Novartis Ag acquired from Gyroscope Therapeutics, due to Gyroscope Therapeutics' patent portfolio. Even though Gyroscope Therapeutics doesn't have many patents, the acquisition by Novartis would allow the company to expand into its technology area even more, while also allowing Novartis to benefit from having a bigger hold on many specific technology areas.

In Summary:

The RNA therapeutics space is extremely exciting with ample possibilities rooting from a single RNA sequence. These include:

- A new path therapeutics path, leading to more lives to be saved.
- Companies racing to protect their novel developments, giving them monopoly over their invention and the drugs that come from it
- The 2025 patent cliff which may open the door for small- and medium-sized pharma companies to move into

Whether it is ASOs or RNAi, using nucleic acids and our own body's mechanisms is such an exciting development and there is a lot more to come from these therapies.

Founded in 2007, PatSnap is the company behind the world's leading Connected Innovation Intelligence platform. PatSnap is used by more than 10,000 customers in over 50 countries around the world to access market, technology, and competitive intelligence as well as patent insights needed to take products from ideation to commercialization. Customers are innovators across multiple industry sectors, including agriculture and chemicals, consumer goods, food and beverage, life sciences, automotive, oil and gas, professional services, aviation and aerospace, and education.

PatSnap's team of 1000+ employees work from its global headquarters in Singapore, London, and Toronto. To learn more about how PatSnap is improving the way companies innovate, visit www.patsnap.com.

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