Reducing the Cost of Biologics with Innovation Intelligence

A PatSnap Report

patsnap

Reducing development costs and increasing ROI of Biologics through Innovation Intelligence

1. Reduce legal expenditure by improving communication between teams

Invention, despite the romantic image of the lone genius, is usually a team endeavor. When a task requires creativity and novelty, as in the case of explorative research and development (R&D), the formation of problem-focused creative teams involving individuals with varied backgrounds has become a staple across organizations.

In the Life Science industry, due to the high capital costs required to research and commercialize an effective drug, this is particularly true. Take Humira, one of the world's bestselling drugs and the first fully human monoclonal antibody approved by the Food and Drug Administration (FDA). The successful development of this drug is a direct result of the effective collaboration between multiple heterogeneous teams spanning various disciplines and organizations (BASF Bioresearch Corporation and Cambridge Antibody Technology). The importance that the role of effective communication had in moving the R&D process forward between these teams can't be overstated.

Of course, discovery and development are not all that's required to develop a successfully commercial product. An effective intellectual property (IP) strategy is also paramount should we want any hope of making a profit on R&D investment. This requires the involvement of the legal team in the R&D process. Affording the legal team as much visibility as possible allows them to effectively offer counsel on avoiding already-protected solutions that are present in the market, reducing the risk of exposure and ultimately allowing them to develop an effective IP strategy for the products that the R&D teams are developing.

IP lawyers are not research scientists, and research scientists are not IP lawyers. However, both groups possess valuable expertise and it's of the utmost importance that these groups do not operate within a vacuum of each other for your business' R&D strategy to be successful.

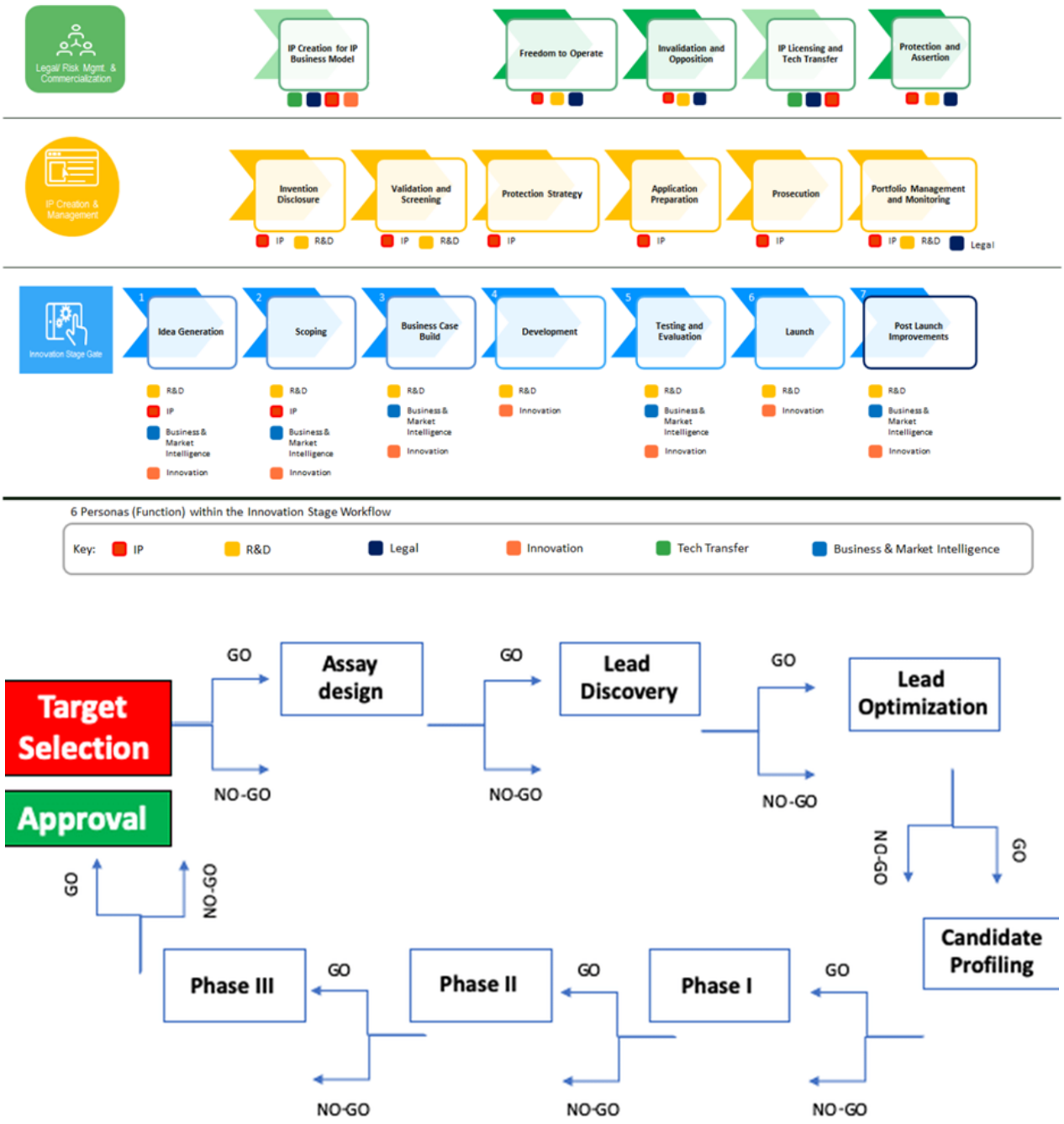
That said, challenges remain around effective communication and information sharing within and across teams. In fact, the higher coordination costs of a creative team that spans multiple disciplinary and/or organizational areas lowers the probability of commercialization success.

Here's the problem: the modern solutions require multiple interdisciplinary teams to collaborate effectively. This collaboration results in higher coordination costs which lowers the probability of commercial success relative to that of smaller R&D teams.

Logically, this follows, as processes involving more people tend to increase the risk of inefficiency. And what do you hear when you hear the word "inefficiency"? You hear the crackle of the flames igniting a pile of money.

This begs the question: how do we go about addressing this problem?

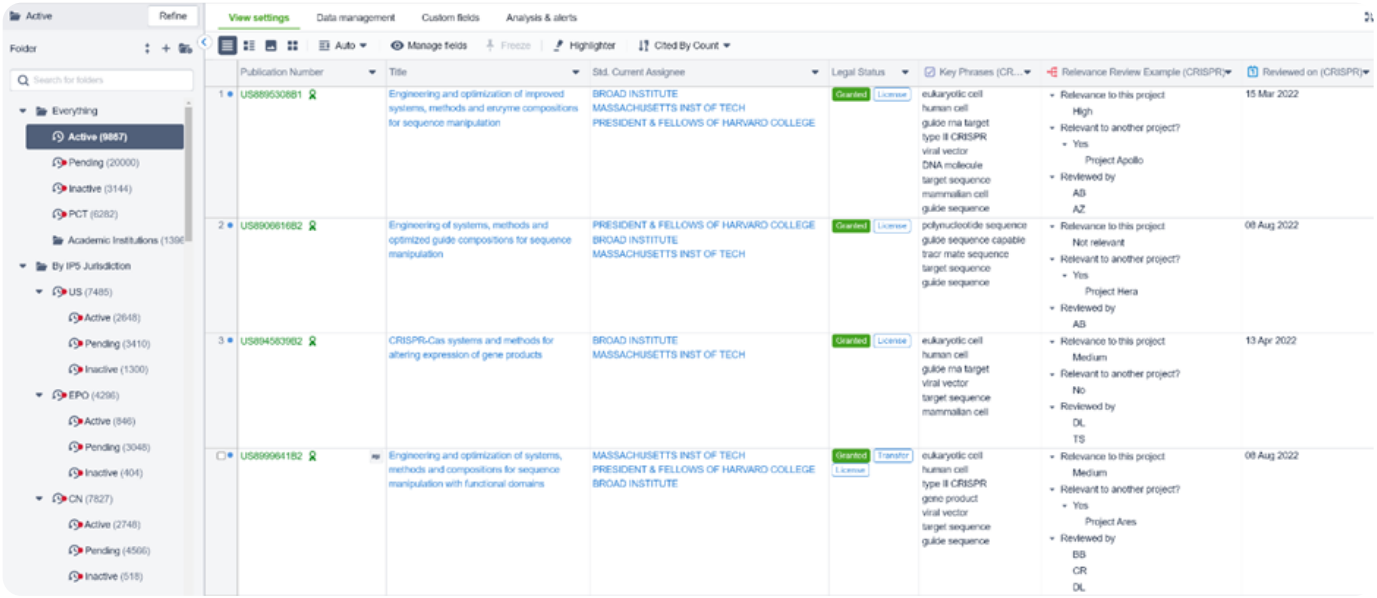
The key to avoiding these issues is to adopt an effective innovation stage-gate. A set of processes that set out the response is to an action and who's responsible. These processes are different for every company, for the development of biologics, a variation on a combination of the two generic workflows shown below are likely to be what you would see, as illustrated on the next page.



Innovation stage gate process, biologic stage gate

To facilitate the success of these processes and reduce R&D overhead in the digital age, fit-for-purpose tools designed for the modern-day R&D infrastructure are a necessity. At PatSnap, we work closely with the world's best, from leading pharmaceutical companies to the next generation of biotech startups. Our goal is to help implement and optimize an effective innovation intelligence strategy involving all teams from R&D to legal.

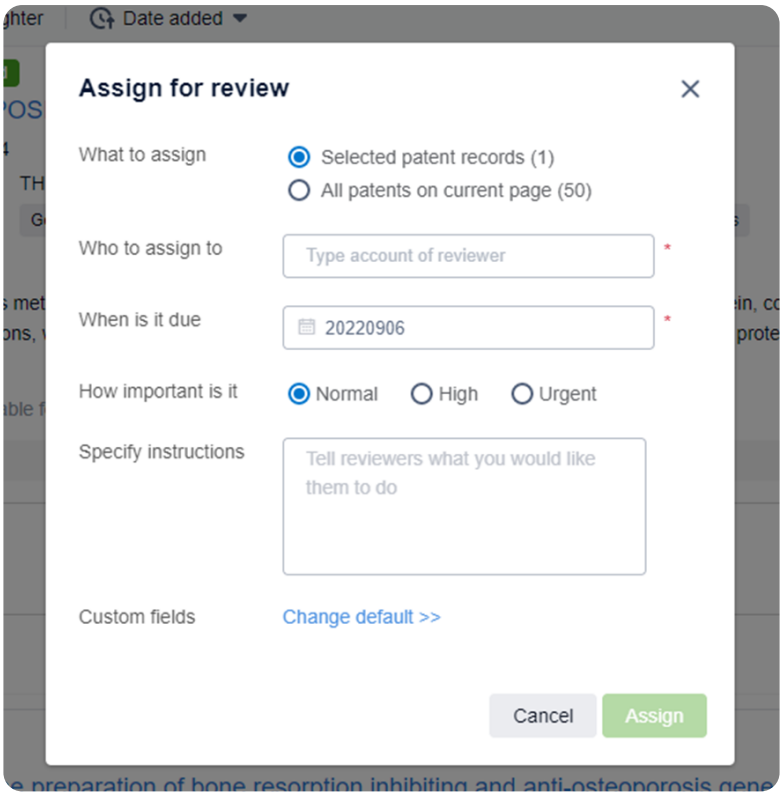
Operationally, the multifaceted nature of today's novel innovation means that inventions often contain compounding features that need to be checked against the broader market for novelty and legal clearance. This means that the greater the scope of the invention, the more complex the validation process becomes. The more checking that is required, the greater the importance of effective communication between teams. The back-and-forth communication between the R&D teams and the legal department must be optimized in order to avoid bottlenecks and delays. To this end, PatSnap's Workspaces offer an effective environment to distribute and manage innovation knowledge across all teams through automatic updating, task assignment, notifications, custom fields, and permission setting across all relevant teams and individuals involved in the process.



Workspaces, PatSnap Analytics

This way, expertise can be easily shared across teams. Allowing R&D to easily share domain knowledge that might be required for a legal decision, and legal teams to effectively share counsel that might affect R&D pathways, without delay.

Workspaces offer distributed insight into the relevant patent and market intelligence data at each stage of the innovation process and are completely customizable to suit your needs. Notifications are sent to the relevant people when certain actions, like reviewing a patent, are completed. Additionally, specific tasks can be assigned to individuals on an ad-hoc basis, allowing you to control the flow of information and prioritize particular documents over others.



Patent assignment, Workspaces, PatSnap Analytics

2. Fail quickly with unpromising or legally problematic candidates

Failing quickly with candidates that are not commercially viable is an important attribute to consider during the R&D process in order to avoid wasting time and money. One of the biggest challenges in the R&D process is determining freedom to operate (FTO) and balancing that versus commercial viability. In an ideal world, this process would be as quick as possible while maintaining decision-making confidence. This way, the expected value of R&D projects can be estimated swiftly, and projects can be moved forward or scuttled in an effective manner.

In order to determine FTO, a comprehensive dataset coupled with an efficient workflow is key. Many tools exist for sequence searching, but they often lack in data comprehensiveness. For instance, a sequence searching tool may allow you to effectively search your reference sequence across a broad database to look for published matches, but the source of that match, let's say a patent publication, will then require you to go to an additional database (this time, the relevant country's patent office website) to understand the context of that subject sequence. This creates a cumbersome experience that only serves to inflate the time required to complete these essential tasks.

Using PatSnap Bio, you can quickly and efficiently run your candidate sequences, prioritize by existing prior art, and collaborate between teams on opinion and pipeline management, all in the most comprehensive sequence searching platform available.

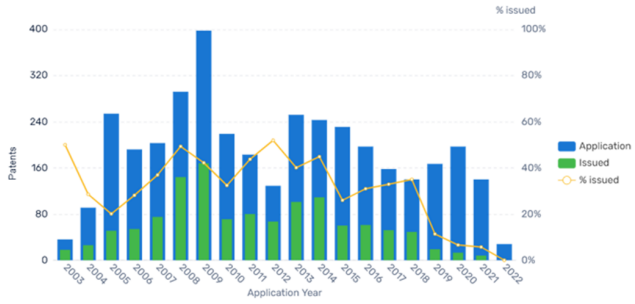
3. Iterate on original to generate new IP opportunities and outcompete biosimilars

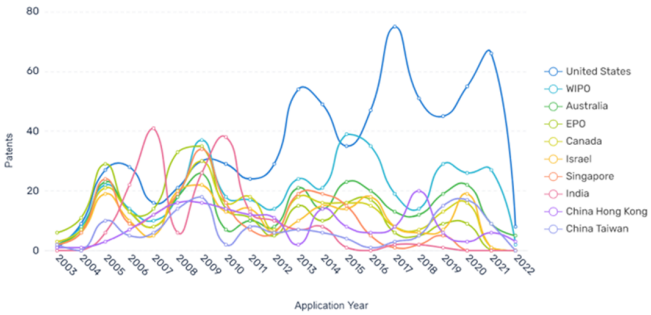
A key strategy for improving the return on investment afforded to a biologic is to mitigate the risk of interchangeable status being afforded to a biosimilar. To tackle this, originators should continue to iterate on their biologic by reducing the frequency of dosing schedules or providing more convenient administration techniques that may extent patent protection or achieve new exclusivity. Other strategies worth mentioning include price decreases, patent defences (and extensions), as well as the use of trade secrets. These strategies will help to foster an overall perception of superiority of branded innovator drugs over their biosimilar counterparts, leading to increased return on investment.

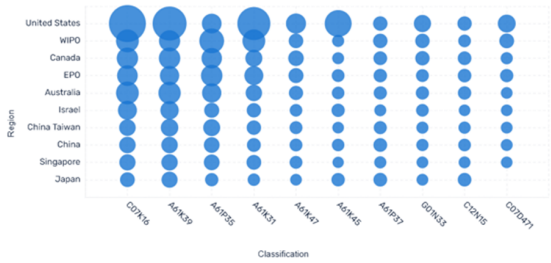
Examples of this include the work of Roche, who, beginning in 2013, developed a new subcutaneous formulation for MabThera that cut treatment time from 2.5 hours to five minutes. Another example is Amgen's first-generation drug Epogen, which required multiple weekly doses. In contrast, the second-generation version of this drug, Aranesp, requires only a weekly injection. These developments improve the perception of superiority by improving healthcare outcomes through increased patient adherence with once-weekly dosing.

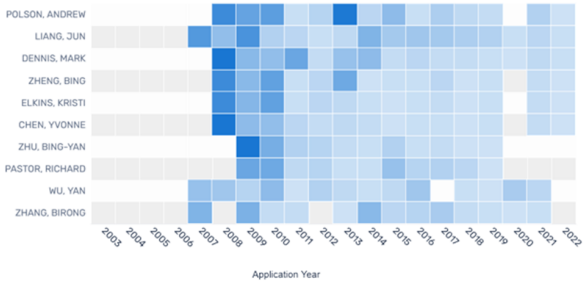
The key to maintaining leadership as an originator is to outmaneuver your biosimilar competitors. To achieve this, a sophisticated competitive intelligence strategy is key. Through a tool such as PatSnap, effective competitor monitoring combined with laser-focused alerts will allow you to keep a pulse on competitor activity. This way, you can be the first to know when information of your competitors activities become publicly available. Of course, publication can sometimes be too late. That's why PatSnap also offers you the ability to infer your competitor's strategy through the creation of bespoke dashboards and innovation tracking, like we've created for Genentech's activity around Rituximab, below.

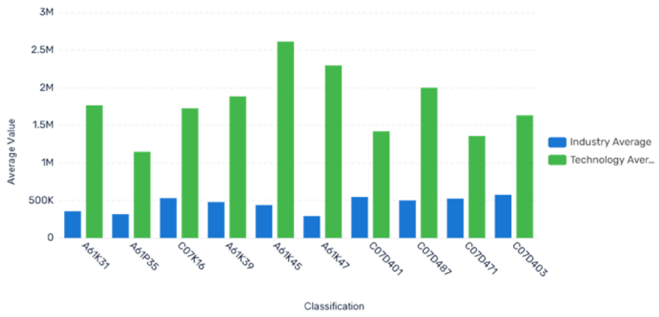
Genentech and Rituximab









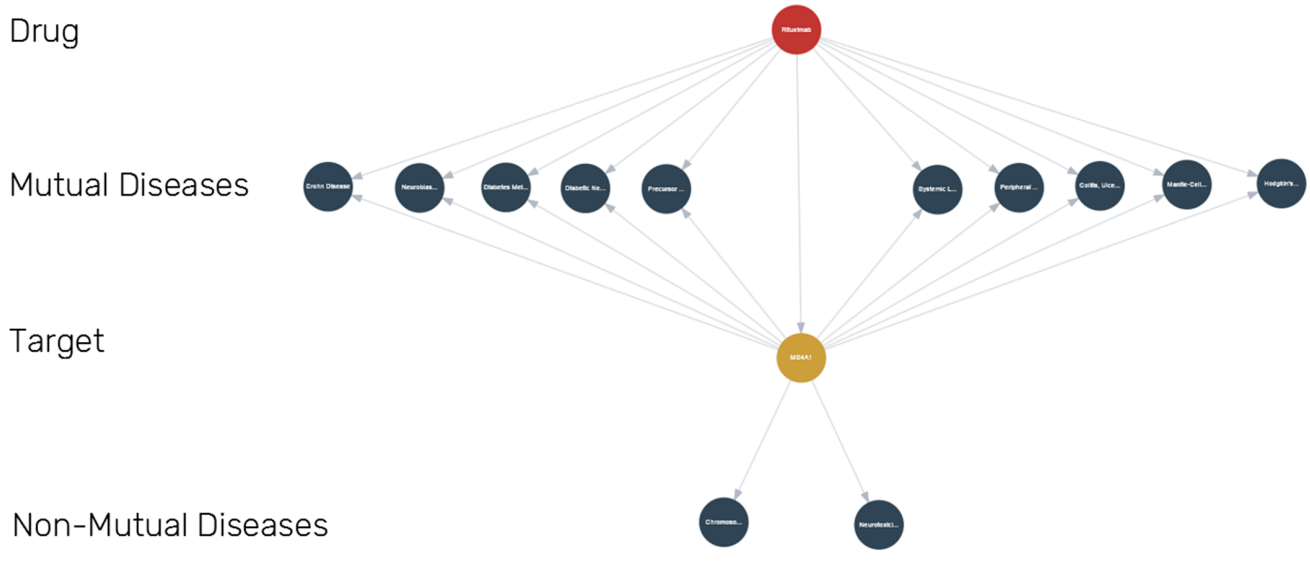


Outmaneuvering your competitors will ultimately lead to increased availability of a superior second-generation biosimilar. It's worth mentioning that the availability of a superior second-generation biosimilar could significantly decrease the demand for an inferior first-generation biosimilar, however, the pricing of a second-generation biosimilar near that of a first-generation biosimilar could help the branded drug to control the market. An example of this is Amgen's Neulasta, a second-generation of Neupogen (filgrastim), which has a single treatment cycle cost of $3,400 compared with Neupogen's cost of $6,000. This is almost a 40% cost reduction. Biosimilars priced at the average reduction of 30% cheaper would not be able to compete with such a second-generation biologic, maintaining Amgen's market share, without cannibalising their ROI opportunity.

4. Increase commercialization opportunity through repurposing

Most of the successful and best-known drug repurposing stories (e.g. sildenafil, minoxidil, aspirin, valproic acid) have emerged, if not from serendipitous observations, from unorganized discovery processes, often relying on the already known pharmacology of a drug (such as an off-target adverse effect) to solve a clinical problem from another domain. Recently though, the drug discovery community has committed to the implementation of organized, systematic, data-driven drug repurposing approaches. Drug repurposing has been advocated as an interesting strategy to explore new pharmaceutical solutions for rare and neglected conditions (in fact, many of the available medications for such conditions can be regarded as repurposed drugs). The pursuit of pharmaceutical solutions for rare and neglected disorders, whereas maybe not particularly profitable in purely economic terms, does imply other forms of value, such as corporate social responsibility and the consequent increased social awareness/perception of pharmaceutical companies. This, in turn, can indirectly increase ROI by improving the selection for treatment of one company's drug over another when an equivalent generic or biosimilar may exist.

PatSnap Synapse offers companies a way to investigate potential repurposing avenues through simple data-driven workflows that equip you with a starting point alongside supporting data that will assist you in validating a particular avenue, such as patents, clinical trial data, academic publications, and approval data. The image below demonstrates the outcome of a simple drug/target comparison using Rituximab. The two non-mutual diseases highlighted are chromosomal disorders and neurotoxicity syndromes.

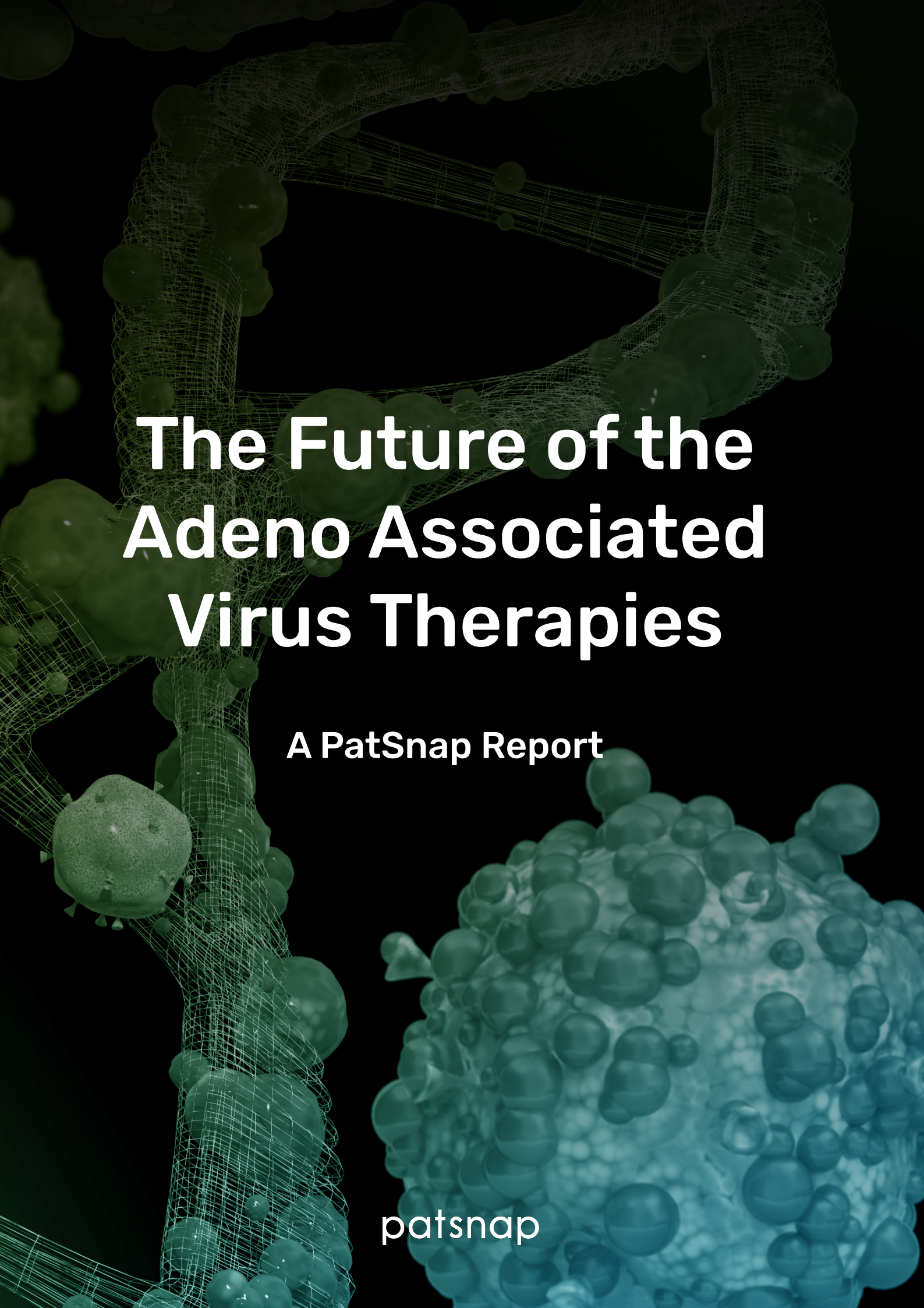


Knowledge graph, PatSnap Synapse

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.

Visit patsnap.com/demo to speak with an innovation specialist or to book a demo.



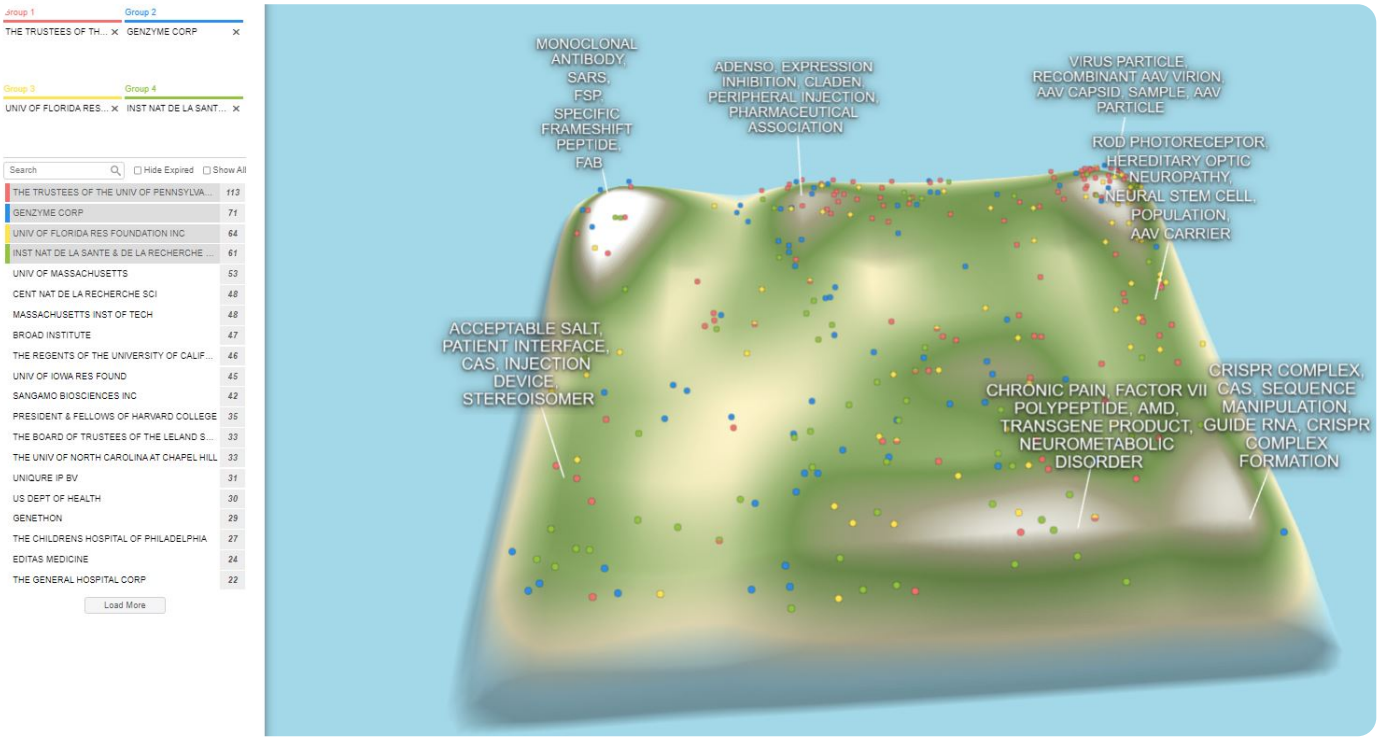
The Future of the Adeno Associated Virus Therapies

A PatSnap Report

patsnap

Part I: Adeno-associated viruses (AAVs) & the patenting landscape

As emerging gene therapies are applauded for their effective and permanent strategies to age old diseases, one therapy has caught the eye of many. Adeno-associated virus' (or AAVs), are a type of non-enveloped virus that are specifically engineered to deliver single strand DNA directly to the cells as a form of therapy. The AAV virus vector encapsulates the treatment of choice and brings it directly to the cells in order to change DNA sequences right at the source. As a result, common challenges of gene therapy such as, detrimental off-target affects (such as in CRISPR therapeutics), or misfiring of single stranded DNA sequences, are mitigated using a highly specific virus vector that is encoded for the target site of choice. Of course, like any promising gene therapy, AAVs also come with their own set of challenges. For example, as the AAVs are a virus vector, the human natural immunity makes it challenging to administer in all patients as the body will often automatically reject and expel the virus as its natural immune system attacks it. This occurs in a whopping 20 - 80% of all eligible patients — a notable figure when considering patenting strategies, investment opportunities, and disease-specific research.

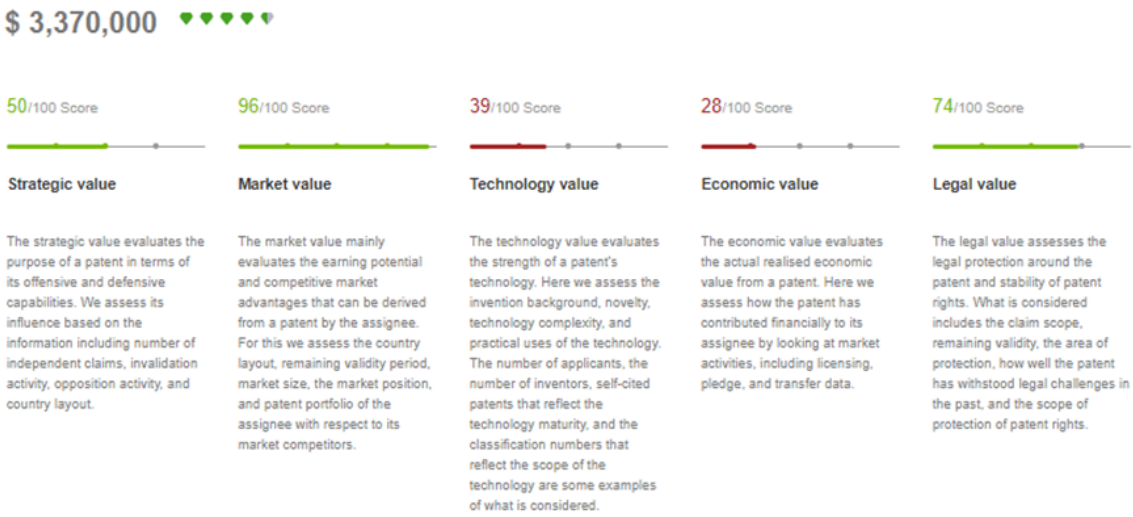


AAV Patent Landscape

Like any biologic domain, AAVs can be quite nuanced when it comes to patenting the technology in and around the area. There are three ways AAVs can be patented: first, the mechanism of how the virus can be detected by the body, second, the production of the virus, and third, the actual AAV vectors, or target sequence. Using PatSnap's proprietary tools and DNA dataset, patent searching, and technology scouting is aggregated on one platform, allowing for Connected Innovation Intelligence to effectively derive insights and to make informed decisions.

1. Patenting the mechanism of how the virus can be detected in the body

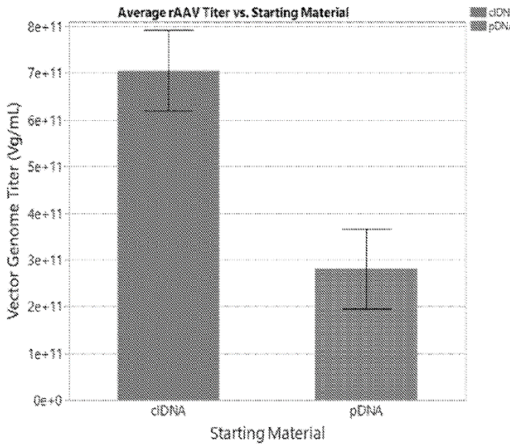
The patent: US11413357B2 Intrathecal delivery of recombinant adeno-associated virus 9 is an example of patenting the intrathecal delivery of AAV9 and the CLN6 gene. The claims include intrathecal delivery to the spinal cord, subarachnoid space, and the arachnoid membrane of the brain. This patent could include therapies for spinal muscular atrophy (SMN1 or SMN2 gene), amyotrophic lateral sclerosis (SOD-1 gene), and other central nervous system diseases that penetrate the blood-brain-barrier. According to PatSnap, this particular patent held by Ohio State Innovation Found/Nationwide Children's Hospital, is valued at $3,370,000 as per its patent holding power, and factors such as commercialization opportunities, litigation chances, and novelty. When filing a patent in the AAV domain, this patent is the gold standard of first-to-market technology, and prior art.



Patent Valuation as per PatSnap Valuation Methodology

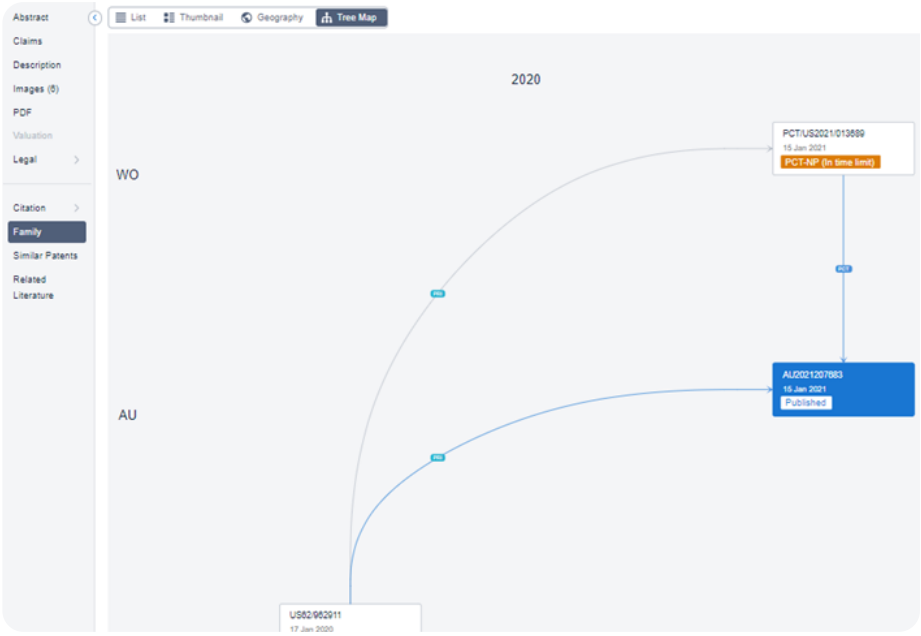
2. Patenting the production of the virus

The patent: AU2021207683A1 Recombinant AAV production is an example of patenting the production of a virus, specifically in the human embryonic cell line. The most significant business challenge for AAVs (which will be discussed in more detail below), is the ability to scale productions and small-scale patient groups which limit the opportunity for economies of scale to be achieved, and lower cost production. This particular patent, held by Asklepios Biopharmaceutical, describes the methodology ofto transfecting a mammalian cell with the AAV2 serotype. As shown in the image below, the output of vector genome in the transfected DNA cell is significantly higher using this method, and as such, this patent is an excellent example of how methodology and production in AAV technology is patented and used as a template for future filing.



Sample Image from AU2021207683A1 describing the benefit of AAV technology

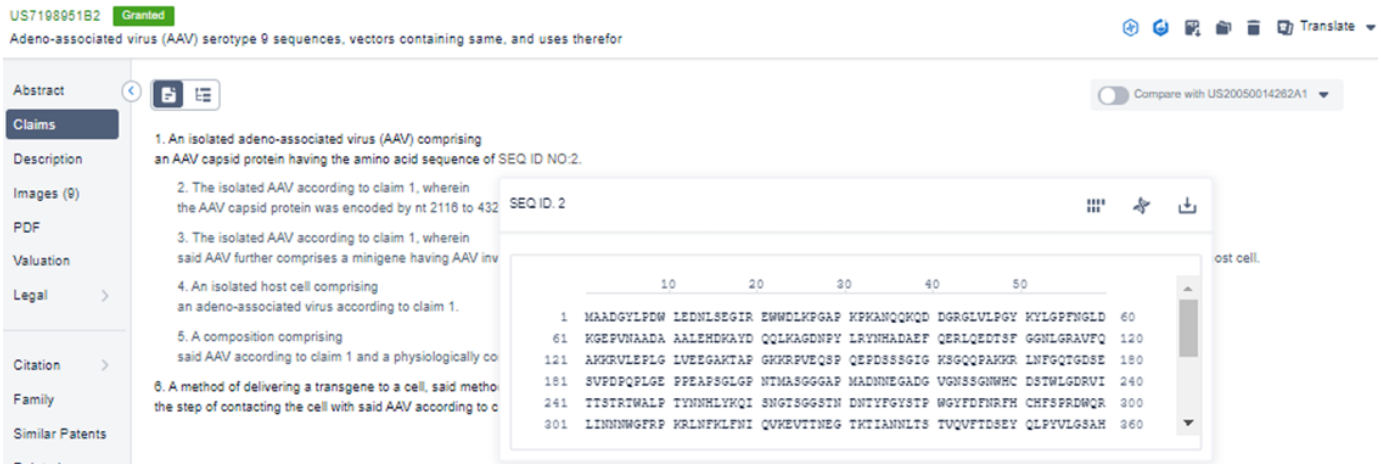
Another notable aspect of this particular patent is the family structure. The US patent of the same was originally filed in 2020, but discontinued as a result of an expired provisional, meaning the patent is not active in the US, and only in Australia. This is an example of when jurisdictions differ in commercial, research, and aggregation potential. The family map in the PatSnap platform displays the transformation of the main patent overtime, with specific jurisdiction aggregation, and causes of discontinuation or patent abandonment.



PatSnap Family Tree Map for AU2021207683A1

3. Patenting AAV vectors and target sequences

The patent: US7198951B2 Adeno-associated virus (AAV) serotype 9 sequences, vectors containing same, and uses therefor describes the single-stranded DNA strands that are used for targeting genomic sites via the AAV vector. This patent is currently held by The Trustees of the University of Pennsylvania and is valued at $710,000 as per PatSnap's valuation system. This particular patent is woven with specific biologic sequences that dictate the exact AAV vectors. In the image below, the patent claims are shown here, along with the specific sequence ID numbers corresponding to the DNA sequence. To understand the overall landscape of the DNA sequence, the PatSnap Bio platform is used to evaluate the patents filed under this specific DNA strand.



Patent View using PatSnap Analytics and PatSnap Bio Modules

In this patent, there are 389 patents corresponding to the DNA sequence. With assignees such as Voyager Therapeutics, CRISPR Therapeutics, and Bayer Healthcare, all patenting with this exact DNA sequence. When patenting in the AAV domain, it's important to note the various ways a particular vector could be patented in order to avoid lack of novelty claims or litigation.

Bio by patsnap

Overview
Patent
Paper
Other Sources

Seq Code 27830

View in Analytics

Found in 59 PatSnap families (389 total) patent(s)

Chemically Modified | In Claims

	Publication Number	Title	Hit Sequences(Seq Position)	Sequence Annotation	Sequence Listing Info
1	US20220195459A1	Regulatable expression using adeno-associated virus (AAV)	SEQ ID. 124	-	SEQ ID.124 [212] PRT [213] Adeno-associated virus 9
2	US20220162609A1	Modulatory polynucleotides	SEQ ID. 151	-	SEQ ID.151 [212] PRT [213] Adeno-associated virus 9
3	WO2022098699A1	Compositions and methods for the treatment of tauopathy	SEQ ID. 135	Seq Code 27830 • adeno-associated viral vector comprising anti-Tau antibodies for prevention, treatment and diagnosis of tauopathies • nucleic acid sequence	-
4	US20220042044A1	Redirection of tropism of aav capsids	SEQ ID. 135	-	SEQ ID.135 [212] PRT [213] Adeno-associated virus 9
5	US20220213501A1	Method of detecting and/or identifying adeno-associated virus (AAV) sequences and isolating novel sequences identified thereby	SEQ ID. 100	-	SEQ ID.100 [212] PRT [213] Unknown [223] capsid protein of AAV serotype, clone...
6	US20220096657A1	Compositions for the treatment of disease	SEQ ID. 124	-	SEQ ID.124 [212] PRT [213] Artificial Sequence [223] Description of Artificial Sequence: Syn...
7	US20220049247A1	Materials and methods for treatment of usher syndrome type 2a and/or non-syndromic autosomal recessive retinitis pigmentosa (ARRP)	SEQ ID. 5137	-	SEQ ID.5137 [212] PRT [213] Adeno-associated virus 9

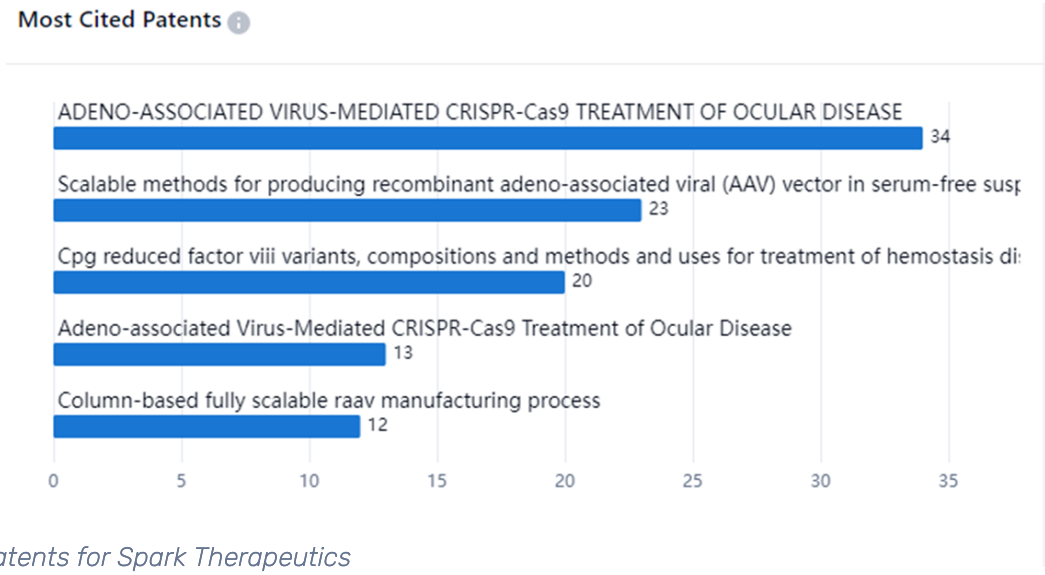
PatSnap Bio Sequence View

Overall, the three patenting opportunities for the AAV technology space are quite similar to most biologic technologies, to either patent exact sequences, or the surrounding methodologies/technologies. In order to understand the AAV patent landscape and where to potentially file as an academic institution, the three areas of patenting are important to note, along with current players, and the corresponding business challenges.

Part II: AAV Business Landscape

The AAV technology domain, although niche, has incredible startup attention and venture capital (VC) funding opportunity. Below are five organizations operating in the AAV space, which will be listed out according to its main academic focus and commercialization goals. *These are not listed in a particular order.

1. Spark Therapeutics: Spark focuses on the RPE65 gene, specifically targeting patients with retinitis pigmentosa. Spark was recently acquired by Roche Holding AG in 2019 for the price of $114.50 per share, for an overall equity value of $4.8 billion.



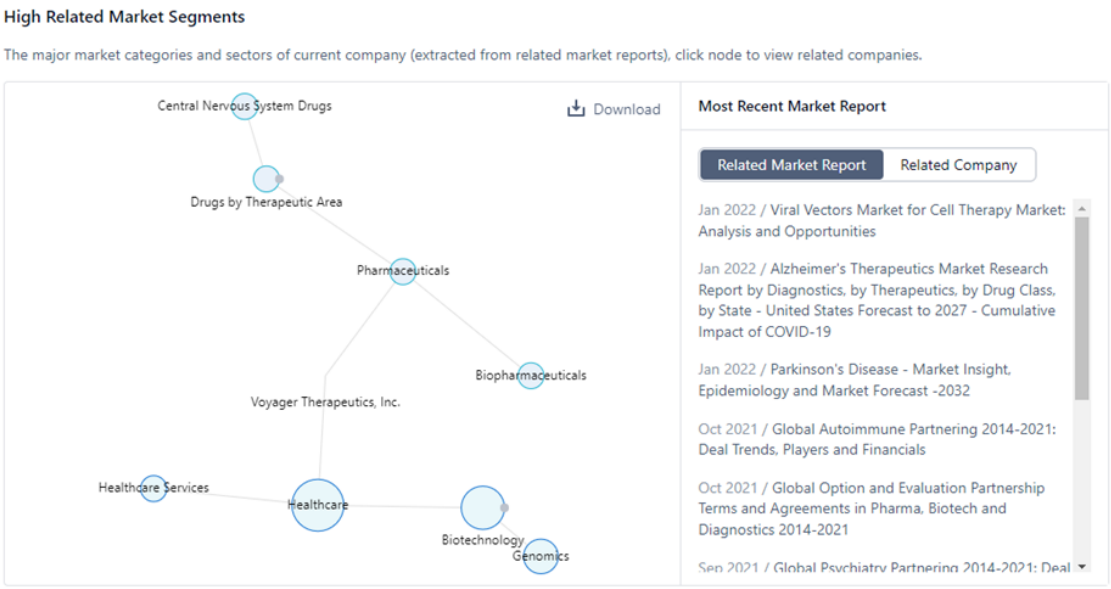
Most Cited Patents for Spark Therapeutics

2. Regenxbio: Regenxbio develops AAV vectors-based treatments for metabolic disorders, muscle diseases, hematologic disorders, ocular diseases, and neurodegenerative disorders. Regenxbio has 408 patents, with nine rounds of funding, notably closing a Series D round of $70.5 million led by Vivo Capital, Venrock, and Brookside Capital. The below table indicates Regenexbio's patent filing strategy as per specific technology topics and therapeutic intersections.

Tech Topic L3	Viruses/bacteriophages	Pharmaceutical delivery mechanism	Genetic material ingredients	Pharmaceutical active ingredients	Recombinant DNA technology	Nervous disorder	Enzymes	Metabolism disorder	Senses disorder	Peptides	Special delivery	Muscular disorder	Neuromuscular disorder	Immunological disorders	Antinoxious agents
Central nervous system	10	10	10	10	9	10	10	8			1	1	1	1	1
Disease	10	10	10	10	9	9	9	7	1	1	1	1	1	1	1
Gene	9	9	9	9	8	9	9	7			1	1	1	1	1
Disease injury	9	9	9	9	8	8	8	6	1	1	1	1	1	1	1
Gene product	9	9	9	9	8	9	9	7			1	1	1	1	1
Adeno-associated virus	8	8	8	8	8	8	8	7							
Blood vessel	8	8	8	8	8	7	7	7	1	1					
Cerebral ventricle	8	8	8	8	7	8	8	7			1	1	1	1	1
Gene transfer	5	5	5	5	5	5	5	5							
Mammal	4	4	4	4	3	4	4	3			1	1	1	1	1
Disease cause	3	3	3	3	2	3	3	2			1	1	1	1	1
Vein	2	2	2	2	1	2	2				1	1	1	1	1
Mucopolysaccharidosis III	1	1	1	1	1	1	1	1							
Mucopolysaccharidosis VI	1	1	1	1	1	1	1	1							
Macular degeneration	1	1	1	1	1				1	1					

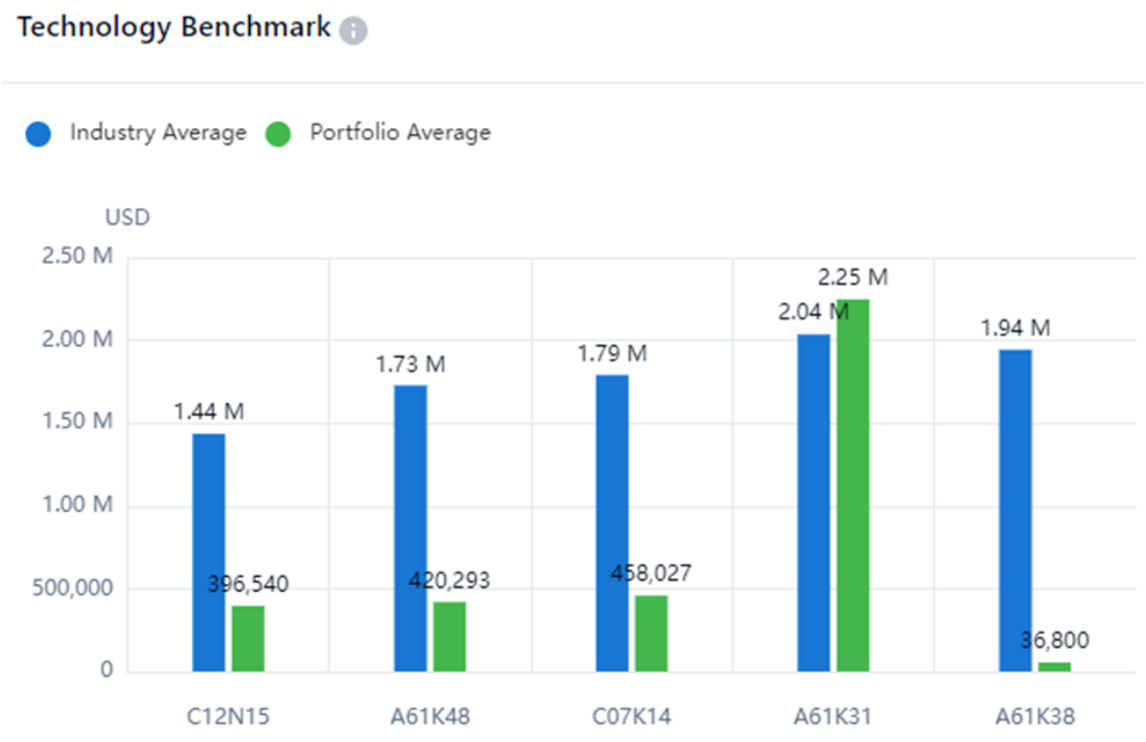
Technology heat map for Regenxbio

3. Voyager Therapeutics: Voyager focuses on AAV treatments for central nervous system diseases, including Parkinson's disease, and ALS. Voyager's most recent funding was led by Brookside Capital at $60M USD in 2015, bringing Voyager to a Series B funding status. The below image depicts the market segments that Voyager operates in, along with recent market reports. As depicted in the image, central nervous system drugs, genomics, and drugs by specific therapeutic areas, are all central to the Voyager pipeline.



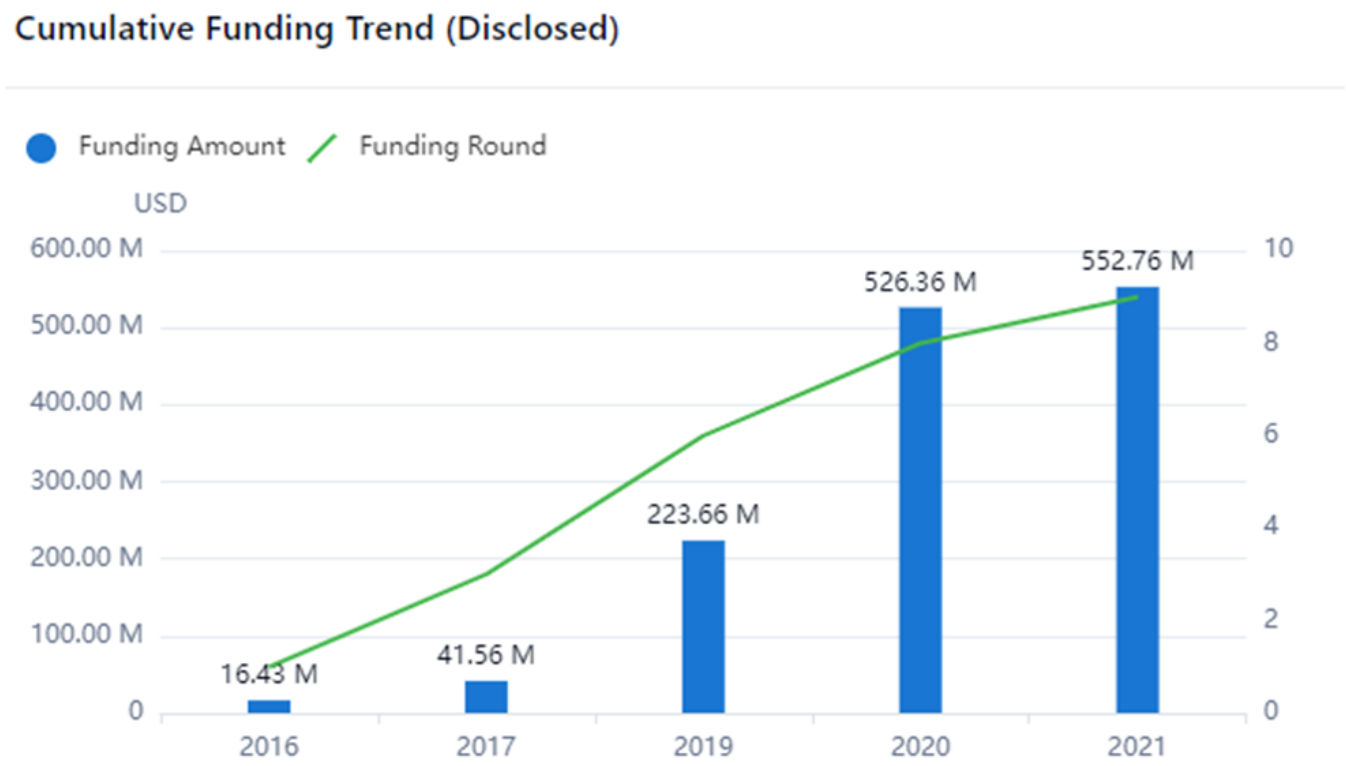
Voyager Therapeutics Market Segments

4. Asklepios Biopharmaceutical: Asklepios Biopharmaceutical is a subsidiary of Bayer AG, and operates in AAV technology pertaining to hemophilia, Duchenne muscular dystrophy, and other CNS disorders. The Asklepios portfolio is above industry average in the A61K31 classification code, medicinal preparations containing organic active ingredients. A recently filed Asklepios patent is CA3163934A1 Methods for treating Huntington's disease, which entered its PCT stage in June 2022.



Technology Benchmark as per Patent Classification codes for Asklepios Biopharmaceutical

5. Rocket Pharmaceuticals: Rocket Pharmaceuticals develops gene therapy treatment options for rare genetic disorders. In August 2021, Rocket raised $26,400,000 in post IPO-equity led by RTW Investments, which will most likely propel Rocket into further academic and commercial development in its technology domain of Pyruvate Kinase Deficiency (PKD) and Leukocyte Adhesion Deficiency-1 (LAD-1) research and development. Rocket has had a steady stream of funding over the past five years, increasing almost tenfold in overall funding amount per year since 2016, as shown in the image below.



Cumulative Funding Trend (Disclosed) for Rocket Pharmaceuticals

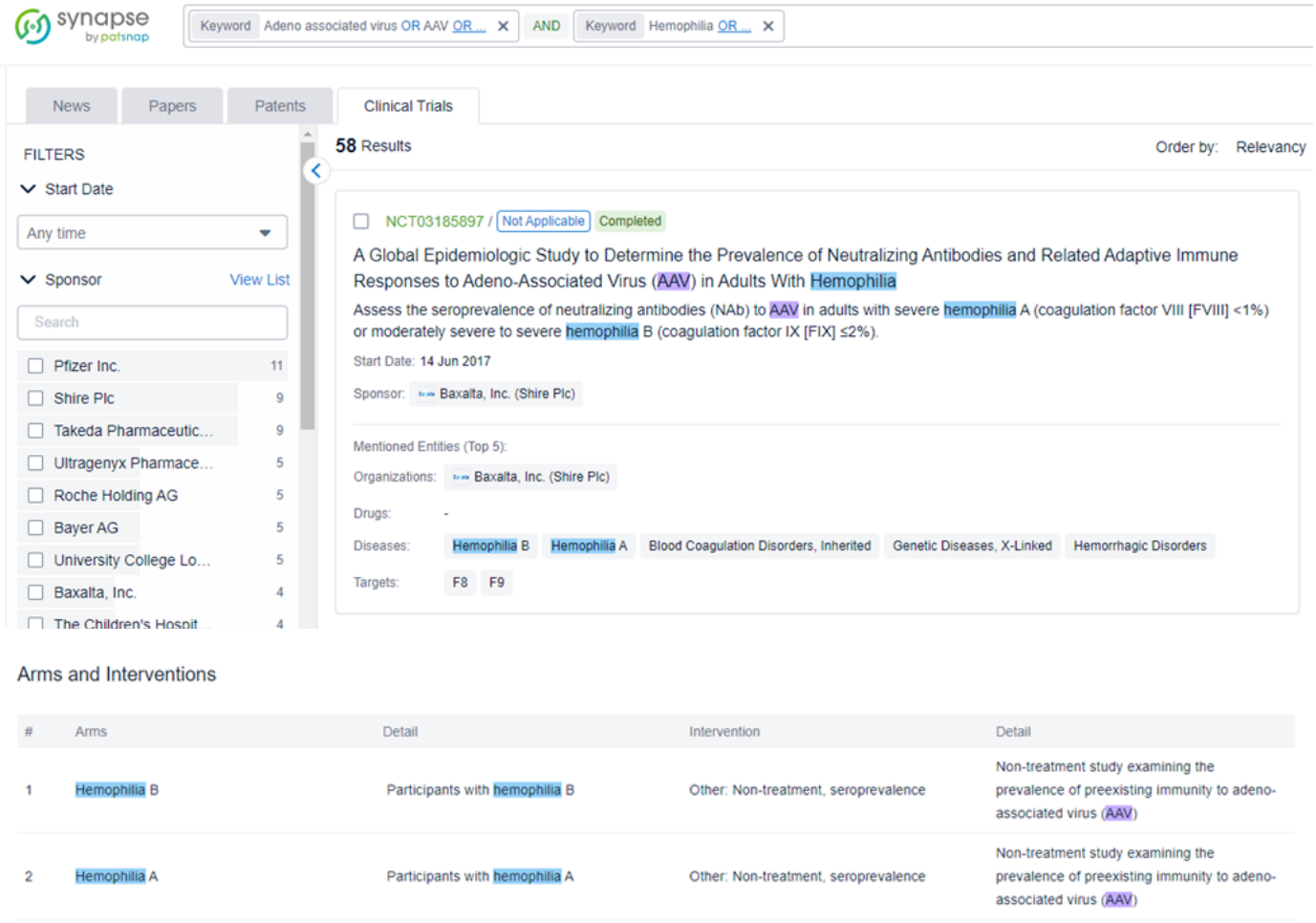
As shown above, the AAV technology space is booming with startup organizations looking to innovate and enter unique disease therapeutics. However, business challenges remain in commercializing and scaling AAV production. Firstly, the large scale manufacturing of the technology requires optimization as a result of small patient groups, secondly, tissue-specific tropism of AAV vectors means the exact direction of a virus is challenging to direct to a desired tissue, thirdly, high quality and high potency recombinant AAV vectors are a challenge to manufacture as a result of lack of research in the area, and lastly, the immune response in the human body to AAV capsids and transgene means the therapy is less effective than expected. As a result, the price per patient for AAV treatment is astronomical, but has the opportunity to be lower in the future as further advancements are made in manufacturing, production, and delivery. For example, it costs upwards of $300,000 to $1,000,000 per treatment currently, which raises many ethical concerns about the distribution of treatments, and the socioeconomic damages to withholding these life-saving treatments from low-income countries and patients.

Part III: Disease-Specific Intellectual Property Deep Dive

There are many ways AAVs can be used to target life-threatening diseases through directed changes in the DNA. However, there are three main diseases that have been researched for its potential in AAV therapy, hemophilia, spinal muscular atrophy (SMA), and Parkinson's disease. By using a tool like PatSnap Synapse, evaluation of current clinical trials, and associated patent filings were aggregated based on clinical trial progression, patent valuation, and efficacy of the treatment.

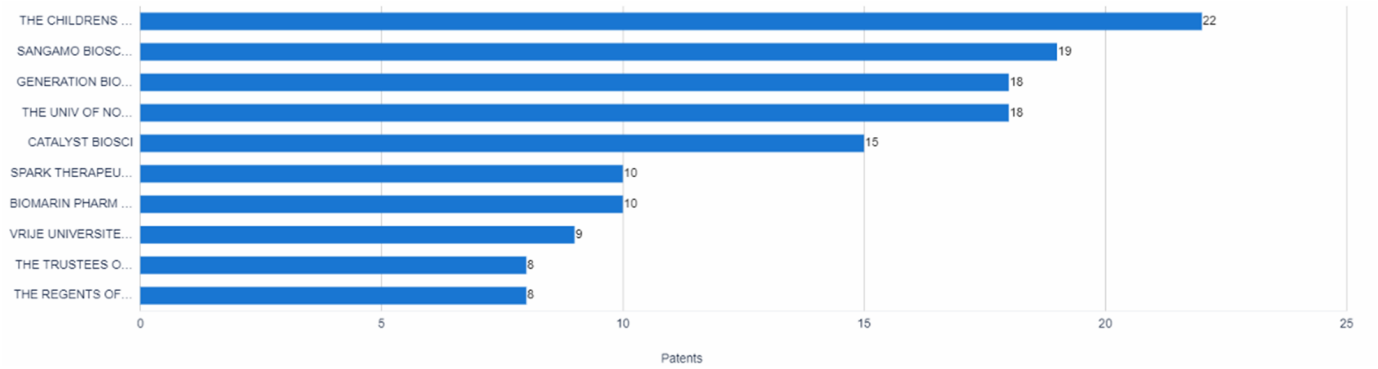
Hemophilia

Hemophilia is an X-linked chromosomal bleeding disorder that has recently been researched alongside AAV vectors for a one-time-administered cure. Furthermore, AAVs can be used in conjunction with CRISPR gene editing for a single nucleotide change in the DNA. Using the PatSnap Synapse platform, a search containing AAV vectors and hemophilia was conducted to evaluate the current clinical trials in the space, along with relevant patents to draw from. Below are direct images from the platform detailing the current research landscape of hemophilia and AAV therapies.



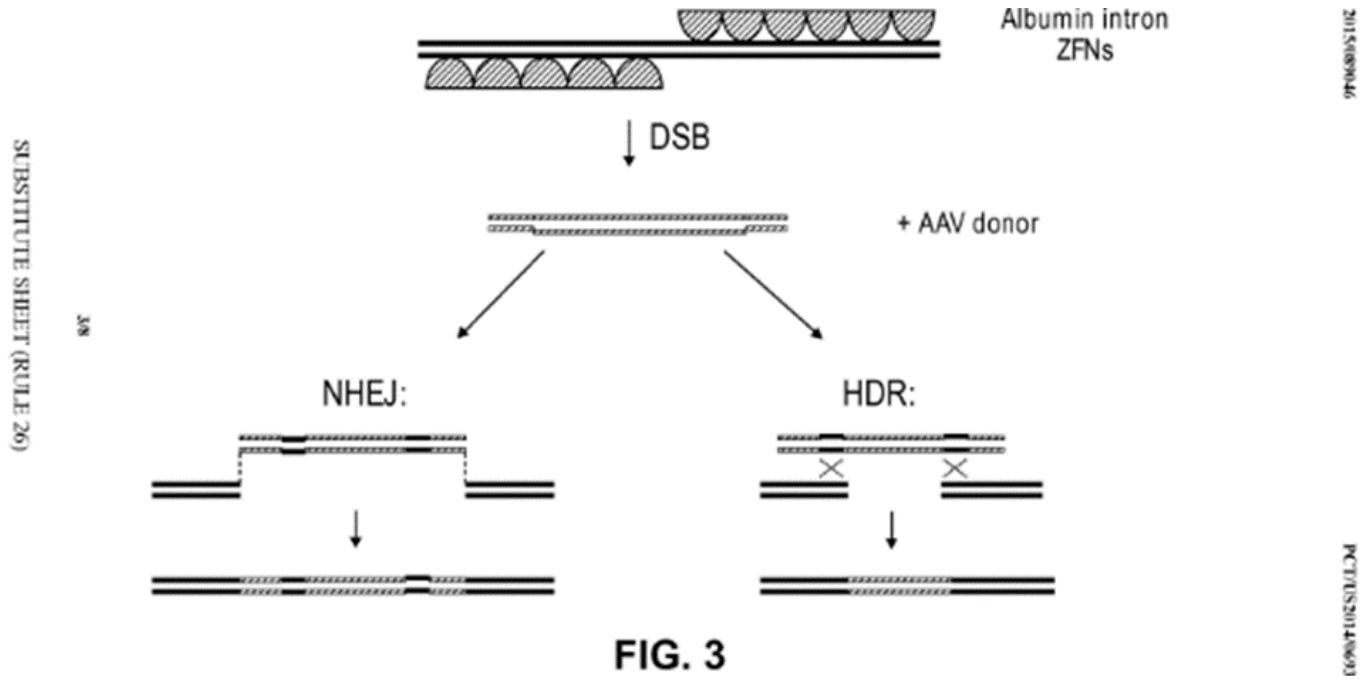
Disease Overview for Hemophilia for PatSnap Synapse

From here, key patents in the AAV and hemophilia target intersect were evaluated, and key assignees in the space are listed in the image below. Currently, the Children's Hospital of Philadelphia and Sangamo Biosciences are in the lead with commercialization and patent filing for AAV hemophilia treatments



Top Assignees operating in Hemophilia research

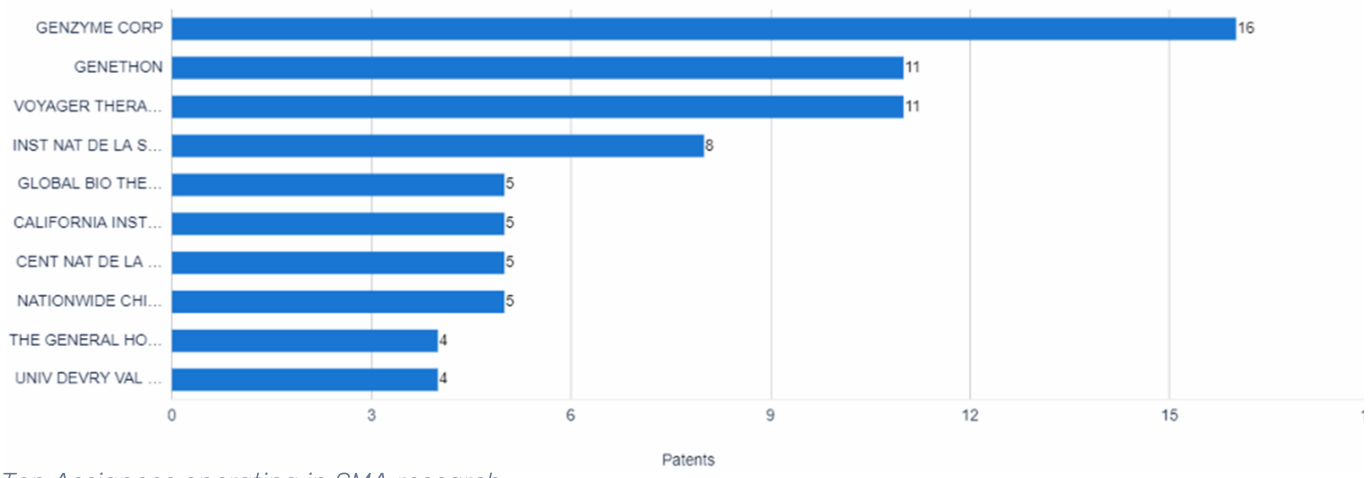
A key patent in this area of research is WO2015089046A1 Methods and compositions for treating hemophilia, held by Sangamo Biosciences, and published in June 2015. The claims of this patent describe the use of AAV2/6 as a vector comprised of zinc finger nucleases, and a specific DNA target sequence. Below is an image describing the use of AAVs as a vector for therapy in hemophiliac patients.



Sample image from WO2015089046A1 describing Hemophilia technology

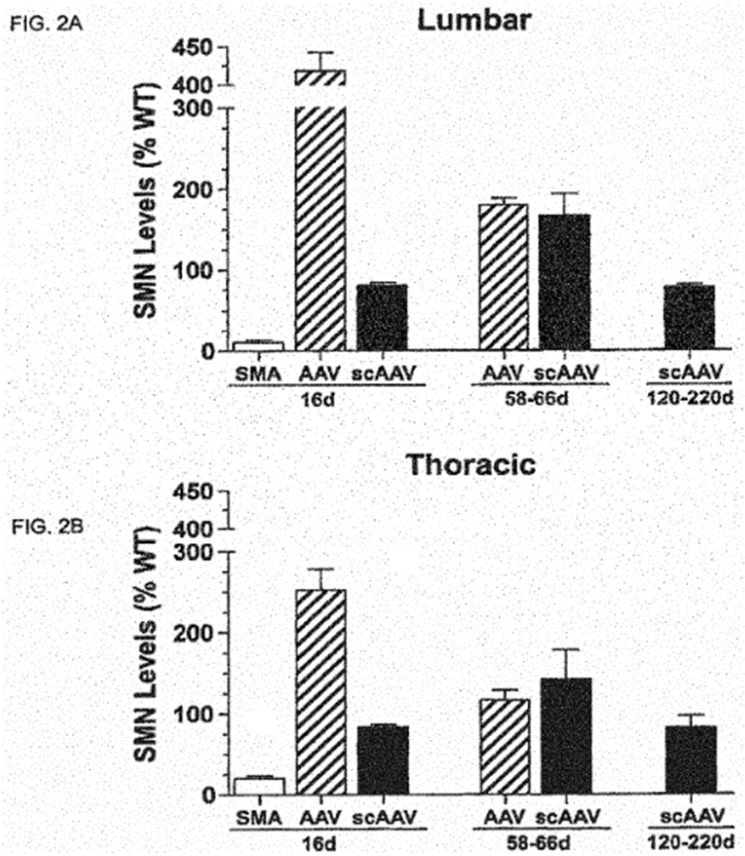
Spinal Muscular Atrophy

Spinal muscular atrophy is a rare neuromuscular disorder that results in the loss of motor neurons and muscle wasting. It's the most common genetic disease pertaining to infant death. Like hemophilia, SMA is a single nucleotide polymorphism, and can be targeted using an AAV vector for a single DNA change. The current lead patent filing assignees are Genzyme Corp, Genethon, and Voyager Therapeutics, all of which originate in the United States.



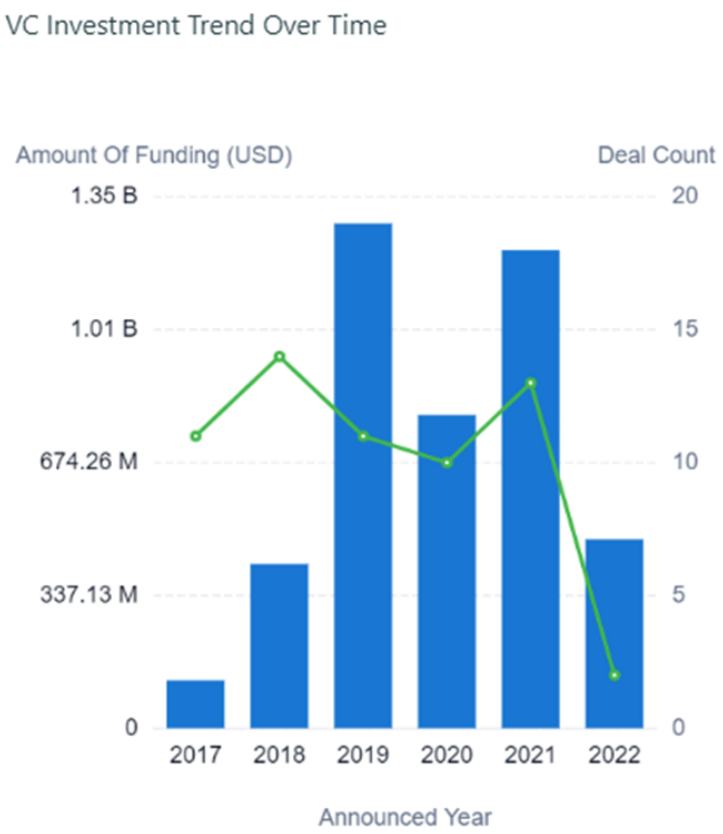
Top Assignees operating in SMA research

A key patent by Genzyme Corporation, the leading patent filer in the AAV and SMA intersect, is US20200384076A1 Gene therapy for neurodegenerative disorders, valued at $7,050,00 given the PatSnap valuation methodology. It describes the use of AAV9 capsid insertion of a specific DNA sequence to the human SMN-1 gene via an intrathecal injection. In the claims of this patent, it details the increased DNA transcription of the SMN-1 gene after the AAV injection in patients, as shown in the image below.



Sample Image from US20200384076A1 describing SMA technology

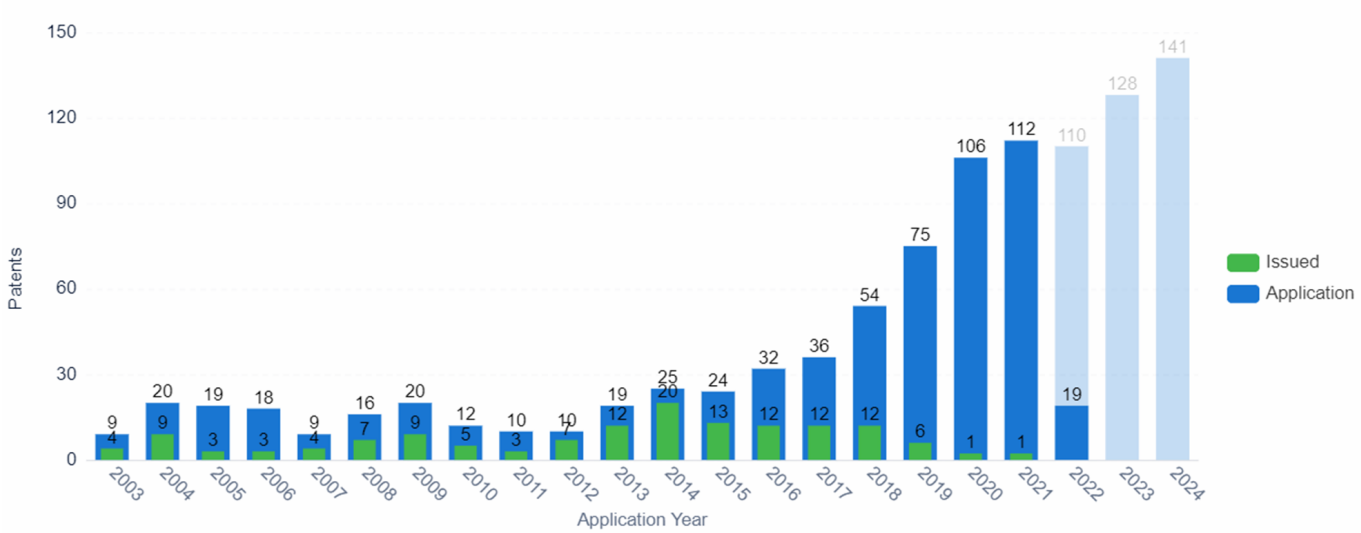
The PatSnap Discovery graph on the next page illustrates how VC investments in the SMA area are showing no signs of slowing. In 2021, there was $1.21 billion of funding poured into the SMA therapeutic area, which consisted of 13 deals. Specifically, ARCH Venture Partners, Obvious Management, and Lux Capital Group are top investors in the SMA investment area, all of which could potentially invest in other disease targets. Because SMA is a rare disease that show itself during infancy, there are often government incentives for academics and patent filers to develop life-changing treatments. As such, an AAV vector directing exact DNA change in the SMN-1 gene is an attractive site for investors, researchers, and corporations to dive into.



VC Investment Trent over time for SMA technology

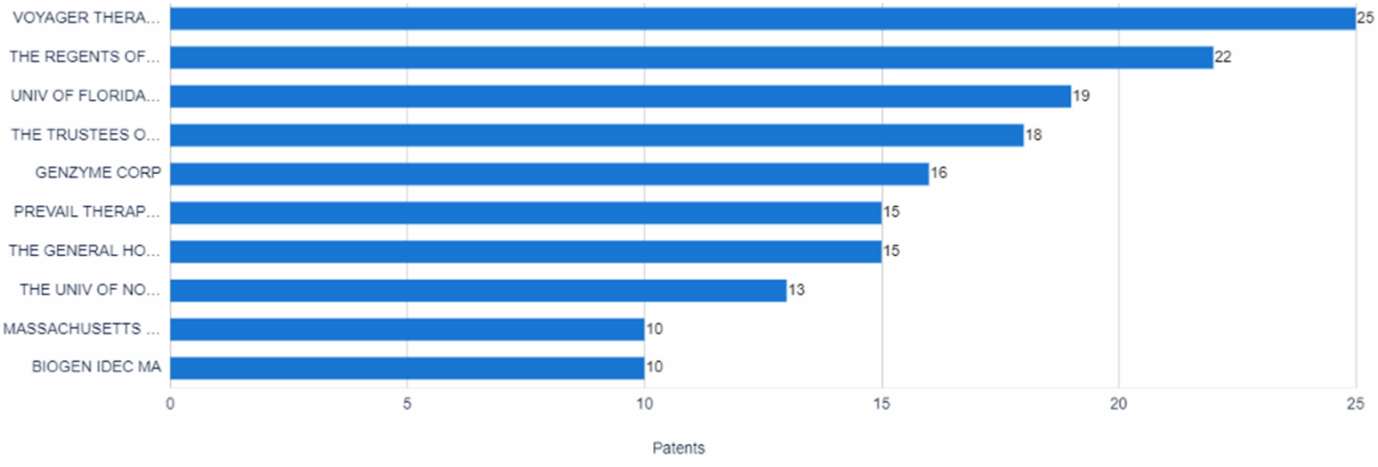
Parkinson's Disease

Parkinson's disease (PD), like SMA, is a neurological disorder which causes a loss of nerve cells in the brain, leading to a significant loss of dopamine in the brain. The decrease of dopamine in the brain results in the dysregulation in body movement, leading to progressive motor function loss such as unwanted movement or slurred speech. In the US alone, nearly one million people live with PD. As such, the need for a lasting therapy is exponential. In the graph below, patent filing reflects this trend as it is predicted to steadily increase in the coming three years.



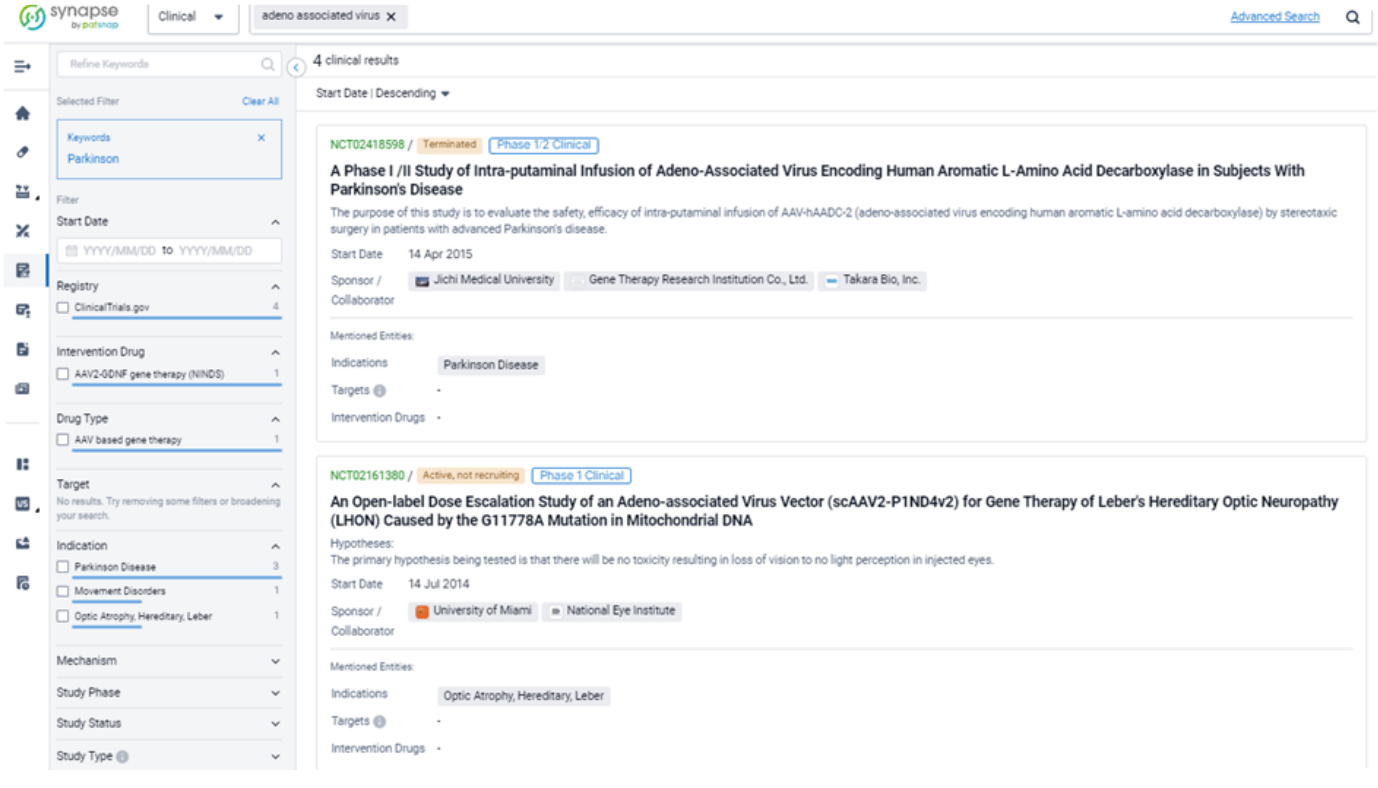
Application trend for Parkinson's Disease patents

The main patent filer in the Parkinson's and AAV intersect is Voyager Therapeutics, which is like that of SMA. This is no surprise as both Parkinson's and SMA are neurological disorders and use the AAV9 vector to penetrate the blood brain barrier for delivery of gene edits.



Top Assignees for Parkinson's Disease patents

To understand the clinical aspect of the current Parkinson's disease and AAV intersect, PatSnap Synapse is used as a tool to aggregate current clinical trials operating in the technology area. The National Institute of Neurological Disorders & Stroke has completed a phase 1 open-label clinical trial as of February 2022 using AAV vectors in conjunction with GDNF gene target to target dopamine production. The nature of Connected Innovation Intelligence allows for a holistic view of the academic and clinical research in a technology area to make informed decisions about where to potentially file patents, or to invest capital.



Disease overview for SMA for PatSnap Synapse

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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.

Visit patsnap.com/demo to speak with an innovation specialist or to book a demo.

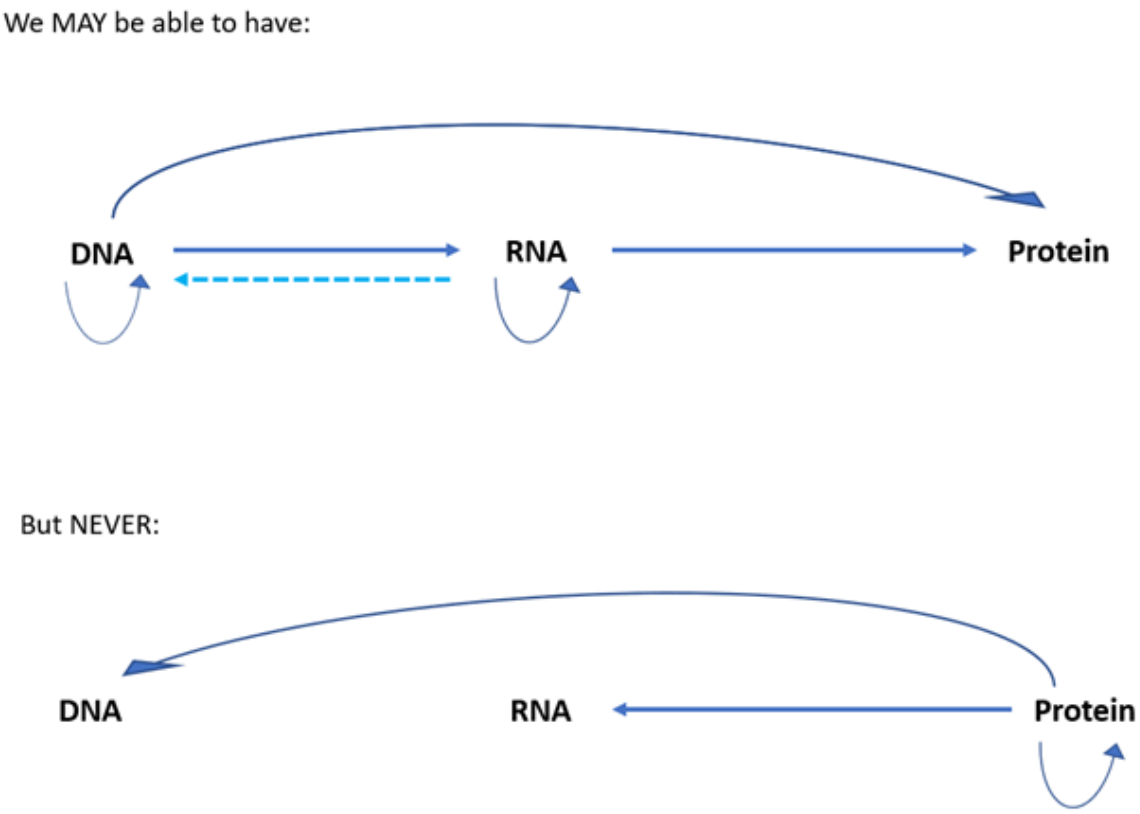
A Deep Dive into RNA Therapies

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

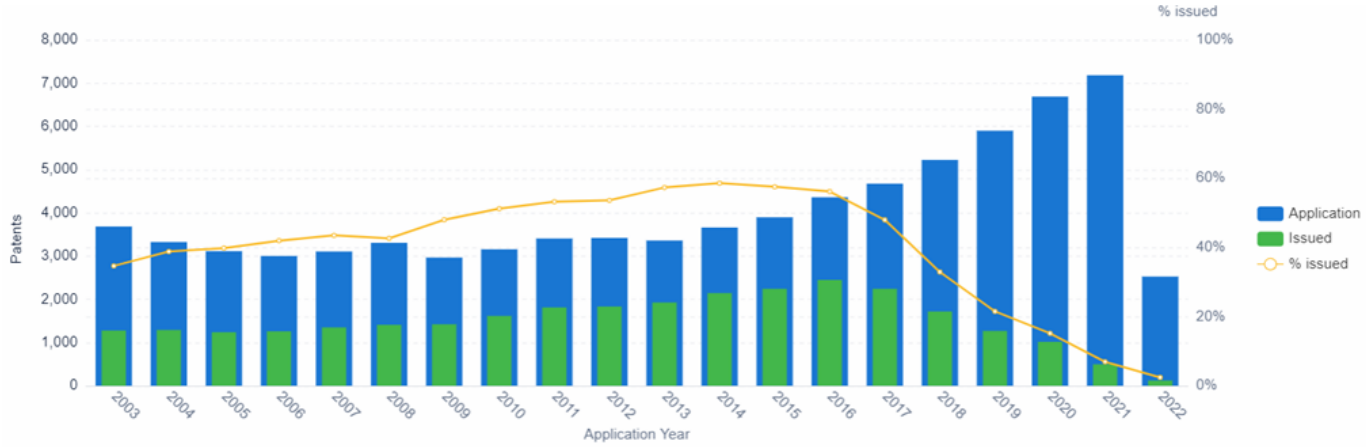
RNA comes in many forms, all of which have different roles within the cell. To name a few, mRNA, and small interfering RNA (siRNA) are some of the RNAs which are gaining a lot of interest within therapeutics. Even though the knowledge of RNA and its role has been around since the 1860s, it's not until 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:

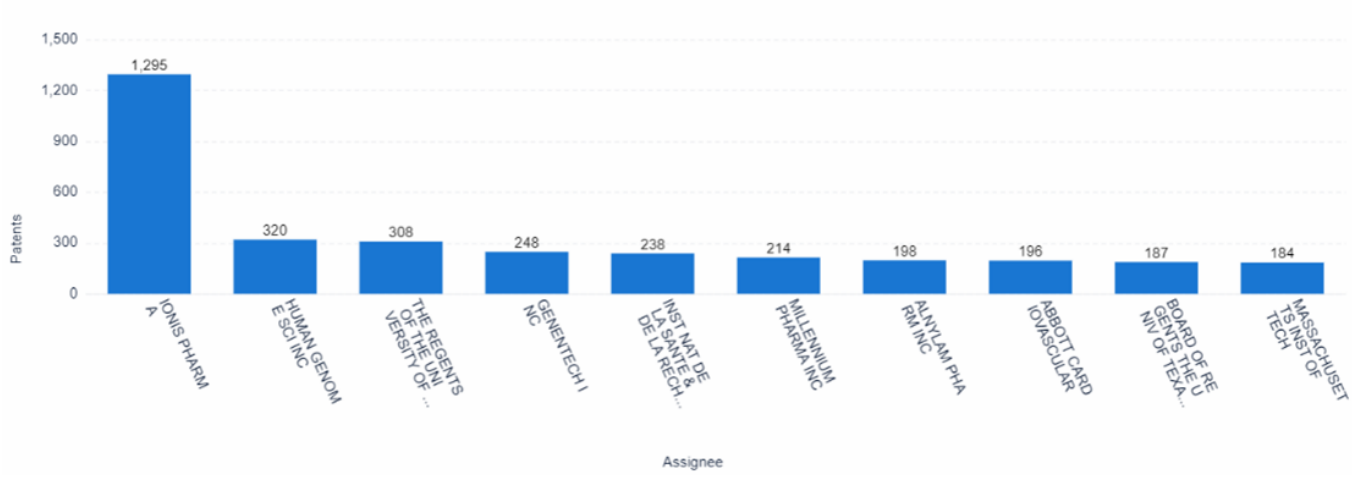
Within the RNA therapeutic scene, there are two main technologies companies are focusing on: Antisense Oligonucleotides (ASOs) and RNA interference (RNAi). These technologies have different mechanisms of action; however, they are both used to target difficult to treat diseases. Here, we discuss how each 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:

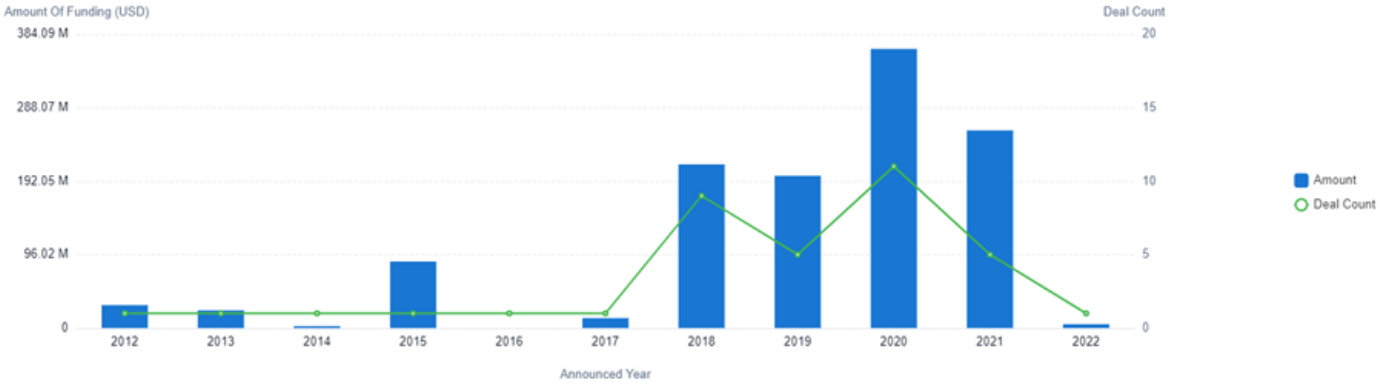
Ionis Pharmaceuticals was the first player in this space that was determined to find a radically different drug discovery technique. Thirty years ago, the company explored the use of using molecules, such as RNA, which had never been used for drug discovery. Within the ASO market, Ionis still maintains 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.

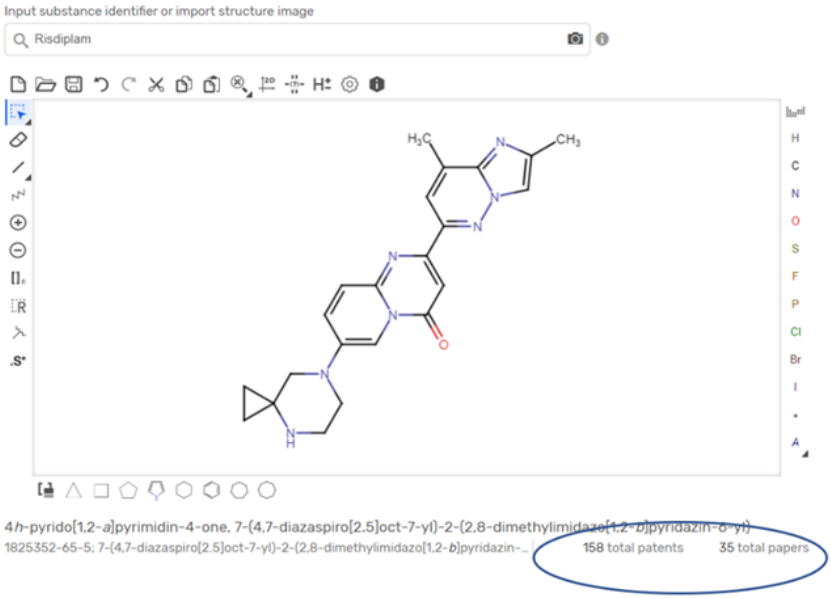
James McArther, Ph.D (CEO of Pepgen) states that "One of the fundamental challenges is that you have these great therapies, but they are not getting into the cells in sufficiently high concentrations to mediate a meaningful therapeutic benefit". Pepgen created a way to develop higher levels of oligonucleotides 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.

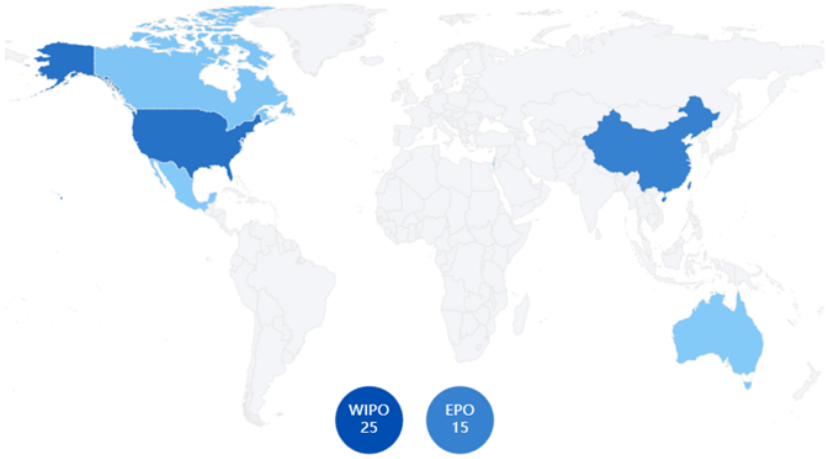
New ASO Drug Spotlight: Risdiplam:

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.

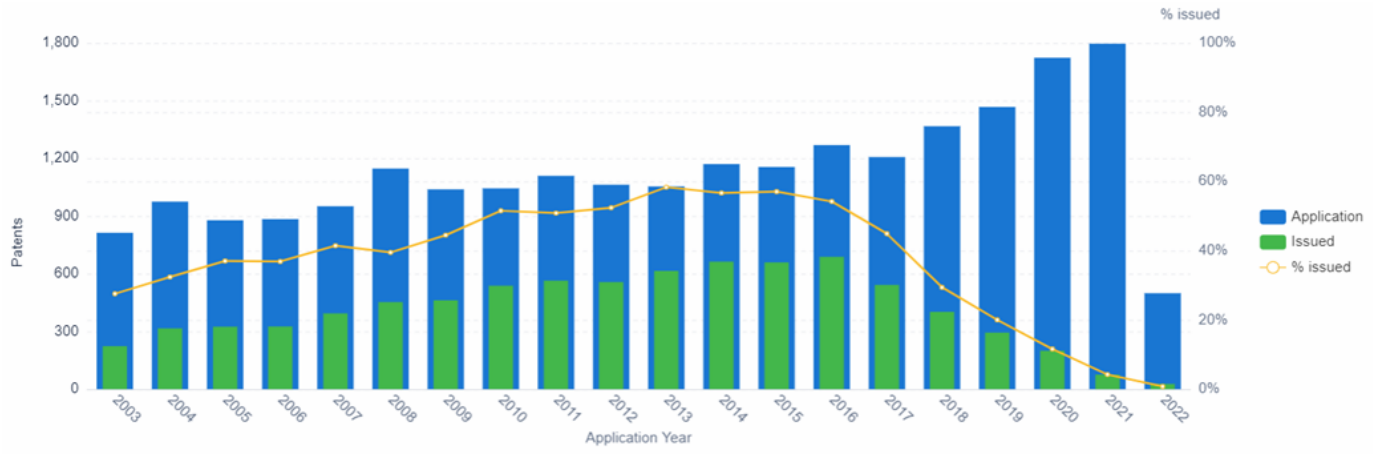
However, it also signifies that there are many different organizations working on therapies for SMA. With the success of Risdiplam, this technology is only going to improve. These diseases which were deemed to be untreatable, now have a chance to be improved and potentially treated. The high amount of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

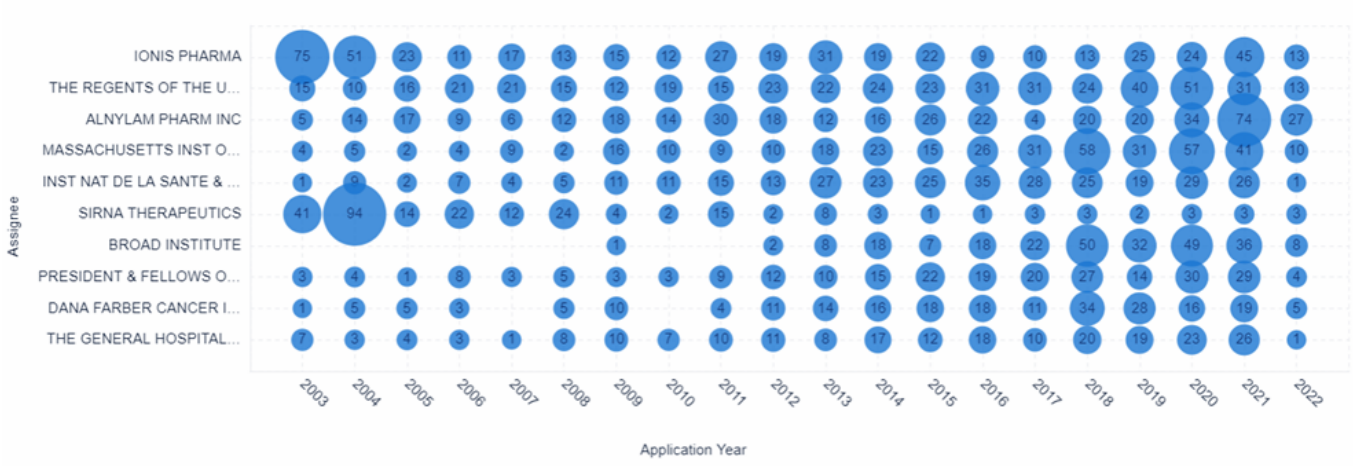
RNAi Patent Landscape:

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.

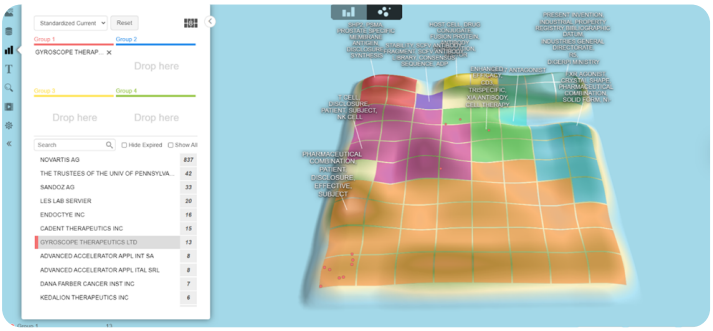
Big Pharma is making big moves — including choosing to partner with smaller companies is due to challenges related to patent cliffs.

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.

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