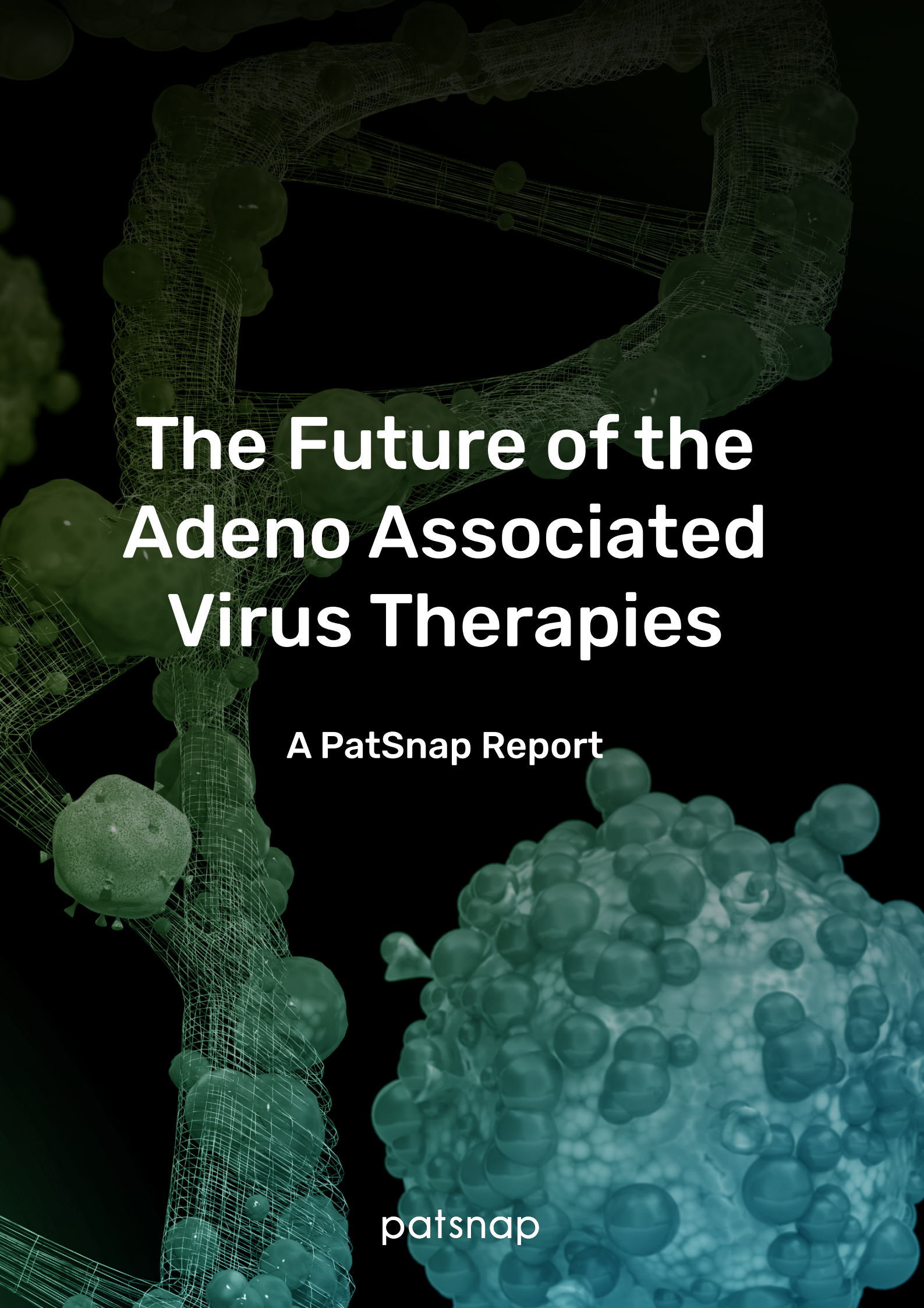


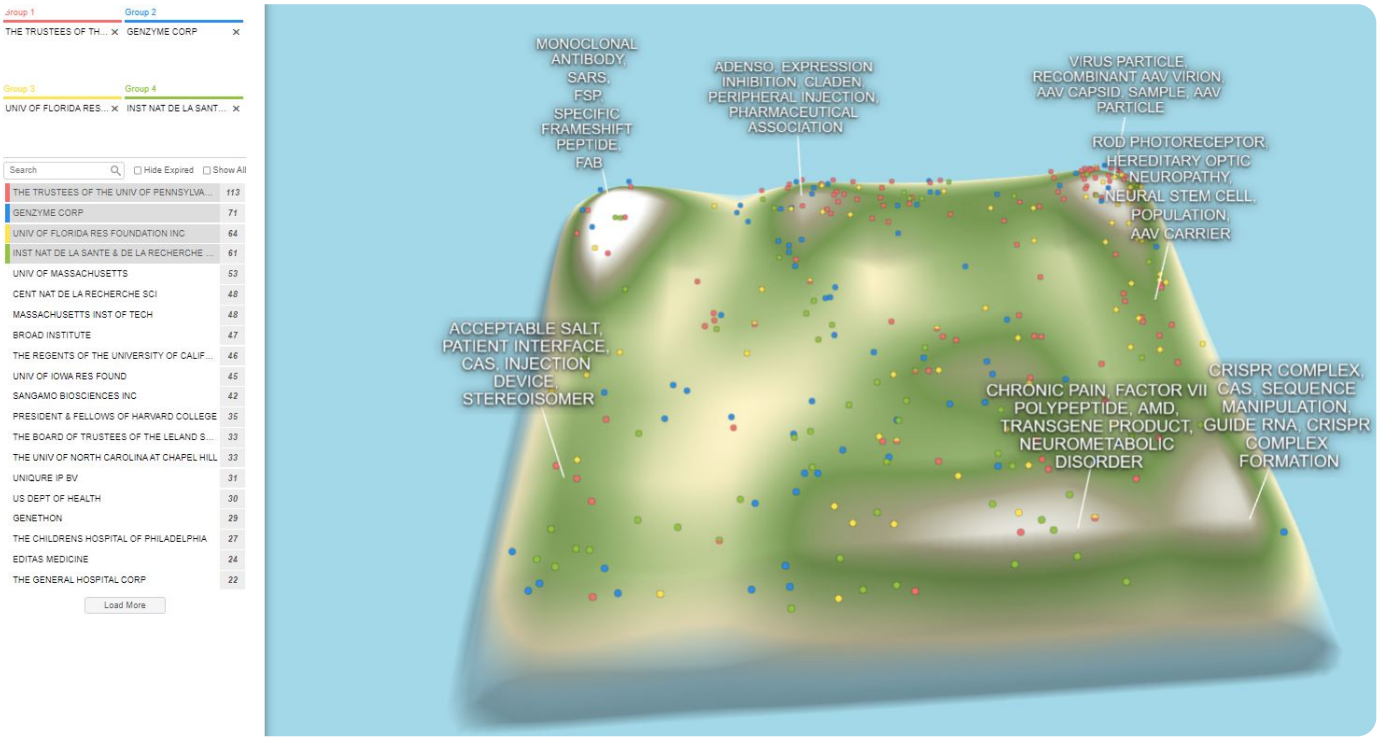
The Future of the Adeno Associated Virus Therapies

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.

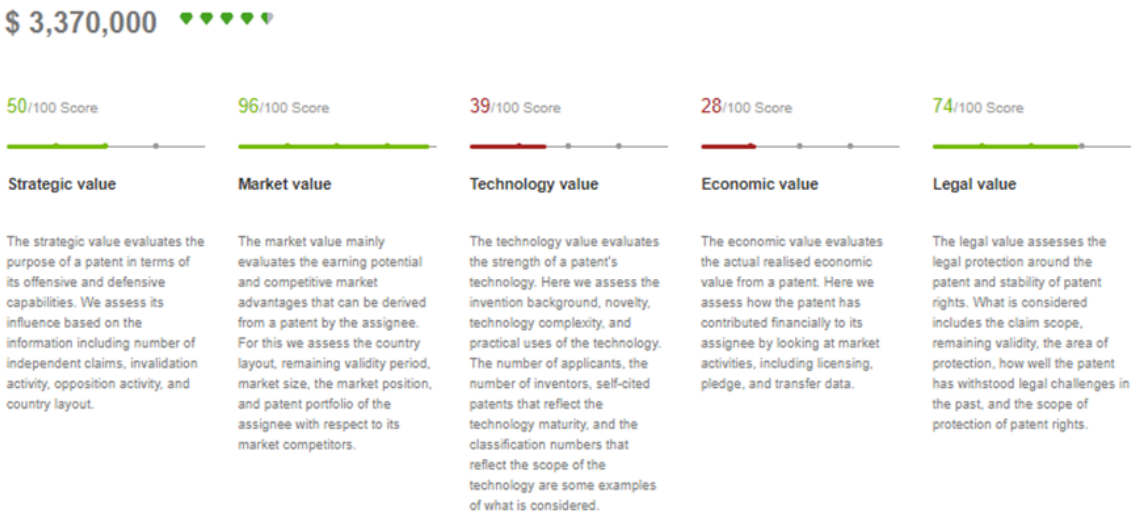


AAV Patent Landscape

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

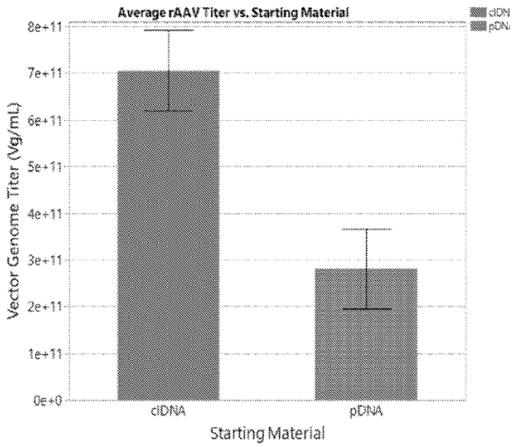
The patent: US11413357B2 Intrathecal delivery of recombinant adeno-associated virus 9 is an example of patenting the intrathecal delivery of AAV9 and the CLN6 gene. The claims include intrathecal delivery to the spinal cord, subarachnoid space, and the arachnoid membrane of the brain. This patent could 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

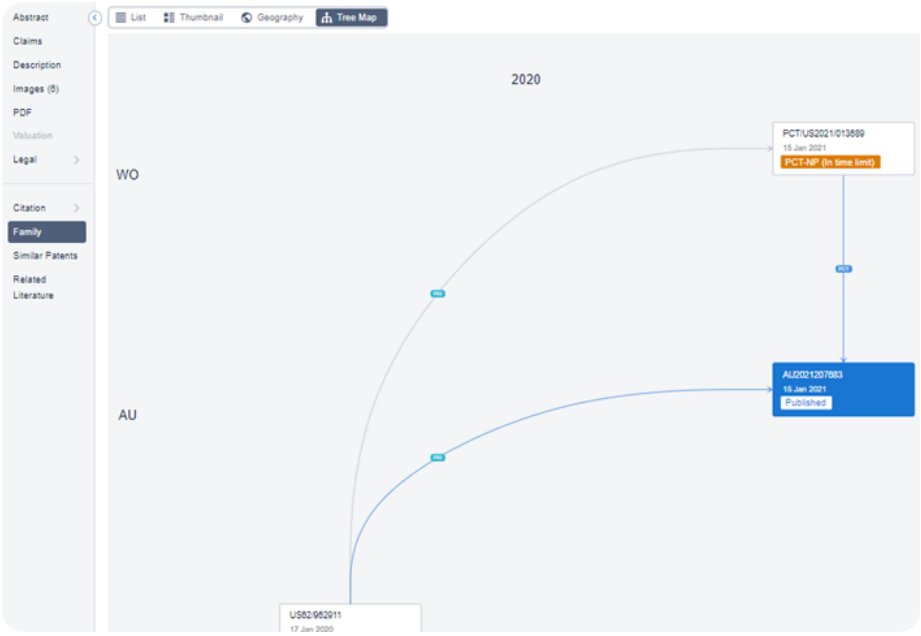
2. Patenting the production of the virus

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

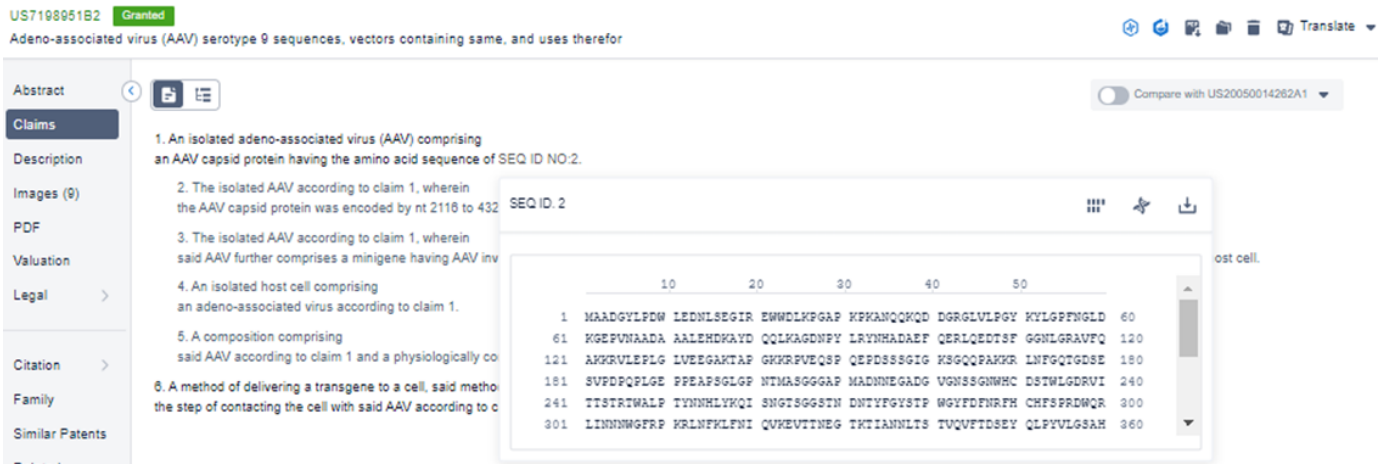
Another notable aspect of this particular patent is the family structure. The US patent of the same was originally filed in 2020, but discontinued as a result of an expired provisional, meaning the patent is not active in the US, and only in Australia. This is an example of when jurisdictions differ 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

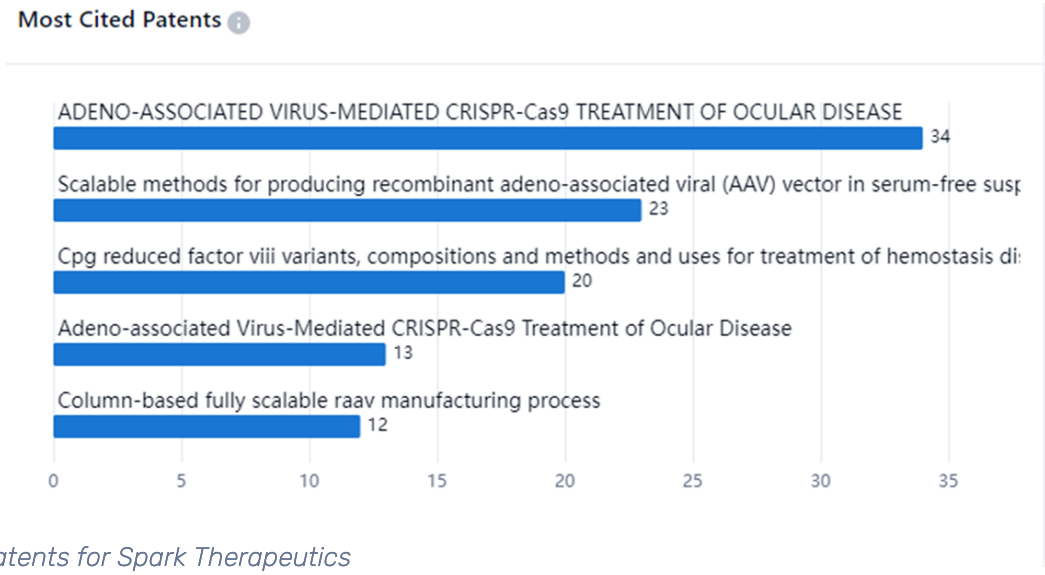
PatSnap Bio Sequence View

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.



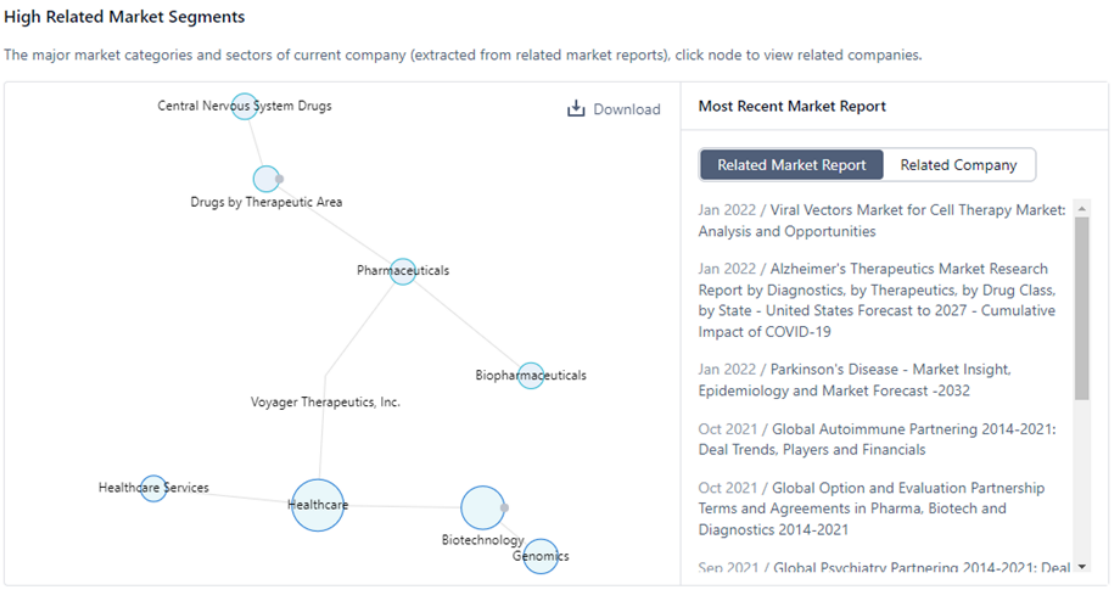
Most Cited Patents for Spark Therapeutics

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					

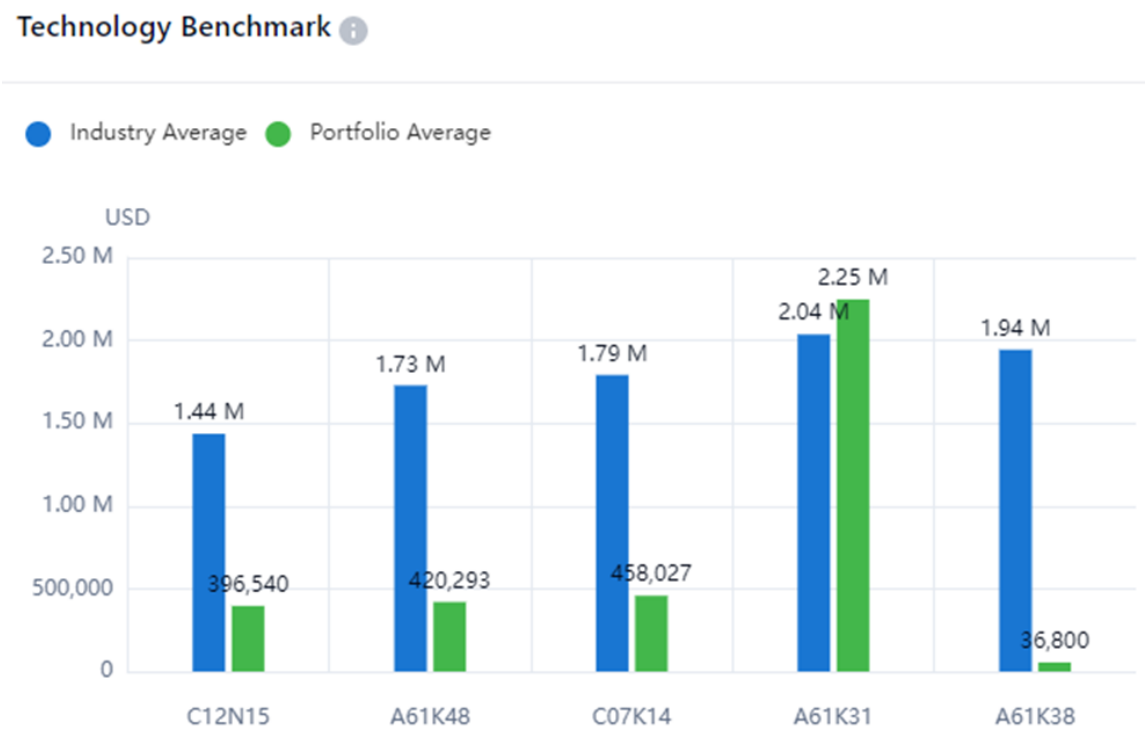
Technology heat map for Regenxbio

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.



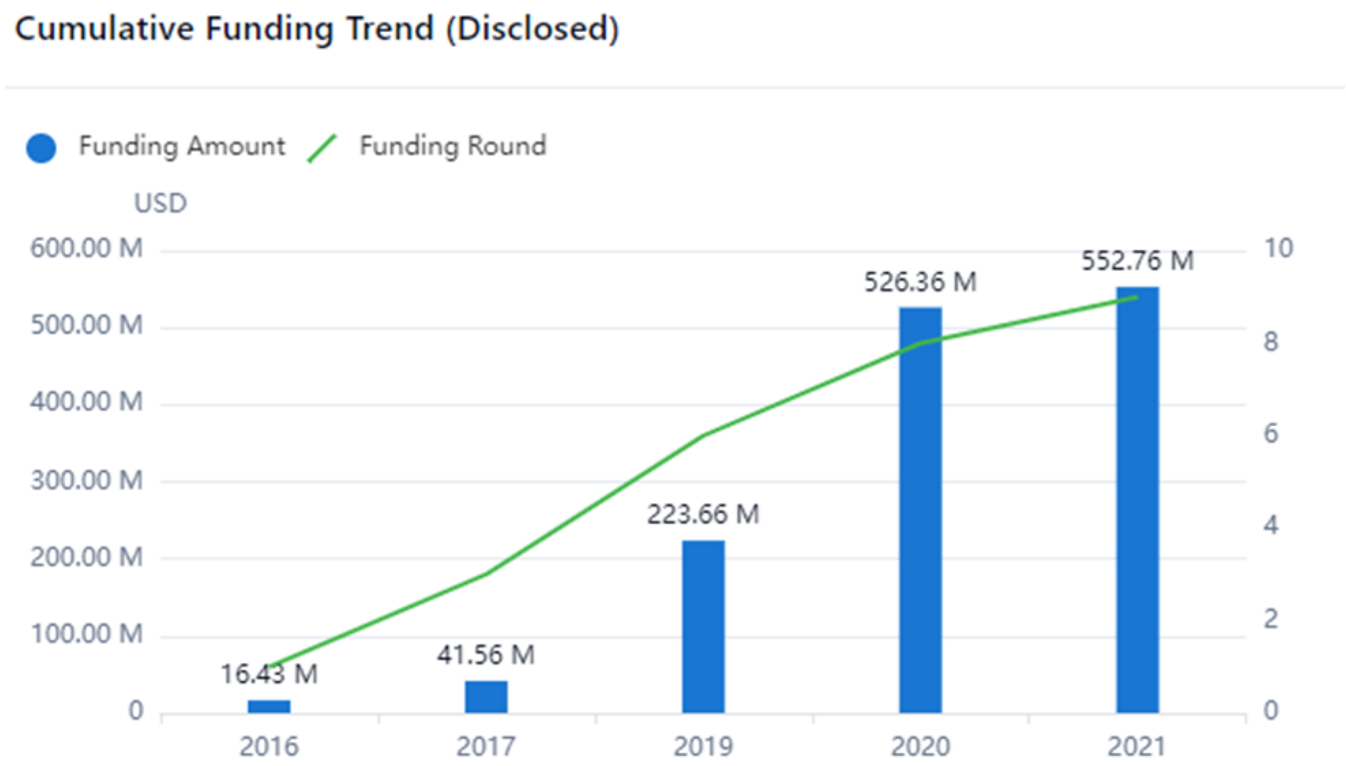
Voyager Therapeutics Market Segments

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

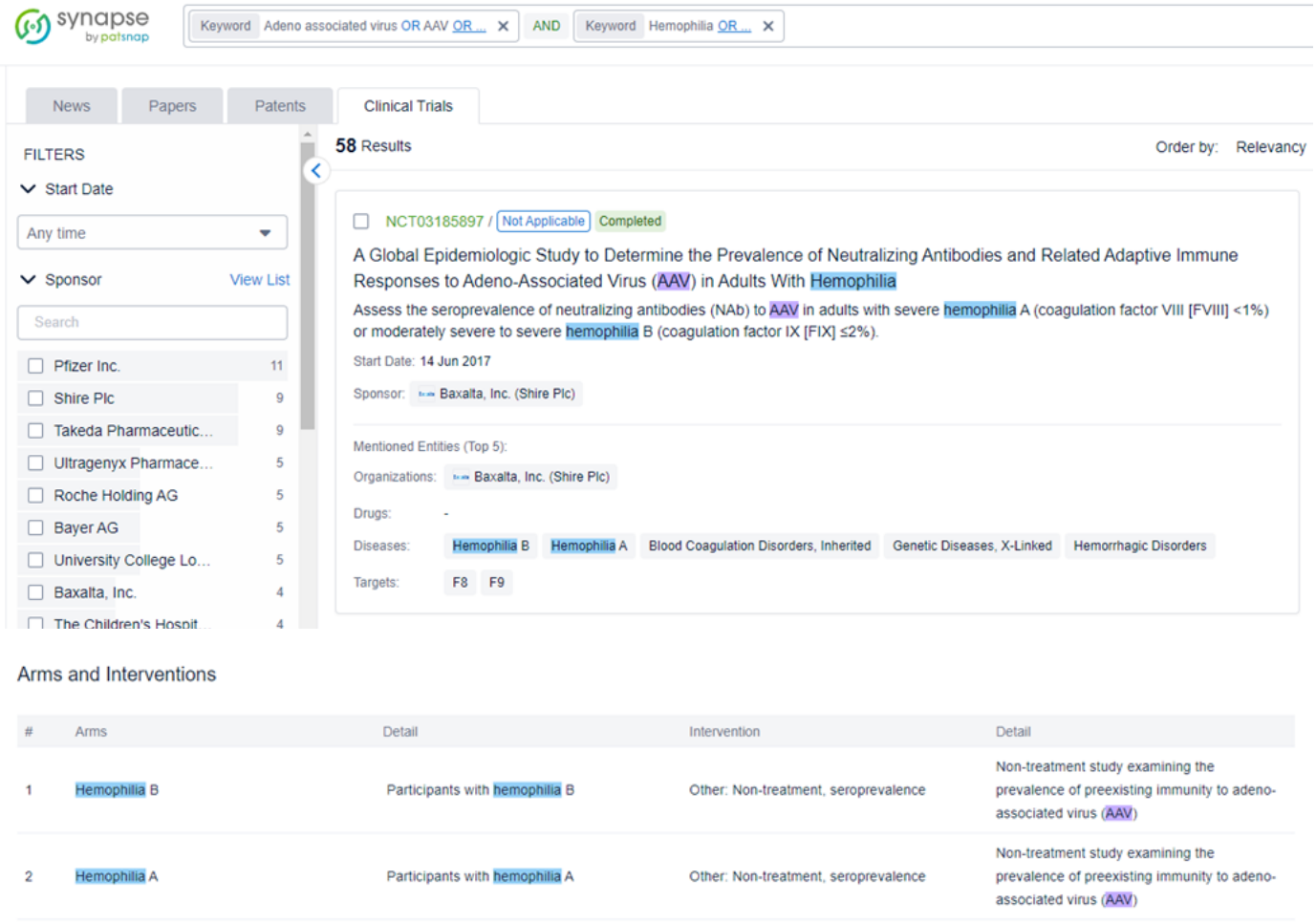
As shown above, the AAV technology space is booming with startup organizations looking to innovate and enter unique disease therapeutics. However, business challenges remain in commercializing and scaling AAV production. Firstly, the large scale manufacturing of the technology requires optimization as 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.

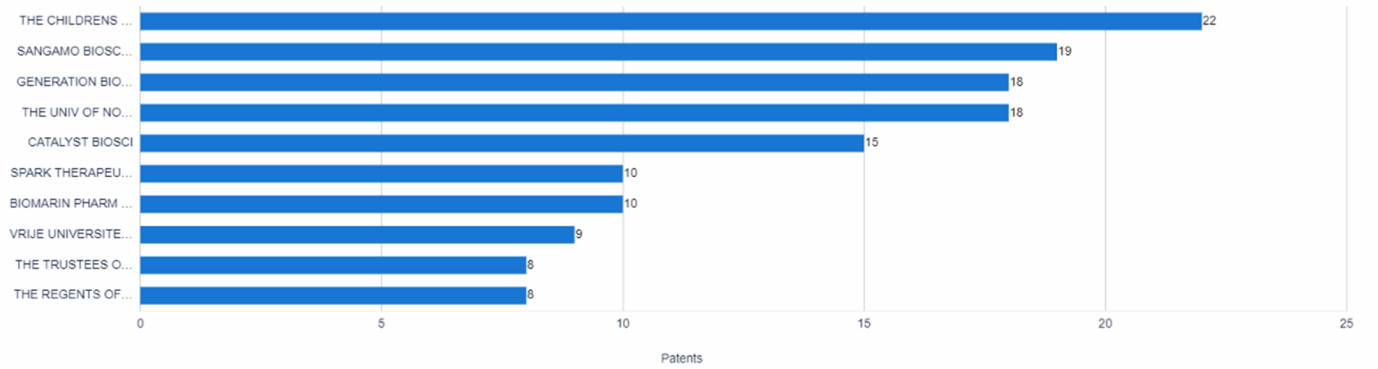
Hemophilia

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.



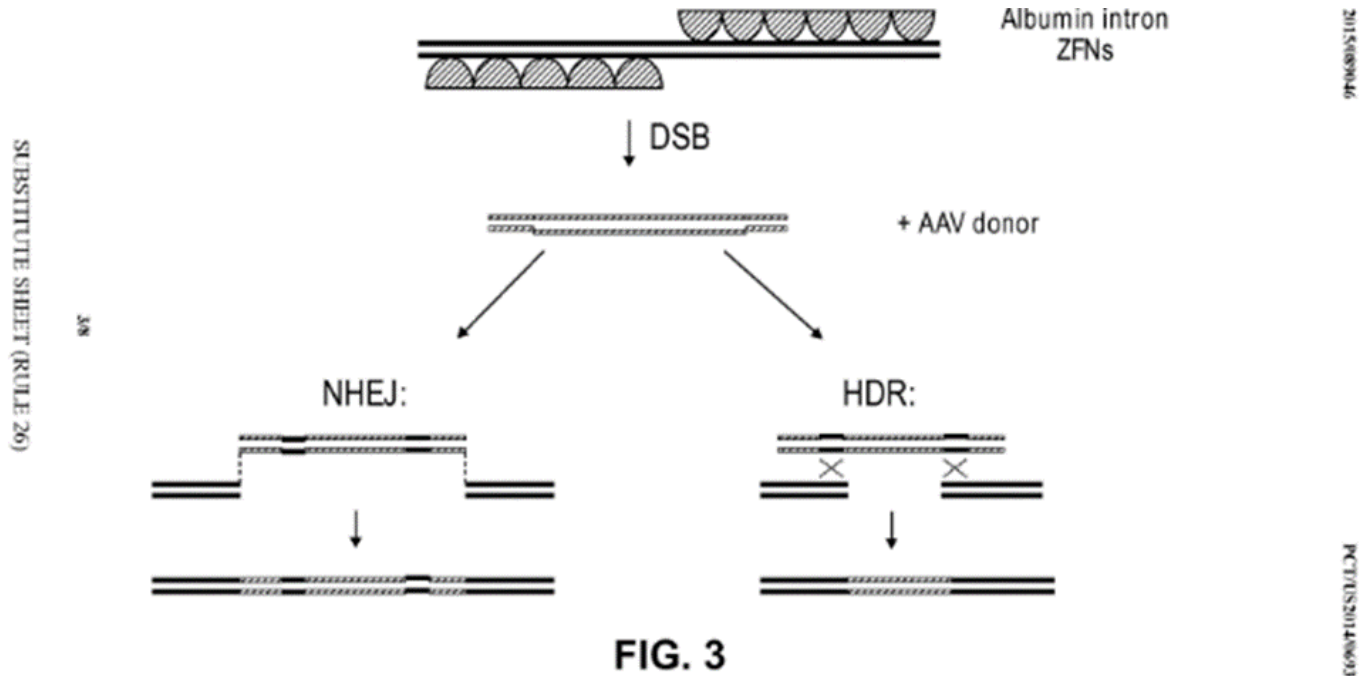
Disease Overview for Hemophilia for PatSnap Synapse

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

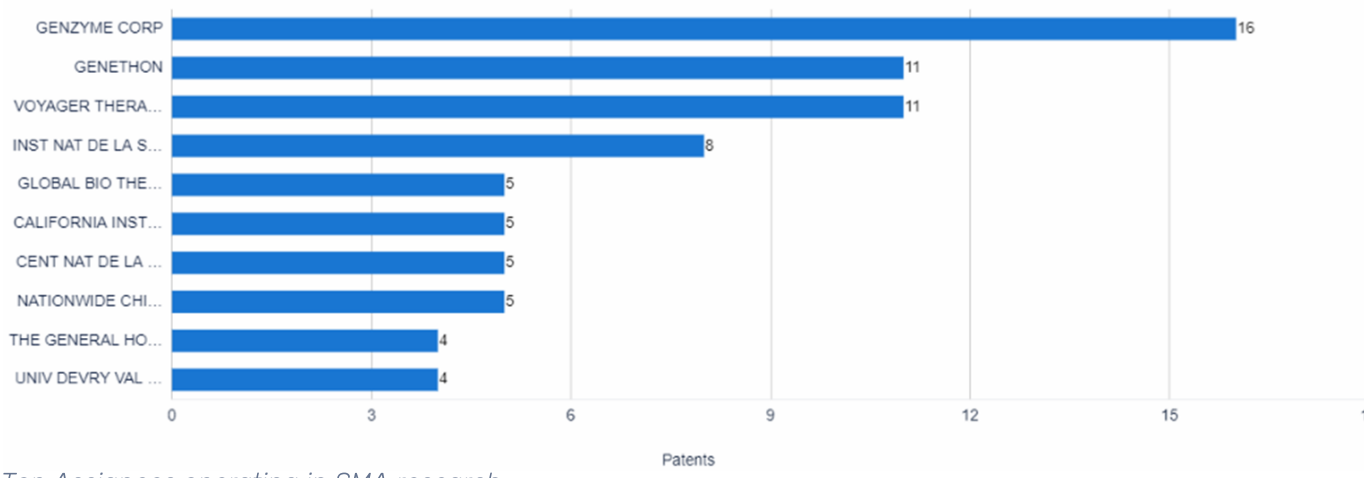
A key patent in this area of research is WO2015089046A1 Methods and compositions for treating hemophilia, held by Sangamo Biosciences, and published in June 2015. The claims of this patent describe the use of AAV2/6 as a vector comprised of zinc finger nucleases, and a specific DNA target sequence. Below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



Sample image from WO2015089046A1 describing Hemophilia technology

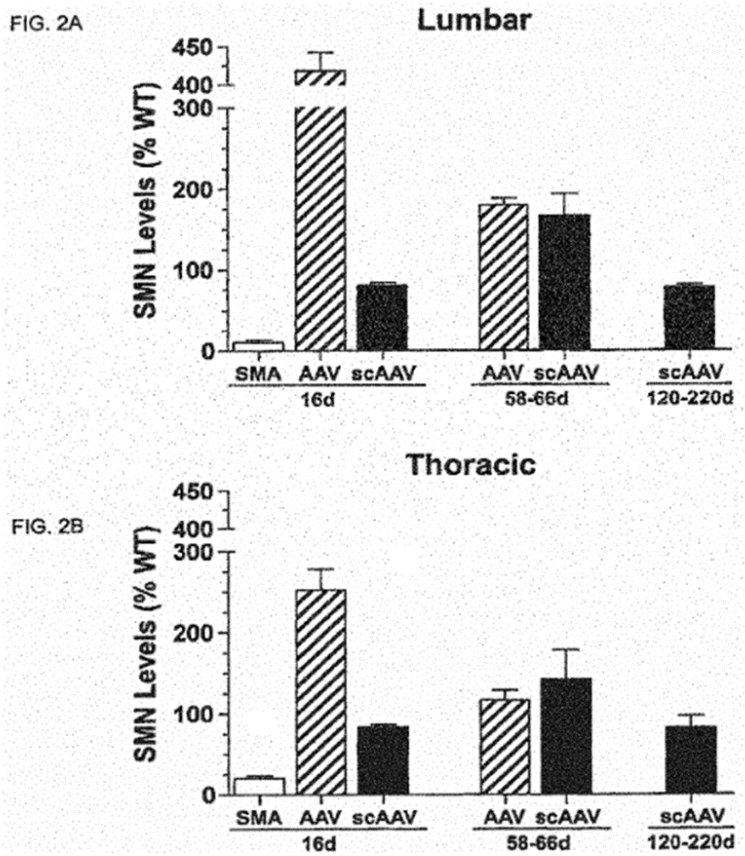
Spinal Muscular Atrophy

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.



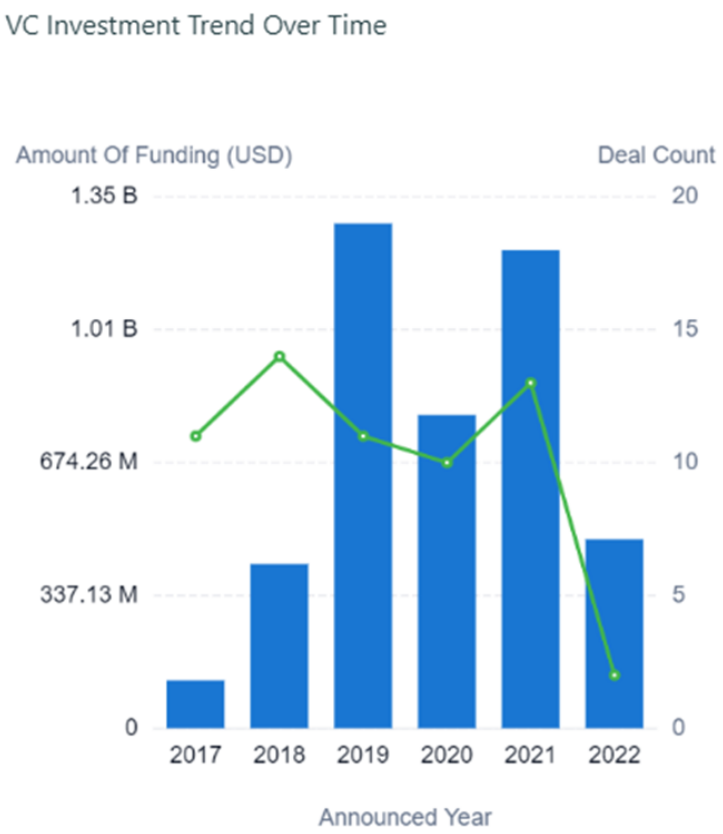
Top Assignees operating in SMA research

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

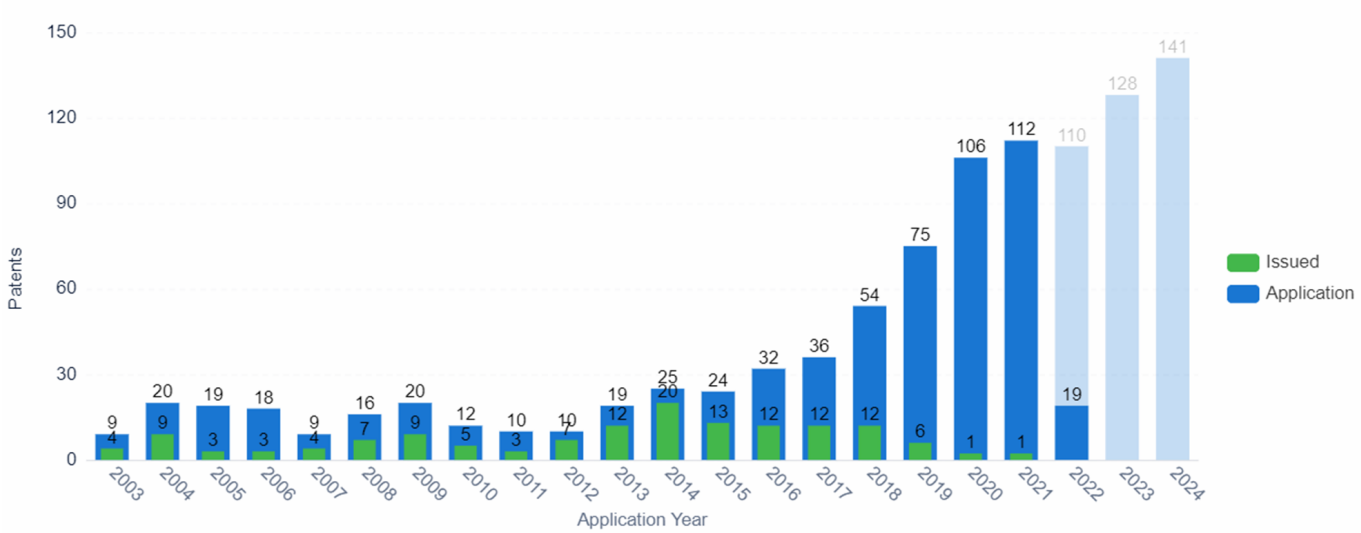
The PatSnap Discovery graph on the next page illustrates how VC investments in the SMA area are showing no signs of slowing. In 2021, there was $1.21 billion of funding poured into the SMA therapeutic area, which consisted of 13 deals. Specifically, ARCH Venture Partners, Obvious Management, and Lux 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

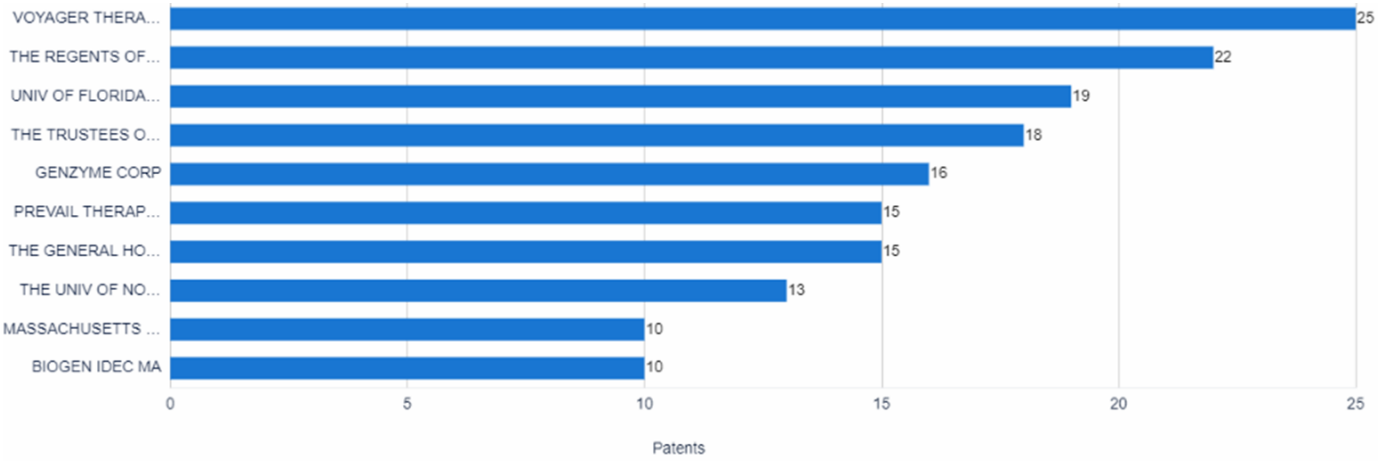
Parkinson's Disease

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.



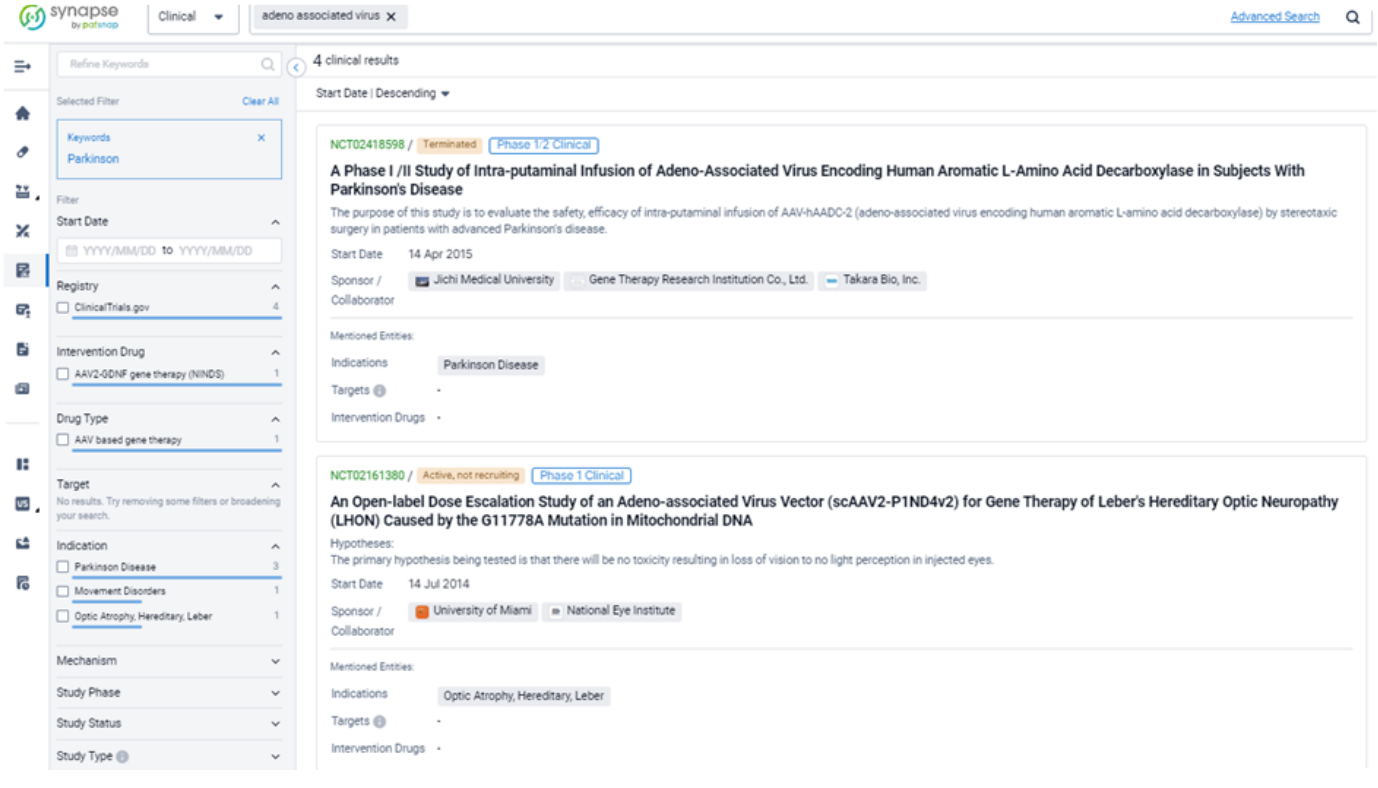
Application trend for Parkinson's Disease patents

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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