Neurological Cell and Gene Therapy Development: Industry Snapshots

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Our Mission

OUR MISSION

Accelerating world class science to deliver transformative regenerative medicine treatments in an equitable manner to a diverse California and world

Industry Landscape: Snapshots

This slide deck contains snapshots of the industry landscape of cell and gene therapy development for neurological disorders to help identify relevant trends.

- Partnering Status of CIRM-funded neuro CGT companies
- Cell Therapies for Parkinson's Disease
- Cell Therapies for Glioblastoma
- AAV Gene Therapies for genetic neurological disorders
- Industry Participation in Non-Profit Gene Therapy Development Efforts
- Industry investment in treatments for Alzheimer's Disease (not CGT)

Example: CIRM Portfolio Partnering (Active For-Profit Neuro Awards)

CIRM is currently funding a wide range of Neurology Biotechs from grant-stage to Publicly listed

Name	Type	CIRM-Funding	Modality	Lead Indication	Total Amount Raised	Last Raise Amount	Most Recent Partnering	Investors/ Partners
Brainstorm Therapeutics	Public	Pivotal	MSC	ALS	$151M	$29.1M	3Q21	Last Raise – Public Offering
Neurona Therapeutics	Private	Phase 1	Cell Therapy	Epilepsy	$135M	$41.5M	2Q21	UCB Ventures, The Column Group
AskBio	Acquired	Phase 1	AAV	PD			3Q20	Acquired by Bayer in 3Q20 for $4B
Ryne Bio	Private	CLIN1	Cell Therapy	PD			2022	Saisei Ventures
Mahzi Therapeutics	Private	TRAN	AAV	Pitt Hopkins	$47.3M	$47.3M	3Q21	Venrock, Ultragenyx, Arrowmark
Navega Therapeutics	Private	DISC	CRISPR	Chronic Pain				NIH and CIRM Grants
BrainXell Therapeutics	Private	DISC	Cell Therapy	SCI				Parent Research Products Company
Vertuis Bio	Private	DISC	AAV	Stargardt				Seed funding

PD – Parkinson's Disease; ALS – Amyotrophic Lateral Sclerosis; SCI - Spinal Cord Injury

Example: Partnering Activity in Cell Therapies for Parkinson's Disease

Academic and industry collaborations continue to advance clinical development of PSC-derived cell therapies for PD

PI/Company	Approach	Investors / Partners	Current Clinical Status	Partnering Notes
Dr. Lorenz Studer, MSK	hESC-derived DA progenitors	Bluerock Therapeutics, Bayer (2019)	Phase 1 trial enrollment completed	Bluerock operates independently
Dr. Malin Parmar, Lund University	hESC-derived DA progenitors	Novo Nordisk (2018)	Phase 1 trial initiated in Sweden, UK	Novo Nordisk funding clinical trial
Dr. Jun Takahashi, Kyoto University	iPSC-derived DA neurons		Phase 1 trial enrollment completed	
Aspen Neuroscience	Autologous iPSC-derived DA neurons	Orbimed, Arch Venture, Frazier Healthcare, GV	IND-enabling	2Q22: $147.5M Series B 4Q22: $40M debt deal
Ryne Bio	iPSC-derived DA progenitors	Fujifilm CDI, Saisei Ventures	IND-enabling	

Example: Cell Therapy for Glioblastoma

Cell-Based Therapies (CAR-T, NK, NSC) are being advanced at NIH and academic institutions

- CIRM is currently funding 7 cell therapy TRAN & CLIN projects at City of Hope, Stanford and UCSF
- CIRM-funded City of Hope CAR-T candidate was licensed to Mustang Bio. Mustang Bio planning to advance combination of COH CAR-T and UAB oncolytic virus

CIRM is participating in early discussions with leading investors and funders to evaluate business models for advancing a portfolio of cell-based therapies for glioblastoma

Example: AAV Gene Therapies for Genetic Neurological Disorders

Zolgensma 2022 Update: Approved in 47 countries; 2 patient deaths from acute liver failure; $1.37B FY22 revenue

Recent Approvals:

- EMA Authorization: PTC Therapeutics' Upstaza AAV gene therapy for aromatic l-amino acid decarboxylase deficiency.

In recent years, several companies launched, raised significant venture financing and public market financing to advance AAV gene therapies for monogenic neurological disorders (i.e. neurometabolic, neurodegenerative).

- In the last year, several late-stage clinical programs have encountered difficulties

Biopharma and investors are partnering with biotechs developing AAV engineering platforms to overcome safety and efficacy limitations for CNS gene delivery.

Example: Clinical AAV Gene Therapies for Genetic Neurological Disorders

Company	Company Type	Lead Clinical Candidates	Clinical Status	Company Status
Lysogene	Public	Phase 2/3 MPS IIIA Phase 1/2 GM1	Endpoints not met.	Insolvency Proceedings. Sarepta ended partnership
SIO Gene Therapies	Public	GM1, GM2, PD	Positive interim safety/efficacy data (Nov 21)	2023 – Company dissolving. 1H22 - Cancelled PD, GM1 and GM2 programs and returned assets to Oxford & UMass.
Taysha Gene Therapies	Public	GAN, Rett	GAN – Type B with FDA on pivotal trial design	4Q22 – Astellas $50M deal to advance GAN, Rett Programs. Leadership changes.
Prevail Therapeutics	Acquired	Clinical: GBA1-PD, Gaucher, FTD-GRN	All 4 trials active	4Q20 – Lilly acquired Prevail for $1B.
Passage Bio	Public	Clinical: GM1, FTD	Positive GM1 interim data	4Q22 – Reduced workforce and cut pipeline to extend runway.
UniQure	Public	HD, ALS	HD: Higher dose cohort restarted in 4Q22	2022 – Hemgenix BLA. 2023 – Clinical ALS candidate acquired from Apic Bio.

MPS IIIA – Mucopolysaccharidosis IIIA; GM1/GM2 – GM1/GM2 gangliosidosis; PD – Parkinson's Disease; GAN – Giant Axonal Neuropathy; FTD – Frontotemporal Dementia; HD – Huntington's Disease; ALS – Amyotrophic Lateral Sclerosis

Example: Investors and Biopharma Partnerships Driving AAV Engineering Platform Biotechs

The wave of company launches and biopharma partnerships accelerated in 2020-2021 and continued into 2023

Company	AAV Engineering Platform	Investments / Partnerships
Shape Therapeutics	AI-driven capsid engineering and RNA-editing	2019 – 2021: $147.5M in investments 2021: Roche (up to $3B) – AD, PD, rare diseases
Dyno Therapeutics	AI-driven capsid engineering	2020: Roche (up to $1.8B) – CNS 2021: $100M Series A
Affinia Therapeutics	Capsid & Promoter Engineering	2020 - 2021: $170M in investments
Apertura Gene Therapy	Capsid & Regulatory Element Engineering	2022: $67M Series A
Capsida	Engineering of BBB penetrating capsids for IV delivery	2021: $50M Series A, $90M Abbvie Partnership, CRISPR Tx Collaboration 2023: Prevail Partnership up to $740M

AI – Artificial Intelligence; BBB – Blood Brain Barrier; IV – Intravenous; AD – Alzheimer's Disease; PD – Parkinson's Disease

Industry Participation in Non-Profit Gene Therapy Companies

Global non-profit/patient-driven approaches are advancing gene therapies to the clinic for rare neurological disorders. Examples include:

- Accelerating Medicinces Partnership Bespoke Gene Therapy Consortium (AMP BGTC)
- CureSPG50/Elpida
- Columbus Children's Foundation (CCF)
- Odylia
- Cure Rare Disease
- Mila's Miracle Foundation

Industry service providers such as CROs and CDMOs are supporting the non-profit organizations with in-kind services, discounted services or access to specialized experts and resources. Examples include:

- Charles River Labs (models, testing, IND) – Elpida, Mila's Miracle Foundation, Cure Rare Disease
- Viralgen (CDMO) – CureSPG50/Elpida, CCF
- Andelyn (CDMO) – AMP BGTC, Cure Rare Disease, Odylia

Example: Alzheimer's Disease R&D Investments

Estimated 235 agents entered into clinical development between 1995-2021*

- 6 commercialized: tacrine, donepezil, rivastigmine, galantamine, memantine, aducanumab
- 117 had negative outcomes
- Estimated Failure Rate: 95%

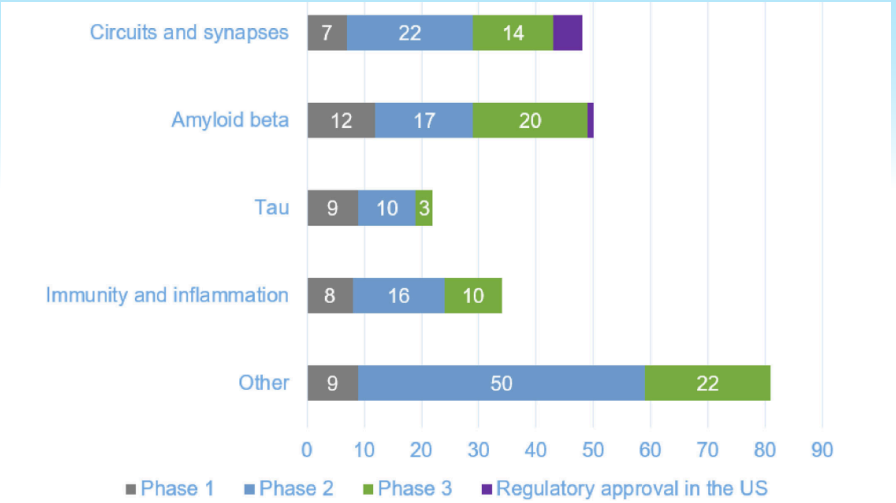

FIGURE 3 Agents in clinical development by key disease targets. The chart summarizes the highest development phase for each agent (n) in clinical development for Alzheimer's disease, categorized by the key disease targets as defined by the Common Alzheimer's Disease and Related Dementias Ontology[16]

$42.5B in industry funding of clinical AD R&D between 1995-2021*

- Phase 2, 3 trials: $33.7B
- Phase 1- phase 3 cost: $462M
- Pre-clinical to FDA Approval#: $5.7B, 13 years

Rate of growth in R&D spending slowed in recent years

Lecanemab received accelerated approval in 2022

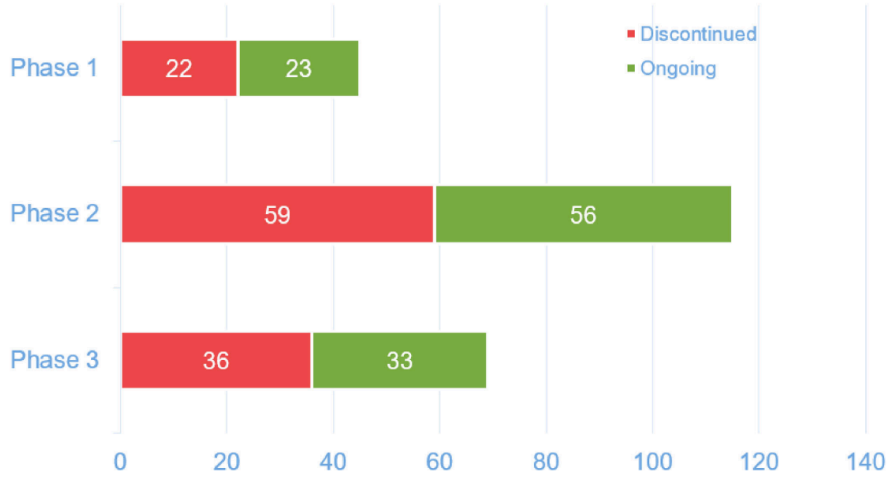

FIGURE 4 Highest clinical trial phase reached for agents in clinical development for Alzheimer's disease (AD). The chart summarizes agents (n) in clinical development for AD from 1995 to 2021, categorized by the highest clinical trial phase reached for discontinued (red) and ongoing (green) agents

*Cummings, et al. Alzheimer's & Dementia 2021. #Scott, et al. Ann NY Acad Sci 2014

Summary

- Current CIRM-funded neurology biotech span all stages of development and financing.
- Industry and academic collaborations are driving PSC-based cell therapies through clinical development for Parkinson's disease.
- Preclinical and clinical development of cell-based therapies for glioblastoma are largely being driven by academic institutions. CIRM is currently funding 8 such programs.
- While some late stage AAV gene therapy companies have faced recent financial difficulties the industry continues to support new biotechs developing AAV engineering platforms to improve CNS gene delivery.
- Non-profit models are progressing AAV gene therapies for rare neurological diseases to clinical trials in partnership with industry CROs and CDMOs.
- Over 25 years of investing in clinical development of Alzheimer's Disease treatments resulted in only 7 FDA-approved treatments.