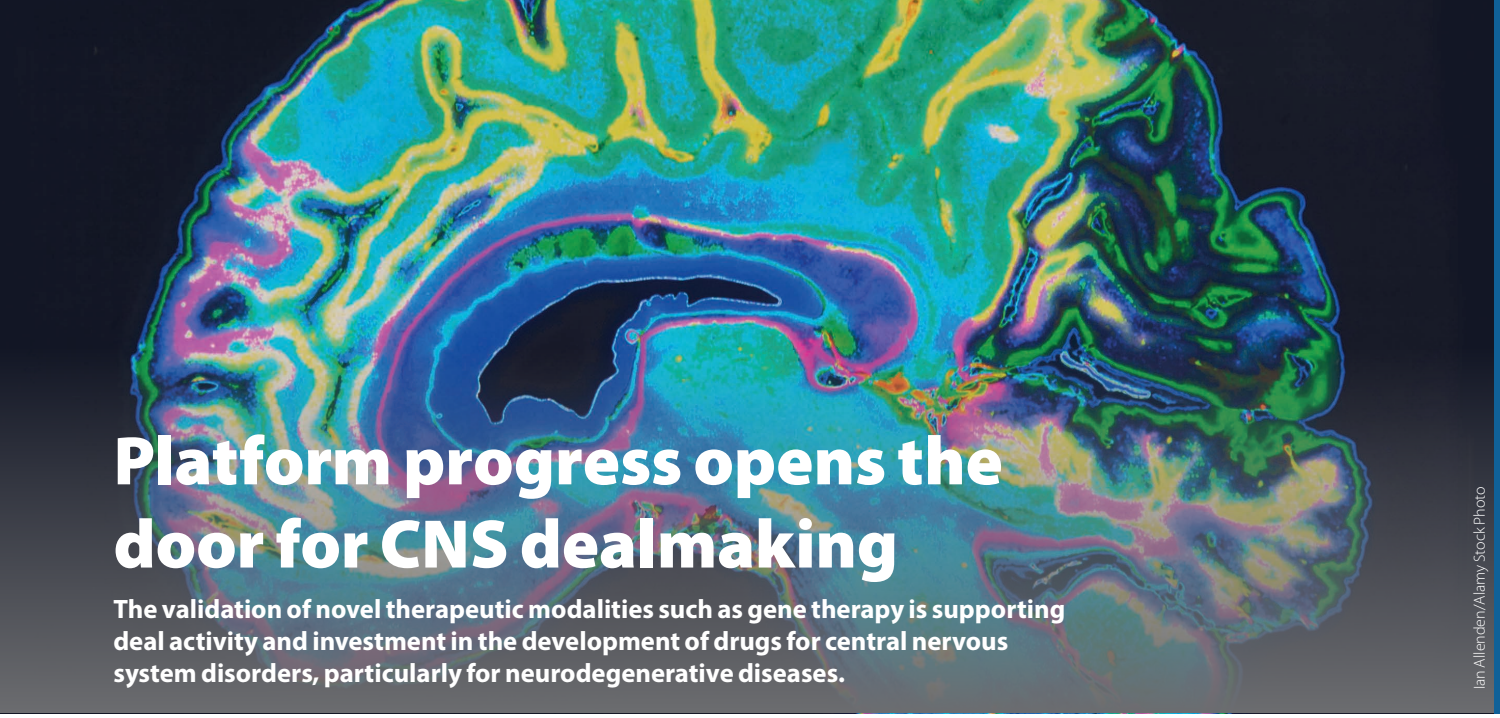

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Platform progress opens the door for CNS dealmaking

The validation of novel therapeutic modalities such as gene therapy is supporting deal activity and investment in the development of drugs for central nervous system disorders, particularly for neurodegenerative diseases.

Cormac Sheridan

While the unmet need for new therapies for many central nervous system (CNS) disorders is huge, the complexity of the brain, combined with our limited understanding of the ways in which brain functions can go awry, make developing drugs for such disorders exceptionally challenging. Indeed, for some disorders such as Alzheimer's disease, vast amounts of money have been invested in the late-stage clinical development of potential drugs over the past decade, with nothing but failure to report so far.

Nevertheless, companies and investors have persisted, encouraged not only by potentially large markets for successful therapies, but also by the emergence of novel therapeutic modalities that can help harness new biological and clinical insights, such as RNA interference (RNAi) and gene therapy based on adeno-associated virus (AAV) vectors. These approaches are fuelling licensing deals and investments, particularly for neurodegenerative diseases, such as Parkinson's disease and spinal muscular atrophy **(Tables 1,2)**.

For example, Regeneron Pharmaceuticals recently established a multicandidate alliance with RNAi pioneer Alnylam Pharmaceuticals, involving an initial outlay of $800 million in cash by Regeneron plus up to $200 million in near-term milestones **(Table 1)**. Although the collaboration is not solely focused on CNS conditions, they are a core component of the ten-year pact. The alliance marries a novel therapeutic modality—Alnylam's maturing RNAi platform—with Regeneron's target discovery capabilities, which are underpinned by its longstanding experience in mouse genetics and more recent deep dive into human population genetics.

Jefferies analyst Maury Raycroft heralded the deal as a win-win. "We believe the combo could offer an interesting blend of technologies and know-how," he wrote in a research note. A key enabler was Regeneron's demonstration last year of the successful delivery of ligand-conjugated small interfering RNA molecules to the CNS of rats by injection into the cerebrospinal fluid.

Breaking through with regenerative medicine

Delivering a therapeutic agent into the brain is typically a necessary, but often challenging, step in any CNS-focused therapeutic development program. Regenerative medicine approaches—based on gene therapy, cell therapy and small molecules—are now providing developers with routes into some CNS diseases. For example, the maturation of CNS-targeted gene therapy vectors, which can be administered by intravenous or intrathecal injection, has been an important technological enabler for a spate of deals.

AveXis is a key exemplar. The highly promising clinical data (*N. Engl. J. Med.* **377**, 1713–1722; 2017) it generated with Zolgensma (onasemnogene abeparvovec; AVXS-101), an intravenously delivered AAV9-based gene therapy for spinal muscular atrophy (SMA), prompted an $8.7 billion buyout from Novartis last year. The therapy has since been submitted to the US Food and Drug Administration (FDA) for regulatory approval, with a decision expected soon after the time of writing. If approved, the treatment will be the first gene therapy approved for a CNS disorder.

Other firms are following in its wake, including Voyager Therapeutics, which has also focused on using AAV vectors for neurodegenerative disorders. In January, the company signed a deal potentially worth $1.8 billion with Neurocrine Biosciences for four of Voyager's gene therapy programs, including VY-AADC, a phase 2 candidate for Parkinson's disease **(Table 1)**. Less than a month later, Voyager teamed up on another Parkinson's disease deal—this time with AbbVie. The deal, which could be worth more than $1.5 billion, will see the companies collaborate on the development of AAV capsids encoding antibodies that target pathological species of α-synuclein in Parkinson's disease.

The promise of gene therapy is also leading to the establishment of new companies in the space, including Passage Bio, a startup cofounded by gene therapy pioneer James Wilson, of the University of Pennsylvania. Following a $116 million series A financing round in February, the company is taking forward five next-generation AAV-based therapies for rare monogenic CNS disorders. Its lead programs include GM1 gangliosidosis, a rare lysosomal storage disorder caused by a lack of β-galactosidase, and a genetically inherited form of frontotemporal dementia, caused by loss-of-function mutations in the gene encoding progranulin, a growth factor that supports neuronal survival and suppresses neural inflammation.

"I think gene therapy has proven itself as a modality that allows you access to the CNS in new and impactful ways," said Tom Woiwode, a managing director at Versant, one of the series A investors in Passage Bio. Rare genetic diseases are in vogue both because they can generally be replicated in preclinical animal models and because objective endpoints can be readily defined for clinical trials.

"Beyond that, it's more complicated," said Versant managing director Jerel Davis. There has, he said, been some success in genetically defining small groups of patients in certain complex CNS indications, such as Parkinson's disease and amyotrophic lateral sclerosis (ALS), and these insights are now being tested in drug development programs.

For example, Denali Therapeutics has won industry and investor backing for its CNS drug development strategy, which is based on the biomarker-guided clinical development of drugs that address novel, genetically validated targets and can cross the blood–brain barrier. Its lead programs include a small-molecule inhibitor of leucine-rich repeat kinase 2, in development for Parkinson's disease—the target is the most common genetic risk factor for the condition—and an inhibitor of

Table 1 | Selected licensing and development deals for CNS disorders

Date	Developer	Partner	Assets	Indications	Terms
April 2019	Alnylam Pharmaceuticals	Regeneron Pharmaceuticals	RNAi drugs directed at up to 30 targets	CNS, ophthalmology and liver disorders	$400 million upfront, $400 million in equity investment and $200 million in milestones
March 2019	Oncodesign	Servier	LRRK2 inhibitors	Parkinson's disease	$3.4 million upfront and $360 million in milestones
February 2019	Voyager Therapeutics	AbbVie	Vectorized antibodies targeting α-synuclein	Parkinson's disease and other synucleinopathies	$65 million upfront, $245 million in preclinical and phase 1 option payments, $728 million in development and regulatory milestones per product and $500 million in commercial milestones
February 2019	SK Biopharmaceuticals	Arvelle Therapeutics	European rights to cenobamate	Epilepsy	$100 million upfront and $430 million in milestones
February 2019	Optinose	Inexia	Nose-to-brain delivery technology for positive modulators of orexin 1 and orexin 2	Narcolepsy	Undisclosed upfront payment and $45 million in development and commercial milestones per product
January 2019	Voyager Therapeutics	Neurocrine Biosciences	Gene therapy	Parkinson's disease, Friedreich's ataxia and two other neurological conditions	$115 million upfront, $50 million in equity investment and $1.7 billion in milestones
January 2019	Skyhawk Therapeutics	Biogen	Small-molecule RNA splice modifiers	Multiple sclerosis, spinal muscular atrophy and other neurological diseases	$74 million upfront and undisclosed milestones
January 2019	C4 Therapeutics	Biogen	Drugs employing a targeted protein degradation mechanism	Alzheimer's disease, Parkinson's disease and other neurological diseases	$415 million upfront plus milestones
January 2019	Click Therapeutics	Otsuka America	CT-152, a prescription digital app	Depression	$10 million upfront plus regulatory milestones, ~$20 million in development funding and $272 million in commercial milestones
December 2018	AC Immune	Eli Lilly	Small-molecule tau aggregation inhibitors	Alzheimer's disease and other tauopathies	$80 million upfront, $50 million in a loan-to-equity conversion instrument and $1.7 billion in milestones
December 2018	Icagen	Roche	Small-molecule ion channel modulators	Undisclosed neurological diseases	Undisclosed upfront and research payments and $274 million in milestones
November 2018	Regenxbio	Abeona Therapeutics	NAV AAV9 vector	Sanfillipo syndrome type A, Sanfillipo syndrome type B, infantile Batten disease and juvenile Batten disease	$40 million in upfront and guaranteed payments and $140 million in milestones
November 2018	Denali Therapeutics	Sanofi	RIPK1 inhibitors	Alzheimer's disease, amyotrophic lateral sclerosis and multiple sclerosis (plus systemic inflammatory indications)	$125 million upfront and >$1 billion in milestones
June 2018	Ionis Pharmaceuticals	Biogen	Antisense drugs	Broad range of neurological disorders	$375 million upfront and $625 million in equity investment

AAV9, adeno-associated virus 9; CNS, central nervous system; LRRK2, leucine-rich repeat kinase 2; RIPK1, receptor-interacting serine/threonine protein kinase 1; RNAi, RNA interference. Sources: company websites.

receptor-interacting serine/threonine protein kinase 1, a master regulator of inflammation and necrosis (a form of programmed cell death), in development for Alzheimer's disease, ALS and multiple sclerosis.

Alzheimer's disease targets shoot blank

But genetic insights into disease biology are no guarantee of clinical success. Despite extensive genetic evidence linking Alzheimer's disease to amyloid-β (Aβ) accumulation, numerous attempts to target the process with either Aβ-directed antibodies or small-molecule inhibitors of β-site amyloid precursor protein cleaving enzyme have floundered. This year looks like a turning point in the evolution of drug development in Alzheimer's disease, as two more antibodies targeting the Aβ cascade failed phase 3 trials.

Roche's decision to discontinue development of crenezumab, which it licensed from AC Immune, was swiftly followed by Biogen's termination of aducanumab, which it had licensed from Neurimmune and was developing in partnership with Eisai. "Obviously it was a big shock for us," said AC Immune CEO Andrea Pfeifer. The company had raised enough cash to fund the rest of its pipeline, which includes antibodies, small molecules and cancer vaccines directed against tau, another key player in Alzheimer's pathology. But its staff had high expectations for crenezumab. "The company was prepared for the event. Psychologically, emotionally, we were not," she said.

The setback raises anew the same question that has always dogged Alzheimer's disease drug development—who to treat and when? "We are selecting patients based on MMSE [mini-mental state examination] scores," Pfeifer said. "Is that good enough to select a patient population that is quite heterogeneous?" Future trials will require more rigorous selection criteria—but further research is needed to refine what they might be. "I think we should work together in certain areas, such as biomarkers, to move the field forward," said Pfeifer. There is, she said, a "generational responsibility" to continue investment in Alzheimer's disease research.

For Angus Grant, CEO of the Dementia Discovery Fund (DDF), a mission-oriented venture capital firm backing new approaches to treating all forms of dementia, "the current failures are a call to arms." Launched in 2015, the DDF completed its fundraising in June 2018, with a final close of £250 million ($350 million). Its backers include the

Table 2 | Selected CNS investment deals

Date	Company	Focus	Transaction	Amount
April 2019	Probiodrug	Alzheimer's disease	Capital increase	€8.2 million ($9.2 million)
February 2019	MeiraGTx Holdings	Gene therapy for Parkinson's disease and amytrophic lateral sclerosis (and non-CNS conditions)	Private share placement	$80 million
February 2019	Axial Biotherapeutics	Therapies targeting the gut–brain axis for neurodegenerative and neuropsychiatric disease	Series B venture capital round	$25 million
February 2019	Arvelle Therapeutics	Epilepsy	Series A	$180 million
February 2019	Passage Bio	Gene therapy for rare monogenic CNS diseases	Series A	$115.5 million
February 2019	Neurogene	Gene therapy for aspartylglucosaminuria, other lysosomal storage disorders and Charcot–Marie tooth disease	Series A	$68.5 million
February 2019	Alector	Immunoneurology drugs for Alzheimer's disease and frontotemporal dementia	IPO	$176 million
December 2018	Diamedica Therapeutics	Stroke	IPO	$16.4 million
November 2018	Alzecure	Alzheimer's disease	IPO	$22 million
November 2018	Rheostat Therapies	Small-molecule modulators of autophagy and mitophagy in neurodegenerative, cognitive and rare diseases	Series A	$23 million
October 2018	Orchard Therapeutics	Gene therapy for neurometabolic disorders (as well as primary immunodeficiencies and hemoglobinopathies)	IPO	$200 million
October 2018	Cerevel Therapeutics	Parkinson's disease, Alzheimer's disease, epilepsy, schizophrenia and addiction	Joint venture between Pfizer and Bain Capital	$350 million
October 2018	Audentes Therapeutics	Gene therapy for rare neuromuscular diseases	Follow-on offering	$150.8 million
July 2018	AC Immune	Alzheimer's disease	Follow-on offering	$117.5 million
July 2018	Alector	See above	Series E	$133 million
June 2018	MeiraGTx Holdings	See above	IPO	$75 million

CNS, central nervous system; IPO, initial public offering. Sources: Nasdaq.com and company websites.

UK Department of Health, Alzheimer's Research UK, the Bill & Melinda Gates Foundation, the American Association of Retired Persons and a biopharma industry consortium. DDF has quickly built a large portfolio of biotech firms and is also backing earlier-stage research projects that need additional validation before they can form the basis of commercial drug development programs.

The key to making progress, it holds, is a better understanding of which patients should—and should not—be included in a trial. "If that is not addressed I think you lose a lot of signal to noise," said DDF chief strategy officer Barbara Tate. "We absolutely believe it is part of the solution." One of the fund's earliest investments, Alector, exemplifies this approach, employing genetic screening and proprietary biomarkers in its inflammation-focused Alzheimer's disease programs.

Alector raised $176 million in its initial public offering in February this year **(Table 2)**, and is now in early clinical development with AL002, an antibody that activates triggering receptor expressed on myeloid cells 2 (TREM2), a signaling protein required for microglial activity. Loss-of-function mutations in the *TREM2* gene are associated with an increased risk of Alzheimer's. Also in the clinic is AL003, an antibody-based inhibitor of sialic acid-binding Ig-like lectin 3 (SIGLEC-3), a receptor with an inhibitory effect on microglial function. Carriers of genetic variants with reduced SIGLEC-3 function have lower risk of late-onset Alzheimer's disease.

These programs are early stage, but their initial readouts, like those of Denali, will be closely scrutinized, given what is at stake. And Grant declares himself to be "inherently optimistic," pointing to the progress in recent decades that has transformed cancer care from a "carpet-bomb" treatment to a precision approach based on identifying and drugging the key pathways that influence an individual patient's tumor.

Pyschiatric disorders still underserved

While investment continues to pour into neurodegenerative disorders, there were no hot startups closing $100 million series A rounds to change the way we treat neuropsychiatric disorders, such as depression or schizophrenia. A 2018 study from BIO analysts David Thomas and Chad Wessel noted that just 29 of the 218 FDA approvals for depression since 1959 involved novel substances (*The State of Innovation in Highly Prevalent Chronic Diseases. Volume I: Depression Therapeutics*. (BIO, 2017))—the vast majority comprised either generics or new formulations of existing products. Scientific uncertainties, including a lack of reliable animal models, combined with challenging regulatory requirements, and a difficult commercial environment, all constitute barriers to innovation.

Nevertheless, the outlook is not completely gloomy. After decades without an FDA approval of an antidepressant with a novel mechanism of action, two received the green light in just one month. In March, the FDA approved Johnson and Johnson's Spravato (esketamine)—an enantiomer of the analgesic and 'party drug' ketamine—for patients with treatment-resistant depression. And shortly after, the agency approved Zulresso (brexanolone), the first drug specifically developed for postnatal depression, which was pioneered by Sage Therapeutics. The company has several other compounds at earlier stages of development for depressive disorders.

"Sage really does stand out," said Woiwode. "They're tough indications, and they've done well there." But the landscape remains wide open for further innovation in CNS disease.

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