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Neuroscience: Advances in research and opportunities ahead

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2024 has proved to be a poignant year of developments in neuroscience. This guide showcases the potential within drug discovery.

In January 2024, Biogen discontinued its Alzheimer's treatment Aduhelm (aducanumab-avwa) for intravenous use and terminated the ENVISION clinical study in an effort to reprioritise its resources in Alzheimer's. This includes Leqembi (lecanemab-irmb), which in July 2023 become the first-ever disease modifying therapy for Alzheimer's to receive traditional FDA approval. The Alzheimer's Association said it was "extremely optimistic about the future of Alzheimer's treatments; a new era that started with the FDA accelerated approval of Aduhelm in 2021".

In March, the FDA revealed plans to convene a meeting of the Peripheral and Central Nervous System Drugs Advisory Committee to discuss the Phase III TRAILBLAZER-ALZ 2 trial, evaluating the efficacy and safety of Eli Lilly's donanemab in early symptomatic Alzheimer's. According to Anne White, Executive VP of Eli Lilly and Company, and President of Lilly Neuroscience, the review process was unexpected but they're confident in donanemab's potential for early symptomatic Alzheimer's.

Exciting clinical developments include positive top-line results for Newron Pharmaceuticals' study in schizophrenia, as well as the discovery by a team at the University of Queensland of a molecular doorway that could help deliver drugs to the brain to treat neurological disorders. Axoltis Pharma and Alto Neuroscience both progressed into Phase II for ALS and major depressive disorder respectively. Not to mention, the repurposing of weight-loss drug Ozempic, which has generated excitement with its potential treatment of addiction and dementia.

Previous decades have been challenging, but disease-modifying drugs such as lecanemab and donanemab have changed this trajectory. The Alzheimer's Society says this could be the "beginning of the end" of Alzheimer's as these milestones mark the first steps in our journey to develop new treatments to slow down and stop the diseases that cause dementia.

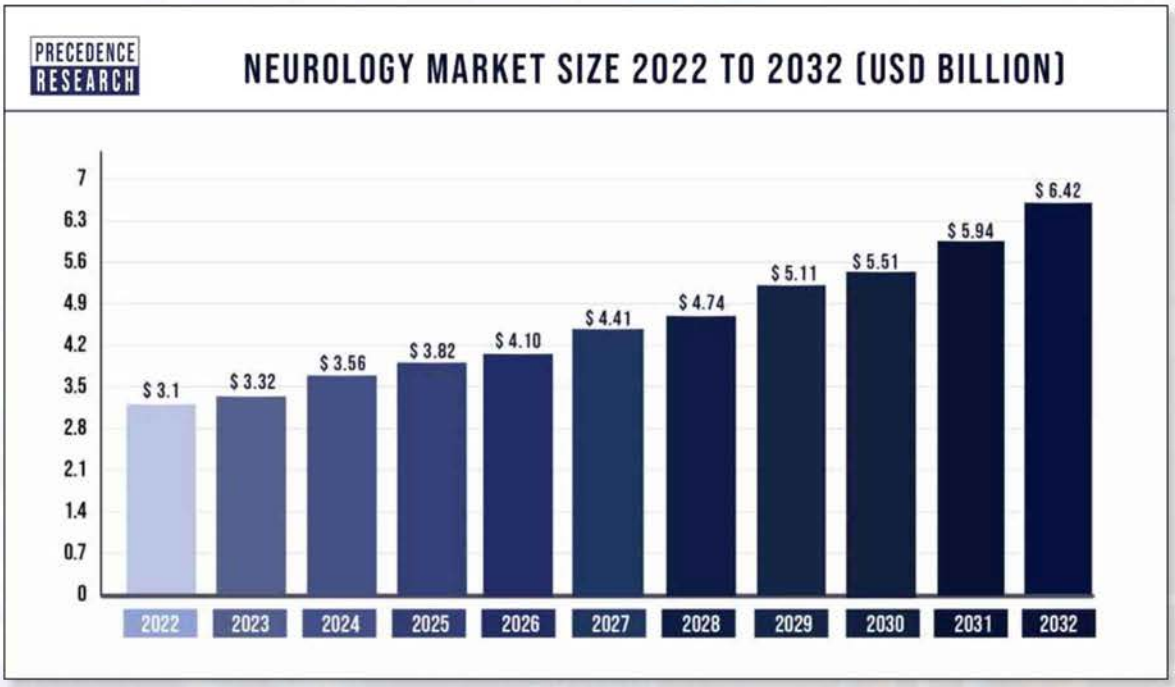
Contents

Neuroscience: A global market overview

An overview of the global market for neuroscience, including the prevalence, value, future outlook and approved drugs as well as those in development.

What is the prevalence?

According to Precedence Research, the global neurology market size was estimated at $3.32 billion in 2023 and is projected to hit around $6.42 billion by 2032, registering a CAGR of 7.60% during the forecast period from 2023 to 2032. This is likely attributable to the increasing prevalence of neurological diseases, including Alzheimer's, brain cancer, epilepsy and traumatic brain injuries.



Source: www.precedenceresearch.com

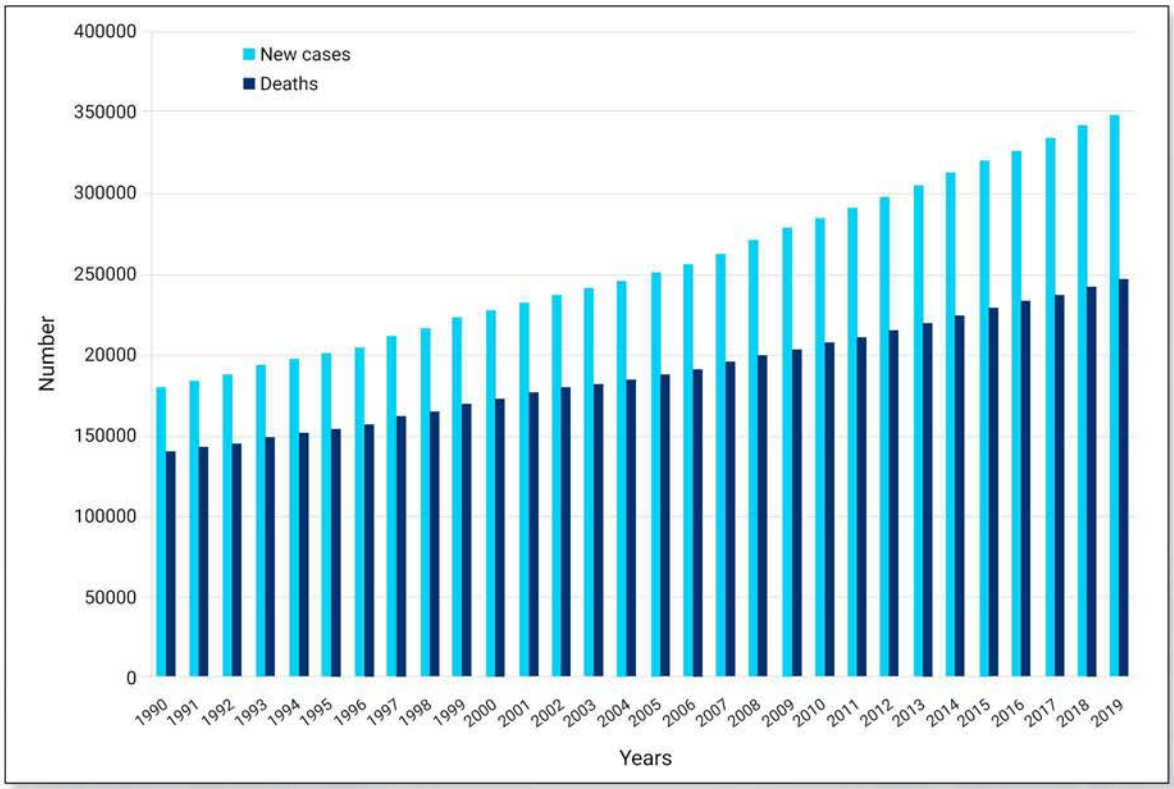
In a paper titled Epidemiology of Alzheimer's Disease, published in Cold Spring Harbor Perspectives in Medicine, the global prevalence of dementia is approximately 24 million, and is predicted to double every 20 years until at least 2040. In the US, an estimated 5.5 million people are affected by Alzheimer's disease, and the prevalence worldwide is believed to be as high as 24 million.

According to The Lancet, Parkinson's is second only to Alzheimer's disease in the list of most common neurodegenerative disorders and, with increasing life expectancies and fewer competing causes of death, its prevalence is expected to increase to 12–17 million people by 2040. Moreover, in an abstract published by the International Parkinson and Movement Disorder Society for the MDS Virtual Congress 2020, researchers estimated the number of individuals living with Parkinson's Disease globally, concluding an estimated 9.4 million lived with Parkinson's disease in 2020.

As for brain cancer, the following open access graph published by Elsevier shows new cases and deaths of brain cancer in the world, 1999–2019.

Drug development and approval

In order to identify what is needed in this industry, it is important to see what has already been achieved, and where this can be expanded. According to Alzheimer's UK, there are 141 drugs being tested in clinical trials for the treatment of Alzheimer's disease - 78% of which are designed to try and slow down how quickly the disease progresses.



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Currently, no medications can cure dementia. However, there are treatments that address the underlying biology such as disease progression and symptom treatment. The table below, created with information from the Alzheimer's Association, indicates FDA-approved treatments for Alzheimer's.

In terms of what to expect from 2024, the Alzheimer's Society says: "We will be investing a record amount into dementia research across many exciting initiatives like our yearly grant round and the blood biomarker challenge. We also expect decisions from the drug regulators later this year on whether new drugs lecanemab and donanemab that can slow down early Alzheimer's will be approved in the UK."

Drug	Category	Treatment
Aducanumab (Aduhelm)	Disease progression	Demonstrates that removing beta-amyloid from the brain reduces cognitive and functional decline in people living with early Alzheimer's. As of January 2024, aducanumab is being discontinued by its manufacturer, Biogen.
Lecanemab (Leqembi)	Disease progression	Removes beta-amyloid from the brain and reduces cognitive and functional decline in people living with early Alzheimer's.
Cholinesterase inhibitors	Cognitive symptom treatment	Treat symptoms related to memory, thinking, language, judgment and other thought processes. Donepezil (Aricept) treats all stages of Alzheimer's, Rivastigmine (Exelon) is approved for mild-to-moderate Alzheimer's as well as mild-to-moderate dementia associated with Parkinson's, and Galantamine (Razadyne) is approved for mild-to-moderate stages of Alzheimer's.
Glutamate regulators	Cognitive symptom treatment	Improve memory, attention, reason, language and the ability to perform simple tasks by regulating the activity of glutamate. Memantine (Namenda) is approved for moderate-to-severe Alzheimer's.
Suvorexant (Belsomra)	Noncognitive symptom treatment	Treatment of insomnia which has been shown in clinical trials to be effective for people living with mild to moderate Alzheimer's disease.
Brexpiprazole (Rexult)	Noncognitive symptom treatment	Treatment of agitation associated with dementia due to Alzheimer's disease.

Source: The Alzheimer's Association

Challenges in neuroscience

In a paper titled Strategies to address challenges in neuroscience drug discovery and development in the International Journal of Neuropsychopharmacology, identifying five primary challenges relating to advances in neuroscience.
These included:

1. Patient populations:	Heterogeneous patient populations are often grouped by clinical symptomatology rather than measurable pathophysiology
2. Target selection:	Novel mechanisms tested so far have not provided positive data
3. Preclinical models:	There is limited understanding of disease pathophysiology and animal models lack complexity of the human brain
4. Clinical endpoints:	Often limited to highly variable, subjective, questionnaire-based endpoints leading to need for a large N in trials
5. Translatable biomarkers:	Lack of translatable molecular biomarkers and access to human tissue
Source: National Institutes of Health (NIH)	

Solutions can be approached in several ways. As for patient populations, these can be improved by patient stratification and the use of biomarkers, which allow pharmaceutical companies to identify patient populations that are most likely to benefit from a new drug. According to Oxford Global, biomarkers "represent a paradigm shift from the traditional one-size-fits-all approach to a more personalised and precise form of healthcare".

When it comes to target selection, the authors of the previously mentioned paper suggest an increased focus on human genetics-defined targets, as well as the adoption of human neurobiology-informed approaches for target identification, based on pathophysiology hypotheses and clinical observations.

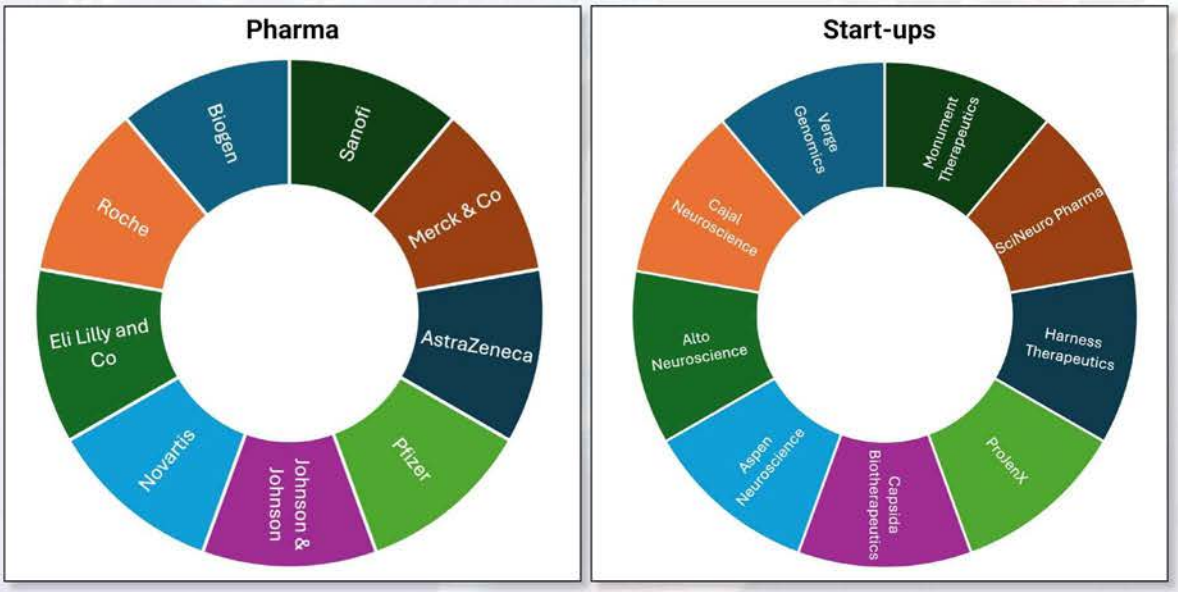
Preclinical models, the authors continue, can be improved by an increased use of translatable biomarkers linked to behavioural assessments and clinical endpoints. On the point of animal models, they say there is an opportunity to address this challenge by adopting animal models that "capture specific domains of pathophysiology, instead of pretending to fully reproduce complex disorders in preclinical species".

As for the challenge of clinical endpoints, the authors argue for increased use of objective biomarker-based endpoints, as well as digitally captured endpoints that allow for repeated testing, increasing statistical power.

Finally, they say the lack of translatable molecular biomarkers and access to human tissue can be overcome through increased use of imaging and electrophysiological biomarkers to show target engagement and central pharmacodynamic activity.

Key players and rising stars

The industry encompasses a range of treatments and drugs in development across neurological disorders, from big pharma to smaller start-ups. The graph below represents pharma companies and start-ups that are heavily involved in R&D, manufacturing and commercialisation in the industry, including the drugs they are developing.



Leveraging the power of molecular communities

Dr Diana Mitrea, Associate Director for Scientific Communications at Dewpoint Therapeutics, shares insight on developing therapeutics targeting biomolecular condensates to address neurological disorders.

Over six decades of target-based drug discovery, extensive effort has been focused on identifying target proteins whose structure and function is disrupted in disease and creating small molecules that repair the defect. This has proved successful in instances where the selected target is the main driver of the disease pathophysiology, and the target happens to present a binding pocket amenable for drug binding in a region of the protein that influences its function. For example, imatinib delivered the first disease-modifying therapy for chronic myelogenous leukaemia by targeting the active site of the disease-driving fusion oncoprotein BCR-ABL; direct acting antivirals can cure >95% of patients infected with Hepatis C virus by selective inhibition of viral proteins. However, the rate of success of this strategy decreases significantly with the increase in complexity of the disease-causing dysregulation, as is the case for many neurodegenerative diseases.

Biomolecular condensates

The biological processes of the cell are compartmentalised in membrane-bound and membrane-less organelles. The latter, also known as biomolecular condensates, are dynamic communities of biomolecules which assemble via phase separation – akin to the separation of oil from vinegar. They respond rapidly to environmental changes and cellular signals to compartmentalise and regulate a wide diversity of biological processes across all life forms.

Condensates integrate the functions of all community members within their microenvironment. Dysfunction in condensates is often responsible for complex causes of disease, that include both loss of function and toxic gain of function of one or more critical biomolecules. This makes them an attractive therapeutic target for diseases and targets that can't be addressed with conventionally developed drugs.

Developing strategies for targeting condensates requires a shift in perspective; condensate targets differ fundamentally from conventional single biomolecule targets because they are effectively a community of molecules, characterised by the structural features of each individual member, as well as collective properties of the community – termed emergent properties. These include local pH, viscosity, porosity, hydrophobicity, and surface tension (Figure 1). Importantly, the emergent properties can be leveraged for the development of a targeted, effective, and safe condensate-modulating drug (c-mods).

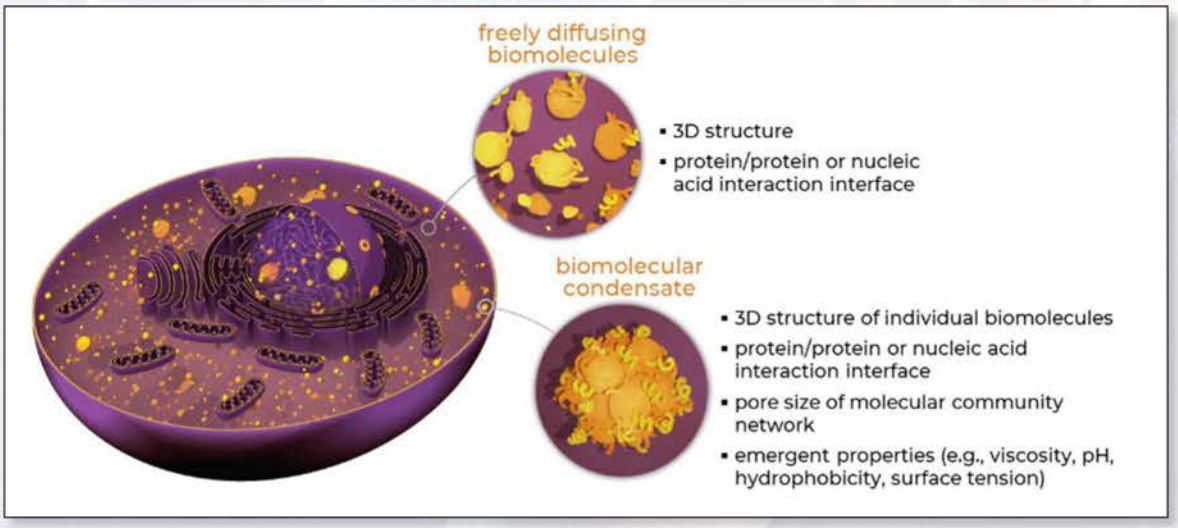


Figure 1 Features that can be leveraged to design and optimise drugs targeting individual biomolecules vs condensates.

Condensatoapthies

A condensatopathy is a condensate aberration that drives disease pathophysiology. An encyclopaedia of condensatopathies by Dewpoint Therapeutics shows their varied disease implications, including neurological disorders, cancer, drug resistance, heart and bone disease, and viral infections.
The high unmet need in neurological disease therapeutics is fuelling increased interest and a steady stream of basic and clinical research efforts. These efforts demonstrate that at the root of many neurodevelopmental and rare diseases lies dysfunction integrated in condensates (Figure 2).

Take amyotrophic lateral sclerosis (ALS), an incurable neurodevelopmental disease: over 40 mutations in a variety of genes have been associated with ALS, each contributing to a small % of patients. Another fraction of patients does not present with any disease associated genetic mutations. Despite this highly variable genetic background, >97% of the patients share a common defect – aberrant cytoplasmic condensates that contain the splicing protein TDP-43 (Figure 3).

Effects of an ALS c-mod

Dewpoint is leveraging this shared condensate defect to develop c-mods for ALS. In its approach, Dewpoint treats the aberrant condensate, and therefore the entire community of biomolecules enclosed within – as the drug target. This serves as a central node of dysfunction in ALS and contributes to multiple downstream misregulated processes, such as TDP-43 loss of splicing function, and gain of toxic function attributed to other proteins that wrongfully join the aberrantly formed biomolecular community. Dewpoint is developing brain-penetrant small molecule c-mods that repair the TDP-43 condensatopathy. The c-mods demonstrate effects on disease pathophysiology metrics (Figure 4); they systemically repair the TDP-43 specific transcriptional and splicing programming, restore neuronal health markers in cultured patient-derived motor neurons, and correct clinically approved ALS-biomarkers in animal models. Importantly, when tested against the current standard of care and other anti-ALS drugs under development, only the c-mod corrected the full complexity of the TDP-43

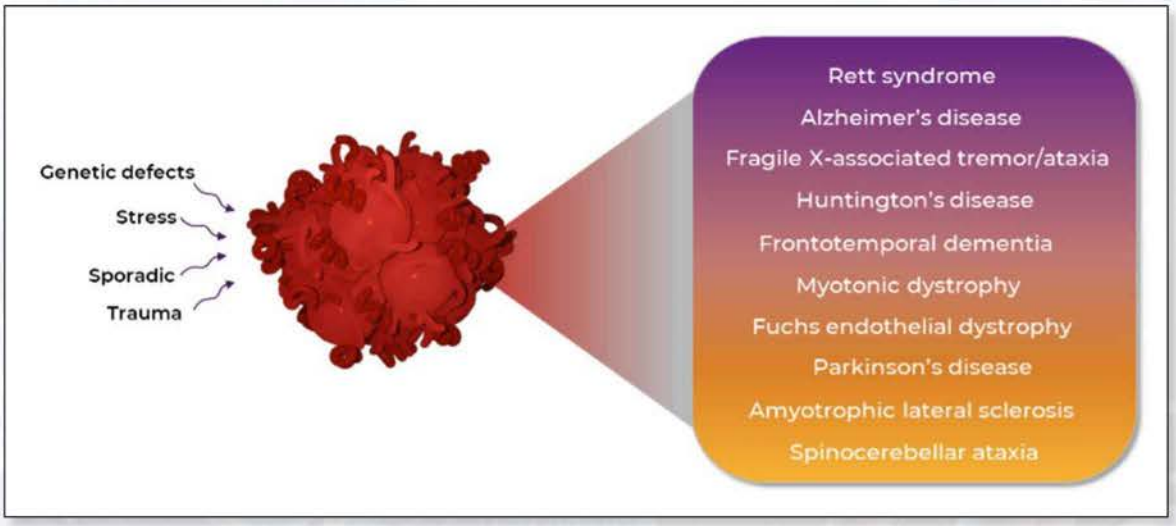


Figure 2 Pathophysiology of many neurodegenerative and rare diseases converges into aberrant condensates.

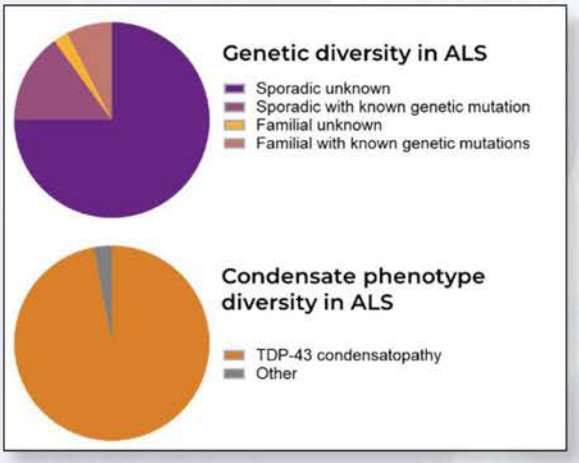


Figure 3 Despite high genetic diversity, >97% of ALS patients share an aberrant cytoplasmic TDP-43 condensate.

transcriptional profile. The c-mod's corrective effects are broad acting, across a panel of over a dozen patient-derived motor neuron cultures, of diverse genetic backgrounds. Collectively, these pre-clinical data show promising progress towards a true ALS disease-modifying treatment.

How is the drug being created?

Dewpoint uses an internal, AI-powered end-to-end platform to identify novel condensate targets, validate the condensate hypothesis, discover and optimise drugs (Figure 5). The platform is disease agnostic and is currently applied across Dewpoint's portfolio, comprised of wholly owned and partnered programmes, spanning neurological, oncology, cardiopulmonary and metabolic diseases.

Mounting evidence demonstrates that condensate structure and function is dependent on its composition and local environment, and can easily be altered by changes in protein levels, stress, cell cycle stage, signalling factors, etc. This also means that engineered systems, either *in cellulo* or *in vitro* are likely to push the system away from its disease-relevant state. After deliberating alternate approaches, Dewpoint chose to embrace the cellular complexity to prioritise biological relevance. As described in the ALS c-mod example, this approach paid off, as it led to translatable success across complex and clinically relevant model systems.

Dewpoint's workhorse discovery assay is high content imaging high throughput screening (HTS), which searches for phenotypic changes relative to the target condensate. This approach combines the advantages of phenotypic assays which cast a wide net, often without prior knowledge or bias on

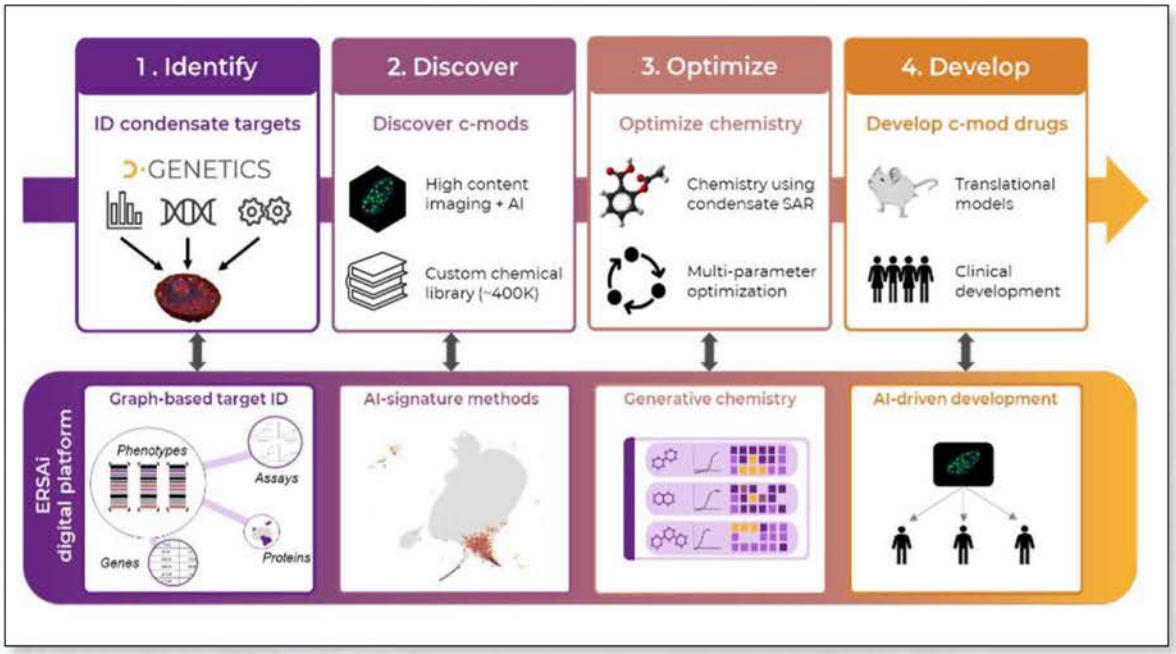


Figure 5 End-to-end, AI-powered drug discovery and development pipeline at Dewpoint Therapeutics.

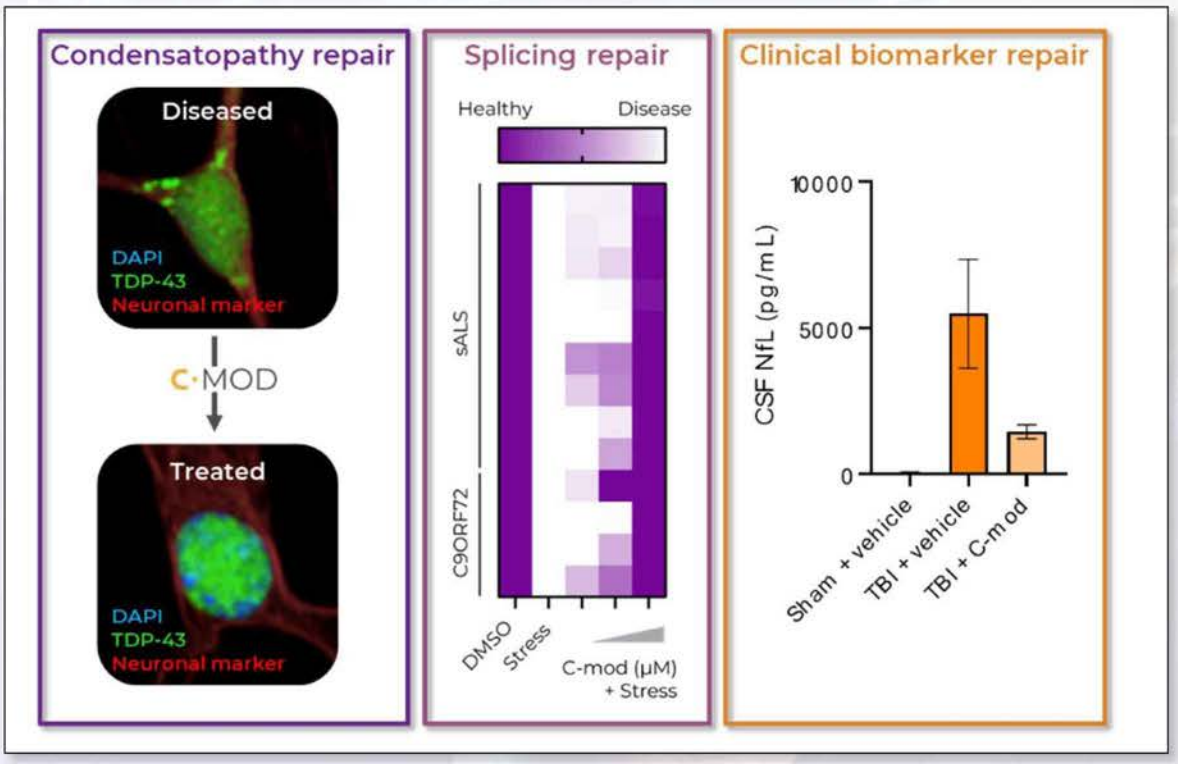


Figure 4 TDP-43 condensatopathy repair in cultured motor neurons (left) with a small molecule c-mod translates into broad-acting repair of TDP-43 splicing function in patient-derived motor neurons (middle) and repair of a clinically accepted biomarker in an ALS mouse model (right).

the pathways that need to be repaired to treat the disease, with those of targeted drug discovery by focusing on the integrating hub of the pathway(s) dysregulation responsible for the disease. The phenotypic perturbations within the condensate are then validated in downstream, functional assays in disease-relevant model systems to confirm the expected systemic and on-pathway effect of the hits.

The direct target can be one of the hundreds of members of the condensate community, or a regulatory factor that acts upstream of the condensate. With efforts to deconvolute the direct target which allows for conventional structure-based drug optimisation, Dewpoint advances its structure-activity relationship efforts based on a combination of condensate and functional assays, to ensure that the disease relevance and efficacy is maintained in the complex cellular setting.

What do we know of c-mods now?

Following Dewpoint's inception in 2018, and the subsequent founding of other biotech companies with the shared goal of developing medicine based on targeting condensates, such as Neriad Therapeutics, Transitions Bio, and ETERN Therapeutics, the industry started hunting for drugs by intentionally targeting condensates.

Recent studies are finding that FDA-approved drugs, developed through conventional methods, function – at least in part, through condensate mechanisms, and/or modulate condensates as part of their off-target effects. Dewpoint's c-mod encyclopaedia recorded 237 compounds experimentally demonstrated to modulate condensates; 63 of which are FDA approved. These c-mods come in multiple modalities – from small molecules to peptides, oligonucleotides, proteins and more. Systematic analysis of this evolving public dataset, further enriched with proprietary data from HTS campaigns and optimisation cycles generated by the biotech industry, will help define unwritten rules that pertain to determining selectivity and specificity towards a community of biomolecules. Together, these novel insights will drive refinement in strategy towards an accelerated path to successful optimisation of c-mods with superior clinical safety and efficacy.

Clinical trial explanation and limitations

To date, there are no drugs discovered or developed through a condensate-centric approach in the clinic. Dewpoint is on track to be the first that brings a drug discovered through a condensate lens into the clinic, scheduled for the H2 of 2025. As part of this journey, several safety and efficacy considerations will have to be revisited and potentially revised, primarily due to the complex nature of the target. For example, while safety studies for c-mods can be designed following well established, conventional approaches, defining selectivity and specificity towards a condensate (ie. a community of molecules) is uncharted territory. The current model that Dewpoint adopted is to define selectivity and specificity relative to the pathways integrated within the condensate as opposed to a single biomolecule. This model will continue to evolve with new data.

Implications for the future of treatment

Refocusing the notion of target from a single biomolecule to a community of biomolecules that function synergistically to perform a specific biological process provides previously unattainable access to effectively modulating the function of molecular targets previously considered 'undruggable'. These targets have earned their 'undruggable' designation due to lack of well-defined pockets where drugs can bind to effectively modulate their function. With c-mods, one gains the ability to modulate this function by altering the structure and environment of the compartment where the 'undruggable' target resides.

C-mods, by virtue of their mode of action of modulating a central node of dysfunction in disease, promise to exhibit disease-modifying effects and activity across broader, more diverse patient populations. Albeit early in the game, Dewpoint's results demonstrate encouraging translatability of outcomes between cell lines, patient-derived cells (eg. iPSCs) and animal models.

There is more work to be done, but the potential implications are substantial. For example, understanding the rules that drive a drug to preferentially accumulate in a specific condensate can be a game changer for optimsing target engagement and improving drug safety and efficacy.

Furthermore, understanding the condensate mechanisms by which the organism responds to stress has the potential to revolutionise how we prevent or combat acquired drug resistance to existing therapies.

Dr Diana Mitrea is the Associate Director for Scientific Communications at Dewpoint Therapeutics. She has a background in biochemistry and protein engineering, and over 14 years' experience in condensate biology and biophysics & structural biology of folded and intrinsically disordered proteins.

Finding a new approach to an old problem

Megan Thomas speaks to ApconiX's Director and Co-founder, Professor Ruth Roberts, and Scientific Lead, Kimberly Rockley, about the state of the neuroscience industry, its significance in drug discovery, the evolution and the future of the field.

MT: Why is neuroscience so important?
Ruth Roberts: With the development of any drug there is the possibility of drug-induced side effects. Neurological side effects can be life-threatening. Any adverse effect detected in the preclinical stage will affect safety margins and potentially lead to compounds becoming no longer viable. In drug discovery and development, this is a waste of time, money and resources. Moreover, possible neurological adverse effects at the clinical stage potentially put patients at risk and can result in a candidate drug being placed on clinical hold.

MT: How has neuroscience research evolved?
RR: Over the past decade or so, there has been an increasing focus on translation. That is, ensuring that laboratory research into new drugs for neurological conditions or into the safety of new drugs in general, is relevant for actual people. I know that seems obvious, but 50 years ago most of this research was conducted in animals and we only gained insight into human safety and efficacy once clinical trials began.

MT: Where are the opportunities?
RR: The key opportunities are in developing and implementing are new approach methodologies (NAMs), based on human information gained using human tissues. All preclinical methods other than animal testing are NAMs, which broadly encompass approaches that aim to refine in vivo methods or improve in vitro testing. This includes 3D tissue culture models and the use of computational methods, such as machine learning. There is increasing interest in NAMs to improve prediction of human safety risks. We are using human ion channels and human-derived brain cells to look at several different neuroscience endpoints in our laboratory.

MT: What are the next steps for research?
There are so many exciting next steps coming up. We are looking at Structure-Activity Relationships (SARs) for seizure, initially. If we have a small molecule drug that interacts with an ion channel to cause seizure, we can potentially modify its chemical structure and design out this effect. It's a very difficult thing to do, but with our expertise and that of our medicinal chemist collaborators, we are confident it is achievable.

We are currently carrying out research in other important applications of the technology we have developed to look at other potential risks in drug development. Specifically, we are looking at sedation (the opposite of seizure), epilepsy (how to block the ion channels responsible) and pain (which we know to be regulated by ion channels in the brain and elsewhere in the nervous system).

MT: What are the challenges?
RR: The main challenge is acceptance of a new approach to an old problem. Fellow research scientists are very enthusiastic about the work we are doing but change takes time and cannot be forced. As well as this acceptance of change, the scientific methods we are using are at the forefront of research and are highly specialised requiring expertise, diligence and determination.

MT: What is your vision for the next 10 years?
RR: My vision is for a new paradigm in the assessment of drug safety when it comes to central nervous system risks such as seizure and sedation. Rather than requiring testing in animals, we could progress to using NAMs using human systems before moving very cautiously into the clinic. Similarly, my vision is for a new paradigm in the development of new drugs for conditions such as pain and epilepsy, again based on human systems rather than on animal models. We do have progress towards this goal within public health internationally so I am optimistic we will get there.

MT: What are the roles of ion channels in the body?
Kimberly Rockley: Ion channels are proteins that regulate electrical activity in the body and have particular importance in the heart and the brain.

One example is hERG, an ion channel in the heart. Drugs affecting hERG can cause fatal arrhythmias. Because of this, regulatory legislation requires all drugs should be tested for activity at hERG.

ApconiX is involved screening drugs for hERG and cardiac liability. In 2017, we discussed the impact of drug-induced seizure and the idea of screening for seizure in the same way as cardiac liability using an ion channel panel and the assessment of electrical activity by microelectrode array (MEA).

MT: What is ApconiX's seizure liability assay?
KR: Our approach is two pronged: Firstly, a microelectrode array assay that utilises human-derived neuronal stem cells to demonstrate potential seizure activity by measuring electrical activity. Secondly, a panel of 15 ion channels that can be screened using automated electrophysiology.

Seizures are characterised by periods of excessive neuronal firing and uncontrolled hyper-excitability. The use of MEA to monitor spontaneous electrical activity and drug responses in hiPSC-neuronal co-cultures stands out as a suitable method to identify seizure liability in vitro. We validated this novel assay by testing 16 drugs known to cause seizure.

Our ion channel panel contains 15 ion channels with strong genetic links to seizure. The activity of these ion channels was tested against the same 16 compounds used on the MEA assay. Our work was recently published in Toxicological Sciences.

MT: How are drugs typically tested for seizure, and where is there room for change/improvement?
KR: Currently animal models are used. These are the rodent and non-rodent studies required to support clinical trials. Anything unusual noted in these studies indicative of aberrant neurological activity would usually trigger a follow-up electroencephalogram (EEG) study for confirmation.

Neurological-related signs can be sporadic, subtle and easily missed. In vivo studies have the limitation of low throughput, high cost, use of animals and potentially problematic translatability to humans.

A significant opportunity for change and improvement is the development of in vitro assays that are high throughput with a quick turnaround time, translatable to humans, and successfully reduce the need for animal testing.

MT: Do you have any case studies of what your clients are working on with this assay?
KR: Over the last few months these assays have been valuable in early de-risking, compound prioritisation and problem solving. We have successfully identified lower risk compounds from a larger series. Previously, this would have required multiple animal studies.

We have also demonstrated good concordance between seizurogenic responses in vitro and concentrations causing convulsions in rodents in vivo. This highlighted the good translation of the assays and reduced the need for further EEG studies.

Additionally, we determined the relevance of seizure observations in nonclinical studies. In this example, nonclinical testing of a compound caused convulsions in dogs. Testing a range of metabolites using the MEA assay showed that only the dog-specific metabolite caused the seizurogenic response.

Early screening of compounds using our assays will undoubtably help identify lower risk candidates as will our work on SARs.

Understanding species differences and the translatability to humans is important research, which we are currently carrying out and expect to finish this summer. This allows us to better help clients bring safe, effective drugs to market without the need for more animal testing than is necessary.

MT: How are you reducing/refining animal testing?
KR: Each clinical project that fails due to seizure will have used around 80-100 rodents and 24 non-rodents in GLP toxicology testing alone to reach this stage. If we can support clients by identifying potentially seizurogenic compounds early in the drug discovery and help understand seizurogenic responses in preclinical studies, we can hopefully reduce the number of failed projects and the number of animals used.

A co-founder of ApconiX, Profess **Ruth Roberts** has over 25 years of experience in leading drug safety. Roberts is also Chair and Director of Drug Discovery at the University of Birmingham, UK and previously Global Head of Regulatory Safety at AstraZeneca.

Dr Kimberly Rockley has a background in cell-based models and joined ApconiX to develop in vitro assays for early detection of seizure liability. Rockley is passionate about the use of *in vitro* techniques to improve preclinical safety and reduce animal testing.

New frontiers for neuroscience

As opportunities arise, who are the key players looking to create impact and what will that mean for the future treatment of neurodegenerative disease?

The next 50 years of neuroscience

On the 50th anniversary of the Society for Neuroscience in 2019, authors published an article in the Journal of Neuroscience reflecting on both the progress that the field has made in understanding the nervous system, as well as the next 50 years.

When published in 2019, the Society predicted equal gender representation of model organisms and studies on the female brain in five years. In 2029, it predicts the acquisition and analysis of genetic information from worldwide populations to study the progression of health, disease, and epigenetic environmental effects. In 2034, it anticipates minimally invasive testing which increases access for early detection and immediate intervention of late-onset diseases, and an understanding of the function of astrocytes, microglia, and the extracellular matrix in whole brain-body function.

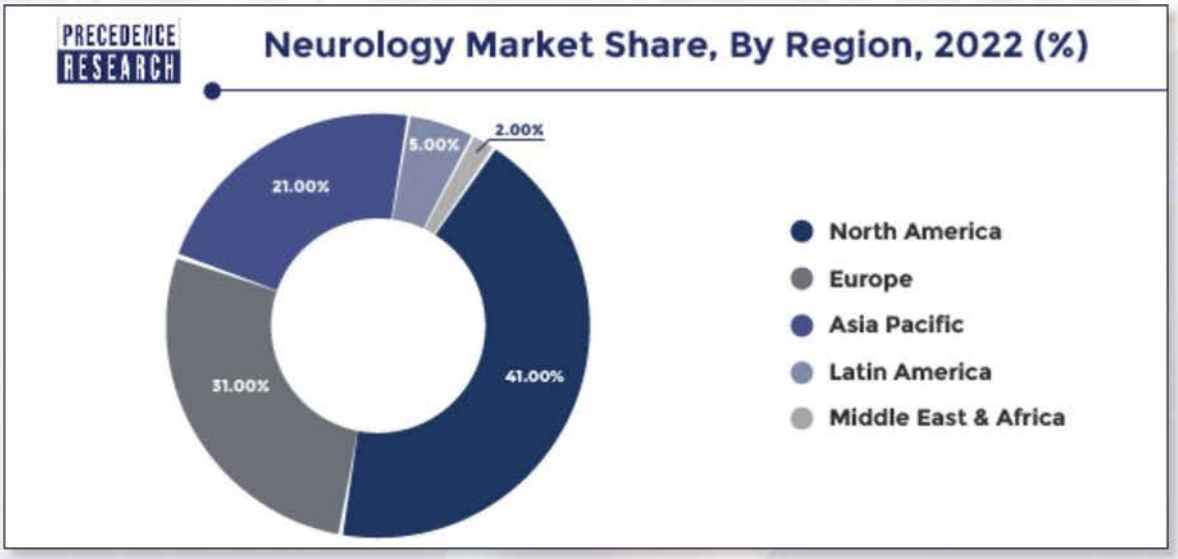
Looking ahead 20 years to 2039, the Society expects to see the highest resolution of whole brain imaging at structural and functional level. After that, in 2049, brain organoids used to screen drugs and efficacy of gene editing techniques implemented to replace damaged tissues. Finally, in 2059, elucidation of the computation of billions of neurons in decision making, used to gain access to artificial limb fluidity through brain activity, as well as machine learning used to recapitulate the perception of visual imagery for the blind and memory revitalisation.

Asia Pacific: a fast-growing market

In a report by Deloitte Insights, the company reported that over 50% of the global neuroscience market revenue arises from North America, while approximately 25% stems from the European market. What remains can be attributed to Asia-Pacific and, to a lesser extent, the Rest of the World (RoW). While this is comparatively a smaller market, its potential is predicted by Precedence Research to be the fastest expansion. This is for several reasons.

First, the emerging demographic trends. The Asia Pacific region makes up 60% of the global population and hosts the two most populous countries in the world: China and India. The UN's Asia Pacific Population and Development Report 2023 reflects that the number of people over the age of 60 is projected to double from 697 million in 2023 to 1.3 billion by 2050. Moreover, compared to other regions of the world, population ageing is "particularly rapid due to the sharp decline in fertility". The report states: "In older age, non-communicable diseases have become the leading cause of death globally and in Asia and the Pacific, while Disability Adjusted Life Years lost to Alzheimer's and diabetes have risen dramatically across the region".

Second, there is an increasing awareness of neurological disorders and improving healthcare access in the region. The IBRO Asia-Pacific Regional Committee (APRC) is a team of elected, voluntary



Source: www.precedenceresearch.com

leaders who focuses on supporting and promoting neuroscience in the Asia-Pacific region based on its specific needs and conditions. The organisation works closely with the Federation of Asian-Oceanian Neuroscience Societies (FAONS), the IBRO Asia-Pacific member societies and other Asia-Pacific and global scientific networks to increase brain research and awareness in the region.

Third, we can consider the neurology-focused research taking place in the region. The following are noteworthy:

- **Zai Lab** (Shanghai) announced in May 2024 that the Center for Drug Evaluation of the China National Medical Products Administration has accepted the supplemental Biologics License Application for efgartigimod alfa injection (subcutaneous injection) (efgartigimod SC) for the treatment of chronic inflammatory demyelinating polyneuropathy.
- **TauRx Pharmaceuticals** (Singapore) is developing therapies targeting tau protein pathology. The company's drug candidate, hydromethylthionine mesylate, aims to prevent the buildup of tau tangles and restore normal brain function.
- **National Brain Research Centre** (Manesar) promotes interdisciplinary research in neuroscience and cognitive sciences. It is an autonomous institute under the Department of Biotechnology, Ministry of Science and Technology, Government of India.

Approaching neurological disease

Alzheimer's disease

Following an awarding of $20 million to The University of Texas MD Anderson Cancer Center to strengthen neurodegeneration research, Jim Ray, Executive Director, Belfer Neurodegeneration saConsortium, said: "Alzheimer's is already the most expensive disease in the US. As our population continues to age, addressing quality-of-life issues and other challenges of treating and living with age-associated diseases must become a priority."

In the Alzheimer's Disease Facts and Figures report, Alzheimer's was the fifth-leading cause of death of people over 65 in 2021. Globally, the Alzheimer's Society estimates that 55 million people live with dementia, which will rise to 139 million by 2050. Of course, there are currently no cures. According to NHS resources, it's unlikely there will be a single cure for dementia, as it's caused by different diseases.

There are, however, drugs approved in the UK, EU and US such as the active drugs of donepezil, rivastigmine, galantamine and memantine to ease symptoms in persons with Alzheimer's, dementia with Lewy bodies, Parkinson's, dementia, and mixed dementia involving any of these types. Formulation variations include combinations like Namzaric in the US (donepezil and memantine).

According to the Alzheimer's Society, there are 127 drugs in 164 clinical trials for Alzheimer's. Moreover, the National Institute on Aging is currently supporting 507 active clinical trials on Alzheimer's and related dementias. Full access to the 57 ongoing clinical trials can be found on the NIA website.

Nordisk's GLP-1 receptor agonist Ozempic (semaglutide) is significant. Although approved for diabetes and weight loss (as Wegovy), it has shown promise for addiction and dementia. Research at the University of Gothenburg investigated Ozempic as a treatment for alcohol use disorder, while a Danish study showed that the dementia rate was lower in patients taking GLP-1 RAs and concluded that they "may provide a new opportunity to reduce the incidence of dementia in patients with type 2 diabetes". Novo Nordisk is currently funding three trials of Ozempic in Alzheimer's, including one into the effect of semaglutide on the rate of accumulation of tau protein in the brain.

At NKGen Biotech, the company's investigational natural killer therapy, SNK01, to treat patients with Alzheimer's, has released data from its Phase I clinical trial and been granted Compassionate Use by the FDA. Reflecting on the future, Dr Paul Song, MD, NKGen, tells DDW: "We remain optimistic that our novel approach will provide an entirely new paradigm in the treatment of this disease and other neurodegenerative diseases as well. We believe our treatment could also complement some of the other targeted antibody-based treatments too."

A patient-centric approach

Biotechnology company Alchemab finds individuals who are susceptible but resilient to specific diseases and uncovers the possible targets that drive their resiliency. By screening the antibody producing B-cell repertoire of individuals, the Cambridge, UK-based biotech identifies specific antibodies that are uniquely present in the resilient subset.

The company has built a workflow that combines computational approaches with advances in antigen display technology to express and screen these unique antibodies in a high-throughput manner. As a result, the platform yields both a novel target linked to modifying the disease, together with potential therapeutic antibodies that could be used to treat the disease. One such programme is ATLX-1088, which was discovered by looking at antibodies from resilient individuals with risk factors for developing Alzheimer's. Despite the risk factors they possessed, the individuals were cognitively healthy and had not gone on to develop the disease.

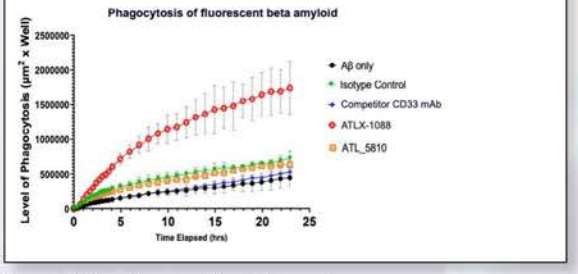
Antibodies to CD33 were identified as being common to these resilient individuals. This was considered

Key clinical drug development trials in Phase I and Phase II				
Project name	**Institution**	**Trial description**	**Population**	**Completion**
Clinical Trials to Prevent Alzheimer's Disease in Down Syndrome	Michael Rafii, University of Southern California	Anti-Aβ immunotherapy to remove amyloid plaques	Non-demented adults with down syndrome (Ages 35 - 55)	2025
A Single Ascending Dose, Multiple Ascending Dose Phase I Study of the GSM 776890 in Healthy Normal Subjects	Douglas Galasko, University of California San Diego	Gamma secretase modulator 776890, an Allosteric modulator of amyloid precursor protein (APP) processing, to attenuate Alzheimer's disease pathology	Healthy adult participants	2025
Phase II Study to Evaluate the Safety and Efficacy of CT1812 in Subjects with Mild to Moderate Alzheimer's Disease	Anthony Caggiano, Cognition Therapeutics	CT1812, a small molecule sigma2 receptor antagonist that displaces Aß oligomers bound to neuronal receptors at synapses	Adults with Mild to Moderate Alzheimer's Disease (Ages 50 - 85)	2024
The LUCINDA Trial: LeUprolide Plus Cholinesterase Inhibition to Reduce Neurological Decline in Alzheimer's	Tracy Butler, Joan and Sanford I Weill Medical College of Cornell University	Lupron, a small molecule gonadotropin-releasing hormone (GnRH) receptor agonist to slow cognitive decline in women with mild to moderate Alzheimer's disease	Women with mild-moderate Alzheimer's disease who are also taking acetylcholinesterase (AChE) inhibitors (Ages 65 - 90)	2025
A Proof of Concept Trial of a Sirtuin-NAD+ Activator in Alzheimer's Disease	Shalender Bhasin, Brigham and Women's Hospital	ß nicotinamide mononucleotide (ßNMN): An NAD+ precursor to slow Alzheimer's disease progression and improve cognition	Mild Alzheimer's disease dementia participants	2025
Phase I Clinical Trial of CMS121, a Novel Therapeutic Candidate for Alzheimer's Disease	William Raschke, Virogenics	CMS121, a small molecule therapy to reduce neuroinflammation	Healthy adult volunteers	2024

Source: The National Institute on Aging (NIA)

significant as CD33, an inhibitory receptor present on microglial cells, is genetically linked to modifying the risk for developing Alzheimer's. ATLX-1088 was selected from a pool of natural human antibodies with the most promising functional characteristics. ATLX-1088 works by competing with the natural CD33 ligand to disinhibit the CD33 receptor on microglial cells, leading to activation of microglia and phagocytosis of the toxic proteins that accumulate during Alzheimer's. While other CD33 inhibitors exert their effects by internalisation of the receptor, ATLX-1088 does not change levels of CD33 on the cell surface, resulting in an improved pharmacokinetic profile. Moreover, the team have found that the antibody has remarkable functional properties. For example, in comparison to known CD33 antibodies, ATLX-1088 leads to greater phagocytosis of amyloid-beta in *in vitro* cellular models and significant reversal of astrogliosis and inflammation in iPSC tri-culture models, suggesting a strong anti-inflammatory effect.

CD33 inhibitor ATLX-1088 causes a significant increase in phagocytosis in human iPSC microglia



Source: https://www.alchemab.com/

Based on the data to date, ATLX-1088 offers a promising and novel therapeutic approach for the treatment of Alzheimer's disease, either as a monotherapy or in combination with existing therapies such as amyloid targeting therapeutics.

Parkinson's disease

The Cure Parkinson's research team and Parkinson's advocates and The Michael J Fox Foundation for Parkinson's Research provide an annual overview of the clinical trials landscape for Parkinson's.

The 2023 report, published in the Journal of Parkinson's Disease, counted 139 active clinical trials in 2022 which are attempting to develop new drugs, with 89 to be completed in 2023. According to a paper published in the National Library of Medicine titled *The Future Burden of Parkinson's Disease,* there are currently three studies from three continents showing an increase in the risk of Parkinson's over time - from the US, Finland, and Taiwan. The stakes are continuously rising and a cure for this debilitating disease needs to be found.

A potential disease-modifying treatment for Parkinson's

Mission Therapeutics are developing deubiquitylating (DUB) enzymes. Its principal target is a DUB called USP30, which inhibits mitophagy. Adding or removing ubiquitins from proteins can influence their behaviour and the physiological pathways. For instance, when a mitochondrion become dysfunctional, particular ubiquitins are added to its surface, which flags it for removal.

In addition, certain situations such as cellular stress and cell injury can cause mitochondria to become dysfunctional, leading to reduced energy production, oxidative stress, inflammation and potentially cell death. Mitophagy defects (ie. faults in genes which code for certain proteins) are associated with neurodegeneration and the development of Parkinson's. Too much USP30 can prevent mitophagy by removing ubiquitins from the surface of dysfunctional mitochondria, leading to a build-up of faulty mitochondria and their by-products in nerve cells, which can damage them or lead to their death.

These situations can cause the death or sub-optimal operation of brain cells that produce dopamine, a neurotransmitter essential for neurological function. The lack of dopamine can cause symptoms of Parkinson's including tremor, rigidity, slow movement, mild memory and thinking problems, sleep problems, pain, and mental health problems.

Mission's lead Parkinson's candidate, MTX325, is a small molecule that is a potent, selective brain penetrant. It is designed to improve mitochondrial quality and function by enhancing mitophagy through inhibition of USP30. Both the target and the drug have been validated in preclinical trials in mice. Researchers from Mission, Harvard University and Cambridge University published results of those trials in the journal Nature Communications.

In March 2024, Mission began a Phase I clinical trial of MTX325. The trial is not powered to show efficacy and further clinical trials will be needed to clinically validate whether MTX325 can produce a disease-modifying effect. Single ascending, multiple dose ascending, and elderly healthy volunteer cohorts are planned to take place in 2024. Parkinson's patients will be the focus of the ongoing trial programme in 2025 and the implications are profound.

Currently, the mainstay treatment is to replace the missing dopamine. Most patients are treated with levodopa, or similar drugs, which are converted into dopamine within the body. These drugs can alleviate the symptoms but not the underlying pathology. Such treatments also tend to become less effective over time, with the affected area of the brain continuing to deteriorate and the condition worsening. They can also result in unpleasant side effects including jerky muscle movements (dyskinesia), and 'off' periods where people rapidly become immobile as the drugs wear off.

Beyond Alzheimer's and Parkinson's

There are several other conditions that hold promise in this field. According to the World Health Organization (WHO), the top ten neurological conditions contributing to loss of health in 2021 were stroke, neonatal encephalopathy (brain injury), migraine, dementia, diabetic neuropathy (nerve damage), meningitis, epilepsy, neurological complications from preterm birth, autism spectrum disorder, and nervous system cancers.

Concussions are the leading form of mild traumatic brain injury and are not limited to any specific population. As a first therapy for concussions, Oxeia Biopharmaceuticals is developing OXE103 (ghrelin), a 28 amino acid peptide hormone discovered in 1999 by Japanese researchers, Kenji Kangawa and Masayasu Kojima. It binds to the growth hormone secretagogue receptor, which stimulates appetite and activates multiple metabolic pathways involved in energy homeostasis and plasticity of dendritic connects in the brain. The pleiotropic activities of OXE103 in the brain match ith the pathologic processes of oxidative damage and connectivity compromise occurring with concussive injury.

The current standard of care is cognitive rest followed by gradual return to normal activity, says Michael Wyand, Chief Executive Officer/ Director of Oxeia. "Treatment is based on symptom management, which has varying efficacy, while waiting for the underlying injury to repair itself. It has been estimated that 80% of concussion patients resolve their symptoms within the first week post injury. The remaining 20% will experience persistent post-concussion symptoms that may persist for weeks to month to years. This persistently symptomatic population represents a significant unmet medical need and is the population that Oxeia selected for its first clinical study."

Oxeia has also completed an exploratory open label Phase IIa trial, conducted at Kansas University Medical Center. The results indicate that OXE103 is a promising and potential therapeutic to treat post-concussion patients suffering from ongoing symptom burdens. A larger, multi-center randomised trial will be the next step.

Conclusion

"We predict a substantial acceleration of our understanding of the nervous system that will drive the development of new therapeutic strategies to treat diseases over the course of the next five decades", confirms the Society for Neuroscience. This progress will manifest itself through a number of new frontiers, from emerging regions such as Asia Pacific, to ground-breaking approaches in the clinic for Alzheimer's, Parkinson's, and beyond. Not only is there promise and potential in the early drug discovery phases, but there are also a substantial number of trials entering later stages and, as time will soon tell, manufacture, distribution and commercialisation.

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