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Insights

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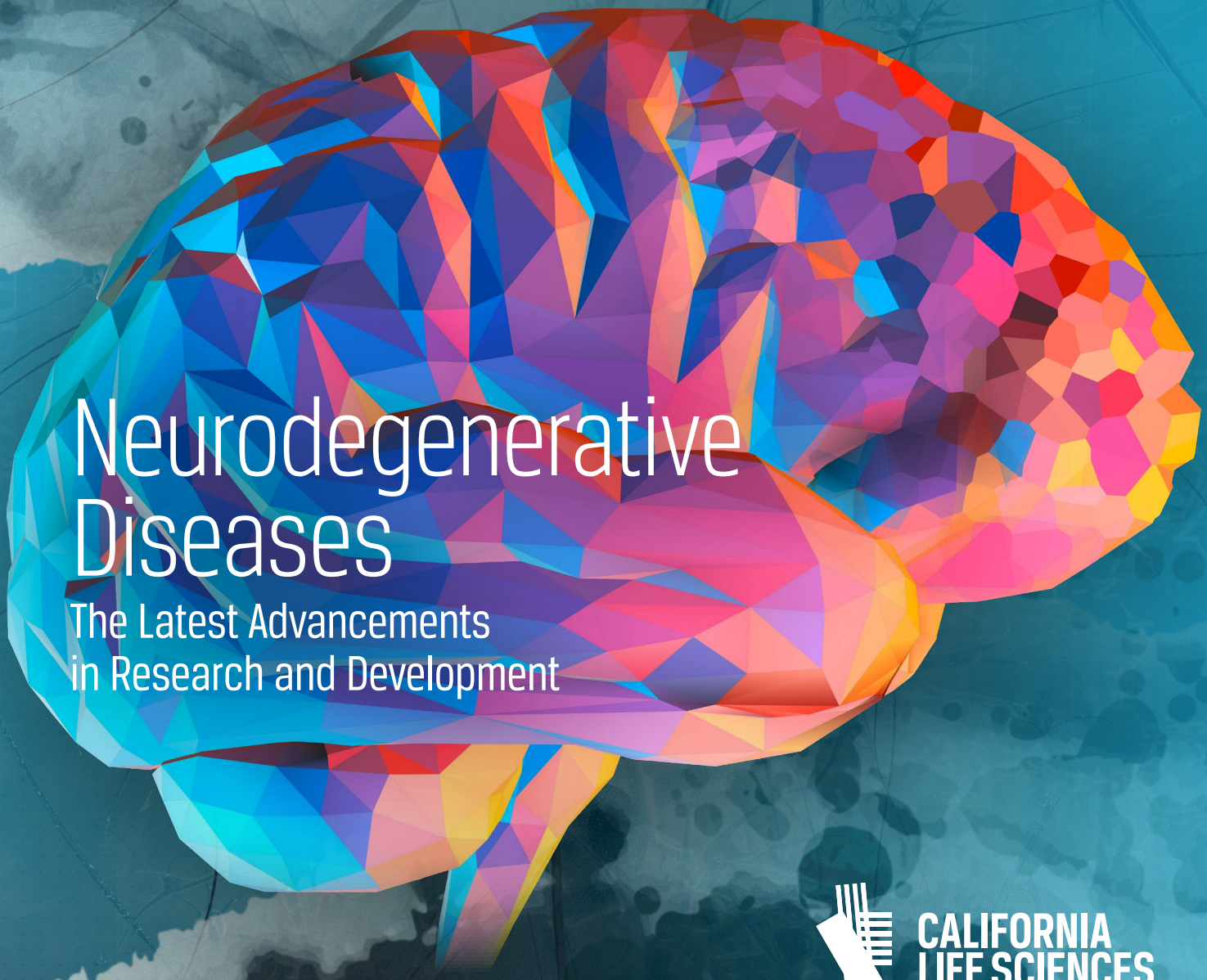

Neurodegenerative Diseases

The Latest Advancements in Research and Development

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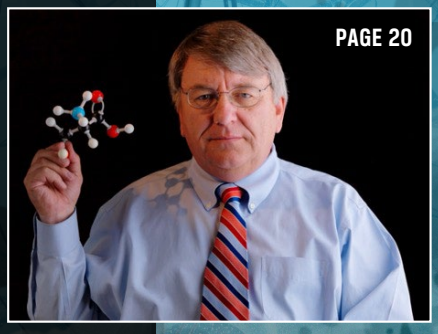
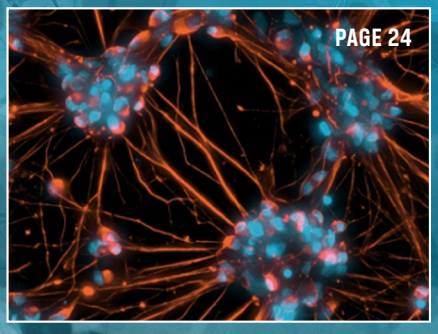
According to the Journal of Clinical Medicine, neurological disorders are the leading cause of physical and cognitive disability across the globe, currently affecting about 15% of the worldwide population. Absolute patient numbers have considerably climbed over the past 30 years.

On top of that, the burden of chronic neurodegenerative conditions is expected to at least double over the next two decades. Because of this evolution, which can largely be attributed to the expansion of the aging population, it will be a huge challenge to keep neurological care accessible to everyone.

CLS is proud to showcase the companies focused on emerging therapeutic developments, more effective and accessible drug treatments, and disease prevention strategies that support precision medicine and further reduce clinical care costs.

Contributing Organizations





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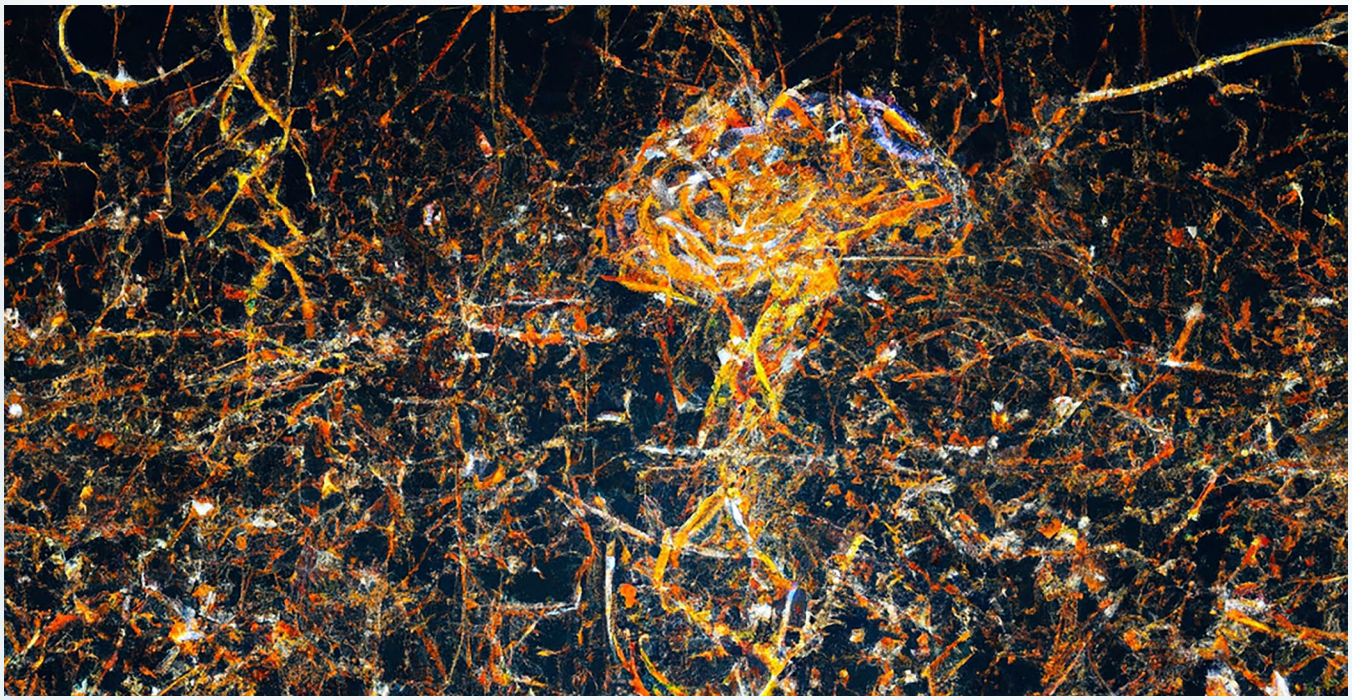
New Technologies Tackling Neurodegenerative Diseases: A Comprehensive Overview

Submitted by Adrián Rubstein, Founder, Ax3.Bio



The World Health Organization (WHO) estimates that approximately one billion people worldwide suffer from neurological disorders.

As the population ages, the number of diagnosed neurodegenerative disease cases is increasing with a potential market expected of USD 53,275 million by 2030. Neurodegenerative disorders (NDs) are characterized by the progressive loss of nervous system cells, which is accompanied by increased depositions of proteins that play important roles in cellular homeostasis. These include amyloid-beta (A) and tau in Alzheimer's disease (AD), -synuclein (-Syn) in Parkinson's disease (PD) as most prevalent examples. The primary goals of ND research today are to improve the diagnosis, treatment, and monitoring of these patients. To achieve these goals, we must improve current biomarkers for diagnosis and monitoring, as well as tools for developing new treatments.

Diagnosis and Monitoring: Non-Invasive Imaging Technologies and Biomarkers

New technologies such as structural magnetic resonance imaging, tau-PET, and susceptibility-weighted imaging are currently being investigated to better understand disease progression and visualize brain architecture with great sensitivity. We can consider the Nigrosome-1 clusters for PD which appear as distinct, hyperintense structures on MRI. In AD, pTau217, can distinguish AD from non-AD dementia with an accuracy of 96%, like tau-PET. While in PD, Phosphorylated -syn was found to be associated with

aggregated forms of -syn and accounts for 90% of the -syn found in Lewy Bodies.

New Treatments: Screening and Development of New Therapies

There is a significant unmet need to identify better targets and understand disease pathophysiology using models other than animal models. On this topic, the Modernization Act approval will help new tools get FDA approved, such as AI and, more specifically for our purposes, Brain on a chip (BoC).

Brain on a Chip: Better Screening

The concept behind BoC is that it can be used to study the human body, which is more complex than any computer model or animal. With this technology, we can improve our screening capabilities for new targets and assess the effect of new treatment on the brain. BoC technology has been developed to address many of the shortcomings of previous models like organoids. While current BoC devices can produce electrical signals like a human organ, they do not fully capture the complexity and variability of real brains.

Gene and Cell Therapy: Precision Treatments

Several major pharmaceutical companies failed to develop treatments for Alzheimer's and Parkinson's disease despite investing more than USD 20 billion and at least 50 compounds in the process. Two new technologies are disrupting the market by potentially curing these patients: cell therapy and gene therapy.

Cell Therapy

The therapeutic potential of various cell types has been investigated in AD animal models, with promising results. Indeed, the primary goal of stem-cell therapy in Alzheimer's disease is to generate new neurons to replace those lost or damaged during disease progression, or, alternatively, to generate glial cells to protect neuronal cells from ongoing degeneration.

Despite promising preclinical data, numerous unresolved safety issues must be addressed before moving this technology from the bench to the bedside and into human clinical trials.

Gene Therapy

The promise of gene therapy has always been built on two pillars: the ability to target etiology and the ability to "achieve permanent correction." A single, long-lasting intervention is especially appealing for CNS diseases because, unlike other organs where repeated doses can easily achieve effective therapeutic concentrations, most peripherally administered agents are unable to cross the blood brain barrier, or only do so poorly. AADC[1] delivery has proven to be more effective than neurotrophic factors and increase the dopamine levels for up to seven years and improving the UPDRS[2] score for up to two years. The main challenge for this therapy is to prove efficacy and safety in the long term and decrease the off-target effects.

The promise of gene therapy has always been built on two pillars: the ability to target etiology and the ability to "achieve permanent correction."

Conclusion

NDs innovations have the potential to transform how we understand and treat these devastating conditions. Cell therapy, gene therapy and advanced imaging techniques could lead us to effective diagnosis and treatments. Despite the difficulties and complexities of these diseases, continued investment in research and innovation is critical to improving outcomes and eventually finding a cure. ■

1 AADC: 1-amino acid decarboxylase
2 UPDRS: Parkinson's Disease Rating Scale

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Closer to Finding the Right Therapeutic Target

Submitted by Springer Nature

As with all major neurodegenerative disorders, many with unmet needs, the developments of disease-modifying therapies have proven challenging for multiple reasons. New working hypotheses that challenge the traditional ideas about how a certain disease develops may aid in forward understanding neurodegenerative diseases. Here, we'd like to focus on two promising research approaches.

Modelling Huntington's Disease Through Direct Neural-Reprogramming

Huntington's disease is a hereditary neurodegenerative disorder caused by an autosomal dominant mutation. The hallmark symptom of Huntington's disease is the presence of progressive chorea (abnormal involuntary movements), which is accompanied by psychiatric symptoms and cognitive decline.

Patient-derived induced pluripotent stem cells are a powerful approach when it comes to modelling brain disorders. However, converting adult fibroblasts into embryonic-like pluripotent cells inevitably wipes any age-related signatures. This can lead to difficulties in modelling neurodegenerative diseases, where age is a risk factor. In recent years, researchers such as the Yoo lab in Washington University School of Medicine, St. Louis, have developed direct neural-reprogramming approaches, in which patient cells can be differentiated directly into neurons, skipping the pluripotent stage and retaining age-associated features. Focusing on Huntington's disease (HD), the Yoo lab have

successfully generated striatal medium spiny neurons (MSNs) from patient fibroblasts using microRNA-based direct neuronal conversion. Such HD-MSNs recapitulated key features of HD pathology, including mutant HTT aggregates, DNA damage, and mitochondrial dysfunction5. They have also provided insights into the progression from pre-symptomatic to symptomatic disease stages, with older, symptomatic patient MSNs developing autophagy impairments that help drive neural death. Boosting autophagy in such cells increased their resilience against neurodegeneration. Similar approaches applied to other neurodegenerative diseases could prove equally fruitful when it comes to insights into disease pathogenesis and progression.

Another recent development has been in the studies of autophagic impairments. Autophagy is a fundamental cellular process that eliminates molecules and subcellular elements, including nucleic acids, proteins, lipids and organelles, via lysosome-mediated degradation to promote homeostasis, differentiation, development and survival.

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Autophagic Impairments Induce Abeta Intraneuronal Build Up and Subsequent Plaque Formation

Autophagy plays a key role in maintaining cellular homeostasis by removing unwanted components through a lysosome-dependent mechanism. Impaired autophagy has been shown in neurodegenerative diseases like Alzheimer's Disease (AD), where abnormal accumulation of proteins leads to neuronal failure. One of the proteins that accumulate in the form of senile plaques is Aβ, which has been traditionally considered of extracellular origin. A recent paper by the Nixon Lab in NYU Neuroscience Institute, New York, challenges the current ideas about the source of plaques in AD. They created a transgenic mice model that allows to monitor autophagy in vivo, and they crossed these mice with five different AD mouse models1. They showed that early deficiencies in lysosomal vATPase activity (that leads to poorly acidified lysosomes) are responsible for autophagy dysfunction. They identified a unique autophagic stress response in compromised neurons characterized by rapid proliferation of autophagocytic vesicles within perikarya and formation of large membrane blebs packed with Aβ/APP-βCTF containing vesicles. They named these Abeta-rich blebs "PANTHOS," after the Greek term for poisonous flower given their resemblance to blossoming flowers. Importantly, they showed that PANTHOS neurons subsequently degenerate to give rise to classical senile plaques and that PANTHOS-like structures were also present in the human brain. The results suggest that Aβ deposition and plaque formation are the consequence of an already highly neurodegenerative status rather than the cause.

New technical approaches such as the use of brain organoids may lead us closer to finding the right therapeutic target.

Could Kibra Be the Key to Alzheimer's?

Submitted by The Buck Institute

Despite recent excitement about new drugs for Alzheimer's disease, there are no truly effective treatments for the debilitating condition yet. The challenge to find targeted therapeutics drives Tara Tracy, Ph.D., Assistant Professor at the Buck Institute in Novato, to approach the problem in a new way.

Most current research looking for treatments on Alzheimer's disease has been focused on reducing the toxic proteins that build up in the brain as the disease progresses. Specifically, a protein called tau accumulates in the brain and becomes toxic to neurons in Alzheimer's disease. Tracy's team is taking a different approach.

"We think that synapse function can be repaired without actually fixing the problem," she said. The tau protein accumulation would remain, but synapses could return to functioning.

The basis of the new concept is that the synapses, which are involved in the transmission of information between neurons, deteriorate during the progression of Alzheimer's disease. Tracy's team has identified a protein located at synapses in the brain that is altered during this progression. The protein is called KIBRA, named because it is found in the kidney and the brain.

Her team found that there is a deficiency of KIBRA associated with toxic tau protein buildup in the brain in Alzheimer's disease. Studies by others have indicated that KIBRA is required for remodeling of synapses that happens during the formation of memories, and that lower levels are associated with dementia.

"We became interested in KIBRA because it is a protein that is specifically important for the mechanism at synapses that is critical for memory," Tracy said.

If there is less of KIBRA, this could be the root of cognitive impairment. Tracy's team is exploring how the protein affects signaling, and whether they could leverage an understanding of that mechanism to repair the synapse and bring memory function back.

So far, Tracy's lab has found that restoring KIBRA function in a mouse model of Alzheimer's disease restored memory in aged mice. They are now looking at human samples to understand how KIBRA levels affect memory during aging in humans.

These studies will provide insight into how to protect memory even when synapses are surrounded by age-related toxic proteins that typically contribute to memory loss. The obvious question arises: Can KIBRA simply be taken as a supplement or injection to provide this resiliency?

"In the most simplified terms, that is what we are trying to get at," Tracy said. "We are hoping to see if we can repair a synapse, and the remodeling that occurs during memory, by reintroducing KIBRA protein into neurons.

KIBRA protein also can be detected in the cerebrospinal fluid (CSF) of humans, and Tracy's team has shown that people with Alzheimer's disease have higher levels of KIBRA in their CSF. Using CSF levels to identify people with KIBRA loss in the brain could indicate those who would most likely benefit from restoration therapy.

"The cool thing about it is that this could be a biomarker of synaptic dysfunction associated with memory loss," she said.

Additionally, Tracy notes that the gene encoding KIBRA has a variant that is associated with risk for Alzheimer's disease and also with diminished memory performance in people without cognitive dysfunction.

"If someone has the 'bad genotype,' we wonder whether that genotype is actually linked to the KIBRA protein expressed in the neurons," she said. If it turns out to be true, it could be an additional indicator of risk for cognitive decline.

The obvious question arises: Can KIBRA simply be taken as a supplement or injection to provide this resiliency?

Tracy envisions a not-too-distant future in which treating a person with Alzheimer's or cognitive decline could be assessed for risk (due to genotype) and KIBRA status (by looking at levels in the CSF), to determine who would be a good candidate for a KIBRA therapeutic.

"Our current goal is to discover KIBRA-specific treatment strategies that will restore synapse function and cognition early enough in disease progression that we can really support healthy brain aging," she said. ■

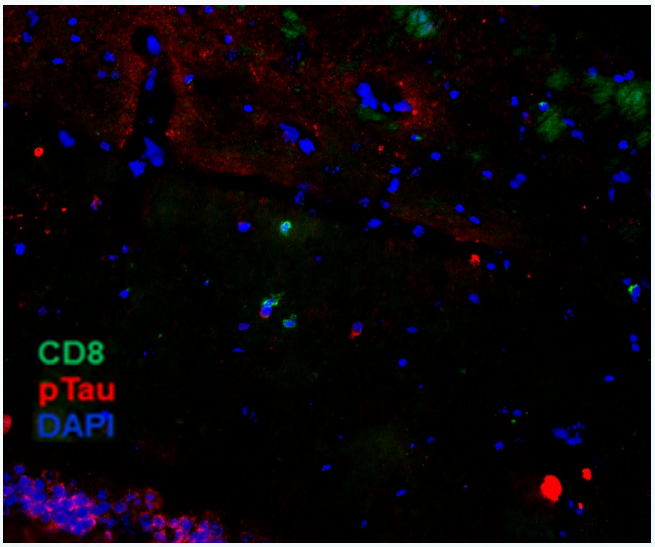
Is Alzheimer's an Autoimmune Disease? The Adaptive Immune System's Emerging Role

Submitted by TNeuroPharma

Alzheimer's disease (AD) is a devastating neurological disorder that affects millions of people around the world. Despite decades of research, the root cause of Alzheimer's disease is not fully understood.

For years, researchers focused on amyloid beta and misfolded tau protein in the brain as two alternative causes. This was logical, as these proteins are key constituents of the amyloid plaques and neurofibrillary tangles characteristic of Alzheimer's brains. It was only in the early 1990s, when patients with inherited forms of Alzheimer's were found to harbor mutations in genes affecting amyloid and not tau, that the debate was thought to be all but settled. However, formal demonstration that amyloid accumulation causes Alzheimer's remained elusive, as these mutant genes failed to reproduce defining features of Alzheimer's in animals. Adding to this uncertainty, many people were shown to harbor amyloid beta plaques in their brains without Alzheimer's dementia. Thus, accumulation of amyloid failed to pass two essential criteria for disease causation: disease reproduction in lab animals, and selective presence in diseased individuals.

A third essential criteria of causation is that blocking the factor prevents or alleviates the disease. Enter two amyloid-reducing Alzheimer's drugs that have recently been in the spotlight—Aduhelm and Leqembi. For Aduhelm, reduction of amyloid beta plaques was observed,



however evidence of disease reduction was deemed insufficient, and ongoing data collection was required by FDA to address this. Leqembi on the other hand slows cognitive decline in AD patients, but so far only incrementally. Many other drugs that effectively removed amyloid from brains repeatedly failed to show any significant effect on dementia or cognitive decline. Thus, the idea that amyloid is a central cause of all the features of Alzheimer's disease fails on two criteria outright and is at best weak on a third.

Studies have now shown that antigen-reactive memory CD8 T cells—the T cells that respond to cancer and mediate autoimmunity in the body—accumulate in the brain and blood of Alzheimer's patients.

This has prompted efforts to identify disease-promoting factors in Alzheimer's that occur before the accumulation of and amyloid beta and tau. In these efforts, genetic risks in Alzheimer's patients largely determine which factors are examined. While these genetic risk studies identified that the immune system may be involved in the pathology of Alzheimer's, the focus has primarily been on the innate immune system's role in promoting

inflammation in the brain. The adaptive immune system, which mediates responses to specific pathogens, cancer, and autoimmunity, has until recently received less attention.

One main reason is that it was long thought that the adaptive immune system didn't operate in the brain. This changed in 2015 when a research team discovered that the adaptive immune access route to the brain had been overlooked because it was hidden in a thin layer of tissue that's often discarded when studying the brain in the lab. This discovery renewed interest in one component of the adaptive immune system in particular: T cells, which may represent one of the earliest events in Alzheimer's development.

Studies have now shown that antigen-reactive memory CD8 T cells—the T cells that respond to cancer and mediate autoimmunity in the body—accumulate in the brain and blood of Alzheimer's patients. This accumulation correlates with tau accumulation and cognitive status, hinting of a more substantive role than previously appreciated. T-Neuro's focus is on defining the role of these T cells in Alzheimer's initiation and targeting these cells for diagnosing and treating Alzheimer's. For example, our T-Track diagnostic detects the T cells responsible for initiating the disease in the blood and represents a minimally invasive diagnostic that could detect the disease much earlier than diagnostics focused on amyloid beta and tau. Additionally, we are exploring therapeutic approaches that suppress the immune system and drugs that target the specific disease-causing T cells to slow or even prevent the progression of Alzheimer's disease.

The potential impact of this research is compelling, with the possibility of earlier detection and more effective treatments that could significantly improve the quality of life for millions of people worldwide. While there is still much to be learned and discovered, the idea of Alzheimer's as an autoimmune disease offers hope and renewed optimism for the future. We at T-Neuro are excited to be working at the forefront of this promising field of study. ■

A Promising Covalent Approach to Treat Alzheimer's Disease and CNS Disorders

Submitted by Kensaku Nakayama, Ph.D., CEO & Founder, JAL Therapeutics

JAL Therapeutics' highly inhibitory, hyperselective, covalent approach to butyrylcholinesterase (BChE) inhibition may become the new frontier for treating and preventing Alzheimer's disease, CNS disorders and other chronic conditions.

At first glance, the idea of using an irreversible organophosphorus compound (OPC) to bind to brain proteins in the treatment of Alzheimer's disease (AD) or other central nervous system (CNS) disorders seems implausible. However, Irvine, California-based JAL Therapeutics is taking this counterintuitive approach—and the current preclinical results show significant promise. In transgenic mouse models of AD, JAL's lead drug candidate, DB2ClPP, inhibits β-amyloid (Aβ) plaque formation with no obvious off-target effects.

Focusing on reducing later-stage Aβ plaque formation is not the company's primary intent. However, reduced plaque is a promising indicator showing that JAL's upstream approach to treating cholinergic dysfunction, or low levels of the chief neurotransmitter, acetylcholine (ACh)—could be a highly effective prophylactic treatment for AD. ACh plays a crucial role in learning, memory, and other cognitive functions. The neurotransmitter is often depleted in people with AD or CNS disorders.

JAL Therapeutics was founded in 2014 after studying the effect of plastics on brine shrimp butyrylcholinesterase (BChE) levels as a possible link to autism. JAL's founders, Dr. Kensaku Nakayama and Dr. Roger Acey, also discovered how OPCs can inhibit BChE

in their collaborative organic and biochemistry research conducted at California State University, Long Beach.

JAL's focus on BChE inhibition centers on the enzyme's role as a toxin fighter. BChE likely served as a safeguard for early humans, whose diets included poisonous berries and mushrooms. In the brain, BChE aids the hydrolysis, or breakdown, of ACh as a backup to the primary enzyme, acetylcholinesterase (AChE).

Interestingly, in Alzheimer's patients, there is a 55-fold increase in brain BChE, dominating AChE by 11:1, resulting in increased hydrolysis of ACh. The downstream effect of this imbalance includes decreased cognitive function and elevated production of amyloid precursor protein (APP), Aβ peptides (Aβ42 and Aβ40), Aβ plaques and tau tangles—all hallmarks of the pathogenesis of AD. Since elevated BChE is central to this process, JAL chose this enzyme as its main target as a potential treatment for AD.

DB2ClPP's potential to treat cholinergic dysfunction upstream compared to other drugs could result in both preventive and disease-modifying treatments not only for AD but also for other CNS indications, including multiple sclerosis and Parkinson's disease.

JAL's use of OPCs to create an irreversible, covalent bond to inhibit BChE turns the enzyme's strength, purpose, and momentum to attack toxins against itself. As a highly inhibitory and hyperselective small molecule, JAL's lead drug candidate, DB2ClPP, is designed to make a significant impact with a very small dose. Of course, using toxins as medicines is commonplace, with warfarin and Botox as key examples.

Although covalent drugs lost some favor years ago due to concern over being irreversible, developers of innovative cancer drugs are now seeing them as a huge benefit, with their pinpoint accuracy affecting their targets with high efficacy.

Does lowering BChE levels cause harm? People with BChE deficiency have no life risks. JAL's intent is not to eliminate BChE, but to reduce the enzyme to normal levels (starting around 4000 U/L), measured by a pseudocholinesterase (BChE) blood test. Levels above 7000 U/L begin to correlate with AD; type 2 diabetes mellitus; and other chronic diseases, such as CNS disorders.

Notably, these diseases all share a common bond—elevated BChE, which suppresses the cholinergic anti-inflammatory pathway. A BChE inhibitor, DB2ClPP is designed to promote healthy cholinergic activity.

Compared to other drugs previously developed, JAL's DB2ClPP has the most laser-focused ability to inhibit BChE, without affecting AChE. This is significant because AChE is needed for brain function. A reason why other drugs have encountered substantial off-target effects is that they also inhibit AChE.

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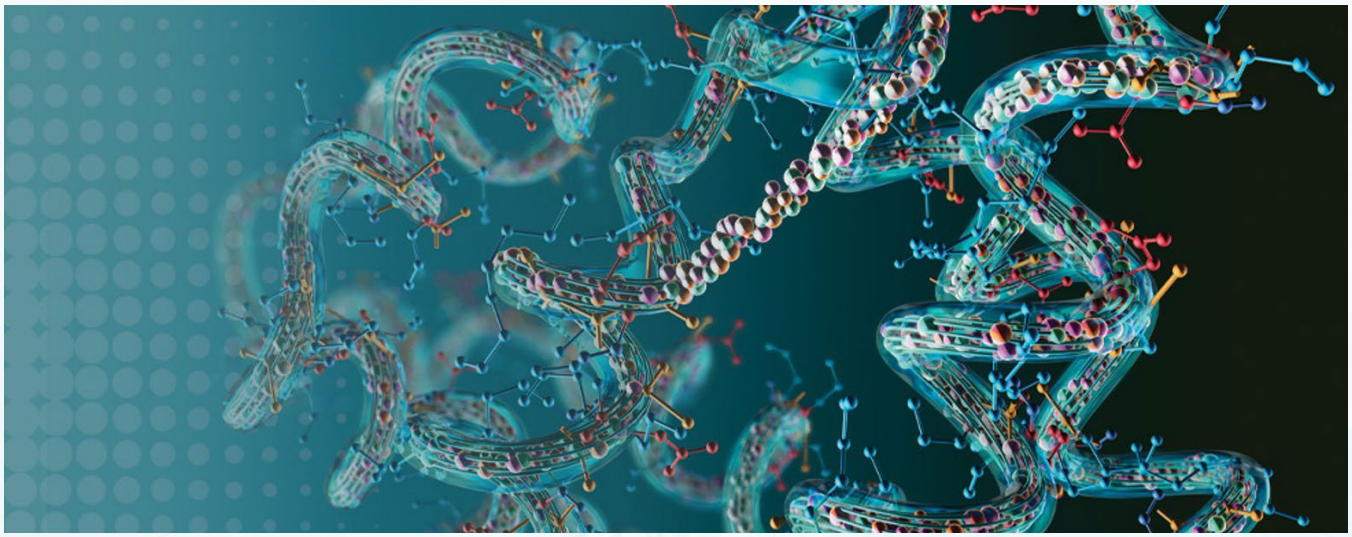
DB2ClPP's potential to treat cholinergic dysfunction upstream compared to other drugs could result in both preventive and disease-modifying treatments not only for AD but also for other CNS indications, including multiple sclerosis (MS) and Parkinson's disease.

JAL is currently focused on completing IND-enabling studies for its lead drug candidate, DB2ClPP, as a treatment for AD. A key step in this process is a pending application for an NIA/NIH grant to help fund preclinical pharmacology, toxicology, metabolism and manufacturing studies.

JAL Therapeutics is currently participating in the California Life Sciences FAST Advisory program's spring cohort and is planning for engagement with potential strategic equity and pharma licensing partners along the journey toward an IND application. ■

Putting a Stopper in (Cell) Death: How Computation Enabled Drug Discovery and AI are Tackling Neurodegenerative Disease

Submitted by ENMedia, an ENTENTE Network Company



It's been said that the advanced stage of neurodegenerative disease is a fate worse than death. But the human suffering, both for the person affected and their families and caretakers, is profound at every stage. Families and patients often say they feel a sense of powerlessness and frustration.

Researchers too have been frustrated by neurodegenerative diseases, making slow progress to understand and treat them over more than four decades. Fortunately, science is beginning to yield viable drugs that can address the fundamental pathophysiology leading to neuronal death. And significant advances in computational drug discovery, including AI, are speeding the quest for new therapeutics.

An exciting development in the treatment of neurodegenerative diseases is the recent conditional FDA approval of Amylyx's RELYVRIO™ for adults living with ALS, a progressive and fatal neurodegenerative disorder caused by motor neuron death. Shown to help slow the loss of physical function, it is believed RELYVRIO may work in part by attenuating neuronal apoptosis—self-destruction of brain cells.

Apoptosis occurs as a normal and controlled process, but it may be accelerated in neurodegenerative disease. Research in the labs of scientists like Loren Walensky, MD, Ph.D., Dana-Farber Cancer Institute, and Evripidis Gavathiotis, Ph.D., Albert Einstein College of Medicine, has brought new understanding to key proteins that regulate apoptosis and their roles in disease. BAKX Therapeutics, a company they founded together with CEO Sree Kant, may help to exploit this understanding for discovery of new therapeutics.

"Apoptosis is a form of cell death that is carefully controlled by a balancing act between two opposing classes of BCL-2 family proteins, pro-survival members like BCL-2 or MCL-1, and death effectors like BAX or BAK. When BAX/BAK are activated, they drive cell death. When blocked, the cell is preserved," Dr. Walensky said. "Proteins like BAX and BAK represent a critical pharmacologic control point. If you have a drug that activates them, you can treat diseases of pathologic cellular excess, like cancer. And if you have a drug that blocks them, you can treat diseases of unwanted cell death, like neurodegeneration."

But targeting BAX/BAK is not easy. Their interplay with other BCL-2 family proteins is tightly regulated, and their interactions are challenging to characterize using structural techniques like X-ray crystallography or NMR.

"One reason for this is that pro-apoptotic BAX has a highly dynamic structure—its shape changes in response to various stimuli," Dr. Gavathiotis said. "It's also cryptic, meaning the sites where a drug could bind to it are hidden. X-ray crystallography effectively takes a snapshot in time. But for a protein that continually morphs and hides its binding sites, a snapshot won't provide enough information for drug discovery."

That's where predictive techniques can help. BAKX uses a suite of computational approaches invented by physicist Yibing Shan during his tenure at D.E. Shaw Research, combined with vast cloud-based supercomputing capability and AI-based predictive approaches developed under Head of Computational Drug Discovery, Dazhi Tan, to predict and crack BAX's code.

The goal is to engineer novel drug candidates that activate BAX for cancer treatment or inhibit it for neurodegenerative disease.

"You can't visualize a conformationally dynamic protein like BAX the way scientists typically do to create new drugs," Kant said. "But BAKX's computational discovery capability—including advanced simulations and predictive AI—combined with structural approaches, allows us to decipher the binding sites on these proteins and design new drugs to latch onto them and in the case of a disease like ALS, keep them from destroying neurons."

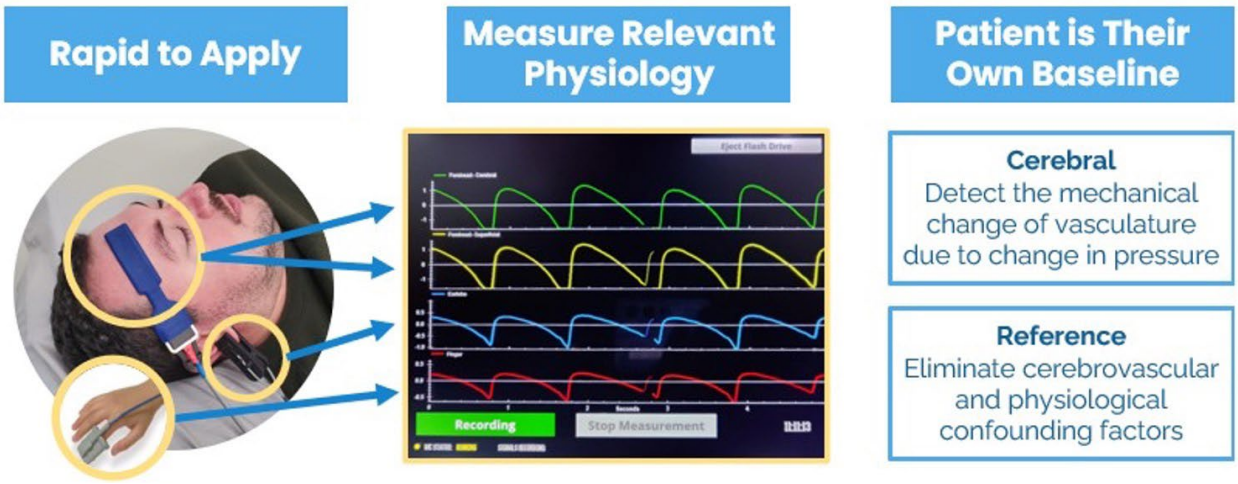
BAKX is currently working to design new drugs that specifically inhibit the BAX protein to keep it from inducing unwanted neuronal cell death. To date, its advanced computational modeling and AI techniques, together with medicinal chemistry, are pointing the way to novel drug-like compounds that could treat ALS and neurodegenerative diseases like Alzheimer's.

The goal is to engineer novel drug candidates that activate BAX for cancer treatment or inhibit it for neurodegenerative disease.

"Computational discovery is giving us a much better platform to drug structurally challenging proteins like BAX, which literally hold the key to cellular life and death," Kant said. "Traditional methods cannot achieve the power or speed needed to drug these challenging proteins. But well-designed approaches that combine cutting edge computational simulations, machine learning, and AI, along with experimental methods can."

Living Up to the "Holy Grail of Neurology" Pedestal

Submitted by CranioSense



The medical community has seen incredible and unbelievable advances in medicine over the past few decades, producing solutions to problems so complex we thought they lived only in our aspirations. By many accounts, the next frontier for medicine is the brain and how we interact with it from a medical perspective, a frontier that is already being explored, and to a measurable level, tamed, by the likes of innovators and disruptors the world over.

Though we still have much to learn in deployable neuroscience, we know that too much pressure on the brain, intracranial hypertension, is not a good thing. Unfortunately, our only means of assessing that pressure in conditions like traumatic brain injury (TBI), stroke, sepsis, and cardiac arrest is to place a pressure sensor directly in the patient's brain or spine. While this is effective, it is also highly invasive and is relegated to only those patients that need relief in pressure, as these external ventricular drains (EVD) double as a therapeutic. This leaves 99% of the population at risk of intracranial hypertension without effective monitoring. As a result, the neurological community often refers to non-invasive intracranial pressure monitoring as the "holy grail" of their practice; those are big words to live up to for a budding startup out of Boston promising to deliver just that.

CranioSense is on a mission to unlock the hidden parameters of brain health by enabling on demand neurological insight and treatment across the neurological care spectrum, and IPASS is the first product that CranioSense is bringing to market to realize

that mission, a noninvasive medical device for initial adjunctive diagnosis and continuous monitoring of intracranial hypertension.

In February, CranioSense, led by long time business partners Ryan Myers, PhD, CEO, and Kristian DiMatteo, COO, signed an exclusive license with Vivonics, Inc. for several issued and pending U.S. and international patents covering non-invasive intracranial pressure assessment. Leveraging this IP, CranioSense is developing a device that is easy to apply, accurate, unobtrusive to the patient, and capable of providing both rapid screening and continuous monitoring, the precise recipe needed to deploy across the entire neurological care spectrum, from pre-hospital to in-hospital to at home care.

The IPASS device consists of a reusable handheld electronic readout unit and a set of disposable sensors, placed on the forehead, ear, and finger. The true differentiation for the CranioSense's groundbreaking technology is in its ability to not only non-invasively look at the physiology of intracranial pressure changes, but to do so in a manner that removes the confounding physiological parameters, like blood pressure, arterial stiffness, and skin tone. By comparing the intracranial waveforms to the waveforms in other areas of the body, we can leverage patients as their own baselines. No other tool available or even under development can boast this, and it sets CranioSense apart in a big way.

Through various completed and ongoing clinical studies, CranioSense is well on the way to demonstrating this advantage is also accurate, a 'must' for clinical adoption. CranioSense has demonstrated that the physiological markers being monitored correlate to intracranial pressure, results that have been published in Intracranial Pressure and Neuromonitoring. They have also demonstrated that IPASS works within the hospital on TBI patients that have invasive pressure monitors placed, showing impressive diagnostic capabilities in a preliminary classification algorithm, which was presented at Neurocritical Care Society 2022 and will be submitted for publication later in 2023.

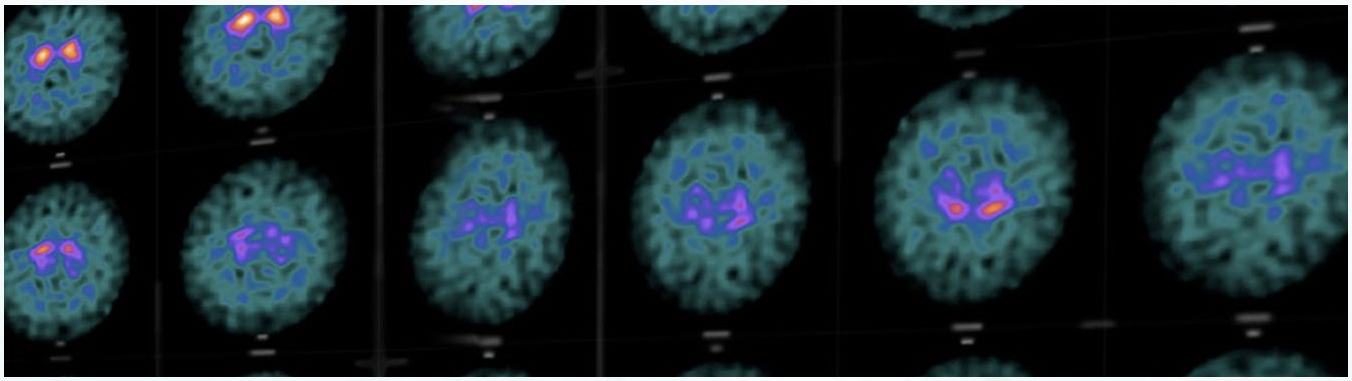
CranioSense is taking on the next frontier in healthcare discovery and is well positioned to disrupt the neurology space by providing early detection, early decision making, and leading to earlier intervention for intracranial hypertension.

By comparing the intracranial waveforms to the waveforms in other areas of the body, we can leverage patients as their own baselines. No other tool available or even under development can boast this, and it sets CranioSense apart in a big way.

"The 'holy grail' moniker is certainly something that we hear often and can seem intimidating on first blush," Myers said. "We choose to use it as a guiding star and a confirmation that we are heading in the right direction. Being a part of the MedTech community, our goal is to help as many patients, caregivers, and providers as we can. Developing something that others see as their 'holy grail' is not scary in my eyes; rather it is exciting, validating, and pushes us that much harder to get IPASS to those people as efficiently as possible."

How Advances in Brain-Imaging Technology and Analytics Will Transform the Way We Visualize, Diagnose, and Treat Neurodegenerative Diseases

Submitted by Peter Savas, Chairman & CEO, LikeMinds



If you have a personal or professional connection to degenerative brain diseases, you've probably seen some grim numbers about the direction we're headed:

- Current estimates show that 150 million people will have Alzheimer's disease by 2050, nearly triple today's number.
- Parkinson's disease cases doubled over the last 25 years, and deaths caused by Parkinson's increased 100% between 2000 and 2020.

Those are unsettling figures, but they aren't alarmist. They reflect what we'll face without breakthroughs in brain disease detection, diagnosis, visualization, and treatment.

Thankfully there are good reasons to expect breakthroughs, and sooner rather than later.

In particular, incredible advances in brain-imaging technology and analytics will revolutionize how doctors, patients, and their families will identify, understand, and respond to neurodegenerative disorders. For example:

- Duke University has developed a high-speed imaging system—Ultrafast Functional Photoacoustic Microscopy—that uses lasers and soundwaves to capture molecular-level changes in the brain in real time.
- Massachusetts General Hospital has created an AI model that analyzed more than 37,000 brain MRIs from over 10,000 patients and identified Alzheimer's disease with 90% accuracy.
- GE HealthCare, in partnership with LikeMinds, is developing Altropane, a brain-imaging tracer that will reduce brain-scanning procedure times for Parkinson's disease by several hours, to as little as 45 minutes.

Just as impressive as these new technologies is the impact they'll have and the sweeping changes they'll enable. In the months and years ahead, they'll reshape the experience and journey for patients dealing with degenerative brain diseases.

Today, patients can go years without receiving a definitive diagnosis. They suffer from symptoms they don't understand while contending with a lack of effective disease-modifying treatment options.

Cutting-edge brain imaging and imaging-data analytics will give doctors and patients the ability to visualize and assess how far Parkinson's has progressed and how it has responded to treatment.

Doctors will soon have the imaging information they need to characterize each patient's condition more accurately and develop patient-specific treatment plans. This will become even more important as pre-symptomatic brain-disease detection technology coupled with next-generation imaging make early intervention a possibility.

Just as patients want to see an x-ray of a broken bone or an image of a cancerous tumor, patients want to see what's happening in their brains. Having a clear picture of their situation will enable them to make better informed decisions about lifestyle changes and treatment options.

The coming improvements to the patient journey mean we're on the brink of being able to offer something that's in short supply for those dealing with brain diseases: hope.

Finally, and perhaps most importantly, the coming improvements to the patient journey mean we're on the brink of being able to offer something that's in short supply for those dealing with brain diseases: hope.

The collective mission of industry, academia, and non-profits is to transform the patient journey for those with neurodegenerative diseases and change the outcome of that journey. We are independently and jointly making remarkable headway.

Every step we take forward with brain-disease detection, visualization, diagnosis, and monitoring is moving us closer to better treatments, and eventually to prevention. My LikeMinds colleagues and I consider ourselves fortunate to be contributing to a next-generation brain-imaging platform that will help us take those steps.

Stopping Protein Misfolds Leads to ALS Diagnosis, Treatment Options

Submitted by Paul Alan Cox, Ph.D., Executive Director, Brain Chemistry Labs

In the shadow of the Tetons, Dr. Sandra Banack uses an immunoaffinity precipitation extraction on an ALS blood sample provided by the CDC. Dr. Rachael Dunlop sequences microRNA extracted from exosomes in the blood samples using a 384-well qPCR instrument.[1,2] At the not-for-profit Brain Chemistry Labs, they are continuing research that began in the jungles of Guam.

Dr.Sandra Banack, pioneer of microRNA ALS diagnostic

Dr. Rachael Dunlop sequencing microRNA from ALS patients at Brain Chemistry Labs, Jackson Hole.

In two remote villages there, 25% of adults died from a mysterious disease with symptoms of ALS, Parkinsonism, or Alzheimer's.[3] Together with Dr. Banack and Dr. Susan Murch, we discovered that the brain tissues of the villagers contained an unusual neurotoxin, BMAA, produced by cyanobacteria.[4,5,6] Together with Drs. Deborah Mash and David Davis, we succeeded in replicating the neuropathology of villagers in vervet monkeys, including misfolded proteins characteristic of Alzheimer's and ALS.[7,8] With Drs. Ken Rodgers and Dunlop, we found that L-serine stopped protein misfolding *in vitro*,[9] with vervets having AD and ALS neuropathology reduced up to 85%. In Ogimi village, Okinawa, where such diseases are unknown, Dr. James Metcalf and I found that the local diet gave villagers 4-5 times the amount of L-serine as in the North American diet.[10]

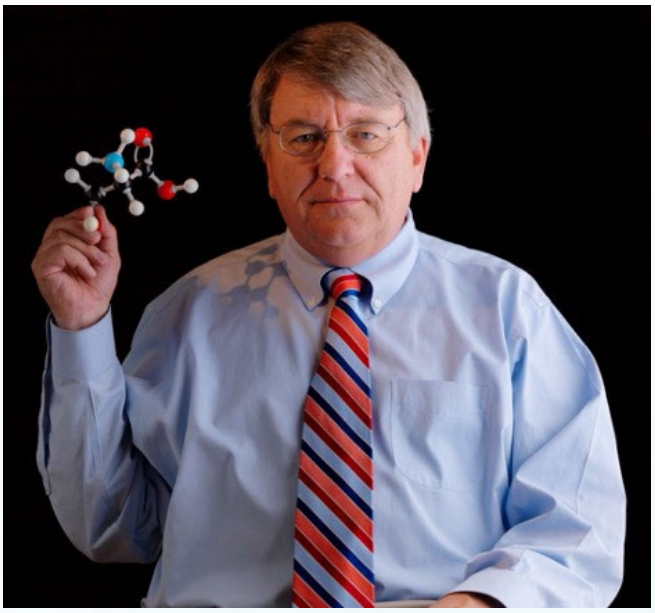
A Phase I clinical trial soon followed. Not only was L-serine found to be safe, but L-serine slowed functional decline in ALS patients.[11] Analysis of 28 ALS patients in a

"Stopping protein misfolding is a viable strategy for treating neurodegenerative illness."

subsequent adaptive Phase II trial confirms this finding. Our team also discovered a unique microRNA fingerprint for ALS.[2] We have now sequenced microRNA from 170 ALS samples and 170 controls.[1] This new diagnostic test offers rapid diagnosis and could assist in the discovery pipeline for new drugs.

Lead patent counsel Dr. John Wetherell in San Diego reports that the Brain Chemistry Labs has a remarkably extensive patent estate.

We are searching for a pharmaceutical partner to license our IP in the U.S., Japan, and Europe, and to conduct a Phase III trial. L-serine modulates the unfolded protein response,[12] so stopping protein misfolding is a viable strategy for ALS and other neurodegenerative diseases. ■



Dr. Paul Cox believes stopping protein misfolding is the key to treating neurodegenerative illness

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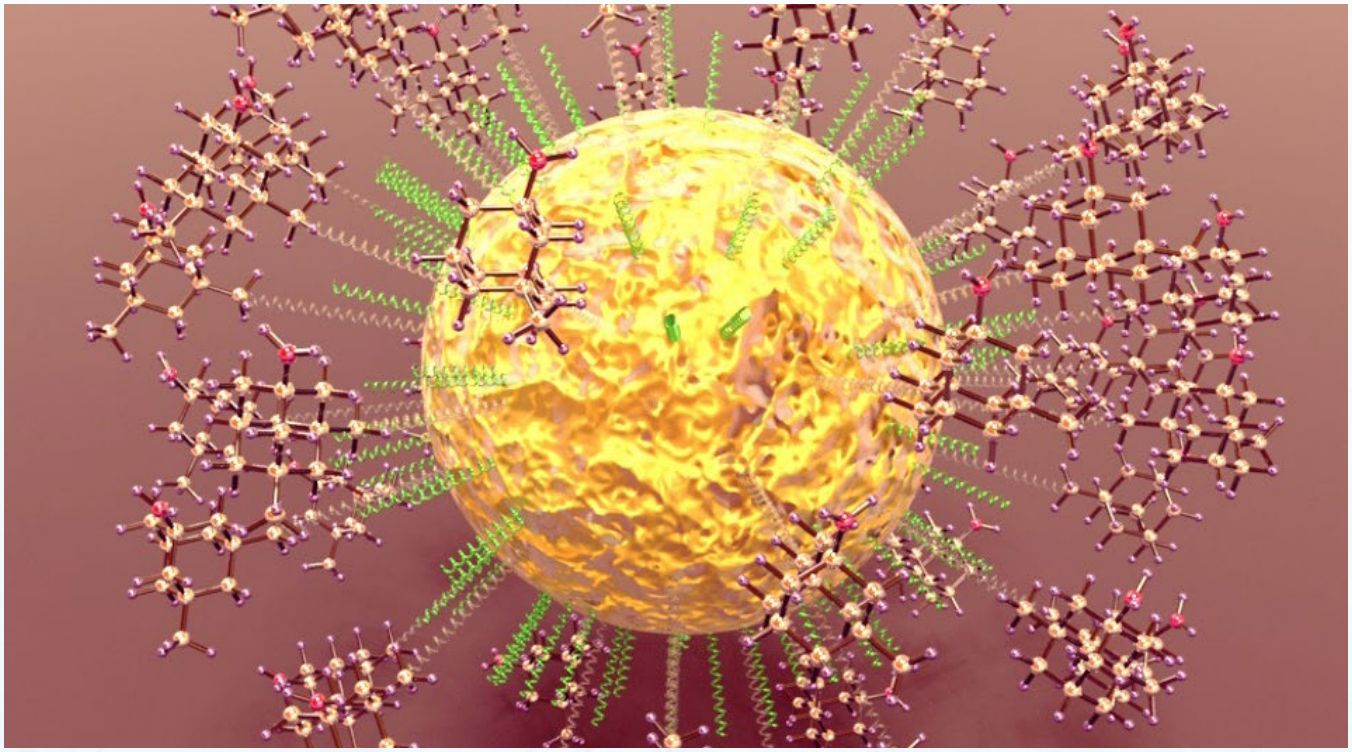
Protecting the Brain with Nanotechnology

Submitted by Elena Molokanova, Ph.D., CEO, NeurANO Bioscience



Neurodegenerative disorders destroy lives, place a heavy burden on caregivers, and lead to devastating socioeconomic impact on our entire society. Due to the incredible complexity of the human brain, neuroscience drug discovery is a challenging and slow process, so most neurodegenerative disorders are still missing effective therapies. Still, many companies, including many in California, are undeterred in their quest to change this unfortunate status quo.

The team at NeurANO Bioscience is one of these groups striving to address this problem. Our company name is portmanteau of **neuro** and **nano**, highlights our mission—the development of novel drugs for **neuro**degenerative disorders using **nano**technology.

While neurodegenerative disorders have very different etiologies, they all have one common feature—glutamatergic excitoxicity: as a disease progresses, neurons start dying, and their intracellular contents are spilled into the extracellular space. Among these contents is glutamate, the most common excitatory neurotransmitter in the brain. Extracellular glutamate can overactivate specialized glutamatergic NMDA receptors on the nearby neurons for extended periods of time causing excitotoxicity, neuronal death, and accelerated neurodegeneration. In addition, overactivated NMDA receptors can reinforce the original triggers of a disease, further worsening disease trajectory.

Under these circumstances, blocking NMDA receptors provides beneficial therapeutics effects. Memantine, a blocker of NMDA receptors (Namenda®, NamendaXR®, Namzaric®), was approved by the FDA for the treatment of moderate-to-severe Alzheimer's disease. However, meta-analysis of memantine effects shows that memantine is simply not sufficiently efficacious, as it produces modest, short-lived, and highly heterogeneous clinical response.

To design a better drug, we considered that memantine's insufficient effectiveness is due to the fact that NMDA receptors that are simultaneously responsible for both glutamatergic excitotoxicity and many physiological processes, including learning, memory, and general body management. Drugs that block overactivation of NMDA receptors will inevitably block synaptic NMDA receptors and may interrupt normal functioning of the brain. This conundrum greatly limits the therapeutic potential of any broad-action blocker of NDMA receptors. For example, memantine is now only used at low concentrations and at late stages of Alzheimer's disease when fewer synapses remain intact.

Our pioneering nanotherapeutics are nano-sized gold nanoparticles embedded with memantine molecules. These nanotherapeutics possess all the might of memantine but without its downsides.

We addressed this conundrum by rationally designing unique first-in-class nanotherapeutics cannot access the narrow synaptic cleft due to their specific dimensions. They therefore cannot block NMDA receptors inside synapses and do not interfere with normal brain functioning, but can block NMDA receptors overactivated by extracellularly spilled glutamate.

Our pioneering nanotherapeutics are nano-sized gold nanoparticles embedded with memantine molecules. These nanotherapeutics possess all the might of memantine but without its downsides. It means that, in contrast to memantine, NeurANO nanotherapeutics

can be used at high concentrations and at any disease stage to provide neuroprotection and slow or stop the disease progression. In certain cases, they have a potential to act as disease-modifying drugs by decreasing amyloid beta oligomers in Alzheimer's patients or aggregates of huntingtin proteins in Huntington's patients.

Over the past few years, the National Institutes of Health funded our drug discovery projects through the Small Business Innovation Research program, NeurANO received funding from the National Institute for Aging, and the National Institute of Neurodegenerative Disorders and Stroke supported preclinical studies using transgenic animal disease models of Alzheimer's disease and Huntington's disease.

The NeurANO team is working alongside the laboratory of Prof. Albert La Spada at the University of California – Irvine (UCI), director of the UCI Center for Neurotherapeutics. To ensure the next generation of neuroscientists have relevant neuroscience and drug discovery experience, we offer internship positions to UC students.

NeurANO Bioscience draws significant support from the local ecosystem. The first push was provided by the Female Founders Group organized by Sybille Hauser, executive director of Innovation Services at California Life Sciences (CLS), under the umbrella of the Mentors, Advisors and Peers Group from the Women In Bio organization.

Last year, NeurANO Bioscience was selected by CLS for the FAST Advisory program that provided customized coaching from industry experts. After graduation from FAST, we presented our programs at the BIO2022 International Convention, and were able to explore the partnering and directly engage with established pharmaceutical companies.

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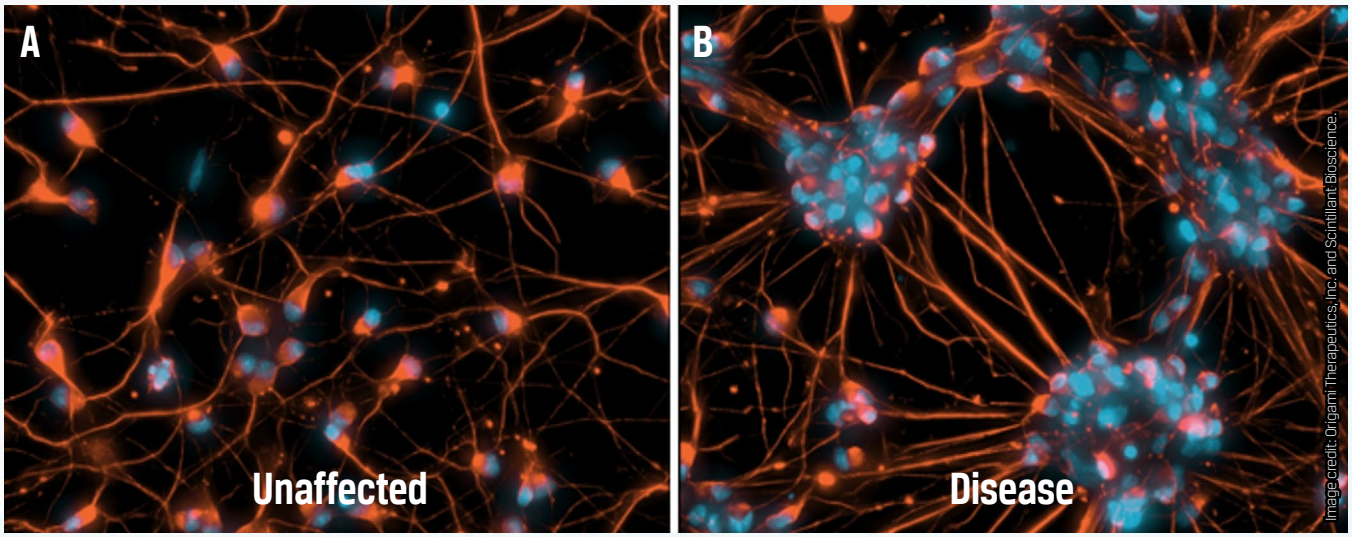
NeurANO Bioscience is strongly committed to helping patients suffering from neurodegenerative disorders. As common for companies working in the field of neurodegenerative disorders, NeurANO still has a very exciting, long, and treacherous path toward bringing our nanotherapeutics to clinic. Since our nanotherapeutics target a common feature of all neurodegenerative disorders and a clinically validated drug target, if successful, NeurANO might be able to develop therapeutic treatments for disorders other than Alzheimer's disease and Huntington's disease. ■

Developing Curative Medicines for Neurodegenerative Diseases

Submitted by Beth J. Hoffman, Ph.D., CEO, Origami Therapeutics



Medium spiny neurons after 12 days in culture have neurites (cytoplasm, orange) and cell bodies (nuclei, blue). ***A.*** *Unaffected neurons.* ***B.*** *HD neurons.*

Despite the recent approvals of Aduhelm and Leqembi for Alzheimer's disease (AD) as well as Relyvrio for ALS, there remains a huge unmet need for disease-modifying treatments of neurodegenerative diseases. At Origami, we're pursuing curative medicines for genetically defined neurodegenerative diseases using a novel approach carefully designed for CNS diseases. In this article, we describe our approach to this historically difficult disease area and why we believe this approach has an excellent likelihood of success.

Many neurodegenerative diseases are caused by protein misfolding, as indicated by the presence of protein aggregates, resulting in toxic gain-of-function. This suggests that eliminating the causative toxic misfolded protein should be efficacious. Focusing on monogenic forms of neurodegeneration enables us to (1) target the specific protein that causes disease and (2) select the right patient population, significantly mitigating the two key areas of risk typically associated with drug failures. Huntington's disease (HD) is the ideal proof point for our drug discovery approach. Here, we use our lead effort to illustrate the success of this approach.

Finding the Right Hits Via Phenotypic Screen

The goal is to selectively eliminate the toxic protein, sparing the normal, non-disease-causing form of the protein to restore normal balanced physiology. However, misfolded proteins are often considered undruggable since they typically do not have a known substrate binding site. Consequently, the common

approaches have been to target the protein aggregates for elimination or select a target within one of the degradation pathways. Given that there are > 2700 different genes involved in protein degradation, it's difficult to know whether modulation of a particular target will be tolerated or whether there are redundancies that make modulation of the target ineffective in the context of a cell or organism.

The alternative is an unbiased approach, using a phenotypic screen to detect all possible degradation mechanisms in human cells by screening for the effect you want to see in patients—namely reduction of the toxic protein. In designing the compound screen, several parameters must be considered: cell type, readout, induction of phenotype in a time-frame compatible with high throughput screening (HTS), and selection of compound library. Set up correctly, this screen should enable the cell to identify which compounds will work without overt toxicity. Origami chose to use primary fibroblasts, a compound library maximized for chemical diversity and a readout of mutant huntingtin (mHTT) aggregation as a monitor of protein misfolding.

Prioritizing Hits Based on Activity in Patient-Derived In Vitro Models

Once the Origami mHTT screen was completed, hits were confirmed and limited hit expansion with a closely related set of analogues was performed. We prioritized the numerous chemotypes based on a high-level assessment of the apparent mechanism of action. By asking simple binary questions, confirmed hits were categorized. For instance, does the compound prevent aggregation by reducing the amount of mHTT protein? If yes, does this occur through reducing mRNA expression? If no, is the mHTT protein lowering through degradation and which pathway?

The key to the prioritization is the use of human patient cells such as fibroblasts, peripheral blood mononuclear cells (PBMCs) and iPSC-induced neurons. Efficacy readouts in cells from individuals with HD increases the likelihood of translation to the clinic and enables biomarker discovery. We found that HD fibroblasts exhibit a deficit in autophagy and saw multiple differences in phenotypes between wildtype and HD medium spiny neurons. We screened our top chemotypes on these cells for activity in reversing the HD phenotypes using cell imaging, biochemistry, transcriptomics, and proteomics.

We found that HD fibroblasts exhibit a deficit in autophagy and saw multiple differences in phenotypes between wildtype and HD medium spiny neurons.

Early Demonstration of In Vivo Proof of Mechanism in Brain

The next step in prioritization of chemotypes was to identify those that were brain penetrant prior to proof of mechanism in vivo. We focused on four chemotypes based on their robust and reproducible effect in lowering mHTT in multiple cell models. All four chemotypes were brain penetrant, and one demonstrated significant reduction of mHTT in the brain after two weeks of intraperitoneal dosing with no change in weight or general appearance.

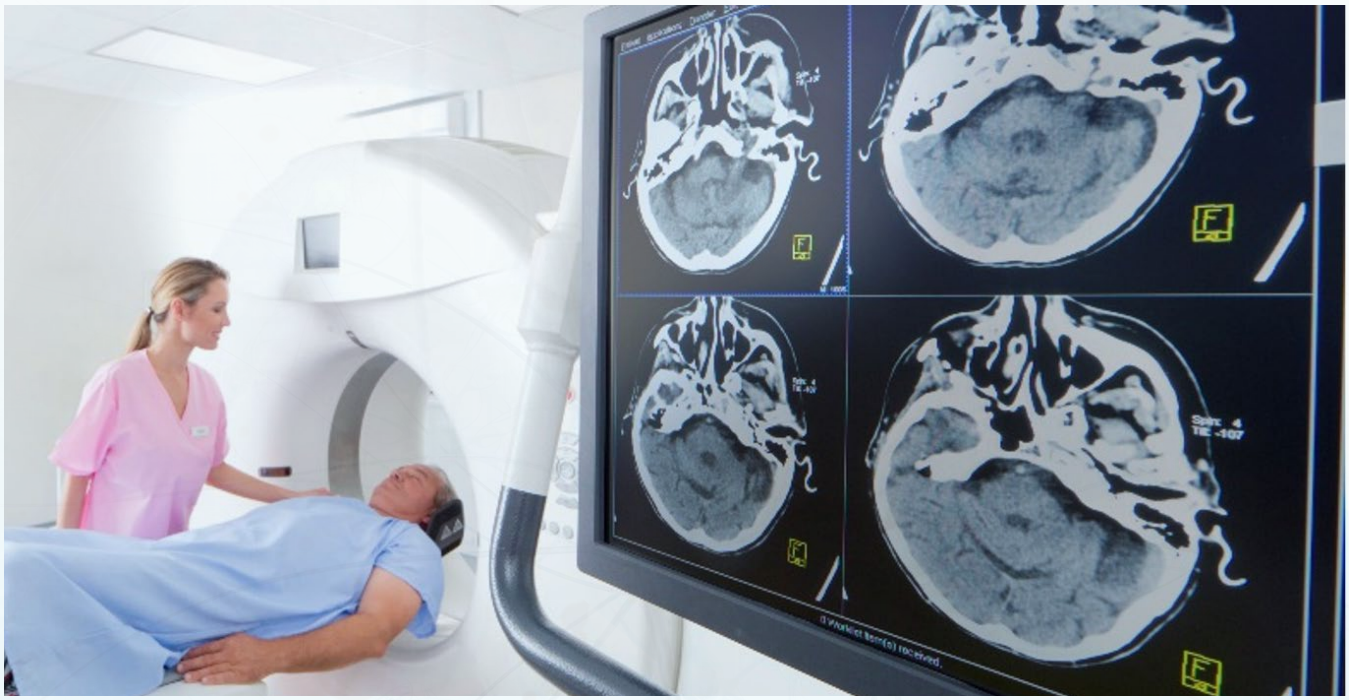
Rapid De-risking and Advancement to Lead Optimization

Further characterization demonstrated selective reduction of mHTT while sparing normal HTT. We measure the reduction of mHTT, the desired effect in patients, to drive optimization and as a pharmacodynamic readout both in lead optimization and in the clinic.

The phenotypic screen enabled the rapid identification of multiple chemotypes with excellent cell permeability, emerging structure-activity relationship, chemical tractability, excellent tissue distribution including brain penetration and in vivo activity after two weeks of dosing, all with limited chemical optimization. Targeting the root cause of disease is applicable to multiple neurodegenerative diseases and promises to provide rapid advancement to the clinic with the prospects of slowing or halting disease progression.

Targeting Misfolded Proteins to Combat Degenerative Diseases

Submitted by Sandra Reynoso, Ph.D., MBA, Co-Founder, ParaMag Biosciences



ParaMag Biosciences is a startup company from the Biochemistry and Molecular Medicine Department at the University of California, Davis School of Medicine.

ParaMag Biosciences' technology is based on years of research by Dr. John Voss at the University of California, Davis, focusing on a "spin label" chemistry platform. Paramag Biosciences has engineered a series of proprietary spin labeled naturally occurring antioxidants that selectively bind to misfolded proteins and prevent neurotoxicity.

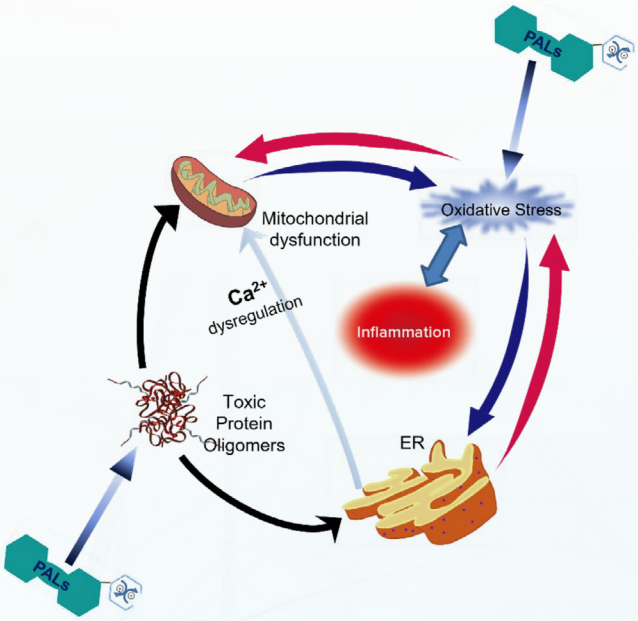
Protein misfolding diseases present challenges due to complex etiology and difficulties in characterizing protein targets that lack a defined structure. Misfolded proteins aggregate and adopt toxic conformations that induce a cascade of oxidative stress, inflammation, and ultimately cell death leading to numerous serious diseases. Protein misfolding is involved in more than 50 medical disorders, including several neurodegenerative and skeletal muscle diseases such as Parkinson's disease (PD), Alzheimer's disease (AD) and Amyotrophic Lateral Sclerosis (ALS). Novel approaches that selectively attenuate oxidative stress and inflammation in diseased tissue have the potential to provide benefit to millions of patients which currently have few or no beneficial treatment options. To date, one drug has been commercialized targeting a protein misfolding disease. Several new candidates are currently in clinical trials.

ParaMag Biosciences has built a broad drug discovery proprietary platform that targets these toxic oligomers which are directly responsible for neuronal death

and neurodegeneration. ParaMag's unique approach allows for the design and synthesis of small molecules which contain an organic paramagnetic moiety that changes the conformation of the toxic oligomer and combats oxidative stress in a highly potent, catalytic manner. These molecules have been termed paramagnetic amyloid ligands (PALs) as they are not only neuroprotective but also able to be visualized in the brain with Magnetic Resonance Imaging (MRI). PALs have a high-affinity binding to misfolded proteins and induce a thermo-dynamic change in conformation. They alter the structure of targeted misfolded proteins, rendering them less toxic. The unique "cyclic nitroxide spin label" gives PAL compounds their potent antioxidative capacity.

Due to their stable unpaired electron, PALs can provide in vivo data on tissue distribution and target engagement. PALs have a unique paramagnetic chemical feature which gives the ability to trace their distribution in vivo using MRI providing not only the potential for imaging but also a means to confirm target engagement and, potentially, measure therapeutic efficacy. This offers an advantage since MRI is lower cost relative to PET imaging and no radioactivity exposure. MRI can be used not only in early clinical development to provide opportunity to asses target engagement, but also repetitively to assess efficacy and disease progression in future clinical trials.

ParaMag's lead program targets alpha-synuclein (α-Syn), the misfolded protein associated with PD. Paramag's approach employs biophysical methods, including CD and EPR spectroscopy, to assay for toxic oligomers on a mechanistic basis. PAL binding of oligomeric α-Syn shows a reduction in α-Syn fibril formation. PALs have also been shown to attenuate α-Syn cytotoxicity in a dose-responsive manner at nanomolar concentrations in cultured human neuronal cell line SH-SY5Y stably transfected with the human α-Syn gene. Use of a transgenic C. elegans α-Syn model also shows PALs have in vivo activity. Collectively, PALs dual mechanism of action detoxifying protein aggregation and reducing oxidative stress offer a competetive advantage in the potential treatment and diagnosis of misfolded protein diseases. ParaMag is currently in conversation with a large pharmaceutical company to further study PALs in PD animal disease models.



Novel approaches that selectively attenuate oxidative stress and inflammation in diseased tissue have the potential to provide benefit to millions of patients which currently have few or no beneficial treatment options.

The next issue of Life Sciences Insights will be published Summer 2023. For advertising and content submission guidelines, please contact Alex Burch at **aburch@califesciences.org**

About California Life Sciences (CLS)

California Life Sciences (CLS) is the state's most influential and impactful life sciences membership organization, advocating for the sector and its diverse innovation pipeline. For more than 30 years, CLS has served the community by supporting companies of all sizes, from early-stage innovators and startups to established industry leaders in the fields of biotechnology, pharmaceuticals, and medical technology. As integral components of a healthy and collaborative ecosystem, CLS also works closely with universities, academic and research institutions, the investment community, and other critical partners that promote this vibrant sector. With offices in South San Francisco, San Diego, Sacramento, Los Angeles, and Washington DC, CLS works to shape public policy, improve access to breakthrough technologies, educate lawmakers, and advance equity within our ecosystem by championing innovative solutions for some of the most pressing challenges of our times. In doing so, CLS fulfills its mission to protect and nurture California's life sciences industry, empowering discoveries that lead to healthier lives around the world. Visit CLS at www.califesciences.org, and follow us on Twitter @CALifeSciences, Facebook, LinkedIn and YouTube.

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