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Releasing the Handbrake on Endogenous Repair – An Alternative Approach to Treating Alzheimer's Disease?

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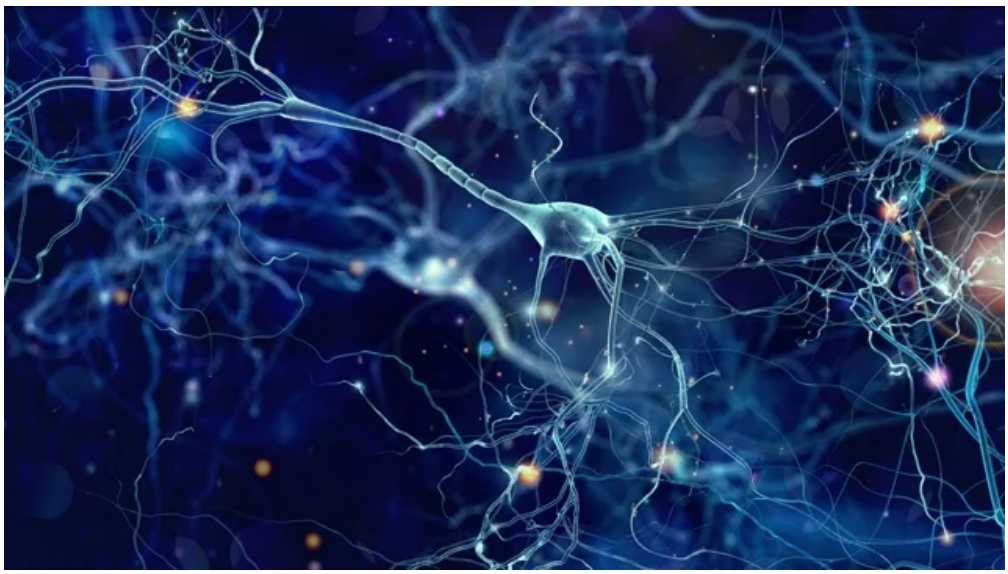

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Over the last 15 years there has been a distinct failure in the development of effective treatments for Alzheimer's disease (AD). As the incidence of AD continues to rise, the medical community and pharmaceutical industry are now exploring novel technologies that target molecular pathways outside of the amyloid-β hypothesis.

One example is the regenerative medicine company NervGen (https://www.nervgen.com/), who recently announced it was advancing its therapeutic technology platform, currently in development for spinal cord injury and multiple sclerosis, to create new treatments for AD.

The technology platform, NVG-291, targets sites of inflammatory damage and removes inhibition of a protein implicated in endogenous repair.

Technology Networks recently spoke with Paul Brennan, President and CEO at NervGen Pharma, to gain his insights on why previous attempts to treat AD have failed, how NVG-291 works and what promise it holds for AD.

Molly Campbell (MC): AD research and development efforts have failed to produce new effective treatments over the last 15 years. In your opinion, what factors have contributed to this failure

Paul Brennan (PB): In my view, there are two key factors that have contributed to the recent failures in AD. The first is that, even today, no one really knows the cause of AD. It's very difficult to develop a new treatment for a disease when you can't specifically target its cause. For example, for several years now it's been known that AD is accompanied by the presence of amyloid-β plaques. But whether or not the plaques are a cause of AD, a symptom of AD, or a combination of both remains unknown.

In the past 15 years both the research community and big pharma have focused a significant amount of their resources on the amyloid-β hypothesis, believing that amyloid plaques are a major cause of AD. This has led to decades of funding directed towards this hypothesis, with very little in the way of positive results. This leads to a second factor. AD is a very slow-developing disease. The formation of amyloid-β plaques occurs 10-15 years before a patient develops symptoms. So, although the amyloid-β hypothesis could be correct, it might be that the trials are starting too late in the progression of the disease to have an effect.

MC: Can you tell us about NervGen's NVG-291 technology platform? How does it unlock the nervous system's ability to repair itself?

PB: NVG-291's platform technology was developed in the laboratory of neuroscientist Dr. Jerry Silver, a world-renowned spinal cord injury and regenerative medicine researcher and Professor of Neurosciences at Case Western Reserve University in Cleveland, Ohio. Dr. Silver's research focused on the glial scar, which forms at the site of a nerve injury to begin the healing process and protect the nervous system.

Dr. Silver's research demonstrated that the glial scar also impedes nerve function as the chondroitin sulfate proteoglycan (CSPG) protein within the glial scar binds and inhibits the damaged nerves from regenerating, repairing or re-growing.Dr. Silver, together with scientists at Harvard University, then identified protein tyrosine phosphatase sigma (PTPσ) as a key neural receptor that binds with the CSPG protein in the scar. The binding of PTPσ to CSPG is the main reason why nerve regeneration was not occurring through regions of scarring.

Because CSPGs naturally occur so widely throughout the body, our technology's mechanisms of action have effects across a broad expanse of traumatic injury, as well as neurodegenerative diseases.

Scar formation is a wound isolation process that takes place throughout the body, including in the nervous system. After injury, whether it be traumatic (as in the case of spinal cord injury), or autoimmune (as in multiple sclerosis), or of unknown etiology (as in Alzheimer's disease), there is an increase in the quantity of CSPGs within the forming scar. These molecules act as a potent barrier which protects the wound and creates a wall to constrain inflammation and isolate the lesion from the remaining healthy tissue. Unfortunately, these barrier molecules are also highly inhibitory to nerve regrowth and nerve repair.

PTPσ is also upregulated after injury to damaged nerve fibres (and other central nervous system (CNS) cell types such as oligodendrocyte progenitor cells and microglia. This receptor recognizes the CSPGs within the scar and binds to these upregulated proteoglycans. The interaction between the receptor and the scar (i.e. PTPσ and CSPG) forms a very strong, synaptic-like bond, effectively trapping the nerves permanently within the scar.

NervGen's compound, NVG-291, binds preferentially to the PTPσ receptor and inhibits receptor activation, releasing the trapped axons and stopping new axons from being trapped in the scar. This allows regrowth in formerly highly inhibited areas. The CSPG-PTPσ interaction also initiates a complex biological cascade which has multiple negative effects in neurodegenerative diseases. NervGen's drug "switches off" the above negative inhibitory effects of the PTPσ signaling, allowing the normal reparative mechanisms to begin the healing process.

MC: NervGen's platform has been shown to activate repair mechanisms, including regeneration, plasticity, and remyelination in a variety of animal models. How reliable are these animal models? What challenges lie in translating these findings to human studies?

PB: Multiple studies with animal models for several diseases and medical conditions have shown that treatment targeting PTPσ receptors with a compound developed by Dr. Silver and his research team, known as intracellular sigma peptide, or ISP, promoted regeneration of damaged nerves and improvement in function.

There are several factors that suggest the results from animal studies will translate to humans. Both CSPGs and PTPσ are highly conserved molecules across mammalian species. We know that PTPσ is a master regulator of axonal growth and seems to control CSPG-based inhibition.We know that humans with mutations in PTPσ have odd axonal pathfinding deficits in development, suggesting this protein's

function is the same in humans and rodents. We also know that human and rodent cells are susceptible to growth inhibition from CSPGs. Our drug, which we call NVG-291 and which is very closely related to ISP binds to mouse and human PTPσ, which then increases regrowth in the presence of CSPG. We also visualized anatomical changes in mouse nerves when treated with NVG-291 *in vivo* (in heart, peripheral nerve, stroke, multiple sclerosis, and spinal cord models).

RM: By what mechanism will NVG-291 exert its effect in AD?

PB: There are several mechanisms in which NVG-291 could exert its effect in AD: axonal sprouting, regeneration, and remyelination as previously discussed can all potentially affect plasticity and thus potentially help the nondamaged sections of the brain regain function that has been lost in AD patients.

However, there are some additional benefits of NVG-291 that may be particularly helpful in AD. Microglia, as the resident macrophage cells, act as the first and main form of active immune defense in the CNS. Microglia express the receptor PTPσ in abundance. The interaction of microglia with CSPGs shifts the microglia to an inflammatory phase which causes them to continually release inflammatory cytokines and reactive oxygen species which lead to nerve cell death. This inflammatory cascade then causes more CSPGs to form (from reactive astrocytes) and the vicious cycle continues. NervGen's NVG-291 shifts the microglia to the housekeeping or phagocytic phase, reducing inflammation **and** allowing them to digest senile plaques.

NVG-291 also decreases the production of amyloid-β plaques by blocking PTPσ signalling, which affects the affinity of a secretase to cleave amyloid precursor protein. This is the precursor step in the production of amyloid plaques. What is exciting about NVG-291 in AD is that there are multiple mechanisms by which it might be beneficial; this is very much a unique characteristic of our approach.

RM: Do you think NVG-291 has the potential to reverse the cognitive effects of AD, or just slow them down?

PB: The extent of the recovery will be dependent on the state of the disease and the rate of the progression of the disease. We believe that NervGen's drug may be able to improve synaptogenesis through the multiple mechanisms described above and, therefore, delay or slow the progression of cognitive impairment. If NVG-291 is able to slow the progression of cognitive impairment it will be a huge win for patients, as currently there is nothing that achieves this effect. It is theoretically possible that the mechanism could also reverse the disease effects, but there is much more work that needs to be performed before we can confidently predict whether or not this is possible.

Paul Brennan, CEO, President & CEO of NervGen Pharma, was speaking to Ruairi Mackenzie and Molly Campbell, Science Writers, Technology Networks.