In this interview, we spoke to Jerry Silver, co-inventor and Scientific Advisor, Ernest Wong, President and CEO, and Bill Radvak, co-founder and Executive Chairman, NervGen Pharma (BC, USA) to learn more about their history, technology and journey to commercialization.

Please introduce yourself and your institution.
Jerry Silver (JS): I received my PhD from Case Western Reserve in 1974 and did post-doctoral work at Harvard University in the Department of Neurosciences at The Children’s Hospital and in the Neuropathology Department at Harvard Medical School. I am currently Professor in the Department of Neurosciences at the Case Western Reserve University School of Medicine.

What are the challenges in attempting to regenerate nerves?

JS: There are two major challenges in regenerating nerves within the central nervous system (CNS). The first is a reduction in the intrinsic growth machinery that occurs within nerves once synaptic connections form and nerve cells mature. Thus, when nerves are severed in the adult spinal cord, the ability to form a rapidly advancing growth cone, the motile apparatus that nerve cells use to elongate, is greatly diminished compared to embryonic neurons.

However, there do exist some subtypes of neurons that maintain a more robust growth motor after injury even in the adult nervous system and these respond especially well to our peptide strategy. Furthermore, there is a phenomenon called neuronal sprouting that can occur in essentially all neurons. This is a process that allows axons that remain after injury to collateralize, albeit very slowly over relatively short distances, in order to reoccupy synaptic territory vacated by the nerve fibers that had been severed by the lesion. This sprouting phenomenon is also highly responsive to our peptide strategy and is stimulated to proceed faster than normal.

"There are two major challenges in regenerating nerves within the central nervous system" (Jerry Silver)

The second major barrier is the secretion of inhibitory extracellular matrix molecules called chondroitin sulphate proteoglycans. In the spinal cord, and elsewhere, there are two important locations where these inhibitory molecules upregulate after injury. They appear in abundance within the vicinity of the lesion in the forming and mature glial scar, and they also increase within the perineuronal net, a cocoon-like ensheathment that normally surrounds many types of synaptic boutons in the mature nervous system.
net is important in stabilizing synapses in the CNS but it also impedes the sprouting phenomenon.

Our peptide strategy helps nerves to overcome both of these barriers since the intracellular sigma peptide (ISP) blocks the major receptor that neurons employ to entrap themselves within the scar and net. Thus, the ultimate strategy to promote regeneration would be to use a combination of approaches that both enhance the intrinsic growth motor while eliminating/overcoming extrinsic barriers.

**What are the advantages and challenges in developing and manufacturing a peptide-based therapeutic?**

Ernest Wong (EW): Peptide therapeutics have played a notable role in medical practice since the advent of insulin therapy in the 1920s. Since then, many peptides have been successfully developed across multiple disease areas and approved as drugs. Around 70 peptides have been approved in the United States, Europe and Japan. 155 peptides are in active clinical development of which half are currently in phase II studies.

Examples of approved peptides include Carfilzomib, developed by Amgen Inc. (CA, USA), which was approved in 2012 for cancer treatment, Plecanatide, developed by Synergy Pharmaceuticals (NY, USA), which was approved in 2017 for chronic idiopathic constipation, and Abaloparatide, which was approved in 2018 for osteoporosis and was developed by Radius Health, Inc. (MA, USA).

"...the future of regenerative medicine looks very bright" (Jerry Silver)

The utilization of peptides as therapeutics has evolved over time and continues to evolve with changes in drug development and treatment paradigms. With the emergence of sequence elucidation and chemical synthesis of peptides in the 1950s, potential drugs based on peptides became easier to identify and manufacture using standard synthetic chemical techniques. The genomic era allowed for the identification and molecular characterization of receptors enabling scientists to pursue novel and selective peptidic ligands for these receptors.
Peptidic drugs can easily be fine-tuned to match the peptide sequences within the binding sites of these receptors. Peptide drug candidates are being generated against a range of molecular targets that reach beyond historically dominant extracellular receptors. Peptides have been shown to disrupt protein-protein interactions, target receptor tyrosine kinases and inhibit intracellular targets better than the alternatives. Unlike small molecule drugs, where issues such as CYP inhibition can lead to drug-drug interactions and side effects caused by off target binding, these problems are less of an issue for peptides.

There are general disadvantages to peptidic drugs, such as short plasma half-life and an inability to be administered orally. The relatively short half-life compared to other drugs would suggest that they may not be suitable in cases where sustained maximum inhibition of a target is required. However, novel synthetic strategies have allowed for the modulation of pharmacokinetic properties and target specificity of peptides through amino acid or backbone modification, incorporation of non-natural amino acids, and conjugation of moieties that extend half-life or improve solubility. Novel formulation strategies allow for reduced injection frequency and improve stability and other positive physical properties.

How did NervGen Pharma come to be founded?

Bill Radvak (BR): Some years back, Harold Punnett, a friend of mine, and his family suffered a tragic event; Codi, his daughter-in-law and mother to his grandchildren, fell into a construction hole and sustained serious spinal cord damage.

Following the event, although Harold quickly found there were no therapeutics available to promote nerve regeneration, he did come across a promising technology invented Dr Silver. Harold reached out to me to support the development of Dr Silver’s research and we created NervGen with the singular mission to commercialize this incredible technology.

You recently completed a $10 million initial public offering. What are you hoping to achieve with this funding?
BR: We expect to make significant advancements in the development and commercialization of our NVG-201 compound. As far as the development of the compound itself, we will complete pre-clinical animal studies, file an investigational new drug application (IND) to FDA and manufacture NVG-291 in ever increasing batches.

Clinically, we will be contracting contract research organizations (CRO) in the coming months to assist with the submission of our IND with FDA towards the end of 2019 and initiation of our first human clinical trial. With that timetable, we expect to start setting up clinical trial sites in the fourth quarter of 2019 so we can initiate a Phase I human safety study on healthy volunteer patients in early 2020.

What are the challenges in securing funding for a regenerative medicine company?

BR: So far, we have had absolutely no challenges financing our regenerative medicine company as we are endeavouring to create a solution for an unmet need. Dr Silver’s reputation of leading neuroscience research brings a tremendous amount of credibility and the technology he created has a very clear and straightforward mechanism of action that is supported by excellent reproducible data generated by numerous independent studies.

There is also the market opportunity to be the first to treat nerve damage, including spinal cord injuries and peripheral nerve injuries. As there are no drugs approved to regenerate nerves, we are confident there is a significant opportunity to have a dramatic impact on a patient’s quality of life and the high cost burden to the healthcare system. Finally, there is the future opportunities as we continue researching secondary applications such as multiple sclerosis, acute myocardial infarction, stroke and other neurodegenerative diseases where multiple research organizations have already independently shown success with our compound.

"...we created NervGen with the singular mission to commercialize this incredible technology" (Bill Radvak)
As is always the case, we will be requiring more and more resources to advance the program to phase II development. We are fully confident in our abilities to fund this program going forward based on a solid proposition of excellent science, great independent data, a solid experienced team advancing the technology and the development of NVG-291 towards clinical trials and a strong finance team working with an excellent capital structure.

What do you think the future holds for regenerative medicine?

JS: In my opinion, the future of regenerative medicine looks very bright. Now that we have finally identified some of the major intrinsic and extrinsic barriers to regeneration, this has opened a door to developing targeted strategies that can optimize the remarkable regeneration potential that exists even in the adult nervous system. A recent publication from my lab, which shows rapid and robust recovery of breathing and forearm function even after a near lifetime of paralysis from a severe cervical spinal cord injury, is evidence for my optimism.
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