Transplanting Specialised Neurons

Cory R Nicholas, PhD, Co-Founder and CEO of Neurona Therapeutics, talks to *Pharmafile* about the world of neurological disorders and transplantation

***Pharmafile:* Can you explain the role neurons play in the central nervous system, and how transplantation of specialised neurons can help treat neurological disorders?**

Cory R Nicholas: The central nervous system, which includes the brain and spinal cord, primarily consists of two types of cells; neurons, or nerve cells, and glia. In simple terms, glia are considered to be 'support' cells providing a variety of specialised functions such as facilitating neuronal activity, supporting synapses, or connections, and providing immune protection. Neurons are the basic working units of the brain, the wiring, and serve to send information to other neurons, muscles, organs, and glands in the body.

Neurons send messages via action potentials, which are brief electrical events that cause the release of chemicals called neurotransmitters into the gap between cells, or the synapse. The action potential and consequent transmitter release allow the neuron to communicate with other cells. There are several types of neurons serving a variety of purposes. They can be classified by their location, shape, connectivity, firing properties, gene expression patterns, and neurotransmitter secretion. Generally, neurons can connect to other cells that are far away (projection neurons), or they can connect to other cells that are in their local environment (interneurons). Neurons can also be excitatory or inhibitory in nature. Excitatory neurons primarily secrete the neurotransmitter glutamate and include many types of motor and sensory neurons. Inhibitory neurons primarily secrete the neurotransmitter gamma-aminobutyric acid (GABA). Glutamate excites other cells, while GABA inhibits them.

There are many disorders of the nervous system that are severe, chronic, and refractory to current drug treatment. For several disorders, a specific cell type in the nervous system is no longer functioning properly or has degenerated.

Examples include the degeneration of GABAergic neurons in epilepsy, dopamine neurons in Parkinson's disease, medium spiny neurons in Huntington's disease, and motor neurons in amyotrophic lateral sclerosis (ALS), and the demyelination, or loss of insulation, in multiple sclerosis. Because most neurons do not effectively regenerate in the adult brain, these diseases are irreversible. Current drugs can, in some cases, provide symptomatic relief for a period of time, however they do not stop disease progression.

Thus, the development of regenerative cell therapies to replace affected cell types has the potential to be significantly disease modifying. Regenerative cell technologies have advanced whereby specific cell types can now be manufactured in cultures from human stem cell lines with unprecedentedly high purity, quantity, consistency, and fidelity to neural cells in the body that they are intended to replace. The manufactured cell therapy products are then delivered by precise stereotactic transplantation into the affected regions of the nervous system so that the grafted neural cells can integrate and persist for the lifetime of a patient. In this way, regenerative cell therapies may provide a more targeted, longer lasting effect from a single dose than could be achieved with a traditional drug.

Can you walk us through the technology involved in the process of neuron identification and transplantation?

Neurona Therapeutics is developing a novel inhibitory cell therapy product comprised of human GABAergic (gamma-Aminobutyric acid) interneurons for the treatment of certain types of chronic epilepsies, neuropathic pain syndromes, and potentially other neurodegenerative and psychiatric indications. In these patient populations, there is a loss of inhibitory tone in specific regions of the nervous system accompanied by dysfunction and degeneration of GABAergic interneurons that can drive disease progression. Consequently, the neural networks in these affected regions become hyperexcitable.

Neurona's first product candidate, NRTX-1001, contains human inhibitory interneurons for one-time direct administration into the seizure onset zones in people living with chronic drug-resistant focal epilepsies. The NRTX-1001 interneurons integrate on-target, replace missing GABA, persist long-term, rebalance neural activity, and provide seizure freedom. In a preclinical animal model of chronic drug-resistant focal seizures (>20 seizures per hour prior to treatment), 70% of cell-treated animals became durably seizure-free, versus 5% in the placebo group.

How are stem cells used in the work you do?

Because adult stem cell progenitors do not exist for most human neuronal lineages, Neurona utilizes human pluripotent stem cell lines to manufacture its product candidates. Pluripotent stem cells have the potential to be infinitely expanded and can be coaxed to develop into virtually any cell type in the body. The expansion is relatively straightforward. The coaxing is more difficult. The stem cells need to be differentiated into highly pure neural cell types that can be consistently manufactured under current good manufacturing practice (cGMP) guidelines for intended clinical use. Neurona has successfully harnessed its stem cell lines. Using a proprietary manufacturing process, the stem cells are differentiated in a stage-wise manner to recapitulate the developmental steps an inhibitory interneuron would normally take in the developing brain. At the end of the process, the neurons are cryopreserved for future administration. With safety being paramount, the NRTX-1001 product candidate contains fully differentiated human interneurons and does not contain residual stem cells.

What disorders are most pertinent in the industry?

Epilepsy is the fourth most common neurological disorder, affecting approximately 3 million people in the United States. One third of people living with epilepsy are resistant to traditional drugs. As the population ages there is an increased need for effective therapies to treat Alzheimer's and Parkinson's diseases. Effective non-opioid therapies are lacking for chronic neuropathic pain as well.

How has COVID-19 impacted the work you do?

While we have experienced the usual issues that any company has faced in how to keep our employees safe and well during the pandemic, Neurona's operations have not been impacted particularly by COVID-19 and we have had a year of great progress as we advance our first programme into the clinic. We are preparing to file our first investigational new drug (IND) this year and had completed the majority of our studies prior to the pandemic lockdown. We have since been principally engaged in completing IND-enabling studies, progressing our other programmes, and focusing on the report-writing process.

What challenges does the neurological industry currently face?

The key challenges include:

- Understanding the mechanisms of disease
- Identification and validation of relevant therapeutic targets
- Ability to intervene early in disease
- Availability of predictive animal models
- Availability of relevant biomarkers for patient stratification and as endpoints for clinical trials

What do you predict for the field in the future?

We expect that the coming decade will bring forth multiple regenerative cell therapies that provide breakthrough, targeted disease modification, where traditional small molecule drugs of the past had failed.

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Prior to Neurona, Dr Nicholas was a faculty member in the Department of Neurology at the University of California, San Francisco (UCSF), where his research focused on determining the origin of human cortical interneurons and pioneering methods to derive interneuron precursors from human pluripotent stem cells for transplantation for the potential treatment of neurological disease. He maintains an adjunct faculty appointment at UCSF. He received his Bachelor's degree from the University of California, Berkeley, and his PhD from Stanford University.