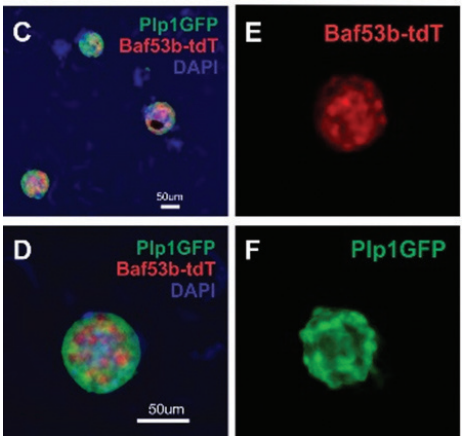

Figure 1: Mouse-derived enteric neurospheres contain neural progenitors, glia cells (PLP1-GFP), and mature neurons (Baf53b-tdT).

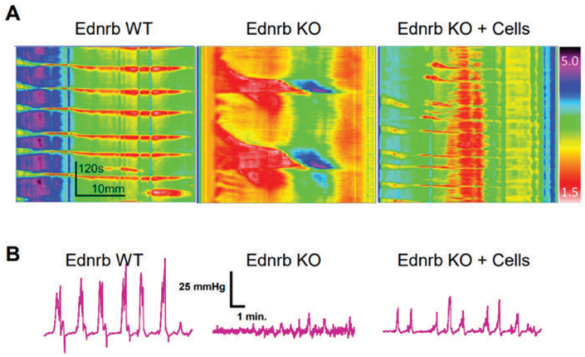

Figure 2: (A) Spatiotemporal mapping of gut contractility shows normal contractions in wild-type mice (left), absent contractions in Ednrb-deficient mice (middle), and improved contractility following cell therapy (right). (B) Luminal pressure recordings show similar findings.

Novel Neural Cell Therapy for Hirschsprung Disease and Related Enteric Nervous System Disorders

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The enteric nervous system (ENS) is the network of neurons and glia throughout the gastrointestinal tract that controls all major functions of the gut, including its motility. As a result, abnormalities of the ENS lead to serious neurointestinal disorders, including esophageal achalasia, gastroparesis, and Hirschsprung disease (HSCR) to name a few. Despite the morbidity associated with these conditions, current treatments target symptom control and are not curative. Our laboratory is developing an autologous neural cell-based therapy as a novel treatment for these disorders.

HSCR is a congenital disorder in which the enteric nervous system fails to develop in the distal end of the gastrointestinal tract, leaving it aganglionic and therefore functionally obstructed. The disease affects 1 in 5,000 newborns and causes severe obstruction in the neonatal period. Current treatment involves major abdominal surgery during infancy to remove the aganglionic segment. While surgery is life-saving, at least 50% of patients experience life-long complications, including fecal incontinence and obstructive symptoms. Regenerative neural cell therapy offers an alternative approach that would restore innervation to the gut and avoid major surgery and its complications.

Our laboratory has developed methods for isolating neural stem cells from the intestinal tract and the subcutaneous adipose tissue of rodents and humans. These cells are expanded as free-floating neurospheres in cultures supplemented with growth factors (Fig. 1). When these neurospheres are transplanted into the aganglionic colon of mice with HSCR, they engraft, migrate, differentiate, and establish neuromuscular connections. Using optogenetics, electrical field stimulation, spatiotemporal mapping, and luminal pressure recordings, we have shown that the transplanted cells restore colonic motor function (Fig. 2).

The preclinical studies are largely completed, and manufacturing work is underway. IND filing is anticipated in the near future, followed soon after by a first-in-human trial. Neural stem cell therapy represents a transformative approach to treating HSCR, and one that can be expanded into other indications, including enteric neuropathies more broadly and traumatic injuries of the peripheral nervous system, increasing the market opportunity and the number of patients that can benefit.