Trainee breaks new ground in enteric nervous system research



outh Australian General Surgery Trainee and PhD candidate Dr David Smolilo has discovered a new colonic circuit involving sensory neurons and excitatory motor neurons that until now has been inferred but never described.

With financial support provided via the RACS Foundation for Surgery WG Norman Research Scholarship, Dr Smolilo used immunohistochemistry and high definition confocal microscopy to identify and trace the circuit which is believed to form the basis of the polarised reflex in the colon

Working on the guinea-pig colon, he found the circuit within the enteric nervous system (ENS) by showing that the sensory neurons of the colon have specialised processes which form basket-like structures around other neurons.

Since his discovery, further work has been performed which confirms and expands his findings while worldfirst trials of several human samples have already shown promising results.

Dr Smolilo said any advances made in the understanding of the ENS could help lead to

treatments for common gastrointestinal disorders such as postoperative ileus, slow transit constipation and chronic bowel obstruction.

He said that despite the importance of the ENS to proper gut function, the neural and mechanical factors that control digestion remained poorly understood.

"The ENS works mostly independently of our central nervous system and is arguably the most primitive part of the nervous system in charge of the digestive tract that evolved ahead of the actual brain," he said.

"The sensory neurons of the gut - also known as the intrinsic primary afferent neurons (IPANS) - make this organ unique because they respond to physical and chemical stimuli and relay this signal directly to the ENS rather than to the brain or the spinal cord.

"They are thought to be the first neurons in reflex pathways of the gut and drive neuronal circuits to initiate a response to the stimulus being 'sensed'."

Dr Smolilo said his research identified how the sensory neurons within the colon activated other neurons by creating basket-like structures to transmit signals.

He said the structures, known as calbindin baskets, were formed from a high concentration of neuronal varicosities and likely directed synaptic output from the sensory neurons.

"The target neurons were determined to be excitatory motor neurons and excitatory interneurons, essentially forming a direct reflex arc triggered by the sensory neuron and resulting in smooth muscle contraction on the oral side of the stimulus," Dr Smolilo said.

"This circuit likely underlies the polarised reflex described in the gut over a hundred years ago and named 'the law of the intestine'.

"This discovery is very exciting because if we understand how the sensory neurons are wired to drive the ENS circuits to make the gut contract normally, we could help in the development of targeted therapeutic interventions to regulate this circuitry and help people with motility related disorders.'

A paper describing Dr Smolilo's discovery has already been published and featured on the front cover of the Journal of Comparative Neurology with his findings described as providing a significant contribution to the field.

He is conducting his research at the Visceral Neurophysiology Laboratory at Flinders University under the supervision of Laboratory Director, Professor Nick Spencer, Colorectal Surgeon Professor David Wattchow and scientist Professor Marcello Costa.

Dr Smolilo was born in Poland and lived in South Africa and Botswana before arriving in Australia in 2001 and later becoming an Australian citizen. He is currently a part-time general surgery registrar at the Flinders Medical Centre in Adelaide.

Dr Smolilo said the importance of the ENS for normal human gut function was exemplified by Hirschsprung's disease, where a segment of the colon is congenitally deficient in enteric neurons, which can lead to babies suffering functional large bowel obstruction from birth.

He said that while a great deal of research had been done on the ENS in recent decades, there were still gaps in understanding how the different neurons interacted with each other, particularly in the large intestine.

"Our understanding of the ENS is a bit like an orchestra in that we know a great deal about individual instruments and how they work but we still don't entirely understand how they all work together to create beautiful music."

"Neurons within the ENS may be classified functionally as sensory neurons, interneurons or motor neurons yet many more distinct neuronal populations have been identified



"Already, the current classification of neurons in the guinea-pig colon reveals up to 17 distinct groups.

"Yet, while we know a lot about the different types of neurons in the ENS we are only starting to make inroads into the exciting area of functional studies, where neuronal circuits described using anatomical methods are linked to specific gut functions.

"Once we have a better understanding of how these neurons communicate then we'll be able to develop a better understanding of disease processes and hopefully develop pharmacological agents to address and counteract them."

ACADEMIC HIGHLIGHTS

- 2018: Flinders Medical Centre, Clinicians' Special Purpose Fund PhD Scholarship
- 2018: Publication of research in Journal of Comparative Neurology titled 'Morphological evidence for novel enteric neuronal circuitry in guinea pig distal colon'.
- 2017: RACS Foundation for Surgery WG Norman Research Scholarship
- 2010: Flinders University Staff Prize for Surgery Finalist

Dr Smolilo thanked RACS and its Fellows for the support offered him through the scholarship.

He said he has greatly enjoying the opportunity to conduct scientific research which he said would allow him a greater understanding of underlying biological processes affecting patients with gastrointestinal diseases.

"I find this work exhilarating in that we are making unique discoveries and adding to the corpus of medical knowledge for the good of humanity," he said.

"It's painstaking work but we have had a couple of Eureka moments when we've switched to a new antibody and the neurons have lit up showing circuits that have never been seen before."

Dr Smolilo joins a cohort of young surgeons who have contributed significantly to research in the pioneering of Neurogastroenterology at the School of Medicine at Flinders University over the last four decades, many of whom are currently practicing colorectal surgeons.

The WG Norman Research Scholarship arose from a bequest to the Foundation for Surgery from the late Dr William Gowan Norman. Thanks to Dr Norman's generosity and forsight this scholarship will continue to fund advances in surgery in South Australia.

> With Karen Murphy Surgical News journalist