Stem cell treatment for Achalasia?

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Career path

2005 - BSc. Biomedical Science
(Queens University of Belfast)

2010 - Ph.D.
(University of Nevada, Reno, USA)
“Transplantation of Interstitial cells of Cajal in the gut.”

2011 - 2017
Research Associate
(UCL Great Ormond Street Institute of Child Health)
“Gut development and enteric stem cell therapy”

2017 - present
Principal Investigator
Guts UK Research Fellow
(UCL Great Ormond Street Institute of Child Health)
“Stem cell therapy for upper GI disorders”
Outline

• What is Achalasia and what are the possible causes?
• How does the gut work?
• Can stem cells transplantation rescue gut disease?
• Discuss implications and future strategy of stem cell transplantation for Achalasia
What is Achalasia?

Achalasia

/ˌakəˈleɪzɪə/ (noun, medicine)

noun: achalasia

A condition in which the muscles of the lower part of the oesophagus fail to relax, preventing food from passing into the stomach.
Possible causes of Achalasia?

Novel mechanism for impaired nitrergic relaxation in achalasia
G E Boeckxstaens

Lower Esophageal Sphincter Is Achalasic in nNOS$^{-/-}$ and Hypotensive in W/W' Mutant Mice
DIGAVALLI V. SIVARAO, HIROSHI L. MASHIMO, HEMANT S. THATTE, and RAJ K. GOYAL
Center for Swallowing and Motility Disorders, Department of Veterans Affairs Medical Center, West Roxbury, and Harvard Medical School, Boston, Massachusetts

OESOPHAGUS
Serum from achalasia patients alters neurochemical coding in the myenteric plexus and nitric oxide mediated motor response in normal human fundus

Journal of Gastroenterology and Hepatology / Volume 29, Issue 10
Gastroenterology Full Access
Murine genetic deficiency of neuronal nitric oxide synthase (nNOS$^{-/-}$) and interstitial cells of Cajal (W/W$^+$): Implications for achalasia?

Pediatrics International / Volume 44, Issue 2
Full Access
Attenuated nitrergic inhibitory neurotransmission to interstitial cells of Cajal in the lower esophageal sphincter with esophageal achalasia in children
Yoshio Watanabe, Hisami Ando, Takahiko Sato, Shinsuke Katsuno, Yuji Marui, Yasuyuki Ono, Shigeno Tonhachi

Initial insult (Viral?)
Myenteric Plexus Inflammation
Inhibitory Neuron Destruction
Achalasia
Genetic Susceptibility
Anti-myenteric Autoantibodies
Relaxatory Nerves (nNOS)
How does the gut work?

Cells in the gut wall

Furness; Nature Reviews 2012
How does the gut work?
Gut Nervous System
How does the gut work? Peristalsis and Motility

Contraction (Acetycholine+ nerves)

Relaxation (nNOS+ nerves)
nNOS neurons and gut disease

Research Question

Is it possible to replace lost nerve cells?

Human gut nervous system stem cells from gut mucosal biopsies

Metzger et al., 2009
Practical steps required for stem cell transplantation

1. Harvesting of cells
2. Enrichment or selection of stem cells
3. Collection and preparation of cells
4. Transplantation
5. Propagation/directed differentiation
6. Culture
7. Manipulation/Gene therapy

Source 'stem' cells from healthy donors and patients
Can stem cells transplantation rescue gut disease?

Donor Mouse Gut Nervous System

Gut Nervous System

Nerve cells

Gut stem cells

All other cells

TRANSPLANTATION TO DISEASED MOUSE
Identification of transplanted ENSC within the nNOS^{−/−} mouse distal colon

McCann et al, 2017
Development of nNOS$^+$ nerves after transplantation

McCann et al, 2017
Stem cell transplantation rescues transit time and motility

• This study provided the first evidence that stem cell transplantation can rescue gastrointestinal function within a disease model

McCann et al, 2017
ENSC Transplantation to treat upper GI disease

Gut stem cells

Nerve cells

All other cells

TRANSPLANTATION TO STOMACH AND OESOPHAGUS

ENSC transplant to nNOS⁻⁻ Antrum

McCann unpublished data
Conclusions

• Research has shown that stem cell transplantation can rescue gut function.

✓ Such a stem cell therapy may allow for the development of targeted therapies for other diseases including Achalasia.

✓ Transplantation studies to oesophagus are currently underway.
Future strategy towards a stem cell therapy for Achalasia
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