### POST-VIRAL GASTROINTESTINAL DISRUPTION & DYSFUNCTION

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#### Disclosures

There are currently no FDA approved therapeutics in this clinical space.

These recommendations are based on clinical expertise of post-infectious disorders.

### **KEY CONCEPTS**

The nervous, immune, & endocrine systems play integral roles in maintaining physiological homeostasis.

Within tissues\* neurons, immune & endocrine cells are in close physical proximity.

\*Consider the implications of connective tissue disorders

There is bidirectional communication between neurons, immune & endocrine cells.

#### POST-VIRAL GASTROINTESTINAL SYMPTOMS

Nausea, headache, cognitive changes, rhinorrhea, oral tingling | burning, dry mouth

Dysphagia, belching, abdominal pain, abdominal bloating, early satiety, constipation, straining with defecation, diarrhea

Adverse reactions to food, flushing, urticaria, rash

THESE SYMPTOMS ARE DRIVEN BY DISTURBANCES IN THE NEUROIMMUNE AXIS

Defining the neuroimmune axis

#### NEUROANATOMY OF THE GASTROINTESTINAL TRACT



### NEUROANATOMY OF THE ENTERIC NERVOUS SYSTEM



THE ENTERIC NERVOUS SYSTEM IS A PART OF THE AUTONOMIC NERVOUS SYSTEM

DOI: 10.1038\NRGASTRO.2012.32

### FUNCTIONS OF THE GASTROINTESTINAL TRACT



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Nature reviews immunology, 2014, 14:667-685.

### THE GASTROINTESTINAL TRACT – LARGEST INTERFACE OF THE NERVOUS, IMMUNE, & ENDOCRINE SYSTEMS



#### THE CRITICAL GASTROINTESTINAL INTERFACE



### The neuroimmune axis in action

A few examples.

### NEUROIMMUNE CROSSTALK – REGULATING GASTROINTESTINAL MOTILITY AND CELL SURVIVAL



CSF1 - COLONY STIMULATING FACTOR 1

BMP2 – BONE MORPHOGENIC PROTEIN 2

### NEUROIMMUNE CROSSTALK – CRITICAL FOR ENTERIC NEURON SURVIVAL DURING INFECTION



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B<sub>2</sub>AR – B<sub>2</sub> ADRENERGIC RECEPTOR

### NEUROIMMUNE CROSSTALK – MAST CELL DEGRANULATION IS NOT JUST AN IGE MEDIATED PROCESS



Our gut microbiota is communicating with our nervous, immune, & enteroendocrine systems.

#### MICROBIOTA-NEUROIMMUNE AXIS – MICROBIAL COMMUNICATION







Substances secreted by microbes enter the blood stream and travel to the CNS. Microbes activate enteroendocrine cells (neuropods) which synapse with the ENS and ANS which in turn communicate with the CNS. Microbes activate enteroendocrine cells which then release hormones that have local and distant effects. Microbes influence immune cell function and inflammation affecting the functions of the ENS, ANS, and CNS.

DOI: 10.1126/science.368.6491.570

# Neuroimmune axis disorders – A systems biology way of thinking about complex conditions.

Will help us accelerate research and clinical care.

Requires next generation tools for diagnosis.

## Making the diagnosis requires leading edge diagnostic tools.

Specialist referral is required.

#### NEXT GENERATION - MOTILITY TESTING



SmartPill wireless motility capsule

#### DIAGNOSE REGIONAL & WHOLE GUT MOTILITY DISORDERS

### NEXT GENERATION BIOPSY TECHNIQUES – FULL THICKNESS BIOPSIES





SAMPLES THE ENTIRE THICKNESS OF THE GASTROINTESTINAL TRACT WALL DOI: 10.4253/wjge.v12.i6.193

### TISSUE LEVEL ENTERIC NERVOUS SYSTEM MAPPING | EVALUATION



#### DIAGNOSE GASTROINTESTINAL NEUROPATHIES

DIAGNOSE DEEP TISSUE LEVEL IMMUNE DISORDERS

DOI: 10.1053/j.gastro.2020.02.035.

#### TISSUE LEVEL IMMUNE PROFILING





PROVIDES VALUABLE INFORMATION FOR SELECTION OF THERAPEUTIC AGENTS

#### DIAGNOSING NEUROIMMUNE DISORDERS

CONTROLS

#### CASES





#### Mast cells

Malagelada et al. (2018) Neurogastroenterol Motil 30(3). doi: 10.1111/nmo.13219.

Emerging diagnostic tools – Diagnosing non-IgE mediated allergies.



### "IRRITABLE BOWEL SYNDROME"



Impacts 15-20% of the global population.



50% contemplate suicide. This is not a benign condition.



Functional gastrointestinal disorders are disorders of the neuroimmune axis.

### DIAGNOSING NON-IGE MEDIATED ALLERGIES

#### **BEFORE ALLERGEN EXPOSURE**

#### AFTER ALLERGEN EXPOSURE



#### CLE – CONFOCAL LASER ENDOMICROSCOPY

DOI: 10.1053/j.gastro.2019.03.046. DOI: 10.1053/j.gastro.2014.07.046.

#### Many Patients With Irritable Bowel Syndrome Have Atypical Food Allergies Not Associated With Immunoglobulin E



Annette Fritscher-Ravens,<sup>1</sup> Theresa Pflaum,<sup>1</sup> Marie Mösinger,<sup>1</sup> Zino Ruchay,<sup>1</sup> Christoph Röcken,<sup>2</sup> Peter J. Milla,<sup>3</sup> Melda Das,<sup>1</sup> Martina Böttner,<sup>4</sup> Thilo Wedel,<sup>4</sup> and Detlef Schuppan<sup>5,6</sup>

#### 70% tested positive for a non-IgE mediated allergy

- Allows for detection of specific antigen
- Allows for a truly prescriptive diet

#### Detects alterations in mucosal barrier

• Currently missed by routine histology (H&E)

#### Detects eosinophil activation

- May also detect mast cell activation
- Mast cells are likely involved in both IgE and non-IgE mediated allergies

50% of patients with IBS may have a non-IgE mediated allergy

## Improving the diagnosis through discovering the mechanism of dysfunction.

Expands therapeutic options.

Moves beyond symptomatic management.

### IN SUMMARY



Gastrointestinal symptoms are common in Post-viral disorders; disorders of the neuroimmune axis.



Specialist referral is required.



We need to leverage leading technologies to improve diagnostics and therapeutics for these disorders.



Early recognition, thorough diagnosis, and targeted interventions are essential to improve patient outcomes.

### REFERENCES

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