BIOGRAPHICAL SKETCH

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NAME: Michael D. Gershon

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POSITION TITLE: Professor of Pathology and Cell Biology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Cornell University	BA	6/58	Zoology
Cornell University Medical School	MD	6/63	Medicine
Cornell University, New York, NY	Post-doc	1963-65	Cell Biology
Oxford University, Oxford, England	Post-doc	165-66	Pharmacology

A. Personal Statement

I began research while still a medical student at Cornell. I focused then on 5-HT in EC cells, which I showed was a mediator of anaphylactic shock in mice. I completed my medical training after that, but did postdoctoral research instead of a clinical training following graduation. I began at Cornell but later moved to Oxford in the UK in the laboratory of Edith Bülbring where I learned to use electrophysiology and pharmacological methods to investigate the peristaltic reflex and other forms of intestinal motility. After returning to Cornell, I worked independently and rose to the rank of Professor before moving to Columbia University as Chair of Anatomy & Cell Biology in Dec. 1975-2005. I have maintained my early focus on 5-HT in the gut throughout my career, showing its roles as a multifunctional GI signaling molecule. I have also investigated many other molecules and expanded my interests to include ENS development, neurogenesis, and intestinal inflammation. I have acquired expertise in light and electron microscopy, molecular and cell biology, as well as multiple methods of investigation of enteric neurophysiology. My work on the ENS has been recognized with honors including the Camilio Golgi Award of the Fidia Fdn, Jacob Javits award from NINCDS, Davenport award in GI Physiology from the American Physiological Society, the Medal of François I from the Collège de France, the Henry Gray award from the American Association of Anatomists (AAA), Masters Award for Sustained Achievement in GI Science, (AGA), the AGA-Rome Lectureship (DDW 2011), Weill-Cornell Alumnus of Distinction, Lifetime Achievement Award from the Federation of Societies of Neurogastroenterology and Motility (FNM2020) and election as a Fellow of the American Association for the Advancement of Science, American Clinical and Climatological Society, AAA, and AGA. I have been President of the AAA and the Cajal Society and I am currently President of the Harvey Society. I have trained over 50 scientists in my career and have mentored young physician-scientists in both pediatric gastroenterology and surgery. Together with Dr. Anne A. Gershon, I have defined functions of varicella zoster virus (VZV) glycoproteins, elucidated the complex process of VZV envelopment, and identified receptors that enable VZV to enter cells and sequester newly enveloped virions. More recently, we have developed the first animal model of VZV reactivation and also demonstrated that VZV establishes latency and is a serious pathogen in the human ENS. Developmental work on the ENS has most recently included regulation of precursor proliferation in enteric neurogenesis, the roles that early-born neurons play in development of neurons born after them during ENS ontogeny, and neuron-neuron interactions in maintaining the adult ENS.

B. Positions and Honors

1966-1969 Cornell University Medical College, Dept. Anatomy, Instructor
1969-1973 Cornell University Medical College, Dept Anatomy, Assistant Professor
1973-1975 Cornell University Medical College, Dept Anatomy, Associate Professor

1975 Cornell University Medical College, Dept Anatomy, Professor.
1975-2005 Columbia University Medical Center, Dept Anatomy & Cell Biology, Professor and Chair
2005- Columbia University Medical Center, Dept of Pathology & Cell Biology, Professor

Other Experience and Professional Memberships (Selected)
1996-2000 AGA Council
2007-2011 Member, Clinical and Integrative Gastrointestinal Pathobiology Study Section (NIH)
Editorial Boards: Gastroenterology, J. Comp. Neurol. J. Neurobiol., Anat. Rec., Synapse, Am. J. Physiol., J. Gastro. Mot., Cell and Tissue Research, Frontiers in Neuroscience.
Sci. Adv. Boards: Pharm. Man. Assoc. Fdn., Chair Panel on Pharmacology-Morphology; Gene Expression

Honors (Selected**)**

State of the Art Lecture, AGA 1986
Tousimis Prize Assoc. Anatomy. Chairs. 1998
Visiting Prof. and Medal of François I, Collège de France 1989
Chair FASEB GI Conf. IV 1990
Guest Editor, Special issue on The Neural Crest , J. Neurobiol 1991
Cajal Club, Pres 1993
Elected Fellow American Association for the Advancement of Science
American Assoc. of Anatomists, President 1994, Fellow 2007
Henry Gray Award, Highest honor of the American Association of Anatomists 1995
American Gastroenterological Association Fellow 2000
AGA Institute Masters Award for Sustained Achievement in Digestive Sciences 2008
Am. Physiol. Assoc, Davenport Distinguished Lecturer in Gastrointestinal Physiology 2010
AGA-Rome Foundation Lectureship at DDW, 2011.
Elected member of the American Clinical and Climatological Association 2011
Elected member of the New York Clinical Society, 2012
Outstanding Alumnus Award, Weill-Cornell Medical College, 2012
The Harvey Society, President, 2015-2016
Lifetime Achievement Award; Federation of Societies of Neurogastroenterology and Motility (FNM2020)

C. Contributions to Science

1. 5-HT mediates anaphylactic shock in mice and facilitates lymphocyte trafficking through venules. Research in my laboratory is focused on the enteric nervous system (ENS). This is the largest and most complex division of the PNS. The ENS is unique in being able to mediate reflex activity and control the behavior of an organ in the absence of input from brain or spinal cord. In general terms, my work on adult ENS has sought to explain, in cellular and molecular terms, the independence of the ENS. I have concentrated on serotonin (5-HT) since my first publications in J. Exp. Med. (1962) and Science (1965) suggesting that 5-HT is released from EC cells and also an enteric neurotransmitter. I went on to confirm the role of 5-HT as an enteric neurotransmitter and later, the multiple roles that 5-HT plays in GI motility and the multiple subtypes of 5-HT receptor in the bowel.

a. Gershon, M.D. and Ross, L.L. (1962). Studies on the relationship of 5-hydroxytryptamine and the enterochromaffin cell to anaphylatic shock in mice. J. Exp. Med. 115:367-382.

b. Gershon, R.K., Askenase, P. and **Gershon**, M.D. (1975). Requirement for vasoactive amines for production of delayed-type hypersensitivity skin reactions. J. Exp. Med. 142:732-747.

2. 5-HT is a neurotransmitter in the ENS This initial work on 5-HT shock and immunity led me to work more broadly on the functions of 5-HT in the gut. That, in turn led me to confirm roles for 5-HT in the initiation of peristaltic reflexes, as a neurotransmitter (of myenteric interneurons) mediating slow EPSPs in Dogiel type II cells, and an action in the vagal pathway mediating gastric relaxation (compliance).

a. Gershon, M.D., Drakontides, A.B. and Ross, L.L. (1965). Serotonin: synthesis and release from the myenteric plexus of the mouse intestine. Science, 149:197-199.

b. Gershon, M.D. and Ross, L.L. (1966). Location of sites of 5-hydroxytryptamine storage and metabolism by radioautography. J. Physiol. (London) 186:477-492.

c. Dreyfus, C.F., Bornstein, M.B. and **Gershon**, M.D. (1977). Synthesis of serotonin by neurons of the myenteric plexus in situ and in organotypic tissue culture. Brain Research 128:125-139.

d. Gershon, M.D. and Tamir, H. (1981). Release of endogenous 5-hydroxytryptamine from resting and stimulated enteric neurons. Neuroscience 6:2277-2286.

3. Two separate 5-HT pools (epithelial and neuronal) exist in gut; SERT inactivates 5-HT in each. Further studies revealed that 5-HT is inactivated primarily by the serotonin reuptake transporter, which is located both in neurons and, surprisingly, in enterocytes. The latter function to terminate the paracrine actions of EC cell 5-HT. I also showed that neuronal and EC cell 5-HT are separate distinct; each is synthesized by a different isoform of tryptophan hydroxylase (TPH1 and TPH2 respectively). As a result, the two pools of 5-HT can be separately deleted to reveal the functions of each. Surprisingly, in addition to initiating reflexes, EC cell 5-HT is strongly pro-inflammatory and functions as a positive regulator of innate immunity. Neuronal 5-HT functions, not only in neurotransmission, but also is anti-inflammatory and acts during development as a growth factor for late-born subsets of neurons, the differentiation of which is 5-HT-dependent. Current work concerns the roles of 5-HT and SERT over activity in the pathophysiology of autism and its frequent co-morbid association with abnormal GI motility.

a. Gershon, M.D. and Altman, R.F. (1971). An analysis of the uptake of 5-hydroxytryptamine by the myenteric plexus of the small intestine of the guinea pig. J. Pharmacol. Exp. Ther. 179:29-41.

b. Wade, P. R., Chen, J., Jaffe, B., Kassem, I.S., Blakely, R.D. and **Gershon**, M.D. (1996). Localization and function of a 5-HT transporter in crypt epithelia of the gastrointestinal tract. J. Neuroscience 16: 2352-2364.

c. Li Z, Chalazonitis A, Huang YY, Mann JJ, Margolis KG, Yang QM, Kim DO, Cote F, Mallet J, **Gershon MD.** (2011) Essential roles of enteric neuronal serotonin in gastrointestinal motility and the development/survival of enteric dopaminergic neurons. J. Neuroscience 31:8998-9009. PubMed PMID: 21677183; PMCID: PMC4442094.

d. Margolis KG, Li Z, Stevanovic K, Saurman V, Israelyan N, Anderson GM, Snyder I, Veenstra-VanderWeele J, Blakely RD, **Gershon MD**. Serotonin transporter variant drives preventable gastrointestinal abnormalities in development and function. **J. Clin Invest.** 2016 Jun 1;126(6):2221-35. doi: 10.1172/JCI84877. Epub 2016 Apr 25. PubMed PMID: 27111230; PubMed Central PMCID: PMC4887174.

4. Processes contributing to ENS development, including guidance of crest cell migration, precursor division, neuron-determined neurogenesis, and the unexpected role of 5-HT, were determined. Studies on development revealed that 5-HT is critical. We discovered that the fate of enteric neurons is dependent on the duration of proliferation of precursor cells and the neurons are born in a stereotyped order. Serotonergic neurons are among the first to be born in the fetal ENS and their activity can sculpt the maturing ENS because sets of late-born neurons are 5-HT-dependent. Studies of the development of the ENS include tests of the idea that neurons generated early in development act through their neurotransmitters to change the enteric microenvironment and influence the fates of neurons generated later. Psychosocial trauma, stress, and inflammation alter neuronal activity and through that activity the neuronal regulation of neuronal development might provide a common pathway for events, from the psychological to the infectious/inflammatory, to affect ENS development and thus shape its character. We have also studied the roles of Hand genes in neurogenesis, netrins in axon guidance, and neuroligins/neurexins in synaptogenesis. Neuronal 5-HT also mobilizes stem cells to form new neurons in adult bowel and promotes proliferation of crypt epithelial cells.

a. Pham, T.D. **Gershon**, M.D. and Rothman, T.P. (1991). Time of origin of neurons in the murine enteric nervous system. J. Comp Neurol. 314: 789-798.

b. Chalazonitis, A., Pham, T.D., Li, Z.S., Roman, D., Guha, U., Gomes, W., Kan, L., Kessler, J.A., **Gershon, M.D.,** (2008) Bone Morphogenetic protein regulation of enteric neuronal phenotypic diversity: relationship to timing of cell cycle exit, J. Comp. Neurology, Aug 10; 509(5): 474-92; PMCID: PMC2592098

c. Liu MT, Kuan YH, Wang J, Hen R, **Gershon MD**. 5-HT_4 receptor-mediated neuroprotection and neurogenesis in the enteric nervous system of adult mice. Journal of Neuroscience. 2009 Aug 5;29(31):9683-99. PubMed PMID: 19657021; PubMed Central PMCID: PMC2749879.

d. Gross ER, **Gershon MD**, Margolis KG, Gertsberg ZV, Cowles RA. Neuronal serotonin regulates growth of the intestinal mucosa in mice. Gastroenterology. 2012 Aug;143(2):408-417.e2. Epub 2012 May 15. PubMed PMID: 22609381; PMCID: PMC3687781.

5. The ENS is a major regulator of the susceptibility of the bowel to inflammation and may thus contribute to the pathogenesis of IBD and Parkinson's disease.

a. Margolis KG, Stevanovic K, Karamooz N, Li ZS, Ahuja A, D'Autréaux F, Saurman V, A, **Gershon MD**. Enteric neuronal density contributes to the severity of intestinal inflammation.

Gastroenterology. 2011 Aug;141(2):588-98, 598.e1-2. doi: 10.1053/j.gastro.2011.04.047. PMID: 21635893 PMCID: PMC4459707

b. Margolis KG, Stevanovic K, Li Z, Yang QM, Oravecz T, Zambrowicz B, Jhaver KG, Diacou A, **Gershon MD.** Pharmacological reduction of mucosal but not neuronal serotonin opposes inflammation in mouse intestine. Gut. 2014 Jun;63(6):928-37. doi: 10.1136/gutjnl-2013-304901. PMID: 23749550; PMCID: PMC4034681.

c. Muller PA, Koscsó B, Rajani GM, Stevanovic K, Berres ML, Hashimoto D, MorthaA, Leboeuf M, Li XM, Mucida D, Stanley ER, Dahan S, Margolis KG, **Gershon MD**, Merad M, Bogunovic M. Crosstalk between muscularis macrophages and enteric neurons regulates gastrointestinal motility. Cell. 2014 Jul 17;158(2):300-13.doi: 10.1016/j.cell.2014.04.050. Erratum in: Cell. 2014 Aug 28;158(5):1210.Dosage error in article text. PubMed PMID: 25036630; PubMed Central PMCID:PMC4149228.

d. Kuo YM, Li Z, Jiao Y, Gaborit N, Pani AK, Orrison BM, Bruneau BG, Giasson BI, Smeyne RJ, **Gershon MD**, Nussbaum RL (2010) Extensive enteric nervous system abnormalities in mice transgenic for artificial chromosomes containing Parkinson disease-associated alpha-synuclein gene mutations precede central nervous system changes. Hum Mol Genet 19:1633-1650; PMCID: PMC2850613.

6. Authoritative reviews have been written in high impact journals covering the ENS manifestations of neurological disorders and the contributions of the ENS to intestinal inflammation.

a. Rao M, **Gershon MD.** The bowel and beyond: the enteric nervous system in neurological disorders. **Nature Rev Gastroenterol Hepatol**. 2016 Sep;13(9):517-28. doi: 10.1038/nrgastro.2016.107. Epub 2016 Jul 20.. PubMed PMID: 27435372; PMCID: PMC5005185.

b. Margolis KG, **Gershon MD.** Enteric Neuronal Regulation of Intestinal Inflammation. Trends Neurosci. 2016 Sep;39(9):614-24. doi: 10.1016/j.tins.2016.06.007. Epub 2016 Jul 20.; PubMed PMID: 27450201 PMCID: PMC5002370.

c. Rao M, **Gershon MD.** Enteric nervous system development: what could possibly go wrong?. Nat Rev Neurosci. 2018 Sep;19(9):552-565. doi: 10.1038/s41583-018-0041-0. Review. PubMed PMID: 30046054; PubMed Central PMCID: PMC6261281.

7. Varicella zoster virus (VZV) is an enteric pathogen VZV is thought to be primarily a pathogen for humans; however, it was grown in guinea pig cells to produce the varicella vaccine. We thus tested the idea that we could grow VZV in neurons, which I was able to isolate from the guinea pig ENS. We found that VZV infects these neurons and, depending on the conditions, could establish latent, lytic, or reactivating infection. We then determined that VZV could establish latency in guinea pigs in vivo and could be reactivated in them by immunosuppression and administration of a stress hormone. We subsequently discovered that VZV establishes latency in the human ENS and can reactivate to cause enteric zoster, which ranges in severity from a cause of occult abdominal pain to perforation of the gut.

a. Gershon MD, Gershon A. Varicella-Zoster Virus and the Enteric Nervous System. J Infect Dis. 2018 Sep 22;218(suppl_2):S113-S119. doi: 10.1093/infdis/jiy407. PubMed PMID: 30247599; PubMed Central PMCID: PMC6151087.

b. Gan L, Wang M, Chen JJ, **Gershon MD,** Gershon AA. Infected peripheral blood mononuclear cells transmit latent varicella zoster virus infection to the guinea pig enteric nervous system. J Neurovirol. 2014 Oct;20(5):442-56. doi: 10.1007/s13365-014-0259-1. Epub 2014 Jun 26. PMID: 24965252; PMCID: PMC4206585.

c. Gershon AA, Chen J, **Gershon MD**. Use of Saliva to Identify Varicella Zoster Virus Infection of the Gut. Clin Infect Dis. 2015 Aug 15;61(4):536-44. doi: 10.1093/cid/civ320. Epub 2015 Apr 16. PubMed PMID: 25882301; PubMed Central PMCID: PMC4607733.

d . Gershon AA, Brooks D, Stevenson DD, Chin WK, Oldstone MBA, **Gershon MD**. High constitutive interleukin 10 level interferes with the immune response to varicella-zoster virus in elderly recipients of live attenuated zoster vaccine. J Infect Dis. 2019 Apr 8;219(8):1338-1346. doi: 10.1093/infdis/jiy660. PubMed PMID: 30445431; PubMed Central PMCID: PMC6601527.

Complete List of 431 publications at:

https://www.dropbox.com/s/uk511wvl8kvqv43/Mike%20Gershon.CV.1.18.18%20copy.docx?dl=0

D. Additional Information: Research Support and/or Scholastic Performance

2R01DK093094 (Gershon, M;Gershon, AA) 03/01/17-02/28/21

"VZV in the enteric nervous system: pathogenesis and consequences". This is the most relevant to the current proposal but concentrates on the intestine, not the esophagus, and on abdominal pain, rather than achalasia. Following primary infection (varicella; chickenpox), varicella zoster virus (VZV) establishes latency in dorsal root (DRG) and cranial nerve (CNG) ganglia; reactivation in DRG or CNG causes a secondary infection (zoster; shingles). VZV latency, however, also almost universally occurs in the enteric nervous system (ENS) after varicella or varicella vaccination. VZV reactivates in the ENS as it does in DRG/CNG, but because enteric neurons lack cutaneous projections, "enteric zoster" occurs without rash and thus is an unsuspected cause of GI dysfunction. We demonstrated that VZV infects guinea pigs, establishes latent infection in DRG/CNG and ENS, and can be reactivated to cause a secondary infection resembling disseminated zoster. Aim 1 will test hypotheses that: (i) evanescent cell fusion transmits VZV from lymphocytes to neurons; (ii) exosomes from VZV-infected lymphocytes transfer stimulator of interferon genes (STING) to neurons; (iii) STING in the neurons induces a type1 interferon response that inhibits VZV proliferation, leading to latency. Aim 2 will determine conditions in guinea pigs that: (i) cause a varicella-like disseminated primary infection; (ii) enable reactivating VZV to be confined to gut or skin; (iii) identify the transduction pathway that regulates the transition from latent to lytic infection in enteric neurons. Aim 3 will to detect enteric zoster non-invasively with salivary VZV DNA in human subjects and characterize endoscopic manifestations of enteric zoster. This research makes the first use a novel animal model in which VZV reactivates in vivo and the first application of a non-invasive technique to identify potential cases of enteric zoster.

1R01NS099270 (Lorenz) 09/30/16-06/30/21
"Modeling Enteric Nervous System Development and Hirschsprung's Disease in Human Pluripotent Stem Cells" This is a grant with Sloan-Kettering on which I am a co-investigator. We are identifying the growth factors and other molecules that induce human pluripotent stem cells to develop as enteric neurons and testing their ability to restore function when grafted into the aganglionic bowel of mouse models of Hirschsprung disease.

2R01NS015547-37 (Gershon) 12/01/79-12/31/22
"Microenvironment in the Enteric Neuron Development". I am the prinicipal investigator., We have demonstrated that enteric neurons are born (undergo terminal mitosis) in a reproducible order in which early-born mature neurons coexist with and innervate still-dividing precursors. Serotonergic and cholinergic neurons are born first, while neurons that contain tyrosine hydroxylase (TH), Gamma-aminobutyric acid (GABA), or calcitonin gene related peptide (CGRP) are born later. This observation led us to frame the hypothesis that the activity of early-born neurons can, through their neurotransmitters, 5-HT and/or acetylcholine (ACh), affect the development of later-born neurons. Supporting of this idea, we showed that 5-HT, through 5-HT_4 receptors, promotes development of TH-, GABA-, and CGRP-containing neurons, that these phenotypes are deficient, and the ENS is hypoplastic when tryptophan hydroxylase 2 (TPH2) is deleted and mice thus lack neuronal 5-HT. The late-born neurons are also deficient and the ENS is hypoplastic in animals that carry an autism-associated human variant of the serotonin transporter (SERT; SERT Ala56 or G56A), which is hyperfunctional and clears 5-HT from its receptors too rapidly. In contrast, mice that lack SERT (SERTKO) or which are exposed during development to a SERT inhibitor have a hyperplastic ENS and excessive numbers of late-born neurons. Recent preliminary data, obtained with mice that under- or overexpress the presynaptic choline transporter, suggest that ACh functions like 5-HT. Because serotonergic and cholinergic neurons are thus essential for ENS development, defects in their signaling during ontogeny lead, not only to ENS hypo-or hyperplasia, but to dysmotilities and abnormally regulated mucosal growth that are readily demonstrated in adult animals. We thus postulate that the defects that arise due to errant serotonergic or cholinergic signaling in ontogeny,

possibly due to environmental perturbations, contribute to dysmotility disorders in adults. Although TPH2-derived 5-HT is more important than that from TPH1 in ENS formation under basal conditions, TPH1-derived 5-HT from “pre-enteric” sources, (placenta, yolk sac, and maternal circulation) may be essential to support ENS neurogenesis prior to development of serotonergic neurons. TPH1-derived 5-HT from mucosal enterochromaffin (EC) cells may also disturb ENS neurogenesis and/or function if it reaches the neuronal compartment. We now plan to test 3 overarching hypotheses: (i) “Pre-enteric” TPH1-derived 5-HT is essential to support enteric neurogenesis before serotonergic neurons develop. (ii) Mucosal SERT activity is essential to prevent 5-HT from overflowing from the mucosa to disturb neurogenesis and/or neuronal function; insults that up- or downregulate SERT thus cause abnormal ENS formation and adult function. (iii) Early-born enteric cholinergic neurons act on muscarinic receptor(s) to stimulate the generation of new neurons and epithelial cells.