BIOGRAPHICAL SKETCH

NAME: Larry S. Miller

eRA COMMONS USER NAME (credential, e.g., agency login): MILLERLS

POSITION TITLE: Chief of Gastroenterology, Professor of Medicine, Zucker school of Medicine at Hofstra/Northwell

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
University of Illinois (Chicago, IL.)	BS	09/1977	Biology with minor in Chemistry
The Chicago Medical School (Chicago, IL.)	MD	06/1981	Medicine
Evanston Hospital, Northwestern University (Evanston, IL)	Residency	06/1984	Internal Medicine
Midwest Nutrition, Education & Research Foundation (Chicago IL.)	Nutrition Board	04/1986	Nutrition
Clinical and Research Fellowship in Gastroenterology, Georgetown University\Washington VA\NIH Combined Gastroenterology Program (Washington D.C.)	GI Board	07/1989	Gastroenterology
Therapeutic Endoscopy Fellowship at the Wellesley Hospital, University of Toronto, Toronto, Canada	Certificate in Therapeutic Endoscopy	06/1990	Therapeutic Endoscopy

A. Personal Statement

I am a third tier trained therapeutic endoscopist and I am also trained, and board certified in clinical nutrition. In addition, I am a trained bench lab and clinical research scientist, having completed a three-year research fellowship at the Digestive Disease Section of the NIDDK. I have had continuous NIH funding for the last 20 years until this year. I currently hold the position as Chief of Gastroenterology at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell. I have spent much of my research career as head of endoscopic research at both Thomas Jefferson University and at Temple University in Philadelphia. I am currently involved in the bioelectronics initiative at the Feinstein Research Center. Part of my research interests is the design and invention of devices. I have invented and patented several different devices. In the early 1990's, I invented a method using simultaneous high-resolution ultrasound and manometry to study the anatomy and physiology of gastrointestinal sphincters. I have spent the last 30 years of my academic career using this technology to study the anatomy and physiology of gastrointestinal sphincters. As part of my previous NIH sponsored research work, I studied the mechanics, physiology, and pathophysiology of the high-pressure zone of the distal esophagus. My first RO1 grant dealt specifically with normal sphincter anatomy and physiology of the distal esophageal anti-reflux barrier. My second NIH RO1 grant clinically investigated the pathophysiology of GERD and we discovered several new pathophysiologic mechanisms in GERD. My recently completed NIH SPARC grant used new endoscopic techniques to implant electrodes on the peripheral branches of the vagus nerve. It was through this work and my collaboration with Dr. Zanos that I became interested in the selective stimulation of efferent and afferent nerve fascicles within the cervical vagus nerve. We have been able to demonstrate selective relaxation and contraction of the gastric pyloric muscle and the lower esophageal sphincter using radial platinum electrodes to stimulate selective nerve fascicles, varying the location, amplitude, and frequency of stimulation. I have successfully administered the projects (e.g., staffing, research, budget), collaborated with other researchers, and produced many peer-reviewed publications from these projects. As a result of these previous experiences, I am aware of the importance of frequent communication among project members and of

constructing a realistic research plan, timeline, and budget. I am a member of the Feinstein Institute for Medical research and have a lab at the Feinstein with access to their animal facility. In summary, I have a demonstrated a record of accomplished and productive research projects in an area of high relevance and my expertise and experience have prepared me to accomplish the proposed project.

Recently completed projects that I would like to highlight include:

1OT2OD026539 Miller (PI) 09/01/2018 – 08/31/2021
Title: Using the GI Tract as a Window to the Autonomic Nervous System in the Thorax and in the Abdomen.
Role: PI

1U18EB021789-01 Miller (PI) 09/30/2015-07/31/2018
Title: An Implantable Wireless System to Study Gastric Neurophysiology
The goal of this study is to design, develop, and validate a wireless, implantable, and high-resolution mapping system that can acquire gastric slow waves.
Role: Co-PI

RO1 DK079954 Miller (PI) 06/01/2010-09/31/2015
Title: Gastroesophageal Anti-reflux Mechanisms
The goal of this study is to identify the anatomic, physiologic, and pharmacologic differences in the gastroesophageal junction high pressure of GERD patients which might play a role in the pathogenesis of GERD.
Role: Co-PI

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

1981-1984	Medical Internship, Junior and senior residency, Evanston Hospital, Northwestern University Training Program in Internal Medicine, Evanston, IL
1984-1986	Fellowship in Clinical Nutrition, Midwest Nutrition, Education and Research Foundation, Chicago, IL
1986-1989	Clinical and Research Fellowship in Gastroenterology, Georgetown University/Washington VA/NIH. Washington D.C.
1989-1990	Therapeutic Endoscopy Fellowship, The Wellesley Hospital, University of Toronto, Toronto, Canada
1990-1993	Assistant Professor of Medicine, Director of Medical Endoscopy, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA
1993-1997	Assistant Professor of Medicine, Director of Endoscopic Research, Temple University School of Medicine, Philadelphia, PA
1997-2006	Associate Professor of Medicine; Associate Director of Gastrointestinal Endoscopy; Director of Endoscopic Research, Temple University School of Medicine, Philadelphia, PA
1994-2012	Endoscopic Ultrasound for the Practicing Physician, Temple University Hospital, Program Chairman
2006-2012	Professor of Medicine, Associate Director of Gastrointestinal Endoscopy; Director of Endoscopic Research, Temple University School of Medicine, Philadelphia, PA
2012- Present	Chief of Gastroenterology, Professor of Medicine, Hofstra Medical School, Northwell Health System, Manhasset, NY

Other Experience and Professional Memberships

1981-	Diplomat, National Board of Medical Examiners
1984-	Diplomat, American Board of Internal Medicine
1986-	Diplomat, American Board of Nutrition
1989-	Diplomat, American Board of Gastroenterology
2001-	Fellows, EUS and GI US course, Program Chairman
2003-	Member, American College of Physicians
2003-2004	President, Komorov GI fellows research forum
2003-2004	President, Philadelphia GI research forum
2004-2012	Member, Patent committee, Temple University
2003-2012	Member, Delaware Valley Endoscopy Society
2007-2012	Chair, Nutrition committee, Temple University Hospital
2012-	Member, Promotions committee, Dept. of Medicine, Hofstra Medical School
2012-	Member, NYSGE (New York Society of Gastrointestinal Endoscopy)

American Medical Association (member)
Chicago Medical Society (member)
American Society of Parenteral and Enteral Nutrition (member)
American College of Clinical Nutrition (member)
Chicago Medical School Alumni Association (member)
American College of Gastroenterology (member)
American Gastrointestinal Association (member)

Honors

1973	Awarded membership Phi Eta Sigma Honor Society, Chicago, IL
1973	Awarded full scholarship from Department of Music University of Illinois, Chicago, IL
1976	Awarded membership, Phi Kappa Phi Honor Society, Chicago, IL
2004	Member, Million Dollar Research Award Club, Temple University, Philadelphia, PA
2012	Golden Apple teaching award for best teacher at Temple University Medical School, Philadelphia, PA

C. Contributions to Science

1. **Bioelectronics with respect to the Gastrointestinal Tract.** My most recent research has been funded by a U18 grant and a SPARC NIH funded project in addition to private industry funding. The privately funded grant used an endoscopic technique to implant electrodes directly into the pyloric muscle and to stimulate the pyloric muscle directly to cause contraction, with the purpose of delaying gastric emptying to treat obesity. The U18 grant developed implantable wireless programmed electrodes for muscle stimulation of the stomach with the potential to treat gastroparesis. During this grant the electrodes were designed and manufactured, and a technique using endoscopic tunneling was developed to implant the electrodes endoscopically in a porcine model. The SPARC NIH funded project used endoscopic techniques to implant electrodes on the vagus nerve. During this project we developed an endoscopic tunneling technique to implant electrodes on the vagus nerve in the thoracic cavity. It was during this project that I became involved with Dr. Zenos. We worked to monitor physiologic functions of the GI tract during vagal nerve stimulation. Initially we implanted cervical ring electrodes that stimulated the entire vagus nerve. Later our group designed and implanted radial cervical electrodes with the capability of stimulating specific fascicles within the cervical vagus nerve to induce specific on target effects within the GI track. For example, relaxation or contraction of the pyloric or lower esophageal sphincter.

    a. Amir Javan-Khoskholgh, Zaid Abukhalaf, Ji Li, **Larry Miller**, Mehdi Kiani, Aydin Farajidavar. An inductive narrow-pulse RFID telemetry system for gastric slow waves monitoring. Annu Int Conf IEEE Eng Med Biol Soc 2016 Aug;2016:4820-4823
    b. Amir Javan-Khoshkholgh, Wahib Alrofati, **Larry S. Miller,** Anil K. Vegesna. A High-Resolution Wireless Power Transfer and Data Communication System for Studying Gastric Slow Waves* Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference 2019:3271-3274 DOI: 10.1109/EMBC.2019.8856619 Conference: 2019 41st Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC
    c. **Larry Miller,** Aydin Farajidavar and Anil Vegesna. Use of Bioeletronics in the Gastrintestinal Tract. Bioelectronic Medicine. Cold Spring Harbor Perspectives in Medicine. Ed. Pavlov and Tracey. September 2018 Cold Spring Harbor Perspectives in Medicine 9(9):a034165. DOI: 10.1101/cshperspect.a034165
    d. **Larry Miller,** Anil Vegesna, Stavros Zenos, Modulation Of The Gastric Pyloric Muscle Using Selective Vagus Nerve Stimulation (In A Porcine Model) Abstract, DDW 2022, San Diego.
    e. The Fourth Bioelectronic Medicine Summit "Technology Targeting Molecular Mechanisms": current progress, challenges, and charting the future. Datta-Chaudhuri T, Zanos T, Chang EH, Olofsson PS, Bickel S, Bouton C, Grande D, Rieth L, Aranow C, Bloom O, Mehta AD, Civillico G, Stevens MM, Głowacki E, Bettinger C, Schüettler M, Puleo C, Rennaker R, Mohanta S, Carnevale D, Conde SV, Bonaz B, Chernoff D, Kapa S, Berggren M, Ludwig K, Zanos S, **Miller L**, Weber D, Yoshor D, Steinman L, Chavan SS, Pavlov VA, Al-Abed Y, Tracey KJ.Bioelectron Med. 2021 May 24;7(1):7. doi: 10.1186/s42234-021-00068-6.PMID: 34024277

2. **Normal anatomy and physiology of peristaltic contraction in the esophagus**: My early publications, as far back as my fellowship in gastroenterology at the NIH, and my first years as an academic gastroenterologist focused on esophageal disease. One of my first publications evaluated the esophageal manifestations of Zollinger-Ellison Syndrome. In an age when gastrin was thought to protect the esophagus from acid damage this paper demonstrated that there was a significant burden of esophageal disease from direct acid exposure in ZES. Another of my early

papers used the new imaging modality of endoluminal ultrasound along with esophageal manometry to determine the underlying pathophysiology of the esophageal disease in scleroderma. My career continued to focus on the normal anatomy and physiology of the esophagus. I developed a technology and method to image the anatomy of the esophagus using high resolution ultrasound and simultaneously evaluate the physiology of the esophagus using manometry (simultaneous endoluminal ultrasound and manometry). By inventing and utilizing these combined modalities I was able to study the anatomy and physiology of esophageal muscle contraction simultaneously. Using this new technology and basic principles of mass conservation in muscle I was able to evaluate esophageal swallowing demonstrating the sequence and coordination of longitudinal and circular smooth muscle contraction and how this sequence increased the efficiency of esophageal luminal closure. Subsequent studies evaluated the global shortening of the esophagus in a quantitative manner demonstrating a greater shortening of the distal esophagus compared to the proximal esophagus and demonstrating for the first time that the circular smooth muscle in the distal esophagus contributes significantly to the shortening of the distal esophagus during peristaltic contraction due to the oblique nature of the muscle fibers in the distal circular smooth muscle.

a) Dai Q, Korimilli A, Thangada VK, Chung CY, Parkman H, Brasseur J, **Miller LS**. Muscle shortening along the normal esophagus during swallowing. Dig Dis Sci. 2006;51(1):105-9. PubMed PMID: 16416220.
b) **Miller L**, Dai Q, Korimilli A, Levitt B, Ramzan Z, Brasseur J. Use of endoluminal ultrasound to evaluate gastrointestinal motility. Digestive diseases (Basel, Switzerland). 2006;24(3-4):319-41. Epub 2006/07/20. doi: 10.1159/000092886. PubMed PMID: 16849860.
c) Vegesna AK, Chuang KY, Besetty R, Phillips SJ, Braverman AS, Barbe MF, Ruggieri MR, **Miller LS**. Circular smooth muscle contributes to esophageal shortening during peristalsis. World Journal of Gastroenterology. 2012;18(32):4317-22. doi: http://dx.doi.org/10.3748/wjg.v18.i32.4317. PubMed PMID: 22969194; PMCID: PMC3436046.
d) Nicosia MA, Brasseur JG, Liu JB, **Miller LS**. Local longitudinal muscle shortening of the human esophagus from high-frequency ultrasonography. Am J Physiol Gastrointest Liver Physiol. 2001;281(4):G1022-33. PubMed PMID: 11557523.

3. **The normal anatomy and physiology of the distal esophageal high-pressure zone (anti-reflux barrier):** During my first funded NIH RO1 grant I used the techniques and methods that I invented and developed (simultaneous ultrasound and manometry), to evaluate **the normal anatomy and physiology of the high-pressure zone of the distal esophagus anti-reflux barrier.** I was the first to quantify the relative alignments, movements, and pressure contributions of the various muscular components (lower esophageal circular muscle, clasp muscle fibers, sling muscle fibers and crural diaphragm) of the distal esophageal high-pressure zone to form the physiologic anti-reflux barrier. I performed these studies using two pharmacologic approaches. In the first approach the skeletal and smooth-muscle pressure contributions to the normal gastroesophageal junction high-pressure zone and the relative position of various muscle components were quantitated using Atropine, a pharmacologic muscarinic antagonist which affects only smooth muscle. The second approach confirmed the results of the first approach and utilized the pharmacologic skeletal muscle paralytic agent cis-atricuronium in patients undergoing general anesthesia to paralyze the crural sphincter and evaluate the pressure generated by the smooth muscle directly measured to determine the smooth-muscle contributions to the gastroesophageal junction HPZ.

a) Brasseur JG, Ulerich R, Dai Q, Patel DK, Soliman AM, **Miller LS**, Brasseur JG, Ulerich R, Dai Q, Patel DK, Soliman AMS, Miller LS. Pharmacological dissection of the human gastro-oesophageal segment into three sphincteric components. J Physiol (Lond). 2007;580(Pt.3):961-75. PubMed PMID: 17289789.
b) Vegesna AK, Sloan JA, Singh B, Phillips SJ, Braverman AS, Barbe MF, Ruggieri MR, Sr., **Miller LS**. Characterization of the distal esophagus high-pressure zone with manometry, ultrasound and micro-computed tomography. Neurogastroenterol Motil. 2013;25(1):53-60.e6. doi: http://dx.doi.org/10.1111/nmo.12010. PubMed PMID: 22998376; PMCID: NIHMS402654 [Available on 01/01/14] PMC3530622 [Available on 01/01/14].
c) McCray WH, Chung C, Parkman HP, **Miller LS**. Use of simultaneous high-resolution endoluminal sonography (HRES) and manometry to characterize high pressure zone of distal esophagus. Digestive diseases and sciences. 2000;45(8):1660-6.
d) **Miller L,** Dai Q, Korimilli A, Levitt B, Ramzan Z, Brasseur J. Use of endoluminal ultrasound to evaluate gastrointestinal motility. Digestive diseases (Basel, Switzerland). 2006;24(3-4):319-41. Epub 2006/07/20. doi: 10.1159/000092886. PubMed PMID: 16849860.

4. **The pathophysiology of gastroesophageal reflux disease (abnormal clasp and sling muscle fibers):** During my second funded NIH RO1 grant I used several techniques to evaluate **the anatomy, physiology and pathophysiology of the esophagus in patients with gastroesophageal reflux disease (GERD).** Many of these studies utilized the clinical technology that I developed. However, I also branched out to evaluate the basic

physiology and molecular physiology of the esophagus in GERD and compare it to the normal esophagus. Using these approaches, I first demonstrated a **significant defect in the pressure profile of the clasp muscle fibers and sling muscle fibers in patients with GERD and an attenuated pressure profile within the lower esophageal circular muscle** of the distal high-pressure zone. I then demonstrated the consequences of these defects showing that the compliance characteristics of the distal esophagus were different in GERD patients than in normal subjects thus accounting for an increase in the distensibility of the high-pressure zone and a mechanistic solution to why these patients have reflux of gastric contents. To explain these changes at a basic physiologic and molecular level my group performed muscle contraction experiments on human clasp, sling and LEC muscle fibers from subjects with and without GERD. We identified various receptors that are responsible for the contraction and the relaxation of the different components of the gastroesophageal high-pressure zone. Most importantly, we have demonstrated that **nicotinic receptor stimulation causes enhanced relaxation of gastric clasp, gastric sling and lower esophageal circular muscle fibers in patients with Barrett's esophagus when compared to that of normal subjects,** and thus identified a possible pathophysiologic mechanism and a target receptor for the treatment of heartburn. We also demonstrated a **unique stoichiometry of the nicotinic receptors in patients with GERD as opposed to normal control subjects**. In addition, we developed a **treatment for non-cardiac chest pain of esophageal origin** (botox injection into the distal esophagus). Our work also branched out to involve other sphincters including the pyloric sphincter (we investigated the use of botulinum toxin injection to **treat gastroparesis**), the ileal cecal valve (we defined the underlying pathophysiology of small bowel bacterial overgrowth), and the upper esophageal sphincter (we defined **the sonographic anatomy of the UES)**.

a) **Miller L**, Dai Q, Vegesna A, Korimilli A, Ulerich R, Schiffner B, Brassuer J. A missing sphincteric component of the gastro-oesophageal junction in patients with GORD. Neurogastroenterol Motil. 2009;21(8):813-e52. doi: http://dx.doi.org/10.1111/j.1365-2982.2009.01294.x. PubMed PMID: 19368661; PMCID: NIHMS120814; PMC2746096.
b) **Miller LS**, Vegesna AK, Braverman AS, Barbe MF, Ruggieri MR, Sr. Enhanced nicotinic receptor mediated relaxations in gastroesophageal muscle fibers from Barrett's esophagus patients. Neurogastroenterology and Motility. 2013;Early View(3):1-10. Epub 15 Dec 2013 doi: 10.1111/nmo.12294. PubMed PMID: 24330081; PMCID: PMID: 24330081.
c) Vegesna A, Besetty R, Kalra A, Farooq U, Korimilli A, Chuang KY, Fisher R, Parkman H, **Miller L**. Induced opening of the gastroesophageal junction occurs at a lower gastric pressure in gerd patients and in hiatal hernia subjects than in normal control subjects. Gastroenterol Res Pract. 2010;2010:857654. doi: http://dx.doi.org/10.1155/2010/857654. PubMed PMID: 20339562; PMCID: PMC2842887.
d) **Miller LS**, Vegesna AK, Sampath AM, Prabhu S, Kotapati SK, Makipour K. leocecal valve dysfunction in small intestinal bacterial overgrowth: A pilot study. World J Gastroenterol. 2012;18(46):6801-8. doi: doi: 10.3748/wjg.v18.i46.6801. PubMed PMID: 23239918; PMCID: PMC3520169.

5. **The pathophysiology of GERD (abnormal muscularis mucosa):** Using simultaneous ultrasound and manometry and another technique that I developed (Transabdominal ultrasound of the distal esophagus) we studied the **anatomy and physiology of the muscularis mucosa of the distal esophagus during peristaltic contraction in normal subjects.** We demonstrated that during swallowing there is longitudinal contraction of the muscularis mucosa which pulls the mucosa within the gastric cardia into the tubular esophagus forming a distal esophageal mucosal plug which acts as an anti-reflux barrier during a period of time when the intra-abdominal pressure exceeds the intra-thoracic pressure. We further demonstrated that this **muscularis mucosa reflex is missing in patients with patients with GERD**. Thus, demonstrating another pathophysiologic explanation for the underlying etiology of why patients reflux gastric contents into the esophagus.

a) Vegesna AK, Patel H, Weissman S, Patel A, Kissel M, Indukuri S, Nimma A, Dai Q, **Miller LS**. Defective Mucosal Movement at the Gastroesophageal Junction in Patients with Gastroesophageal Reflux Disease. Dig Dis Sci. 2014. Epub 2014/03/13. doi: 10.1007/s10620-014-3091-9. PubMed PMID: 24610481.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/larry.miller.1/bibliography/49441586/public/?sort=date&direction=ascending