

BIOGRAPHICAL SKETCH

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NAME: Mark Pimentel, MD, BSc(Med), FRCP(C)

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

POSITION TITLE: Associate Professor of Medicine (in-residence)

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 Manitoba, Winnipeg, Canada	Undergrad	06/1988	Biochemistry and Microbiology
University of Manitoba, Winnipeg, Canada	MD	06/1992	Medicine
University of Manitoba, Winnipeg, Canada	BSc (med)	06/1992	Degree in medical research
University of Manitoba, Health Sciences Center	Residency	06/1996	Internal Medicine
UCLA, Los Angeles, California	Fellowship	06/1999	Gastroenterology

NOTE: The Biographical Sketch may not exceed five pages. Follow the formats and instructions below.

A. Personal Statement

Over the past 15 years, my lab and I have dedicated our effort to unearthing the mechanisms for the development of IBS. The hypothesis in 1999 was that a subset of IBS subjects may have small intestinal bacterial overgrowth. This happened at a time that predated the microbiome revolution. This nidus of information led to a continuous series of discoveries and treatments. On this basis, we discovered the use of antibiotics and more specifically rifaximin for the treatment of IBS. Following this work, my lab discovered that bacterial overgrowth is seen in IBS based on breath testing, culture, qPCR and now deep sequencing. We later showed that methane on breath testing was associated with constipation, and identified *M. smithii* as the organism responsible for this methane production. To determine why these bacterial changes occur, we turned to emerging data that IBS could develop after a bout of acute gastroenteritis. Over an 8 year period we developed and validated the first animal model of post-infectious bacterial overgrowth and altered bowel function similar to IBS in humans. This model allowed us to understand the role of specific toxins in *C. jejuni*. Specifically, the CdtB toxin was associated with the development of the IBS-like phenotype in rats. Through a broad series of experiments, we showed that through molecular mimicry, anti-CdtB antibodies cross react with the cell adhesion protein vinculin in the host gut. Most significantly, levels of circulating antibodies to CdtB and autoantibodies to vinculin as measured by ELISA correlated with the levels of small intestinal bacterial overgrowth (SIBO) in these animals. Antibodies to CdtB also cross react with vinculin in the human gut, and based on these data, our group assessed circulating anti-CdtB and anti-vinculin antibodies as biomarkers for D-IBS in human subjects. This measurement of serum anti-vinculin and anti-CdtB antibodies by ELISA was the basis for the world's first diagnostic test for D-IBS, IBSChek™ (Commonwealth Laboratories, Inc). In this study, we will utilize these ELISAs for CdtB and vinculin to determine the role of acute gastroenteritis in the subsequent development of post-infectious IBS.

Recently, we recruited Dr. Nipaporn Pichetshote to join the academic enterprise of the GI Motility Program at Cedars-Sinai. She has great academic potential and is highly motivated. She will be an important clinical scientist nationally over time given her determination. She has trained in functional GI disorders and has a great interest in post-infectious IBS research. If awarded this study, it will be an important milestone in growing her academic career.

1. **Pimentel M**, Chatterjee S, Chang C, Low K, Song Y, Liu C, Lezcano S, Conklin J, Finegold S. A new rat model links two contemporary theories in irritable bowel syndrome. *Dig Dis Sci* 2008;53:982-9.

2. Pokkunuri V, **Pimentel M**, Morales, Jee S-R, Alpern J, Weitsman, Marsh Z, Low K, Hwang L, Khoshini R, Barlow G, Wang H, Chang C. Role of cytolethal distending toxin and bowel phenotypes in a rat model of post-infectious irritable bowel syndrome. *J Neurogastroenterol Motil* 2012;18:434-42.
3. **Pimentel M**, Morales W, Pokkunuri V, Brikos C, Kim SM, Kim SE, Triantafyllou K, Weitsman S, Marsh Z, Marsh E, Chua KS, Srinivasan S, Barlow GM, Chang C. Autoimmunity Links Vinculin to the Pathophysiology of Chronic Functional Bowel Changes Following *Campylobacter jejuni* Infection in a Rat Model. *Dig Dis Sci*. 2015 60(5):1195-205
4. **Pimentel M**, Morales W, Rezaie A, Marsh E, Lembo A, Mirocha J, Leffler DA, Marsh Z, Weitsman S, Chua KS, Barlow GM, Bortey E, Forbes W, Yu A, Chang C. Development and validation of a biomarker for diarrhea-predominant irritable bowel syndrome in human subjects. *PLoS One*. 2015 May 13;10(5):e0126438.

B. Positions and Honors

Positions and Employment

1999-2001	Associate Director, GI Motility Program, Cedars-Sinai Medical Center
2001-present	Director, GI Motility Program, Cedars-Sinai Medical Center.
2014-present	Professor of Medicine (In-residence series), UCLA Geffen School of Medicine

Other Experience and Professional Memberships

1996-present	Member, American Gastroenterological Association
1996-present	Member, American College of Gastroenterology
1998-present	Member, American Motility Society

Honors

1984-88	Dean's List- Undergraduate, University of Manitoba.
1986	Highest achievement Notice in Mathematics, University of Manitoba
1987	Morris Neaman Memorial Scholarship for most outstanding BSc. Med. Research Project
1988	Highest Standing in Chemistry Medallion, University of Manitoba
1994-95	Teacher of the Year, Resident, Honorable Mention
1995-96	Chief Medical Resident, University of Manitoba
1996	Allan R. Ronald Book Prize, for Research Day
1998	Young Investigator Award. 10 th Biennial Meeting of the American Motility Society, Philadelphia, PA
2004	Rubinstein Award (mentorship of resident research) 1 st prize
2007	Rubinstein Award (mentorship of resident research) 1 st prize
2008	Cedars-Sinai Friends of Nursing Award. In recognition of support of nursing
2008	Rubinstein Award (mentorship of resident research) 1 st prize
2009	Research Award for our group (trainee). Neurogastroenterology and Motility Meeting, Chicago
2012	CTSI Researcher award, Cedars-Sinai Medical Center
2013	ACG Governors Award for Excellence in Clinical Research for paper entitled, "Anti-vinculin antibodies: Multicenter Validation of a diagnostic blood test for irritable bowel syndrome."
2013	Healthnetwork Service Excellence Award

C. Contribution to Science

My most significant contributions to science are as follows:

1. **Small intestinal bacterial overgrowth is common in IBS subjects.** While the concept of small intestinal bacterial overgrowth was not a controversial subject, the finding that it could be seen in IBS was highly controversial initially. However, continued efforts to validate breath testing through meta-analysis and later culture and sequencing of the small bowel, there is now good evidence that SIBO is seen in a subset of IBS subjects. New data is now expanding the concept that there may be

interactions between the gut microbes and the “brain-gut axis” blending the evolving understanding of IBS.

- a. **Pimentel M**, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome: A double-blind, randomized, placebo controlled study. *Am J Gastroenterol* 2003;98:412-9.
- b. Shah ED, Basseri RJ, Chong K, **Pimentel M**. Abnormal breath testing in IBS: A meta-analysis. *Dig Dis Sci* 2010;55:2441-9.
- c. Pylaris E, Giamarellou-Bourboulis EJ, Tzivras D, Koussoulas V, Barbatzas C, **Pimentel M**. The prevalence of small intestinal bacterial overgrowth by small bowel culture: Relationship with irritable bowel syndrome. *Dig Dis Sci* 2012; 57:1321-9.
- d. Giamarellou-Bourboulis E, Tang J, Pylaris E, Pistiki A, Barbatzas C, Brown J, Lee CC, Harkins TT, Kim G, Weitsman S, Barlow GM, Funari VA, **Pimentel M**. Molecular assessment of differences in the duodenal microbiome in subjects with irritable bowel syndrome. *Scandinavian journal of gastroenterology*. 2015; 50(9):1076-87.

2. **Methane and methanogenic archaea cause constipation.** In the pursuit of understanding the spectrum of IBS symptoms, we noted that when methane was seen on lactulose breath testing, subjects were nearly universally constipated. Through a series of studies, we showed that *M. smithii* is the organism responsible for this methane and the constipation.

- a. **Pimentel M**, Lin HC, Enayati P, van den Burg B, Lee H-R, Chen LJ, Park S, Kong Y, Conklin J. Methane, a gas produced by enteric bacteria, slows intestinal transit and augments ileal contractile activity. *Am J Physiol Gastrointestinal Liver Physiol* 2006;290:G1089-95.
- b. Chatterjee S, Park S, Low K, Kong Y, **Pimentel M**. The degree of breath methane production in IBS correlates with the severity of constipation. *Am J Gastroenterol* 2007;102:837-841.
- c. Hwang L, Low K, Khoshini R, Melmed G, Sahakian A, Makhani M, Pokkunuri V, **Pimentel M**. Evaluating breath methane as a diagnostic test for constipation predominant IBS. *Dig Dis Sci* 2010;55:398-403.
- d. Kim G, Deepinder F, Morales W, Hwang L, Weitsman S, Chang C, Gunsalus R, **Pimentel M**. *Methanobrevibacter smithii* is the predominant methanogen in patients with constipation-predominant IBS and methane on breath. *Dig Dis Sci* 2012;57:3213-8.

3. **Rifaximin produces a sustained relief of IBS.** Based on the emerging concept of bacterial overgrowth in IBS, we began exploring the use of antibiotics as a treatment for IBS. This culminated in 3 randomized controlled trials demonstrating that IBS is relieved by rifaximin. Moreover, this was the first time that patients received a therapy, and had a sustained benefit after cessation of therapy in IBS.

- a. **Pimentel M**, Park S, Kane, SV, Kong Y. Rifaximin, a non-absorbable antibiotic improves the symptoms of irritable bowel syndrome: A randomized, double-blind, placebo-controlled study. *Ann Intern Med* 2006;145:557-563.
- b. **Pimentel M**, Lembo A, Chey W, Zakko S, Ringel Y, Yu J, Mareya S, Shaw A, Bortey E, Forbes WP. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med* 2011;364:22-32.
- c. **Pimentel M**, Morales W, Chua K, Barlow G, Weitsman S, Kim G, Amichai MM, Pokkunuri V, Rook E, Mathur R, Marsh Z. Effects of rifaximin treatment and retreatment in nonconstipated IBS subjects. *Dig Dis Sci* 2011;56:2067-72.

4. **Developed the first animal model with IBS-like features after acute gastroenteritis in the US.** While groups were looking at various models of post-infectious IBS in animals, few were exploring the use of conventional human bacterial pathogens. Over the last decade we developed the techniques for and validated the first US animal model of post-infectious IBS. In this model, rats develop SIBO, altered stool form and increased rectal lymphocytes. Using this model we began to explore the role of bacterial toxins in the development of PI-IBS. This led to the studies that suggest that cytolethal distending toxin B (CdtB) might be important in the development of IBS.

- a. **Pimentel M**, Chatterjee S, Chang C, Low K, Song Y, Liu C, Lezcano S, Conklin J, Finegold S. A new rat model links two contemporary theories in irritable bowel syndrome. *Dig Dis Sci* 2008;53:982-9.

- b. Jee S-R, Morales W, Low K, Chang C, Zhu A, Pokkunuri V, Chatterjee S, Soffer EE, Conklin JL, **Pimentel M**. Interstitial Cell of Cajal Density Predicts Small Intestinal Bacterial Overgrowth in a Rat Model of Post-infectious IBS Secondary to *Campylobacter jejuni*. *World J Gastroenterol* 2010;16:3680-6.
 - c. Pokkunuri V, **Pimentel M**, Morales W, Jee S-R, Alpern J, Weitsman, Marsh Z, Low K, Hwang L, Khoshini R, Barlow G, Wang H, Chang C. Role of cytolethal distending toxin and bowel phenotypes in a rat model of post-infectious irritable bowel syndrome. *J Neurogastroenterol Motil* 2012;18:434-42.
5. **Discovered that serum antibodies to CdtB and vinculin are predictors of IBS forming the basis for the first blood test for IBS.** On the basis of antibodies to CdtB, it appears that through molecular mimicry, antibodies to CdtB might cross-react with human and rat vinculin. Studies now suggest this is true and this has culminated in a major work testing this approach as a diagnostic test to be used clinically.
- a. **Pimentel M**, Morales W, Pokkunuri V, Brikos C, Kim SM, Triantafyllou K, Weitsman S, Marsh E, Marsh Z, Chua KS, Srinivasan S, Barlow GM, Chang C. Autoimmunity links vinculin to the pathophysiology of chronic functional bowel changes following *Campylobacter jejuni* infection in a rat model. *Dig Dis Sci* 2015; 60(5):1195-205.
 - b. **Pimentel M**, Morales W, Rezaie A, Marsh E, Lembo A, Mirocha J, Leffler DA, Marsh Z, Weitsman S, Chua KS, Barlow GM, Bortey E, Forbes W, Yu A, Chang C.. Development and validation of a biomarker for diarrhea-predominant irritable bowel syndrome in human subjects. *PloS one*. 2015; 10(5):e0126438.

Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/1VksbUWH6htQc/bibliography/46056402/public/?sort=date&direction=ascending>

D. Research Support

Ongoing Research Support

Principal Investigator. Gut Family Fund. This philanthropic family has contributed yearly to the development of IBS models and solving IBS. September, 2014-present. The goal of this project is to further the understanding of the role of vinculin in IBS. This includes homology studies between CdtB and vinculin to identify the specific epitope of vinculin that may be susceptible to molecular mimicry.

Principal Investigator. Salix Pharmaceuticals. Developing a blood test for irritable bowel syndrome. Sept 2013-August 2014. In this study, we performed a large scale validation of anti-CdtB and anti-vinculin as a diagnostic test for D-IBS.

Principal Investigator. Synthetic Biologics. Anti-methanogenic properties of HMG Co-A Reductase Inhibitors. June 2014-present. In this project, we helped develop a proprietary statin product that inhibits methanogenesis. To inhibit methane might have the effect of reducing constipation in IBS-C.

Principal Investigator. Salix Pharmaceuticals. Effect of Rifaximin on Clinical and Downstream events in Post-infectious IBS using a Rat Model. August 2011-August 2012. In these projects, we assess the effect of rifaximin in an animal model of post-infectious IBS.

Principal Investigator. Salix Pharmaceuticals. The Effect of Rifaximin on Gastrointestinal Flora and Bacterial Resistance, August 2011-August 2012. In this study we assess the effect of rifaximin on gut microbial resistance over time.

Principal Investigator. Foundation Grant. To examine the role of intestinal infection in the pathophysiology of functional diseases (animal models). 2009-2012. This anonymous donor provided funding that helped develop the animal model of post-infectious IBS.

