

**BIOGRAPHICAL SKETCH**

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NAME: DAVID IRA SOYBEL

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

POSITION TITLE: Professor of Surgery

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 Chicago, Chicago, IL	B.A.	06/1978	Biology (Honors)
University of Chicago, Chicago, IL	M.D.	06/1982	Medicine (Honors)
Barnes Hospital, St. Louis, MO	Intern/Jr. Res.	06/1984	General Surgery
Washington Univ. Sch. Med., St Louis, MO	Research Fellow	06/1987	Surgery & Physiology
Barnes Hospital, St. Louis, MO.	Senior/Chief Res.	06/1990	General Surgery

**A. Personal Statement**

My initial and mid-career efforts in investigation (1990 to 2011), funded by VA and NIH awards, were directed at clarifying mechanisms of injury in gastric and colonic mucosa and their responses to inflammation at the cellular level. More recently, my efforts in investigation have focused gaps in our understanding of the biological mechanisms that drive recovery and convalescence after surgical illness and major operations. While the early stages of systemic injury and innate immune response seem well described, and programs of wound healing have been extensively studied, it remains unclear how patients get well after major illness or operations, and why some do not. In my most recent efforts, my research team has tested the hypothesis that hyperglycemia represents an important marker of early post-operative stress and provides clues to potentially important genetic and metabolic drivers of delays in healing and convalescence.

**Key publications:**

1. Won EJ, Lehman EB, Geletzke AK, Tangel MR, Matsushima K, Brunke-Reese D, Pichardo-Lowden AR, Pauli EM, **Soybel DI**. Association of postoperative hyperglycemia with outcomes among patients with complex ventral hernia repair. *JAMA Surg*. 2015 May;150(5):433-40. PMID: 25786088
2. Ssentongo P, Ssentongo AE, Dykes T, Pauli EM, **Soybel DI**. Nonalcoholic Fatty Liver Disease as a High-Value Predictor of Postoperative Hyperglycemia and Its Associated Complications in Major Abdominal Surgery. *J Am Coll Surg*. 2018 Oct;227(4):419-429. Epub 2018 Jul 27. PMID: 30059745
3. Brunke-Reese D, Ssentongo P, Ssentongo AE, Phillips BE, Pauli EM, Berg A, Kelleher SL, **Soybel DI**. The Role of Genetic Variant rs13266634 in SLC30A8/ZnT8 in Post-Operative Hyperglycemia after Major Abdominal Surgery. *J Clin Endocrinol Metab*. 2019 Apr 10 (online ahead of print). PMID 31220282
4. Oh JS, Ssentongo AE, Ssentongo P, Dykes T, Keeney L, Armen SB, **Soybel DI**. Image-based assessment of sarcopenic obesity predicts mortality in major trauma. *Am J Surg*. 2021 Jun 18 (online ahead of print) PMID: 34172258

## **B. Positions, Scientific Appointments, and Honors**

1990 - 1992	Assistant Professor of Surgery, Yale University School of Medicine
1990 – 1992	Associate in Surgery, Yale New Haven Hospital; Attending Surgeon, West Haven VAMC
1993 – 1996	Assistant Professor of Surgery, Harvard Medical School
1996 – 2001	Chief of General Surgery and Associate Chief of Surgical Services, West Roxbury V.A.M.C. and Boston V.A. Healthcare System
1993 - 2011	Senior Staff Surgeon, Brigham and Women's Hospital
1996 - 2008	Associate Professor of Surgery, Harvard Medical School
2001 - 2002	Associate Director for Graduate Medical Education, Partners HealthCare System
2002 - 2011	Consulting and Active Staff, Dana Farber Cancer Institute
2008 - 2011	Professor of Surgery, Harvard Medical School
2011 - 2020	David L. Nahrwold Professor of Surgery, Penn State Hershey School of Medicine
2011- 2020	Professor of Surgery, Cellular and Molecular Physiology, and Nutritional Sciences.
2011 - 2020	Vice-Chairman (Research), Department of Surgery, Penn State Hershey College of Medicine
2011 - 2020	Division Chief for General Surgery Specialties, Penn State Hershey College of Medicine and Penn State Hershey Medical Center, Hershey, PA
2020 – present	Chief of Surgical Services at the Department of Veterans Affairs Medical Center, White River Junction, VT
2020 – present	Professor of Surgery at the Dartmouth College Geisel School of Medicine

## **Other Experience**

1995 - 1999	V.A. MERIT REVIEW Study Section Surgery (member)
1997	NIH IRG Study Section Surgery and Bioengineering (ad hoc)
1999 - 2000	V.A. MERIT REVIEW Study Section Gastroenterology (ad hoc)
2002 - 2004	NIH Center for Scientific Review Advisory Council-CSRAC (member)
2008	Brigham and Women's Hospital/Harvard Business School Leadership Program
2012 2013	NIH SBIBY12 Small Business Grant Study Section (ad hoc)
2013	Harvard Law School Program in Negotiation

## **Honors**

1982	Catherine Dobson Research Award, University of Chicago
1985 - 1987	National Research Service Award, NIH/NIADDK
1990	Alpha Omega Alpha, Washington University School of Medicine
1996	Faculty Prize for Teaching Excellence, Harvard Medical School
1999 - 2000	President-Elect/President, Association for Academic Surgery
2004	Faculty Prize for Teaching Excellence, Harvard Medical School
2006	Outstanding Teacher of the Year, Association for Surgical Education
2008, 2009, 2010	Awards for Outstanding Teaching in the Core Surgery Clerkships, Brigham and Women's Hospital, Harvard Medical School
2018	Dean's Award for Excellence in Teaching, Penn State-Hershey College of Medicine

## **C. Contributions to Science (chronological order)**

- 1. Cellular ion homeostasis and intracellular pH regulation in acid-secreting parietal cells and surface epithelial cells of the gastric mucosa.** A longstanding problem in cellular physiology has been to understand how parietal cells maintain intracellular pH and ion composition during stimulation of large volumes of hydrochloric acid (HCl) secretion. Our work in the early 1990s provided evidence that acid-secreting cells of the stomach (amphibian oxyntopeptic cells and mammalian parietal cells) utilize redundant antiport or cotransport mechanisms linking pH regulation and HCO<sub>3</sub><sup>-</sup> movements to the transport of other ions (Na<sup>+</sup>, K<sup>+</sup> and Cl<sup>-</sup>), as well as describing the regulation of these mechanisms by the secretagogue-trophic hormone, gastrin. This work provided evidence for greater complexity of intracellular pH regulation in gastric cells than had previously been supposed. I was the principal investigator in this work, performing the studies or directly supervising students and surgical resident trainees in their career development.

## Citations

- a. **Soybel DI**, Davis, MBE, Cheung LY. Characteristics of basolateral Cl<sup>-</sup> transport in Necturus antral mucosa. *Am J Physiol - Gastrointest Liver Physiol* 1993; 264: G910-G920. PMID: 8498517
- b. **Soybel DI**, Gullans SR, Delpire E. Role of basolateral Na-K-Cl cotransport in acid secretion by amphibian gastric mucosa. *Am J Physiol- Cell Mol Physiol* 1995; 269: C242-C249. PMID: 7631751
- c. Klingensmith M, Hallonquist H, McCoy B, Cima R, Delpire E, **Soybel DI**. Pentagastrin selectively modulates expression of mRNAs encoding apical H/K ATPase and basolateral Na-K-Cl cotransport in rat gastric fundic mucosa. *Surgery* 1996; 120:242-247. PMID: 8751589
- d. Klingensmith ME, Cima RR, Gadacz AE, **Soybel DI**. Evidence for Cl<sup>-</sup>-independent HCO<sub>3</sub><sup>-</sup> transport in basolateral membranes of oxyntopeptic cells of Necturus gastric mucosa. *Am J Physiol-Cell Mol Physiol* 1996; 271: G1096-G1103. PMID: 8997254

2. **Expression and functional characterization of the extracellular calcium ion receptor (CaR) in gastrointestinal epithelial cell systems not directly involved in systemic calcium homeostasis.** In 1993, Hebert and Brown isolated and cloned the CaR from parathyroid and renal tissues, and demonstrated its role in managing systemic calcium homeostasis. Collaborating with these investigators, we demonstrated for the first time the presence and functional capabilities of the CaR in gastrointestinal mucosa, including stomach, small intestine and colon. In addition, our team demonstrated that the CaR was capable of detecting and being activated by small disturbances in calcium ion concentration generated by release of Ca<sup>2+</sup> ions from neighboring cells, thereby providing the first evidence that Ca<sup>2+</sup> ions might serve as “first messengers” that regulate signature functions in tissues not directly connected to calcium homeostasis. I was a co-principal investigator in this work (with Dr. Edward Brown), directly supervising students and trainees in their early career development.

## Citations

- a. Cima RR, Cheng I, Klingensmith ME, Chattopadhyay N, Kifor O, Hebert SC, Brown EM, **Soybel, DI**. Identification and functional assay of an extracellular calcium-sensing receptor in Necturus gastric mucosa. *Am J Physiol - Gastrointest Liver Physiol* 1997; 273: G1051-G1060. PMID: 9374702
- b. Chattopadhyay N, Cheng I, Rogers K, Riccardi D, Hall A, Diaz R, Hebert SC, **Soybel DI**, Brown EM. Identification and localization of an extracellular Ca<sup>2+</sup> sensing receptor in rat intestine. *Am J Physiol - Gastrointest Liver Physiol* 1998; 274: G122-G130. PMID: 9458781
- c. Cheng I, Chattopadhyay N, Butters R, Cima RR, Rogers KV, Hall AE, Hebert SC, Brown EM, **Soybel DI**. Expression of an extracellular calcium-sensing receptor in rat stomach. *Gastroenterol* 1999; 116: 118-126. PMID: 9869609
- d. Hofer, AM, Curci, S, Doble, MA, Brown, EM, **Soybel, DI**. Intercellular communication mediated by extracellular Ca<sup>2+</sup> receptor. *Nature Cell Biol* 2000; 2:392--398. PMID: 10878803.

3. **Role of Zinc ions (Zn<sup>2+</sup>) in regulation of gastrointestinal mucosal function and responses to inflammation/oxidate stress.** The biological importance of zinc has long been recognized for different stages of life, including: infant nutrition, childhood and adolescent growth, reproductive functions (including breast feeding) in women and men, and immunity in the elderly. In the course of studying calcium homeostasis in the GI tract, we became aware of the possibility that intracellular management of Zn<sup>2+</sup> might play previously unsuspected roles in regulation of important gastrointestinal functions. Our work in mammalian multicellular glandular systems (isolated gastric glands or colon crypts) has demonstrated that Zn<sup>2+</sup> ions are transported (through exchange with H<sup>+</sup> ions) into the acid-secreting tubulovesicle compartment of the gastric parietal cell and are required for the compartment to insulate itself from back-diffusion of those same H<sup>+</sup> ions. We have shown that intracellular stores of Zn<sup>2+</sup> are released, in both gastric and colonic mucosal cells, in the presence of oxidants that are generated when products of bacterial metabolism (ammonia NH<sub>3</sub>) come into contact with oxidants (hypochlorous acid, HOCl) generated by activated neutrophils or macrophages. In collaboration Dr. Shannon Kelleher (currently located at UMass-Lowell), we demonstrated that Zn<sup>2+</sup>

ions are transported by a specific transporter (SLC30A2 or ZnT2) into the secretory granules of Paneth cells, located in the crypts of the small intestine; we also provided evidence of the importance of this Zn<sup>2+</sup> transport pathway for the viability and bacterio-static/cidal capabilities of the Paneth Cell. Taken together, our observations (all firsts) provided evidence for the mechanisms by which cellular Zn<sup>2+</sup> homeostasis may play a significant role in protecting the organism from threats by luminal microorganisms in all segments of the GI tract. In the development of this work, I was the Principal Investigator for the team or a co-principal investigator in this work (with Dr. Shannon Kelleher), directly supervising students and trainees in those aspects of the work that focused on GI function.

#### Citations

- a. Gerbino, A, Hofer, AM, McKay BM, Lau BW, **Soybel, DI**. Divalent cations regulate acidity within the lumen and tubulovesicle compartment of gastric parietal cells *Gastroenterol* 2004; 126:182-195. PMID: 14699499
- b. Cima, RR, Dubach, JM, Wieland, AM, Walsh, BM, **Soybel, DI**. Intracellular Ca<sup>2+</sup> and Zn<sup>2+</sup> Signals During Monochloramine-Induced Oxidative Stress in Isolated Rat Colon Crypts. *Am J Physiol - Gastrointest Liver* 2006; 290: G250-G261. PMID: 16002562
- c. Liu JJ, Kohler JE, Blass AL, Moncaster JA, Mocofanescu A, Marcus MA, Blakely EA, Bjornstad KA, Amarasiwardena C, Casey N, Goldstein LE, **Soybel DI**. Demand for Zn<sup>2+</sup> in Acid-Secreting Gastric Mucosa and its Requirement for Intracellular Ca<sup>2+</sup>. *PLoS One* 2011;6(6):e19638. Epub 2011 Jun 15.
- d. Podany A, Wright J, Lamendella G, **Soybel DI**, Kelleher SL. ZnT2-mediated zinc import into Paneth cell granules is necessary for coordinated secretion and Paneth cell function in mice. *Cell Mol Gastroenterol Hepatol* 2016 Jan 8;2(3):369-383. doi: 10.1016/j.jcmgh.2015.12.006. PMID: 28174721

4. **Systemic zinc imbalance in the response to surgical stress.** In partnership with Dr. Shannon Kelleher (at that time in the Department of Nutritional Sciences at Penn State, University Park), we embarked on studies directed at understanding whether systemic imbalances in micronutrients such as zinc might be present and consequential in medically complex patients undergoing major abdominal operations. We established that such imbalances were common among such patients, especially when obesity and Type-2 Diabetes (T2D) were present and correlated with the likelihood of post-operative hyperglycemia and wound occurrences. Subsequently we established animal models for studying the effects of pathologically relevant, diet-induced imbalances in zinc stores on the early response to modest and severe surgical stress. In collaboration with Dr. Charles Lang (Department of Cell and Molecular Physiology at Penn State Hershey) we also established a model of surgical stress complicated by peritonitis, in order to simulate circumstances in which patients would undergo a major abdominal operation and then have catastrophic procedure-related complications. Our studies suggested that even modest zinc imbalances (not obvious zinc deficiencies) have diverse downstream effects on nutrition, immunity, and metabolic function, as well as disturbances in fat and skeletal muscle metabolism.

#### Citations

- a. Kelly E, Mathew J, Kohler JE, Blass AL, **Soybel DI**. Hemorrhagic Shock and Surgical Stress Alter Distribution of Labile Zinc within High and Low Molecular Weight Plasma Fractions. *Shock* 2012; 38(3):314-9. (Epub 2012 June 12). PMID:22744307
- b. Geletzke AK, Rinaldi JM, Phillips BE, Mobley SB, Miller J, Kaag M, Dykes T, Hollenbeak CS, Kelleher SL, **Soybel DI**. Prevalence of Systemic Inflammation and Micronutrient Imbalance in Patients with Complex Abdominal Hernias. *J Gastrointest Surg* 2014 Apr;18(4): 646-55. PMID:24356980
- c. Phillips BE, Geletzke AK, Smith PB, Podany AB, Chacon A, Kelleher SL, Patterson AD, **Soybel DI**. Impaired recovery from peritoneal inflammation in a mouse model of mild dietary zinc restriction. *Mol Nutr Food Res* 2015 60(3):672-81 PMID: 26627196
- d. Crowell KT, Soybel DI, Lang CH. Inability to replete white adipose tissue during the recovery phase of sepsis is associated with increased autophagy, apoptosis and proteasome activity. *Am J Physiol- Reg Integr Comp Physiol* 2017; 312: R388-R399. PMID: 28100477

5. **Addressing medical complexity in patients undergoing major operations.** In collaboration with a well-recognized health economist at Penn State University Park, Dr. Christopher Hollenbeak and more recently with colleagues here at the VA Medical Center in White River Junction, studies have been undertaken to more fully understand the environment in which medically complexity patients undergo major abdominal operations. In a series of cohort studies, data-mining studies, and systematic reviews, we have tried to understand barriers to managing such complex patients. Such barriers include the failure of health systems to recognize that low surgical volume centers often care for surgical patients who carry higher comorbidities for adverse outcome; and the need for health systems to identify medically and socially complex patients (such as the elderly) and understand how their care is influenced by systems designed to care for higher volumes of low complexity patients. The opportunities include economic incentives or disincentives for low-cost risk interventions in areas such as tobacco use and opioids for pain control. This work has had variable visibility. It has, however, been carried on in the spirit that any opportunity to pursue new ideas and innovations in patient care should be measured (at the outset) against both cost and the economic incentives and disincentives that influence decisions of surgeons, insurers, policy advisors, and patients themselves. In all of these efforts, the work was done collaboratively and with interdisciplinary oversight of trainees/students.

### **Citations**

- a. Matsushima K, Schaefer EW, Won EJ, Armen SB, Indeck MC, **Soybel DI**. Positive and negative volume outcome relationships in the geriatric trauma population. *JAMA-Surgery* 2014 Apr;149(4):319-26. 2013 (On-Line First Jan 22, 2014) PMID:24452778
- b. Wilson MZ, **Soybel DI**, Hollenbeak CS. Case Volume and Outcomes following Colectomy: The Results of a Matched Cohort Analysis. *Am J Med Qual* 2015; 30(3):271-282. PMID:24671097
- c. Kulaylat AS, Hollenbeak CS, **Soybel DI**. Cost-utility analysis of smoking cessation to prevent operative complications following elective abdominal colon surgery. *Am J Surg* 2018; 216:1082-1089. PMID30262122
- d. Liu JY, Anderson JC, Franklin JS, Gesek FA, **Soybel DI**. Nudging patients and surgeons to change ambulatory surgery pain management: Results from an opioid buyback program. *Surgery* 2021; 170: 485-492. PMID: 3367673