BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: **Sharkey, Keith A.**

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

POSITION TITLE: Professor of Physiology & Pharmacology

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 London, London, UK	BSc (Hons)	06/1981	Nutrition
University of Liverpool, Liverpool, UK	PhD	03/1985	Physiology
University of Bristol, Bristol, UK	Postdoctoral	12/1987	Neurogastroenterology
University of Calgary, Calgary, AB, Canada	Postdoctoral	03/1990	Neurogastroenterology

A. Personal Statement

I have focused, for most of my >30 year independent career, on understanding neural control of the gastrointestinal (GI) tract in health and inflammatory bowel disease. My laboratory has identified and characterized the effects of intestinal inflammation on neuronal, and enteroendocrine physiology in the GI tract, providing a mechanistic understanding of how altered neural signaling in the gut gives rise to functional alterations in inflammatory bowel disease. We have studied the impact of inflammatory bowel disease on the brain and in a series of studies have demonstrated central neural mechanisms of dysfunction leading to behavioural abnormalities associated with inflammatory bowel disease. We are actively studying the role of the gut microbiota on central and peripheral control mechanisms in the GI tract.

Before their roles had been widely appreciated, we proposed that endocannabinoids regulate secretory and motor functions in the GI tract. In a series of well-cited papers, we have shown novel actions of endocannabinoids working through the enteric nervous system. We discovered that cannabinoid CB_2 receptors localized on enteric nerves modify intestinal motility in inflammation, therefore providing a unique mechanism for the maintenance of intestinal homeostasis that may have implications and therapeutic potential in other inflammatory states. With the use of novel compounds that can modify endocannabinoid signaling, we have provided evidence for functional roles of the components of the endocannabinoid system in regulating motility, secretion and neurotransmission in the GI tract.

B. Positions and Honors

Positions:

1999-present Professor, Dept. Physiology & Pharmacology, University of Calgary, Calgary, AB, Canada
2017-2018 Director, Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada
2010-2017 Deputy Director, Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada
1995-1999 Associate Professor, Dept. Physiology & Biophysics, University of Calgary, Calgary, AB, Canada
1990-1995 Assistant Professor, Dept. Physiology & Biophysics, University of Calgary, Calgary, AB, Canada

Selected Honors and Representative Professional Activities:

2021 Distinguished Research Award, Gastrointestinal & Liver Physiology Section, American Physiological Society (presented at Experimental Biology, 2022)

2016	Finkelstein Award for Excellence, Crohn's and Colitis Canada
2015	*Fellow of the Canadian Academy of Health Sciences*
2014	Fellow of the *Canadian Association of Gastroenterology*
2013	Killam Annual Professor Award, *University of Calgary*
2012	"Smith" Distinguished Achievement Award for Senior Faculty, *Faculty of Medicine, University of Calgary*
2009	Research Leadership Award, *Crohn's and Colitis Foundation of Canada (CCFC)*
2006-2021	CCFC Chair in IBD Research, *Cumming School of Medicine, University of Calgary*
2006	Research Excellence Award, *Canadian Association of Gastroenterology*
2002	Janssen Masters Award in Gastroenterology, *American Gastroenterological Association*

2013-2017	Reviewing Editor, *The Journal of Physiology*
2013-present	Member, *Expert Advisory Board, Nature Reviews Gastroenterology and Hepatology*
2006-2011	Basic Science Editor, *Neurogastroenterology and Motility*

C. Contributions to Science

H index 68 (>16,800 total citations, 46 papers cited ≥100 times; ISI Web of Science, All database search)

- 264 Peer-reviewed publications including significant discoveries published in:
    - Science (IF: 47.7) 2005; Nature Medicine (IF: 53.4) 2001, 2012; Gastroenterology (IF: 22.7) 19 papers including, 2012, 2015, 2016; Nature Communications (IF: 14.9) 2020; Microbiome (IF 14.7) 2021; PNAS (IF: 11.2) 2008, 2019

PubMed Bibliography: https://www.ncbi.nlm.nih.gov/myncbi/1NaGasBE90LAG/bibliography/public/

Enteric nervous and enteroendocrine systems in intestinal inflammation. I proposed that the disturbances of gastrointestinal motility and secretion observed in intestinal inflammation were due to alterations in the processing of information in the gut wall because the detection systems, the intrinsic primary afferent neurons and enteroendocrine cells, were changed as a result of the inflammation. Using animal models and tissue from individuals with inflammatory bowel disease (IBD), my longstanding collaborator Dr. G.M. Mawe (University of Vermont) and I performed rigorous mechanistic analyses of the intestinal sensory system, both the primary afferent neurons and the enteroendocrine cells. We discovered that the properties of the sensory system are markedly altered in inflammation, with changes in neuronal excitability and increased release and availability of serotonin in animal models of inflammation and in IBD. We showed that specific changes persist over time and many also occur at a distance from the site of inflammation. Taken together, these changes alter the signaling in the gut and lead to reduced motility and secretion. During these studies we found a unique molecular defect in the gut associated with IBD. These findings represent the first systematic and mechanistic account of how neuronal signaling in the gut is altered in intestinal inflammation and in IBD and the first detailed analysis of the properties of major classes of enteric neurons in gut inflammation. These studies explain many of the functional deficits of IBD and are of further significance for the identification of specific molecular targets for the treatment of motor and secretory disturbances. Representative publications:

Coates, M.D., Mahoney, C.R., Linden, D. R., Sampson, J.E., Chen, J., Blaszyk, H., Crowell, M.D., **Sharkey, K.A.**, Gershon, M.D., Mawe, G.M., Moses, P.L. (2004). Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. Gastroenterology, **126**, 1657-1664.

Lomax, A.E., Mawe, G.M. and **Sharkey, K.A.** (2005). Synaptic facilitation and enhanced neuronal excitability in the enteric nervous system during experimental colitis. Journal of Physiology (London), **564.3**, 863-875.

Roberts, J.A., Durnin, L., **Sharkey, K.A.**, Mutafova-Yambolieva, V.N and Mawe, G.M. (2013). Oxidative stress disrupts purinergic neuromuscular transmission in the inflamed colon. Journal of Physiology (London), **591**, 3725-3737.

MacEachern, S.J., Keenan, C.M., Papakonstantinou, E., **Sharkey, K.A.*** and Patel, B.A.* (2018). Alterations in melatonin and serotonin signalling in the colonic mucosa of mice with dextran-sodium sulfate-induced colitis. British Journal of Pharmacology, **175**, 1535-1547 (*co-senior authors).

Enteric glia and their roles in intestinal inflammation and host defense. Neurons of the enteric nervous system are surrounded by a unique type of peripheral glial cell - enteric glia. My laboratory has defined many of the features of enteric glia in the normal and inflamed gut. We were the first to show that enteric glia respond to inflammation and inflammatory mediators, undergoing a process called reactive gliosis. With Drs. D.M. McKay (University of Calgary) and B. Patel (University of Brighton), we discovered that enteric glia express inducible nitric oxide synthase under normal physiological conditions and that nitric oxide from enteric glia plays a significant inhibitory role in the regulation of intestinal secretion in the normal and inflamed colon. We showed that enteric glia are important participants in enteric neurotransmission, particularly involving them as a novel target for sympathetic nerve terminals in the GI tract. These studies explain how stressful events can manifest themselves in the gut and alter its function through actions at the level of the enteric nervous system. Importantly my laboratory have shown that enteric glia are active players in neural signaling (as they are in the brain) and play an essential role in maintaining homeostasis, especially in disease states such as intestinal inflammation, where they contribute to the regulation of motility and secretion. Representative publications:

MacEachern, S.J., Patel, B.A., McKay, D.M. and **Sharkey, K.A.** (2011). Nitric oxide regulation of colonic epithelial ion transport: a novel role for enteric glia in the myenteric plexus. Journal of Physiology (London), **589** (Pt 13), 3333-3348.

Gulbransen, B.D., Bashashati, M., Hirota, S.A., Roberts, J.A., Beck, P.L., MacDonald, J.A., Muruve, D.A., McKay, D.M., Mawe, G.M., Thompson, R.J. and **Sharkey, K.A.** (2012). Activation of neuronal P2X7 receptor-pannexin-1 mediates death of enteric neurons during colitis. Nature Medicine, **18**, 600-605.

MacEachern, S.J., Patel, B.A., Keenan, C.M., Chapman, K., McCafferty, D.-M., Savidge, T., MacNaughton, W.K. and **Sharkey, K.A.** (2015). Inhibiting inducible nitric oxide synthase in enteric glia restores electrogenic ion transport in experimental colitis. Gastroenterology, **149**, 445-455.e3.

Vicentini, F.A., Keenan, C.M., Wallace, L.E., Woods, C., Cavin, J.-B., Flockton, A., Macklin, W.B., Belkind-Gerson, J., Hirota, S.A. and **Sharkey, K.A.** (2021). Intestinal microbiota shapes gut physiology and regulates enteric neurons and glia. Microbiome, In press.

Endocannabinoid regulation of motor and secretory function in the GI tract. Before their roles had been widely appreciated, we proposed that endocannabinoids regulate secretory and motor functions in the GI tract. In a series of landmark papers, in collaboration with Dr. Alexandros Makriyannis (Northeastern University) and others we have shown novel actions of endocannabinoids working through the enteric nervous system. We discovered that cannabinoid CB_2 receptors localized on enteric nerves can modify intestinal motility in inflammation, therefore providing a unique mechanism for the maintenance of intestinal homeostasis that may have implications and therapeutic potential in other inflammatory states. With the use of novel compounds that can modify endocannabinoid signaling, we have provided evidence for functional roles of the components of the endocannabinoid system in regulating motility, secretion and neurotransmission in the GI tract. Representative publications:

Hons, I.M., Storr, M.A., Mackie, K., Lutz, B., Pittman, Q.J., Mawe, G.M. and **Sharkey, K.A.** (2012). Plasticity of mouse myenteric synapses mediated through retrograde endocannabinoid and purinergic signaling. Neurogastroenterology and Motility, **24**, e113-e124.

Bashashati, M., Storr, M.A., Nikas, S.P., Wood, J.T., Godlewski, G., Liu, J., Ho, W., Keenan, C.M., Zhang, H., Alapafuja, S.O., Lutz, B., Mackie, K., Kunos, G., Patel. K.D., Makriyannis, A., Davison, J.S. and **Sharkey, K.A.** (2012). Inhibiting fatty acid amide hydrolase normalizes endotoxin-induced enhanced gastrointestinal motility in the mouse. British Journal of Pharmacology, **165**, 1556-1571.

Keenan, C.M., Storr, M.A., Thakur, G.A, Wood, J.T., Wager-Miller, J., Straiker, A., Eno, M.R., Nikas, S.P., Bashashati, M., Hu, H., Mackie, K., Makriyannis, A. and **Sharkey, K.A.** (2015). AM841, a covalent cannabinoid agonist, powerfully slows gastrointestinal motility in normal and stressed mice in a peripherally-restricted manner. British Journal of Pharmacology, **172**, 2406-2418.

Central mechanisms of behavioural dysfunction in intestinal inflammation. Intestinal inflammation leads to alterations in the central nervous system that manifest as pain, and behavioural comorbidities including anxiety and depression. The neural mechanisms of behavioural dysfunction and pain are not well understood. We investigated changes in the brain in colitis and discovered altered excitability of central neurons due to

activated microglia that release cytokines centrally to alter the expression of ion channels in central neurons. We have found that central cytokines upregulate the expression of the degradative enzyme for the endocannabinoid anandamide, reducing levels of this molecule, which leads to alterations in corticolimbic circuits that mediate anxiety. Reversing this change by improves the behavioural symptoms. We have also shown that the gut microbiota contributes to sensitization of visceral afferent nerves leading to chronic pain in animals that have recovered from colitis. Representative publications:

Riazi, K., Galic, M.A., Kuzmiski, B., Ho, W., **Sharkey, K.A.** and Pittman, Q.J. (2008). Microglial activation and TNFα production mediate altered CNS excitability following peripheral inflammation. Proceedings of the National Academy of Sciences USA, **105**, 17151-17156.

Riazi, K., Galic, M.A., Kentner, A.C., Reid, A.Y., **Sharkey, K.A.** and Pittman, Q.J. (2015). Microglia dependent alteration of glutamatergic synaptic transmission and plasticity in the hippocampus during peripheral inflammation. Journal of Neuroscience, **35**, 4942-4952.

Vecchiarelli, H.A., Morena, M., Keenan, C.M., Chiang, V., Tan, K., Qiao, M., Leitl, K., Santori, A., Pittman, Q.J., **Sharkey, K.A.** and Hill, M.N. (2021). Comorbid anxiety-like behaviour in a rat model of colitis is mediated by an upregulation of corticolimbic fatty acid amide hydrolase. Neuropsychopharmacology, **46**, 992-1003.

Esquerre, N., Basso, L., Defaye, M., Vicentini, F.A., Cluny, N., Bihan, D., Hirota, S.A., Schick, A., Jijon, H.B., Lewis, I.A., Geuking, M.B., **Sharkey, K.A**., Altier, C. and Nasser, Y. (2020). Colitis-induced microbial perturbation promotes postinflammatory visceral hypersensitivity. Cellular and Molecular Gastroenterology and Hepatology, **10**, 245-244.

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

Ongoing Research Support

Sharkey, K.A. **(PI)**	Canadian Institutes of Health Research. Foundation grant. Enteric neural control of the GI tract in health and inflammatory disease.	$336,486/yr	FDN148380	1 July 2016 - 31 March 2024

The goal of this grant is to the study enteric neural and glial mechanisms of motility and barrier function in health and inflammatory disease.

Pittman, Q.J. **Sharkey, K.A.** & Hill, M.N. **(Co-I)**	Canadian Institutes of Health Research. Project grant. Peripheral inflammation and anxiety: role of endocannabinoid signaling in the amygdala.	$173,655/yr	PJT159454	1 Oct 2018 - 30 Sept 2023

The goal of this grant is to study the mechanism of action of the endocannabinoid system in the regulation of anxiety.

Gruber, A. **Sharkey, K.A.** & Altier, C. **(Co-I)**	Alberta Innovates Operating grant. Novel therapeutic potential of non-psychotropic cannabinoids in pain, inflammation and depression.	$148,500/yr		1 June 2020 - 30 Sept 2022

The goal of this grant is to study non-psychotropic cannabinoids in visceral pain and colitis

Sharkey, K.A. **(PI)**	Abalone Inc. Operating grant The actions of CB2 agonists in colitis	$38,750		1 October 2020 - 30 September 2021

The goal of this grant is to study CB2 agonists in colitis.

Reimer, R.A., **Sharkey, K.A.**, Hart D.A., & Fortuna, R. **(Co-I)**	The W. Garfield Weston Foundation. Operating grant. Weston Family Microbiome Initiative Role of prebiotic supplementation in	$147,800		1 July 2019 - 30 June 2022

reducing inflammation and improving
physical function in adults with knee osteoarthritis and obesity.

The goal of this grant is to study the role of the gut microbiome in osteoarthritis.

Completed Research Support

Sharkey, K.A. **(PI)**	Millennium Pharmaceuticals (Takeda). Operating grant Studies of gene expression in the enteric nervous system of mouse models of GI disease	$166,415/yr		1 January 2018 - 30 June 2021

The goal of this grant is to study gene expression in enteric glia and neurons in inflammation.

Swain, M.G. + 9 others including **K. A. Sharkey (Co-I)**	Canadian Institutes of Health Research. Team grant. Brain dysfunction in chronic inflammatory disease: reciprocal effects of CNS and periphery crosstalk.	$458,496/yr	THC135321	1 July 2014 - 30 June 2020

The goal of this grant is to study the mechanisms of brain dysfunction in inflammatory bowel and liver disease.

Sharkey, K.A. **(PI)**	MedImmune Inc. Operating grant Expression profile and modulation of the enteric nervous system by a tumor necrosis factor (TNF) – family cytokine	$57,500		1 May 2017 – 30 April 2021

The goal of this grant is to study to expression of a TNF family member in the enteric nervous system.

Sharkey, K.A. **(PI)**	Lallemand Health Solutions Operating grant *In vivo* studies on Pediococcus acidilactici M5/18	$30,000		1 Oct 2016 – 30 Sept 2019

The goal of this grant was to examine the actions of this probiotic bacterium on GI function.

Sharkey, K.A. (PI)	Canadian Institutes of Health Research. Operating grant Endocannabinoids in the regulation of gastrointestinal motility disorders.	MOP38185		1 April 2013 - 31 March 2018

The goal of this project was to understand the role of the endocannabinoid system in disordered intestinal motility.

Sharkey, K.A. **(Co-I)** (PI: L. Parker)	Canadian Institutes of Health Research. Operating grant Endocannabinoid regulation of nausea in the visceral insular cortex.	MOP137122		1 October 2014 - 30 September 2016

The goal of this grant was to understand the role of endocannabinoids in the regulation of nausea.

Sharkey, K.A. **(PI)**	Canadian Institutes of Health Research. Operating grant Purinergic signalling and the role of enteric glia in the enteric nervous system in intestinal inflammation	MOP106569		1 October 2010 - 30 September 2015

The goal of this project was to understand the role of enteric glia in neurotransmission in health and in states of intestinal inflammation.