## BIOGRAPHICAL SKETCH

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NAME: Hanrahan, John William

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

POSITION TITLE: Professor of Physiology

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 |
|---|---|---|---|
| Dalhousie Univ., Halifax, Nova Scotia | B.Sc. (Hon.) | 06/76 | Biology |
| Univ. British Columbia, Vancouver, B.C. | Ph.D. | 03/82 | Zoology |
| Yale Univ. School of Medicine, New Haven, CT | PostDoc | 11/85 | Physiology/Biophysics |

### A. Personal Statement

I have a longstanding interest in epithelial anion and $Cl^-$ channels, especially CFTR. As a graduate student I studied insect epithelial $Cl^-$ transport using ion-sensitive microelectrodes and 2D cable analysis. As a postdoc I studied $Cl^-$ channels in the rabbit urinary bladder using current fluctuation analysis and patch clamping. After setting up my own lab at McGill I helped identify a cAMP regulated chloride channel in T84 epithelial cells, then recorded identical single channel activity in cells made to express the newly-cloned CFTR gene. That provided early evidence that CFTR is a chloride channel. Since then we have studied its regulation by kinases, serine/threonine phosphatases, and the roles of various phosphorylation sites on the R domain. The tyrosine kinase Src was shown by others to modulate CFTR gating and my lab observed surprisingly robust stimulation of CFTR by tyrosine kinases. We engineered a biotinylation target sequence into the 4th extracellular loop of CFTR and used image correlation spectroscopy, fluorescence recovery after photobleaching, and single particle tracking to study its lateral mobility. We are also interested in how CFTR regulates bicarbonate secretion into the airway surface liquid (ASL) and have analyzed the buffer capacity of airway secretions, airway bicarbonate transport by apical CFTR and pendrin and basolateral AE2, and most recently found bicarbonate-dependent pH oscillations on the airway surface that have far-reaching implications for airway physiology and host-defense.

### B. Positions and Honors

Positions

| | |
|---|---|
| 1982-1985 | Postdoctoral Fellow, Department of Physiology, Yale Univ. School of Medicine |
| 1986-1991 | Assistant Professor, Department of Physiology, McGill University |
| 1991-present | Medical Scientist, Montreal Chest Institute, McGill University Health Centre |
| 1991-present | Associate Member, Meakins-Christie Laboratory, McGill University Health Centre |
| 1992-1999 | Associate Professor, Department of Physiology, McGill University |
| 1999-present | Professor, Department of Physiology, McGill University |

Honors

| | |
|---|---|
| 1980 | Scholarship, Natural Sciences and Engineering Research Council Canada |
| 1982 | Thesis Award, Outstanding Ph.D. of 1982, Canadian Society of Zoologists |
| 1982-84 | NSERC/NATO Fellowship, Yale University School of Medicine |
| 1984 | Brown-Coxe Fellowship, Yale University School of Medicine, declined |

| | |
|---|---|
| 1984-85 | Post-doc Fellowship, Medical Research Council Canada, Yale University |
| 1987-91 | Research Scholarship, Medical Research Council Canada (salary award) |
| 1992 | J.A.F. Stevenson Professor Award, Canadian Physiological Society |
| 1992 | Milbury Fellow, Mount Desert Island Biological Laboratory, Maine |
| 1993 | Senior Scientist II, Fonds de la recherche en santé du Québec (salary award) |
| 1994-98 | Scientist, Medical Research Council Canada (salary award) |
| 1999-04 | Senior Scientist, Medical Research Council Canada (salary award) |
| 2001 | Visiting Professor, Burroughs-Wellcome Foundation |
| 2003 | Benjamin Meaker Visiting Professorship, University of Bristol |
| 2005-09 | Council Member and Trustee, Physiological Society (UK) |

**C. Contributions to Science - selected publications**

We have characterized epithelial transport, focusing on chloride and bicarbonate secretion by airway epithelial cells and the roles of CFTR, pendrin and SLC26A9:

Sato Y, Mustafina KR, Luo Y, Martini C, Thomas DY, Wiseman PW, **Hanrahan JW**. 2021. Nonspecific binding of common anti-CFTR antibodies in ciliated cells of human airway epithelium. Sci Rep. Dec 1;11(1):23256.

Kim D, Liao J, Scales N, Martini C, Luan X, AbuArish A, Robert R, Luo Y, McKay GA, Nguyen D, Tewfik MA, Poirier CD, Matouk E, Ianowski JP, Frenkiel S, **Hanrahan JW.** 2021. Large pH oscillations promote host defense against human airways infection. J Exp Med. 218(4):1-15.

Sato Y, Thomas DY, **Hanrahan JW.** 2019. The anion transporter SLC26A9 localizes to tight junctions and is degraded by the proteasome when co-expressed with F508del-CFTR. J. Biol. Chem. 294(48):18269-1828415.

Kim D, Huang J, Billet A, AbuArish A, Goepp J, Matthes E, Tewfik MA, Frenkiel S, **Hanrahan JW.** 2019. Pendrin mediates bicarbonate secretion and enhances CFTR function in airway surface epithelia. Am J. Resp. Cell Mol. Biol. 60(6):705-716.

Huang J, Kim D, Shan J, Abu-Arish A, Luo Y and **Hanrahan JW**. (2018). Most bicarbonate secretion by Calu-3 cells is mediated by CFTR and independent of pendrin. Physiol Rep.6(5): e13641.

Kim D, Liao J, **Hanrahan JW**. 2014. The buffer capacity of airway epithelial secretions. Front Physiol.5: 188.

Shan J, Liao J, Huang J, Robert R, Palmer ML, Fahrenkrug SC, O'Grady SM, **Hanrahan JW.** 2012. Bicarbonate-dependent chloride transport drives fluid secretion by the human airway epithelial cell line Calu-3. *J Physiol.* 590:5273-5297.

Huang J, Shan J, Kim D, Liao J, Evagelidis A, Alper SL, **Hanrahan JW**. 2012. Basolateral chloride loading by AE2: Role in fluid secretion by the human airway epithelial cell line Calu-3. J Physiol. 590:5299-5316. doi: 10.1113/jphysiol.2012.236919

We have studied the regulation of cAMP levels and CFTR activity by phosphodiesterases and protein kinases

Turner MJ, Sato Y, Thomas DY, Abbott-Banner K, **Hanrahan JW**. 2021. Phosphodiesterase 8A Regulates CFTR Activity in Airway Epithelial Cells. Cell Physiol Biochem. 55:784-804.

Turner MJ, Abbott-Banner K, Thomas DY, **Hanrahan JW**. 2021. Cyclic nucleotide phosphodiesterase inhibitors as therapeutic interventions for cystic fibrosis. Pharmacol. Ther. 224:1-144.

Turner MJ, Dauletbaev N, Lands LC, **Hanrahan JW**. 2020. The phosphodiesterase inhibitor ensifentrine reduces production of proinflammatory mediators in well differentiated bronchial epithelial cells by inhibiting PDE4. J Pharmacol Exp Ther. 375(3):414-429

Turner MJ, Luo Y, Thomas DT, **Hanrahan JW**. 2020. The dual phosphodiesterase 3/4 inhibitor RPL554stimulates rare class III and IV CFTR mutants. Am. J. Physiol-Lung Cell and Mol. Physiol. 318(5): L908- L9209.

Billet A, **Hanrahan JW.** 2013 The secret life of CFTR as a calcium-activated chloride channel. J. Physiol. 591:5273-5278. doi: 10.1113/jphysiol.2013.261909

Billet A, Luo Y, Balghi H, **Hanrahan JW**. 2013 Role of Tyrosine Phosphorylation in the Muscarinic Activation of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). J. Biol. Chem. 288(30): 21815-23. doi: 10.1074/jbc.M113.479360

Billet A, **Hanrahan JW**. 2013. The secret life of CFTR as a calcium-activated chloride channel. J. Physiol. 591(21): 5273-8.

Seavilleklein G, Amer N, Evagelidis A, Chappe F, **Hanrahan JW** and Chappe V. 2008. PKC phosphorylation modulates PKA-dependent binding of the R domain to other domains of CFTR. Am. J. Physiol. Cell Physiol. 295:C1366-75.

Chappe V, Irvine T, Liao J, Evagelidis A and **Hanrahan JW**. 2005. Phosphorylation of CFTR by PKA promotes binding of the regulatory domain. EMBO J. 24:2730-40.

Chappe FG, Loewen ME, **Hanrahan JW** and Chappe VM. 2008. VIP increases CFTR levels in the apical membrane of Calu-3 cells through a PKC-dependent mechanism. *J. Pharmacol. Exp. Ther.* 327:226-38.

Chappe V, Hinkson DA, Howell LD, Evagelidis A, Liao J, Chang X-B, Riordan JR and **Hanrahan JW**. 2004. Stimulatory and inhibitory protein kinase C consensus sequences regulate the cystic fibrosis transmembrane conductance regulator. *Proc. Natl. Acad. Sci (USA)* 101:390-395.

Chappe V, Hinkson DA, Zhu T, Chang X-B, Riordan JR and **Hanrahan JW**. 2003. Phosphorylation of protein kinase C sites in NBD1 and the R domain control CFTR channel activation by PKA. *J. Physiol.* 548:39-52.

Mathews CJ, Tabcharani JA, Chang X-B, Jensen, TJ, Riordan JR and **Hanrahan JW**. 1998. Dibasic protein kinase A sites regulate bursting rate and nucleotide sensitivity of the cystic fibrosis transmembrane conductance regulator chloride channel. *J.Physiol.* 508: 365-377.

Jia Y, Mathews CJ and **Hanrahan JW**. 1997. Phosphorylation by protein kinase C (PKC) is required for acute activation of CFTR by protein kinase A (PKA). *J. Biol. Chem.* 272: 4978-4984.

Seibert FS, Tabcharani JA, Chang X-B, Dulhanty AM, Mathews CJ, **Hanrahan JW** and Riordan JR. 1995. cAMP-dependent protein kinase-mediated phosphorylation of cystic fibrosis transmembrane conductance regulator residue ser-753 and its role in channel activation. *J. Biol. Chem.* 270: 2158-2162.

Chang X-B, Tabcharani JA, Hou Y-X, Jensen TJ, Kartner N, Alon N, **Hanrahan JW** and Riordan JR 1993. Protein kinase A (PKA) still activates CFTR chloride channel after mutagenesis of all ten PKA consensus phosphorylation sites. *J. Biol. Chem.* 268: 11304-11311.

Tabcharani JA, Chang X-B, Riordan JR and **Hanrahan JW**. 1991. Phosphorylation-regulated Cl- channel in CHO cells stably expressing the cystic fibrosis gene. *Nature* 352: 628-631.

Kartner N, **Hanrahan JW**, Jensen TJ, Naismith AL, Sun S, Ackerley CA, Reyes EF, Tsui LC, Rommens JM, Bear CE and Riordan JR. 1991. Expression of the cystic fibrosis gene in non-epithelial invertebrate cells produces a regulated anion conductance. *Cell* 64: 681-691.

We have studied the selectivity of CFTR and the outwardly rectifying anion channel to bicarbonate and other anions:

Tabcharani JA, Linsdell P and **Hanrahan JW**. 1997. Halide permeation in wild-type and mutant cystic fibrosis transmembrane conductance regulator chloride channels. *J. Gen. Physiol.* 110: 431-354.

Linsdell P, Tabcharani JA, Rommens JM, Hou Y-X, Chang X-B, Tsui L-C, Riordan JR and **Hanrahan JW**. 1997. Permeability of wild-type and mutant cystic fibrosis transmembrane conductance regulator chloride channels to polyatomic anions. *J. Gen. Physiol.* 110: 355-364.

Linsdell P, Tabcharani JA and **Hanrahan JW**. 1997. Multi-ion mechanism for ion permeation and block in the cystic fibrosis transmembrane conductance regulator chloride channel. *J. Gen. Physiol.* 110: 365-377.

Tabcharani JA, Rommens JM, Hou Y-X, Chang X-B, Tsui L-C, Riordan JR and **Hanrahan JW**. 1993. Multi-ion pore behaviour in the CFTR chloride channel. *Nature* 366: 79-82.

Tabcharani JA, Chang X-B, Riordan JR and **Hanrahan JW**. 1992. The CFTR chloride channel: Iodide block and permeation. *Biophys. J.* 62: 1-4.

Tabcharani JA, Jensen TJ, Riordan JR and **Hanrahan JW**. 1989. Bicarbonate permeability of the outwardly rectifying anion channel. *J. Membrane Biol.* 112: 109-122.

We have screened libraries of drug-like molecules and natural products for novel correctors of F508del-CFTR and characterized their modes of action:

Sampson HM, Lam H, Chen PC, Zhang D, Mottillo C, Mirza M, Qasim K, Shrier A, Shyng SL, **Hanrahan JW**, Thomas DY 2013. Compounds that correct F508del-CFTR trafficking can also correct other protein trafficking diseases: an in vitro study using cell lines." Orphanet Journal of Rare Diseases 8:11. doi: 10.1186/1750-1172-8-11.

Carlile GW, Keyzers RA, Teske KA, Robert R, Williams DE, Linington RG, Gray CA, Anjos SM, Sampson HM, Zhang D, Liao J, **Hanrahan JW**, Andersen RJ, Thomas DY 2012. Correction of delF508-CFTR trafficking by inhibition of PARP with the sponge alkaloid Latonduine. Chemistry & Biology 19:1288-1299. doi: 10.1016/j.chembiol.2012.08.014

Anjos SM, Robert R, Waller D, Zhang D, Balghi H, Sampson HM, Ciciriello F, Lesimple P, Carlile GW, Goepp J, Liao J, Pasquale F, Phillipe R, Dantzer F, **Hanrahan JW**, Thomas DY 2012. Decreasing Poly(ADP-ribose) Polymerase activity restores ΔF508 CFTR trafficking. Frontiers in Pharmacology 3:165. doi: 10.3389/fphar.2012.00165.

Sampson HM, Robert R, Liao J, Matthes E, Carlile GW, **Hanrahan JW**, Thomas DY. 2011. Identification of a NBD1-binding pharmacological chaperone that corrects the trafficking defect of F508del-CFTR. Chemistry & Biology. 18:231-242.

Robert R, Carlile GW, Liao J, Balghi H, LeSimple P, Liu N, Kus B, Rotin D, Wilke M, De Jonge HR, Scholte BJ, Thomas DY, **Hanrahan JW.** 2010. Correction of the Delta phe508 cystic fibrosis transmembrane conductance regulator trafficking defect by the bioavailable compound glafenine. Mol. Pharmacol. 77:922-930.

Robert R, Carlile GW, Pavel C, Liu N, Anjos S, Liao J, Luo Y, Zhang D, Thomas DY and **Hanrahan JW**. 2007. Structural analogue of sildenafil identified as a novel corrector of the F508del-CFTR trafficking defect. Mol. Pharmacol. 73:478-489.

We have investigated the effects of cigarette smoke on CFTR function, demonstrating it causes a robust initial stimulation and inhibition after prolonged exposure at low concentrations.

Wong F, Abu-Arish A, Matthes E, Turner MJ, Greene LE, Cloutier A, Robert R, Thomas DY, Cosa G, Cantin AM, and **Hanrahan JW**. 2018. Cigarette smoke activates CFTR through ROS-stimulated cAMP signaling in human bronchial epithelial cells. American Journal of Physiology: Cell Physiology. 314: C118-C134.

Cantin AM, Bilodeau G, Liao J, and **Hanrahan JW**. 2006. Oxidant stress suppresses CFTR expression. Am. J. Physiol. Cell Physiol. 290:C262-70.

Cantin AM, **Hanrahan JW**, Bilodeau G, Ellis L, Dupuis A, Liao J, Zielenski J, Durie P. 2006. Cystic Fibrosis Transmembrane Conductance Regulator function is suppressed in cigarette smokers. Am. J. Respir. Crit. Care Med. 173:1139-44.

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

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|---|---|
| May 2014-21 | Co-organizer and host, annual CFTRc/Fibrose Kystique Quebec symposium |
| Jan 2010-19 | NACFC Conference organizing committee, North American CF Conferences in Anaheim CA, Orlando FL, Salt Lake City UT, Atlanta GA, Phoenix AZ, Orlando FL |
| July 2011 | Symposium Speaker and co-organizer, Epithelial transport during infection and nflammation, Physiology 2001, Oxford Univ., UK |
| Mar 2011 | Co-Chair, Basic Science Conference, European CF Society, Ste. Maxime, France |