McGill | Faculty of Medicine and Health Sciences | Faculté de médecine et des sciences de la santé

## Committee for Oversight of Research Units

## Annual Reporting for Faculty Supported Research Centres and Networks

---

All Centres (provisional Centres; McGill Centres), Research groups and Networks that receive funding from the Faculty of Medicine and Health Sciences (FMHS) are required to provide an annual report to the Committee for Oversight of Research Units (CORU)

The reporting period is May 1, 2021 – April 30, 2022.

Please submit your report to the Research Office, Faculty of Medicine and Health Sciences (**riac.med@mcgill.ca**) before the following deadline:

# Monday, May 2, 2022

**Continued support from the Faculty is contingent on:**

1. the receipt of the reporting documents on time,
2. the evaluation of reported activities by the Faculty's Committee for Oversight of Research Units (CORU),
3. the availability of Faculty funds.

Your strong engagement in the Faculty's mission for continued research excellence and financial stewardship is truly appreciated.

## Annual Report of Activities and Outcomes

Name of the Unit: **McGill Cystic Fibrosis Translational Research Centre (CFTRc)**

Name of Unit leader & email address:

Director: **Dr. John Hanrahan**
john.hanrahan@mcgill.ca
514-398-8320

Co-Director (Clinical): **Dr. Larry Lands**
larry.lands@mcgill.ca
514-412-4444

Associate Director: **Dr. David Thomas**
david.thomas@mcgill.ca
514-398-2973

Manager: **Dr. Annick Guyot**
annick.m.guyot@mcgill.ca
514-398-4323 x1

If the Unit is **a Senate-approved** McGill Research Centre, indicate date of approval: **October 8th, 2015**

**Mission statement** of the Unit (~ 2 sentences):

The mission of the Cystic Fibrosis Translational Research Centre (CFTRc) is to accelerate the development of a cure for cystic fibrosis. To achieve this goal, the it provides a platform for basic CF research and the development of therapies targeting the basic defect that underlies cystic fibrosis and other protein trafficking diseases.

**Total number of Unit members: 17 regular members** and **17 associate members**

**Number of members affiliated with McGill's FMHS: 14 regular members** and **7 associate members**

**Unit's website:**

**Please note the website needs to feature:**

- all sources of funding support (including the FMHS logo),
- the list of Members and their institutional affiliation with appropriate links,
- the activities supported by the Unit,
- all previous Annual Reports.

Website address (URL): **https://www.mcgill.ca/cftrc**

**Please respect the page limits, where indicated.**

*(minimum font size of 11 pts, use lay language)*

**1. Explain the significance of the Unit's mission at McGill and beyond** (1/2 page max.)

To accelerate the development of a cure for cystic fibrosis, the CFTRc serves as a base for scientific networking/collaboration and training, and offers specialized resources that are needed to carry out mechanistic studies of CF disease and develop new therapeutics. More specifically, the CFTRc provides:

-a stimulating training environment for students and postdocs that is enhanced by collaboration with other centres, virtual international conferences and seminars by leading researchers.

-a structure that facilitates liaison with Cystic Fibrosis Canada, the US Cystic Fibrosis Foundation, UK CF Trust, and the European CF Society, and which can promote the awareness of CF through outreach activities and publicity.

-training on, and access to, state-of-the-art core equipment for fundamental CF research, including electrophysiology (Ussing chamber setups and automated patch-clamp), large scale (bioreactor) culture of mammalian cells for biochemical studies, spectro-fluorometry, and imaging of protein trafficking in live cells using confocal and TIRF fluorescence microscopy.

-access to expertise in assay development, screening and hit validation.

-pulmonary cells isolated from the lungs of CF patients undergoing transplantation and from non-CF donors. The Primary Airway Cell Biobank (PACB) isolates and distributes lung cells, tissue and biofluid samples to researchers across Canada and internationally. The PACB also biobanks cells from donors with other respiratory diseases including asthma, COPD, emphysema, IPF and has seen requests for these increase during the pandemic. The biobank is certified by the International Society of Biological and Environmental Repositories (ISBER). It is promoted by the US CF Foundation (https://www.cff.org/Research/Researcher-Resources/Tools-and- Resources/CF-Foundation-Biorepository/), the UBC Office of Biobank Education and Research Biobank Certification Program (https://biobanking.org/biobanks/view/218), and the Association of Biomolecular Resource Facilities (ABRF) core marketplace (https://abrf.org/abrf-core-marketplace). The PACB is a member of the Canadian Network of Scientific Platforms (CNSP (cnsp-rcps.ca)), a pan-Canadian network of professionals working on technical, managerial and administrative levels in scientific platforms (i.e. core facilities and technology resources). The network represents diverse technologies and institutions across the country and its mandate is to raise awareness and increase the value of scientific platforms, educate research personnel, set and promote best practices, enhance communication and cooperation within the research community, and promote interaction with industry.

**2. Alignment with the Faculty's Strategic Research Plan** (1/2 page max.)

The activities of the CFTRc are fully consistent with the strategic research plan and mission of the Faculty of Medicine and Health Sciences. The centre aligns with Strategic Priority 4.3 of the FHMS Strategic Research Plan "Key Determinants of Health and Disease: gene, Behavior and Environment ". ''Our Faculties will continue to support research efforts towards gene discovery and treatment in rare diseases and in common complex disorders,….''. The CFTRc will support this vision in several ways:

- it provides a structure that promotes collaboration between members
- it provides an international footprint that is recognized worldwide. For example the PACB has attracted customers from Scotland, Northern Ireland, England, Japan, Germany, The Netherlands and many centres across Canada and the USA. The CFTRc supplies airway epithelial cells, other cells and lung samples (alveolar cells, smooth muscle, fibroblasts, sputum), media, and expertise. It enhances the international profile of group members and stimulates innovative research programs within the unit and externally.
- it provides an enhanced training environment for postdocs and students.
- it attracts funding from industry thanks to its emphasis on translational research and its resources and expertise. New opportunities have emerged with partners (EnGene, Laurent Pharma, Feldan Therapeutics, Verona Pharma, etc) in large part because CFTRc is known as a translational research centre. This collaboration with industry maximizes the benefit obtained from previous CFI investments in CFTRc infrastructure (approx. $5M from CFI6). The centre is of strategic importance for CF research and also for studies in other areas related to protein folding and long QT syndrome type 2 (Lukacs), alpha1 antitrypsin deficiency (Thomas), COPD (Thomas and Hanrahan), asthma (Martin, Lands) and COVID19 (Hanrahan, Lukacs).

3. **Major joint publications over the past 12 months** (including shared software, data repositories; with links) co-authored by at least two PI members of the Unit:

**1.** Long-term bone mineral density changes and fractures in lung transplant recipients with cystic fibrosis.
Durette G, Jomphe V, Bureau NJ, **Poirier C**, Ferraro P, **Lands LC**, Mailhot G.
***J Cyst Fibros.*** 2021 May;20(3):525-532. doi: 10.1016/j.jcf.2020.09.012. Epub 2020 Oct 21.

**2**. A Precision Medicine Approach to Optimize Modulator Therapy for Rare CFTR Folding Mutants.
Veit G, Velkov T, Xu H, Vadeboncoeur N, Bilodeau L, **Matouk E**, **Lukacs GL**.
***J Pers Med.*** 2021 Jul 7;11(7):643. doi: 10.3390/jpm11070643.

**3**. Characterizing Vocal Fold Injury Recovery in a Rabbit Model With Three-Dimensional Virtual Histology.
Kolosova K, Gao Q, Tuznik M, Bouhabel S, Kost KM, Wang H, Li-Jessen NYK, **Mongeau L**, **Wiseman PW**.
***Laryngoscope.*** 2021 Jul;131(7):1578-1587. doi: 10.1002/lary.29028. Epub 2020 Aug 18.

**4**. Cyclic nucleotide phosphodiesterase inhibitors as therapeutic interventions for cystic fibrosis.
Turner MJ, Abbott-Banner K, **Thomas DY**, **Hanrahan JW**.
***Pharmacol Ther.*** 2021 Aug;224:107826. doi: 10.1016/j.pharmthera.2021.107826. Epub 2021 Mar 1.

**5**. Differential Regulation of the Asthmatic Phenotype by the Aryl Hydrocarbon Receptor.
Traboulsi H, de Souza AR, Allard B, Haidar Z, Sorin M, Moarbes V, Fixman ED**, Martin JG**, Eidelman DH, **Baglole CJ**.
***Front Physiol.*** 2021 Oct 21;12:720196. doi: 10.3389/fphys.2021.720196. eCollection 2021.

**6**. Nonspecific binding of common anti-CFTR antibodies in ciliated cells of human airway epithelium.
Sato Y, Mustafina KR, Luo Y, Martini C, **Thomas DY**, **Wiseman PW**, **Hanrahan JW**.
***Sci Rep.*** 2021 Dec 1;11(1):23256. doi: 10.1038/s41598-021-02420-x.

**7**. Phosphodiesterase 8A Regulates CFTR Activity in Airway Epithelial Cells.
Turner MJ, Sato Y, **Thomas DY**, Abbott-Banner K, **Hanrahan JW**.
***Cell Physiol Biochem.*** 2021 Dec 23;55(6):784-804. doi: 10.33594/000000477.

**8**. Rescue of mutant CFTR trafficking defect by the investigational compound MCG1516A.
Lopes-Pacheco M, Bacalhau M, Ramalho SS, Silva IAL, Ferreira FC, Carlile GW, **Thomas DY**, Farinha CM, **Hanrahan JW**, Amaral MD.
***Cells.*** 2022 Jan 1;11(1):136. doi: 10.3390/cells11010136.

**9**. Lipid-driven CFTR clustering is impaired in cystic fibrosis and restored by corrector drugs.
Abu-Arish A, Pandžić E, Luo Y, Sato Y, Turner MJ, **Wiseman PW**, **Hanrahan JW**.
***J Cell Sci.*** 2022 Mar 1;135(5):jcs259002. doi: 10.1242/jcs.259002. Epub 2022 Mar 7.

**10**. Conducting an Endoscopic Sinus Surgery Dissection Course via Telesimulation: An Initial Experience.
Tham AC, Himdi L, Nguyen LHP, **Frenkiel S**, **Tewfik MA**.
***OTO Open.*** 2022 Mar 4;6(1):2473974X221083981. doi: 10.1177/2473974X221083981. eCollection 2022

**11**. The NSAID glafenine rescues class 2 CFTR mutants via cyclooxygenase 2 inhibition of the arachidonic acid pathway.
Carlile GW, Yang Q, Matthes E, Liao J, Birault V, Sneddon HF, Poole DL, Hall CJ, **Hanrahan JW**, **Thomas DY**.
***Sci Rep.*** 2022 Mar 17;12(1):4595. doi: 10.1038/s41598-022-08661-8.

**12**. Co-Operative Biofilm Interactions between Aspergillus fumigatus and Pseudomonas aeruginosa through Secreted Galactosaminogalactan Exopolysaccharide.
Ostapska H, Le Mauff F, Gravelat FN, Snarr BD, Bamford NC, Van Loon JC, McKay G, **Nguyen D**, Howell PL, **Sheppard DC**.

***J Fungi (Basel).*** 2022 Mar 24;8(4):336. doi: 10.3390/jof8040336.

**13**. Characterization of skeletal muscle wasting pathways in diaphragm and limb muscles of cystic fibrosis mice.
Gusev E, Liang F, Bhattarai S, Broering FE, Leduc-Gaudet JP, Hussain SNA, **Radzioch D**, **Petrof B**.
***Am J Physiol Regul Integr Comp Physiol.*** 2022 Apr 12. doi: 10.1152/ajpregu.00225.2021.

4. **Major joint research projects funded over the past 12 months** (involving at least two PI members of the Unit:

**Hanrahan JW** and **Thomas DY**. Pharmacological chaperones that bind F508del-CFTR and their mechanisms of action, ***CIHR***

**Lukacs GL**, **Matouk E** and **Rousseau S**. Mechanism and pharmacological modulation of intrinsic and acquired pro-inflammatory state of the airway epithelia in cystic fibrosis, ***CIHR***

**Lukacs GL** and **Matouk E**. Rational optimization of CFTR modulators and assessment of predictive potential of novel cystic fibrosis (CF) airway epithelial models for clinical outcome, ***CIHR***

**Lukacs G** and **Matouk E**. Molecular basis of and preclinical approaches to overcome therapy-resistant cystic fibrosis mutations, ***CIHR***

**Thomas DY** and **Hanrahan JW**. Research Funding agreements for projects on alpha-1 anti-trypsin deficiency and acquired CFTR deficiency, ***McGill/CQDM/Pfizer/Traffick Therapeutics***

**Baglole C** and **Fritz JH** Immunological consequences of inhaled cannabis and selected cannabinoids, ***CIHR***

**Fritz JH** and **Gruenheid SL** Role of the cystic fibrosis transmembrane conductance regulator (CFTR) in intestinal homeostasis, ***CIHR***

5. **Major outreach activities** (e.g., seminar series, general public events):

**-Annual symposium**: held on Zoom on May 27-28 2021. Number of attendees: 100. See program in **Appendix 1**.

**-Seminar Series:** cutting edge *seminars* were organized through the Centre and held on Zoom due to the pandemic. Number of attendees: 50 in average. See advertising posters in **Appendix 2**.
Deborah Baines – January 18 2022
Cedric Govaerts – March 17 2022
Ann Harris – April 21 2022

**-Communications:**
http://www.mcgill.ca/cftrc
https://www.mcgill.ca/lifesciencescomplex/facilities/cystic-fibrosis-translational-research-centre-platforms
https://navigator.innovation.ca/index.php/en/facility/mcgill-university/cystic-fibrosis-translational-research-centre-cftrc

6. **Major training activities** (e.g., summer schools, co-supervision of trainees, practical workshops):

**CFTRc workshop – Cell Culture Methods I** - Thursday 14 April at 4 pm EDT – On Zoom -

Presentation by

Syeda Sadaf Zehra Zaidi - Lung cell isolation and primary culture

Mark Turner - gene knockdown using CRISPR/Cas9

Number of attendees: 25

See announcement in **Appendix 3**

**7.** If applicable, **list new members** who joined the Unit in the past 12 months (indicate: Name, title, full/associate member, affiliation):

**Ajitha Thanabalasuriar**, Assistant Professor, Full member, Pharmacology and Therapeutics, McGill University - intravital lung imaging

**Caroline Wagner**, Assistant Professor, Full member, Bioengineering, McGill University - mucus biophysics

**Luc Mongeau**, Professor, Full member, Mechanical Engineering, McGill University - lung on chip

**Carolyn Baglole**, Associate Professor, Full member, Medicine, McGill University - acquired CFTR deficiency

**8.** If applicable, **list members who have left the Unit** in the past 12 months (indicate: Name, title, full/associate member, affiliation):

**Jason Young**, Associate Professor, Associate member, Biochemistry, McGill University (sadly passed away February 2022)

**Appendix 1**


# PROGRAMME DE L'ÉVÉNEMENT

## JOURNÉE SCIENTIFIQUE - JEUDI 27 MAI 2021

C'est avec plaisir que je vous invite à participer à la journée scientifique du Symposium québécois des chercheurs et cliniciens FK qui se tiendra virtuellement le jeudi 27 mai 2021. Cet événement, axé sur la recherche, comptera sur la présence de conférenciers internationaux de premier plan dans le domaine de la FK.

**Dr John Hanrahan**
Professeur, Département de Physiologie et Institut de Recherche du Centre Universitaire de Santé McGill
Directeur, Centre de Recherche Translationnelle sur la Fibrose Kystique

| | | |
|---|---|---|
| **12 h 55** | Ouverture de la salle d'attente | |
| **13 h 00** | Mots de bienvenue | Olivier Jérôme,<br>*Fibrose kystique Canada*<br>Dr Gergely Lukacs,<br>*Université McGill, Montréal* |
| **13 h10** | CLCA1 regulates airway mucus production and ion secretion through TMEM16A | Dr Karl Kunzelmann,<br>*Regensburg University, Germany* |
| **13 h 40** | Analysis of airway epithelium composition and function | Dr Luis Galietta,<br>*Giannina Gaslini Institute, Italy* |
| **14 h 10** | Acid ceramidase: a future therapy for cystic fibrosis? | Dr Aaron Gardner,<br>*Newcastle University, UK* |
| **14 h 40** | Pause | |
| **15 h 00** | A journey on airway epithelial ER stress, calcium signals, and inflammation: relevance to CF airway disease | Dre Carla Ribeiro,<br>*Marsico Lung Institute/UNC Cystic Fibrosis Center, USA* |
| **15 h 30** | Cholesterol regulation in cystic fibrosis | Dr Thomas Kelley,<br>*Case Western Reserve University, USA* |
| **16 h 00** | Plénière – A new airway epithelial hierarchy and its implications for lung disease | Dr Jay Rajagopal,<br>*Harvard Medical School, USA* |
| **17 h 10** | Remerciements et fin de l'événement | Dr John Hanrahan,<br>*Université McGill, Montréal* |

Le Symposium québécois des chercheurs et cliniciens FK 2021 a été rendu possible grâce à la contribution financière de notre partenaire VERTEX.

Cystic Fibrosis Canada Fibrose kystique Canada | TOUJOURS PLUS LOIN

# JOURNÉE DES CLINIQUES - VENDREDI 28 MAI 2021

**Dr Zofia Zysman-Colman, MDCM**
Professeure adjointe en clinique
Pneumologie pédiatrique
CHU Sainte-Justine

C'est en mon nom et celui de toute l'équipe de la clinique FK de l'Hôpital Sainte-Justine que nous sommes fiers de pouvoir vous proposer une édition virtuelle condensée de la journée des cliniques. Bien que notre quotidien et notre pratique professionnelle soient encore impactés par la pandémie, le comité organisateur de cette journée est heureux de rassembler les professionnels, chercheurs et cliniciens FK du Québec et de vous offrir un programme riche en contenu. Nos conférenciers couvriront de nombreux sujets d'intérêts de même que plusieurs ateliers destinés aux diverses professions de notre réseau québécois de clinique FK.

| | | |
|---|---|---|
| **7 h 45** | Ouverture de la salle d'attente | |
| **8 h 00** | Mot de bienvenue | Dre Zofia Zysman-Coleman<br>Olivier Jérôme |
| **8 h 15** | Vapotage chez les patients atteints de maladies pulmonaires | Dr Alain Desjardins |
| **9 h 00** | Comment faire face à des situations difficiles avec les patients et familles : techniques et pistes de réflexion | Dominique Pallanca, Ph. D. |
| **9 h 45** | Épidémiologie, transmission et éradication du *Pseudomonas aeruginosa* chez les enfants atteints de fibrose kystique | Dre Ana Blanchard |
| **10 h 30** | Pause | |
| **10 h 45** | Le dépistage néonatal : les expériences d'un centre | Dr Jacques-Édouard Marcotte |
| **11 h 30** | Les multiples facettes de la recherche clinique en fibrose kystique : Des nourrissons aux greffés pulmonaires | Geneviève Mailhot, Ph. D. |
| **12 h 15** | Pause Dîner | |
| **13 h** | Revue annuelle | Dr André Cantin |
| **13 h 45** | Fibrose kystique Canada – 60 ans de recherche, de traitements et de soins | John Wallenburg, Ph. D. |
| **14 h 10** | Groupes par spécialités | |
| | Cliniciens et pharmaciens | Dre Zofia Zysman-Colman et Myriam Guèvremont |
| | Personnel infirmier | Isabelle Tellier et Manon Caissy |
| | Psychologues et travailleurs sociaux | Dominique Pallanca, Ph. D. et Anne-Elizabeth Journet |
| | Nutritionnistes | Marie-Hélène Denis |
| | Inhalothérapeute et physiothérapeute | Sarah Wilhelmy |
| | Patients/proches-aidants/organismes | Olivier Jérôme |
| **14 h 45** | Allocution du Ministre de la Santé et des Services Sociaux du Québec | Ministre Christian Dubé |
| **15 h 00** | Remerciements et fin de l'événement | |

***ACCRÉDITATION DE FORMATION MÉDICALE CONTINUE***

*Cette activité est accréditée par le Centre de formation continue (CFC) de la Faculté de médecine et des sciences de la santé de l'Université de Sherbrooke qui est pleinement agréé par le Collège des médecins du Québec (CMQ) et par le Comité d'agrément de l'éducation médicale continue (CAÉMC). Pour les professionnels de la santé, le CFC remet une attestation de présence de **4 heures 30 minutes** de formation accréditée. Les participants doivent réclamer un nombre d'heures conforme à la durée de leur participation.*

*Selon le règlement du Collège des médecins du Québec (CMQ), cette formation correspond **4 heures 30 minutes** d'activités de développement professionnel reconnues (catégorie A).*

*La présente activité est une activité d'apprentissage collectif agréée (section 1) au sens que lui donne le programme de Maintien du certificat du Collège royal des médecins et chirurgiens du Canada (CRMCC). Vous pouvez déclarer un maximum de **4 heures 30 minutes** de section 1.*

Le Symposium québécois des chercheurs et cliniciens FK 2021 a été rendu possible grâce à la contribution financière de la pharmaceutique **VERTEX**

Cystic Fibrosis Fibrose kystique Canada

TOUJOURS PLUS LOIN

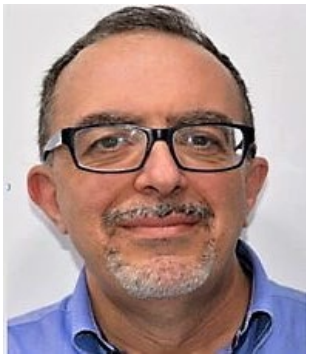
**CLCA1 regulates airway mucus production and ion secretion through TMEM16A**

Raquel Centeio, Jiraporn Ousingsawat, Khaoula Talbi, Rainer Schreiber, Karl Kunzelmann

*Department of Physiology, University of Regensburg, Germany*

TMEM16A is a $Ca^{2+}$ activated chloride channel (CaCC) that belongs to a family of 10 proteins, operating as phospholipid scramblases and CaCCs. TMEM16A and its regulator CLCA1 are associated with inflammatory airway disease and goblet cell metaplasia. CLCA1 is a secreted protein with protease activity that was demonstrated to enhance expression of TMEM16A. Expression of CLCA1 is enhanced in goblet cell metaplasia and is associated with various lung diseases. However, mice lacking expression of CLCA1 showed the same degree of mucous cell metaplasia and airway hyperreactivity as asthmatic wild-type mice. Moreover, $Ca^{2+}$ activated $Cl^-$ currents were reported to be identical in wt and CLCA1-/- mice. To gain more insight into the role of CLCA1, we applied *in vitro* produced secreted N-CLCA1 to mice *in vivo* using intratracheal instillation. We observed no upregulation of TMEM16A by CLCA1 and no differences in ATP-induced short circuit currents (Isc). However, intraluminal mucus accumulation was observed by treatment with N-CLCA1 that was not observed in control animals. The effects of N-CLCA1 were augmented in ovalbumin-sensitized mice. Mucus production induced by N-CLCA1 in polarized BCi-NS1 human airway epithelial cells was dependent on TMEM16A-expression. IL-13 upregulated expression of CLCA1 and enhanced mucus production, however, without enhancing purinergic activation of Isc. In contrast to polarized airway epithelial cells and mouse airways, which express very low levels of TMEM16A, nonpolarized airway cells express large amounts of TMEM16A protein and show strong CaCC. The present data show an only limited contribution of TMEM16A to airway ion secretion, but suggest a significant role of both CLCA1 and TMEM16A for airway mucus secretion

📖 Dr. Kunzelmann graduated from Medical School at the University of Freiburg in 1985. He then carried out clinical work at the County Hospital in Karlsruhe for 1 year and obtained his habilitation and *venia legendi* in physiology in 1993. He trained with Professor Rainer Greger (University of Freiburg), Professor Jay Nadel and Dr. Dieter Gruenert (UCSF), Professor John Riordan (Mayo Clinic Scottsdale) and Professor David Cook (University of Sydney). He is currently Professor in Physiology C3 at the University of Regensburg and holds an Honoree Professorship at the School of Biomedical Sciences, University of Queensland (St. Lucia, Australia). He is also a permanent visiting Professor at the Department of Science of the University of Lisbon (Portugal). Dr. Kunzelmann has published 227 original papers in peer reviewed journals, 47 reviews and 24 book chapters.



**Analysis of airway epithelium composition and function**

Luis Galietta

*Telethon Institute of Genetics and Medicine of Pozzuoli, Italy*

The airway epithelium plays a fundamental protective role in the respiratory system against pathogens delivered by inhaled air. One of the major innate protective mechanisms is mucociliary clearance (MCC), which involves release of mucus, ciliary beating, and secretion of fluid. Different epithelial cell types may have specific roles in MCC. However, the contribution of each cell type to MCC is unclear. In particular, the site of expression of CFTR, the channel responsible for cAMP-activated chloride secretion, is unclear. The presence in airway epithelia of ionocytes as a rare cell type endowed with high CFTR expression is a recent intriguing finding. We are analyzing the cell type composition of the airway epithelium in vitro and in ex vivo samples to assess the localization of CFTR and of other channels and transporters to possibly understand the implications in coordinated ion transport.

📖 Born in Caracas (Venezuela) in 1959, Luis Galietta graduated in Biological Sciences from the Federico II University of Naples. He initially carried out research with a scholarship from the Giannina Gaslini Institute. After training in the United States, he returned to Italy as a researcher and manager of the Molecular Genetics Laboratory of the Giannina Gaslini Institute in Genoa. Since 2017 he has been an investigator at the Telethon Institute of Genetics and Medicine TIGEM of Pozzuoli (Naples) and since 2018 has been associate professor of Medical Genetics at the University of Naples. Frederick II. He has been involved in the study of ion channels in human fibroblasts and keratocytes at the Gaslini Institute and the Institute of Cybernetics and Biophysics (CNR). He helped develop new fluorescent proteins for the study of anionic channels and transporters and is involved in the high-throughput screening of chemical compounds for the identification of pharmacological modulators of the CFTR protein, bicarbonate transport, and airway epithelial cell biology. He has published over 200 papers in international journals.

**Acid ceramidase: a future therapy for cystic fibrosis?**

Aaron Gardner

*Children's Respiratory Group, Newcastle University, United Kingdom*

Cystic fibrosis lung disease is characterized by inflammation and susceptibility to infection, however, the pathogenesis of cystic fibrosis lung disease is not fully elucidated, and both of these processes remain problematic even for people with cystic fibrosis who are receiving modulator therapies. Sphingolipids form specialized membrane domains that modulate a diverse range of biological processes. Increased levels of the sphingolipid ceramide have been reported in the airway epithelium of cystic fibrosis murine models that when normalized reduced inflammation and susceptibility to the key pathogen, *Pseudomonas aeruginosa*.
Using a variety of gold standard techniques (primary human ALI culture, mass spectrometry, bacterial co-cultures) we were able to definitively demonstrate a similar increase in the levels of ceramide in airway cells from people with CF, which is associated with increased inflammation and also susceptibility to infection. We identified that this increase in ceramide was driven by a deficiency in both the production and activity of the enzyme acid ceramidase, which typically processes ceramide to sphingosine. Excitingly, treatment with a recombinant human acid ceramidase (rhAC) was able to normalize ceramide levels whilst also reducing key inflammatory markers and susceptibility to infection. This places rhAC as an ideal target for future therapeutic development, but important questions about its exact mechanism of action remain.

📖 Aaron is currently employed at Newcastle University in the United Kingdom as a senior scientist in the Children's Respiratory Group, led by Dr Malcolm Brodlie. Aaron's major focus is translation research relating to cystic fibrosis, with a specific interest in the role of sphingolipids and host pathogen interactions. This interest in CF was sparked during his undergraduate degree when he was fortunate enough to be awarded a yearlong placement with the UK CF Gene Therapy Consortium at Imperial College. He maintained this research interest through his PhD and several post-doctoral positions until starting at Newcastle University in 2015. Aaron is currently attempting to develop research independence (major interests include leveraging machine learning on CF clinical and genomic metrics and investigating novel culture methodologies) within the group whilst also continuing to drive the exciting sphingolipid/acid ceramidase work that he will talk about.

**A journey on airway epithelial ER stress, calcium signals, and inflammation: relevance to CF airway disease**

Carla Ribeiro

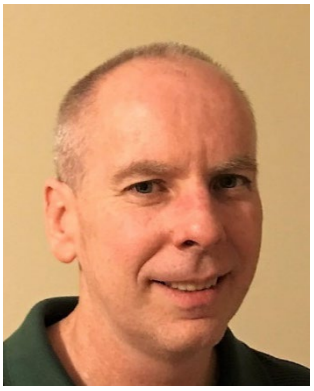
*Marsico Lung Institute and Cystic Fibrosis Center, The University of North Carolina at Chapel Hill, USA*

Cystic fibrosis (CF) patients suffer from chronic airway infection and inflammation. The CF airway milieu induces an airway epithelial adaptation consisting of expansion of endoplasmic reticulum (ER) calcium stores; in turn, the ER/calcium store expansion mediates exaggerated inflammatory responses, e.g., increased cytokine production, in CF airway epithelia. The ER/calcium store expansion and increased inflammatory responses of CF airway epithelia result from ER stress-triggered activation of the unfolded protein response (UPR). Our recent studies have implicated the ER stress transducer inositol requiring enzyme 1α (IRE1α) as a key UPR pathway responsible for CF airway epithelial cytokine production. We will discuss our current research in this area and the notion that targeting the IRE1α UPR pathway may be a therapeutic strategy for CF airway disease.

📖 Dr. Ribeiro received her PhD degree from Duke University, Durham, NC (1992) and did her postdoctoral studies at NIH/NIEHS, Research Triangle Park, NC (1993-1998). She subsequently joined the Cystic Fibrosis Center at the University of North Carolina at Chapel Hill, NC, where she followed a career as a pulmonary biologist. Dr. Ribeiro is a Professor of Medicine and a Joint Professor of Cell Biology and Physiology.

Research in the Ribeiro laboratory focuses on studying mechanisms of airway inflammatory responses relevant to the pathogenesis of airway diseases characterized by mucus obstruction, inflammation, and oxidative stress, such as cystic fibrosis, asthma, and chronic obstructive pulmonary disease. In particular, the Ribeiro laboratory studies the functional roles of the endoplasmic reticulum (ER) and the mitochondria in the regulation of intracellular calcium ($Ca^{2+}_i$) signals and $Ca^{2+}_i$-mediated inflammation, and ER stress responses pertinent to the pathophysiology of these pulmonary diseases.

The Ribeiro group was the first to implicate the ER stress pathway mediated by the ubiquitous inositol requiring enzyme 1α (IRE1α) in cytokine production by human bronchial epithelia, using translational models relevant to CF. Dr. Ribeiro and colleagues also made the key discovery that the isoform IRE1β is only expressed in mucous cells, is up-regulated in CF and asthmatic airway epithelia, and is required for allergic inflammation-induced airway epithelial mucin overproduction. The recent findings implicating IRE1β in the pathogenesis of idiopathic pulmonary fibrosis associated with airway epithelial mucin overproduction expanded the importance of IRE1β in lung diseases characterized by increased mucus production and airway obstruction.



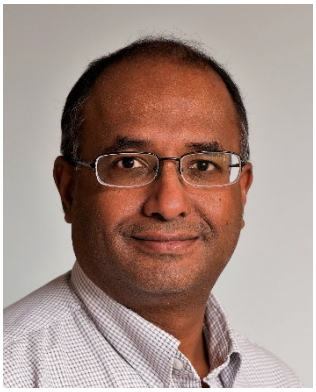
**Cholesterol regulation in cystic fibrosis**

Thomas Kelley

*Department of Genetics and Genome Sciences, Case Western Reserve University, USA*

Serum lipid differences in CF patients were first identified over fifty years ago. Our research initially focused on cellular lipid regulation, particularly the cholesterol synthesis pathway, as it related to inflammatory signaling. Through the course of these studies, it was identified that cholesterol regulation in CF cells and tissues consists of elevated rates of *de novo* cholesterol synthesis, excess cholesterol content in plasma membranes, and disrupted intracellular distribution characterized by perinuclear accumulation of free cholesterol in endosomes. Current research focuses on exploiting these cellular cholesterol manifestations to develop biomarkers to better follow responsiveness to therapies, as well as a focus on the mechanisms that lead to CF-related cholesterol regulatory changes. These mechanistic studies have identified that cholesterol distribution alterations in CF cells are due to microtubule-mediated changes that impact endosomal transport. How these cellular changes impact broader CF phenotypes are also discussed.

📖 Thomas J. Kelley, Ph.D., is a Professor in the Depts of Genetics and Genome Sciences and Pediatrics at Case Western Reserve University in Cleveland, Ohio. Dr. Kelley received his B.A. degree in Chemistry from the College of Wooster, Wooster, Ohio and his Ph.D. in Biochemistry from the University of Notre Dame. Dr. Kelley completed his postdoctoral training at Case Western Reserve University and then joined the faculty in 1998. Dr. Kelley's research is focused on cystic fibrosis and he has published on various aspects of CF cell biology and cell signaling regulation. He is active with the Cystic Fibrosis Foundation, serving on various committees and working groups.



**A new airway epithelial hierarchy and its implication for lung disease**

Jay Rajagopal

*Center for Regenerative Medicine, Harvard Stem Cell Institute, Massachusetts General Hospital, USA*

Here, we combined single cell RNA-seq (scRNA-Seq) and *in vivo* lineage tracing to study the cellular composition of the murine tracheal epithelium and validate putative transcriptional cell types by establishing their distinct developmental origins and tissue organization. We detected all of these known cell types, and discovered a novel rare cell type. The rare cell, termed the ionocyte, has a unique morphology, is present in both mouse and human, is the human airway epithelial cell type that specifically expresses *CFTR*, and is marked by the unique transcription factor *FOXI1*. A loss of function of FoxI1 results in a CF-like phenotype demonstrating that much of the biology of CF can be attributed to a rare cell type. We also identify previously uncharacterized subsets of both tuft and goblet cells, associate these cells with novel functional attributes, and establish their developmental provenance. Surprisingly, all these progenitors arise from basal cells, thus revising the current standard model of epithelial lineage in the trachea. We further discovered a novel progenitor population that resides in a previously unrecognized epithelial structure, which we term a "hillock". Finally, we determine some of the epithelial cells which host the functional loci of action of several key disease genes in asthma, infection, and cystic fibrosis.

📖 Jay Rajagopal is a Professor at Harvard Medical School, an HHMI Faculty Scholar, and a member of the MGH Center for Regenerative Medicine where his laboratory is interested in modern cellular approaches to lung regeneration and reframing the cellular basis of lung disease. His laboratory focuses on lung developmental biology, stem cell biology, and Regenerative Medicine. The lab has contributed to the areas of cell plasticity and has recently published a revised epithelial hierarchy of the murine airway using that has identified new cell types and cell subtypes and macroscopic epithelial structures, including the pulmonary ionocytes and "hillocks". Current interests include establishing new general mechanisms of epithelial regeneration, metaplasia, and the functions of different newly identified lung cell types.

**Appendix 2**

Cystic Fibrosis Translational Research CENTRE de Recherche Translationnelle sur la Fibrose Kystique

McGill School of Biomedical Sciences | École des sciences biomédicales

# CFTRc Seminar Series

## Dr. Deborah Baines

***Professor of Molecular Physiology***
***Infection and Immunity Research Institute***
***St George's University of London***

## Interrogating the constituents of airway surface liquid/sputum – friends and foes

The lungs are lined with a thin film of airway surface liquid (ASL) which contains a complex array of molecules that play a key role in innate defence and mediate communication between the epithelium, the immune cells, and the external environment. The ASL contains hundreds of proteins. Proteases and anti-proteases present in the ASL regulate the cleavage of these proteins and the generation of peptides. Our investigation of the sputum peptidome from people with and without Cystic Fibrosis (CF) has identified novel peptides with cellular, antimicrobial and antiviral bioactivity. In CF disease, changes to the relative abundance of proteases, anti-proteases and their activity alter the proteomic and peptidomic profile of sputum and modify the ion transport properties of the airway epithelium *in vitro*.

**Date:** **Tuesday, January 18, 2022**

**Time:** **11:00 a.m.**

**Online via Zoom:**

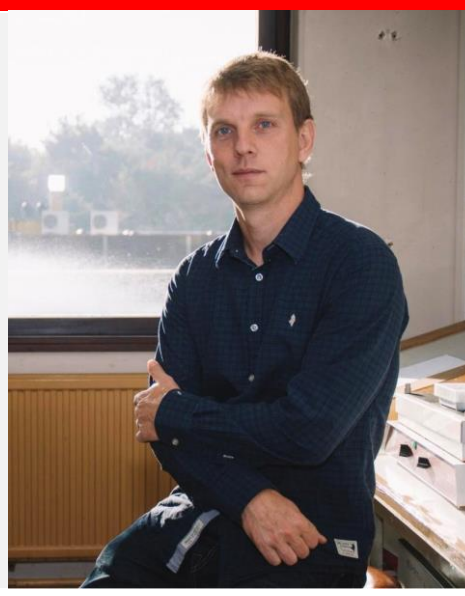
**https://mcgill.zoom.us/j/83877380528?pwd=dmxlNWdFV1I4bjJDZ00zbHlvQi9lUT09**

**Meeting ID: 838 7738 0528**

**Password: semCFTRc**

# Joint Seminar - Department of Anatomy and Cell Biology & McGill Cystic Fibrosis Translational Research Centre (CFTRc)

## *Cedric Govaerts, Ph.D.*



Permanent researcher (Senior Associate Professor)
***Université libre de Bruxelles***

*Hosted by: John Hanrahan , PhD*
*Director, McGill Cystic Fibrosis Translational Research Centre (CFTRc)*

Cystic Fibrosis Translational Research CENTRE de Recherche Translationnelle sur la Fibrose Kystique

***Thursday, March 17, 2022***
***11:30 a.m.***

## *"Nanobodies against CFTR : from discovering novel conformations to new therapeutic routes"*

Functional impairment cystic fibrosis transmembrane conductance regulator (CFTR) anion channel by mutation causes Cystic Fibrosis (CF). The most frequent mutation is the deletion of phenylalanine 508 (F508del) in the first nucleotide-binding domain (NBD1) that affects the thermodynamic stability of the domain. We have developed nanobodies targeting NBD1 of human CFTR and demonstrate their ability to stabilize both isolated NBD1 and full-length protein. Crystal structures of NBD1-nanobody complexes provide an atomic description of the epitopes and reveal the molecular basis for stabilization. These stabilizing nanobodies, promote maturation and cell-surface expression of F508del-CFTR. This effect is highly synergistic with that of approved correctors indicating that their modes of correction are different. Subsequently, we have shown that this rescue leads to recovery of CFTR activity in cellular assays but also forskolin-induced swelling of organoids derived from CF patients.

Our nanobodies also revealed that NBD1 can spontaneously adopt an alternative conformation that departs from the canonical NBD fold previously observed for CFTR and related transporters. Crystallography studies reveal that this conformation involves a topological reorganization of NBD1. Single-molecule fluorescence resonance energy transfer microscopy shows that the equilibrium between the conformations is regulated by ATP binding. However, under destabilizing conditions, such as the prominent disease-causing mutation F508el, this conformational flexibility enables unfolding of the β-subdomain. Our data indicate that in wild-type CFTR this conformational transition of NBD1 regulates channel function, but, in the presence of the F508del mutation, it allows domain misfolding and subsequent protein degradation. Our work provides a framework to design conformation-specific therapeutics to prevent noxious transitions.

Cystic Fibrosis Translational Research CENTRE de Recherche Translationnelle sur la Fibrose Kystique

McGill School of Biomedical Sciences | École des sciences biomédicales

## CFTRc Seminar Series

# Dr. Ann Harris


***Leonard C. Hanna Professor***
***Ohio Eminent Scholar in Stem Cell Genomics***
***Vice Chair for Research***
***Department of Genetics and Genome Sciences***
***Case Western Reserve University, Cleveland***


# A cell type-selective hierarchy for regulation of the *CFTR* gene


Recent progress using functional genomics approaches has generated a cell type-selective model for regulation of expression of the *CFTR* gene. The talk will present new data on the *cis* regulatory elements, transcription factor and structural features that are required to coordinate CFTR expression in secretory cells in the airway and intestinal epithelium. The model provides valuable information for the development of gene-editing therapeutics.


**Date:** Thursday, April 21, 2022

**Time:** 4:00 p.m.

**Online via Zoom:**

https://mcgill.zoom.us/j/87440083516?pwd=SFd0cXJHVVFDLzJ4ZmJWVmZQKzhGUT09

**Meeting ID: 874 4008 3516**

**Password: 792521**

**Appendix 3**

| | |
|---|---|
| **From:** | Annick Michelle Guyot, Dr |
| **To:** | Annick Michelle Guyot, Dr |
| **Cc:** | John W. Hanrahan, Dr.; Syeda Sadaf Zehra Zaidi, Miss; Mark John Turner, Dr |
| **Subject:** | CFTRc workshop - Cell culture methods I - Thursday, April 14 at 4:00pm - on Zoom |
| **Date:** | 4 avril 2022 17:13:45 |

---

Dear CFTRc members,

Please see invitation below to attend a workshop about cell culture methods.

Best regards,

Annick

# CFTRc workshop - Cell culture methods I

All CFTRc members and their laboratories are invited to a 1 hour zoom workshop on cell culture methods.
Thursday 14 April at 4 pm

Presentations in this session will be:
Syeda Sadaf Zehra Zaidi - Lung cell isolation and primary culture
Mark Turner - gene knockdown using CRISPR/Cas9

Zoom link: https://mcgill.zoom.us/j/82041642313?pwd=eGRlaEI4UStlOWcxVFlhcWZLOFptUT09

Meeting ID: 820 4164 2313
Passcode: 779093