



UN SOUFFLE DE COLLABORATION

Symposium québécois des chercheurs et cliniciens FK



27 MAI 2021

Journée scientifique

28 MAI 2021

Journée des cliniques

Édition virtuelle - sur invitation

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, <i>Fibrose kystique Canada</i> Dr Gergely Lukacs, <i>Université McGill, Montréal</i>
13 h 10	CLCA1 regulates airway mucus production and ion secretion through TMEM16A	Dr Karl Kunzelmann, <i>Regensburg University, Germany</i>
13 h 40	Analysis of airway epithelium composition and function	Dr Luis Galiotta, <i>Giannina Gaslini Institute, Italy</i>
14 h 10	Acid ceramidase: a future therapy for cystic fibrosis?	Dr Aaron Gardner, <i>Newcastle University, UK</i>
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, <i>Marsico Lung Institute/UNC Cystic Fibrosis Center, USA</i>
15 h 30	Cholesterol regulation in cystic fibrosis	Dr Thomas Kelley, <i>Case Western Reserve University, USA</i>
16 h 00	Plénière - A new airway epithelial hierarchy and its implications for lung disease	Dr Jay Rajagopal, <i>Harvard Medical School, USA</i>
17 h 10	Remerciements et fin de l'événement	Dr John Hanrahan, <i>Université McGill, Montréal</i>

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



TOUJOURS
PLUS LOIN

JOURNÉE DES CLINIQUES - VENDREDI 28 MAI 2021



Dr Zofia Zysman-Coleman, 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 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 <i>Pseudomonas aeruginosa</i> 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-Coleman 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	

ACCREDITATION 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.

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CLCA1 regulates airway mucus production and ion secretion through TMEM16A

Raquel Centeio, Jiraporn Ousingawat, 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 (I_{sc}). 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 I_{sc}. 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 1 α (IRE1 α) 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 IRE1 α 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 1 α (IRE1 α) 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 IRE1 β 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 IRE1 β in the pathogenesis of idiopathic pulmonary fibrosis associated with airway epithelial mucin overproduction expanded the importance of IRE1 β 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 *Foxl1* 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.