Fibrose kystique Québec

*Donnez le souffle de vie*MD

25e anniversaire du CFTR

Lundi 26 mai 2014, *New Residence Hall* (*McGill University*)

avec la collaboration de

Cystic Fibrosis Translational Research Center

CFTRc

Centre de Recherche Translationnelle sur la Fibrose Kystique

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En collaboration avec le Centre de recherche translationnelle sur la fibrose kystique de l'Université McGill (CFTRc), la fondation Fibrose kystique Québec est ravie de convier chercheurs, cliniciens, étudiants ainsi que le personnel scientifique et clinique à commémorer la découverte du gène CFTR responsable de la fibrose kystique.

Cette importante découverte faite en 1989 par une équipe canadienne a marqué un tournant dans l'histoire de la maladie. La connaissance du gène a permis de progresser non seulement en matière de diagnostic mais a également ouvert de nouvelles perspectives en termes de compréhension de la physiopathologie de la maladie, avec l'espoir de mise au point de thérapies spécifiques.

Ce sont des années de recherche fondamentale qui ont permis la découverte récente de molécules susceptibles de restaurer ou de stimuler la fonction de la protéine CFTR. Mieux connaître la protéine CFTR et son environnement va éventuellement permettre de pallier aux anomalies engendrées par la mutation du gène.

Au Québec, la fondation subventionne de nombreuses équipes de recherche liées à la fibrose kystique. Nous avons naturellement accepté de collaborer avec Renaud Robert, Ph.D. et ses collègues de l'Université McGill afin de créer un événement à Montréal qui célèbre les progrès accomplis depuis 25 ans et explore les pistes prometteuses de guérison pour les personnes atteintes à travers le monde.

La contribution des chercheurs, cliniciens, médecins et étudiants combinée au généreux soutien d'entreprises et du public ainsi que le temps précieux consacré par d'innombrables bénévoles font une grande différence dans la recherche d'une solution et dans l'avancement de la cause. Il y a ainsi de l'espoir pour un remède ou un traitement au cours de notre vie.

Au nom des personnes atteintes, nous vous remercions de votre présence, merci de contribuer à faire la différence.

Le président du conseil d'administration,

Marc Giroux

In collaboration with the McGill Cystic Fibrosis Translational Research Center (CFTRc), the foundation Fibrose Kystique Québec is glad to gather researchers, clinicians, students, scientific and clinical personnel and interested lay people to celebrate the discovery of the CF gene at this symposium.

The program will recap how the CFTR gene was discovered and provide an overview of recent advances in basic and translational research that provide hope for longevity and a better quality of life for those with CF.

We are grateful to Renaud Robert, Ph.D. and his colleagues to have submitted the idea of this symposium. We naturally got involved in making this happen since we all are seeking solutions for Cystic Fibrosis. Thanks to all these years of research, there is now hope for a cure in this lifetime.

Merci! Aucun autre mot ne me vient à l'esprit pour vous exprimer notre joie et notre immense fierté face au succès de ce symposium. Deux mois de travail qui se concrétisent par une participation nombreuse et une collaboration avec l'Université McGill ainsi que des partenaires enthousiastes qui permettent d'espérer de nouveaux projets ensemble.

Votre engagement et votre participation à ce symposium permet à Fibrose kystique Québec de ressortir plus fort et encore plus engagé à soutenir la recherche. « L'engagement » est l'élément central de toutes les actions de Fibrose kystique Québec. Et sans engagement de donateurs, bénévoles et employés, le monde de la philanthropie n'existerait tout simplement pas. J'espère que cette journée en bonne compagnie vous permettra de garder un bon souvenir et, qui sait, vous convaincre de vous engager vous aussi davantage envers la cause!

Merci de croire à d'éventuelles solutions pour combattre la fibrose kystique, et merci de considérer nous appuyer éventuellement lors de l'une de nos activités!

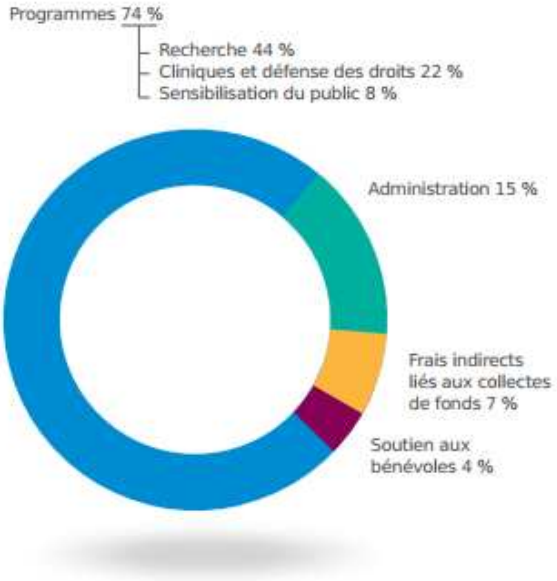
Je profite également de l'occasion pour remercier Vertex pour son engagement à titre de commanditaire principal et inconditionnel ainsi que la faculté de Médecine de l'Université McGill et Novartis pour leur partenariat enthousiaste. Et merci à tous les exposants et autres partenaires de l'événement. Tous ensemble, vous permettez à cette journée d'être non seulement possible mais de devenir – je l'espère – un jalon d'une longue aventure de collaboration.

Le président-directeur général,

Mark Bordeleau

AFFECTATION DES FONDS

(Exclut les frais directs liés aux collectes de fonds)



Les états financiers vérifiés complets sont offerts sur le site Web de Fibrose kystique Canada à www.fibrosekystique.ca

Horaire / *Schedule*

8h00	Inscription et mise en place des affiches / *Registration and poster set-up*
9h00	Mots de bienvenue / *Welcome words*: **Marc Giroux** & **Mark Bordeleau**, Fibrose Kystique Québec
9h05	Animation de la séance du matin / *Morning Session Chair*: **David Y. Thomas**, PhD., McGill University
9h10	*CFTR and more genes; walking and running* **Johanna Rommens**, Ph.D, Hospital for Sick Kids (Toronto)
10h00	*Mucus et immunité: une harmonie complexe orchestrée par le CFTR* **André Cantin**, M.D. Université de Sherbrooke
10h35	Pause offerte par Vertex / *Vertex Coffee Break*
11h05	*Analyse du transcriptome en fibrose kystique:* *une nouvelle source de données afin d'explorer la pathophysiologie* **Yves Berthiaume**, M.D., M.Sc., FRCP, Université de Montréal
11h40	*Whey Protein Supplementation for Cystic Fibrosis* **Larry C. Lands**, M.D., Ph.D., Children's / CHUM
12h15	**Rose Goldstein**, Ph.D., Vice-Principal Research and International Relations, McGill University
12h30	Dîner offert par Vertex: choix de sauté asiatique, bœuf braisé ou lasagne végé / *Lunch offered by Vertex : choice of asian stir-fry, braised beef or veggie lasagna*
13h45	Animation de la séance de l'après-midi / *Afternoon Session Chair*: **John Orlowski**, PhD., McGill University
13h50	*Personalized medicine in CF: opportunities and challenges* **Fredrick Van Goor**, Ph.D., Vertex Pharmaceuticals
14h25	*Towards the deconstruction of the peripheral membrane protein quality control (QC) in cystic fibrosis and beyond* **Gergely L. Lukacs**, M.D., Ph.D., McGill University
15h00	Communications affichées / *Poster session* Pause-café offerte par Vertex, pommes offertes par Molecular Devices / *Coffee Break offered by Vertex, apples by Molecular Devices*
15h45	*Development and characterization of new correctors of F508del CFTR* **John W. Hanrahan**, Ph.D., McGill University
16h20	*CF, from the patient to discovery and back* **John R. Riordan**, Ph.D., University of North Carolina
17h05	Récapitulation & toast au 25e anniversaire offert par Traffick Therapeutics / *Closing words & Toast to the 25th Anniversary offered by Traffick Therapeutics*

Johanna Rommens, Ph.D,

The identification of *CFTR* as the causal gene in 1989 heralded a new era to improve management and treatment of cystic fibrosis (CF). Over 1,800 *CFTR* gene variants have been reported to lead to CF to date. Although improved and earlier diagnosis has been realized with newborn screening being practised in many countries, the avenues to improved treatments have been challenging and more difficult than initially envisioned. The CFTR gene product is a large multi-domain protein that locates to the apical plasma membrane of epithelial tissues where it operates as an anion channel contributing to fluid flow in the airways, sweat glands, pancreatic ducts, intestines and male reproductive tract. Understanding the pathobiology of CF has required the development of cell and animal models to learn how organs fail when CFTR does not work. Tremendous insights have been achieved that are guiding current efforts to develop better therapeutic strategies. An aspect of CF that is not yet clearly understood is the variable presentation amongst patients. Ongoing genome-wide association analyses by the *Cystic Fibrosis Gene Modifier Consortium* with patients from Canada, United States and France are underway to address this issue. *CFTR* and its variants are the major determinant of CF, but a number of modifier genes have been identified that also contribute to disease presentation.

Dr. Rommens received her doctorate degree in Chemistry from the University of New Brunswick (Canada). She then moved to The Hospital for Sick Children in Toronto and trained with Dr. Lap-Chee Tsui as a post-doctoral fellow. This period is fondly remembered for the excitement of the identification of the cystic fibrosis gene (CFTR), work led by the Tsui and Riordan laboratories at the hospital. Dr. Rommens is currently a Senior Scientist in the Program of Genetics & Genome Biology of the Hospital's Research Institute, and is also a Professor in Molecular Genetics at the University of Toronto.

The fundamental interests of Dr. Rommens' laboratory include mechanisms that underlie genetic diseases and their presentations. Dr. Rommens has extensive experience in positional cloning and disease gene identification. She also has interests in genome analysis, gene expression and disease model studies. Her current research is focused genetic diseases of the exocrine pancreas including cystic fibrosis and Shwachman-Diamond syndrome.

André Cantin, M.D.

Le mucus recouvrant l'épithélium bronchique a une tâche difficile. Il doit fournir un environnement protecteur pour les cellules des voies aériennes, tout en s'assurant que les pathogènes ne profitent pas de ses largesses. Il accomplit cette tâche grâce à un travail d'équipe impliquant les principales glycoprotéines du mucus, soit les mucines Muc5B et Muc5AC, les cils bronchiques et le CFTR. Les mucines définissent les propriétés viscoélastiques du mucus selon la disponibilité de deux substances clés, l'eau et le bicarbonate. Le contenu d'eau et de bicarbonate du mucus est orchestré par le CFTR. Au moment d'une agression aigue des voies aériennes, soit par des pathogènes ou par des produits électrophiles polluants tels que la fumée de cigarette, les glandes de mucus se vident violement dans les

voies aériennes, et le CFTR s'active et pour fournir au mucus l'eau et le bicarbonate. Cette réaction urgente est nécessaire pour permettre l'évacuation efficace des substances néfastes vers la gorge. Par contre si l'agression est soutenue de façon prolongée, les glandes de mucus subissent une hyperplasie, la transcription de Muc5AC augmente, et la fonction du CFTR s'éteint. Ces réponses ont pour but de fournir le temps qu'il y a agression, une couche encore plus protectrice de mucus aux cellules bronchiques. Une fois le danger passé, le CFTR retrouve sa fonction et permet au mucus plus fluide, mais moins protecteur, de reprendre son déplacement caudocéphalique à la surface des cils. Ce processus dynamique et délicat est absent chez les personnes atteintes de fibrose kystique. Il en résulte une accumulation permanente de mucines excessivement déshydratées, anioniques et acides. Les organismes pathogènes inhalés stagnent dans cette couche anormalement riche en mucines à la surface bronchique. Il s'en suit un appel des neutrophiles qui doivent maintenant tenter de tuer les pathogènes dans un mucus déficient en eau et en bicarbonate. Or, il s'avère que la principale arme des neutrophiles pour tuer les bactéries, la synthèse des oxydants par l'enzyme NADPH oxydase, est neutralisée par la charge anionique des mucines et par un pH acide. De plus, la présence de NADPH oxydase fonctionnelle sur les neutrophiles est essentielle pour permettre la résolution de l'inflammation. L'absence soutenue de CFTR induit donc secondairement une déficience fonctionnelle sévère de NADPH oxydase, ce qui provoque un grave défaut immunitaire. L'absence de NADPH oxydase fonctionnel est fortement associée à l'infection par des pathogènes catalase-négatifs, et à une hyper-inflammation non-résolutive. Le moyen le plus efficace de corriger ces défauts devrait être la correction de la fonction du CFTR. En attendant il serait opportun d'explorer des stratégies pouvant rétablir le bicarbonate dans le liquide à la surface des bronches, d'hydrater le mucus et de neutraliser la charge anionique des mucines responsables de l'inhibition de l'activité NADPH oxydase des neutrophiles.

Travail subventionné par Fibrose Kystique Canada.

📖 Dr Cantin a fait une formation de recherche en biologie pulmonaire aux National Institutes of Health avant de se joindre comme pneumologue au service de pneumologie du Centre hospitalier universitaire de Sherbrooke. Il est professeur de médecine au Département de médecine de la Faculté de médecine et des sciences de la santé de l'Université de Sherbrooke. Il est également le directeur de la clinique des adultes porteurs de fibrose kystique et de la clinique de fibrose pulmonaire au Centre hospitalier universitaire de Sherbrooke.

Ses travaux de recherche en fibrose kystique et en fibrose pulmonaire idiopathique sont subventionnés par Fibrose Kystique Canada et par le Centre de recherche clinique du CHUS. Il a publié plus d'une centaine d'article et des chapitres de livres. Ses thèmes de recherche portent sur les mécanismes de la pathophysiologie pulmonaire et les nouvelles approches thérapeutiques en fibrose pulmonaire idiopathique. Il travaille également sur l'inflammation bronchopulmonaire de la fibrose kystique et ses traitements.

Yves Berthiaume, M.D., M.Sc., FRCP

Afin d'identifier de nouveaux gènes impliqués dans la pathophysiologie de la fibrose kystique, nous avons fait une analyse du transcriptome des cellules épithéliales bronchiques FK. Cette analyse nous a permis d'identifier 2 nouveaux mécanismes qui pourraient avoir un rôle à jouer dans la pathophysiologie de la maladie. Premièrement, nous avons observé que le gène chitinase 3 like 1 (CHI3L1), est surexprimé dans les cellules épithéliales FK. Ce gène code pour la protéine YKL-40 qui a été identifiée comme un biomarqueur de plusieurs pathologies tel que le diabète, le cancer ou même la maladie pulmonaire obstructive chronique. Nos résultats préliminaires suggèrent aussi que cette protéine pourrait avoir un rôle prédictif de l'intolérance au glucose chez les patients atteints de fibrose kystique. Dans un deuxième temps, nous avons observé que plusieurs gènes qui sont surexprimés dans les cellules FK sont localisés sur un même locus chromosomique. Cette colocalisation pourrait s'expliquer par des changements épigénétiques au niveau de ces locus chromosomiques. En utilisant une technique d'immunoprécipitation de l'ADN méthylé, nous avons observé que certains gènes sont hyperméthylés en FK. Un de ces gènes, c'est le gène RGS2 qui code pour une protéine régulatrice des protéines G et dont l'expression est accentuée par le stress oxydatif. Nos résultats démontrent que l'expression du gène et de la protéine RGS2 est diminuée dans les cellules FK et que cette diminution est associée à une surexpression de gènes inflammatoires (S100A12, TNF, YKL-40). Donc ces résultats démontrent que l'utilisation d'une analyse de la réponse transcriptomique nous permet d'identifier de nouvelles pistes d'investigation afin de mieux comprendre la pathophysiologie de la fibrose kystique.

Dr Yves Berthiaume a obtenu un diplôme de médecine de l'Université de Sherbrooke en 1980 et par la suite s'est spécialisé en pneumologie à la même université de 1980 à 1983. Il a aussi obtenu une maîtrise en physiologie respiratoire de la même université en 1983. Il est membre du Collège royal des médecins et chirurgiens du Canada (pneumologie) depuis 1984. Il a complété des études post-doctorales en recherche fondamentale au Cardiovascular Research Institute de l'Université de California, San Francisco de 1983 à 1986. De 1986 à 1992, il a été professeur adjoint et professeur agrégé au Département de médecine de l'Université de Calgary. Depuis 1992, Il est devenu membre du service de pneumologie et du Centre hospitalier de l'Université de Montréal où il est présentement professeur au Département de médecine. En 2012, il a accepté le poste de Directeur exécutif de la clinique et de la recherche clinique à l'Institut de recherches cliniques de Montréal. Il est présentement récipiendaire de la Chaire de recherche Gosselin-Lamarre de l'Institut de recherches cliniques de Montréal. Les intérêts de recherche du Dr Yves Berthiaume se concentrent sur le rôle de l'épithélium pulmonaire dans la pathophysiologie de maladies telles que la fibrose kystique ou de l'œdème pulmonaire.

Larry C. Lands, M.D., Ph.D.

Cystic Fibrosis patients are at risk for malnutrition and have elevated protein requirements. Cystic Fibrosis is also characterized by chronic lung inflammation and oxidative stress. Whey protein is rich in branched chain amino acids and cysteine, the essential substrate for glutathione synthesis. Whey is thus considered a high quality protein. We have treated whey protein with hyperbaric pressure. Hyperbaric

treatment of whey protein results in enhanced protein digestibility and increased availability of essential amino acids. This enhances whey's anti-inflammatory and antioxidant properties. This presentation will review preclinical and clinical results with pressurized whey and its potential for Cystic Fibrosis patients.

📖 Larry C. Lands, MD, PhD, is a tenured full professor in the Department of Pediatrics of McGill University, Director of Pediatric Respiratory Medicine and Director of the Cystic Fibrosis Clinic at the Montreal Children's Hospital. He is also the longest-standing member of the Quebec Lung Transplant Clinic at Hôpital Notre Dame-CHUM and respiratory consultant to the CF Clinic in Rouyn Noranda. His research interests focus on modulation of inflammation and enhancing functional capacity, with over 100 peer-reviewed articles. Dr. Lands is Vice-Chair of Cystic Fibrosis Canada's Research Advisory Council, Chair of Cystic Fibrosis Canada's Knowledge Translation Platform Committee, and a member of Cystic Fibrosis Canada's Canadian Patient Data Registry Oversight Committee. He is Chair of the Canadian Lung Association/Canadian Thoracic Society's Studentship and Fellowship Committee. He is a member of the Respiratory and Cystic Fibrosis Clinical Study Group of the Medicine for Children Research Network of the United Kingdom's National Institutes of Health Research. He is also a member of the editorial boards of Paediatric Respiratory Reviews and Frontiers in Pediatric Pulmonology.

Fredrick Van Goor, Ph.D.

This presentation will outline the benefits and challenges of the Class system; offer a proposal to describe *CFTR* mutations using a list of key attributes; incorporate key aspects of the Class system; will account for the inherent variability due to the range in severity, number, and type of CFTR mutations; show a brief overview of next generation CFTR correctors and the potential impact on personalized medicine in CF.

📖 Dr. Van Goor joined Vertex Pharmaceuticals in 2001 to help identify new medicines for the treatment of cystic fibrosis. While at Vertex Pharmaceuticals, Dr. Van Goor was the Lead Biologist on the research and clinical teams that identified multiple investigational drugs and the marketed drug KALYDECO that target the underlying molecular defects in the cystic fibrosis gene product, the CFTR chloride channel. Currently, Dr. Van Goor is the Lead Biologist for the cystic fibrosis program at Vertex Pharmaceuticals, Inc., providing the scientific leadership for the preclinical, clinical, and commercial teams. Prior to joining Vertex Pharmaceuticals, Dr. Van Goor was a Postdoctoral Fellow at the National Institutes of Health where he published several scientific articles on the pattern of electrical membrane signaling underlying the temporal release of reproductive hormones from the pituitary. Dr. Van Goor received his Ph.D. and B.Sc. from the University of Alberta.

Gergely L. Lukacs, M.D., Ph.D.

Overlapping proteostasis networks have evolved to meet the distinct requirements of polypeptides' intrinsic designs at distinct subcellular locations, such as the nucleus, mitochondria, endoplasmic reticulum, cytosol and the plasma membrane. Although these biological machines evolved to ensure the timely disposal of structurally impaired polypeptides to avoid proteotoxicity, inherent to their limited fidelity, partially functional proteins may be subjected to

premature elimination, which exacerbate a loss-of-function disease phenotype. I will discuss the emerging paradigm of the cellular and molecular basis of the plasma membrane or peripheral protein quality control (QC) that contributes to the elimination of non-native polypeptides from the cell surface, including the partially folded or unfolded mutant CFTRs that escaped either constitutively the endoplasmic reticulum QC or upon exposure to low temperature or "corrector" molecules (e.g. VX-809, an investigational corrector under clinical trial) that can partially revert the channel folding defect. Mechanistic understanding of the peripheral QC machinery may foster the development of therapeutic approaches to alleviate the clinical manifestation various conformational diseases, including cystic fibrosis.

📖 Gergely L. Lukacs, *MD, PhD. Professor, CRC, - Dept of Physiology and Biochemistry, McGill Univ.* Dr. Lukacs is graduate of the Dept. Physiology, Semmelweis Medical School, Budapest and received his postdoctoral training at Yale Medical School and The Hospital for Sick Children. In 1995 he joined the Gene Therapy Initiative and subsequently the Cell Biology and Respiratory Program at the Hospital for Sick Children Research Institute. From 2007 he is on faculty at McGill. Dr. Lukacs' research focuses on the folding, traffic and quality control of CFTR and other plasma membrane proteins to elucidate the underlying molecular mechanism of orphan conformational diseases. As a member of the CFTRc, GRASP and the US CF Folding Consortium his laboratory is also involved in assay development for the identification and mechanistic dissection of CF corrector molecules.

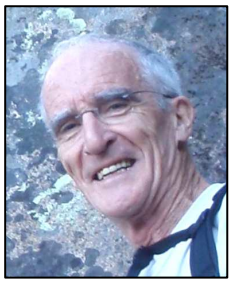
John W. Hanrahan, Ph.D.

CFTR correctors identified in cell-based screens are surprisingly diverse, suggesting they may have different targets and/or modes of action. This is encouraging because it implies there are multiple distinct ways to correct F508del-CFTR trafficking. The majority of the hits in our screens have no clear similarity to compounds of known function, however searching adjacent chemical space has revealed structurally related molecules with known cellular targets including phosphodiesterases, histone deacetylases, kinases, E3 ligases, polyADP-ribose polymerases (PARP also termed ARTD), cyclooxygenase 2 and Na/K ATPase. Many of these compounds inhibit enzymes involved in the post-translational modification of proteins. While serine and tyrosine phosphorylation of CFTR has been implicated in biogenesis and trafficking and protein ubiquitination plays a central role in quality control, other post translational modifications such as ADP ribosylation remain to be explored. Using hits from the McGill HTS campaign as the starting point, computational methods were used to identify analogues in the GSK compound collection. One of these underwent extensive (>400 derivatives) medicinal chemistry development in collaboration with GSK. This McG339 series is interesting because some members of the family have significant levels of correction alone and are also synergistic with the Vertex compound VX-809, giving significantly greater correction than what is currently thought to be the threshold needed for clinical benefit. We have also identified other combinations of compounds which display significant corrector synergy. These are being pursued using a bicistronic adenovirus to deliver dual fluorophores into primary HBE cells for ratiometric halide influx assays.

📖 John Hanrahan is a Professor in the Department of Physiology, McGill University, a member of the Research Institute of the MUHC, and an associate member of the Meakins Christie Labs. He is also a member

of GEPROM (Groupe d'étude des protéines membranaires) and the director and co-founder of the McGill CF Translational Research centre (CFTRc). Dr. Hanrahan obtained his BSc (Hon) in Biology at Dalhousie, PhD in Zoology (Physiology) at UBC, and Postdoctoral training in the Yale Univ. School of Medicine. He has received Fellowship, Scholar, Scientist and Senior Scientist awards from CIHR, and the Chercheur Boursier Senior II award from FRQS. His research interests relate to epithelial transport and channels at the cellular and molecular level, and are focused on cystic fibrosis and CFTR function. His lab studies basic mechanisms of channel regulation, the role of CFTR in airway epithelial host defense, and the development new therapeutics for CF.

John R. Riordan, Ph.D.



Although infants with symptoms now recognized as characteristic of cystic fibrosis are mentioned in historic accounts of life in Europe in earlier centuries, CF was described as a defined disease entity only 75 years ago. As a heterogeneous disease of multiple epithelial tissues, recognition of the root cause was mystifying. Mucovisidosis was the prominent feature. Detection of altered electrolytes in sweat and other exocrine secretions and later measurement of increased bioelectric potential across airway (Knowles et al. *New Eng J Med* 305, 1489-95, 1981) and sweat duct (Quinton. *Nature* 301,421-22 1983) epithelia led to extensive investigations of ion conductances and discovery of a somewhat unexpected anion permeability defect. However with even this information at hand identification of the primary defect at the molecular level remained extremely challenging.

The recognized autosomal recessive inheritance of CF then came to the fore with the general proposal of Botstein and colleagues (*Am J Hum Genet* 32, 314-31, 1980) that restriction fragment length polymorphisms (RFLPs) could be used to locate Mendelian disease loci. Lap-Chee Tsui seized upon this approach to CF and during the 1980s succeeded in locating the CF gene by what since has come to be known as positional cloning as described by Johanna this morning. During the same period my laboratory decided to pursue the sweat gland in which Paul Quinton had demonstrated the chloride permeability defect. Glands were dissected from skin biopsies of individuals with and without CF and primary cell cultures established. Attempts to detect disease related differences at the protein level by 2D electrophoresis for example failed to detect consistent changes. However, RNA and cDNA from the cultures that retained native electrophysiological properties were tested for hybridization to genomic fragments in the neighborhood of the CF genomic locus. One hybridizing partial cDNA was used to reprobe cDNA libraries from normal and CF cells to identify additional overlapping sequences covering a nearly complete open reading frame. Comparison of sequences of CF and control origins revealed a single codon deletion (**Δ**F508) in the former. Sequence similarities with other members of a family of transporters identified the product as a membrane protein and the pattern of expression in tissues was consistent with those affected by the disease. Additional experiments in Lap-Chee's lab identified the same sequence difference on ~ 2/3 of CF chromosomes.

The greatest initial impact of finding the gene was to provide a focus for research in what had been a very broad and diverse field. The mutation consortium initiated by Lap-Chee and his fax machine led to the uncovering of ~2000 different mutations. The many detailed

genotype/phenotype studies in combination with the output of high throughput modulator screens have already led CF into the era of personalized medicine.

My laboratory along with a great many others have concentrated on attempts to understand structure-function of the unique ABC ion channel and the impact of mutations. These studies are incomplete because although CFTR's channel function can be studied at the single molecule level in cell membranes, its low abundance and instability make it difficult to purify and characterize by biophysical methods. Thermodynamic instability currently limits both efforts to crystallize the protein for 3D structure determination and to overcome the further destabilizing affect of the **Δ**F508 mutation. However progress is being made on this front and it is likely that the required fine rebalancing of thermal stability will be achieved. The success of Kalydeco™ in treating several function-disrupting mutants promises that additional compounds acting on still other mutants will emerge. Technologies utilizing gene editing hold hope for treatment of some missense mutants and new advanced gene replacement methodologies are likely to be developed. Thus, the cycle from patient to discovery and back is not entirely complete but is well on the way and continuing at an intense pace. (Supported by the NIH and CFF).

John Riordan is Michael Hooker Distinguished Professor of Biochemistry and Biophysics in the Faculty of Medicine at UNC Chapel Hill, North Carolina. Dr. Riordan received his Ph.D. in Biochemistry from the University of Toronto then moved as a post-doc fellow to the Max-Planck-Institutes for Molecular Genetics and Biophysics in Frankfurt. He played a major role in cloning the CF gene and has been a leader in the characterization of its protein product CFTR. He was Director of the Cystic Fibrosis Research Development Program at the Hospital for Sick Children when the CF gene was identified and has received numerous awards including the Paul di Sant'Agnese Distinguished Achievement Award from the US CF Foundation; Pharmaceutical Manufacturers Association of Canada Gold Medal of Honour; Royal Society of Canada Centenary Medal, Gairdner International Award; Mila Mulroney Cystic Fibrosis Research Award, Doris F. Tulcin Award for Excellence in Cystic Fibrosis Research; Canadian Biochemical Society Boehringer-Mannheim Award; and Officer of the Order of Canada. The primary research focus of Dr. Riordan's lab remains the structure, function and biosynthetic processing of CFTR and the prospects for therapy.

Communications affichées / *Poster Session*

1. New opportunities for progress in CF research: The Cystic Fibrosis Translational Research centre (CFTRc).

- Auteurs /Authors: Renaud Robert, Aurélie Cleret-Buhot, Julie Goepp, Stevo Radinovic, Elizabeth Matthes, Carmen Lampron, Annick Guyot, David Y. Thomas, John W. Hanrahan
- Affiliations/Affiliations: The Cystic Fibrosis Translational Research centre (CFTRc), McGill University.

2. Impact of Pseudomonas aeruginosa infection on airway epithelial repair.

- Auteurs/Authors: Manon Ruffin[1, 2], Nguyen Thu Ngan Trinh[1, 2], Claudia Bilodeau[1, 2], Émilie Maillé[1], Trevor Beaudoin[3, 4], Dao Nguyen[4, 5], Simon Rousseau[3, 4], Emmanuelle Brochiero[1, 2]
- Affiliations/Affiliations: [1] Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM), [2] Département de médecine, Université de Montréal, [3] Meakins Christie Laboratories, [4] McGill University, [5] Montreal General Hospital Research Institute

3. Calibration of Wide-field Deconvolution Microscopy for Quantitative Fluorescence Imaging

- Auteurs/Authors: Lee J.S., Wee T.L, Brown C.M.
- Affiliations/Affiliations: McGill University, Advanced BioImaging Facility (ABIF)

4. Triaging the folding and degradation function of Hsp70 using CFTR as a substrate model

- Auteurs/Authors: Patrick Kim Chiaw, Christine Hantouche, Yogita Patel, Jason C. Young
- Affiliations/Affiliations: McGill University

5. McGill University Flow Cytometry Core Facility

- Auteurs/Authors: Dr. Russell Jones, Ken McDonald and Diane Ethier
- Affiliations/Affiliations: McGill University

6. Impact of CFTR correction on CF airway epithelial repair in non-infectious and infectious conditions

- Auteurs/Authors: Claudia Bilodeau[1,2], Nguyen Thu Ngan Trinh[1,2], Émilie Maillé[1], Emmanuelle Brochiero[1,2]
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7. Tyrosine phosphorylation regulation of the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) chloride channel

- Auteurs/Authors: Billet, A.[(1,2)]; Jia, Y.[(1)]; Riordan, J.R.[(3)]; Hanrahan, J.W.[(1,2)]
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8. The protein kinase TPL2 and the EGF receptor contribute to ERK1/ERK2 activation in CF airway epithelial cells exposed to Pseudomonas aeruginosa

- Auteurs/Authors: Guy Martel, Lucie Roussel, Simon Rousseau
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9. The buffer capacity of airway epithelial secretions

- Auteurs/Authors: Dusik Kim[1], Jie Liao[1] and John W. Hanrahan[1, 2, 3]
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10. Pseudomonas aeruginosa increases IL-33 expression in airway epithelial cells: a novel inflammatory mediator in cystic fibrosis lung disease

- Auteurs/Authors: Raquel Farias and Simon Rousseau
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11. McGill Life Sciences Complex, Advanced BioImaging Facility (ABIF)

- Auteurs/Authors: Cleret-Buhot A., Wee T.L., Brown C.M.
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12. The Role of SMPD1 in the Innate Immune System's Response to Bacterial Infection

- Auteurs/Authors: Elyse MacFadden-Murphy, Dr. Simon Rousseau
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13. Identification of CFTR and KCa3.1 potentiators from in silico high throughput screening of the ZINC bank

- Auteurs/Authors: MF Lavoie, A. Riopel, A. Leblanc, P.Morales, E. Brochiero, & R. Sauvé
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14. Airway Smooth Muscle Dysfunction in Cystic Fibrosis

- Auteurs/Authors: Marina Simeonova, Anne-Marie Lauzon, James G. Martin
- Affiliations/Affiliations: Meakins-Christie Laboratories, McGill University

15. On the road to clinical trial in cystic fibrosis patients infected with Pseudomonas aeruginosa following a discovery of therapeutic potential of fenretinide in preclinical studies.

- Auteurs/Authors: Radzioch D.[1,2,5,6], Wojewodka G.[2,6], De Sanctis J.[3,6], Guilbault C.[1,6], Lachance C.[1,6] Kopriva F.[4], Hajduch M.[4], Cupri S.[6,7], Colin P.[5], Pislariu R.[5], Matouk E.[1,6,7]
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16. Differential activation of Airway Epithelial Cells by Planktoinc and Biofilm Pseudomonas aeruginosa and the onset of innate immune activation.

- Auteurs/Authors: Beaudoin T., Lafayette S., Roussel L., Bérubé J. Nguyen D and Rousseau S.
- Affiliations/Affiliations: McGill

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