VITAL SIGNS

THE NEWSLETTER OF MCGILL UNIVERSITY DEPARTMENT OF MEDICINE

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A GIANT HAS FALLEN

Dr. David Eidelman
Chair, Department of Medicine

This issue of the Newsletter is dedicated to the memory of Dr. Peter Macklem, former Chair of the Department of Medicine and Physician-in-Chief of the Royal Victoria Hospital, whose obituary appears on page 6. It is no exaggeration to say that Dr. Macklem was a giant. Indeed, he was one of the most important medical leaders in our history. By virtue of his originality, outspokenness and generosity of spirit, he led our department with distinction and exerted an extraordinary influence on the science and practice of respiratory medicine during his long career. This influence is still felt at the bedside and in daily clinical practice. More importantly, during the five decades of his research career, Peter contributed to the training and mentoring of generations of researchers and clinicians. In recognition of his passion for research, this issue is focused on translational research, featuring the innovative work of Drs. Danuta Radzioch and Brent Richards. I am sure that Peter would have been very excited by their projects.

LDI GENETIC EPIDEMIOLOGY PROGRAM

Dr. Brent Richards
Assistant Professor, Division of Endocrinology, JGH

Since the discovery of the double helix by Watson and Crick, physicians and scientists have hypothesized that predisposition to common disease must be transmitted, at least in part, through variations in base pair sequences. Yet, despite much endeavor, most of the genetic factors that influence common disease have remained elusive until recently.

Major advances in genotyping technologies have permitted massively paralleled genotyping of the genome, such that common variations in base pairs (also called single nucleotide polymorphisms or SNPs) can be assayed reliably in thousands of individuals. Techniques have been pioneered here at McGill, by scientists such as Rob Sladek and Constantin Polychronakos, to use such genotyping arrays to identify SNPs that are reproducibly associated with common disease through a study methodology termed genome-wide association (GWA) studies.

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IN THIS ISSUE:

The **McGill University Department of Medicine's RESEARCH SYMPOSIUM** will be held on Friday, May 27, 2011 at the McGill Faculty Club. Details will be sent out by email in March.

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To date, GWA studies have identified 3,720 SNPs to be associated with 452 diseases or traits, representing a deluge of potentially important insights into etiology of many common diseases. Importantly, these studies are often limited in power and have generally identified small effects on the disease or trait of interest. This suggests much of the genetic predisposition to disease remains to be identified.

Our research program, based at the Lady Davis Institute, is focused on identifying the genetic determinants of common, aging-related disease. Focusing mainly on osteoporosis, we have led and co-led several large-scale studies which have reproducibly identified genetic determinants of bone mineral density, osteoporotic fractures and bone-related traits such as vitamin D levels. These studies have only been possible through collaborations with large international teams of investigators, in order to streamline study procedures and replicate of our findings. After the identification of the genetic determinants we then work closely with physiologists and functional genomicists, such as David Goltzman and Tomi Pastinen, respectively, to try to understand how the identified base-pair changes influence bone metabolism.

Our team has grown over the past 2 years to now include 4 postdoctoral fellows and 3 part-time research assistants and programmers. Celia Greenwood, a statistical geneticist was recently recruited to the Lady Davis Institute, as a principal investigator, and has brought with her a team of post-docs and expertise in this area. Celia's recruitment has been instrumental in creating the critical mass of researchers needed to build a more cohesive research program. The CIHR, FRSQ, CFI, LDI and several other national and provincial research partners have provided funding for our activities.

As we move forward to a better understanding of the relationship between the genome and disease, we will focus on the role of rare base-pair changes and epigenetic mutations, such as changes in methylation. To this end, we will genome-wide re-sequence 300 individuals who have suffered early osteoporotic fractures, thus creating among the first cohorts of study subjects who have had their entire genomes re-sequenced. As members of TwinsUK (a Wellcome Trust supported population-based cohort of twins), we will measure methylation across the genome in 5,000 identical and fraternal twins, which should permit us insights into the role of methylation in causing divergence of phenotypes between these sibling pairs. Our research group is well positioned to be among the first to be able to deal with such datasets as we are building the computational infrastructure to deal with dozens of terabytes of data and are developing novel statistical methodologies to identify the epigenetic and rare base-pair variants that influence risk of common disease.

Our overall research vision is to improve the patient care for individuals suffering from common diseases by identifying the genes that play an important part in their etiology. Doing so will help to better understand the disease pathophysiology, provide drug targets, and in some cases will help to identify groups of individuals at highest risk, such that preventive therapies can be implemented.

MCGILL'S NOVEL ORPHAN DRUG GIVES NEW HOPE TO CYSTIC FIBROSIS PATIENTS

Dr. Danuta Radzioch
Professor, Departments of Medicine and Human Genetics

The diagnosis of a child with a rare disease can be devastating. These diseases are often due to genetic defects and usually there is no cure. Research on these diseases is limited by the funding available and pharmaceutical companies focusing mostly on those diseases with larger market potential. However, the hope for finding an efficient treatment, or even better, a cure is very much alive for rare diseases, partly due to endorsement of the

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(Continued from page 2 / Orphan Drug)
U.S. Food and Drug Administration (FDA) and the European Medicine Agency (EMA) who, through their Orphan Drug Designation programs, promote research in rare diseases. This designation provides privileged access to the regulators in the USA and Europe, reduced filing fees for orphan drugs and offers market exclusivity for either seven (USA) or ten (EU) years thereby increasing pharmaceutical companies interest in the drug and facilitating efforts to secure funding for clinical trials.

Cystic fibrosis (CF), categorized as a rare disease, involves multiple organ pathology causing patients to live with many symptoms such as malabsorption of nutrients, low body mass, malfunction of the pancreas, diabetes, infertility and osteoporosis. However, the most plaguing symptoms are the chronic pulmonary infections which cause lungs to deteriorate, eventually leading to respiratory failure. In addition to the physical symptoms, patients and their families must deal with the psychological aspect of the disease, the frequent hospitalisations, the difficult treatments and numerous medications. In 1989, the gene responsible for CF was discovered. Both families of patients suffering from CF as well as the scientific community thought that this disease would be cured in the foreseeable future. However, more than twenty years later, there still is no cure and while progress has been made to improve the lives of patients, the progressive lung disease still remains the primary immediate cause of death despite the impressive progress made in developing new antibiotics and specific protocols for CF patient care.

McGill University has applied for and recently received the Orphan Drug Designation from the FDA for a new promising drug called fenretinide, a derivative of Vitamin A, for the treatment of CF patients suffering from chronic bacterial lung infections with Pseudomonas aeruginosa. This important achievement is the result of several years of intense research, culminating with a patent submission by the Commercialization Group at McGill's Office of Sponsored Research (OSR). Our laboratory has been pursuing research on CF lung disease for more than 15 years. These studies have been funded by the Canadian Cystic Fibrosis Foundation and also by a Proof of Principle Phase I grant from CIHR.

Following these exciting findings, our research focus shifted to study the lipids important in the regulation of inflammation, namely docosahexaenoic acid (DHA, an omega-3 fatty acid) and arachidonic acid (AA, an omega-6 fatty acid). Defects in these lipids have been known in CF since 60s, 20 years before the gene involved in the disease was discovered. However, correcting these defects has proven to be an arduous task. Dr. Claudine Guilbault corroborated the fatty acid imbalance in the laboratory's mouse model of cystic fibrosis (CF mice), discovered a reduction in another class of lipids mediators called ceramides, and demonstrated that all these lipid imbalances associated with CF can be corrected by fenretinide. Subsequently, the results indicated that the normalizing effect of fenretinide on lipid mediators also helped the CF mice to resist lung infection with Pseudomonas aeruginosa and prevented the early onset of osteoporosis in CF mice, as demonstrated by the research done by Sahar Saeed, a graduated master's student from the laboratory. Recently Gabriella Wojewodka, a PhD student currently working on this project in our laboratory, has discovered that the imbalance in AA and DHA, the two essential fatty acids, can be seen in the leukocytes of CF patients and that it can be normalized by the treatment of CF cells derived from CF patients with fenretinide in vitro. Over the last few years, the fatty acid imbalance was meticulously studied and corroborated among patients with CF at the adult clinic directed by Dr. Elias Matouk at the Montreal Chest Institute.

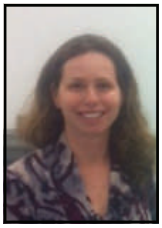
Together, these results have led to the pursuit of clinical trials to treat patients with CF using fenretinide. The first step was receiving the Orphan Drug Designation from the FDA, a first for McGill; we are also planning to secure the Orphan Drug Designation from the EMA for the European Union. Combining solid research results in vitro and in vivo with this major accomplishment, Dr. Matouk and I obtained significant funding through the *Programme de soutien à la valorisation des technologies – volet 3* (PSVT-3) from the Quebec *Ministère du Développement économique, de l'Innovation et de l'Exportation* (MDEIE) and from MSBiValorisation to begin a Phase 1B/2 clinical trial at the Adult Cystic Fibrosis Clinic at the Montreal Chest Institute. Overall, this drug seems to be a promising therapy for CF especially by helping to improve the lung's ability to fight infections. Ultimately, this treatment is hoped to result in fewer infections, less hospitalizations, a better preservation of lung function and ultimately a significant increase in life expectancy for patients with CF.

RECRUITMENTS

We are pleased to welcome the following new members to our Department:

Dr. Geneviève Gyger, Assistant Professor to the Division of Rheumatology and based at the Jewish General Hospital. Dr. Gyger completed her fellowship in rheumatology at Université de Montréal and has done a year of *formation complémentaire* at McGill. She has become an expert in the diagnosis, investigation and management of patients with scleroderma as well as in the use of video capillaroscopy for the diagnosis of multiple rheumatic diseases. Dr. Gyger will be involved in clinical activities and pursue her research interests in scleroderma and capillaroscopy.

Dr. Istvan Mucsi, Associate Professor to the Nephrology Division and the Multi-Organ Transplant Program as well as Attending at the MUHC. Dr. Mucsi holds an M.D. (1988) and a PhD (2000) from Semmelweis University, Budapest. He completed his residency in internal medicine in Hungary and a clinical fellowship in adult nephrology at the University of Toronto. Dr. Mucsi worked as a nephrologist at the Humber River Regional Hospital in Toronto between 2003 and 2007. His clinical and research interests include renal anemia, sleep disorders and psycho-nephrology, bone and mineral disorders and inflammation in patients with chronic disease in general, and in kidney transplant recipients in particular.

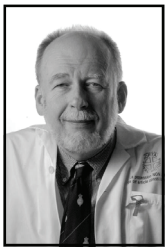


Dr. Fabienne Parente, Assistant Professor to the Medical Biochemistry Division and Attending at the MUHC. Dr. Parente received her medical degree from Université de Montréal in 2004 and then came to McGill, at the Montreal Children's Hospital (MCH) for her medical biochemistry training. She recently completed additional training at the CHUM and will finalize a fellowship next year through the Canadian College of Medical Geneticists. Dr. Parente's primary site will be at the MCH, where she will be in charge of the core laboratory and biochemical genetics laboratory. She will also pursue research in the field of biochemical genetics.

Dr. Osama Roshdy, Assistant Professor to the Division of Dermatology and based at the Jewish General Hospital. Dr. Roshdy completed his training in Dermatology in Egypt, a Masters in immunopathology at McGill, a Masters in molecular and cell biology at Laval University and a year of additional training at the JGH. His area of interest is the role of the recently described T helper lymphocyte (TH17) in skin diseases. He has been investigating this cell in atopic dermatitis for the last three years, and will explore its role in cutaneous melanoma and basal cell carcinoma. He will also be involved in clinical activities.

NEW CHALLENGES

Dr. Robyn Tamblyn has been appointed as incoming **Scientific Director of CIHR's Institute of Health Services and Policy Research** (CIHR-IHSPR), effective January 1, 2011. Professor in the Departments of Medicine and Epidemiology and Biostatistics, she is also the Scientific Director of the Clinical and Health Informatics Research Group at McGill University. More on this story.



As part of the redevelopment process at the MUHC, we hope to harmonize the care and treatment of HIV infected adults now being seen at the Immune Deficiency Treatment Centre (IDTC) and at the Montreal Chest Institute (MCI), along with the associated education and research programs. **Dr. Norbert Gilmore** has taken on the task of leading the merged HIV and chronic viral disease units of the MGH and RVH. Dr. Gilmore comes to this position with a wealth of experience and a long standing relationship with both sites. He succeeds Dr. Richard Lalonde, who has stepped down as Director of the MCI and Dr. Chris Tsoukas, who ably led the IDCT since its inception.

HONOURS

Dr. Jonathan Campbell Meakins (1882-1959) will be posthumously inducted into the **Canadian Medical Hall of Fame** in April 2011. One of McGill's most illustrious graduates and professors, Dr. Meakins was appointed Director of Experimental Medicine in 1912 before being recruited to the University of Edinburgh for several years. He was recruited back to McGill in 1924 as Chair of Medicine and Physician-in-Chief of the Royal Victoria Hospital, where he established the McGill University Clinic, dedicated to what we now call translational research. The founding father of the Royal College of Physicians and Surgeons of Canada, Dr. Meakins eventually became Dean and was the recipient of numerous honours. His many contributions to McGill University have been commemorated in the Meakins-Christie Laboratories. More on this story.

Dr. Albert Aguayo will be inducted into the **Canadian Medical Hall of Fame** in April 2011. Emeritus Professor in the Departments of Medicine and Neurology & Neurosurgery, Dr. Aguayo joined McGill in 1967 and was Director of the Centre for Research in Neuroscience from 1985 to 2000. He has made significant contribution in the areas of neural regeneration and repair and his work has had important influences in treating injuries to the nervous system once considered untreatable. More on this story.

Dr. Sylvia Cruess, endocrinologist, Professor in our Department and Core Faculty Member at the McGill Centre for Medical Education**,** has been named **Officer of the Order of Canada** in recognition of her pioneering contributions to the understanding of medical professionalism and its relationship with medicine's social contract. More on Dr. Cruess.

Dr. Maurice McGregor, Emeritus Professor in our Department, has also been named **Officer of the Order of Canada** for having pioneered and championed the field of health technology assessment in Canada, and for his leadership in medical education and cardiology. More on Dr. McGregor.

Dr. Errol Marliss, Professor in the Divisions of Endocrinology and Gastroenterology and Head of the McGill Nutrition and Food Science Center, has been named **Fellow of the American Society for Nutrition**. Dr. Marliss is internationally known for his work on body protein metabolism and its abnormalities.

Dr. Brian Chen, Assistant Professor in the Departments of Medicine and Neurology & Neurosurgery , has received a **Sloan Research Fellowship** to continue his research, which focuses on the "cellular and molecular mechanisms of how neural circuits wire up with precision". Awarded annually since 1955, the fellowships are given to early-career scientists and scholars in recognition of achievement and the potential to contribute substantially to their fields.

Photo: Owen Egan

Dr. Robert Sladek is the 2011 recipient of the **Joe Doupe Young Investigator Award** of the **Canadian Society for Clinical Investigation**. This award recognizes outstanding research accomplishments in the first eight years of an investigator's career. Dr. Sladek, Assistant Professor in the Division of Endocrinology and Metabolism and in the Department of Human Genetics, is known for his innovative work in genomics, particularly in relationship to diabetes mellitus.

IN MEMORY OF DR. PETER MACKLEM

By Drs. David Eidelman and Mara Ludwig

We are profoundly saddened by the unexpected death, on February 11, 2011 at age 79, of **Dr. Peter Macklem**, Emeritus Professor of Medicine. A former Chair of the Department of Medicine and Physician-in-Chief at the Royal Victoria Hospital, Dr. Macklem was one of the most dynamic and influential leaders in the history of McGill's Faculty of Medicine.

A graduate of Queen's University, Dr. Macklem came to McGill to pursue his medical studies, receiving his MD,CM in 1956. He subsequently pursued training in internal medicine and respiratory medicine at McGill, and became a Fellow of the Royal College of Physicians and Surgeons of Canada in 1963. Although originally intending to become a clinician, he became involved in research at an early stage and it became the passion of his life. Over the course of 5 decades, Dr. Macklem remained active in research. Indeed, he was still working on protocols with colleagues in Europe at the time of his death.

Among his numerous scientific achievements, Dr. Macklem pioneered the study of small airway function and thereby identified the early pulmonary damage effected by smoking. His work constitutes the scientific basis for the ongoing campaign against smoking. He demonstrated that normal respiratory muscle function is compromised during acute respiratory failure, and delineated the mechanisms for both dyspnea and respiratory muscle fatigue. This work continues to inform the development of novel approaches to the management of COPD, as well as optimal ventilatory management. In later years, Dr. Macklem's intense curiosity and boldness led him to the study of the theory of complexity and its implications for pulmonary function.

In addition to his preeminent role in respiratory research, Dr. Macklem was an outstanding medical leader. First as the founding director of the Meakins-Christie Laboratories and then as Director of the Inspiraplex, the Respiratory Health Networks of Centres of Excellence, Dr. Macklem inspired and fostered the careers of many physicians and scientists who currently hold positions of leadership in universities around the world. In 1980 he was made Physician-in-Chief of the Royal Victoria Hospital and Chair of Medicine at McGill University. In 1985 he was appointed as Massabki Professor of Medicine at McGill before becoming Physician-in-Chief of the Montreal Chest Hospital in 1987.

Dr. Macklem has been widely recognized for his achievements. He was a medalist of the American College of Chest Physicians (1979), was elected as a Fellow of the Royal Society of Canada (1982) and received an Honorary Doctorate from the *Université Libre de Bruxelles* (1987). Dr. Macklem was chosen as the James Burns Amberson Lecturer of the American Thoracic Society in 1986. In 1988, Dr. Macklem was granted the Order of Canada and in 1991 was the recipient of the John B. Sterling Medal given to an outstanding graduate of Queen's University. In 1999, in recognition of his enormous contributions, Dr. Macklem was awarded the Trudeau Medal of the American Thoracic Society, the highest honour bestowed by the international respiratory community. Also in 1999, he was named a Wightman awardee of the Gairdner Foundation in recognition of having demonstrated outstanding leadership in medicine and medical science.

Peter Macklem was a brilliant, charismatic and outspoken thinker. He was original in his research and dynamic in his leadership. He fostered the careers of too many to name. Throughout his career, he maintained his scientific curiosity and enthusiasm and imparted these to his many trainees and colleagues. For those of us who were fortunate to have had the privilege to work with him and to be mentored by him, the loss is profound. We are left with a debt of gratitude that cannot be repaid. He will be missed.

Donations in his memory may be made to TIARA (www.tiara.on.ca), Frontenac Arch Biosphere (www.fabr.ca), Dans la rue, of Montreal (www.danslarue.com), or a charity of your choice.

IN MEMORIAM

By Dr. Henri Ménard

Dr. David Hawkins was born in St. John's, Newfoundland and ended his earthly life peacefully, in the ICU of the Ottawa General Hospital on Saturday, February 12, 2011, following complications of an acute respiratory illness.

Dr. Hawkins received his MD from Dalhousie University and did post graduate training at Dalhousie, McGill and the Scripps Research Foundation in La Jolla, California. In 1968, he returned to McGill as a Medical Research Council (MRC) of Canada Scholar and subsequently became Professor of Medicine and Director of Rheumatology at the Montreal General Hospital. In 1980, he became Chair of Medicine at Memorial University. and in 1987, Memorial's 3rd Dean of Medicine. In 1991, he was VP of the MRC (Canada) and served as interim President. He has also served for many years as a volunteer board member for a number of medical and health associations, notably the Arthritis Society of Canada.

In 1993 the MRC and Memorial University jointly endowed the David Hawkins Lectureship in Health Sciences Research. In 1995 he became Executive Director of the Association of Canadian Medical Colleges, in Ottawa. In the same year he was named Alumnus of the Year by the Dalhousie Medical Alumni Association. From 1995-2009 he was an adjunct professor of pediatrics at University of Ottawa with a consulting clinical practice in pediatric rheumatology at the Children's Hospital of Eastern Ontario.

David is widely known and loved as a clinician, mentor, scientist, teacher, humorous and witty raconteur, friend and supporter of students and colleagues, general enthusiast, adventurer, skier, sailor, innovator, cook, party host and patriotic Newfoundlander. Farewell David!

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The Department of Medicine's number of successes is prolific. Although every attempt is made to acknowledge them all at the time we go "to press", some announcements may be delayed. Do not hesitate to contact us to let us know of your successes.