Message from the Director, Robert Friesel, PhD

2015 was an exciting year at the Center for Molecular Medicine (CMM) as we saw the awarding of two highly competitive R24 program grants to Leif Oxburgh DVM/PhD and Cliff Rosen MD. These prestigious multi-million dollar grant awards are collaborative multi-institutional grants in highly focused areas of translational and clinical importance. We also welcomed three new faculty members to CMM, Michaela Reagan PhD, who came to CMM from the Dana Farber Cancer Institute in Boston; Katherine Motyl PhD, who was formerly a postdoctoral researcher in the laboratory of Cliff Rosen; and Aaron Brown PhD, formerly a postdoctoral researcher in the laboratory of Leif Oxburgh. Both Dr. Motyl and Dr. Brown were advanced to faculty status due to their significant scientific achievements and potential to be successful independent investigators. These young investigators will bring new and exciting expertise and scientific perspective that will complement our existing faculty.

Last year I spoke about the importance of discoveries in biomedical research and their impact on how human diseases are diagnosed and treated. CMM has a cadre of investigators poised to make exciting and important discoveries in kidney disease, cardiovascular disease, anemia, osteoporosis, obesity, and cancer. These investigators are among the brightest in their fields with many great projects and ideas, some of which they cannot investigate because of the scarcity of research funding.

Often these ideas require proof of concept in the form of preliminary data to develop a competitive external grant application for funding of the project. Fortunately, CMM and Maine Medical Center Research Institute have a pilot project program that enables early stage funding of some of these highly meritorious ideas. Funding for these pilot projects comes from our two Centers of Biomedical Research Excellence (COBRE) grants and institutional funds. It is a competitive process involving writing a pilot grant application, which is then peer reviewed by senior investigators to identify the most highly impactful projects. Because the goal is for these projects to lead to significant external funding for more fully developed research ideas, we view the program as an investment in the future success of our investigators. In 2015, eight pilot projects were awarded from our COBRE programs, including awards to Sergey Ryzhov MD/PhD, to investigate the role of myeloid cell-derived factors in the heart after myocardial infarction; Aaron Brown and Cliff Rosen to develop human iPS cells that can form brown fat; Robert Koza to study genes impacting obesity in mouse models; and Liangru Contois and Peter Brooks to study regulators of angiogenesis. In addition, our programs supported technical projects to advance our core facility resources, including projects to perform multiplex global transcriptome analysis (Leif Oxburgh) and skeletal histomorphometry (Volkhard Lindner).

CMM is fortunate to have the support of the National Institutes of Health and Maine Medical Center, which provide funding for these pilot studies, and enables our investigators to pursue their innovative ideas.

Cover photos

Top row (left) B16 mouse melanoma cells transfected with red fluorescent protein targeted to mitochondria (red) with tubulin stain in green; (right) duct of a mouse mammary gland stained to detect cytokeratin 5 (green), cytokeratin 8/18 (red), and nuclei (blue). Both from Oleg Tikhomirov.

Middle row (left) section from mouse heart muscle stained to detect collagen IV (green) and filamentous actin (red), Oleg Tikhomirov; (right) whole primary mouse bone marrow cells (green) grown in a 3D silk scaffold (pink/purple) recapitulate the bone marrow microenvironment in vitro - these models are used to study adipogenesis, osteogenesis, and cancer-stromal cell interactions. Michaela Reagan and the Confocal Microscopy Facility (Igor Prudovsky).

Bottom row (left) microCT image of a healing bone fracture of the mouse femur, showing callus formation at the point of break. Xuehui Yang and the microCT facility (Terry Henderson); (right) human endothelial cells stained to detect collagen IV (green), filamentous actin (red), and nuclei (blue), Beau Rostama.
For more information about the Center for Molecular Medicine, please contact:

Bob Friesel, Ph.D.
Director, Center for Molecular Medicine
friesr@mmc.org

For more information on our research training programs, please contact:

Lucy Liaw, Ph.D.
Associate Director, Center for Molecular Medicine
Director, Research Training Programs
liawl@mmc.org

If you are a student looking for job shadow or internship opportunities, please contact our Education Coordinator, Liz Bergst: Bergse@mmc.org

Your support of the Maine Medical Center Research Institute allows for our world-class scientists to truly be innovative and take risks in their research. You are a key partner in helping us make advances in biomedical research. Thank you! To discuss how you can help support our research and education programs, please contact our Research Leadership Gift Officer, Kendra Allen: KAllen@mmc.org

Please visit our website at: mmcri.org
Michaela Reagan, PhD

Q: How do you envision your research impacting patients with multiple myeloma?

Michaela: I envision that research from my lab will discover new ways to treat multiple myeloma patients by targeting the bone marrow microenvironment. I aim to develop therapies that will both stop tumor growth and strengthen and heal the bone, which is commonly eroded as these tumors grow in the marrow. My lab is researching how certain cells in the bone marrow support tumor growth. With this knowledge, we are designing, developing, and testing better treatment strategies to interfere with this process.

Q: How will the environment at Maine Medical Center Research Institute support you as you establish your own research laboratory?

Michaela: Maine Medical Center Research Institute offers everything a cancer researcher could want. Major assets are the clinical connections, especially the clinical faculty, BioBank tissue repository, the translational catalysts, and connections with NE Cancer Specialists, Tufts Medical Center, and Dana-Farber. The scientific resources and the collaborative environment make an incredibly strong and supportive environment for young investigators. The kind and helpful staff in the administration have all been crucial in getting my lab off the ground. I have outstanding mentors, collaborators, and lab members, who have all welcomed me here. The reliable support from leadership is very meaningful, and these resources will continue to be extremely important as my lab evolves. I cannot imagine a better environment in which to pursue biomedical science, especially for a newly independent investigator.
Katie Motyl, PhD

Q: What was the best advice you have received that helped you get to this point in your career?

Katie: The best advice I have received was to never give up. All of my mentors have helped me to believe in my ability to reach this point in my career and even when faced with setbacks, I have been encouraged to persevere at every stage.

Katie: I hope to contribute to the skeletal health of patients through discovering novel mechanisms regulating bone remodeling. I also hope to give the young investigators that I train every chance to succeed and pursue their unique career goals.

Aaron Brown, PhD

Q: Why did you choose to start your research lab in Maine?

Aaron: I chose to do my research here because of the expanding biomedical science infrastructure and as a lifelong Mainer, I have always enjoyed the diverse landscapes, wildlife, and rich seasons that Maine has to offer.

Q: What is the main goal of your research?

Aaron: The main goal of my research is to study how adipose tissue develops and is regulated to find biological mechanisms that can be exploited to aid in the fight against obesity, which is correlated with an increased risk for diabetes, stroke, heart disease and cancer.

“...as a lifelong Mainer, I have always enjoyed the diverse landscapes, wildlife, and rich seasons that Maine has to offer.”
Q: What are you trying to learn from your program?

A: We are trying to understand how stem cells become either bone or fat cells, and how this influences obesity and osteoporosis. Both diseases are very prevalent and the pathophysiology of each disease goes back to the earliest stem cell, found in the bone marrow. Identifying the progenitor for each cell type will allow us to design therapies that could change the course of the disease.

Q: How does it help to have multiple institutes involved in this program?

A: This program is based on a single biologic question that could not be addressed by one investigator or one institution. For example, the clinical studies with anorexia nervosa are done at Mass General Hospital, the world's leading center for understanding and treating this disease. At Yale, new techniques for tracing the origin of these bone and fat cells are being implemented, work that could not be done elsewhere. By working together towards a common goal, everyone benefits.

Q: Give one example of a recent, exciting contribution this program has made to advance progress in this field.

A: We have developed a new technique for visualizing and quantifying marrow fat. This is the first advance in the field in forty years, and is now being utilized around the world by most laboratories since it combines technology already available. It also allows us to understand in rodent models, the origin and regulation of marrow fat. Moreover, it is also being applied in other fields.
Q: What recent scientific advances have made this research possible?

A: We have traditionally studied development of the kidney in a descriptive way, and that is how we have discovered many of the basic signals between cells essential for formation of functional structures. Recently, we developed technology that harnesses our basic understanding of signals governing organ development to create new kidney tissue entirely in the laboratory. This has strong potential for translation into a medical device, and our multidisciplinary team is one of the founding members of the (Re)building a Kidney Consortium that focuses international research efforts towards this goal. Although laboratory-grown kidneys for transplantation remain a relatively long-term goal, perhaps coming to clinic for human use in 20 or 30 years, we now understand that the essential principles are feasible, making it a realistic goal. As a point of comparison, the refinement of kidney transplantation to a therapy with over 90% success rate from an experimental trial took approximately as long.

“To address complex questions such as engineering new kidney tissue, we need to assemble the best team, irrespective of geographic location. With this funding we have built a team of experts with complementary research expertise from three different academic research centers from Maine to Texas.” Leif Oxburgh

Three dimensional modeling of a single glomerulus isolated from a postnatal mouse kidney stained with podocyte marker Wilms’ Tumor 1 (blue), endothelial marker Griffonia simplicifolia isolectin B4 (green), and mesangial marker alpha smooth muscle actin (red). The volume rendering shown is based on 3D reconstruction of serial confocal micrographs.
Other new grant awards in 2015

Our research programs are supported by grants from the National Institutes of Health and other federal agencies, private foundations, and corporate funders. Congratulations to our other new grant and fellowship recipients in 2015!

NIH F32 postdoctoral fellowship

Kathleen Bishop was awarded a postdoctoral fellowship from the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the NIH. Her project focuses on the DOCK7 protein and its function in osteoblasts in the bone.

Hyundai Hope on Wheels

Above, left to right: Eric Larsen (Maine Children’s Cancer Program), Donald St. Germain, (Director of Maine Medical Center Research Institute and VP of Research, Maine Medical Center), Pradeep Sathyanarayana (Hope on Wheels grant awardee), East Coast Executive Manager, Hyundai Motors America. Dr. Sathyanarayana received a grant to study microRNAs in acute myeloid leukemia.

Acorda and BioPact

Douglas Sawyer leads a project with a sponsored research agreement from Acorda Therapeutics, Inc. to study heart progenitor cells from patients who undergo open heart coronary artery bypass graft surgery. Dr. Sawyer’s group will study ERBB and glial growth factor 2 functions in cardiac progenitor cells.

Michaela Reagan was awarded a grant from BioPact, the developer of specialized and proprietary carbon nanotubes for medical therapies. Dr. Reagan will develop bone-targeting or multiple myeloma-targeting nanoparticles that will deliver therapies to eradicate multiple myeloma cells. This project will test the ability of drug-loaded carbon nanotubes to be effective anti-cancer therapies.

Maine Cancer Foundation

Anne Breggia, the Director of our BioBank, received a grant to expand our existing human specimen repository to include blood and bone marrow from cancer patients. Researchers in the Center for Molecular Medicine directly utilize the resources of the BioBank for their translational studies.
New graduates from the University of Maine

Graduate School of Biomedical Science and Engineering

The Graduate School of Biomedical Science and Engineering is celebrating its 10 year anniversary. This program is housed at the University of Maine Orono, and is a state-wide partnership including Maine Medical Center Research Institute, The Jackson Laboratory, Mount Desert Island Biological Laboratory, the University of Southern Maine, and the University of New England. Graduate students in this program work towards the Ph.D. degree in either Biomedical Science or Engineering, and can choose to perform thesis research at any of the cooperating institutions. At Maine Medical Center Research Institute, we have trained 26 UMaine graduate students who have earned their Ph.D. degree working in our research laboratories.

From left: Lucy Liaw, Beau Rostama, Sarah Peterson, Deepthi Muthukrishnan, and Leif Oxburgh. Beau, Sarah, and Deepthi successfully achieved their PhD degrees from University of Maine in 2015. Beau and Sarah performed their thesis work in the Liaw lab, and Deepthi performed research in the Oxburgh lab.
Center for Molecular Medicine
Publications 2015

The bone-fat interface: basic and clinical implications of marrow adiposity. Devlin MJ, Rosen CJ. *Lancet Diabetes Endocrinol*

Inhibition of tumor-associated αvβ3 integrin regulates the angiogenic switch by enhancing expression of IGFBP-4 leading to reduced melanoma growth and angiogenesis in vivo. *Contois LW, Akalu A, Caron JM, Tweedie E, Cretu A, Henderson T, Liaw L, Friesel R, Vary C, Brooks PC. Angiogenesis*

3,5-diiodo-L-thyronine (t2) in dietary supplements: what are the physiological effects? *Hernandez A. Endocrinology*


Marrow fat in mice is increased following a high fat diet. *Casey Doucette, Cliff Rosen et al.*

Dynamic interplay between bone and multiple myeloma: emerging roles of the osteoblast. *Reagan MR, Liaw L, Rosen CJ, Ghobrial IM. Bone*

SLUG is a direct transcriptional repressor of PTEN tumor suppressor. *Uygur B, Abramo K, Leikina E, Vary C, Liaw L. Prostate*


Serum FGF-21 levels are associated with worsened radial trabecular bone microarchitecture and decreased radial bone strength in women with anorexia nervosa. **Fazeli PK, Faje AT, Cross EJ, Lee H3, Rosen CJ, Bouxsein ML, Klibanski A. Bone**


Emerging EPO and EPO receptor regulators and signal transducers. **Kuhrt D, Wojchowski DM. Blood**

Racial differences in bone loss and relation to menopause among HIV-infected and uninfected women. **Sharma A, Flom PL, Rosen CJ, Schoenbaum EE. Bone**


Adipose tissue Mest and Sfrp5 are concomitant with variations of adiposity among inbred mouse strains fed a non-obesogenic diet. **Anunciado-Koza RP, Higgins DC, Koza RA. Biochimie**

Energy excess, glucose utilization, and skeletal remodeling: new insights. **Lecka-Czernik B, Rosen CJ. J Bone Miner Res**


Parent stem cells can serve as niches for their daughter cells. **Pardo-Saganta A, Tata PR, Law BM, Saez B, Chow RD, Prabhu M, Gridley T, Rajagopal J. Nature**


Cthrc1 in neurons in the brain, **Volkhard Lindner**

Macrophenage-derived osteopontin induces reactive astrocyte polarization and promotes re-establishment of the blood brain barrier after ischemic stroke. **Gliem M, Krammes K, Liaw L, van Rooijen N, Hartung HP, Jander S. Glia**

Pericyte structure and distribution in the cerebral cortex revealed by high-resolution imaging of transgenic mice. **Hartmann DA, Underly RG, Grant RI, Watson AN, Lindner V, Shih AY. Neurophotonics**

A synthetic niche for nephron progenitor cells. Brown AC, Muthukrishnan SD, Oxburgh L. Dev Cell

Kidney progenitor cells grown ex vivo induced to produce markers of distal kidney tubules, Aaron Brown, Leif Oxburgh et al.

Igfbp2 deletion in ovariectomized mice enhances energy expenditure but accelerates bone loss. DeMambro VE, Le PT, Guntur AR, Maridas DE, Canalis E1, Nagano K1, Baron R1, Clemmons DR1, Rosen CJ. Endocrinology


The past 10 years—new hormones, new functions, new endocrine organs. Bouillon R, Drucker DJ, Ferrannini E, Grinspoon S, Rosen CJ, Zimmet P. Nat Rev Endocrinol


Type 2 diabetes and the skeleton: new insights into sweet bones. Shanbhogue VV, Mitchell DM, Rosen CJ, Bouxsein ML. Lancet Diabetes Endocrinol

Proportionate dwarfism in mice lacking heterochromatin protein 1 binding protein 3 (HP1BP3) is associated with alterations in the endocrine IGF-1 pathway. Garfinkel BP, Arad S, Le PT, Bustin M, Rosen CJ, Gabet Y, Orly J. Endocrinology

Targeting EPO and EPO receptor pathways in anemia and dysregulated erythropoiesis. Rainville N, Jachimowicz E, Wojchowski D. Expert Opin Ther Targets


Mutation in the DLL4 gene in a mouse model leads to altered lung vascular structure (right) compared to the lung vasculature in normal mice (left). Beau Rostama, Chris Norton, Tom Gridley, et al.

Arteriovenous malformations of blood vessels in a mouse endoglin mutant embryo, Kira Young, Luke Krebs, Calvin Vary et al.


Adipose tissue residing progenitors (adipocyte lineage progenitors and adipose derived stem cells (ADSC). Berry R, Rodeheffer MS, Rosen CJ, Horowitz MC. Curr Mol Biol Rep


Navigating the bone marrow niche: translational insights and cancer-driven dysfunction. Reagan MR, Rosen CJ. Nat Rev Rheumatol

New insights into bone marrow adipocytes: Report from the First European Meeting on Bone Marrow Adiposity (BMA 2015). Hardouin P, Marie PJ, Rosen CJ. Bone

Concurrent BMP7 and FGF9 signalling governs AP-1 function to promote self-renewal of nephron progenitor cells. Muthukrishnan SD, Yang X, Friesel R, Oxburgh L. Nat Commun

Molecular correlates of fat mass expansion in C57BL/6J mice after short-term exposure to dietary fat. Anunciado-Koza RP, Manuel J1, Koza RA. Ann N Y Acad Sci


The chick chorioallantoic membrane (CAM) is a model for angiogenesis and inflammation. The CAM on the right was stimulated with FGF2, and shows inflammation and blood vessel recruitment. Jackie Ames, Peter Brooks et al.

Passenger gene mutations: unwanted guests in genetically modified mice. Ackert-Bicknell CL, Rosen CJ. J Bone Miner Res

Twenty years in Maine: integrating insights from developmental biology into translational medicine in a small state Gridley T. Current Topics in Develop Biology


Mouse model of neointimal lesion formation induced by carotid artery ligation. β-galactosidase activity staining highlighting the smooth muscle layers of a ligated mouse carotid artery in blue. Sarah Peterson, Jacqueline Turner et al.

>6800: the number of hours of internship training provided to high school, college, and post-baccalaureate students in our laboratories.

22: the number of job shadow students we hosted in 2015.

200: the number of hours of research training for medical residents.

>2700: the number of hours of training for international scholars.
Chris: What did you research and why do you think it is important?

Rayne: I’m studying the growth of the heart after failure. We are characterizing the expression of NRG and ERBB receptor in cardiac progenitors. It is important to understand how it recovers after failure, and discovering how to regrow damaged cells after heart failure could save a lot of lives.

Jennifer: I’ve been doing caveolin research. Caveolins are a family of proteins found in the plasma membrane of heart cells. They are involved in receptor-independent endocytosis, which is when a cell absorbs molecules by engulfing them. I’ve been making plasmids and running fluorescence resonance energy transfer to see how the insulin receptor interacts with caveolin.

Anna: I’ve been studying the effect of the Notch signaling pathway on smooth muscle cells derived from plaques taken from endarterectomies performed on patients with obstructed blood vessels. Atherosclerosis is a disease that causes plaque to build up inside your arteries, and it can be life threatening, so it is important for us to understand what causes it and how to prevent it.

Chris: What are your day-to-day activities?

Jennifer: I rarely do the same thing every day. The one repetitive thing is maintaining the cell cultures, but other than that, it is something new every day.

Chris: What did you enjoy most about your internship?

Rayne: I’ve really enjoyed the learning aspect. Getting to learn about the lab and everyone’s excitement has been a good experience.

Anna: I love all of the techniques I’m learning. Cell culture, microscopy, and materials, and resources I wouldn’t have at school – it’s great.

Jennifer: You have to know what you’re doing and double check everything when running an experiment. If you aren’t careful, you can set yourself back by a few weeks!

Chris: How do you think this internship has prepared you for your career?

Anna: Working in a professional environment is very different than a school lab. Having professional relationships with the other scientists teaches you how to interact and work in a lab environment.

Jennifer: It helps you gain a deep understanding of the basic science behind the topics you study. Then this can help you understand the more complex topics you come across later.

Rayne: It has helped me in deciding what kind of career I want. It gave insight into how research is done, and has encouraged my future pursuits.
Maine Medical Center Research Institute

Center for Molecular Medicine

81 Research Drive

Scarborough, ME 04074

207-396-8181

mmcri.org