Department of Chemistry & Biochemistry

School of Integrated Science and Humanities

Departmental Seminar Announcement

Epigenetic Reprogramming Due to DNA Repair: A New Mechanism for Permanent Variations in Gene Expression in Animal Cells.

Dr. Mark Muller

TopoGen Inc., Orlando

Abstract:

We have characterized the changes in chromatin structure, DNA methylation and transcription during and after homologous DNA repair (HR) and Non-Homologous End Joining (NHEJ) in human cells. We have discovered that both major repair pathways can potentially revise DNA methylation patterns. NHEJ is error prone and a prominent repair path in animals and these repair products are strongly silenced. HR is a high fidelity pathway that effectively regenerates the wilds type DNA sequence following a DS break. Even when repair is error free, the resulting repair products display new DNA methylation patterns that are either over-written or completely modified from the parental cells (prior to repair). This leaves behind an imprinting 'scar' and virtually any repaired gene may be silenced permanently in the offspring of the original repair. The imprinting or DNA methylation scar maps to the 3' of the DS break in HR and at both 3' and 5' locations in NHEJ. In studying this new source of gene expression variation in somatic cells, we have developed a deeper understanding of the process by mapping the DNA-Chromatin loops connecting the 5' and 3' ends of the repaired gene. In addition, during a two-week period after HR, transcription-associated demethylation promoted by Base Excision Repair enzymes further modifies methylation of the repaired DNA. Subsequently, the repaired genes display stable but diverse methylation profiles. These profiles govern the levels of expression in each clone. Our data argue that DNA methylation and chromatin remodelling induced by HR may be an important source of permanent variation of gene expression in somatic cells.

In a related project, we are using the same cell context HR and NHEJ platforms to screen for novel effectors that influence the DNA methylation revisions in DNA repair. Using *in silico* screening for example, we were able to carry out a drug repurposing analysis to show that an already FDA approved small molecule has the potential to alter DNA methylation outcomes that attend repair. In a second project, we have used the cell-screening platform to demonstrate the presence of miRNAs in the serum of advanced stage cancer patients, that can alter DNA methylation status in a neutral gene. Collectively our goal is to identify novel epi-therapeutics, either as small molecules or non-coding RNAs for application in acute and chronic human diseases.

Date: **Friday, October 21, 2016**
Time: **11:00 am to 12:00 pm**
Location: GL-100 MMC (Live)
Marine Sciences Building Room 105 (MSB-105) – BBC (via Polycom)

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Phone: 305-348-2605
Fax: 305-348-6700
E-mail: chemistry@fiu.edu
http://chemistry.fiu.edu

Career Summary.

Mark T. Muller received his Ph.D. from the University of British Columbia (Vancouver) in Molecular Virology and Microbiology. He joined the Department of Microbiology at Ohio State University in 1980 and by 1990 was a full professor. He has been an NIH funded cancer researcher for over 30 years with multiple patents, publications and seminars around the globe. At The Ohio State, Dr. Muller, along with several colleagues, founded a new Department of Molecular Genetics, the first of its kind in the US, and actively collaborated with clinical researchers in the NCI designated Comprehensive Cancer Center at OSU in anticancer drug discovery projects. Dr. Muller was a Program Leader of the Cancer Center's Program in Experimental Therapeutics. While at OSU in the late 1990s, Dr. Muller took a leadership role in establishing a Research Incubator with the Edison Foundation, and was on the board to develop and grow new start-ups in the Columbus community. During this time, Dr. Muller was instrumental in getting new state legislation to change laws prohibiting faculty from starting new companies with high equity positions. He founded several biotech start-ups which occupied OSU Incubator space. One of the companies, TopoGEN, Inc. continues today as a profitable entity located in Central Colorado and Dr. Muller was instrumental in bringing NIH SBIR funding for a new platform of epigenetics. In 2004, Dr. Muller was recruited to the University of Central Florida to build a research base for the new UCF College of Medicine, where he was Chair of the Central Florida Cancer Consortium. Dr. Muller left academia (2015) to become CEO of TopoGEN, Inc., where he is growing the Company using resources and incentives from the State of Colorado and active NIH funding.