McGowan Institute for Regenerative Medicine
A program of the University of Pittsburgh and UPMC

Dr. Andrew Duncan Receives NIH Grant Focused on Obtaining a Better Understanding of Liver Biology

Nearly 25 million Americans are affected by liver dysfunction, and liver diseases are the 10th leading cause of death in the US. There is a clear and urgent need for developing new alternatives to whole organ replacement. A better understanding of liver biology is required to improve existing approaches and to innovate therapies for the treatment of liver diseases, including viral hepatitis and steatohepatitis. McGowan Institute for Regenerative Medicine faculty member Andrew Duncan, PhD, assistant professor in the Department of Pathology at the University of Pittsburgh with a secondary appointment in the Department of Bioengineering of the Swanson School of Engineering, recently received a 5-year, $2,174,309 grant from the National Institute of Health's National Institute of Diabetes and Digestive and Kidney Diseases. The project title is "Mechanisms of Polyploidy and Aneuploidy in the Liver."

Hepatocytes, the primary functional cell type in the liver, display a range of chromosomal diversity resulting from prevalent physiological polyploidy (>90% in mice and 50% in humans) and aneuploidy (60% in mice and 30-90% in humans). In eukaryotic organisms, cells usually contain a diploid genome comprised of pairs of homologous chromosomes.

Polyploidy refers to gains in entire sets of chromosomes, and aneuploidy refers to gains and losses of individual chromosomes. The roles of hepatic polyploidy and aneuploidy represent a major gap in our current understanding of liver biology. Dr. Duncan and the team recently found that aneuploidy enhances the regenerative capacity of the mouse liver. In response to Tyrosinemia-induced injury, that is normally toxic to the liver, they identified a subset of aneuploid hepatocytes that was resistant to the disease. The data suggest that aneuploid hepatocytes are endowed with enhanced capacity for adaptation and regeneration.

Dr. Duncan's central hypothesis is that aneuploidy functions as an adaptive mechanism in response to hepatic injury. The goals of his project are to identify mechanisms regulating hepatic aneuploidy/polyploidy and to unravel how aneuploidy affects liver function. To investigate these questions, he and the team propose to determine whether polyploid hepatocytes are necessary for development of aneuploid livers. Experiments will characterize hepatic cell divisions, karyotypes, and stress response in E2f7/E2f8 knockout mice, which have normal liver function but are depleted of polyploid hepatocytes. Next, the researchers will dissect the role of a novel regulator of hepatic polyploidy, recently identified in Dr. Duncan's laboratory, microRNA-122 (miR-122). Experiments will determine how miR-122 alters ploidy and aneuploidy throughout life. The scientists will also identify cellular and molecular mechanisms by which miR-

122 regulates hepatic ploidy. Finally, the team will determine how random karyotypes (in aneuploid hepatocytes) affect function in the liver. They will utilize a novel xenotransplantation model to examine clonal nodules of regenerating human hepatocytes. Experiments will measure aneuploidy and determine gene expression profiles in these nodules. Together, these studies will define the extent to which aneuploidy affects liver repair/regeneration as well as the molecular mechanisms that control this process. Understanding how aneuploid hepatocytes arise and function will provide new and crucial insights into liver homeostasis, diseases, and treatments.

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Duncan Laboratory: Genetic Diversity in Liver Development and Regeneration

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