

Mike A. Leonis, MD, PhD

Instructor

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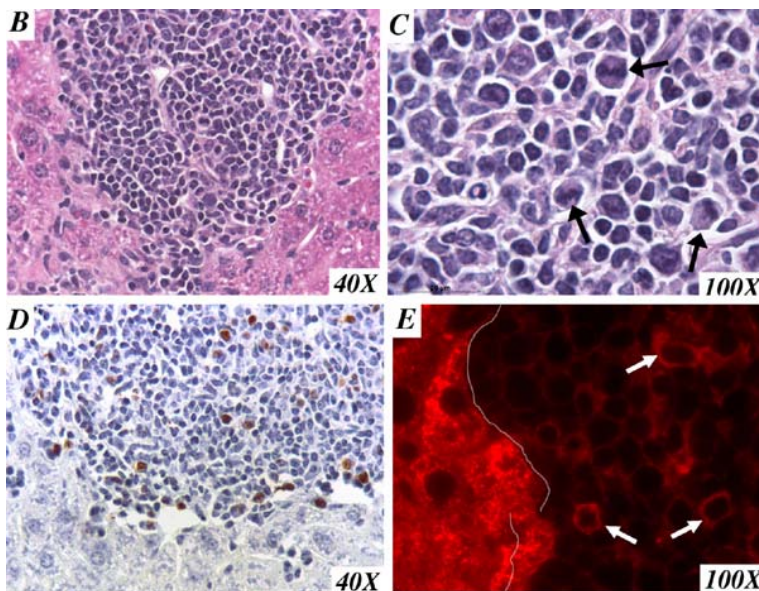
Description of Research:

Dr. Leonis investigates the mechanisms of hepatic tumorigenesis. The long term goal of his research is to define the role of the tyrosine kinase Ron receptor in liver pathophysiology, focusing primarily on the role of Ron receptor gain-of-function in hepatic tumorigenesis. He has previously used the well-characterized lipopolysaccharide-induced murine model of acute liver failure in galactosamine-sensitized mice to show that mice containing a deletion in the tyrosine kinase domain of the Ron receptor have a reduction in the number of liver cells undergoing apoptosis compared to wild-type mice. Currently he is testing the hypothesis that gain-of-function of the Ron receptor leads to hepatic tumorigenesis, possibly via activation of the beta-catenin transcriptional cascade. To test this hypothesis both in vitro and in vivo, he has established hepatic cell lines which over-express either the wild type or a constitutively active form of the Ron receptor and generated a transgenic mouse line with liver-specific over-expression of wild type Ron receptor. Dr. Leonis is also developing two lines of translational research. In the first, he has begun investigating human hepatoblastoma tumor specimens for their degree of Ron receptor expression and activation of intracellular signaling pathways relevant to carcinogenesis. And in the second, he is the Center Leader in a multi-center prospective study funded by the NIDDK-Pediatric Acute Liver Failure Study investigating the use of N-acetylcysteine in the recovery of children with idiopathic acute liver failure.

Collaborations:

Dr. Leonis has used the **Integrative Morphology Core** in collaboration with Dr. Waltz to study the role of Ron in the hepatic protection against apoptosis. He is also collaborating with Dr. Yazigi in studies of the role of N-acetylcysteine as an adjunct treatment of children with idiopathic acute liver failure. Dr. Leonis is using the **Microarray and Bioinformatics Cores** to search for prominent molecular signatures in hepatoblastoma.

Representative Figure:



Development of liver tumors in *Ron* transgenic mice. Tumorigenic foci develop spontaneously in the liver of transgenic mice with the hepatic overexpression of *Ron* (B), with variable levels of stromal accumulation and nuclear pleomorphism (arrows in C). These tumorigenic foci have abundant proliferating cells, as demonstrated by increased BrdU uptake in D. In E, albumin immunostaining shows cytoplasmic signal within normal liver lobule (left portion of the panel) as well as in neoplastic cells (white arrows). *Leonis et al., manuscript in preparation.*