

## ABSTRACT

### ENVIRONMENTAL LIVER DISEASE

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This seminar will provide an overview of environmental liver diseases (ELD). It will identify: (i) relevant exposures and liver pathologies focusing on toxicant associated steatohepatitis; (ii) key hypotheses; and (iii) current challenges and proposed solutions to move the field forward in the context Dr. Cave's RIVER award.

Over the last twenty years, deaths due to liver cirrhosis have increased by 65% while liver cancer-related deaths have doubled. Nonalcoholic fatty liver disease alone affects greater than 25% of the global population. The hepatotoxicity of industrial chemicals has long been recognized. Due to its role in xenobiotic metabolism, the liver is the most common target organ for chemical toxicity. However, chronic liver diseases remain understudied in the environmental health sciences. There is an unmet medical need for new medications for all chronic liver diseases, with the possible exception of hepatitis C. A better understanding of the environmental contribution to chronic liver disease is required to develop preventative and therapeutic interventions.

Dr. Cave became interested in this field as a clinical gastroenterology fellow at the University of Louisville, when he serendipitously discovered steatohepatitis occurring in polyvinyl chloride production workers at the Rubbertown chemical manufacturing complex. Dr. Cave's subsequent career development in environmental health could be considered a success story of the professional pipeline goal of the NIEHS Strategic Plan. He first received an NIEHS P30 career development award with subsequent R01 and R35 awards from the institute. Along the way, intellectual support from collaborating intramural NIEHS scientists as well as investigators at EPA, ATSDR, and academia was critically important to his EHS development. Because Dr. Cave is an active clinician, the RIVER award has been helpful to provide protected time for research.

The Cave laboratory currently takes a reverse translational approach consistent with the NIEHS translational research framework to answer fundamental questions related to environmental liver disease. Cohort studies are used to determine relevant chemicals warranting further investigation in model systems. Because this approach is tied to organ injury and not any one specific chemical, it might not be possible were it not for the RIVER award. The laboratory has elucidated new mechanisms for ELD such as tyrosine kinase receptor inhibition and signaling disruption by PCBs. However, the RIVER award's greatest impact has been the recruitment of investigators into the field. These investigators include (i) trainees; (ii) established environmental health scientists new to liver; and (iii) established liver investigators new to EHS. For example, investigators from multiple major cohort studies (e.g., the Anniston Community Health Surveys, GuLF Study, the C8 Health Project, etc.) have recently collaborated with Dr. Cave to add or enhance liver assessments in their research. RIVER projects leverage resources at interacting NIEHS P30 and P42 centers as well as interagency collaborations. Due, in part, to these efforts the field is gaining momentum with increasing numbers of peer-reviewed publications investigating the contribution of environmental exposures to liver disease.