

**Final Recommendations of the NIAAA Extramural Advisory Board
'Gut-Liver-Brain Interactions in Alcohol-Induced Pathogenesis'
February 3-4, 2009**

- 1. There is evidence that moderate alcohol consumption has health benefits whereas high consumption is harmful. To understand the mechanisms behind observed differences in health effects with variation in amounts and patterns of alcohol consumption and to address the biphasic effects of ethanol, it is important for NIAAA sponsored research programs to incorporate studies with varied doses and patterns of ethanol exposure.** To achieve this goal, it will be important to understand the influences that multiple variables have as related to the beneficial and pathologic effects of alcohol on liver, gut, brain and other organs. Complete dose-response and time course studies need to be performed that emphasize the quantity and frequency of drinking ranges. The critical variables (and their interactions) that should be considered include quantity, frequency, duration, and temporal pattern of drinking, as well as the influence of gender, ethnicity, genetic differences, nutritional status, exercise/life style, medications (e.g. statins, antidepressants), age and circadian rhythms.
- 2. It is important to characterize endocrine, paracrine, and other signaling molecules involved in alcohol's pathological effects and to study the interactions between multiple organ systems [liver, gut, brain (including blood brain barrier), adipocyte, immune system], with an emphasis on development of therapies.** Examples of signaling molecules and pathways involved in alcohol-induced pathogenesis to be studied include modulators of endocannabinoid systems, cytokines, and peptides mediating energy homeostasis. It is important to study innate immune mediators that contribute to brain, liver and other system pathology and to determine how ethanol and its metabolites alter these systems. These studies should also include analysis of the neuroprotection conferred by these molecules and pathways.
- 3. It is important to measure alcohol metabolism and the concentrations (and time courses) of metabolites that are generated.** An emphasis should be given to how changes in levels of metabolites affect key enzyme and signaling systems and how changes in these enzyme and signaling systems affect redox states in different tissues. Investigations should include effects of alcohol dose, time, gender and genetic variation.
- 4. Investigate the pharmacology of acetate, lactate, and other ethanol-induced metabolic changes.** Analyses should include effects of key metabolites (acetate, lactate, others) on different systems (brain, gut, liver, endocrine) and on behavior.

5. **It is important to explore how alcohol influences pathogen and gut biome derived factors.** Explore the effects of alcohol on the gut biome, small intestine/colon/gut permeability, liver clearance and activation of the immune system via gut permeable factors. Conduct multilevel basic and clinical studies of the relationship of the gut biome to alcohol-induced human organ disease. Explore the contribution of gut biome alterations in acute and chronic disease development.
6. **Collect and accumulate biosamples, including DNA, RNA, protein and gut biome, to allow biobanking and eventual analyses.** Use metabolomics, genomics, and proteomics to study the interactions of organ systems leading to alcohol-derived liver and brain disease across the course of illness and the lifespan.
7. **It is important to explore bidirectional interactions among obesity/metabolic syndrome and alcohol metabolism, alcohol-use disorders and alcoholic toxicity to brain and liver.** Studies should include both moderate (possibly beneficial) and heavy alcohol consumption.
8. **Investigate the course and progression of alcohol-induced brain and liver disease to better inform the development of experimental models, including a focus on minimal hepatic encephalopathy.** Explore collaborative mechanisms to bring together researchers in areas of liver, brain, gut, immune, endocrine and other relevant systems.
9. **Investigate how alcohol acts on physiological barriers and their role in mediating interactions among various organs.** The barriers to be studied include the blood-brain-barrier, blood-CSF-barrier, and the gut barrier. Are there common elements that contribute to dysregulation or disruption of these protective barriers?