Final Recommendations of the NIAAA Extramural Advisory Board
'Mechanisms of Alcohol Action and Injury (MAAIT I)'
May 24-25, 2005

1. Common and interactive mechanisms of alcohol-induced injury and impairment of repair across tissues, organs, and systems.

Opportunities exist to better understand alcoholic tissue injury related to endocrine, immune, nervous, gastrointestinal, cardiovascular, renal, adipose and other systems that contribute to health and pathology. Studies should include investigations of how alterations in one organ system relate to alcoholic injury in other systems and to overall pathology. The roles of known mechanistic factors in rendering injurious effects across different organ systems should be examined by identifying their effects on gene transcription, translation and cellular biology. Both the acute and chronic effects of alcohol induced tissue injury require investigation to better understand the progressive nature of alcoholic pathology. Interactions between different organs under acute and chronic alcohol exposure need to be explored to improve the understanding of how pathological mechanisms underlie adverse effects of alcohol on multiple organs.

In addition to the interaction of multiple physiological systems contributing to alcohol induced injury, there are common factors that may contribute to injury across multiple organ systems. These factors include redox state, metabolites, adducts, cytokines, oxidant stress, hypermetabolism, low energy state, common intracellular signaling processes and altered immune function. There are opportunities to better understand how alcohol induced alterations in cellular metabolism, formation of biologically active agents and other modifiers of cell biology contribute to progressive cellular and multiple tissue pathology. This could create opportunities in therapies designed to reverse and/or block alcoholic tissue injury.

The effects of ethanol on natural mechanisms of regeneration and repair are also key issues, to which new techniques in stem cell biology can contribute.

2. Drinking patterns should be examined in relation to tissue injury.

Tissue injury is likely to be affected by both peak alcohol levels and total exposure, so accurate measurements of alcohol and metabolite concentrations (both peak and area under the curve) are needed to better understand both acute and chronic mechanisms of injury. Opportunities exist for discoveries that provide technology to better follow BEC and metabolite measures over time. These include biosensor technologies and isotope-labeled ethanol. Studies should be encouraged to gather more detailed data on the pattern of alcohol exposure and the relationship to tissue injury.

3. Mechanisms of alcohol toxicity across the lifespan.

Opportunities exist to better understand the role of developmental factors (especially during adolescence) on the risk of developing alcoholism, behavioral pathology and/or organ injury. Age related factors in susceptibility to alcohol-related injury and impairment of repair in the fetus, adolescent, adult, and geriatric populations

should be explored, including studies that link exposures and injuries that can be years apart in humans. Identification of treatments that prevent the onset or progression of organ-specific damage at different times across the lifespan is important.

4. Determination of the genetic, behavioral, and environmental factors governing individual differences in susceptibility to alcohol induced injury.

Opportunities exist for identification of critical genetic, behavioral, and environmental risk factors that govern susceptibility to alcohol-induced injury. These factors may include nutrition, genetics, inflammation, psychiatric disease, tobacco, exposure to other pharmaceutical and non-pharmaceutical agents, the amount and pattern (constant vs. binge) of drinking. Individual differences in vulnerability to disease should include psychiatric disease and neurodegeneration as well as liver disease and tissue injury. Collecting well annotated genetic samples can aid in these studies.

5. Alcohol as a co-factor in risk and protection for a variety of diseases and the influence of alcohol on therapeutics.

The role of alcohol in contributing to diseases with multiple causes should be explored via partnership with other institutes, with NIAAA focusing on alcohol-unique mechanisms and/or alcohol-critical mechanisms involved in diseases associated with alcohol consumption. There are opportunities to build initiatives across institutes focused on diseases where alcohol is a co-factor in causation or protection, or might influence therapy (either directly or through alcohol-induced damage to key organs such as liver and brain). The influence of alcohol on medications, including polypharmacy for the elderly is important. One example is the investigation of synergistic alcohol effects with viral hepatitis and tobacco on the incidence of liver cancer. Opportunities for discovery also exist on the interactions between obesity, diabetes, and alcohol.

Biomarkers of organ injury, particularly at early stages of disease, should be explored. Well annotated tissue banks and repositories can contribute to this effort by allowing genetic, genomic and proteomic studies, and should be encouraged. Animal models can be used to discover markers of early disease and to test early treatment strategies.

6. Use new and existing tools and technology in appropriate circumstances.

While it is not appropriate for the agency to sponsor major efforts directed toward *development* of general technologies (genomic, proteomic, metabolomic, imaging), the *use* of such technologies as imaging (brain, liver, fetus), genomics, proteomics, metabolomics and biocomputational models to investigate targeted questions related to alcohol action and injury should be encouraged. Development of specific biosensor technology for ethanol and metabolites is warranted, as noted above, and could provide opportunities to understand how alcohol pathology relates to the pattern of BEC.

7. Agency initiatives that could advance these areas include proactive efforts to link different kinds of studies and to support extensions of existing studies.

These could include promoting supplements for banking well annotated samples from epidemiological or treatment studies for genetic, genomic and/or proteomics, and

banking and encouraging sharing of tissues from human subjects and animal models that have undergone different treatments. Program officers could encourage collaboration across disciplines, possibly using small supplements to cover marginal costs.