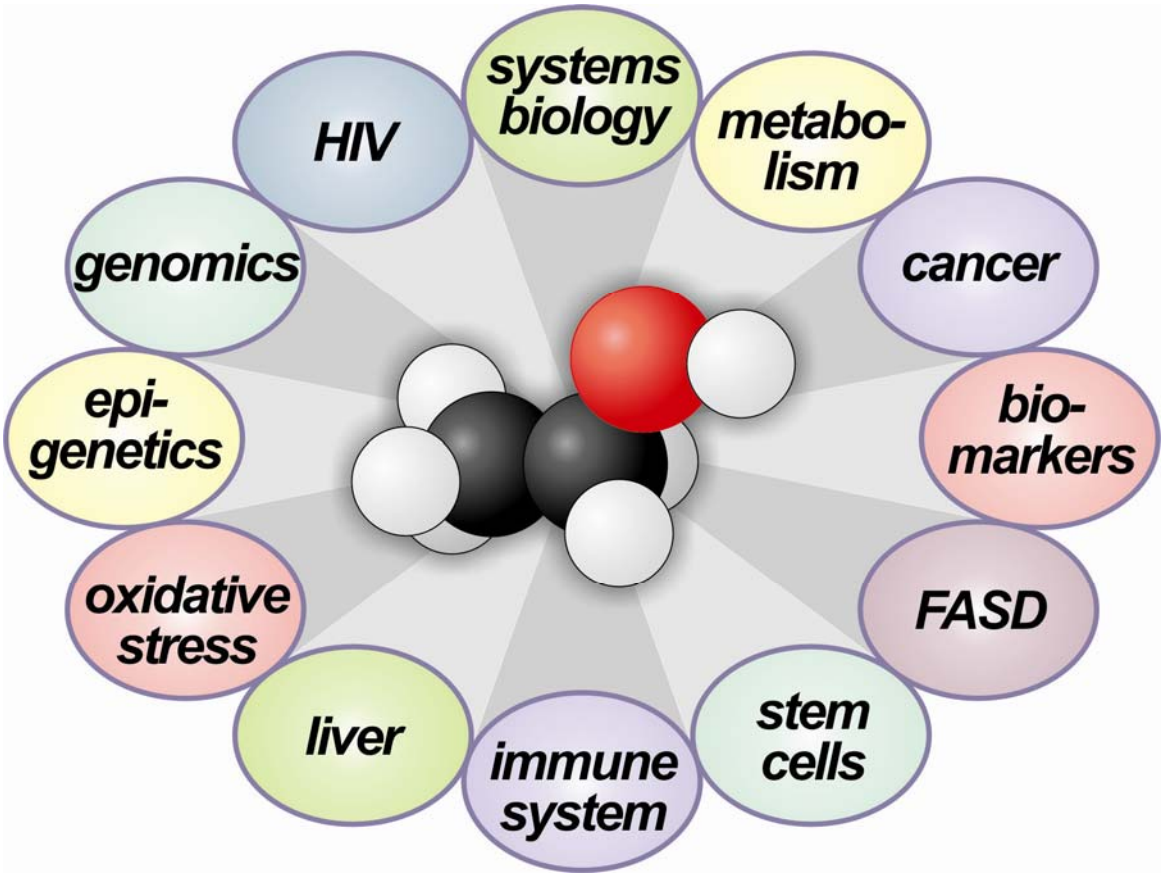
NIAAA
National Institute on Alcohol Abuse and Alcoholism
Division of Metabolism and Health Effects

Research Opportunities in

ALCOHOL METABOLISM & HEALTH EFFECTS



June 2008

Division of Metabolism and Health Effects

National Institute on Alcohol Abuse and Alcoholism

Mission Statement

The Division of Metabolism and Health Effects (DMHE) plans, stimulates, develops, and supports programs of research on the many factors including genetic, inter-individual variation, and dietary factors that influence alcohol metabolism and its sequelae. Utilizing the full spectrum of award mechanisms, DMHE supports research on alcohol metabolism, emphasizing metabolic pathways, enzyme kinetics, thermodynamics, metabolite measurements, adduct formation, non-enzymatic metabolism, and various substrates that may be affected by alcohol or alcohol metabolites; genetic studies involving alcohol-metabolizing enzymes and their role in reducing risk of alcohol consumption and tissue injury; identification of molecular pathways by which alcohol causes tissue and organ damage; genetic and metabolic variations that contribute to alcohol's impact on the initiation and progression of medical disorders including osteoporosis, type 2 diabetes, obesity, hypertension, immune and respiratory diseases, liver cirrhosis, cardiomyopathy, endocrine dysfunction, fetal alcohol spectrum disorders, and certain cancers; the use of systems biology, bioinformatics, and real-time imaging methods to uncover biological pathways and networks involved in alcohol metabolism and organ damage; the use of genomic, proteomic, metabolomic, and lipidomic approaches to develop relational databases; and biomarker development to detect and monitor alcohol-induced pathologies.

DMHE encourages multidisciplinary approaches that integrate genetic, molecular, cellular, and animal models to understand mechanisms of alcohol action and injury.

Acknowledgments

We are extremely grateful to Dennis Twombly for developing and contributing the section on Research Training and Career Development Programs and to Dale Hereld for his editorial contributions.

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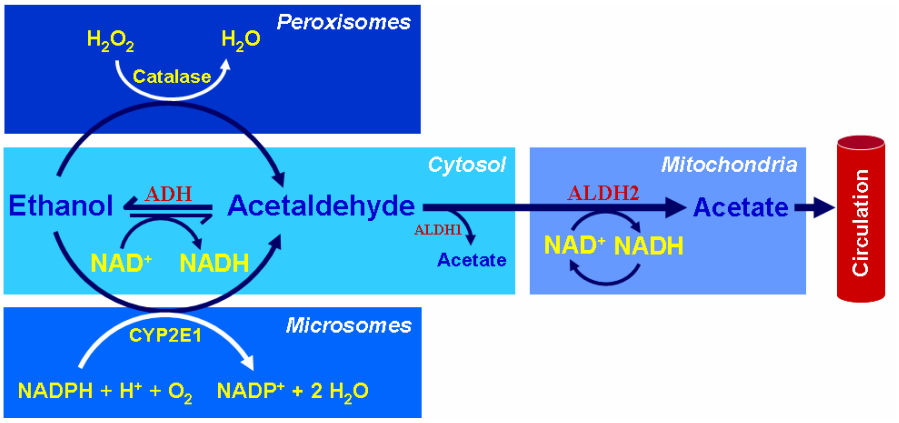
Alcohol Metabolism and Pharmacokinetics

Ethanol is metabolized to acetaldehyde by several isozymes of alcohol dehydrogenase (ADH), by catalase in a H_2O_2-dependent reaction, and by various cytochrome P450s (CYPs), particularly the ethanol-inducible CYP2E1, which is largely responsible for the increased rate of alcohol metabolism associated with chronic exposure. Acetaldehyde, in turn, is further oxidized to acetate by mitochondrial and, to a lesser extent, cytosolic aldehyde dehydrogenases (ALDH2 and ALDH1, respectively). Differences in the activities of these enzymes due to genetic variation can significantly affect blood alcohol and acetaldehyde concentrations and, thereby, influence alcohol intake and tissue damage. Moreover, metabolism of alcohol generates reactive oxygen species and lipid peroxidation products, which contribute to tissue damage and affects health. Thus, DHME invites research on alcohol metabolism and its contribution to the pathophysiological sequelae of alcohol exposure:

- Enzymology of ADH, ALDH, catalase and CYPs (e.g., CYP2E1) and the factors that impact their *in vivo* activity.
- Genetic variation in each of the alcohol metabolizing enzymes and distribution of differences across individuals and populations; environmental factors that interact with genetic variation to exacerbate or mitigate pathophysiological effects of alcohol.
- Manipulation of the metabolism of alcohol or acetaldehyde, or their effects on signaling pathways, to diminish tissue injury.
- Role of non-oxidative pathways of alcohol metabolism in tissue damage.



- Induction of CYP2E1 and perhaps other adaptive mechanisms that alter dispositional tolerance and metabolism of alcohol.
- Role of epigenetic mechanisms in the regulation of alcohol metabolism.
- Examination of the role of mitochondrial CYP2E1, the regulatory factors that control its subcellular targeting, and the physiological consequences of that targeting.

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Alcohol Metabolism and Pharmacokinetics (Cont'd)

- Understanding of the controlling mechanisms and consequences of subcellular localization of enzymes that metabolize alcohol (e.g., CYP2E1) or acetaldehyde (ALDH).
- Temporal variations in enzyme activity and alcohol metabolism, including swift increase in alcohol metabolism (SIAM), and dramatic multi-day cyclic variations observed during constant alcohol infusion.
- Effect of alcohol metabolism on redox state and co-factor concentrations as well as the impact of large alcohol loads on lipid and carbohydrate metabolism and overall energy balance.
- Metabolism of alcohol in extrahepatic tissues.

In vivo pharmacokinetics of alcohol refers to alcohol absorption, distribution through body tissues and disposition by metabolism, excretion or other means. Pharmacokinetic issues of interest include:

- Effect of dose, beverage type, body weight and composition, gender, age, prandial state, time of day, etc. on blood alcohol and acetaldehyde levels.
- Effect of the pattern of alcohol consumption on blood alcohol and acetaldehyde levels during binge and chronic drinking and including time-frames from minutes to months.
- Integration of the enzymology, genetic variation of the alcohol metabolizing enzymes, dispositional tolerance, etc. into a unified *in vivo* pharmacokinetic model.

Application of innovative technology to study alcohol pharmacokinetics:

- Biosensors to monitor continuous alcohol and acetaldehyde concentrations in natural conditions.
- Application of nanotechnology to access subcellular kinetics of alcohol metabolism and the physiological consequences of that metabolism.
- Use of pharmacokinetic/pharmacodynamic modeling to unify analysis of how patterns of drinking affect outcomes.
- Development of unique biomarkers for alcohol's effects on various tissues at early stages of pathology.

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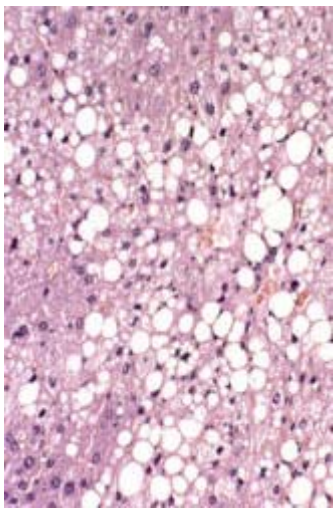
Alcoholic Steatosis and Diabetes

Steatosis (fatty liver) is the first stage of alcoholic liver disease (ALD); it occurs in a majority of chronic heavy drinkers and can progress to the more severe stages of alcoholic hepatitis, alcoholic fibrosis and cirrhosis. While hepatic steatosis may be reversible, it is associated with other pathologies and, thus, may offer an opportunity for effective therapeutic intervention. Areas of research interest include:

- Alcohol's actions on the enzymes that promote hepatic fatty acid (FA) synthesis (e.g., ACC, FAS, ACL, SCD1), reduce FA mobilization and block β-oxidation by for example inhibiting CPT1-dependent mitochondrial transport of FAs.
- The actions of alcohol on signaling factors that regulate enzymatic control of FA metabolism, including SREBP, PPARα, PPARγ and PGC-1α.
- Alcohol's effects on AMPK (5'AMP-activated protein kinase), which serves as a 'master' regulator of energy storage and metabolism, as well as adiponectin, leptin, and other adipokines.
- Role of alcohol metabolism in shifting the redox-state so as to possibly promote steatosis.
- Action of cytokines, including tumor necrosis factor (TNFα) in shifting lipid metabolism toward adipocyte FA mobilization and hepatocyte lipogenesis and FA sequestration.
- Alcohol-induced suppression of plasminogen activator inhibitor (PAI-1) and the consequent increase in VLDL synthesis as well as subsequent fibrosis (see below).
- Activated biosynthesis of the endocannabinoid, 2-arachidonoylglycerol (2-AG) in hepatic stellate cells and its subsequent paracrine induction of lipogenesis, and suppression of FA oxidation in hepatocytes.
- Changes in the NAD^+/NADH ratio due to alcohol metabolism and the consequent effect on SIRT1 and its relationship to PPARγ and PGC-1α function and hepatic lipid metabolism.



Additional interest focuses on steatosis as a precursor to subsequent inflammatory hepatitis, fibrosis, and cirrhosis, including:

- Steatosis-related dysregulation of the immune system, increased susceptibility to endotoxins (LPS), and induction of pro-fibrotic cytokines.
- Relationships between steatosis, functional changes in tight junctions and claudins, and novel signaling factors such as osteopontin.
- Role of alcohol-induced PAI-1 and consequent fibrin deposition in promoting liver inflammation (steatotic hepatitis) and fibrosis.

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Alcoholic Steatosis and Diabetes (Cont'd)

Alcoholic steatosis manifests many of the histological and functional abnormalities characteristic of non-alcoholic fatty liver disease (NAFLD), including insulin resistance, hyperglycemia, hypertriglyceridemia, hypertension, and an increased risk for cardiovascular disease. Moreover, NAFLD can progress from simple steatosis through non-alcoholic steatohepatitis (NASH) to fibrotic cirrhosis analogous to stages of alcoholic liver disease. The similarities (and differences) offer opportunities for research including:

- Role of hepatic and abdominal fat (in apparent opposition to overall obesity) in the metabolic syndrome and particularly in the development of Type-2 Diabetes.
- Hepatic insulin resistance as primary or secondary to the overall metabolic syndrome.
- The significance of NAFLD-related induction of CYP2E1 even in the absence of alcohol.
- Develop *in vivo* and *in vitro* models to assess combined effects of alcohol use and obesity that recapitulate the process in humans.

One important aim is to develop improved strategies for the treatment of alcoholic steatosis, expanding on previous research on both alcoholic and non-alcoholic steatosis. Examples include, but are not limited to: metformin, AICAR, thioglitazones, adiponectin, leptin, PAI-1 antagonists, ACE-inhibitors, olmesartan, cannabinoid CB1-receptor antagonists such as rimonabant, and the SIRT1 agonist, resveratrol.

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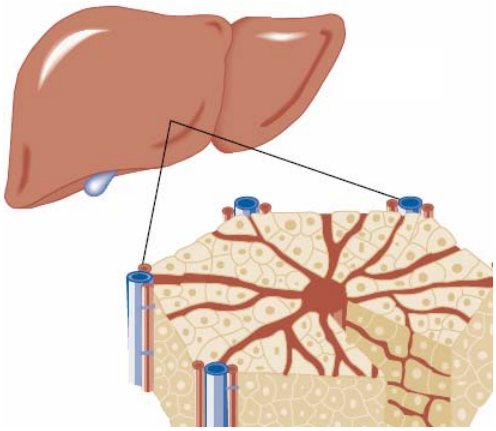
Alcohol and Liver Damage

The liver is the primary site of alcohol metabolism. Thus, it is frequently exposed to toxic metabolites and is vulnerable to severe, chronic injury. Excessive alcohol consumption generally leads to three pathologically distinct liver diseases: steatosis, hepatitis (acute or chronic), and cirrhosis/cancer. While the mechanisms underlying alcohol-induced tissue injury and resolution or progression to chronicity are very complex and not fully understood, emerging evidence indicates that the dysregulation of hepatic homeostasis (resulting from imbalance of damaging and protective signals) is crucial for alcoholic liver disease development. All mature liver cell types as well as liver adult stem cells have been implicated in the development of alcohol-induced liver injury, chronic alcoholic hepatitis, hepatic inflammation, and hepatocarcinogenesis. Numerous signaling cascades involving growth factors, cytokines, matrix remodeling, and feedback stimulation and inhibition of growth-related signals are involved in these complex processes. The liver has a remarkable capability to restore its mass and function after injury. However, alcohol promotes cell-cycle arrest and apoptosis of hepatocytes, extensive extracellular matrix deposition, and activation of proinflammatory cytokines, conditions that interfere with tissue regeneration and repair. Dissecting the precise roles of distinct liver cell populations and signaling pathways in hepatic homeostasis, toxicity and regeneration will enable us to effectively design therapeutics for alcohol-induced liver diseases. DMHE invites new applications to study alcohol's impact on emerging frontiers in the following areas:

- Transcriptional and epigenetic controls of liver regeneration and repair.
- Liver immunity, hepatic stellate cells, and fibrosis.
- The NOD-like receptors (NLRs) function in pathogen-induced liver inflammation and cell-death signaling.
- The role of different subpopulations of resident and recruited macrophages during hepatic injury, repair and disease progression.
- Adult liver stem cell activation and differentiation.
- The regulatory effect of innate immune cells on liver injury and regeneration.



- Telomerase activity/regulation in various liver cell types at distinct phases of alcohol liver disease and recovery.
- The role of endocannabinoids in the regulation of hepatic metabolism, injury, and fibrosis.
- Mechanisms involved in alcohol's interactions with iron, novel iron regulatory proteins, and zinc with respect to liver damage and regeneration.

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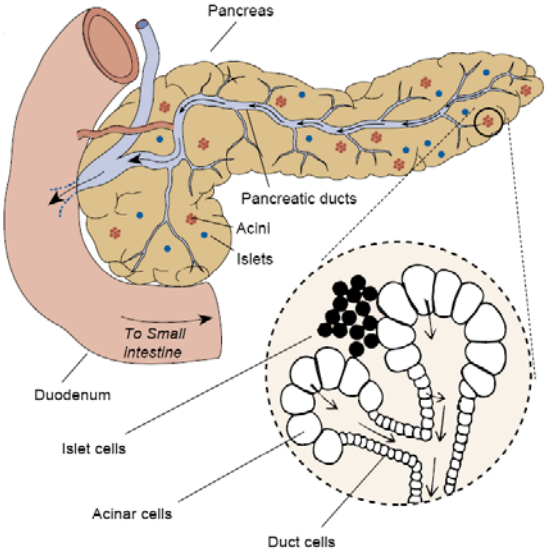
Division of Metabolism and Health Effects

Alcoholic Pancreatitis

Alcohol abuse is a major cause of pancreatitis in the Western world. Alcohol-induced pancreatitis can manifest itself as acute necrotic inflammation and/or chronic damage, including acinar atrophy and fibrosis. The metabolism of alcohol in the pancreas via oxidative and non-oxidative pathways produces toxic metabolites, such as acetaldehyde and fatty acid ethyl esters (FAEEs). It is generally accepted that the pancreatic injury is a consequence of the toxic effects of the above metabolites, oxidative stress, and inflammatory cytokines/chemokines released during pancreatic necroinflammation.

The Division of Metabolism and Health Effects supports research on the effects of alcohol on the pancreas and the injuries caused by alcohol abuse. Possible areas of investigation include, but are not limited to:

- The role of alcohol and its metabolites in the inflammatory, necrotic, and fibrotic responses in alcoholic pancreatitis.
- Molecules playing important roles in the process of ethanol-induced pancreatitis, including genes/proteins in the kinase system, transcription factors involved in the inflammatory response, and mediators of apoptosis and necrosis.
- Genetic abnormalities that may predispose to chronic pancreatitis induced by alcohol abuse.
- Biochemical markers for diagnosis of susceptible individuals and disease severity.
- Mechanisms by which chronic alcohol consumption may promote carcinogenesis and pancreatic cancer.
- Animal models that recapitulate the sequence of pathologic responses of alcoholic pancreatitis and alcohol-related pancreatic cancer.



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Alcohol and the Lung

Alcohol has multiple effects on lung function and homeostasis. It is conventional wisdom that chronic alcoholics often succumb to bacterial pneumonia, but there is evidence that even acute alcohol exposure can compromise lung homeostasis. Both alveolar integrity and pulmonary immune function are affected by alcohol exposure, and alcohol is known to contribute to oxidative stress in the lung.

The Division of Metabolism and Health Effects invites research on the effects of alcohol on the lung, including, but not limited to, the following topics:

- Mechanism by which alcohol increases the occurrence of Acute Respiratory Distress Syndrome (ARDS), with the goal of developing potential protective measures.
- Factors contributing to the dysregulation of oxidative balance and glutathione levels.
- Mechanisms contributing to the reduced efficiency of alveolar macrophages in the presence of alcohol consumption.
- The mechanism by which alcohol alters the innate immune response and the adaptive immune response. This may include the proliferation and function of hematopoietic cell types and also the altered regulation of cytokine expression.
- Effects of alcohol on mucociliary clearance of pathogens from the upper airways.
- Reduced host defense against infection due to reduced secretion of phospholipids into the alveolar fluid, leading to impaired surfactant function.
- Effects of alcohol on alveolar barrier function, including the function of alveolar type 1 and alveolar type 2 cells, and tight junctions.
- The mechanism by which trauma or infection at physiological sites distant from the lung negatively affect lung function and lung homeostasis.
- The development of non-invasive clinical measures of biomarkers in lung tissues or fluids as a means to measure compromised pulmonary function (such as oxidative stress) prior to evidence of organ damage, with the goal of enabling early preventative measures.
- The understanding of how alcohol promotes the progression from infection or trauma to sepsis, and why the most severe outcomes are more common with chronic alcohol consumption.
- Mechanisms leading to the combined damage due to alcohol consumption and tobacco smoke.

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Alcohol and the Cardiovascular System

Alcohol's effects on the cardiovascular system are dependent on the amount consumed and pattern of drinking. Thus, moderate consumption of one drink daily by women and two drinks daily by men were found in epidemiological studies to be associated with reductions in coronary artery disease and total mortality. In addition, moderate consumption has favorable effects on insulin actions and inflammation, which may be particularly beneficial for individuals with diabetes and metabolic syndrome. On the other hand, chronic heavy drinking is associated with cardiomyopathy, arrhythmias, and hypertension. Alcohol consumption associated with these effects varies among individuals, suggesting an interaction between genetic predisposition and the quantity and pattern of drinking.

Several potential mechanisms have been postulated for both the beneficial and detrimental effects of alcohol on the cardiovascular system. However, studies are needed to determine the relative contribution of genes and the environment to mechanisms underlying these effects.

The Division of Metabolism and Health Effects invites research on the mechanisms of alcohol effects on the cardiovascular system, including, but not limited to, the following topics:

- Role of pattern of consumption of alcoholic beverages (rather than the amount of alcohol consumed) in the putative beneficial or detrimental effects of alcohol.
- How alcohol metabolism (alcohol dehydrogenase, aldehyde dehydrogenase, CYP2E1) influences the outcome.
- Fatty acids, glucose, and lactate can be taken up by the heart as metabolic fuels. Alcohol consumption and its metabolism influence these substrates, and the change in NADH/NAD^+ ratio could influence the tricarboxylic acid (TCA) cycle. How derangements in the metabolic pathways of these substrates by alcohol affect energy substrate preference and results in pathology.
- Role of alcohol's effects on AMPK, carnitine, and long chain acyl-CoA transport through mitochondrial membranes on mitochondrial damage and alcohol-induced pathology.
- Effects of alcohol on myocardial glycogenesis and glycogenolysis.
- How alcohol influences myocardial preconditioning and postconditioning. The extent these effects have on favorable outcomes (decreasing damage after sublethal ischemia) due to moderate alcohol consumption.
- Acetate and ketone bodies (especially β-hydroxybutyrate) produced by alcohol metabolism in the liver are substrate for cardiac metabolism. Cardiac acetyl-CoA synthase transforms acetate into acetyl-CoA, and, based on their blood concentrations, ketone bodies are also used by the heart. Consequences of using acetate and ketone bodies on fatty acids pathways.

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Alcohol and the Cardiovascular System (Cont'd)

- Non-oxidative metabolism of alcohol to fatty acid ethyl ester (FAEE) results in the accumulation of FAEE in the mitochondrial inner membrane. The role of FAEE in mitochondrial damage and cardiac pathology due to alcohol needs to be further delineated.
- How alcohol consumption influences uncoupling proteins (UCP2 and UCP3) in the heart and how that may lead to impaired mitochondrial energy production and alcohol-induced cardiac muscle disease.
- Biomarkers for individuals prone to either beneficial or detrimental effects of alcohol are needed. The development of sensitive and selective biomarkers using proteomics and metabolomics is needed.
- Systems biology analyses of alcohol's actions on the biochemical and biophysical aspects of cardiac bioenergetics are needed.
- The peroxisome proliferators-activated receptor-α (PPAR-α) is an important regulator of fat metabolism, and is expressed in the heart, liver and skeletal muscle. Activated PPAR-α induces expression of genes encoding proteins involved in FA uptake, transport into mitochondria, and β-oxidation. Alcohol's effects on myocardial PPAR-α need to be studied.
- PPAR-γ co-activator α (PGC-1α) is selectively expressed in highly oxidative tissues like the heart, and is modulated by SIRT1. Stimuli that increase PGC-1α activity and expression include: p38 MAP kinase, NO, AMPK, and Ca^{++}-calmodulin kinase. PGC-1α also increases mitochondrial biogenesis. Alcohol's effects on these major players need to be investigated.

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Alcohol and Musculoskeletal Disorders

Chronic heavy alcohol consumption induces a dose-dependent noxious effect on skeletal muscle, leading to progressive functional and structural damage of myocytes and gradual reduction in muscle mass. Alcohol consumption is also considered as a risk factor for osteoporosis based on the frequent finding of a low bone mass, decreased bone formation rate, and increased fracture incidence in alcoholics. Studies showed that alcohol could reduce bone formation and inhibit proliferation of cultured osteoblastic cells.

The Division of Metabolism and Health Effects supports research on alcohol-induced muscle damage and the effects of alcohol on bone and mineral metabolism, which includes, but is not limited to:

- Molecular and cellular events and pathogenic mechanisms involved in the development of alcohol-induced muscle diseases, such as:
  - Disturbances in carbohydrate, protein, and energy metabolism.
  - Impairment of the rate of protein synthesis of myofibrillar proteins.
  - Cell turnover.
  - Signal transduction.
  - Apoptosis and pre-apoptotic pathways.
  - Oxidative damage in the pathogenesis of alcoholic myopathy.
  - Gene expression changes in alcohol exposed muscle.
- Association between alcohol consumption and osteoporosis and mechanism by which alcohol influences bone density and bone repair.
  - Cellular mechanism of osteopenia induced by alcohol.
  - Mechanism of action of alcohol on bone metabolism, such as direct and secondary changes in calcium-regulating hormones and mineral homeostasis.
  - Effect of chronic alcohol consumption on differentiation of bone marrow stromal cells and osteoblasts, and the association with bone formation and repair.
  - Effect of chronic alcohol abuse on other factors involved in osteoporosis.

One alcoholic drink per day reduces one's risk of hip fracture, while two drinks per day increases the risk.

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Alcohol, Trauma, and Shock

A large fraction of emergency room cases of trauma or injury involve subjects with elevated blood alcohol levels. While it is obvious that the state of inebriation can contribute to the occurrence of injury, chronic and even acute alcohol exposures can also worsen one's prognosis for recovery from injury, trauma and shock. The incidence of acute respiratory distress syndrome (ARDS) triggered by trauma is elevated nearly four-fold in alcohol-exposed patients. Recovery from ARDS is only 50% under the best of circumstances. Tissue injury at remote sites affects the immune homeostasis of two important organs, the lung and the gut. Consequently, trauma victims are more susceptible to infection after acute or chronic alcohol exposure, which sometimes leads to a systemic inflammatory response. Furthermore, morbidity and mortality due to sepsis and to shock are greater in patients exposed to alcohol prior to or at the time of injury. In general, prior alcohol exposure leads to a more severe outcome with poorer healing.

In order to reduce the health burden due to trauma and injury, the Division of Metabolism and Health Effects encourages research including, but not limited to, the following areas:

- The mechanism by which the alcoholic lung is predisposed to acute respiratory distress syndrome, and establishing therapeutic interventions. This may include studies on modifications of immune cells, their receptors, of the cytokine and chemokine profile, the integrity and function of alveolar epithelial cells, or the role oxidative stress.
- How prior exposure to alcohol alters the neuroendocrine response to hemorrhagic shock or septic shock, and how this knowledge can be translated into therapeutic intervention.
- The alteration by alcohol of the immune homeostasis of the gut and its barrier capabilities. Downstream effects of endotoxin and bacteria that escape the gut to reach the blood stream. Studies may include immune cells, lymphoid organs, cytokines derived from immune cells, endothelial cells, or keratinocytes, and the resulting effects on target cells.
- Effects of chronic or acute alcohol exposure on specific mechanisms of wound healing.
- The mechanisms by which burn injury leads to subsequent compromised pulmonary function and overall increases in morbidity and mortality.
- The effects of alcohol exposure on bone metabolism, including bone integrity and prognosis for recovery after injury.
- How alcohol exposure increases the likelihood of infections progressing to a systemic inflammatory response, sepsis, and ultimately multiple organ failure. An identification of various steps in this process that represent targets for therapeutic intervention.
- An understanding of the gender differences in the prognosis for recovery after trauma.

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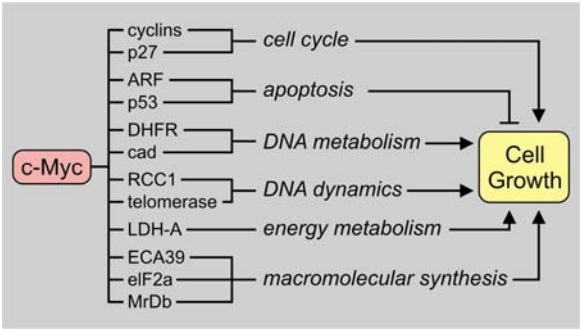
Alcohol and Cancer

Chronic alcohol consumption is a strong risk factor for cancer of the upper aerodigestive tract (esophagus, pharynx, larynx, and oral cavity) and is a strong causal factor in liver and colon cancers. For pancreatic and lung cancer, an association is suspected. In addition, chronic alcohol consumption is associated with breast cancer in women, especially post-menopausal women.

Although the exact mechanisms by which alcohol induces cancer are not known, several have been advocated, including: (1) formation of acetaldehyde, (2) induction of CYP2E1 which produces reactive oxygen species (ROS, leading to lipid peroxidation) and enhances the metabolism of procarcinogens (such as nitrosamines) present in tobacco smoke and the diet, (3) changes in folate and methionine metabolism, (4) alcohol-induced increase in estrogen formation in breast cancer, (5) suppressed immune function, (6) nutritional deficiencies such as vitamin E, zinc, selenium, folate, pyridoxal phosphate, etc., and (7) alcohol's solvent action enhancing the bioavailability of carcinogens from tobacco and diet.

The Division of Metabolism and Health Effects invites research on the mechanisms of alcohol carcinogenesis, including, but not limited to, the following topics:

- Role of polymorphisms in genes encoding enzymes for alcohol metabolism (e.g., alcohol dehydrogenase, aldehyde dehydrogenase, CYP2E1), folate metabolism (especially MTHFR), and DNA repair in alcohol-induced cancer.
- Whether or not moderate alcohol consumption increases breast cancer risk. If yes, what are the mechanisms? Does alcohol increase breast cancer risk in women carrying the *BRCA1* and *BRCA2* mutations?
- Role of epigenetic effects due to alcohol through the folate and methionine cycles in producing cancer, especially hepatocellular carcinoma.
- Extent to which acetaldehyde interferes with DNA repair, if any.
- Variations in ADH genotypes and susceptibility for breast cancer.



- Effects of alcohol on the p53 gene products and cell cycle control.
- Role of alcohol in lung cancer etiology, independent of cigarette smoking.
- Alcohol's actions on normal tissue stem cells, which are a likely target for the initial carcinogenic insult because they possess the longevity necessary for accumulating the multiple genetic or epigenetic changes required for malignant transformation.

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Alcohol and Cancer (Cont'd)

- Impact of immune suppression, especially T cells, by alcohol on cancer development.
- Systems biology analyses of alcohol's actions on the biochemical and regulatory circuitries that link the cell-cycle checkpoint, apoptotic, and DNA repair pathways.
- Identification of molecular targets affected by alcohol for enhancing programmed cell death in response to DNA damage, particularly by investigating p53-independent pathways.
- Identification of biomarkers useful for assessing risk, for earlier diagnosis and for identifying persons susceptible to alcohol-induced cancers, with extremely high sensitivity.
- Understanding how alcohol impacts repair pathways, epigenetic changes, and protein and lipid function, and how they alter cancer susceptibility, which will lead to novel targets for prevention and therapy.

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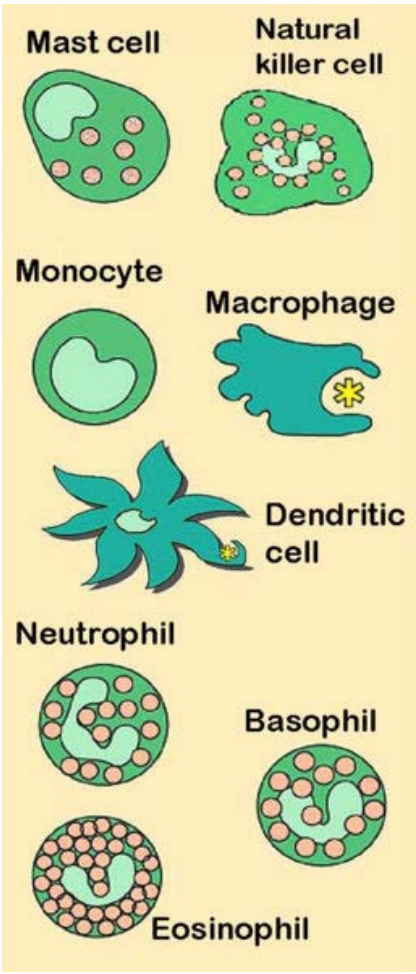
Alcohol and the Immune System

Alcohol consumption affects immune function in complex and seemingly contradictory ways: excessive alcohol consumption is immunosuppressive, but with a paradoxical increase in specific T cell populations. The detrimental effects of alcohol on the immune system are not limited to chronic alcohol exposure as acute single doses of alcohol can affect host responses to infection and to trauma. Both innate and adaptive immune responses are altered by exposure to alcohol. The mechanism by which alcohol causes these alterations is not yet clear, and is likely to be complex, due to the redundancy and pleiotropy of immune effector cell function, cytokine expression, and cytokine target cells. While the mammalian immune system can be viewed as a direct target of alcohol damage, the imbalance in the immune response is also implicated in alcohol's damage to other organs, including liver.

The Division of Metabolism and Health Effects supports research on the effects of alcohol on the immune system, including, but not limited to, the following topics:

- Effects of alcohol on the differentiation, maturation and function of immune effector cells, such as monocytes, macrophages, neutrophils, mast cells, dendritic cells, T cells, and B cells. This includes blood- and lymph-borne cells as well as tissue-resident cells.
- Alterations in the function of lymphoid tissues, including bone marrow, thymus, lymph nodes (mesenteric), spleen, and Peyer's patches.
- Characterization of the expression and function of cytokines, whether pro-inflammatory, anti-inflammatory, proliferative or suppressive. Also, alterations in the cytokine-producing cells (immune and non-immune) and in the target cells.
- Characterization of the function of surface active receptors and the signaling pathways they activate, including toll-like receptors, (TLR), nucleotide binding oligomerization domain like receptors (NLR), T cell receptors, B cell receptors, and the multitude of cytokine receptors and their subunits. Also, involvement of adhesion molecules. The signaling process and the transcription factors involved.
- The many factors that contribute to inflammation, including pro-inflammatory cytokines, reactive oxygen species, chemokines, and the recruitment and function of phagocytic cells.



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Alcohol and the Immune System (Cont'd)

- Role of alcohol in the impairment of barrier function.
- Effect of alcohol on the function of antigen presentation, linking innate immunity with adaptive immunity.
- In adaptive immunity, the differentiation, maturation, and polarization of T cells into $CD4^+$, $CD8^+$, Th1, Th2, regulatory T cells (Treg), or Th17 cells. The development of specific B cells populations.
- Humoral factors.
- Epigenetic effects of alcohol that modulate immune response.
- The regulatory balance of pro-inflammatory and anti-inflammatory cytokines and the regulatory balance between effector and suppressor function in adaptive immunity.

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Division of Metabolism and Health Effects

Alcohol and Viral Infections

Alcohol abuse increases human susceptibility to opportunistic infections and can accelerate disease progression, enhance drug toxicity, and/or reduce the effectiveness of medications. Mechanisms underlying these adverse impacts of alcohol may include innate and adaptive immune suppression, tissue/organ damage, metabolic alterations, and alcohol-drug interactions. A comprehensive understanding of these mechanisms is critical for developing effective treatments for the consequences of alcohol abuse. Viral hepatitis and HIV/AIDS are among high research priorities of NIAAA because of the enormous health problems associated with these diseases and the significant impact of alcohol use on disease progression.

The Division of Metabolism and Health Effects supports basic and translational research on the impact of acute and chronic alcohol abuse on viral diseases, including, but not limited to, the following topics:

- Effect of alcohol on the viral infection (e.g., HCV, HBV, HIV), replication, transmission, selection of genetic variants, and disease progression.
- Alcohol's impact on antiviral immune responses, including activation/maturation, function, and survival of immune cells of the innate and adaptive immunity, such as dendritic cells, macrophages, NK/NKT cells, T and B lymphocytes, and intrahepatic immune cells.
- Effect of alcohol on antiviral drugs (e.g., combined pegylated interferon and ribavirin therapy for HCV infections or HCV/HIV coinfections, antiretrovirals for HBV and HIV infections, etc.), including pharmacokinetics, metabolism, alcohol-drug interactions, and toxicity.
- Effect of alcohol on coinfections (e.g., HIV/HCV): anti-HCV and/or anti-HIV immune response; changes at molecular, cellular, and tissue levels that may inform disease progression and/or therapeutic responses; and host and viral factors (e.g., inflammatory cytokines, viral genotype, oxidative stress) that may influence disease progression, etc.
- The impact of alcohol on complications associated with HIV infection including, but not limited to, liver disease, renal failures, muscle wasting, cardiovascular complications, and diabetes. For HIV/AIDS-related research, also see Trans-NIH AIDS Research Plan at:

  http://www.oar.nih.gov/strategicplan/fy2009/index.asp.
- Combined effects of alcohol and other factors, such as smoking, non-specific medications, malnutrition, gender, race, and genetic background, on viral disease.
- Develop and refine in vivo and in vitro models for studying viral diseases in the context of alcohol use.

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Fetal Alcohol Spectrum Disorders

Alcohol consumption during pregnancy all too often has tragic and lasting consequences for the exposed fetus, including mental and growth retardation as well as learning, memory, and attention deficits. These varied outcomes, including Fetal Alcohol Syndrome, fall under the umbrella of Fetal Alcohol Spectrum Disorders (FASD). Remarkably, FASD affects roughly 1% of births in developed countries and exacts an annual economic toll in the billions of dollars in the United States alone.

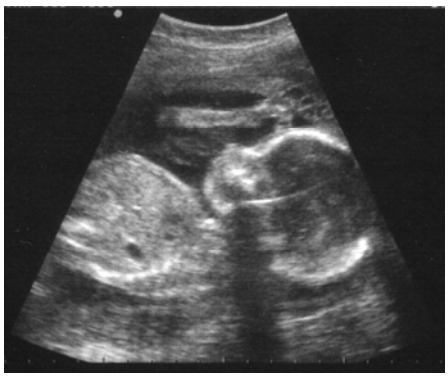
In recent decades, much progress has been made toward defining the anatomical, cellular, and molecular alterations in FASD and elucidating the underlying pathogenic mechanisms. *In utero* ethanol exposure causes significant losses of neurons due to apoptosis and impairs new synapse formation between surviving neurons (or "plasticity"), which is critical for post-natal brain development, learning, and memory. In addition, a growing body of evidence indicates that ethanol impairs the outgrowth of axons from differentiating neurons by inhibiting the function of neural cell adhesion molecule L1. Fetal development and growth can be further compromised by the deleterious effects of ethanol on placental development. Depression of maternal thyroid hormone levels by alcohol is also thought to contribute to cognitive and behavioral deficits in offspring.

Roughly one percent of children born in the United States are affected by FASD.

These and other advances toward understanding the mechanisms by which alcohol promotes FASD have lead to promising therapeutic interventions, including: antioxidants and serotonin receptor-1A agonists to prevent neuronal apoptosis due to ethanol exposure; treatments that promote neuronal plasticity, such as environmental enrichment (i.e., sensory, cognitive, and motor stimulation) and pharmacologic agents (e.g., phosphodiesterase inhibitors, choline); agents that antagonize ethanol's inhibitory effects on neural cell adhesion molecule L1; and thyroid hormone replacement.

The Division of Metabolism and Health Effects invites applications aimed at extending our understanding of FASD pathogenesis and promoting the development of safe and effective interventions for preventing or treating the effects of fetal alcohol exposure. Possible areas of investigation include, but are not limited to, the following:

- Develop effective, practical biomarkers of maternal drinking, fetal alcohol exposure, and its consequences to the developing fetus.
- Determine mechanisms by which alcohol exposure impairs fetal neural development (e.g., neuronal apoptosis, migration, plasticity) and develop therapeutic strategies related to these.



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Division of Metabolism and Health Effects

Fetal Alcohol Spectrum Disorders (Cont'd)

- Identify epigenetic effects, especially gene imprinting, of intrauterine alcohol exposure on the developing fetus and examine the contributions of these epigenetic changes to developmental deficits commonly associated with FASD.
- Identify nutritional or hormonal deficiencies of the mother or fetus and evaluate the benefits of correcting these deficiencies.
- Investigate alcohol's effects on placentation and the consequences of compromised placental function on intrauterine development.
- Apply genomic and other "-omic" approaches to broadly define ethanol's effects on the developing fetus in order to reveal novel mechanisms at work in FASD and/or potential biomarkers.
- Establish and refine animal models of FASD to facilitate elucidation of pathogenic mechanisms, discovery and assessment of potential biomarkers, and validation of novel therapeutic approaches for FASD prevention and treatment.

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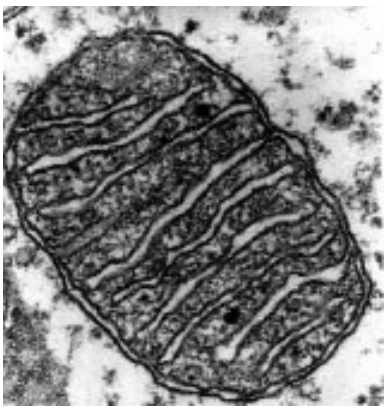
Susan Maier, PhD *maiers@mail.nih.gov* 301-451-7583

The Role of Mitochondria in Alcohol-induced Pathology

Alcohol metabolism impacts the structure and function of mitochondria, which play central roles in cellular energy production, reactive oxygen species (ROS) generation, and programmed cell death. Studies of alcohol's effects on mitochondrial structure and function are critical to understanding the mechanisms of alcohol-induced injuries and to developing new strategies for their diagnosis and treatment. DMHE encourages research (1) to better understand how acute or chronic alcohol consumption affects mitochondrial structure and function and, in turn, how these mitochondrial changes contribute to the alcohol-induced injuries; (2) to investigate how pre-existing variations in the mitochondrial proteins, either mitochondrion- or nucleus-encoded, or in the control of their expression or function, including cellular signaling pathways, contribute to an individual's response to acute or chronic alcohol intake; and (3) to identify alcohol-induced mitochondrial changes that can serve as useful biomarkers for the diagnosis and prognosis of tissue injury or that lead to novel targets for therapeutic interventions. DMHE aims to foster the utilization of innovative experimental design and emerging technologies, such as genomics, proteomics, metabolomics, bioinformatics, as well as state-of-the-art microscopic imaging techniques, to better understand mitochondrial functions in intact cells and tissues. The ultimate goal of this research area is to decipher the molecular events and interconnecting metabolic and signaling networks that would explain how alcohol affects mitochondria to cause tissue injury. This knowledge may provide new avenues for diagnostic and therapeutic interventions.



Examples of appropriate studies in this area include, but are not limited to:

- Examine the alteration in mitochondrial structure and dynamics, fusion and fission, and biogenesis and turnover that are caused by acute or chronic alcohol intake.
- Determine the nature of mitochondrial DNA damage and repair in the cellular response to acute or chronic alcohol exposure.
- Elucidate alcohol's effects on mitochondrial DNA replication, transcription, protein synthesis, and metabolism.
- Analyze alcohol's effect on the expression, post-translational modification, transport, and function of nuclear-encoded mitochondrial proteins.
- Examine the effects of alcohol on the assembly of mitochondrial complexes consisting of nuclei- and/or mitochondria-encoded proteins.
- Investigate the comparative roles of mitochondrial and microsomal CYP2E1 in the metabolism of alcohol and its subsequent consequences, including the production of ROS.

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Division of Metabolism and Health Effects

The Role of Mitochondria in Alcohol-induced Pathology (Cont'd)

- Study mitochondrial function and transcriptional regulation in response to alcohol-induced oxidative stress and metabolic changes.
- Examine alcohol's effects on signaling pathways that affect mitochondrial function, including those that are common to "low-powered" mitochondria associated with co-morbid conditions such as type-2 diabetes and metabolic syndrome.
- Investigate whether genetic variations of mitochondrial proteins, encoded either in the nucleus or mitochondria, contribute to the susceptibility or resistance of individuals to alcohol-induced tissue injury.
- Define the functional role of PPARs and the PGC-1 family of coactivators in the regulation of mitochondrial function and cellular energetics and how alcohol may influence these functions.
- Investigate the function of mitochondrial genes, proteins, and metabolites in alcohol-induced tissue injuries.
- Develop potential mitochondria-related biomarkers for the diagnosis and prognosis of alcohol-induced tissue injuries.
- Identify potential mitochondrial targets for therapeutic intervention in alcohol-induced tissue injuries.

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Biomarkers of Alcohol-induced Tissue Injury

The development of biomarkers for alcohol-induced disorders is important for their successful prognosis, diagnosis, and treatment. There is a well-recognized but unmet need for alcohol-induced organ damage in clinical practice. Although several alcohol biomarkers have been used in clinics for years, their accuracy, sensitivity, or specificity needs to be improved. Currently no clinically available laboratory test can reliably diagnose excessive alcohol use or predict the progression of alcohol-induced organ damage. Biomarkers of alcohol exposure and alcohol-induced organ damage have several fundamental purposes in alcohol research and clinical practice. First, they can be indicators of problematic drinking and alcohol-related organ damage. Biomarkers capable of detecting organ damage at an early stage can provide not only valuable information for patients to seek early medical intervention but also a tool of screening in a large population. Second, they can monitor or predict the progression of organ damage. Third, biochemical tests of alcohol intake could provide objective measurement during pharmacological clinical trials and identify individuals who respond to treatment. Finally, they can disclose recent drinking in social and problematic drinkers in high-risk situations, such as during pregnancy. The discovery of novel biomarkers for diagnosis and prognosis and for monitoring alcohol exposure, alcohol-induced organ damage, and response to treatment is of great importance for both alcohol research and clinical practice.

DMHE encourages the use of both traditional approaches and new functional genomic studies for developing more effective biomarkers. In addition to providing accurate, reliable, and reproducible results, useful biomarkers must also be sensitive, requiring only reasonable amounts of readily attainable samples (e.g., blood, urine, saliva, and hair).

Appropriate areas of investigation include, but are not limited to:

- Identification of genes, genetic variants, or epigenetic alterations as biomarkers that are associated with alcohol-induced organ damage in animal models or in humans.
- Identification of new biomarkers at the RNA, protein, or metabolite levels to assess the acute or chronic, moderate or excessive alcohol exposures that are associated with alcohol-induced organ damage in animal models or in humans.
- Identification of prognostic and diagnostic biomarkers that can monitor or predict the progression of alcohol-induced organ damage.
- Identification of early biomarkers in animal models that can be used in predicting the risk for fetuses by in utero alcohol exposure.
- Application of bioinformatic and computational tools to analyze or integrate new or existing genomic, proteomic, and metabolomic information, as well as other experimental and clinical measurements, to identify novel biomarkers for alcohol exposure or alcohol-induced organ damage.

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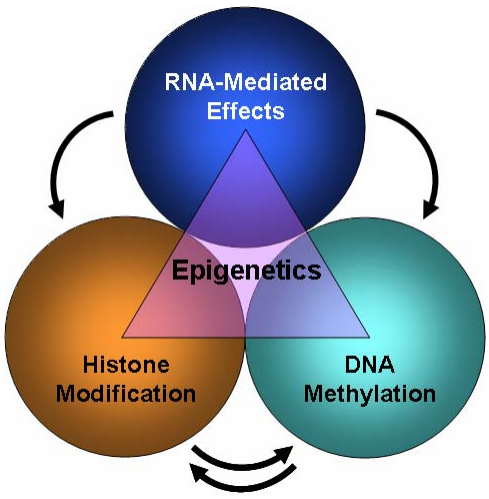
Epigenetics: DNA Methylation, Histone Modification, and RNA-mediated Gene Regulation

Epigenetics refers to the study of heritable changes in gene function that are not due to alteration of DNA sequence. Increasing evidence has demonstrated that epigenetic mechanisms play an important role in gene activity and chromosomal instability. Epigenetic mechanisms that have been associated with silencing or activation of gene transcription include DNA methylation, histone modification such as acetylation, methylation, phosphorylation, ubiquitination, sumoylation, and ADP-ribosylation, as well as small RNA-mediated gene regulation.

An emerging area of research involves the identification of epigenetic mechanisms of alcohol-induced organ damage. This damage reflects the genetic and epigenetic make-up of the individual and the cumulative responses to alcohol exposure and environmental perturbations over time. Many alcohol-induced pathophysiological changes are long-lasting and persist even after cessation of ethanol consumption. Although acetaldehyde, the first metabolite of ethanol, can form DNA adducts and causes sequence alteration of the DNA, most of the short or long-lasting effects of alcohol may be mediated through the changes that do not involve DNA sequence alteration. Many environmental risk factors such as age, diet, lifestyle, smoking, and stress, which may also contribute to alcohol-induced disorders, have been documented to cause epigenetic alterations.

That the alcohol-induced pathogenesis may involve epigenetic responses represents an exciting area of future research. Both genetic and epigenetic mechanisms are crucially important for susceptibility, initiation, progression, and pathogenesis of alcohol-induced disorders. Together, they will improve our understanding of alcohol-induced disorders, broaden insights into the nature of the diseases, and provide new prognostic, diagnostic, and therapeutic avenues. Because of their potential to be modulated and perhaps even reversed, epigenetic modifications are attractive targets for the development of novel pharmacologic interventions if they are proven to be critically involved in the pathogenesis of alcohol-induced tissue injury.



DMHE is interested in understanding the role of epigenetic mechanisms in the susceptibility, initiation, progression, and pathogenesis of alcohol-induced tissue injury due to acute, chronic, or excessive alcohol consumption. The goal of this program is to stimulate and support research that focuses on how these alcohol exposures change epigenetic modifications and how these changes modulate gene expression that are associated with alcohol-induced tissue injury in human subjects or in animal and cellular models.

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Division of Metabolism and Health Effects

Epigenetics: DNA Methylation, Histone Modification, and RNA-mediated Gene Regulation (Cont'd)

DMHE fosters multidisciplinary collaborations using state-of-the-art technologies. Appropriate research topics may include, but are not limited to:

- Identification of epigenetic changes, such as DNA methylation, histone modifications, and miRNA-mediated interference, induced by acute, chronic, or excessive alcohol consumption using either genome-wide or hypothesis-driven candidate gene approaches.
- Determination of epigenetic alterations, influenced by the dose or duration of alcohol administration, that are associated with the initiation, progression, and pathogenesis of alcohol-induced organ damage.
- Identification of epigenetic changes induced by alcohol-exposure at different stages of the lifespan, including *in utero* fetal development, adolescence, and adulthood.
- Determination of the role of epigenetic mechanisms, such as DNA methylation, histone modifications, and miRNA-mediated interference, on specific signaling or metabolic pathways or networks that have been implicated in alcohol-induced organ damage.
- Integration of epigenetic information into genetic or genomic studies, such as linkage, whole-genome associations, or gene expression profiling studies.
- Evaluation of epigenetic effects that respond to therapeutic interventions.
- Assessment of epigenetic alterations as biomarkers for alcohol exposure or for prognosis, diagnosis, and treatment of alcohol-induced organ damage.
- Application of bioinformatics and computational tools to analyze and manage epigenetic data that may be linked and integrated with other experimental and clinical information.

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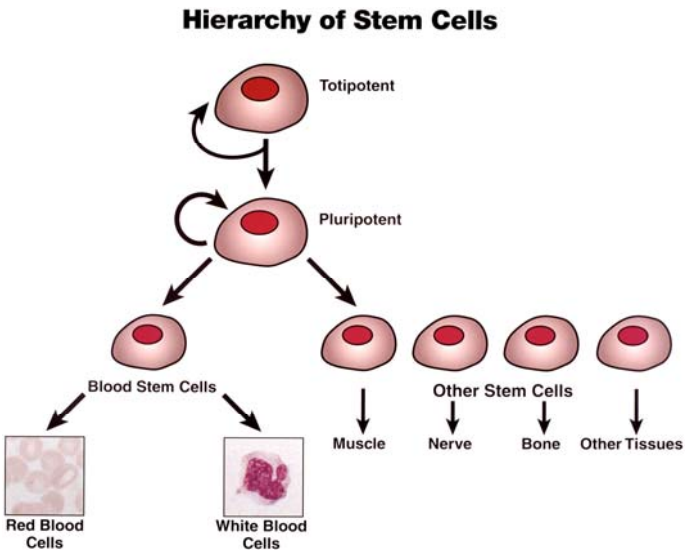
Alcohol, Epigenetics, and Stem Cells

Recent progress in stem cell (SC) research is opening up unprecedented opportunities for the development of new strategies to repair alcohol-damaged organs. This may also lead to a better understanding of the pathological mechanisms underlying the development of chronic alcohol-induced disease and provide the necessary knowledge for possible prevention strategies in the most-at-risk population. Epigenetic processes have recently been shown to be responsible for the differential gene expression that shapes a stem cell's identity and function in development, tissue regeneration, and neoplastic transformation. Epigenetic changes including DNA methylation, histone modifications, nucleosome remodeling, and RNAi components are heritable modifications to the genome that are not encoded in the nucleotide sequence; they instead serve as signals to chromatin modifying complexes to alter chromatin into transcriptionally repressive or permissive configurations. During differentiation, genes that are crucial for pluripotency and self-renewal are silenced, whereas tissue-specific genes begin to be expressed. For example, a cluster of nearly identical cells at the blastula stage undergo a well-orchestrated series of epigenetic modifications that establish specific programs of gene expression, triggering differentiation into specialized cell types and eventually resulting in the development of different organs and tissues. Although epigenetic modifications are established early in development and maintained throughout life, they are reversible and responsive to environmental interventions and exposure to alcohol and its toxic metabolites. Our current knowledge of the influence of alcohol on the epigenetic status of stem cells is limited and therefore further studies are needed to understand fundamental epigenetic processes involved in failed stem cell activation and differentiation required for regeneration of organs damaged by alcohol.



Thus, DMHE invites research that (1) explores epigenetic profiles of SC in an alcohol-induced environment versus normal tissue and establishes their consequences for SC plasticity and tissue repair; (2) elucidates the molecular mechanisms by which alcohol dysregulates epigenetic control governing the renewal and cell lineage specification of SC and induces abnormal gene expression. Research goals consistent with these objectives include, but are not limit to:

- Identify stem- and lineage-specific loci in SC genome that are targets of epigenetic changes by alcohol.

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Alcohol, Epigenetics, and Stem Cells (Cont'd)

- Identify alcohol-induced epigenetic modifications in genes encoding signals from the SC niche (e.g., BMPs, Wnt, SHH and IGF1/IGF2) and their subsequent consequences on stem cell plasticity and tissue repair.
- Identify what extracellular cues related to alcohol metabolism and toxicity (acetaldehyde, acetate, nutritional deficiency, oxidative stress, cytokines, growth factors) are capable of initiating and carrying out epigenetic reprogramming.
- Explore the possible effects of alcohol on bivalent chromatin domains and Polycomb group proteins, the underlying regulatory mechanisms, and how they affect "stemness" and differentiation of SC.
- Establish how alcohol affects methylation profiles of master regulatory genes in embryonic SC, adult SC and their differentiated normal and diseased progenies.
- Determine how alcohol affects chromatin modifications in SC with respect to transcriptional regulation and the differentiation pathway; which factors and enzymes contribute to these processes.
- Examine if epigenetic modifications in SC and their progenies are followed up by any genetic changes at each pathological stage of alcohol-induced chronic disease progression.
- Establish epigenetic aberrations in SC and their progenies during the progression of alcohol-induced disease to identify new biomarkers for disease risk and early diagnostic.

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Division of Metabolism and Health Effects

Alcohol, Retinoic Acid, and Stem Cells

Chronic alcohol consumption affects every organ of the body, often resulting in life-threatening diseases. Successful disease resolution and organ regeneration subsequent to alcohol injury depend on the ability of resident or transplanted stem cells to overcome the local environmental restrictions on survival and growth signals and temporarily shift towards proliferation and lineage-specific differentiation. A large body of evidence indicates that retinoic acid (RA) controls cell proliferation, differentiation and apoptosis and that a loss or excess of RA signaling affects many aspects of stem cell biology. Since alcohol interferes with RA biosynthesis and metabolism, it can significantly change RA viability and thus modulate the stem cell function and outcome of organ repair and regeneration. The development of Fetal Alcohol Syndrome that is associated with varied levels of RA is strong evidence that through RA signaling alcohol interferes with the normal developmental processes and organogeneseis that are closely linked to stem cell biology. However, the mechanisms underlying stem cell behavior in alcohol-induced RA changes are not well understood. Many actions of the RA are mediated directly trough its nuclear receptors that bind to specific DNA sequences in the promoter of target genes or indirectly, reflecting the actions of intermediate transcription factors. Moreover, recent evidence indicates that RA can also influence gene expression via epigenetic modifications. The spatial-temporal expression pattern of RA synthesis/catabolic enzymes and components of the RA signaling pathway that are, in turn, responsive to extrinsic cues from microenvironment add further complexity to the RA-induced cell growth control. This implies that alcohol's interfere with RA signaling has the potential to disturb a broad variety of cellular processes, including cell proliferation, differentiation and apoptosis. Critical factors are dose, onset and duration of exposure, cell type involved and environmental conditions. Investigation of how alcohol affects the endogenous RA levels and expression of different components of RA signaling in different cell types and its cross-talks with other factors and pathways known to elicit stem cell functions will provide further insight into the general mechanism of organ homeostasis and regeneration. Research areas of interest include, but are not limited to, the following examples:

- Study of alterations in retinoid metabolism and signaling in various cell types during alcohol-mediated disease progression to chronicity or cancer.
- Identification of the expression profile of RA-dependent genes in various tissues after alcohol exposure with respect to cell proliferation, differentiation and apoptosis.
- Assessment of the impact of alcohol on RA interactions with other signal transduction pathways and transcriptional factors that underlie tissue-specific differentiation.
- Elucidation of the molecular mechanisms by which alcohol dysregulates RA-inducible gene expression.
- Validation of the efficacy of RA administration on disease resolution and organ regeneration subsequent to alcohol injury.

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Division of Metabolism and Health Effects

Genetics, Genomics and Alcohol-induced Tissue Injury

Alcohol-induced pathophysiological changes are affected by intrinsic and environmental factors. Alcohol and its metabolites alter cellular functions through changes at the levels of DNA, RNA, protein, metabolite, and other molecules. Studies in animal models and humans have generated a large amount of genetic data and identified various chromosomal regions responsible for some alcohol-related phenotypes or symptoms. The phenotypes of alcohol-related illnesses appear to be controlled by both genes and dynamic networks, which include metabolic and signaling pathways. Revealing the identities of these genes and players in the networks is critical not only for understanding the underlying mechanism of alcohol-related diseases but also for developing prognostic, diagnostic, and therapeutic means to prevent or treat these diseases. Identification of common variations in the form of single nucleotide polymorphisms (SNPs) and haplotype blocks will be extremely useful for mapping the disease susceptibility genes in the genome. Ideally, high-density of SNPs and haplotype markers can be identified on a genome-wide scale across various populations.

The integration of genetics and genomics could accelerate the identification or prioritization of candidate susceptibility genes for alcohol-induced disorders. DMHE supports studies using various complementary approaches to identify the genes and pathways that are related to alcohol-induced organ damage. Both genetic and epigenetic mechanisms are crucially important for susceptibility, initiation, progression, and pathogenesis of alcohol-induced disorders. A better understanding of epigenetic mechanisms will complement information obtained from genetic, genomic, and functional genomic studies. The information can also be integrated with other experimental and clinical measurements to identify complex systems-level responses to alcohol.

DMHE fosters multidisciplinary collaborations using state-of-the-art technologies to investigate areas that may include, but are not limited to:

- Genome-wide association studies in human subjects or animal models to identify candidate genes or pathways involved in alcohol-induced organ injury
- Identification of genetic variations associated with susceptibility to alcoholism and individual responses to alcohol using genomics, proteomics, metabolomics, glycomics, bioinformatics, and imaging technologies
- Fine mapping of previously identified chromosomal regions using high density SNPs or haplotype markers
- Characterization of genetic components in alcohol-induced organ damage using in vivo functional imaging in animal models

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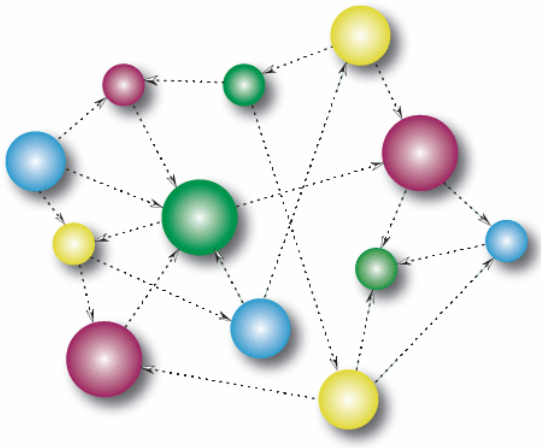
Systems Biology Approaches in Alcohol

Systems biology studies the behaviors of complex biological organizations or processes through the integration of diverse quantitative information and mathematical modeling to generate predictive hypotheses regarding the functions of the biological system. Alcohol-induced organ damage reflects the genetic and epigenetic make-up of an individual and the cumulative responses to alcohol exposure and environmental perturbations over time. Each of these factors may contribute only a small fraction to the phenotype. At the molecular level, the effects of alcohol and its metabolites are the consequences of changes in DNA, RNA, proteins, metabolites, and other molecules. At the systems level, alcohol affects organs by influencing biochemical and signaling pathways. This high degree of complexity in alcohol-induced disorders renders the traditional gene-by-gene or single discipline studies limited because they only provide a fragmented view of a very complex picture. An integrated approach, such as systems biology, is essential for revealing the global nature of the perturbations leading to disease. From either pathogenetic or etiological perspectives, alcohol-induced organ damage is indeed a system biology disorder.

Genomics and functional genomics are the driving forces behind the systems biology approach for alcohol-induced disorders. At the DNA level (genome and epigenome), various technologies and information can be applied to study genetic variation, gene mutation, gene mapping, and genetic or epigenetic regulation. Both genetic and epigenetic mechanisms are crucially responsible for susceptibility, initiation, progression, and pathogenesis of alcohol-induced disorders. Evidently, approaches to the study of gene regulation purely based on gene sequence would not be sufficient to explain alcohol-induced pathogenesis. An understanding of epigenetic mechanisms will complement information obtained from genetic, genomic, and functional genomic studies. At the RNA level (i.e., transcriptome), DNA microarray and other technologies can be used to study the quantity of RNAs and their alternative splicing. In the past several years, a significant amount of microarray data has been generated and is reaching the critical mass required for systems biology studies. At the protein level (i.e., proteome), proteomic technologies can systematically survey the identity, quantity, modification, localization, interaction, and function of all proteins in a cell, often in a high-throughput manner. At the metabolite level (i.e., metabolome), metabolomics involves a detailed quantitative analysis of low molecular weight metabolites after alcohol administration in a biological system. Metabolites are the intermediate and end products of cellular functions, and their levels and modulation reflect an organism's response to genetic or environmental perturbations. The determination of these metabolites can be achieved by us-



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Systems Biology Approaches in Alcohol (Cont'd)

ing mass spectrometry, nuclear magnetic resonance spectroscopy, capillary electrophoresis, and high-performance liquid chromatography, in conjunction with a wide range of bioinformatic, statistical, and computational tools. A virtual snapshot image can be obtained of the myriad of small molecules within the biological system and how these molecules are modulated in individual time frames. Metabolomic studies in alcohol research are complementary to studies of the genome, transcriptome, or proteome, because they can extract latent biochemical information of diagnostic or prognostic value, reflecting actual biological events and can serve as a sentinel for diseases. Another emerging area for systems biology is glycomics, which is a global approach to study complex carbohydrates for their structure and function and their interaction with other carbohydrates, proteins, lipids, and nucleic acids. Carbohydrates and their interaction with other molecules are involved in a wide spectrum of cellular functions. Glycomic studies may reveal glycan changes and provide novel avenues for understanding alcohol's actions, especially on post-translational modifications of proteins.

For systems biology studies, bioinformatics, computation, statistical analysis, and mathematical modeling are pivotal for integrating large, complex datasets generated through the high-throughput -omic technologies. The integration and modeling of diverse information, including other biological and clinical measurement, would vastly enhance the power of any single-discipline approach, help to decipher the mechanisms of alcohol-induced disorders, and provide new avenues for their prognosis, diagnosis, and treatments.

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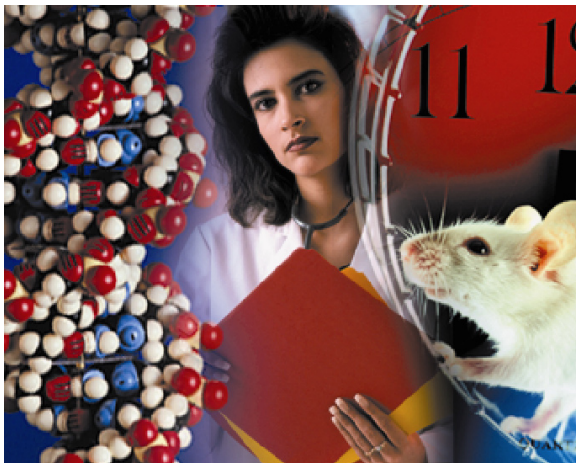
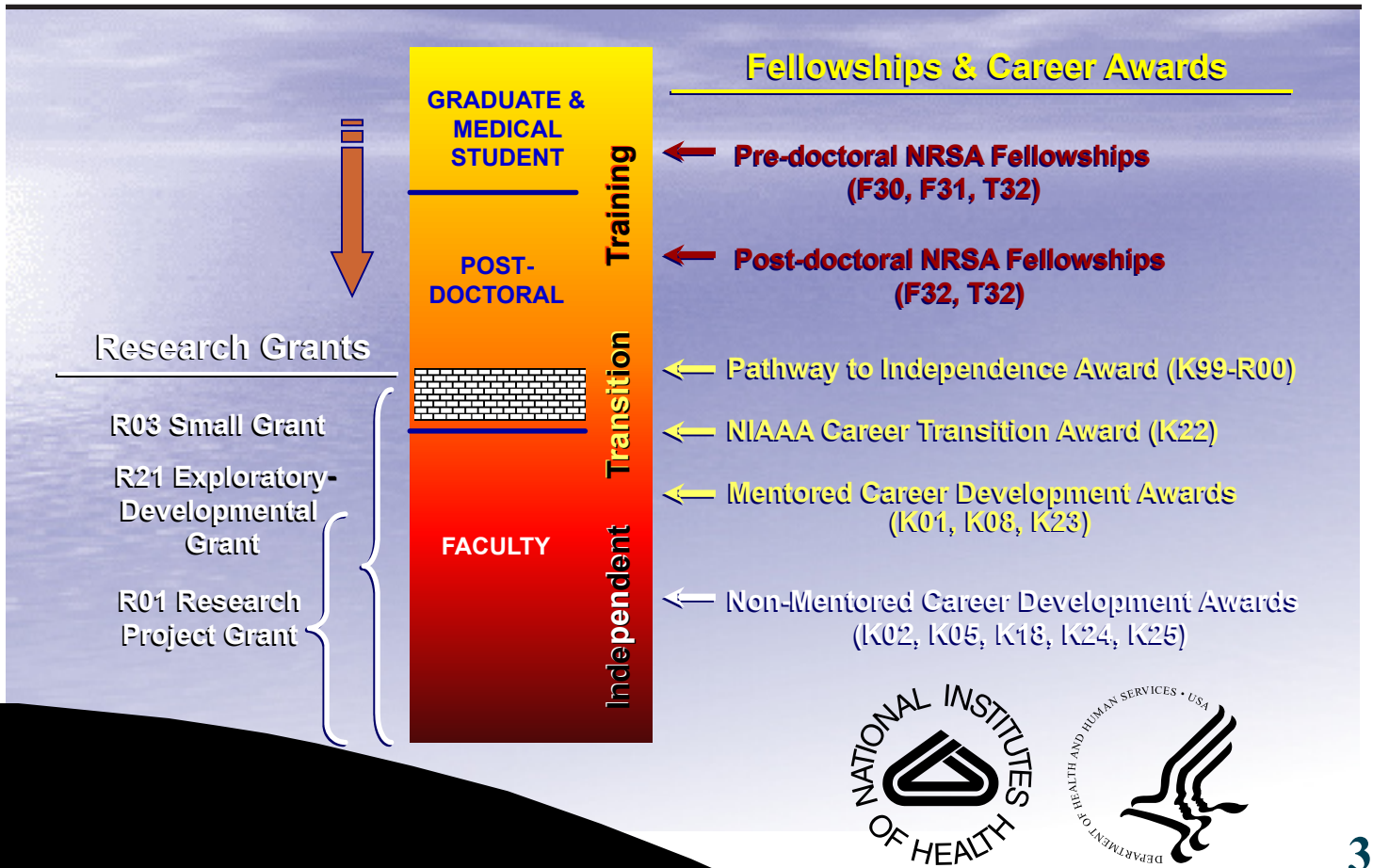
NIAAA
National Institute on Alcohol Abuse and Alcoholism

Research Training and Career Development Programs



NIAAA sponsors training and career development programs at the predoctoral, postdoctoral, and faculty levels, including opportunities for under-represented minorities and women. Basic and clinical research training is available in social, behavioral, biological, and mathematical sciences as related to alcohol actions and consequences. Pre- and postdoctoral support is provided via Ruth L. Kirschstein National Research Service Awards (NRSA). NRSA awards are made as individual fellowships or as institutional training programs that support multiple pre- or postdoctoral fellows. After completion of postdoctoral training, the next step in research career development is to obtain a faculty position and become an independent investigator with research grant support. Career Development Awards (K-awards) provide salary and limited research funds for investigators at specific stages of their careers. Mentored career awards are used to support individuals who have completed their postdoctoral training and wish to gain further mentored research experience as they transition to independent faculty status. Mentored awards are also available for established investigators who seek specialized training in a new research field. These programs are designed to provide multidisciplinary expertise in research related to alcohol, and to build competence in areas essential to success as independent investigators.



NIAAA
National Institute on Alcohol Abuse and Alcoholism

Research Project Grants

Research-Related

R 01 **Research Project Grant**
To support a discrete, specified, circumscribed project on health-related research and development based on the stated program interests of one or more of the NIH Institutes and Centers (PA-07-070; http://grants.nih.gov/grants/guide/pa-files/PA-07-070.html)

R 03 **Small Research Grant**
To provide research support specifically limited in time and amount for studies in categorical program areas such as pilot/feasibility studies, secondary analyses, method/technology development. Small grants provide flexibility for initiating studies which are generally for preliminary short-term projects and are non-renewable.
(PA-06-180; http://grants.nih.gov/grants/guide/pa-files/PA-06-180.html)

R 15 **Academic Research Enhancement Awards (AREA)**
To support individual research projects in the biomedical and behavioral sciences conducted by faculty, and involving their undergraduate students, who are located in health professional schools and other academic components that have not been major recipients of NIH research grant funds.
(PA-06-042; http://grants.nih.gov/grants/guide/pa-files/PA-06-042.html)

R 21 **Exploratory/Developmental Grant**
To encourage new, exploratory and developmental research activities in their early stages of development. Such projects may involve considerable risk but may lead to a breakthrough in a particular area, or to the development of novel techniques, agents, methodologies, models or applications that could have major impact on a field of biomedical, behavioral, or clinical research.
(PA-06-181; http://grants.nih.gov/grants/guide/pa-files/PA-06-181.html)

Small Business

R41 **Small Business Technology Transfer (STTR) Grants – Phase I (R41) / Phase II (R42)**
To support cooperative research and development (R&D) projects between small business concerns and research institutions, limited in time and amount. Phase I projects establish the technical merit and feasibility of ideas that have potential for commercialization. Phase II awards support development of projects whose feasibility has been established in Phase I.
(PA-07-281; http://grants.nih.gov/grants/guide/pa-files/PA-07-281.html)

R 43 **Small Business Innovation Research (SBIR) Grants – Phase I (R43) / Phase II (R44)**
To support small businesses in developing products or services that may ultimately lead to commercialization. Phase I projects establish the technical merit and feasibility of R&D ideas. Phase II awards support the development of projects whose feasibility has been established in Phase I and which are likely to result in commercial products or services.
(PA-07-280; http://grants.nih.gov/grants/guide/pa-files/PA-07-280.html)

NIAAA
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National Research Service Awards

Individual Fellowship Awards

F 30 **Individual Predoctoral NRSA for M.D./Ph.D. Fellowships**
Provides support for predoctoral training which leads to the combined M.D./Ph.D. degrees. Addresses the need for training physicians to become physician-scientists including those conducting translational and patient-oriented research.
(PA-05-151; http://grants.nih.gov/grants/guide/pa-files/PA-05-151.html)

F 31 **Predoctoral Individual National Research Service Award**
Provides predoctoral individuals (doctoral candidates) with supervised research training in specified health and health-related areas leading toward the research degree (e.g., Ph.D.).
(PA-07-002; http://grants.nih.gov/grants/guide/pa-files/PA-07-002.html)

F 31 **Predoctoral Individual National Research Service Award to Promote Diversity**
Seeks to improve the diversity of the health-related research workforce by supporting the training of predoctoral students from groups that have been shown to be underrepresented. Such candidates include individuals from underrepresented racial and ethnic groups, individuals with disabilities, and individuals from disadvantaged backgrounds.
(PA-07-106; http://grants.nih.gov/grants/guide/pa-files/PA-07-106.html)

F 32 **Postdoctoral Individual National Research Service Award**
Provides support for postdoctoral research training within the broad scope of biomedical, behavioral or clinical research to individuals to broaden their scientific background and enhance their potential for research in specified health-related areas.
(PA-07-107; http://grants.nih.gov/grants/guide/pa-files/PA-07-107.html)

F33 **National Research Service Award for Senior Fellows**
Provides support to experienced scientists to make major changes in the direction of their research careers, to broaden their scientific background, to acquire new research capabilities, to enlarge command of an allied research field, or to take time from regular professional responsibilities for the purpose of increasing capabilities to engage in health-related research.
(PA-07-172; http://grants.nih.gov/grants/guide/pa-files/PA-07-172.html)

Institutional Training Grants

T 32 **National Research Service Award Institutional Research Training Grant**
Provides support to institutions to create and develop a graduate and postdoctoral research training program in biomedical, behavioral, or clinical research. This grant enables the director of the program to select the trainees and to develop a curriculum of study and research experiences necessary to provide high quality research training.
(PA-06-468; http://grants.nih.gov/grants/guide/pa-files/PA-06-468.html)

NIAAA
National Institute on Alcohol Abuse and Alcoholism

NIH & NIAAA Web Resources

General Resources

The NIH Homepage:
http://www.nih.gov

NIAAA Web Site (strategic plan, mission, transdisciplinary research):
http://www.niaaa.nih.gov

Policy Issues

NIH Office of Extramural Research Grants Policy: http://grants1.nih.gov/grants/policy/policy.htm

Multiple Principal Investigators: http://grants1.nih.gov/grants/multi_pi/index.htm

NIH Modular Grant Information, Q&A, Sample Budget and Biosketch:
http://www.nih.gov/grants/funding/modular/modular.htm

NIH Data Sharing Policy: http://grants1.nih.gov/grants/policy/data_sharing/index.htm

NIH Grants to Foreign Institutions: http://www.nih.gov/grants/policy/nihgps/part_iii_5.htm#awardsforeign

New Limits on Appendix Materials: http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-07-018.html

NIH Policy on Late Submission of Grant Applications and new submission receipt dates:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-026.html

Continuation of pilot program to Shorten Review Cycle for New Investigators:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-013.html)

The NIH Guide for Grants and Contracts

Office of Extramural Research: http://grants1.nih.gov/grants/

Types of NIH Grant Programs:
http://grants.nih.gov/grants/funding/funding_program.htm
http://grants.nih.gov/grants/oer.htm

Program Announcements (PAs) and Request for Applications (RFAs):
http://www.nih.gov/grants/guide/index.html
http://grants.nih.gov/grants/guide/pa-files/index.html
http://www.grants.gov

NIH & NIAAA Web Resources (cont.)

NIAAA National Institute on Alcohol Abuse and Alcoholism

The Application Process

Center for Scientific Review: http://www.csr.nih.gov/

Application Receipt, Referral and Review: http://www.nih.gov/grants/funding/submissionschedule.htm

NIH Grant Application (SF 424, PHS 398) Instructions, Guidelines and Forms:
http://www.nih.gov/grants/forms.htm

Answers to Frequently Asked Questions about NIH Grants: http://www.nih.gov/grants/funding/giofaq.htm

CSR Advice to Applicants Submitting Clinical Research Applications:
http://cms.csr.nih.gov/ResourcesforApplicants/AdvicetoInvestigatorsSubmittingClinicalResearchApplications.htm

NCI's Guide for New Investigators: http://www.nci.nih.gov/researchandfunding/grantprocess

NIAID Grant Tutorial: http://grants.nih.gov/grants/new_investigators/resources.htm

NIGMS Tips for New NIH Grant Applicants: http://www.nigms.nih.gov/Research/Application/Tips.htm

Electronic Submission and Transition Process

Submitting Your Grant Application: http://grants1.nih.gov/grants/submitapplication.htm

Converting to SF424 Research and Related [R&R]) forms: http://www.grants.gov

Information and registration for electronic submission:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-067.html
http://era.nih.gov/ElectronicReceipt

Grants.gov Registration:
http://grants.gov/applicants/get_registered.jsp
http://www.grants.gov/contactus/contactus.jsp [Customer Service: support@grants.gov; 1-800-518-4726]

NIH eRA Commons grantee organization registration: https://commons.era.nih.gov/commons/
http://era.nih.gov/ElectronicReceipt/preparing.htm [eRA Help Desk web support http://ithelpdesk.nih.gov/eRA/;
Email commons@od.nih.gov; 1-866-504-9552, 301-402-7469]

Updates regarding the transition process: http://era.nih.gov/ElectronicReceipt/

Forms transition and questions on NIH's overall plan for electronic receipt:
Email grantsinfo@nih.gov; 301-435-0714

NIAAA
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NIH & NIAAA Web Resources (cont.)

The Review Process:

Peer Review Policy and Issues: http://grants1.nih.gov/grants/peer/peer.htm

The Peer Review Process: http://cms.csr.nih.gov/AboutCSR/OverviewofPeerReviewProcess.htm

Descriptions of Initial Review Groups at the Center for Scientific Review:
http://www.csr.nih.gov/review/irgdesc.htm

NIH Center for Scientific Review Study Section Rosters:
http://www.csr.nih.gov/committees/rosterindex.asp

CSR Web Site Video on NIH Peer Review:
http://www.csr.nih.gov/video/video.asp

Human Subjects Regulations and Resources:

Office of Extramural Research Human Subjects Policies, Regulations, and Guidance:
http://grants1.nih.gov/grants/policy/hs/index.htm

NIH Implementation of Office for Human Research Protections (OHRP) Guidance on Research Involving Coded Private Information or Biological Specimens:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-020.html

NIH Human Subjects Review Criteria: http://grants1.nih.gov/grants/peer/hs_review_inst.pdf

HHS Office for Human Research Protections (OHRP): http://www.hhs.gov/ohrp/

Data on Active Grants:

NIH Award Data and Trends: http://grants1.nih.gov/grants/award/award.htm

CRISP, NIH-funded research projects: http://crisp.cit.nih.gov/

NIAAA
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Career Development Awards (K-awards)

Career Transition Awards

K 22 **NIAAA Career Transition Award**
Assists the career transition of postdoctoral fellows or equivalent investigators into independent faculty positions by providing research support after obtaining an independent (tenure or non-tenure track) academic appointment. The program is designed for; 1) advanced postdoctoral fellows at extramural research institutions who are currently supported under a NIAAA-sponsored Individual NRSA Postdoctoral Fellowship award or Institutional Research Training Grant, and 2) current Intramural Research Training Awardees (IRTA) or equivalent staff fellows within the NIAAA Division of Intramural Clinical and Biological Research.
(PAR-06-096; http://grants.nih.gov/grants/guide/pa-files/PAR-06-096.html)

K 99 **NIH Pathway to Independence (PI) Award (K99-R00)**
Facilitates the career transition of postdoctoral fellows by providing support for both an additional period of mentored research (K99) and support for independent research (R00) upon obtaining an independent (tenure or non-tenure track) academic appointment. The program is designed for current postdoctoral trainees with up to 5 years of experience, including U.S. and non-U.S. citizens.
(PA-07-297; http://grants.nih.gov/grants/guide/pa-files/PA-07-297.html)

Mentored Career Development Awards

K 01 **Mentored Research Scientist Development Award**
Provides support for supervised research and training in biomedical, behavioral or clinical sciences that will further develop research independence. The career development experience must be in a research area new to the applicant and/or one in which an additional supervised research experience will substantially add to or enhance the research capabilities of the applicant.
(PA-06-001; http://grants.nih.gov/grants/guide/pa-files/PA-06-001.html)

K 08 **Mentored Clinical Scientist Research Career Development Award**
Provides support and protected time for outstanding research scientists with clinical doctoral degrees to pursue an intensive, supervised research experience in the fields of biomedical and behavioral research, including translational research. The supervised research experience may integrate didactic studies with laboratory or clinically-based research, or focus solely on research.
(PA-06-512; http://grants.nih.gov/grants/guide/pa-files/PA-06-512.html)

K 23 **Mentored Patient-Oriented Research Career Development Award**
Provides support for the supervised career development of clinically trained professionals who have made a commitment of focus their research endeavors on patient-oriented (human subjects) research, and who have the potential to develop into productive, clinical investigators.
(PA-05-143; http://grants.nih.gov/grants/guide/pa-files/PA-05-143.html)

Career Development Awards (K-awards) (cont.)

K 25 **Mentored Quantitative Research Development Award**
Supports the supervised career development of investigators with quantitative scientific and engineering backgrounds outside of biology or medicine who are transitioning to or have made a commitment to focus their research endeavors on biomedical and behavioral research that addresses health and disease.
(PA-06-087; http://grants.nih.gov/grants/guide/pa-files/PA-06-087.html)

Non-Mentored Career Development Awards

K 02 **Independent Scientist Award**
Supports the continuing development of newly independent scientists who can demonstrate the need for a period of intensive research focus to enhance and expand the potential of their research programs to make significant contributions within the field of alcohol research.
(PA-06-527; http://grants.nih.gov/grants/guide/pa-files/PA-06-527.html)

K 05 **Senior Scientist Research and Mentorship Award**
Supports outstanding senior scientists who have demonstrated a sustained, high level of research productivity, and whose expertise, research accomplishments, and contributions to the alcohol field have been and will continue to be critical to the mission of NIAAA, to further focus on their research programs. The candidate is also expected to serve as a mentor to newly independent investigators and junior faculty.
(PA-06-555; http://grants.nih.gov/grants/guide/pa-files/PA-06-555.html)

K 18 **Career Enhancement Award for Stem Cell Research**
Provides short-term support to enable investigators to enhance or change the direction of their research programs by acquiring new research skills and capabilities in the study and use of human or animal embryonic, adult, or cord blood stem cells. This program is designed for; 1) independent junior faculty who wish to expand their research through the use of stem cells, and 2) more senior, established investigators who wish to re-direct their research, in whole or in part, to include the use of stem cells. Applicants need to enlist an expert in stem cell research to serve as a sponsor.
(PAR-06-115; http://grants1.nih.gov/grants/guide/pa-files/PAR-06-115.html)

K 24 **Midcareer Investigator Award in Patient-Oriented Research**
Provides support for clinician researchers to allow them protected time to devote to patient-oriented (human subjects) research and to act as research mentors for clinical residents, clinical fellows and junior clinical faculty.
(PA-04-107; http://grants.nih.gov/grants/guide/pa-files/PA-04-107.html)

NIAAA
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NIAAA / NIH Career Transition Awards

NIH Pathway to Independence (PI) Award (K99-R00)

The NIH Pathway to Independence (PI) Award is an innovative program designed to enable promising postdoctoral scientists to receive both mentored and independent research support from the same award. Most NIH Institutes including NIAAA are sponsoring these awards. The initial 1-2 year mentored phase (using a K99 mechanism) allows postdoctoral scholars to complete their supervised research work, publish results, and search for an independent faculty position. Beginning in FY09, NIAAA provides 100% of salary support for the K99 awardee up to a maximum of $105,000, and up to $50,000 for research expenses. The second, independent R00 phase provides up to 3 additional years of support. This phase enables an awardee who secures an assistant professorship or equivalent position to establish his or her own independent research program. Total costs for the R00 phase will be up to $249,000 per year. This amount includes salary, fringe benefits, and research expenses. F & A costs will be reimbursed at the extramural sponsoring institution's full negotiated rate. Extramural and intramural postdoctoral fellows may apply for this program. U.S. citizens and non- U.S. citizens are eligible. Applications (new or revised) must be submitted within 5 years of the candidate's receipt of a research or clinical doctoral degree. Individuals are NOT eligible if they have currently or previously held research faculty or other professorships or their equivalent in academia, industry or elsewhere, or if they have been a principal investigator on major NIH research grants (such as R01, P01 or subprojects of such grants). NIAAA intends to issue 3 new PI awards per year, depending upon the quality of applications received and the availability of funds. Standard receipt dates for K-awards apply (Feb/Jun/Oct 12). To be considered for NIAAA funding, the research proposal must be related to alcohol. Prior to preparing an application, prospective applicants should discuss their competitiveness for this funding opportunity with NIAAA program staff.
(see http://grants.nih.gov/grants/guide/contacts/pa-06-133_contacts.htm)

The link for the new Pathways to Independence (K99/R00) Program is:
http://grants1.nih.gov/grants/new_investigators/index.htm

The link for the Program Announcement is:
http://grants.nih.gov/grants/guide/pa-files/PA-07-297.html

A list of common questions and answers is posted at:
http://grants1.nih.gov/grants/new_investigators/QsandAs.htm

NIAAA Career Transition Award (K22)

The goal of this program is to facilitate the transition of outstanding postdoctoral fellows into new faculty positions and to provide core financial support as they begin establishing independent research programs. The award will provide salary and research support for up to three years after candidates receive appointments at academic research institutions. To be eligible, applicants must propose basic or clinical research related to the health risks or benefits of alcohol consumption, or the prevention and treatment of alcohol-related problems. NIAAA anticipates selecting 2 - 5 new K22 awardees per year, depending on

NIAAA / NIH Career Transition Awards (cont.)

the quality of applications and availability of funds. Eligible applicants for the K22 program include individuals with a research or health professional doctoral degree and 2-6 years of postdoctoral experience. The program is designed for:

- Advanced postdoctoral fellows at extramural research institutions who are currently supported by an NIAAA-sponsored National Research Service Award (NRSA) for Individual Postdoctoral Fellows (F32) or an Institutional Research Training Grant (T32);
- Current Intramural Research Training Awardees (IRTA) or equivalent staff fellows in the NIAAA Division of Intramural Clinical and Biological Research (DICBR).

Eligible individuals should apply while they are still in a "mentored" postdoctoral position. Candidates must be U.S. citizens or non-citizen nationals, or individuals lawfully admitted to the United States for permanent residence.

Successful applicants will receive a Letter of Intent to Commit Funds from the NIAAA. To activate the award, candidates must obtain a formal offer of appointment to a tenure-track or equivalent faculty position at a U.S. academic institution. Candidates will have up to 18 months to activate the award. Starting in FY09, the K22 award will provide up to 100% of the candidate's institutional base salary up to a maximum of $105,000, as well as $75,000 per year for research-related expenses. For full details of the NIAAA career Transition (K22) Program, read the Program Announcement posted at:
http://grants.nih.gov/grants/guide/pa-files/PAR-06-096.html

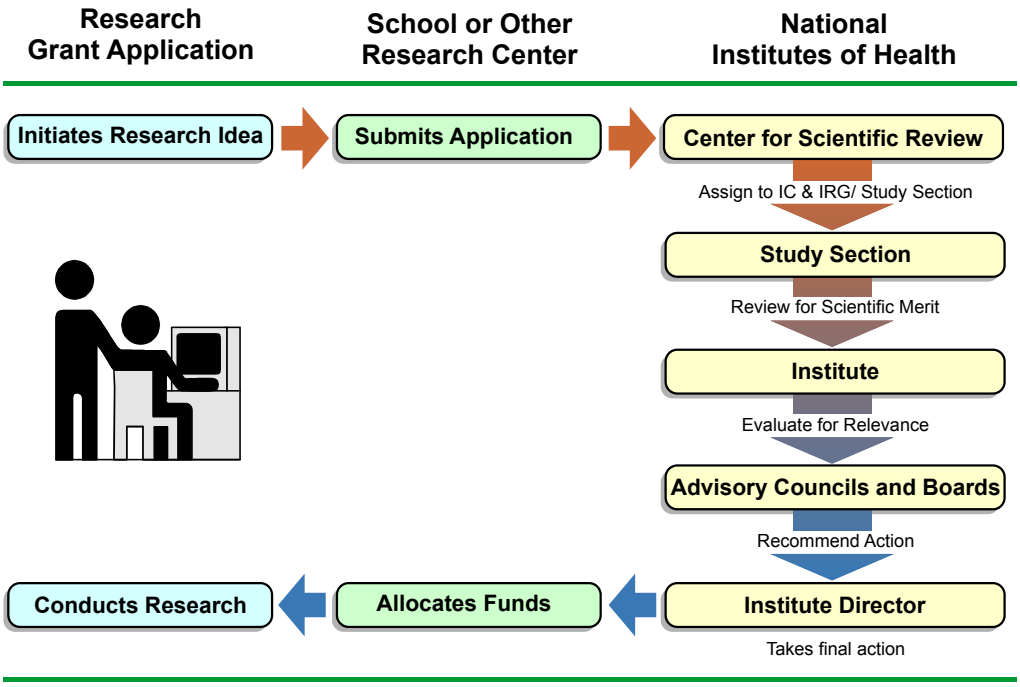
Interested postdoctoral fellows should review both the K99-R00 and K22 Program Announcements to determine the appropriate mechanism of support. Some key differences in the two programs are:

- K22 awards are restricted to NRSA fellows currently receiving NIAAA support (T32 or F32); the K99/R00 program allows any postdoctoral fellow with up to 5 years of experience to apply;
- K22 awards are restricted to US citizens, non-citizen nationals, or individuals admitted to the U.S. for permanent residence; the K99/R00 program also allows non-citizens to apply;
- The K22 award does not provide any support until the candidate receives a faculty appointment; the K99 provides financial support for up to 2 years of mentored postdoctoral training, followed by a transition to R00 support upon receipt of a faculty appointment;
- The K22 award reimburses Facilities and Administrative (F & A) Costs at a rate of 8%. The K99 phase uses an 8% F & A rate, whereas the R00 phase uses the full institutional F & A rate.

Both of these new career transition programs are intended for postdoctoral fellows whose formal research training is nearly complete, and who will soon begin searching for faculty positions. Individuals whose career development would benefit from further technical or theoretical training should strongly consider the mentored Career Development Awards offered by NIAAA (e.g., K01, K08, K23, K25). After consulting the relevant Program Announcements, interested individuals may seek additional guidance by contacting: *Dennis A. Twombly, Ph.D., Division of Neuroscience and Behavior, National Institute on Alcohol Abuse and Alcoholism, 5635 Fishers Lane, Bethesda, MD 20892-9304. Telephone: (301) 443-9334; Email: dtwombly@mail.nih.gov*

NIAAA
National Institute on Alcohol Abuse and Alcoholism

Grant Submission, Review, and Administration: Who does what at NIH?



Center for Scientific Review (CSR): This is the component of NIH that manages the peer review of most grant applications. After a proposal is submitted, staff in the Division of Receipt and Referral analyze the scientific areas involved and assign the application to an appropriate Initial Review Group (IRG) or Study Section. The Study Section is managed by an SRA.

Scientific Review Officer (SRO): The SRO oversees the scientific and technical review of the applications assigned to a particular Study Section, either at CSR or in the Review branches of NIH Institutes. The SRO analyzes the scientific areas involved in a group of applications, selects members of the peer review committee, assigns reviewers to applications based on topic areas and methodology, manages the study section meetings, and prepares summary statements after the review is conducted.

Program Director (Project Officer): Program Staff administer research programs as part of the scientific Divisions within the NIH Institutes. Grant applications are assigned to Project Officers on the basis of scientific field and technical approach. PO's provide policy & program guidance, assist applicants in interpreting summary statements, make funding recommendations on the basis of priority scores and program priorities, monitor grants after funding, and review progress reports.

National Advisory Council: Each NIH Institute has a Council comprised of senior scientists as well as lay members. The Council provides guidance to the Institute on policy and budgetary issues, and conducts the second-level review of new and competing grant applications. In this capacity, Council members review applications and summary statements for each of three cycles per year. In general they concur with the recommendations and priority scores of the study sections.

Institute Director: The Institute Director sets the overall goals and funding priorities for the Institute, and makes the final decisions for funding on all grant applications assigned to the Institute.

Grants Management Staff: GM staff process new and competing grant awards, assure that grants adhere to Institute and NIH policies and fiscal guidelines, and administer grants after funding. Applications that are recommended for funding are assigned to a staff member who processes financial aspects of the award and manages the grant throughout its duration.

NIAAA
National Institute on Alcohol Abuse and Alcoholism

Alcohol Research Centers

The NIAAA Centers program provides leadership in conducting and fostering interdisciplinary, collaborative research and is a major contributor to the development of cutting-edge research, new research methods and strategies for translating research into clinical practice.

NIAAA utilizes four Center Mechanisms each with specific goals. These include:

P 20 **Developmental/Exploratory Alcohol Research Centers**
Supports groups of researchers to create a cohesive, interdisciplinary team focused on a significant alcohol research theme and to assist them in establishing the necessary collaborations, facilities and research projects to justify a subsequent application for a Specialized (P 50) or a Comprehensive (P 60) Alcohol Research Center.

P 30 **Resource Core Alcohol Research Centers**
Provides support for centralized resources and facilities shared by alcohol research investigators both within and outside the sponsoring institution. Resource Core Centers are expected to act as regional or national resources in their particular area of expertise and provide the means to develop new research ideas and encourage new investigators.

P 50 **Specialized Alcohol Research Centers**
Sustains an integrated, multidisciplinary, multi-investigator, long-term program of research and innovation development planned around an important research theme. Specialized Centers are also expected: to function as a regional or national resource in their particular area of expertise; to provide opportunities for research training; to develop research collaborations with outside investigators and to provide the means to develop new research ideas and encourage new investigators via pilot projects.

P 60 **Comprehensive Alcohol Research Centers**
Serves all the same goals as the P 50 Specialized center and develops an effective research translation or information dissemination component to help accelerate the implementation of research findings for the benefit of public health.

For information about existing NIAAA Alcohol Research Centers see:
http://www.niaaa.nih.gov/ResearchInformation/ExtramuralResearch/ResCtrs1198.htm

Additional information on NIAAA Alcohol Research Centers may be obtained by contacting R. Thomas Gentry, PhD (tgentry@niaaa.nih.gov, 301-443-6009).

NATIONAL INSTITUTES OF HEALTH

DEPARTMENT OF HEALTH AND HUMAN SERVICES • USA

Division of Metabolism and Health Effects

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Additional information on NIAAA grants and programs can be found at:

http://www.niaaa.nih.gov