

Interim Report of the Research Priorities Committee, RSA
Michael E. Charness, M.D.
Committee Chair

The Research Priorities Committee met in Chicago on Wed, July 11, 2007. The committee voted to continue its current approach of having each member submit a set of priorities to the Chair. An additional step will occur this year, the integration of several priorities lists into three final lists. The original and final draft lists will be posted on the RSA web site and will be available for comment from the RSA membership. Using input from the membership, the draft lists will be finalized by March 1, 2008 in time for consideration as NIAAA updates its annual strategic planning document.

The following subgroups were designated

- A. Buck (Chair), Bonci, Mihic, Hodge, Grant, Platt
- B. Hasin (Chair), Saitz, Zweben, Anthenelli, Moore
- C. Mattson (Chair), Hutchison, Nagy, Tapert, Wall

The research priorities committee currently operates out of phase with the NIAAA strategic planning process, which ends in September. A new timetable was proposed to bring the activities of the committee in line with the NIAAA strategic planning process. The current year will provide a transition to a more permanent, better-aligned timetable.

2007-2008

July 31: Submit individual research priority lists to the Chair and the subgroup chairs

Dec 31: Subgroup chairs will work with their subgroups to distill and synthesize the submitted priorities of individual members into a single set of subgroup recommendations and submit to the Chair. The individual priority lists and the three distilled lists will be posted on the RSA web site.

Jan 1 - March 1: The RSA membership will have the opportunity to comment on the posted research priorities through an RSA website chat room. The subgroups will modify their recommendations, based on input from the membership. Final research priorities will be posted on the RSA website. The RSA president or the president's designee will present the RSA research priorities to the NIAAA National Advisory Council.

Late June: Committee meets at RSA to review and improve its process.

The new timetable and process will allow for input from the membership and more timely communication with NIAAA to better inform the NIAAA strategic planning process.

Research Priorities Committee Group A

Kari Buck, PhD; Antonello Bonci, MD; Donna Platt, PhD; John Mihic, PhD (Buck, Chair)

1. New research approach likely to have a high impact

- Increase funding for high-risk projects. As we well know, most NIH funded projects tend to be quite conservative in order to increase their chances of being funded. It would be valuable to put a funding program in place aimed at financing innovative, high-risk ideas with good potential for high impact.
- Determine why early alcohol use/exposure increases risk for alcohol abuse/dependence/withdrawal. Further characterize who is at risk for alcohol abuse/dependence/withdrawal (genetically; age and environmentally determined periods of vulnerability) using informative human and animal populations.

2. New research approach with an unknown impact

- Improve imaging technologies so that brain structure and function can be examined in genetic models currently possible only in mice (e.g., in gene knockouts that reduce self-administration of alcohol).
- Develop new reagents (e.g., antibodies) and approaches (e.g., antibody arrays) to quantify proteins to obtain a more complete understanding of alcohol's effects. [The measurement of expression and post-translational modification of many proteins has been stalled/misled by the lack of specific antibodies.]
- Apply new methodologies (e.g., exon arrays) to examine alcohol effects on the expression of alternative gene forms (splicing) to obtain a more complete understanding of alcohol's effects on gene expression.
- Examine epigenetic effects of alcohol across the lifespan, including alterations in embryonic and fetal development, adolescent and young adult brain maturation and disease. Identify additional mechanisms by which alcohol may alter gene expression and influence risk for alcohol use/abuse/dependence/withdrawal (e.g., alternations in transcription factors, small inhibitory RNA, etc).
- Use nonhuman primates selected on the basis of genotype to “naturally model” alcohol physiogenetics.
- In collaboration with NCCR, develop a genotype/phenotype database for nonhuman primates.

3. Research approach is already present and funded but needs to be kept as a high priority

- Continue to identify the relative influence of gene and environment on risk for developing alcohol abuse/dependence/withdrawal using informative human and animal model populations.
- Incorporate alcohol use disorders, family history of alcoholism, endophenotypes, and detailed measures of alcohol consumption into the National Health and Nutrition Examination Survey (NHANES) and other surveys to facilitate translational research building on animal model and human research.
- Continue to identify genes associated with vulnerability for alcohol dependence by employing proven (e.g., QTG) and emerging technologies using informative human and animal model populations.
- Define the full range of pharmacodynamic effects of alcohol on CNS function and the variability associated with unique genetic and gene-environment profiles.
- Continue to investigate how alcohol alters the oxidative state of cells and the pathologic consequences of changes in oxidative state in the brain and other organs.
- Refine successful youth alcohol interventions, ensure that programs are developmentally appropriate and attention grabbing, and focus on preventing the consumption of large volumes of alcohol. Also refine successful alcohol interventions in women of child-bearing age, ensure that programs are attention grabbing and focus on preventing the consumption of large volumes of alcohol.
- Medications development with emphasis on collaborations between medicinal chemists, preclinical and clinical scientists (e.g., lack of selective GABA-A $\alpha 4/\delta$ receptor ligands prohibits *in vivo* evaluations).
- Continue to study the basic physiology of brain areas heavily involved in ethanol-dependent behaviors, including the functional consequences of acute ethanol exposure and the effect of chronic ethanol exposure on receptors and ion channels, on a wide variety of ethanol-dependent behaviors.

- In a variety of brain regions, test if ethanol generally affects neurotransmitter release or if specific neurotransmitter release mechanisms are more susceptible to modulation by ethanol. Encourage a whole-synapse approach with concurrent study of pre- and post-synaptic elements of synaptic function.
- Secondary validation of potential targets that show differential gene expression as a result of alcohol administration/abuse/dependence/withdrawal. Emphasis should be on identifying changes in patterns of gene/protein expression (functional networks) and to determine if these vary among brain regions.
- Continued creation of genetically-engineered animals, especially tissue-specific & inducible knock-ins.

4. Research approach is already here but under funded and therefore the potential is unrealized

- Develop new animal models that more closely resemble diverse human traits regarding alcohol use, including improved models of ethanol drinking in rodents that better resemble alcohol abuse in humans.
- Program project type mechanism to fund the creation and phenotypic analysis of knock-in animals.
- Expand collaborative opportunities with NIMH (alcoholism comorbidity with other mental conditions) and NIAID (the influence of alcoholism on HIV and other infectious diseases expression/progression).

5. Training/education

- Train young investigators, with attention to diversity.
- Develop training grant opportunities that integrate all facets of research from bench to bedside.
- Train/support young investigators investigating alcohol and gene/environmental interactions using informative human and animal model populations.

Kari Buck, Ph.D.

1. New research approach likely to have a high impact

- Characterize who is at risk (genetically; age or environmentally determined periods of vulnerability to alcohol dependence and associated behaviors that may contribute to continued alcohol use/abuse and relapse to drinking) using informative human and animal model populations.
- Determine why early alcohol use/exposure increases risk for alcohol dependence and associated behaviors (e.g., withdrawal, etc.) that can contribute to continued alcohol use/abuse and relapse using informative human and animal model populations.

2. New research approach with an unknown impact

- Improve imaging technologies so that brain structure and function can be examined in genetic models currently possible only in mice (e.g., in gene knockouts that reduce self-administration of alcohol).
- Develop new reagents (e.g., antibodies) and apply new techniques (e.g., antibody arrays) for quantifying proteins to obtain a more complete understanding of alcohol's effects on these systems. [The ability to measure expression and post-translational modification of many proteins is currently stalled by the lack of specific antibodies. It is widely recognized that commercially available antibodies for some GABA-A receptor proteins don't even recognize the right protein. The generation of new, specific antibodies will likely involve generating antibodies using nonmammalian (e.g., avian) species.]
- Apply new methodologies (e.g., exon arrays) to examine the acute and chronic effects of alcohol on the expression of alternative gene forms (alternative splicing) to obtain a more complete understanding of alcohol's effects on gene expression.
- Examine the acute and chronic effects of alcohol on normal processes associated with chemical modification of DNA and histones, and the consequences of these modifications on gene

expression. In addition to epigenetics, identify other mechanisms (e.g., alternations in transcription factors, small inhibitory RNA, etc) by which alcohol may alter gene expression and influence vulnerability to alcohol dependence and associated behaviors that contribute to continued alcohol use/abuse and relapse.

- Examine epigenetic effects of alcohol across the lifespan, including alterations in embryonic and fetal development, adolescent and young adult brain maturation and disease.

3. Research approach is already present and funded but needs to be kept as a high priority

- Continue to identify the relative influence of gene and environment on risk for developing alcohol dependence and associated withdrawal using informative human (e.g., discordant twin pairs) and animal model (e.g., inbred strain panels) populations.
- Continue to identify genes associated with vulnerability for alcohol dependence by employing proven (e.g., QTG) and emerging technologies using informative human and animal model populations.
- Define the full range of pharmacodynamic effects of alcohol on central nervous system function and the variability associated with unique genetic and gene-environment profiles.
- Continue to investigate how alcohol alters the oxidative state of cells and the pathologic consequences of changes in oxidative state in the brain and other organs.
- Work to incorporate alcohol-related measures, including alcohol use disorders, alcohol dependence associated behaviors including endophenotypes, family history of alcoholism, and detailed measures of alcohol consumption, into the National Health and Nutrition Examination Survey (NHANES) and other surveys so future efforts can be undertaken for translational research building upon animal model and human research and to study the effects of gene and environmental factors as risk factors.
- Refine successful youth alcohol interventions, ensure that programs are developmentally appropriate and attention grabbing, and focus on preventing the consumption of large volumes of alcohol. Also refine successful alcohol interventions in women of child-bearing age, ensure that programs are attention grabbing and focus on preventing the consumption of large volumes of alcohol.

4. Research approach is already here but under funded and therefore the potential is unrealized

- Train/support young investigators investigating alcohol and gene/environmental interactions using informative human and animal model populations.
- Develop new animal models that more closely resemble diverse human traits regarding alcohol use, to aid the study of alcohol dependence and pharmacotherapy development. [not confounded by activity]

Antonello Bonci, M.D.

1. Research approach is already present and funded but needs to be kept as a high priority

1. Need to increase funding on projects focused on understanding the basic physiology of brain areas heavily involved in ethanol-dependent behaviors.
2. We need to expand our knowledge about the functional consequences of acute ethanol exposure. There is still an enormous amount of work to do.
3. Third, we need to fully understand the effect of chronic ethanol exposure on receptors and ion channels, on the whole variety of ethanol-dependent behaviors.

4. Fourth, we need to develop behavioral models of ethanol drinking in rodents. Although the current models are incredibly valuable, we need to invest more efforts in creating behavioral models of ethanol addiction that will better resemble alcohol abuse in humans.

New research approach likely to have a high impact.

1. Increase funding for high-risk projects. As we well know, most NIH funded projects tend to be quite conservative, in order to increase their chances of being funded. I believe that it would be valuable to put a funding program in place aimed at financing specifically innovative, high-risk ideas that have potential for success.

S. John Mihic:

Genetically-engineered animals

The use of genetically-engineered mice, and more recently rats, represents an extremely powerful tool for elucidating the molecular mechanisms of alcohol actions in the CNS, particularly in determining which specific behavioural effects are mediated by which specific proteins. The continued creation and use of these animals should be a research priority. This is especially true for knockin animals in which subtle modifications can be made, compared to knockouts in which entire genes are silenced. The alcohol research field can and should be at the forefront of the development of novel knockin animal technologies, including the development of tissue-specific and inducible knockin mice, as well as fostering the developments of these technologies in rats. A possible complication with the creation of these future lines of knockin mice is that the labs possessing the skills required to make these animals may have no idea of exactly what knockin animal might be best to create. For example, if one wishes to make a knockin of a subunit of a ligand-gated ion channel, one must first very carefully characterize that particular mutant electrophysiologically. Once the particular mutation is decided upon and the knockin mouse is made, it must be characterized behaviourally, biochemically and perhaps electrophysiologically. No one lab can do all these things well. Thus to best utilize this approach perhaps a program project mechanism of research funding should be explored, such that several labs possessing different and complementary experimental skills can all simultaneously work to best create and utilize these animals.

Integration of pre- and post-synaptic effects of ethanol

The last two decades has seen enormous research effort expended on elucidating the post-synaptic effects of ethanol, particularly studies on alcohol actions on GABA-A and NMDA receptors, as well as a number of other ligand-gated ion channels. Much less intensively studied have been possible pre-synaptic effects of ethanol that would be expected to affect neurotransmitter release at pre-synaptic neurons. More detailed studies are required, in a variety of brain regions, to determine if ethanol generally affects neurotransmitter release or if, as is more likely, to determine which specific neurotransmitter release mechanisms are most susceptible to modulation by ethanol. In addition, for specific neurotransmitters, does the magnitude of this modulation occur equally in different brain regions? Finally, studies proposing the concurrent study of both pre- and post-synaptic elements of synaptic function (i.e. a whole-synapse approach) should be encouraged.

Genomics, proteomics and pathways

In the last few years a number of microarray papers have been published in the alcohol research field, focusing on alcohol-induced changes in RNA levels in both humans and laboratory animals. An obvious common finding is that many gene expression changes are seen following ethanol administration, tolerance development as well as alcohol withdrawal. Much secondary validation of these potential alcohol targets remains to be done. Emphasis should also be placed on identifying changes in patterns of protein expression following alcohol administration and withdrawal. In addition, it is important to develop and use computational approaches to identify global patterns of gene and protein expression changes (i.e., functional networks) and to determine if these vary among brain regions.

Donna Platt, Ph.D.

1. New research approach with an unknown impact

- Support the development of a database of genotype/phenotype data across nonhuman primate users (perhaps in collaboration with NCCR).
- Explore the use of nonhuman primates selected on the basis of genotype to “naturally model” alcohol physiogenetics.
- Conduct collaborative studies with NIDA examining interactions of alcohol with other drugs of abuse on subsequent behavior.
- Examine the behavioral effects of GABA-A $\alpha 4/\delta$ ligands in *in vivo* models of alcohol abuse.

2. Research approach is already present and funded but needs to be kept as a high priority

- Medications development with particular emphasis placed on collaborative projects between medicinal chemists, preclinical and clinical scientists – see point 4 above: lack of ligands with selectivity for $\alpha 4/\delta$ prohibits *in vivo* evaluations.

3. Research approach is already here but under funded and therefore the potential is unrealized

- Expand collaborative opportunities with NIMH researchers examining alcoholism co-occurring with other mental health conditions.
- Expand collaborative opportunities with NIAID researchers examining the influence of alcoholism on HIV (and other infectious diseases) expression and/or progression – from molecular/cellular to behavior/cognition.

4. Training/education

- Train young investigators, with attention to diversity.
- Develop training grant opportunities that integrate all facets of research from bench to bedside.

Research priorities for alcohol research (Group B)

Compiled by Deborah Hasin, Ph.D.

Integrates lists from Robert Anthenelli, Deborah Hasin, Roland Moore, Richard Saitz, Allen Zweben

1. New research approach likely to have a high impact

- Genetic research: genes as modifiers of self-administration and reinstatement in animals and humans, as modifiers of behavioral and pharmacological treatment response, as interacting with

environment and development in onset, persistence and offset of alcohol disorders, as validators of alcohol phenotypes for DSM-V.

- Return to samples studied longitudinally to collect DNA
- Expand etiologic and treatment research on comorbidities/co-addictions: tobacco/nicotine, cannabinoid and opioidergic interactive effects, substance abuse and psychiatric disorders, obesity, HIV and HCV (including determining risk thresholds for alcohol)
- Study success of alcohol control policies in specific areas (e.g., college campuses) by level of alcohol availability in adjacent areas

2. New research approach with an unknown impact

- Cost-effectiveness research, including improving validity and standardization of measures and use of measures from other areas of health
- Research on methods to reduce stigmatization of alcohol problems and increase public awareness that intervention can be successful, in the general public and among health professionals
- Studies on alcohol across stages of the lifespan, for example, effects of early alcohol exposure on pubertal development and brain functioning, subjective and objective responses to alcohol by age group including transition from early to mid-adulthood, ethnographic studies of teen parties

3. Research approach already present, funded but needs to be kept as a high priority

- Expand collaborations across NIH institutes, academia and the pharmaceutical industry
- Conduct research on alcohol industry marketing efforts, alcohol taxation changes
- Continue studies on gene discovery as well as clarification of the reasons for inconsistent results concerning some genetic effects

4. Research approach is already here but underfunded and thus potential is unrealized

- Cross-national, cross-cultural studies
- Untreated “natural recovery” studies: biological/genetic as well as psychosocial aspects
- Mechanisms, access for secondary analyses of data sets (COMBINE, COGA, NESARC)
- Identify strategies to enhance screening, brief intervention and appropriate referral within “real world” primary care setting.

5. Funding mechanisms that should be developed to enhance career development

- Pay full overhead on K awards to make them more appealing to institutions.
- For mid-career and senior scientist mentoring awards, expand period of eligibility to more than one renewal
- Provide administrative “new investigator” supplements (similar to minority supplements) to K02s, K05s and the R01 grants of mid-career and senior investigators to increase mentored access to pilot funding for junior new investigators
- Develop mechanisms to establish partnerships with minority institutions to improve mentoring and support for minority investigators

Roland S. Moore, Ph.D. (Prevention Research Center, PIRE)

1. New research approach likely to have a high impact

- Compare the relative success of alcohol control policies on college campuses with varying degrees of alcohol availability in the communities that surround them.
- Attempt to reduce violence in and around bars through interventions affecting the speed or duration of alcohol consumption in on-premise outlets, especially bars.
- Evaluate coordinated trainings of district attorneys, judges, and law enforcement personnel on consistent approaches to DUI and other alcohol-related crime, with associated time-series analyses of conviction rates and other evidence of deterrence.
- Assess the differences in the ways that light, moderate, and heavy drinkers interpret and act upon community-level policy changes such as stepped-up DUI enforcement and sales restrictions.

2. New research approach with an unknown impact

- Deter high-risk drinkers' consumption of common household products containing alcohol through a national program to strengthen denaturants.
- Facilitate natural experiments in reducing alcohol availability immediately adjacent to "dry" counties and "dry" Native American reservations.
- Increase understandings and assessments of the work-related hazards of coming to work with a hangover.
- Conduct ethnographic research on teen parties, parental hosting rationales, and effectiveness of party patrols.

3. Research approach is already present and funded but needs to be kept as a high priority

- Encourage innovative methods grants to increase analytical precision and measurement of alcohol consumption.
- Identify key points in the lifespan where susceptibility to alcoholism is heightened.
- Facilitate cross-national research, especially comparing drinking patterns of migrant groups in the United States with cultures of origin to shed light on risk/protective factors.

4. Research approach is already here but underfunded and therefore the potential is unrealized

- Translate psychosocial research regarding cue reactivity, expectancies and norms into brief interventions for problem drinkers.
- Carry out research on alcohol industry marketing efforts, analogous to the productive National Cancer Institute-supported analyses of tobacco industry documents.
- Use economic and epidemiological methods to assess the long-term repercussions of alcohol taxation changes, including weakening through inflation.
- Link alcohol research to obesity prevention studies through collaboration with other NIH Institutes by investigating caloric, metabolic and nutritional characteristics of alcohol as it is consumed with or without other foods.

5. Education/Career Development

- Nurture participatory action research partnerships between established alcohol centers and predominantly minority universities (e.g., tribal colleges) to increase research mentoring opportunities for their students.
- Pay full overhead on K-series awards to make them more appealing to institutions.
- Offer mentoring fellowships with funding for both mentors and mentees, specifying goals for methods mastery and publication outcomes.

Robert M. Anthenelli, M.D.

1. Research approach likely to have high impact
 - Cross-validate human laboratory paradigms attempting to model alcohol relapse with the reinstatement models simulating alcohol relapse in experimental animals
 - Elucidate gender-/sex-sensitive pathways affecting risk to develop alcoholism and treatment responsiveness
 - Identify and test gene x environment interaction effects influencing alcohol self-administration and reinstatement in experimental animals and cross-validate in humans
 - Expand research on alcoholism with other co-addictions emphasizing tobacco/nicotine, cannabinoid and opioidergic interactive effects
2. New research approach with an unknown impact
 - Elucidate the roles of the endocannabinoid system in alcohol's intoxicating effects
 - Explore effects of early alcohol exposure on pubertal development and brain functioning
 - Test new drug delivery systems including nanotechnology
 - Elucidate the roles of orexigenic and anorexigenic neuropeptides and neurosteroids in alcohol's reinforcing effects
3. Research approach already present and funded but needs to be kept as a high priority
 - K-Awards of all types; Expand Mid-Career K-24 Award period of eligibility
 - Expand the Integrative Neuroscience Initiative on Alcoholism (INIA) to include more projects translating the basic research findings into human clinical models
 - Alcoholism treatment in dually-diagnosed and co-addicted patient populations
 - Research that supports the interplay among genetic, environmental and developmental factors in the etiology of alcoholism in humans
4. Research approach is already here but under-funded and therefore the potential is unrealized
 - Expand research on the concurrent or sequential treatment of tobacco dependence in alcohol dependent individuals
 - Expand focus of NIDA's Clinical Trials Network (CTN) to examine alcohol and concomitant other drug treatment
 - Expand collaborations across NIH institutes, academia and the pharmaceutical industry
 - Facilitate greater access to major NIAAA-funded initiatives (i.e., COGA, Project COMBINE) and industry-sponsored trials to spawn secondary data analyses of these large data sets

Allen Zweben

1. **New research approach likely to have a high impact**
 - Develop mechanisms to fund collaborative networks among government, academia and industry to study medications for the treatment of alcohol problems.
2. **New research approach with an unknown impact**
 - Study of genotypic and phenotypic subtypes of alcohol dependent patients (e.g., opioid mu receptor) that respond positively (efficacy and safety) to specific pharmacologic agents.

- Define and validate assessment measures that are suitable for capturing an array of benefits and costs derived from particular interventions or combinations of pharmacological and behavioral treatment modalities.

3. Research approach is already present and funded but needs to be kept as a high priority

- Focus on mediators and moderators that contribute to the decisional/motivation processes to change drinking behavior on their own or via professional help.
- Examine the common factors such as optimism, empathy, alliance, and expectancy that are specific to a particular treatment approach and subsequently lead to improved outcomes.
- Increase the understanding of the role of social context (marital relationship, other partners and kin networks, employment, legal and economic factors) in promoting or interfering with positive change in drinking behavior.
- Develop models for integrating behavioral and pharmacological treatments that facilitate medication compliance, sustain patients in treatment and lead to improved outcomes across different patient populations and/or settings. .

4. Research approach is already here but under funded and therefore the potential is unrealized

- Identify strategies to enhance screening, brief intervention and appropriate referral within “real world” primary care setting.
- Examine models for incorporating medications into the alcohol treatment delivery system in primary care settings.
- Develop and test engagement and adherence techniques that will sustain patient in treatment and enhance medication compliance, factors closely associated with improved outcomes.
- Develop adaptive or conceptual treatment models that will address the treatment needs of nonresponders in combined medication and behavioral treatment trials.
- Expand the application of medications that manage the care of individuals with range of alcohol-related problems in primary care and specialty settings including individuals with co-morbidities (i.e., alcohol and drug use disorders and/or psychiatric problems).
- Develop a more comprehensive understanding of how natural recovery occurs targeting individuals who do not typically seek help for alcohol problems.

5. Funding mechanisms that should be developed to enhance career development

- Develop mechanisms to provide education and training programs for minority investigators to conduct studies on health disparities.
- Develop mechanisms to establish partnerships with minority institutions to improve mentoring and support for minority investigators interested in alleviating health disparities among individuals with alcohol related problems.

Deborah Hasin, Ph.D.,

1. New research approaches likely to have a high impact

- Include non-invasive DNA collection techniques (e.g., saliva kits) in all large-scale surveys and ongoing longitudinal studies.
- Conduct surveys (direct and vignette questions) on negative attitudes and beliefs about alcohol use disorders and treatment among health care professionals and the general public, and the reasons for these beliefs.
- Conduct cross-national surveys on alcohol consumption and DSM-IV alcohol use disorders in countries with contrasting per capita consumption rates, alcohol practices, policies and/or advertising policies. Include drinking norms, exposure to early and adult fateful stressful/traumatic events, and ecological information on alcohol policies and advertising.

2. New research approach with an unknown impact

- Compare subjective and objective responses to alcohol (positive, negative, intoxication, other) between young and middle-aged adults (the ages of well-established decline in onsets and persistence of alcohol disorders in the general population).
- Study the effectiveness of public information/advertising interventions to reduce stigmatization and improve understanding of treatment efficacy (informed by successful efforts from the mental health area, e.g., major depression).
- Incorporate genetic information in randomized trials of behavioral as well as pharmacological treatments to determine how genetic variants that affect risk for alcohol dependence modify treatment effects.
- Conduct survey research on beliefs about the inevitability of underage drinking and the reasons for this among children, adolescents and adults.

3. Research approach already present and funded but needs to be kept as a high priority

- Longitudinal studies of risk and protective factors for excess drinking across the lifespan.
- Studies oriented to gene discovery as well as clarification of the reasons for inconsistent results concerning some genetic effects.

4. Research approach already here but under-funded and potential is unrealized

- Identify existing epidemiologic samples exposed to contrasting environmental influences on alcohol and add a wave of data collection to update alcohol information and collect DNA.
- Substantive studies via secondary analyses of large, existing datasets (specific RFAs).
- Nosological studies relevant to DSM-V through secondary analyses of large existing datasets (specific RFAs)
- Nosological research relevant to DSM-V (i.e., alternative phenotypic representation of alcohol use disorders) that incorporates biological indicators (genetic, endophenotypic).

5. Funding mechanisms to enhance career development

- Extend senior investigator mentoring funding to mentoring pre-docs.
- Extend mentoring senior scientist awards to more than one renewal if the mentoring is successful (e.g., mentees receive grants, publish, advance academically).

- Provide administrative “new investigator” supplements (similar to minority supplements) to R01 grants of senior investigators to increase mentored access to pilot funding.
- Provide “partial sabbatical” support to mid- and senior-level scientists to develop knowledge and expertise in a specific area that will expand their research capabilities.

Richard Saitz

1. New research approach likely to have a high impact

- Longitudinal studies of alcohol use initiation in children, excessive drinking in young adults, and risks for later consequences (particularly study of life transition points)
- Longitudinal studies of alcohol consumption and other detailed assessments, and risk for consequences (particularly specific medical illnesses), in healthy people and in those with key conditions (e.g. HIV, hepatitis C), with identification of risk thresholds
- Population attributable (to alcohol) risks for health conditions (e.g. HIV, hypertension, hepatitis C, cardiomyopathy, pneumonia, child abuse, trauma, health care utilization).
- Placebo-controlled trials of moderate drinking (primary and secondary prevention)
- Studies with adaptive designs (e.g. testing strategies that depend on patient response to initial strategy)
- Efficacy studies of alcohol dependence interventions in general (not specialty) healthcare settings including pharmacotherapy
- Studies of how to implement treatments with known efficacy
- Studies of systems interventions to achieve better quality of care
- Pragmatic (effectiveness) trials of interventions to identify and engage non-treatment seekers

2. New research approach with an unknown impact

- Cost-effectiveness research, using metrics that allow comparison with other health states (utilities, quality-adjusted life years)
- Studies of education and clinician behavior and systems/organizational change

3. Research approach is already present and funded but needs to be kept as a high priority

- Large, long-term efficacy studies of brief intervention (in person & electronic), with individual and population-level health outcomes/consequences, varying intensity and models, in varied, particularly general healthcare and nonclinical settings, and integrated with other health behavior interventions

4. Research approach is already here but under funded and therefore the potential is unrealized

- Statistical methods to combine clinical outcome measures and tests of the validity/importance of combined clinical outcome measures (e.g. consumption, consequences) across domains, time and data sources
- Quantification of “second-hand” effects of drinking (including nondependent use) on social, legal and economic consequences
- Biomarkers for screening in nonspecialty care settings

5. Funding mechanisms that should be developed to enhance career development

- Faculty development award for clinician educators (disseminating alcohol research to practice), either via establishment of centers of educational excellence that would in turn support a number of faculty [teams], or to individuals. Awards would support research on education and implementation [science], and education itself (development of and dissemination of materials)
- Mentored awards to support research of junior faculty researchers (e.g. first several years on faculty before eligibility for traditional K series awards)

Research Priorities Committee, Group C

Contributors: Sarah Mattson, Tamara Wall, Susan Tapert, Laura Nagy (Mattson, Chair)

1. New research approach likely to have a high impact

- Compare brain structure/function of youth with alcohol use disorders, including FASDs, to other clinical groups.
- Increased research in the area of basic mechanisms, risk factors, early treatments, periods of vulnerability, recovery, and the clinical profile of alcohol use disorders, including FASDs.
- Conduct a large cross-national epidemiological study of alcohol consumption and alcohol use disorders, including FASD; involve alcohol and tobacco prevention efforts.
- Examine the acute and chronic effects of alcohol exposure on executive functioning, decision-making, and social information processing, including processes involved in the maintenance or interruption of drinking behaviors.
- Investigate relationship between short term impact of ethanol on cellular/organ systems and the development of long-term pathology, e.g., liver or bone disease.

2. New research approach with an unknown impact

- Develop standardized methodological and assessment measures to permit more meaningful comparisons across studies; identify or improve screening tools and brief interventions for alcohol use disorders, including FASD; better characterize developmental trajectories.
- Prevent the escalation of drinking immediately following active duty in the military, particularly following traumatic combat situations.
- Evaluate role of parenting practices, peer influences, on youth risk behaviors.

3. Research approach is already present and funded but needs to be kept as a high priority

- Examine neurocognitive underpinnings of alcohol use disorders, including FASD, using both brain imaging and neuropsychological methods, improve identification/diagnosis of at-risk individuals; identify mechanisms of vulnerability.
- Support longitudinal investigations of risk and protective factors for alcohol involvement across the lifespan; address combined influence of other exposures.
- Longitudinally examine brain structure and function of high-risk children to determine the effect of alcohol on adolescent neuromaturation.
- Use of “-omics” strategies (genomics, proteomics, metabolomics, etc) along with modeling of integrated pathways looks to be a promising strategy to try to predict/model what the fundamental targets of ethanol action are in individual cell types and then to predict if these targets are susceptible to ethanol action across cell types.

- 4. Research approach is already here but under funded and therefore the potential is unrealized**
- Examine the relationships between alcohol use disorders, including FASD, and other psychiatric and medical conditions, with attention to developmental course and intervention.
 - Identify individuals, groups, and environments at highest risk for alcohol problems and improve prevention efforts, incorporate genetic analysis into ongoing longitudinal studies.
 - Optimize the accuracy of alcohol research instruments, including further examination of transdermal or other in vivo assessment approaches.
 - Use of alternative model organisms to study the developmental, behavioral and pathological effects of ethanol
- 5. Funding mechanisms that should be developed/strengthened that would enhance career development**
- Expand funding to senior investigators to improve mentorship of the next generation of alcohol-related researchers, build or expand current research areas, examine existing data, and provide bridge funds to those who experience funding lapses.
 - Train young investigators, with attention to diversity, particularly among minority groups currently under-represented among NIH/NIAAA grant recipients, with advantageous allocation of postdoctoral fellowships, travel awards, and funded workshops; increase access to pilot funding, preliminary review and guidance by senior investigators.