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Midwest Alcoholism Research Center: Future directions

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Midwest Alcoholism Research Center: Future Directions

- **Dept. of Psychiatry, Washington University School of Medicine, St. Louis**
- **Dept. of Psychology, University of Missouri, Columbia**

Collaborations with:

- **Palo Alto Veterans Administration, California**
- **Saint Louis University School of Public Health**
- **Queensland Institute of Medical Research, Brisbane, Australia**
- **Dept. of Psychiatry, University of Iowa (under development)**



Broad Theme

- **Understanding the etiology of alcohol use disorders and their comorbidity with other psychiatric disorders.**

- **Focus on general community samples.**



Why Important?

In the coming years, multiple genes will be identified that contribute to AUD risk. Urgent need to understand:

- **Developmental unfolding of their effects, including effects on disorders comorbid with alcoholism;**
- **Interplay with environmental risk-factors (from conception onwards);**
- **Effects in general population samples (not just high density pedigrees);**

Need to have refined approaches that will allow characterization of effects at multiple levels of analysis (not just diagnostic interview!):

- **human experimental paradigms**
- **human ecological paradigms**



Levels of Analysis

- **Basic science studies (pre-natal alcohol exposure);**
- **Gene-mapping & molecular genetic studies;**
- **Prospective epidemiologic & genetic epidemiologic surveys;**
- **Human experimental studies, neuroimaging studies**
- **Human “ecological” studies (palm pilot assessment);**
- **Methods development - quantitative methodology;**
 - **assessment methodology**



Integrative Hypotheses

Testing three inter-related models for genetic and environmental influences on AUD risk.

- ⇒ **“Pharmacologic vulnerability”**: differences in level of response to alcohol, nicotine, cognitive aspects of alcohol use (expectancies, motives)
- ⇒ **“Negative affect regulation”**: understanding the associations between AUDs and depression, anxiety disorders, suicidality.
- ⇒ **“Behavioral undercontrol”**: understanding the associations between AUDs and externalizing disorders – attention deficit hyperactivity disorder, conduct problems, adult antisocial behavior.

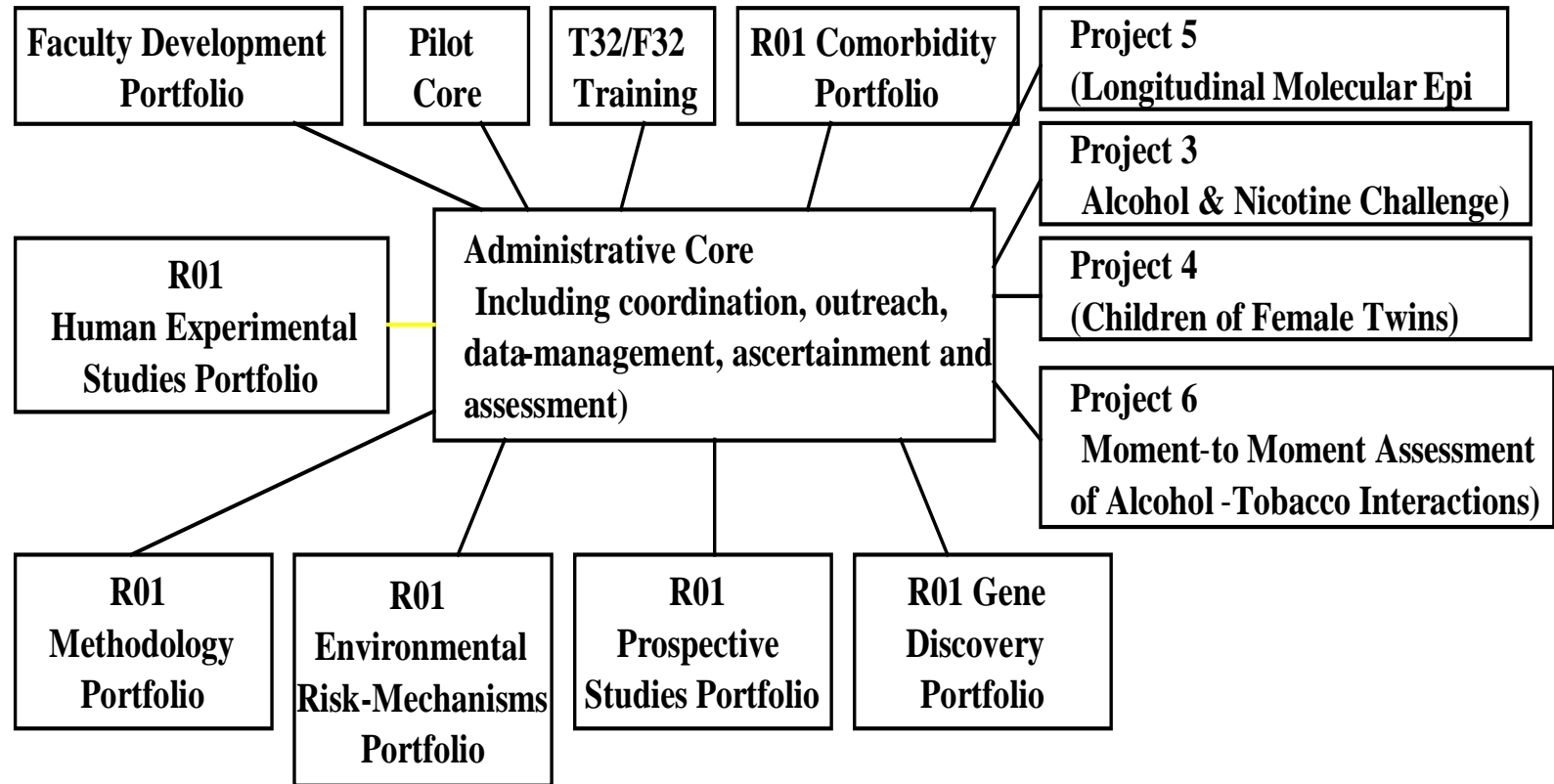


Individual genetic epidemiologic studies are expensive

- ⇒ **Integrated program of research combining P50-based projects, RO1-funded projects, K-awards for junior faculty development, career development.**
- ⇒ **Most center-based research is RO1-based.**

Structure of MARC

B) Structure for Competing Continuation (Years 06 -10)





- 38 Investigators (including basic science, including 22 core faculty at W.U. and Mizzou, 16 affiliate investigators)**
- 8 K-awardees (2 pending submission)**
- 29 RO1s /project grants (several pending review)**

⇒ Multiple funding sources (NIAAA, NIDA, NIMH, NINDS, NCI)



Genetics Methodology Research

How do we best identify predictors of transitions in adolescent substance use?

How do we optimize phenotype definition for gene-mapping studies?

How do we best investigate the inter-play between genetic and environmental risk-factors?

How do we define quantitative phenotypes for gene-discovery efforts?

How do we make best use of longitudinal data-sets?



Environmental Risk-Mechanisms/ Children-of-Twins Portfolio...

**Bucholz, Cadoret, Eisen, Glowinski, Heath, Jacob, Nelson,
Slutske, True**

Comparing outcomes in offspring of twins from 4 groups:

Parent AUD (or drug dependent)

Parent unaffected, MZ cotwin AUD;

Parent unaffected, DZ cotwin AUD;

Parent unaffected, cotwin unaffected.

Use of children-of-twins design to separate genetic and environmental influences on offspring risk

		Level of risk to children due to:		
		Genetic Effects	Familial Environmental Effects ^a	Genotype x Environmental Interaction Effects
Parental AD history	Cotwin's History			
Alcohol dependent	Any	High	High	High
Non-dependent	Alcohol dependent, MZ	High	Low	Low
Non-dependent	Alcohol dependent, DZ	Intermediate	Low	Low
Non-dependent	Non-dependent	Low	Low	Very Low



Vietnam – Era Twin Panel Children-of-Twins Studies (PI's Jacob, True)

<i>Parent</i>	<i>Cotwin</i>	<i>Alcohol Use Disorders in Offspring's (Aged 18-25)</i>
Alcohol Dependent	Any	42.9
Alcohol Abuse	MZ cotwin AD	54.3
Unaffected	MZ cotwin AD	26.7 ^{NS}
Alcohol Abuse	DZ cotwin AD	36.6 ^{NS}
Unaffected	DZ cotwin AD	27.8 ^{NS}
Unaffected	Unaffected	29.6

(Jacob et al, in review)



G x E interaction effects more important in the etiology of AUDs than we had anticipated.



Australian Twin Panel Children-of-Twins Studies

P50-Project 4 (Female alcoholic twins)

	Childhood ADHD ^a in offspring (%)
Mother AD	18.0
Mother AB	17.7
Mother unaffected, MZ cotwin AD/AB	23.8
Mother unaffected, DZ cotwin AD/AB	1.6 ^{NS}
Mother unaffected, cotwin unaffected	8.3

^a Broad phenotype – similar results for narrow phenotype



Genetic transmission is a major determinant of the increased risk of ADHD to offspring of alcoholic parents. Association cannot be explained by parental rating bias or high risk environmental exposures associated with parental alcoholism.

BUT, controlling for parental genetic risk of alcoholism, maternal smoking during pregnancy remains a significant predictor of risk (OR = 3.83)



Other Environmental Risk-Mechanism Priorities:

- (1) Childhood physical/sexual abuse (Nelson)**
- (2) Maternal smoking & drinking during pregnancy, studied using mothers with both “clean” and “dirty” pregnancies (Knopik – under development)**
- (3) Interactions between high-risk environmental exposures associated with parental alcoholism, & offspring genetic risk of depression/suicidality – a major determinant of the comorbidity of depression & alcoholism? (Glowinski)**



Prospective Studies Portfolio (Missouri-based)

Longitudinal (including genetic epidemiologic) studies of children, adolescents, young adults.

- Cooper** - adolescent alcohol use & sexual risk-taking (follow-up in adulthood);
- Sher** - long-term consequences of collegiate drinking;
- Sher** - new college cohort;
- Heath** - prospective adolescent female twin study (follow-up in adulthood);
- prospective adolescent male twin study (P50, closing down);
- Anokhin** - twin study of collegiate drinking;
- Madden** - adolescent male twin study of smoking;
- Bucholz** - high-risk adolescent family study (African-American over-sample)
- Todd** - prospective study of twins with ADHD.

Heath, Anokhin, Madden, Bucholz, Todd studies all use birth record ascertained families (recontact rates as high as 95%).



Gene Discovery Projects Portfolio

Studies using general community samples. Designed to complement studies using clinically ascertained probands and their relatives (e.g. COGA).

- IRPG1 (Martin)** - 1000 AD cases, 1000 controls.
- IRPG2 (Todd)** - large sibships, used with quantitative index of consumption/tolerance that is highly correlated with alcoholism risk.
- IRPG3 (Heath)** - sibships selected for extreme concordance or discordance on quantitative index.
- NAG (Madden)** - focused on heavy smoking sib pairs (but will contribute information about alcohol phenotypes).
- Mutation screening (Todd)** - system-based approach, screening for individuals with comorbid alcohol & nicotine dependence with variants in ~ 80 dopamine system genes.



Bridging the Gap

- **Community-based adult samples to address gene effects in the general population**

BUT, also need to take advantage of prospective studies to address developmental unfolding of gene effects and their interplay with environmental risk-mechanisms.

⇒ P50/Project 5 (pending)



Project 5 (pending)

Molecular epidemiologic study to obtain blood samples for DNA extraction, genotype 4 existing longitudinal panels:

- (a) Chassin – 400 adolescents (50% from families with a biologic and custodial alcoholic parent) followed prospectively from adolescence into young adulthood (4 assessment waves completed, 5th in progress), plus 240 adult siblings. Includes Hispanics. Age range 10-16 at wave 1, 24-29 by wave 5.**

- (b) Cooper – 2000 adolescents (40% African-American) followed prospectively in a study of drinking and sexual risk-taking. 10-16 at initial assessment, 19-24 by wave 4.**



Project 5 (pending) - II

- (c) Heath – 2400 female adolescent twins (15% African-American) followed prospectively from adolescence (13-20) into young adulthood (25). Parental as well as adolescent interview data (informative for studying gene effects associated with childhood externalizing disorders).**

- (d) Sher – 400 college students (50% with paternal history of alcoholism, 50 % with no alcohol or drug use disorders in 1st or 2nd degree relatives) followed prospectively into their early 30s, across 7 waves of assessment.**



Human Experimental & Neuroimaging Portfolio

Investigating under controlled experimental conditions associations observed in epidemiologic/genetic epidemiologic surveys.

- **Neuroimaging & neuropsychology study of MZ twin pairs discordant for heavy alcohol use during adolescence (Rohrbaugh/Buckner)**
 - **Importance of early-onset drinking as a predictor of later alcohol dependence risk.**
- **Nicotine & alcohol challenge study of effects on ataxia (assessed using dynamic posturography (P50/Project 3: Rohrbaugh))**
 - **Does moderation of alcohol effects by tobacco (or vice versa) contribute to the striking comorbidity of alcohol & nicotine dependence.**



Human Experimental & Neuroimaging Portfolio (II)

- **Nicotine challenge studies using twin pairs concordant and discordant for smoking status to identify heritable components of human response to nicotine, in both non-smokers and smokers (Sirevaag)**
 - Informative because of the genetic overlap of smoking and alcoholism (c.f. MZ pairs discordant for regular smoking).
- **Noncontact (laser doppler) studies of emotion and stress (Rohrbaugh, DoD). Future potential for neuroimaging studies.**



Ecological Assessment Project (P50/Project 6, pending: Sher)

- **Again designed to “bridge the gap”, between diagnostic interview surveys (comorbidity of smoking and alcoholism) and human experimental studies (nicotine & alcohol challenge).**
- **PDA (palm pilot) based prompted assessments of smoking and drinking to describe their naturalistic co-occurrence and associations with contexts and stressors.**



Adult Comorbidity Projects

- **Personality/Personality Disorder in Australian twin panel**
(Trull, in resubmission)
- **Pathological gambling**
 - **Vietnam Era twin panel (Eisen)**
 - **Australian twin panel (Slutske)**

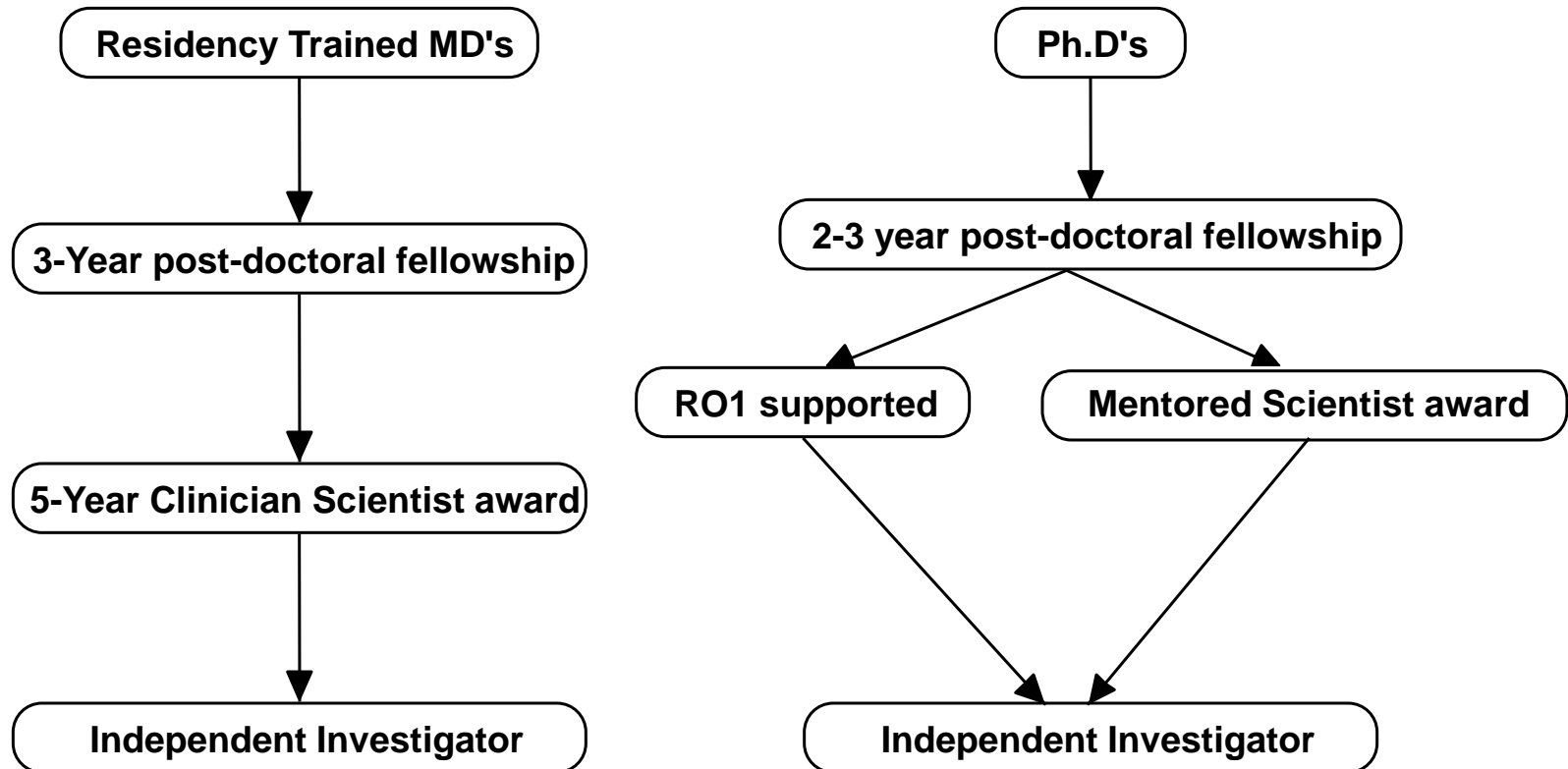
**(In Australia, high proportion of gaming machines
("Pokies") are based in bars)**



Overview of Education and Outreach

- Predocctoral**
- Psychology (University of Missouri T32)
 - Medicine (Wash. U. – including summer interns)
- Postdoctoral**
- Psychology (University of Missouri T32)
 - Broadly biomedical (Wash. U. T32)
 - Training of residents in psychiatry, fellows in child psychiatry (Bucholz)
- Junior Faculty**
- Mentored scientist/clinician scientist awards
 - Weekly/biweekly mentoring meetings
- Outreach**
- Community Advisory Board
 - Guze Symposium & associated poster presentations

Career Development Post-doctoral trainees





Educational & Training Resources

Washington University

- **Strong program in Medicine (but heavy basic science orientation)**
- **Strong residency program in Psychiatry (40 residents)**
 - Strong fellowship program in Child Psychiatry (6 fellows)**
 - Strong departmental seminar programs (Grand Rounds; Psychiatry Research; Genetics; Epidemiology; Neuroscience)**
- **Strong post-doctoral training program in Psychiatry (25 post-doctoral trainees, both Ph.D. and M.D., including more senior investigators retraining)**
- **Top social work program (#2 in US) – not fully exploited**
- **Strong Ph.D. program in biomedical sciences (not yet exploited)**
- **Strong tradition of faculty mentoring in Psychiatry, use of mentored scientist awards**

NEED MORE POST-DOCTORAL TRAINEES!



Educational & Training Resources **University of Missouri, Columbia**

Core additions faculty in Psychology

- **Many undergrads participate in research, may use data from projects for honors theses**
- **Strong track-record of predoctoral training (NIAAA T32)**
- **Growing post-doctoral training program**
- **Strong mentoring of junior faculty, 2 K-awardees;**

Weekly proseminar on alcohol studies (2 hours) with contributions from other MARC sites;

Weekly alcohol research methods/analyses meeting.



Development of Junior Investigators

Post-doctoral training: apprentice model, supplemented by:

Departmental seminars;

P50 research/methods seminar;

Seminars in quantitative methodology, grantsmanship; addictions journal club;

tutorial-based research training (meeting one on one);

Junior faculty – see above (both as teachers/presenters and students).

Senior faculty – see above (both as presenters /teachers and students).



Outreach

(1) Community Advisory Board (Chair: Kathy Bucholz)

- former state legislators;**
- local media representatives;**
- those active in work with young people, other high-risk groups;**
- director of State Alcohol & Drug division.**

⇒ **Receive reports about what we are finding**

⇒ **Provide input about perceived local research needs.**



Outreach (Cont.)

(2) Annual Guze Symposium

- different “research theme” each year:

 - e.g. alcoholism etiology (2001)

 - e.g. college drinking (2002)

 - e.g. alcohol and the high school student (2003)

- different “target” audiences:

 - e.g. physicians and other clinicians (2001)

 - e.g. college administrators (2002)

 - e.g. school administrators and teachers (2003)

Format: - invited speakers, both local & national

- poster session at which P50 investigators & trainees present research findings relevant to meeting theme.

⇒ Encourages use of our data for Outreach.