Washington State University Alcohol and Drug Abuse Research Program (ADARP)

Fiscal Years 2009, 2010, and 2011

Barbara A. Sorg, Director
360-546-9719, sorg@vetmed.wsu.edu

Jenny Baylon, Program Coordinator
509-335-5676, baylonj@vetmed.wsu.edu

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Executive Summary

Mission Statement

The mission of the Alcohol and Drug Abuse Research Program (ADARP) is to promote substance abuse research at Washington State University and to provide the university, its scientific community, and the public with the knowledge gained from this research.

In accordance with its mission, the Alcohol and Drug Abuse Research Program carries out the following activities:

- Funds research, including pilot grants, graduate student grants, and undergraduate research fellowships
- Provides bridge funds
- Awards equipment grants
- Provides funds for recruitment of new faculty
- Brings many prominent researchers to WSU to give seminars and meet with faculty and students

WSU Alcohol and Drug Abuse Researchers secured a 10:1 ratio of extramural to intramural funding.

- Throughout its history, the WSU Alcohol and Drug Abuse Research Program has regularly maintained or exceeded this return on the dollar and has played a key role in the success of WSU researchers.

Alcohol and Drug Abuse Research Program expenditures were consistent with its overall mission.

- ADARP funded research in 23 different departments on four campuses.
- More than 85% of all funds went to support substance abuse research through pilot grants, graduate student grants, equipment grants, and start-up awards.
- Rigorous grant competitions and constructive critiques improved proposals and enhanced the chances of extramural funding.
- Just over one percent of funds supported the seminar series and other special events, thereby enriching the campus environment and helping to build connections between WSU and the wider scientific community.

Alcohol and Drug Abuse Research Program
September 2012

Mission Statement

The mission of the Alcohol and Drug Abuse Research Program is to promote substance abuse research at Washington State University and to provide the university, its scientific community, and the public with the knowledge gained from this research.

Background

The Alcohol and Drug Abuse Research Program (ADARP) at Washington State University was established in its present form in 1987-88. The ADARP is supported by funds received in accordance with Washington State Initiative 171, which sets aside a portion of liquor license fees to be used for research. Initiative 171 support has been in the range of $120,000 to $300,000 per year, depending upon receipts from liquor licenses. The program is administered by the Director, who consults with an advisory committee when establishing and enforcing new policies.

In accordance with its mission, the ADARP carries out the following activities:

1. **Funds research, especially pilot grants. The ADARP has given research money to faculty from the following departments, schools, and colleges:**

Animal Sciences
Anthropology
Chemistry
Communication
Comparative American Cultures
Counseling Psychology
Genetics and Cell Biology
Health Research and Education Center
Human Development
Kinesiology
Mathematics
Molecular Biosciences
Neuroscience
Nursing
Pharmaceutical Sciences
Pharmacy Practice
Political Science/Criminal Justice
Psychology
Sociology
Speech and Hearing Sciences
Veterinary and Comparative Anatomy, Pharmacology and Physiology
Veterinary Microbiology and Pathology
Wellness Center

   a. **Pilot grants** help faculty to obtain preliminary data to allow them to obtain extramural funding in substance abuse research.

   b. **Graduate student grants** provide salary support for graduate students actively participating in substance abuse research. Benefits: The

graduate student grant program gives graduate students practice writing grants, provides graduate students with "ownership" of a project, allows graduate students to study substance abuse issues when lack of funds might otherwise have made that impossible, and provides graduate students with individual recognition.

c. **Undergraduate student grants** provide wages and supplies for small faculty-mentored projects. Benefits: Minimal output of funds (less than 10% of total budget) furthers WSU's ideal of being "World Class. Face to Face." Also, funding undergraduates appears to encourage them to continue on to graduate school.

2. **Provides bridge funds.** These are limited funds for established substance abuse researchers who are temporarily without a federal grant. Bridge funds have been provided six times since 1995, and amounts have ranged from $10,000 to $35,000 (average $21,905).

3. **Recruits new faculty members.** The ADARP has provided start-up funds to augment departmental start-up packages for substance abuse researchers six times since 1993, and amounts have ranged from $17,000 to $100,000 (average $66,750).

4. **Awards equipment grants**. Equipment grants provide funds for shared equipment essential to substance abuse researchers.

5. **Brings many prominent researchers to WSU to present seminars and meet with researchers and students.** In addition to exposing the WSU community to cutting-edge substance abuse research, the seminar series has helped WSU researchers to forge several key long-term collaborations with invited guests.

6. **Regularly collaborates with many other units.** The ADARP has collaborated with departments from across campus in the following areas:

   a. **Start-up funds.** The ADARP has contributed to departmental start-up packages for top-notch faculty recruits in Psychology, Pharmaceutical Sciences, and VCAPP. Without ADARP help, these departments may not have been able to recruit such strong faculty.

   b. **Faculty collaboration.** Substance abuse researchers from different departments share information and ideas during ADARP events. Relationships are forged that lead to collaborations and equipment sharing.

   c. **Seminar speakers.** The ADARP has collaborated with the Wellness Center, the Murrow College of Communications, Psychology, VCAPP, and Pharmaceutical Sciences to bring in speakers beneficial to many faculty and students.

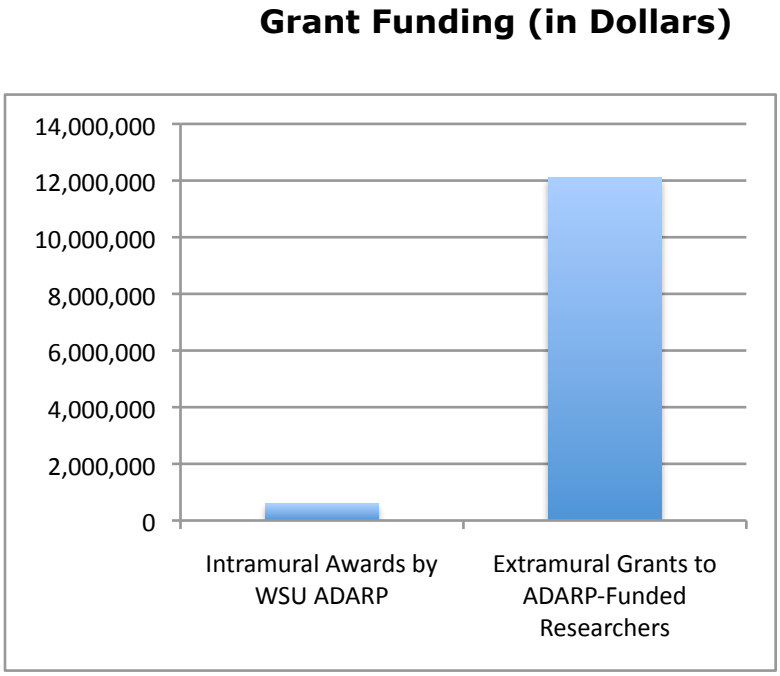
Return on Investment

Based on years of experience, we estimate that it takes approximately three years to turn ADARP pilot grant funding into an extramurally funded grant. Therefore, we compared pilot grant expenditures in Fiscal Year (FY) 2006, 2007, and 2008 to extramural grants received during FY 2009, 2010, and 2011 (see below).

During FY 2006, 2007, and 2008, the ADARP spent $587,179 on pilot grants, graduate student grants, bridge funds, and equipment grants. The $587,179 does not include start-up funds or undergraduate grants.

During FY 2009, 2010, and 2011, ADARP-funded researchers received $12,103,110 in extramural funding partially or entirely attributable to ADARP grants.

WSU ADARP-funded researchers secured better than a 20:1 ratio of extramural to intramural funding. Throughout its history, the WSU Alcohol and Drug Abuse Research program has generally maintained or exceeded a 10:1 return on the dollar and has played an integral role in the success of WSU researchers. Approximately fifty percent of ADARP-funded researchers go on to secure extramural funding on their research topic.

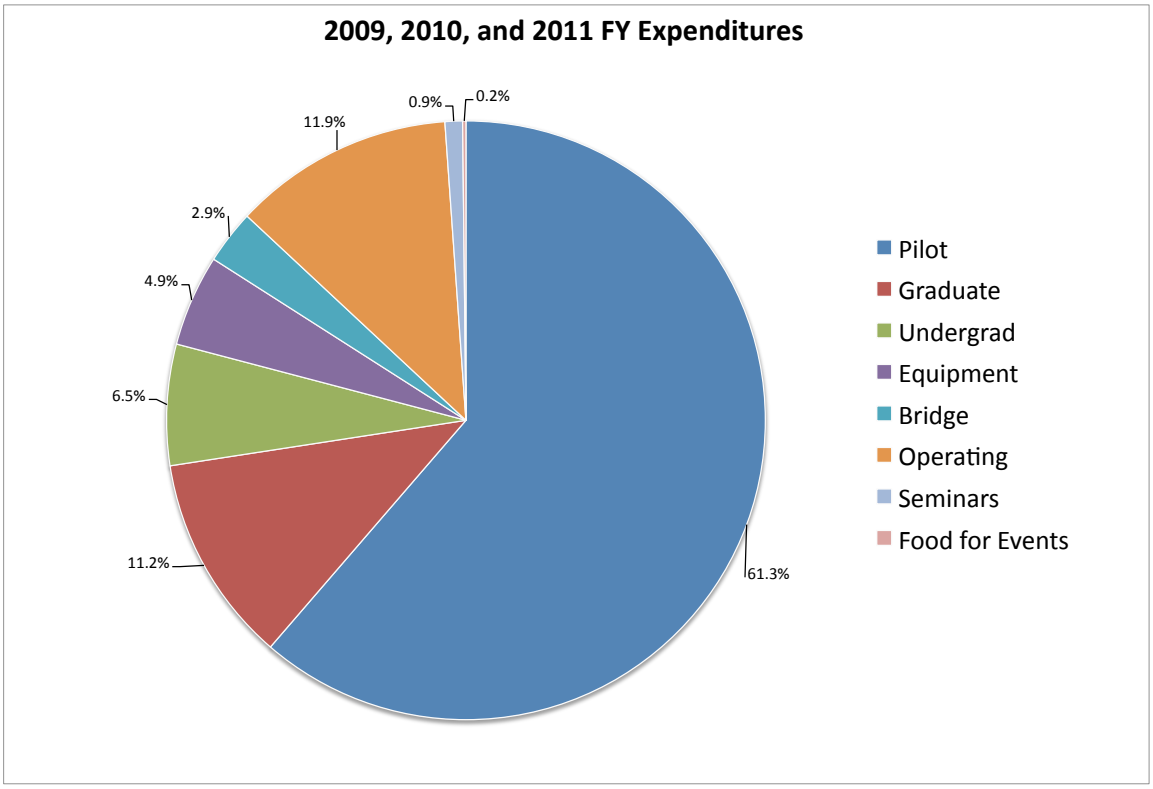


Extramural Grants Received (FY 09, 10 & 11)

Name	Amount	Dates	Details
Austin, Erica	$731,081	7/2009-6/2011	104978 (Washington State Department of Social and Health Services). Manage the Aged, Blind, or Disabled (ABD) Cost Offset and Treatment Expansion Evaluation Project.
Austin, Erica	$1,655,858 + $68,428 + $44,446	7/2009-6/2011	20585 (Washington State Department of Social and Health Services). The goal of this project is to facilitate the delivery of substance abuse prevention services by personnel located throughout the state.
Austin, Erica	$104,500	7/2008-6/2009	104707 (Tobacco Prevention and Control Program). The goal of this project was to advise the state of Washington on tobacco prevention campaigns and perform focus groups with adolescents to test prevention messages.
Dong, Yan	$149,500	3/2011-2/2013	"The Nucleus Accumbens NMDA Receptor in HIV-Induced Motivational Disorders."
Dong, Yan	$373,750	4/2011-3/2013	"Labeling of Cocaine-Generated Nascent Excitatory Synapses."
Hill, Laura Griner	$660,000	2/2009-4/2014	"Creating Culturally Competent Programs for Families"
Huang, Yanhua (Yan Dong and Barbara Sorg, mentors)	$993,448	3/2011 - 2/2016	K99 DA029565-01 NIH/NIDA. "Regulation of Nucleus Accumbens Neurons by Sleep Deprivation."
Lee, Brian	$124,140	7/2010–6/2013	NIH – F31DA028020 (PI) "Neurocircutiry Plasticity after Cocaine Seeking."

Name	Amount	Dates	Details
Morgan, Mike	$3,781,236	9/2009 – 7/2014	R01 NIH/NIDA R01 DA027625 "Psychostimulants Induce Long-Term Changes in Nociception." Role: Multiple PIs (Morgan, Aicher, & Ingram) Coordinate project and conduct behavioral experiments.
Morgan, Mike	$331,030	8/2009 – 7/2011	R01 DA 015498-07 (PI) "Cellular Mechanisms of Opioid Tolerance."
Morgan, Mike	$149,500	5/2009 – 4/2011	R03 DA026591 NIH/NIDA. "Neural Mechanisms of Enhanced Cannabinoid/Opioid Antinociception."
Schwartz, Jennifer	$140,000	2010 - 2012	R03 NIH "Public Policy and Policy Enforcement Effects on Changes in Female and Male Drunk Driving."
Shelden, Eric	$334,984	4/2008 - 6/2011	"Small Heat Shock Protein Regulation and Function in Zebrafish"
Sorg, Barbara	$398,750	8/2011 - 09/2013	NIH NIDA (R21DA030647) (PI) "Matrix Metalloproteinases and Cocaine"
Walker, Brendan	$1,829,258	4/2011 – 3/2016	R01AA020394-01 NIAAA (NIH) (PI) "Role of Dynorphin/Kappa-Opioid Systems in Alcohol Dependence"
Walker, Brendan	$110,000	1/2011 – 12/2012	Hope for Depression Research Foundation, Research Grant. "Role of Central Kappa-Opioid Receptors in Altered Ultrasonic Vocalizations as a Measure of Depressive Affect Induced by Addictive Drugs."
Walker, Brendan	$123,201	9/2009 – 8/2011	Research grant from Lundbeck Research USA, Inc. "Kappa-Opioid Mechanisms of Nalmefene"
TOTAL	**$12,103,110**		

Expenditure History by Category



Alcohol and Drug Abuse Research Program Expenditures

- ADARP funded research in seventeen different departments on three campuses.
- More than 86% of all funds went to support substance abuse research through pilot grants, graduate student grants, undergraduate student grants, equipment grants, and bridge funds.
- Rigorous grant competitions and constructive critiques improved proposals and enhanced the chances of extramural funding.
- Just over 1% of funds supported the seminar series and other special events, therefore enriching the campus environment and helping to build connections between WSU and the wider scientific community.
- Approximately 12% of expenditures went toward operating costs.

Expenditure History by Category (2009, 2010, and 2011 FY)	
Pilot	$ 740,473.00
Graduate	135,555.80
Undergraduate	78,757.00
Equipment	59,599.74
Bridge	35,000.00
Operating	143,848.47
Seminar Series	11,386.53
Food for Events	2,150.57
TOTAL	**$1,206,771.11**

Grant History by Department
(2009, 2010, and 2011 FY)

Department	# Submitted	# Funded	Pilot	Graduate	Undergrad	Other[6]	% Funded
Animal Sciences	1	0		0 of 1			0.0
Anthropology - WSUV	3	2	1 of 1	1 of 2			66.7
Chemistry	7	2	1 of 3	1 of 4			28.6
Communications	8	3	2 of 7	1 of 1			37.5
Health and Wellness	1	0	0 of 1				0.0
Human Development	12	5	2 of 6	1 of 3	2 of 3		41.7
Math. & Sci. - WSUV	1	0	0 of 1				0.0
Nursing	3	3	3 of 3				100.0
Pharmaceutical Sci.	5	1	1 of 4		0 of 1		20.0
Pharmacotherapy	1	1	1 of 1				100.0
Psychology	13	9	2 of 2	2 of 5	5 of 6		69.2
Psychology - WSU-TC[1]	1	0	0 of 1				0.0
Psychology - WSU-V[2]	10	5		1 of 2	4 of 8		50.0
SMB[3]	1	1	1 of 1				100.0
Sociology	2	1	1 of 1	0 of 1			50.0
VCAPP[4]	17	11	2 of 5	3 of 4	5 of 7	1 of 1	64.7
WWAMI[5]	4	2	2 of 4				50.0
	90	**46**	**19/41 46%**	**10/23 43%**	**16/25 64%**	**1/1 100%**	**51.1**

[1] WSU Tri Cities

[2] WSU Vancouver

[3] School of Molecular Biosciences

[4] Veterinary and Comparative Anatomy, Pharmacology, and Physiology

[5] Washington, Wyoming, Alaska, Montana, and Idaho Regional Medical Education Program

[6] Equipment or Start-Up

Grants Approved for Fiscal Years 2009, 2010, and 2011

Amount	7/1/2008 - 6/30/2009	Budget	Project	
35,000.00	Dong (VCAPP) Pilot (7/1/08 - 12/31/09)	2550	1216	
35,000.00	Craft (Psych.) Pilot (9/8/08 - 3/31/10)	2474	1219	
14,230.00	Parks (Psych.) Pilot (9/25/08 - 3/31/10)	2474	1220	
35,000.00	Tarnai (SESRC) Pilot (11/19/08 - 5/31/10)	3905	1222	Pilot grants
35,000.00	Dong/Brown (VCAPP) Pilot (1/14/09 - 7/31/10)	2550	1225	
26,673.00	Jansen (VCAPP) Pilot (2/3/09 - 8/31/10)	2550	1228	
35,000.00	Sorg (VCAPP) Pilot (5/14/09 - 11/30/10)	2550	1232	
9,755.00	Cyr/Morgan (Psych./Vanc.) Graduate (1/1/09-12/31/09	5810	1224	Graduate Student Grants
2,020.00	Cunningham/Diversi (Hum. Dev. Vanc.) UG Sem. (8/21/08-12/31/08)	5814	1217	
2,020.00	Ingram/Williamson (Psych./Vanc.) UG Sem. (1/1/09 - 5/31/09)	5810	1223	
2,020.00	Lyman/O'Brien/Rodgers (Human Dev.) UG (1/27/09-5/31/09)	2144	1226	
2,020.00	Bond/Jansen (VCAPP) UG (2/3/09 - 5/31/09)	2550	1227	Undergraduate
5,320.00	Haseman/Morgan (Psych./Vanc.) UG-Summer (5/1/09 - 8/31/09)	5810	1229	Student Grants
5,320.00	Fyfe/Ingram (Psych./Vanc.) UG-Summer (5/1/09 - 8/31/09)	5810	1230	
5,320.00	Rooney/Simasko (VCAPP) UG-Summer (5/1/09 - 8/31/09)	2550	1231	
5,320.00	Craft/Laggart (Psych.) UG-Summer (6/3/09 - 8/31/09)	2474	1233	
35,000.00	Morgan (Psych./Vanc.) Bridge Funds (9/1/08-8/31/09)	5810	1218	Bridge Funds
25,821.74	Walker/Craft/Wright (Psych.) Equip. (10/3/08 - 6/30/09)	2474	1221	Equipment Funds
315,839.74	**Total for Fiscal Year 2009**			

Amount	7/1/2009 - 6/30/2010	Budget	Project	
22,089.00	Hust (Com) Pilot (7/8/09 - 1/31/11)	2434	1234	
32,403.00	Wisor (WWAMI-Spokane) Pilot (8/5/09 - 3/31/11)	5850	1239	
27,886.00	Vandermause (Nursing) Pilot (8/17/09 - 3/31/11)	2483	1240	
33,525.00	White (Pharmacotherapy) Pilot (9/9/09 - 3/31/11)	2958	1241	
34,372.00	Hindman (Comm.) Pilot (1/1/10 - 6/30/11)	2434	1244	Pilot grants
35,000.00	Hagen (Anthro. WSU-V) Pilot (3/26/10 - 9/30/11)	5810	1245	
35,000.00	Krueger (VCAPP) Pilot (7/1/10 - 12/31/11)	2550	1251	
35,000.00	Craft (Psych.) Pilot (7/1/10 - 12/31/11)	2474	1252	
34,908.00	Walker (Psych. Pilot (7/1/10 - 12/31/11)	2474	1253	
34,337.00	McGuire (Hum. Dev.) Pilot (7/1/10 - 12/31/11)	2144	1254	
20,042.00	Wakley (Psych) Grad (8/15/09 - 8/31/10)	2474	1235	Graduate Student Grants
23,179.00	Lee (VCAPP) Grad (8/1/09 - 7/31/10)	2550	1236	
14,624.00	Suter (Human Dev.) Grad (7/23/09 - 7/31/10)	2144	1237	
4,038.00	Bond/Jansen (VCAPP) UG - AY (8/16/09 - 5/31/10)	2550	1238	
2,019.00	Walker/Smith (Psych.) UG-Sem (1/1/10 - 5/31/10	2474	1242	
2,019.00	McGuire/McBride/Marlow (HD) UG-Sem (1/1/10 - 5/31/10)	2144	1243	
5,320.00	Beets/McGuire (Hum. Dev.) UG-Summer (5/1/10 - 8/31/10)	2144	1246	Undergraduate Student Grants
5,320.00	Bennett/Sorg (VCAPP) UG-Summer (5/1/10 - 8/31/10)	2550	1247	
5,320.00	Smith/Walker (Psych.) UG-Summer (5/1/10 - 8/31/10)	2474	1248	
5,320.00	Cole/Morgan (Psych. WSUV) UG-Summer (5/1/10 - 8/31/10)	5810	1249	
5,320.00	Rooney/Simasko (VCAPP) UG-Summer (5/1/10 - 8/31/10)	2550	1250	
417,041.00	**Total for Fiscal Year 2010**			
25,279.00	Lee (VCAPP) Grad (8/1/10 - 7/31/11) Received NIH grant, returned all of ADARP grant.	New Competition, but award added to 1236		

Amount	7/1/2010 - 6/30/2011	Budget	Project	
32,976.00	Kang/Schenk (Mol. Bios.) Pilot (7/1/10 - 12/31/11)	2428	1255	
34,563.00	Schwartz (Soc.) Pilot (7/27/10 - 12/31/11)	2480	1258	
17,095.00	Shishani (Nursing) Pilot (8/30/10 - 2/29/12)	2483	1259	
35,000.00	Ishikawa (VCAPP) Pilot (1/20/11 - 7/31/12)`	2550	1262	Pilot grants
35,000.00	Hill/Schenk (Chem.) Pilot (3/16/11 - 9/30/12)	2452	1263	
35,000.00	Zhang (Pharm. Sci.) Pilot (3/11/11 - 9/30/12)	2957	1264	
26,712.00	Howell (Nursing) Pilot (3/16/11 - 9/30/12)	2483	1265	
19,764.00	Roulette/Hagen (Anthro.) Grad. (8/1/10 - 7/31/11)	2482	1257	
20,367.00	Davis/Walker (Psych.) Grad. (5/16/11 - 5/15/12)	2474	1268	Graduate Student Grants
24,298.00	Bobeck/Morgan (Psych. WSUV) (5/16/11 - 8/15/12)	5810	1269	
2,019.00	Reis/Walker (Psych.) UG-Sem (1/1/11 - 5/31/11)	2474	1260	
2,019.00	Wyrick/Sorg (VCAPP) UG-Sem (1/1/11 - 5/31/11)	2550	1261	Undergraduate
5,320.00	Kandasamy/Craft (Psych) UG-Summer (5/1/11-8/31/11)	2474	1266	Student Grants
5,320.00	Drapala/Ingram (Psych. WSUV) UG-Summer (5/1/11-8/31/11)	5810	1267	
33,000.00	Jansen/Sorg (VCAPP) Equip. (7/1/10 - 12/31/10)	2550	1256	Equipment Funds
328,453.00	**Total for Fiscal Year 2011**			

BRIDGE FUND DETAILS
(Entire History)

Faculty	Amount	Year	Department
Schenk	$16,434.00	1995	Chemistry
Meadows	10,000.00	1997	Pharmaceutical Sciences
Jerrells	25,000.00	1998	Pharmaceutical Sciences
Craft	25,000.00	2002	Psychology
Quock	20,000.00	2005	Pharmaceutical Sciences
Morgan	35,000.00	2008	Psychology (WSU Vancouver)
Total	**$131,434.00**		
Average	**$21,905.67**		

START-UP DETAILS
(Entire History)

Faculty	Amount	Year	Department
Craft	$50,000.00	1993	Psychology
Jerrells	50,000.00	1997	Pharmaceutical Sciences
Quock	50,000.00	1998	Pharmaceutical Sciences
Ouimette	17,000.00	2001	Psychology
Dong	100,000.00	2006	Veterinary and Comparative Anatomy, Pharmacology, and Physiology
Walker	100,000.00	2008	Psychology
Total	**$367,000.00**		
Average	**$61,166.67**		

Alcohol and Drug Abuse Research Program Seminars
July 2008 to June 2011

Date	Name	Affiliation	Title
2008 – 9/11	Danny Winder	Department of Molecular Physiology and Biophysics, *Vanderbilt University School of Medicine*	"Modulation of Glutamatergic Transmission in the Extended Amygdala by Drugs of Abuse and Stress"
2008 – 11/6	Brendan Walker	Department of Psychology, *Washington State University*	"The Role of Kappa-Opioid/ Dynorphin Systems in Alcohol Abuse"
2009 – 3/11	Jennifer Stuber	School of Social Work, *University of Washington*	"Smoking and Socioeconomic Status: What Explains the Relationship?"
2009 – 9/3	George Koob	*Scripps Research Institute*	"The Dark Side of Addiction: Neurobiological Mechanisms"
2009 – 11/16	Janis Kupersmidt	*Innovation Research & Training ("iRT")*	"Media Literacy Education for Substance Abuse Prevention: Results of Randomized Efficacy Trials of Elementary and Middle School Programs."
2010 – 4/16	Jenny Wiley	Department of Psychiatry, *Research Triangle Institute*	"Sugar, Spice, and Everything Nice? Cannabinoid Pharmacology in Females"
2010 – 5/6	Yavin Shaham	Behavioral Neuroscience Branch, *National Institute on Drug Abuse*	"Incubation of Drug Craving"

Date	Name	Affiliation	Title
2010 – 9/3	Paul Vezina	Department of Psychiatry and Behavioral Neuroscience, *University of Chicago*	"Dopamine-Glutamate Signaling and Amphetamine Sensitization"
2010 – 10/8	Michela Marinelli	*RFUMS/Chicago Medical School*	"Age, Stress, and Dopamine Neurons: Factors Facilitating Cocaine Addiction"
2010 – 10/14	John Neumaier	Department of Psychiatry, *University of Washington*	"Probing Striatal Function using Pathway-Selective Viral Vectors and Neoceptors"
2010 – 10/29	Paul Phillips	*University of Washington*	"Coupling Value to Action: Dopamine and Decision Making"
2010 – 12/10	David Lovinger	Laboratory for Integrative Neuroscience, *NIAAA*	"Synaptic Plasticity in the Dorsal Striatum: Roles in Learning and Memory"
2011 – 2/18	Stacey Hust	Edward R. Murrow College of Communication, *Washington State University*	"Framing Adolescent Marijuana Use as a Societal Problem: The Effects of Media Advocacy Editorials on Marijuana Users and Non-Users"
2011 – 3/24	Katie Witkiewitz	Department of Psychology, *Washington State University - Vancouver*	"Fall(s) from the Wagon: Mechanisms of Behavior Change following Alcohol Treatment"

Date	Name	Affiliation	Title
2011 – 4/14	Alan Rosenwasser	University of Maine	"Chronobiology of Alcohol and Alcoholism"
2011 – 4/29	Andrea Hohmann	Indiana University	"Endocannabinoid Mechanisms of Pain Suppression"
2011 – 5/6	Terry Robinson	University of Michigan	"The Touch of Temptation: Individual Differences in the Ability to Resist Reward Cues and Implications for Addiction"

Pilot and Graduate Student Grant Abstracts

Grants Awarded during FY 2009

Anabolic-Androgenic Steroids Ameliorate Pain via Opioid Activation.
Department of Psychology, Rebecca Craft, Professor ($35,000).

There is a fundamental gap in understanding how anabolic-androgenic steroids (AAS) affect pain. The *long-term goal* is to elucidate how chronic AAS use and its termination alter the endogenous opioid system, and how that alters pain, analgesia and mood, as well as contributing to AAS dependence. The *objective of this application* is to demonstrate that chronic AAS use significantly decreases sensitivity to inflammatory pain, and that this is an opioidergic effect. The *central hypothesis* is that chronic administration of non-aromatizable AAS (those that act primarily at androgen rather than estrogen receptors) decrease inflammatory pain, and this AAS effect is blocked by the opioid antagonist naltrexone. Guided by preliminary data, this hypothesis will be tested by pursuing three *specific aims: (1)* Demonstrate that AAS decrease chronic inflammatory pain; (2) Demonstrate opioid involvement in AAS effects on pain; (3) Demonstrate "rebound" increases in pain sensitivity during AAS withdrawal. Under the first aim, the effects of non-aromatizable AAS vs. aromatizable AAS will be compared on multiple acute (non-inflammatory) vs. chronic inflammatory pain tests, to demonstrate that only non-aromatizable AAS effectively decrease inflammatory (but not acute) pain. Under the second aim, the ability of non-aromatizable vs. aromatizable AAS to modulate opioid analgesia and to be blocked by an opioid antagonist will be determined, to demonstrate that AAS effects involve the opioid system. Under the third aim, inflammatory pain sensitivity will be examined 1 to 4 weeks after termination of chronic AAS treatment. *The proposed research is significant* because it will demonstrate for the first time that non-aromatizable AAS decrease inflammatory pain, and that this effect is mediated by a neurotransmitter known to be integral to pain inhibition in the CNS. These findings will provide an explanation for reports of hastened recovery from exercise-induced injury in AAS abusers, and increased muscle and joint pain in patients treated with anti-androgens for various medical conditions. This research also will broaden our understanding of how AAS-induced opioid release in AAS users contributes to the addictive properties of AAS, the lethal effects of AAS overdose, and increased opioid abuse observed in AAS users.

Methylphenidate Enhancement of Morphine Antinociception.
Department of Psychology, Michelle Catherine Cyr, Graduate Student.

Attention-Deficit/Hyperactivity Disorder is the most prevalent childhood psychiatric disorder in the USA. Methylphenidate (MPH) is often utilized to reduce symptomatology. Early MPH treatment in rats has been shown to enhance adult morphine drug seeking behavior (Crawford et al., 2007). We have extended these findings by showing that MPH treatment in young rats enhances morphine antinociception and tolerance when tested as

an adult (manuscript in preparation). These findings indicate a long-lasting change in neuronal functioning within opioid receptor containing areas of the brain. Given that MPH exerts its effects on DA neurons, brain structures where dopamine and opioids interact probably underlie the MPH-induced enhancement of morphine effects. For example, the ventrolateral periaqueductal gray (v-PAG) contains both dopaminergic and opioid networks (Hokfelt et al., 1976) and contributes to opioid-induced analgesia (Lane et al., 2005). Thus, it is hypothesized that MPH enhances morphine antinociception by altering the v-PAG. The purpose of this study is to test this hypothesis by microinjecting morphine into the v-PAG of adult rats pretreated with MPH from Day 11 - 20 following birth. It is predicted that (1) rats exposed to MPH during the preweanling period will show enhanced acute antinociception in adulthood following microinjection of morphine into the v-PAG and (2) that morphine tolerance will develop more rapidly in rats exposed to MPH during the preweanling period. Male Sprague-Dawley rats will receive daily IP injections of saline (SAL) or MPH (5 mglkg) for 10 consecutive days beginning on PD 11. At 55 days of age, rats will be implanted with a guide cannula aimed at the v-PAG. Following a seven-day recovery period, morphine-induced antinociception to microinjection into the v-PAG will be assessed. Rats will be tested on the hot plate and by tail flick tests with cumulative microinjection of quarter log doses of morphine into the v-PAG (1, 1.8, 3.2, 5.6, and 10 µg/O.4 µl). One day later, tolerance will be induced by two daily microinjections into the v-PAG of either SAL or morphine *(5µg/OA* µl) for two consecutive days. On the following day (PD 65), cumulative doses of morphine will be administered as before to assess the development of tolerance. Morphine dose response curves and the half maximal antinociceptive effect (Dso) will be calculated for hot plate and tail flick tests using non-linear regression.

Homeostatic Synapse-Driven Membrane Plasticity in Cocaine Addiction. ***Department of VCAPP. Yan Dong, Assistant Professor ($35,000).***

Drug-induced functional deviation of nucleus accumbens (NAc) neurons underlies a major pathophysiology of addiction. Homeostatic neural plasticity is a powerful self-correcting mechanism through which neurons use neuroplasticity machinery to functionally compensate "undesirable" cellular alterations and thus stabilizing their functional output. Are there any forms of homeostatic neural plasticity in NAc neurons that may help these neurons regain normal form of homeostatic crosstalk between excitatory synaptic input and intrinsic membrane excitability? In contrast to regulated synapse-driven membrane plasticity, this form of homeostatic plasticity enables NAc neurons to adjust their intrinsic membrane excitability to functionally offset alterations in excitatory synapses. As a consequence, the integrated function of NAc neurons is maintained stably. Our *long-term goal* is to utilize the endogenous homeostatic mechanisms in repairing the cocaine-distorted functional output of NAc neurons. As the first step to attain our long-term goal, the *objective* of this ADA application is to determine the molecular mechanism(s) mediating the synapse-membrane homeostatic crosstalk in

NAc neurons. Our central hypothesis is that the synaptic N-methyl-D-aspartate receptors (NMDARs) detect the strength of excitatory synapses and, in turn, homeostatically regulate the intrinsic membrane excitability of NAc neurons. The *rationale* behind this application is that, once the molecular basis underlying this NAc homeostatic neuroplasticity is defined, more comprehensive studies can be conducted 1) to determine why this homeostatic neuroplasticity fails to restore the normal function of NAc neurons following cocaine exposure, and 2) to develop a homeostasis-based treatment for addiction. Our objective will be achieved by pursing two *specific aims*: 1) determine the NMDAR subunits that mediate the synapse-membrane homeostatic crosstalk; and 2) establish an *in vivo* approach based on synapse-membrane homeostatic crosstalk to repair cocaine-induced depression of intrinsic membrane excitability of NAc neurons. This application is *innovative* because it takes an unprecedented step to characterize a *novel* form of homeostatic plasticity in an addiction-related brain region (NAc), in which no concrete forms of homeostatic plasticity have been demonstrated before. The proposed work is also *significant* because understanding how endogenous homeostatic mechanisms function in NAc will provide significant insights into using the homeostatic mechanism for addiction treatment.

MMP Regulation of Cocaine-Induced Synaptic Plasticity within Nucleus Accumbens Neurons. ***Veterinary & Comparative Anatomy, Pharmacology and Physiology, Yan Dong, Assistant Professor, and Travis Brown, Postdoctoral Fellow.***

A hallmark of addiction is a preoccupation/anticipation of the drug and related cues, which ultimately consumes the individuals' motivation to pursue other rewards. Evidence has accumulated over the last decade demonstrating that drugs of abuse can co-opt synaptic plasticity mechanisms in brain circuits involved in reinforcement and reward. Although many molecular changes occur with acute drug exposure, few are persistent enough to account for the importunate life-long neuroadaptations observed in the nucleus accumbens (NAc) and other related brain regions. In the NAc, we previously showed that cocaine exposure generated nascent, premature excitatory synaptic connections (synapses expressing only functionally stable N-methyl-D-aspartic acid (NMDA) receptors). Given that synapses are the basic connecting units within the neural network, these nascent synapses may represent an ongoing circuitry re-development/re-organization within NAc following cocaine exposure. To become fully functional, these cocaine-generated nascent, premature excitatory synapses must recruit α-amino-3-hydroxy-5-methylisoxazole-propionic acid (AMPA) receptor. Thus, a key unsolved question is whether or how these nascent synaptic connections are matured such that a new, fully functional set of circuits is established. To address this question, this proposal focuses on matrix metalloproteinases (MMPs). MMPs are important extracellular molecules that are upregulated following cocaine exposure, essential for a variety of addiction-related behaviors, and implicated in synaptic reorganization. Based on our preliminary data (see below) as well as published results, we hypothesize

that the newly generated nascent synapses recruit MMPs to the post synaptic density (PSD), thus allowing for the transformation of premature synapse to mature synapse. To test this hypothesis, we will use both electrophysiological and morphological approaches to determine the role of MMPs in the maturation of cocaine-generated nascent synapses in the NAc. This application is innovative because it will be the first study to link generation of new neural circuitry to the development of addiction, which is a novel angle in understanding the neural basis of addiction. The proposed work is also highly significant because it may identify MMPs as potential therapeutic targets for future anti-addiction drug development.

Internal Desynchronization as a Property of Addiction: Hijacking our Biological Clocks with Drugs of Abuse. ***Veterinary and Comparative Anatomy, Pharmacology and Physiology, Heiko T. Jansen, Ph.D., Associate Professor, and David Rector, Associate Professor.***
Drug addiction represents a common problem worldwide with extraordinary negative consequences for society, families, and individuals alike. Accumulating evidence suggests that the propensity for drug seeking, drug relapse, and efficacy of treatment may all be dependent on temporal (e.g., time of day and time of year) variables. Our ongoing research efforts have elucidated an important role of the body's master clock located in the suprachiasmatic nucleus (SCN) in the expression of various drug-seeking behaviors via a temporally regulated process we have coined "reward potential." This process predicts that biological clocks in the SCN play an important mechanistic role in the time of day variation in drug seeking behaviors. However, molecular clocks are also expressed in other brain areas, even in ones known to play direct roles in the etiology of addictive behaviors. To elucidate the importance of clocks in different brain regions to the development of a condition of internal deschyronization, we propose to visualize clock gene expression in two key brain regions, the SCN and ventral tegmental area (VTA) *in vivo* using a transgenic rat model expressing a luciferase-containing clock gene promoter. Transgenic rats will be trained to self-administer cocaine, and the temporal organization of the two clocks monitored during the development of cocaine addiction behaviors. Additional animals will be monitored for clock function during food self-administration trials to discriminate between normal rewarding behaviors and those that ultimately lead to drug addiction. Together, these results will yield entirely novel information about the underlying role of biological clocks in the addiction process.

Alcohol Consumption in a Group Context and its Effects on Group and Individual Cooperation in a Public Goods Dilemma. ***Department of Psychology, Craig D. Parks, Professor & Principal Investigator, Sterling M. McPherson, Graduate Student & Co-Investigator, Kacy Pula, Graduate Student & Co-Investigator***
There is a large gap in the alcohol research literature given nearly all investigations are concerned with the behavior of individuals, while alcohol is most often consumed in some type of group setting. The proposed research

adds to the small but growing literature on behavior in groups under moderate alcohol consumption. This area deserves considerably more attention, given that drinking moderate amounts of alcohol frequently occurs in a social or group setting. The primary goal of this proposal is to further explore how alcohol can affect group processes in a more generalizable situation that mimics real world situations where individuals and groups are asked to decide between selfishness or generosity. Participants will play a public goods game individually or in a three-person group after consuming either alcohol or a placebo. This research mimics the real-world situation of group members having to decide whether to contribute money towards collective gain as opposed to not contributing for individual gain. By examining how a group context impacts the effect of alcohol on cooperation in a mixed motive situation, the proposed project contributes to gaining an understanding of how group processes manifest themselves among intoxicated individuals and what impact this has on decision-making. Specific methods and hypotheses are laid out in detail, along with the benefits to Washington State University and the Alcohol and Drug Abuse Research Program.

Reconsolidation and Disruption of Cocaine-Associated Memories.
Veterinary & Comparative Anatomy, Pharmacology and Physiology, Barbara A. Sorg, Professor.

The ability to disrupt drug-associated memories in drug addicts is important because this disruption is expected to suppress the cycle of relapse to drugs. Drug memories are reactivated during exposure to the drug and drug-related cues, and these memories are thought to undergo reconsolidation, a process that strengthens memories. Conversely, reconsolidation can be disrupted by amnestic agents present during reactivation of the memory, causing the memory to be *weakened.* Thus, even long-term memories may become unstable upon recall if appropriate conditions and amnestic agents are both present. The ability to weaken drug memories suggests that animals or humans may be returned to some level of pre-addicted state, at least regarding the motivation to seek or take drugs. Only one other investigator to date has examined reconsolidation of drug-associated memories in the drug self-administration model. They demonstrated the ability of amnestic agents to disrupt a cocaine-cue-associated memory in cocaine self-administering rats. However, an important question is whether a cocaine relapse in which drug is again paired with the cue would re-establish the ability of the cue to maintain drug-seeking behavior. Moreover, drug-associated memories consist of contextual cues and discrete cues. A gap in our knowledge is that we do not know the extent to which each of these types of drug-associated memories can be diminished using the reconsolidation disruption strategy. Also importantly, we do not know (1) the extent to which a memory weakened by amnestic agents could potentially be strengthened again by a relapse to drug-taking behavior if no amnestic agent is present, and (2) whether manipulations that optimize lability of the memory prior to disruption could be used to produce a more persistent suppression in the wake of a drug relapse. The objectives are to define the

impact of a cocaine relapse after disruption of reconsolidation on 1) cue-induced relapse and 2) context-induced relapse; and 3) in both objectives, to enhance the lability of cocaine memories in an attempt to sustain disruption of these memories. We will use the protein synthesis inhibitor anisomycin to disrupt reconsolidation. *The most compelling reason to address these questions is that most human cocaine addicts will relapse, and without knowledge on the extent to which this relapse may reestablish cocaine-associated memories, we will not be well-positioned to address the next question of how to maximize the disruption of cocaine-associated memories.*

Seattle and Tacoma Community Resident Views of Alcohol Impact Area Policies. ***Social & Economic Sciences Research Center, John Tarnai, Director.***

The proposed study is part of an ongoing evaluation of Alcohol Impact Areas (AlA) in Washington State. This study proposes to assess community opinions and views two years after the implementation of AlAs in Seattle and five years after the AlA implementation in Tacoma. Alcohol Impact Areas are deslqnated by the Washington State Liquor Control Board (WSLCB) at the request of a community, and restrict the sale of single high alcohol content beer and wine products within the area. The purpose of these restrictions is to control and reduce chronic public inebriation and illegal activity associated with alcohol sales or consumption. Surveys of community residents have previously been conducted in both Seattle and Tacoma to assess public opinion prior to or concurrent to the implementation of these AlAs. This proposed study will focus on the public's views after some period of time that the AlA policy has been in place, and is designed to evaluate the effectiveness of the AlA rules and product restrictions based on the views of people who live inside and outside the AlAs. Because there are two different locations, with different lengths of time since the AlA implementation, the results will be particularly useful in addressing the sustainability of AlA policy. This kind of policy has not been attempted elsewhere, and initial findings in Tacoma suggest that the policy is effective at controlling some aspects of chronic public inebriation. This study will provide additional data regarding the effectiveness of the AlA policies in place in Seattle and Tacoma. There is substantial interest among many communities in Washington State and elsewhere in the nation. The WSLCB is very interested in this study and supports this proposal.

Grants Awarded during FY 2010

Sex Differences in Cannabinoid Analgesia: Brain Mechanisms. ***Psychology, Pharmaceutical Sciences. Rebecca Craft, Professor, Ray Quock, Professor and Chair.***

Although there is growing evidence of sex differences in cannabinoid (CB) analgesia, the *mechanisms* by which cannabinoids modulate pain differentially in females vs. males remain unknown. Our *long-term goal* is to improve pain management in women. The *overall objective of this application* is to identify brain mechanisms underlying sex differences in CB antinociception against chronic pain in the rat. Our *central hypothesis* is that sex differences in CB antinociception are due to estradiol enhancement of brain CB_1 and CB_2 receptor density and/or affinity. Behavioral and neurochemical approaches will be used to address the following specific aims: (1) Identify the brain CB receptor types that contribute to sex differences in CB antinociception against chronic pain; (2) Identify sex differences in CB receptor density and affinity in pain-relevant areas of the brain. Experiments under Aim 1 will test the hypothesis that activation of CB_1 and CB_2 receptors in the brain leads to greater antinociceptive effects of cannabinoids in female compared to male rats. Receptor-selective antagonists will be administered intracerebroventricularly *(i.c.v.)* to determine the contribution of brain CB_1 and CB_2 receptors to sex differences in anti-allodynic and anti-hyperalgesic effects of the CB agonist ~9-tetrahydrocannabinol (THC), using an animal model of chronic inflammatory pain. Using radioligand binding techniques, Aim 2 will test the hypothesis that CB_l and CB_2 receptor density/affinity in pain-relevant areas of the brain is greater in females compared to males. The results of these studies will provide a strong basis for future research elucidating the cellular and molecular mechanisms underlying sex differences in and gonadal hormone modulation of CB antinociception. Our findings will contribute to the development of CB analgesics that may be particularly useful in women.

Impact of Helminth Treatment on Smoking Behavior among Aka Foragers and Ngandu Farmers. ***Department of Anthropology, Washington State University, Vancouver. Edward H. Hagen (P.I.), Barry S. Hewlett (Co-P.I.).***

Current neurobiological theory of drug use is based on the observation that all addictive drugs interfere with reward processing, enhancing drug seeking and consumption, whereas current theory of drug origins views almost all major drugs of abuse as plant neurotoxins that evolved to punish and deter herbivores. According to this latter view, plants should not have evolved compounds that reward or reinforce plant consumption. Mammals, in turn, should not have evolved reinforcement mechanisms easily triggered by toxic substances. Situated in an ecological context, drug reward is a paradox. This project will test one potential resolution of the paradox, namely that humans, like other animals, might have evolved to counter-exploit plant neurotoxins. The plant defensive chemical nicotine, in particular, is an effective anthelmintic. Two rural African populations, the Aka and Ngandu,

have high levels of helminth infection yet little access to Western anti-worm medicines, and so might be motivated (consciously or unconsciously) to increase consumption of certain readily available substances such as tobacco, which is heavily used in both groups. To determine whether human helminthiasis increases smoking and other forms of tobacco consumption, a double-blind, placebo-controlled clinical trial will be conducted in which a random 50% of the sample will then be treated with a commercial anthelminitic, and the remaining sample will receive placebo. Compared to the placebo control group, the group treated for helminth infections is predicted to exhibit reduced smoking behavior, as indexed by salivary cotinine, a nicotine metabolite.

Adolescent and Young Adult Responses to Television Ads for Alcoholic Beverages: A Receiver-Oriented Message Analysis. *Edward R. Murrow College of Communication. Douglas Blanks Hindman, Associate Professor, Erica Austin, Professor. Bruce Pinkieton, Professor, Stacey Hust, Assistant Professor.*

This project is designed to examine age and situational differences in receivers' (8^{th} to 11^{th} graders versus college students) interpretations of televised alcoholic beverage advertising, to compare receiver interpretations of televised alcoholic beverage advertising to the analysis of the same ads by trained content coders, to examine the association between receivers' perceptions of content in televised alcoholic advertising content and their alcohol-related beliefs and expectancies, and to establish the reliability of instruments designed to measure specific elements of industry codes for responsible advertising and marketing. The members of the study team intend to apply the findings and research measures produced by the present study toward grant applications that support the establishment of new methods in social science research and for multi-site and statewide efforts directed at strengthening youth and young adult media literacy regarding televised alcohol commercials.

Ambiguous Advertisements: Effects on Beliefs and Behavioral Intentions Related to Alcohol Consumption. Edward R. *Murrow College of Communication.* Stacey J.T. Hust, Assistant Professor, Jessica K. Fitts, Graduate Student

The alcohol industry is charged with advertising and promoting products that are simultaneously considered beneficial and harmful. In an attempt to appropriately advertise alcohol, the industry has established codes of responsible advertising practices, largely to ensure that advertisements do not appeal to underage drinkers and do not encourage abuse of the alcohol. Yet scholars have identified that some advertisements do not adhere to these guidelines, even though they do not clearly violate the guidelines. Instead, these ambiguous ads blur the guidelines that ensure alcohol advertisements are not especially appealing to underage youth. The purpose of this project is to explore the effects of the ambiguous alcohol advertisements on viewers' beliefs about alcohol advertising and alcohol consumption. Considering that scholars have posited that ambiguous

advertisements allow advertisers to hint at restricted content that would likely appeal to underage drinkers, this study also considers whether ambiguous ads affect underage college students differently than of-age college students.

A 3 x 2 pre- and post-test experiment will be used to examine the role of ambiguous content in alcohol advertising. Six hundred participants (300 underage students and 300 of-age students) will be randomly selected from college locations in the Palouse area including Washington State University and the University of Idaho and will be offered a $10 incentive to participate in the project. Participants will then be randomly assigned to one of three conditions (ambiguous advertisements, unambiguous advertisements, and a control) so that there are 200 participants in each condition with an equal mix of people less than 21 years of age and of legal drinking age in each condition.

Two hundred participants will view ambiguous advertisements, 200 will view advertisements that have been digitally altered so that the content is no longer ambiguous, which means the ads will be modified so the questionable content is replaced with content that clearly meets the regulatory guidelines, and 200 people will serve as a control group by viewing advertisements unrelated to alcoholic beverages. The experimental stimuli will be pretested in focus groups so the advertisements look realistic and so it can be determined that the content of the ambiguous advertisements has been adequately altered.

Regulation of Addiction-Related Behaviors by Sleep Deprivation.
Department of Veterinary and Comparative Anatomy, Pharmacology, and Physiology. Jim Krueger, Professor, Yanhua Huang, Postdoctoral Fellow.

Sleep profoundly affects emotional and motivational states. Sleep disturbance is a prominent co-morbidity in almost all emotional and motivational disorders including drug addiction. Clinical studies also show that people with insomnia are more prone to drug addiction. Despite such apparent significance, little is known about how sleep disturbance alters the function of brain regions that control addiction-related emotional and motivational states. This application focuses on this important yet under-explored research area; the proposed research attempts to characterize how sleep deprivation (SD) regulates both the excitatory and inhibitory synapses as well as the intrinsic membrane properties of neurons within the nucleus accumbens (NAc), a brain region that gates emotional and motivational outputs. Malfunction of the NAc contributes to several pathological emotional and motivational states, such as drug addiction, anxiety, and depression. Although clinical statistics show a clear correlation between the intensity of sleep disturbance and the degree of these emotional disorders, it is not understood how the NAc neurons are altered in sleep-disturbed subjects. By characterizing the effect of SD on the synaptic transmission and the membrane properties of NAc neurons, the proposed work will provide a comprehensive mechanistic understanding about how sleep disturbance affects the function of the NAc. The central hypothesis guiding the proposed

research is that SD differentially regulates excitatory and inhibitory synaptic transmission as well as alters the membrane excitability of NAc neurons, resulting in distorted functional output of NAc neurons. This hypothesis will be tested by pursuing three specific aims: 1) characterize SD-induced synaptic adaptations in NAc neurons; 2) characterize SD-induced membrane adaptations in NAc neurons; and 3) explore the impact of SD on NAc-based emotional and motivational behaviors. The proposed work is closely relevant to NIH's mission in that the expected outcome will provide essential understanding about how sleep and sleep disturbance regulate a key brain region that is critically involved in a large number of emotional and motivational disorders.

Neurocircuitry Plasticity after Active Cocaine Seeking. ***Veterinary and Comparative Anatomy, Pharmacology and Physiology. Brian Lee, Graduate student.***

Purpose of this Application:

The primary purpose of this application is to seek continued support for my ongoing graduate research and to reapply for a pre-doctoral fellowship from NIH. Thanks to the support from ADARP, my research has been funded since last year with the pre-doctoral award. The proposal, which I submitted last year and still remains valid, is a three-year research plan, covering all the intended research for the rest of my graduate studies at WSU. As indicated in the last submission, proposing this three-year plan will help the committee to evaluate my research as a whole rather than being segmented each year. The current application aims to report to the review committee the progress I made over the past funding period and to apply for support for next year.

Over the past funding period, I have accomplished about 1/3 of the research proposed in the ADARP application (see below), published one co-author paper and submitted one first author paper (under review), and submitted an NIH application for a pre-doctoral award. Indeed, it is the support from ADARP that encouraged me for my first NIH submission. Although my application was not funded, the priority score (38) and comments from the review committee are highly promising. I will revise my proposal and submit again early next year.

For the next couple of years, I will continue doing my thesis work in Dr. Yan Dong's laboratory, co-advised by Dr. Barb Sorg. Although there is no doubt that Drs. Dong and Sorg or the department will support my graduate study and research continuously, I strongly believe that applying for the ADARP grant is an excellent opportunity for me. This will provide an objective evaluation of my scientific ability among experienced WSU investigators. It is also an honorable recognition for my early scientific career.

Two specific aims, slightly modified from previous submission, are elaborated below. I will accomplish aim two during the first two months and hope to accomplish aim one within the funding year. Again, the reasons that I propose two aims are: 1) to demonstrate to the review committee that the proposed research is comprehensive, 2) to provide an effective outline for

the review committee about the future direction of my research, and 3) to provide me with valuable advice for my own studies.

Alcohol and Drug Use among Transgender Youth. ***Human Development, Sociology. Jenifer K. McGuire, Assistant Professor, Meredith Williams, Graduate Student, Sociology.***

Transgender adolescents are at increased risk for a variety of internalizing and externalizing behaviors, including alcohol and drug use. The pathways that lead to increased risk taking among this population are not well understood; however, links between contextual risk factors and adolescent drug use have been established for Lesbian, Gay and Bisexual (LGB) populations. The proposed study examines alcohol and drug use among transgender youth by conducting interviews with transgender adolescents and a parent where available. We begin with an examination of social systems that may provide risk or protective factors, with a particular focus on family relationships and a secondary focus on other social systems such as schools, medical establishments, peers, work and religious contexts. Links between contextual risk and protective factors and adolescent alcohol and drug use provide the foundation for this investigation. We seek to interview 80 parent-adolescent pairs. Funds are requested for travel (7 trips to collect data from 10-15 families on each trip), subject compensation, and research assistant costs for transcription, coding, and analyses of the data.

Cost-Benefit Analysis of a Community-Based, Alcohol Use Prevention Program. ***Department of Human Development. Casey R. Suter, Graduate Student/Teaching Assistant, Advisor/PI: Dr. Laura G. Hill.***

Abstract: Economic evaluations of prevention programming provide policymakers with critical information on the true costs and benefits of preventative program. The objective of the proposed study is a cost-benefit analysis of a community-based, alcohol use prevention program in the state of Washington. Detailed cost information will be collected from program participants, facilitators, and site-coordinators. Programs operating throughout the state will be included in the study to provide representative estimates of program functioning. Effectiveness data from the randomized clinical trial of the program combined with national estimates on the cost of alcohol disorders will allow for calculation of benefit-cost ratios and net benefit in 2009 dollars.

A Multi-method Pilot Study Exploring Relational Health of Adolescent Women in Inpatient Chemical Dependency Treatment*. College of Nursing. Roxanne Vandermause, Assistant Professor, Merry Armstrong, Associate Professor, Kris Miller, Associate Professor.*

Adolescent substance use (SU) endures as a priority concern to communities. The increasing risk of SU in young women is a rising concern. Therefore, it is important to conduct research that emphasizes protective factors in the mental health and positive development of female adolescents. The importance of relationships and "connectedness" as aberrant behavior protective factors has been validated extensively in the literature of several

disciplines over the past decade. Less well described are the components and qualities of relational engagement among adolescents involved in substance abuse treatment.

Further, *how* relationships affect SU treatment success remains unclear and is a compelling question for research. This multi-method study will use both quantitative and qualitative approaches to accomplish a broad analysis of the nature of relational health among two groups of 16-17 year old girls, those enrolled in an inpatient substance abuse treatment program and a comparison group of 16-17 year old girls attending high school in the same community as the treatment center. The specific aims of the study are to: 1) Assess the usefulness of the Relational Health Indices (Liang, et. aI., 2002) in measuring differences between groups (16-17 year old girls in an inpatient SU treatment program and girls in the community without known SU problems) in three dimensions and three domains of supportive relationships, 2) Determine common patterns and meanings of the relational experiences of 16-17 year old girls in SU treatment, from in-depth hermeneutic interviews, and 3) Generate a comprehensive analysis of the dimensions, domains, patterns and meanings of supportive relationships among 16-17 year old girls in SU treatment, comparing selected findings. Researchers will analyze survey data (RHI and demographic questions) from 30 girls admitted to Daybreak, an in-patient chemical dependency treatment facility, and data from extended in-depth interviews from 15 of these girls, collected within 2 weeks of admission. The survey will be repeated 1 week before discharge and 3 months after discharge. Similar index survey data will be collected once from a matched group of girls attending high school, who have not exhibited SU problems. The purpose of this exploration is to determine the essential nature of relational experiences in girls in SU treatment, as revealed through hermeneutic phenomenological analysis, and to measure and explicate specific dimensions and domains of relational health that can be targeted for intervention. *The hermeneutic analysis of in-depth interviews provides the necessary complement to the measured dimensions and domains of the RHI, providing an exploration of meaning that cannot be apprehended using existing tools.* Results will inform an expanded study to further explore the relational domains and dimensions of significance and to assess the therapeutic impact of treatment on these indices. Results will be foundational to the overall goal of our program of research: improving interventions and age and gender-responsive treatment strategies for adolescent substance users.

Sex Differences in Antinociception and Sedation Following Central Administration of D9-Tetrahydrocannabinol. ***Department of Psychology. Alexa Wakley, Graduate Student. Mentor: Rebecca Craft, Ph.D.***

Previous research has shown that systemically administered cannabinoids produce greater antinociceptive and sedative effects in female compared to male rats. There is also some evidence for sex differences in the brain endocannabinoid system. Therefore, the aim of this study is to determine whether sex differences in cannabinoid effects can be attributed to

supraspinal mechanisms. This lab has previously demonstrated that systemically administered D9-tetrahydrocannabinol (D^9-THC) produces sex-dependent effects in antinociception and sedation that can be attributed to pharmacokinetic factors and to estradiol. The proposed experiments will test the hypothesis that females are more sensitive than males to D9-THC induced antinociception and sedation following central drug administration *(i.* c. *v.).* Results supporting this hypothesis would suggest that sex differences in behavioral effects of cannabinoids could be attributed to sex differences in supraspinal mechanisms. The proposed studies will also determine if estradiol modulates *i.c.v.* D9-THC-induced antinociception and sedation in females. The present study will provide a foundation for examination of specific supraspinal mechanisms that may be involved in sex differences in cannabinoid effects.

Role of Kappa-Opioid *I* Dynorphin Systems in Negative Affective States Produced by Alcohol*. Department of Psychology. Brendan M. Walker, Assistant Professor.*

A fundamental characteristic of excessive alcohol use is the comorbidity of alcohol dependence and disorders of affect. Self-medication of these negative affective states likely contributes to excessive alcohol use and relapse. Negative affective states produced by chronic alcohol exposure result from neuroadaptations in motivational and affective neurocircuitry that are not yet understood. The principal investigator's *long-term goal* is to identify novel, effective pharmacotherapeutic targets for the treatment of alcoholism. The *objective of this application,* which is the next step in pursuit of that goal, is to understand the neuroadaptations that occur in response to chronic alcohol exposure and contribute to attenuated motivational and affective states. The *central hypothesis* is that compensatory neuroadaptations within opioid peptide systems alter positive and negative affect. The *rationale* for the proposed studies is that identification of speciflc opioid targets will enable the development of pharmacotherapies designed to alleviate motivational and affective symptoms produced by alcohol dependence. The hypothesis will be tested by pursuing the following two *specific aims:* 1) Evaluate the role of dynorphin systems in negative affective behaviors produced by alcohol dependence using two separate animal models and 2) further characterize negative affective behaviors during acute and protracted withdrawal using an extended dependence induction period. These aims will use animal models of affective behavior to allow for the systematic investigation of neurotransmitter systems and neurocircuitry that contribute to altered motivational and affective states produced by chronic ethanol exposure. These specific aims will collectively help to identify important neuroadaptations that result from chronic alcohol exposure and provide much needed information regarding the neurocircuitry involved in altered affective systems. Such a *contribution is significant* because it will help to develop pharmacotherapeutic targets for the treatment of alcoholism that focus on the removal of attenuated negative affective states, a strategy that should greatly increase medication compliance and decrease rates of relapse.

The Bioavailability of Two Different Formulations of Intranasal (IN) Naloxone. ***Department of Pharmacotherapy. John R. White, Jr., Professor.***

Death rates due to drug overdose have escalated dramatically over the past two decades in the United States and in Washington State. Much of this increase is due to the increased use and availability of potent narcotic analgesics (ex. Oxycontin, methadone, heroin, and others). The definitive treatment for narcotic analgesic overdose is intravenous (IV) naloxone. However, there are several problems associated with the use of IV naloxone, the most salient of these being the time lag between recognition of the overdose and treatment by a health care provider. Additional problems include difficulty cannulating the patient, potential spread of infectious diseases (ex. Hep B, Hep-C, HIV) due to accidental needle stick, and reticence on the part of bystanders to contact 911 (with illicit drug use). In response to this, researchers and health care professionals have attempted to circumvent these problems with the use of intranasal (IN) naloxone. Currently, several programs across the United States support the use of IN naloxone for the infield treatment of narcotic overdose. Following this trend, the Washington State Medical Association adopted a resolution supporting the dissemination and use of IN naloxone on September 28, 2008. However, recent studies have suggested that the rescue rates and the bioavailability of the currently used formulation of IN naloxone do not support its widespread use. In an attempt to rectify this problem, this study would evaluate the pharmacokinetics and the bioavailability of two novel IN formulations of naloxone and compare them to the conventional IV formulation. The results of this study will contribute to the understanding of the treatment of narcotic overdose with IN naloxone and may provide dose/concentration information regarding a more appropriate IN formulation.

Suppression of Cerebral Microglial Activation Attenuates Methamphetamine-induced Hypersomnolence. ***Department of Veterinary and Comparative Anatomy, Pharmacology and Physiology and WWAMI Medical Education Program, Jonathan P. Wisor, Assistant Professor.***

Hypersomnolence occurring as a consequence of methamphetamine withdrawal may result in dose escalation and increase the likelihood of relapse among methamphetamine abusers. Methamphetamine exposure results in increased levels of pro-inflammatory cytokines and other markers of microglial activation in the brain. Cerebral levels of pro-inflammatory cytokines are known to increase the propensity for sleep. It is thus likely that effects of methamphetamine on sleep are mediated by microglial activation. Yet, the degree to which microglial activation and the resulting release of pro-inflammatory signals underlie changes in sleep subsequent to methamphetamine exposure remains to be determined. Using rodent models, we will determine the degree to which hypersomnolence subsequent to methamphetamine exposure is dependent on microglial activation. *Our working hypothesis* is that microglial activation is required for the hypersomnolence that occurs after methamphetamine exposure. *We will test*

this hypothesis by measuring the effect of methamphetamine on electroencephalographically-defined sleep in laboratory mice in which brain microglial activation is suppressed by genetic and pharmacological manipulations. This project will ascertain whether microglial activation is essential for the hypersomnolence that occurs in association with methamphetamine exposure. The proposed experiments will provide valuable preliminary data for a *planned National Institutes* of *Health RO1 application* that proposes to demonstrate the requirement for pro-inflammatory effector mechanisms in regulating methamphetamine-induced changes in sleep and their neurochemical underpinnings.

Grants Awarded during FY 2011

The Role of the Adenylyl Cyclase Pathway in Morphine Tolerance.
Department of Psychology. Erin Bobeck, Graduate Student. Mentor: Michael Morgan, Ph.D.

Opioids, such as morphine, are the most commonly prescribed drugs to treat chronic pain. However, the development of antinociceptive tolerance limits their effectiveness over time. Many cellular changes have been implicated in the development of morphine tolerance. *In vitro* studies have shown that chronic morphine pretreatment causes upregulation of adenylyl cyclase and an increase in GABA release within the ventrolateral periaqueductal gray (vlPAG). The vlPAG is a key component of a descending pain modulatory pathway and is known to contribute to morphine antinociception and tolerance. The objective of the proposed studies is to expand on these *in vitro* studies to determine the role of adenylyl cyclase in causing morphine tolerance within the vlPAG of intact rats. If the adenylyl cyclase pathway is important for tolerance, it is hypothesized that inhibition of adenylyl cyclase would prevent morphine tolerance and the enhanced GABA release. Our preliminary results indicate that repeated microinjections of an adenylyl cyclase activator (NKH 477) cause a rightward shift in the morphine dose-response curve as what is seen with the development of morphine tolerance. In order to assess the behavioral effects of changes in GABA release *in vivo*, the competitive $GABA_A$ antagonist, bicuculline, will be administered following repeated morphine or inhibition of the adenylyl cyclase pathway. Given that there are many messengers within this pathway, Specific Aim 1 will determine if inhibition of two main components (adenylyl cyclase and Protein Kinase A) alters the development and expression of morphine tolerance. Specific Aim 2 will evaluate the role of adenylyl cyclase in increasing GABA release within the vlPAG. The results of these studies will reveal whether morphine tolerance causes an increase in GABA release via upregulation of adenylyl cyclase that attenuates morphine-induced antinociception.

Ethanol Dependence and Impulsive Responding in Rats. Department of Psychology. *Seth M. Davis, Graduate Student. Mentor: Brendan Walker, Ph.D.*

Previous research has shown that acute exposure to ethanol increases multiple facets of impulsive responding in rats. Evidence suggests that the transition from a non-dependent to a dependent state corresponds to a shift from impulsivity to compulsivity; however measures of impulse control with regard to ethanol dependence have largely been ignored. The aim of the current study is to identify cognitive/behavioral differences between ethanol dependent and non-dependent animals and to identify precursors that may lead to a better understanding of alcoholism in humans. The central hypothesis is that animals dependent on ethanol will exhibit an inability to suppress motor responses in a stop-signal paradigm and also show an increased choice of a small immediate reinforcer versus a larger delayed reinforcer in a delay discounting paradigm compared to non-dependent controls. Changes in both the stop-signal reaction time and delay discounting tasks would both be suggestive of an overall lack of impulse control. The proposed studies will also observe changes in impulsive responding from multiple time points, from acute to protracted ethanol withdrawal in order to better characterize changes in regulatory systems. Lastly, the use of pharmacological treatments that have been shown to reduce self-administration in dependent animals will be explored as to their effects on the behavioral component of impulsivity.

Cocaine and the Neuronal Metabolomics of Tyrosine and Glucose by Ion Mobility Mass Spectrometry. *Department of Chemistry. Herbert Hill and Jim Schenk, Professors of Chemistry*

One of the PIs (Hill) has recently developed a high resolution ion mobility spectrometer which he has interfaced to a time-of-flight mass spectrometer. Ion mobility spectrometry appears to have potential for application to drug abuse research and has been designated by the National Institutes of Drug Abuse as one of the most promising analytical methods for research on drug metabolism. In this proposal, funds are requested for a pilot project to determine if Hill's high resolution ion mobility mass spectrometer can be used to quantify and identify metabolites associated with drug exposure. The model system that will be used in this project is the effect on the glucose metabolome of cocaine exposure. Results of recent reports in the literature suggest that administration of cocaine alters the metabolism of glucose in areas of the brain containing dopamine, norepinephrine, and serotonin transporters and that these transporters are involved in the effects of cocaine. One impediment to seeing the complete picture with regard to these (and other) multiple systems is the analytical chemical challenge of making measurements of multiple neurochemical systems simultaneously. We propose to use ion mobility mass spectrometry (IMMS) to simultaneously measure the glucose metabolome as well as that of tyrosine in dopaminergic areas (striatal, nucleus accumbens, and medial prefrontal cortex) and norepinephrine and serotonin areas (the thalamic

nuclei) of the rat. We shall first optimize analytical procedures for obtaining information from dissected tissues about the metabolomes, show that differences can be observed following pharmacological manipulations of synthesis and metabolism, and finally show what effects acute and daily doses of cocaine have on these metabolomes.

An Analysis of the Reinforcing Value of Cigarettes and e-Cigarettes among Nicotine-Dependent Cigarette Smokers using the Multiple Choice Procedure. ***Program of Excellence in the Addictions & Program of Excellence in Rural Mental Health and Substance Abuse Treatment,College of Nursing. Donelle N. Howell, Ph.D., Jennifer M. Cameron, Ph.D.***

Electronic cigarettes (e-cigarettes) have been marketed as devices capable of reducing the toxic effects of cigarette smoking and helping nicotine-dependent smokers overcome addiction (Pauly, Li, & Barry, 2007). Manufacturer claims that the e-cigarette can be used as a safer alternative to cigarette smoking or as an effective means of smoking cessation have yet to be fully evaluated by the FDA (Wollscheid & Kremzner, 2009). To date, only three laboratory studies on e-cigarettes have been conducted that provide initial data on the physiological and subjective effects of e-cigarette use. The next logical step in e-cigarette research is a laboratory study designed to evaluate the reinforcing value of e-cigarettes. The proposed study will use the Multiple Choice Procedure (MCP; Griffiths, Troisi, Silverman, & Mumford, 1993) to evaluate the reinforcing value of e-cigarettes among nicotine-dependent cigarette smokers when compared to money or use of their usual cigarette brand. Participants will complete two unrestricted smoking sessions (one with cigarettes and one with e-cigarettes) and three MCP sessions where they will choose between (1) a cigarette and money, (2) an e-cigarette and money, and (3) a cigarette, an e-cigarette, and money. Subjective and physiological ratings of e-cigarette and cigarette effects as well as qualitative reports of smoking experience will also be obtained. Results of this pilot study will be used to inform future behavioral (e.g., contingency management analog studies) and pharmacological studies with e-cigarettes among nicotine-dependent cigarette smokers, cigarette smokers who are currently attempting to stop smoking, and current e-cigarette smokers.

Homeostatic Dysregulation in Nucleus Accumbens. ***Veterinary & Comparative Anatomy, Pharmacology and Physiology. Masago Ishikawa, Research Assistant Professor.***

Several forms of homeostatic neuroplasticity have been characterized in different brain regions, all of which act to stabilize the overall functional output of the neurons toward their prior "set-point." Nucleus accumbens (NAc) neurons play a central role in gating/regulating emotional and motivational behaviors including craving and seeking drugs of abuse; drug-induced functional alterations of NAc neurons underlie a major

pathophysiology of addiction. Our recent work demonstrates a novel form of homeostatic crosstalk between excitatory synaptic inputs and intrinsic membrane excitability in NAc neurons. Through this homeostatic plasticity, NAc neurons adjust their intrinsic membrane excitability in response to prolonged changes in excitatory synaptic inputs such that the integrated neuronal output may remain stable. Our *long-term goal* is to determine the potential of homeostatic plasticity-based approach for correcting drug-induced cellular alterations, thus possibly providing a novel therapeutic strategy for the anti-addiction treatment. To accomplish this goal, we first need to clarify two critical points: 1) what molecular substrates mediate and regulate the synapse-membrane homeostatic crosstalk in NAc neurons; and 2) what role does homeostatic plasticity play in cocaine-induced functional alterations in NAc neurons. This grant application is designed to obtain these two specific sets of knowledge, which will serve as a technical and theoretical foundation for our subsequent application for more comprehensive experimentation. The *central hypothesis* that guides our current research is that synaptic NR2B-containing N-methyl-D-aspartate receptors (NMDARs) mediate the excitatory synapses-to-membrane homeostatic plasticity. This application is *significant* because it will provide a well-defined molecular basis for an endogenous homeostatic mechanism in the NAc neurons; the expected results will provide an essential conceptual and technical footstone for our subsequent application in determining the therapeutic potential of the endogenous self-correcting mechanisms for treating drug addiction.

Molecular Mechanism of the Lethal Arrhythmic Effects of Cocaine.
School of Molecular Biosciences and Department of Chemistry.
ChulHee Kang, Professor and James O. Schenk, Professor.

Cocaine use in the United States continues to be a serious problem; as many as 19% of Americans have used cocaine. In addition to many systemic complications due to both acute and chronic uses, cocaine intoxication is the most frequent cause of drug-related death and emergency room visits in the US, greatly accelerating cardiovascular disease and initiating sudden cardiac death. However, the underlying molecular mechanism for the devastating cardiotoxicity of cocaine has not been clearly elucidated. A slight functional alteration in the cardiac sarcoplasmic reticulum (SR) is enough to cause those serious pathophysiological problems. The main SR proteins responsible for the cardiac excitation-contraction coupling are the Ca^{2+} transport ATPase, the Ca^{2+} storage protein calsequestrin (CSQ), the Ca^{2+} release channel (RyR) and several regulatory proteins. Our preliminary data indicate that cocaine and certain classes of related compound drugs, which have been associated with cardiotoxic effects, bind cardiac CSQ, warranting further systematic study. In addition, cocaine binding to CSQ results in a significant disruption of Ca^{2+} binding capacity of CSQ. The physiological and biomedical relevance of this is very high and provides a compelling case for the continuation of our systematic approach written in this proposal. Our hypothesis, "cocaine binds CSQ and alters the normal Ca^{2+} regulation in SR," will be further strengthened by multidisciplinary approaches, biophysical, biochemical, and electrophysiological methods. Characterizing and understanding the effects of

cocaine will not only reveal the underlying cause of lethal arrhythmia, but will also help us to obtain a long-term research support from NIH. Revealing the molecular mechanisms of cardiac adverse effects of cocaine and many other drugs are the long-term goals of our research.

Cultural Models, Patterns of Smoking, and Acculturation Among Aka Foragers and their Ngandu Farming Neighbors. ***Department of Anthropology. Casey Jordan Roulette, Edward H. Hagen, and Barry S. Hewlett***

Tobacco and similar plants are regularly consumed by peoples the world over despite their negative health effects. Aka forest foragers of the Central African Republic smoke two different tobacco products: what Aka call bangaya (Nicotiana sp., Solanaceae), a tobacco plant grown locally by Ngandu farmers; and manufactured cigarettes, often called blancs. Aka also smoke tunga, leaves of Polyalthia suaveolens (Engler and Diels) (Annonaceae), a forest tree. Collectively these are referred to as ndako (things one smokes). The proposed research will examine the cultural and demographic factors involved in tobacco use behaviors among Aka forest-foragers and their Ngandu trading partners. The relationship between the Aka and the Ngandu, and of acculturation in particular, will be considered in order to assess its impact on patterns of tobacco use and associated health problems.

Pills Anyone? An Exploratory Study of College Men's and Women's Opportunities and Motivations for Non-Medical Prescription Drug Use. ***Department of Sociology. Jennifer Schwartz, Ph.D., Kristin A. Cutler, PhD. Candidate***

National surveys on substance use indicate that the prevalence of non-medical prescription drug use is now greater than the prevalence of illicit drugs other than marijuana (National Survey on Drug Use and Health, 2005, 2008). Of the persons misusing prescription drugs, young adults, aged 18-25 report the highest prevalence of misuse, with males and females misusing these drugs at comparable rates. This absence of a gender-gap in the misuse of prescription drugs runs counter to data on the misuse and abuse of illicit drugs (e.g., cocaine, ecstasy and heroin) and on problem alcohol use which indicate that men use and abuse these substances at a much higher rate than women. Studies on prescription drug use also indicate that being a college student is a risk factor for prescription drug abuse and misuse and show that on the most "prescription prone" college campuses 1 in 4 students are misusing prescription drugs (McCabe, Boyd, and Teter, 2006). Motivations underlying non-medical prescription drug use are varied—including pain relief, better sleep, better focus, a quicker high, and experimentation—but have yet to be sufficiently explored using qualitative methodological techniques. I, therefore, propose an in-depth study that explores the motivations underlying non-medical prescription drug use. My analysis will be informed by social learning theories that emphasize the importance of learned motives and techniques of acquiring and appropriately using prescription drugs. It will focus on identifying gender similarities and

differences in key aspects of the "context of offending." This includes reasons for using prescription drugs, opportunities and methods for obtaining these drugs, diversion efforts, and poly-drug use. I plan to employ qualitative methodological techniques in the form of semi-structured, open-ended interviews with individuals 18-25 years of age attending Washington State University.

Physiological and Subjective Effects Associated with Nicotine-Containing Hookah Smoking. ***College of Nursing. Kawkab Shishani, PhD, BSN, Donelle Howell, PhD.***

Although the use of cigarettes has declined, the use of other tobacco products has remained steady. Hookah (waterpipe) smoking is the most common form of tobacco smoking after cigarettes in the U.S. (Eissenberg, Ward, Smith-Simone, & Maziak, 2008; Primack et al., 2008). Hookah smoking is growing rapidly in the U.S., and in particular, is becoming increasingly popular among young adults (American Lung Association, 2007). One concern is that the intermittent, but heavy hookah use over the time may lead to later dependent use (via increased hookah use or the transition to cigarette smoking) or be associated with other significant health risks. To date, very few studies have been conducted on hookah smoking, and with few exceptions (Eissenberg & Shihadeh, 2009), the majority of studies have been conducted in foreign countries. Furthermore, to the best of our knowledge, no studies have evaluated intermittent hookah users. The purpose of the current proposal is to conduct a rigorous pilot test of the physiological and subjective effects related to hookah smoking in frequent, nondependent hookah users. Results from this pilot study will be an important first step in furthering research efforts examining the risks of hookah smoking.

Mechanism of Alcohol Regulation of NKT Cells in Melanoma-Bearing Mice. ***Department of Pharmaceutical Sciences. Hui Zhang, Ph.D.***

Alcohol is a well known immunosuppressor. Chronic alcohol consumption has been associated with increases in the incidence of cancer and decrease in the survival of cancer patients. The immune system plays an important role in tumor immunosurveillance and the control of tumor growth and progression. The effect of chronic alcohol consumption on tumor immunity is an underexplored area of research. Our previous data indicate that long term alcohol consumption decreases the survival of mice inoculated with B16BL6 melanoma and that the decrease in survival is related to loss of effective anti-tumor immune responses. Our long-term goal is to find ways to enhance the anti-tumor immune responses in order to extend survival. Cancer immunotherapy is a promising approach being explored to extend the survival of cancer patients. However, lack of knowledge regarding the basic mechanisms that inhibit the beneficial immune responses elicited by tumors and specifically how alcohol facilitates the decline of these immune responses hampers the development of immunotherapeutic approaches to treat cancer in general and also in relation to high alcohol consumption. Our long-term goal is to understand how chronic alcohol consumption modulates anti-tumor

immunity in established tumors. The objective of this application is to determine how chronic alcohol consumption induces natural killer (NK) T cells in melanoma-bearing mice and how these cells regulate anti-tumor immune responses. The central hypothesis of this application is that chronic alcohol consumption increases NKT cells in melanoma-bearing mice by enhancing the production of tumor-derived factors. We further hypothesize that these NKT cells inhibit anti-tumor immunity by producing T-helper 2 cytokines and negatively regulate dendritic, NK and CD8+ T cell responses. To test the central hypothesis and accomplish the objective of this application, the following two specific aims will be pursued: Specific aim 1: Determine the origin of increased NKT cells in the peripheral blood from alcohol-consuming, B16BL6 melanoma-bearing mice. Specific aim 2: Determine the biological function of the increased NKT cells with regard to their cytokine profile. The completion of the research proposed in this application will not only greatly fill the gap between the effects of alcohol consumption on tumor immunity and tumor immunotherapy, but also will lay the foundation of continued research in this area. The identification of the factors that induce NKT cells in tumor-bearing mice will allow us to study the precise mechanism of how alcohol consumption combined with melanoma regulates NKT cell function, and subsequently other tumor immune responses. Identifying these factors will also allow for the selection of appropriate targets that regulate NKT cell function and for the future development of immunotherapeutic agents to treat alcoholics with cancer. Thus, this project will fundamentally advance the fields of NKT cell research, tumor immunology, and immunotherapy.