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

Fiscal Years 2012, 2013, and 2014

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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 greater than a 9:1 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 79% 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 two 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

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. 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 $350,000 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, ADARP carries out the following activities:

1. **Funds research, especially pilot grants. 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
Nursing
Pharmaceutical Sciences
Pharmacotherapy
Pharmacy Practice
Political Science/Criminal Justice
Psychology
Sleep and Performance Research
Social and Economic Sciences Research Center
Sociology
Speech and Hearing Sciences
Veterinary and Comparative Anatomy, Pharmacology and Physiology (changed name to Integrative Physiology and Neuroscience in 2013)
Veterinary Microbiology and Pathology
Wellness Center
Washington Institute for Mental Illness Research and Training (WIMIRT)
WWAMI Medical Sciences

   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.** ADARP has provided start-up funds to augment departmental start-up packages for substance abuse researchers ten times since 1993, and amounts have ranged from $17,000 to $100,000 (average $54,325).

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.** ADARP has collaborated with departments from across campus in the following areas:

   a. **Start-up funds.** ADARP has contributed to departmental start-up packages for top-notch faculty recruits in Psychology, Pharmaceutical Sciences, and IPN (formerly 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.** ADARP has collaborated with the Wellness Center, the Murrow College of Communication, Psychology, VCAPP, and Pharmaceutical Sciences to bring in speakers beneficial to many faculty and students.

Return on Investment

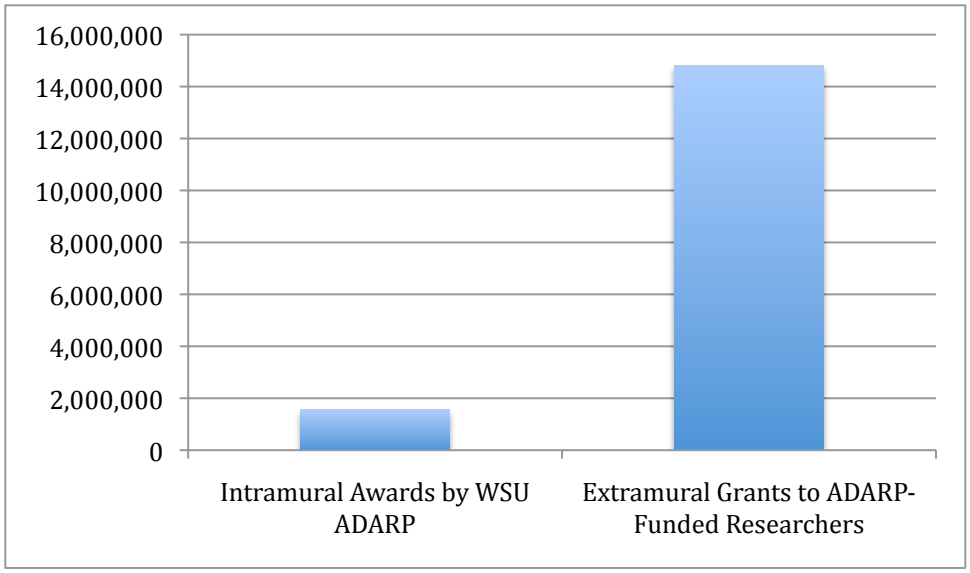
Based on years of experience, we estimate that it takes approximately three years to turn ADARP pilot grant funding into an extramurally funded grant. Therefore, we compared pilot grant expenditures in Fiscal Year (FY) 2006-2011 to extramural grants received during FY 2009-2014 (see below).

During FY 2006-2011, ADARP spent $1,557,808 on pilot grants, graduate student grants, bridge funds, and equipment grants. The $1,557,808 does not include start-up funds or undergraduate grants.

During FY 2009-2014, ADARP-funded researchers received $14,776,022 in extramural funding partially or entirely attributable to ADARP grants.

WSU ADARP-funded researchers secured greater than a 9:1 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.

Grant Funding (in Dollars)



Extramural Grants Received (FY 12, 13 & 14)

Name	Amount	Dates	Details
Craft, Rebecca	$413,460	9/2012 – 8/2017	DA016644 (R01) NIDA "Sex Differences in Cannabinoid Dependence and Analgesia" (co-I subcontractor; J. Wiley, PI, Research Triangle Institute).
Shishani, Kawkab & McPherson, Sterling	$273,896	9/2013 – 8/2016	K01D A037661-01A1 Shishani (PI) NIDA "The Role of Contingency Management in Waterpipe Smoking Cessation"
Sorg, Barbara	$414,000	8/2011 – 9/2013	R21DA030647 NIDA "Matrix Metalloproteinases and Cocaine"
Sorg, Barbara	$1,178,662	6/2012 – 5/2017	R01DA033404-01 NIDA "Extracellular Matrix, Cocaine, and Memory"
Wisor, Jonathan	$392,894	4/2014 – 3/2016	R21DA037708 "Chronic Methamphetamine Disrupts Sleep-Dependent Molecular/Energetic Homeostasis"
TOTAL	**$2,672,912**		

PUBLICATIONS

1. Bobeck, E. N., Chen, Q., Morgan, M. M. & Ingram, S. L. Contribution of Adenylyl Cyclase Modulation of Pre- and Postsynaptic GABA Neurotransmission to Morphine Antinociception and Tolerance. Neuropsychopharmacology 39, 2142-2152, doi:npp201462 [pii]10.1038/npp.2014.62 (2014).
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3. Browning, J. R., et al. Positive affective vocalizations during cocaine and sucrose self-administration: a model for spontaneous drug desire in rats. Neuropharmacology 61, 268-275, doi:S0028-3908(11)00157-2 [pii]10.1016/j.neuropharm.2011.04.012 (2011).
4. Browning, J. R., Jansen, H. T. & Sorg, B. A. Inactivation of the paraventricular thalamus abolishes the expression of cocaine conditioned place preference in rats. Drug Alcohol Depend 134, 387-390, doi:S0376-8716(13)00400-6 [pii] 10.1016/j.drugalcdep.2013.09.021 (2014).
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6. Cearley, C. N., Blindheim, K., Sorg, B. A., Krueger, J. M. & Churchill, L. Acute cocaine increases interleukin-1beta mRNA and immunoreactive cells in the cortex and nucleus accumbens. Neurochem Res 36, 686-692, doi:10.1007/s11064-011-0410-9 (2011).
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11. Craft, R. M., Wakley, A. A., Tsutsui, K. T. & Laggart, J. D. Sex differences in cannabinoid 1 vs. cannabinoid 2 receptor-selective antagonism of antinociception produced by delta9-tetrahydrocannabinol and CP55,940 in the rat. J Pharmacol Exp Ther 340, 787-800, doi:jpet.111.188540 [pii] 10.1124/jpet.111.188540 (2012).
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model and implications for age and sex differences in drug consumption. Front Psychiatry 4, 142, doi:10.3389/fpsyt.2013.00142 (2013).
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Biochem Behav 124C, 269-277, doi:S0091-3057(14)00177-4 [pii] 10.1016/j.pbb.2014.06.007 (2014).
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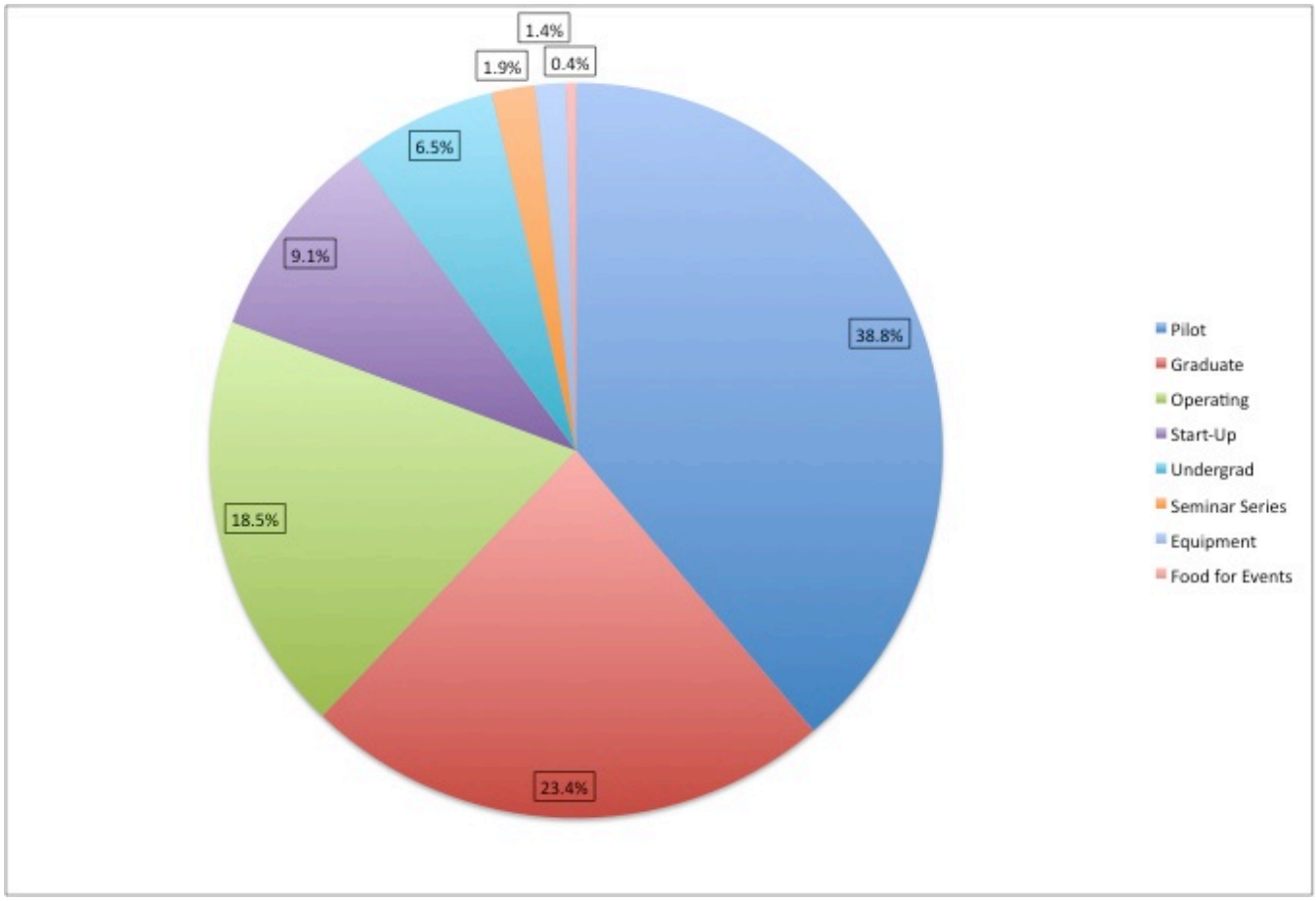
PRESENTATIONS

1. Craft, Rebecca. Sex differences in cannabinoid analgesia. In: "Vulnerability to Pain: Sources of Female-Male Differences and the Challenge of Understanding Them," International Association for the Study of Pain, Milan, Italy (8/26/2012)
2. Craft, Rebecca. Sex differences in cannabinoid analgesia. Gill Center for Biomolecular Science, Indiana University-Bloomington, IN (3/5/2014)
3. Craft, Rebecca. Sex differences in sensitivity to cannabinoid drugs. Psychology Dept., UNC-Chapel Hill, NC (10/30/2013)
4. Craft, Rebecca. Vive la diffèrence: Sex differences in the behavioral pharmacology of opioids. In: "The Behavioral Pharmacology of Drugs of Abuse and Drug Dependence: A Tribute to Steve Holtzman and Bob Schuster," American Society for Pharmacology and Experimental Therapeutics, San Diego, CA (4/23/2012)
5. Craft. Rebecca. Sex differences in cannabinoid analgesia. RTI International, Durham, NC (3/14/2013)
6. E. N. Bobeck, S. L. Ingram, & M. M. Morgan. Ligand-biased mechanisms of opioid antinociception. International Narcotics Research Conference, Cairns, Australia. Hot Topic #6 (July 17, 2013)
7. E. N. Bobeck, S. M. Taff, M. M. Morgan. Co-administration of morphine and fentanyl into the PAG protects against tolerance to either opioid. Neuroscience 43rd Annual Meeting. San Diego. Abstract #158.04 (Nov. 10, 2013)
8. Hagen, Ed. Does treating intestinal helminth infections reduce smoking behavior? Results of a double-blind, placebo-controlled, randomized control trial among Central African foragers. American Association of Physical Anthropologists Annual meeting (2011)
9. Hagen, Ed. Drug toxicity, not reward, explains large age and sex differences in substance use. American Association of Physical Anthropologists Annual meeting, Calgary (2014)
10. Hagen, Ed. Drugs are bad...for pathogens: Tobacco and cannabis vs. helminths in Central African foragers. Human Behavior and Evolution Society Annual Meeting, Albuquerque, NM (2012)
11. Hagen, Ed. Nicotine — candy or cure? Testing an evolutionary alternative to the reward model of psychoactive substance use. Invited Symposium, Association for Psychological Science Annual Meeting, Chicago, IL (2012)
12. Hagen, Ed. Nicotine: candy or cure? A longitudinal study of smoking vs helminth reinfection among African hunter-gatherers. American Association of Physical Anthropologists Annual meeting, Portland, OR (2012)
13. Hagen, Ed. Sugar and ice and everything nice: an evolutionary approach to age and sex differences in substance use. Human Behavior and Evolution Society Annual Meeting, Miami, Florida (2013)
14. Hagen, Ed. The highly polymorphic human cytochrome P450 (CYP) 2A6 gene: examining diversity and nicotine metabolism in a central African foraging population. American Association of Physical Anthropologists Annual meeting, Portland, OR. Presented by Hayley Mann (2012)
15. Hagen, Ed. Tobacco, cannabis, parasites, and life history strategies in an African population of hunter-gatherers. American Association of Physical Anthropologists Annual meeting. Portland, OR. Presented by Casey Roulette (2012)

16. Howell, D., Cameron, J., McPherson, S., Byers, A., Meyer, H., Falk, S., Zipperer, L., & Roll, J. M. Analysis of the reinforcing value of cigarettes and e-cigarettes among nicotine-dependent cigarette smokers using the multiple choice procedure. Poster presented at the Association for Behavioral Analysis International in Seattle, WA (May, 2012)
17. Howell, D., Shishani, K., McPherson, S., & Roll, J. Physiological and subjective effects of waterpipe (hookah) smoking. Poster presented at the College on Problems of Drug Dependence in San Diego, CA (June, 2013)
18. Mehalick, M. L. & Morgan, M. M. Comparison of a traditional stimulus evoked pain response assay with pain suppressed locomotor behavior in the rat. Society for Neuroscience 42st Annual Meeting. New Orleans. Abstract #376.14 (October 15, 2012)
19. Morgan, M. M., Kallio, S. W., & Reid, R. A. Comparison of acute morphine withdrawal in male and female rats using a conditioned place avoidance procedure. Society for Neuroscience 42st Annual Meeting. New Orleans. Abstract #171.02 (October 14, 2012)
20. R. A. Reid, S. W. Kallio, M. M. Morgan. Conditioned place aversion to naloxone-precipitated withdrawal following a single microinjection of morphine into the periaqueductal gray of male and female rats. Neuroscience 43rd Annual Meeting. San Diego. Abstract #158.01 (Nov. 10, 2013)
21. Shishani, K., Howell, D., McPherson, S., & Roll, J. Direct Health Effects of Waterpipe Smoking in Intermittent Young Adult Waterpipe Smokers. Symposium presented at the Society for Research on Nicotine and Tobacco in Boston, MA. (March, 2013)
22. Shishani, K., Howell, D., McPherson, S., & Roll, J. Physiological and Subjective Effects of Waterpipe Smoking. Presented at the International Meeting on Waterpipe Tobacco Smoking in Abu Dhabi (United Arab Emirates) (October, 2013)
23. Sorg, Barbara. Legacy Research Institute, Portland, OR (2013)
24. Sorg, Barbara. Oregon Health & Science University, Behavioral Neuroscience, Portland, OR (2012)
25. Sorg, Barbara. University of Chicago, Department of Psychiatry and Behavioral Neuroscience (2011)
26. Sorg, Barbara. University of Wyoming, School of Pharmacy, Laramie, WY (2012)
27. Sorg, Barbara. Washington State University – Spokane Riverpoint Campus, Spokane, WA (2011)

Expenditure History by Category
2012, 2013, and 2014 FY



Alcohol and Drug Abuse Research Program Expenditures

- ADARP funded research in fourteen different departments on four campuses.
- More than 79% of all funds went to support substance abuse research through pilot grants, graduate student grants, undergraduate student grants, equipment grants, and start-up funds.
- Rigorous grant competitions and constructive critiques improved proposals and enhanced the chances of extramural funding.
- Just over 2% 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 18.5% of expenditures went toward operating costs.

Expenditure History by Category
(2012, 2013, and 2014 FY)

Pilot	$332,249.99
Graduate	200,212.71
Operating	158,527.16
Start-Up	78,325.44
Undergrad	55,403.37
Seminar Series	16,362.92
Equipment	11,700.00
Food for Events	3,679.81
	$856,461.40

Grant History by Department (2012, 2013, and 2014 FY)

Department	# Submitted	# Funded	Pilot	Graduate	Undergrad	Other[4]	% Funded
Animal Sciences	3	3	1 of 1	1 of 1	1 of 1		100.0
Anthropology	1	1		1 of 1			100.0
Chemistry	2	1	0 of 1	1 of 1			50.0
Chemistry/Pol. Sci.	1	1	1 of 1				100.0
Communication	7	1	1 of 6	0 of 1			14.3
Counseling Psych.	1	0		0 of 1			0.0
Counseling Services	2	0	0 of 2				0.0
Exp. & Systems Phar.	1	0	0 of 1				0.0
Human Development	1	1	1 of 1				100.0
IPN[1] (was VCAPP[2])	13	9	3 of 4	2 of 4	2 of 3	2 of 2	69.2
IPN/Sleep Center	3	2		1 of 2		1 of 1	66.7
Mathematics	2	1	1 of 2				50.0
Molecular Biosciences	1	0	0 of 1				0.0
Nursing	2	1	1 of 2				50.0
Pharmaceutical Sci.	1	1	1 of 1				100.0
Pharmacotherapy	2	2			2 of 2		100.0
Psychology	30	25	5 of 8	8 of 10	10 of 10	2 of 2	83.3
Psychology - Basic S.	20	17	2 of 4	5 of 6	10 of 10		85.0
Psychology - Clinical	10	8	3 of 4	3 of 4		2 of 2	80.0
Sleep & Performance	2	1	0 of 1	1 of 1			50.0
Sociology	1	0		0 of 1			0.0
WWAMI[3]	1	1		1 of 1			100.0
	77	**51**	**15/32 47%**	**16/24 67%**	**15/16 94%**	**5/5 100%**	**66.2**

[1] **Integrative Physiology and Neurosciences**
[2] **Veterinary and Comparative Anatomy, Pharmacology, and Physiology**
[3] **Washington, Wyoming, Alaska, Montana, and Idaho Regional Medical Education Program**
[4] **Equipment or Start-Up**

Basic Science vs. Clinical and Social Science

Category	# Submitted	# Funded	Pilot	Graduate	Undergrad	Other[4]	% Funded
Basic Sci.	43	32	8 of 15	8 of 11	13 of 14	3 of 3	74.4
Clin. & SS	34	19	7 of 17	8 of 13	2 of 2	2 of 2	55.9
	77	**51**	**15/32 47%**	**16/24 67%**	**15/16 94%**	**5/5 100%**	**66.2**

By Campus

Campus	# Submitted	# Funded	Pilot	Graduate	Undergrad	Other[4]	% Funded
Pullman	49	30	8 of 19	10 of 17	9 of 10	3 of 3	61.2
Spokane	7	4	2 of 5	2 of 2			57.1
Tri Cities	1	1	1 of 1				100.0
Vancouver	17	14	4 of 7	3 of 3	6 of 6	1 of 1	82.4
Pull./Spk.	2	1		1 of 2			50.0
Vanc./Spk.	1	1				1 of 1	100.0
	77	**51**	**15/32 47%**	**16/24 67%**	**15/16 94%**	**5/5 100%**	**66.2**

New vs. Revised (Pilot and Graduate Student Grants Only)

	# Funded	% Funded	# Funded	% Funded	# Funded	% Funded
Category	**All Grants**	**All Grants**	**Pilot**	**Pilot**	**Graduate**	**Graduate**
New	22 of 44	50.0%	10 of 25	40.0%	12 of 19	63.2%
Revised	9 of 12	75.0%	5 of 7	71.4%	4 of 5	80.0%
	31 of 56	**55.4%**				

Grants Approved for Fiscal Years 2012, 2013, and 2014

Amount*	7/1/2011 - 6/30/2012	Budget	Project	
30,000.00	Szentirmai (WWAMI)(7/1/11 - 12/31/12)	5750	1272	Pilot grants
28,782.00	Dimitrov (Mathematics. WSUV)(1/1/12 - 6/30/13)	5807	1277	
16,344.00	Morgan (Psych. WSUV)(1/1/12 - 6/30/13)	5810	1278	
29,014.00	Jansen/Simasko (VCAPP)(1/1/12 - 6/30/13)	2550	1279	
30,000.00	Trobridge (Pharm. Sci.)(1/9/11 - 7/31/12)	2957	1280	
29,995.00	Tragesser (Psychology - WSU-TC)(4/24/12 - 11/30/13)	5610	1285	
24,066.00	Chiu/Schenk (Chemistry)(8/16/11-8/15/12)	2452	1270	Graduate Student Grants
25,892.00	Winters/Dong (VCAPP)(8/16/11-8/15/12)	2550	1271	
7,369.00	Yamamoto/Hindman (Com.)(8/16/11 - 8/15/12)	2850	1273	
8,997.00	Madden/Newberry (VCAPP)(5/16/12 - 12/31/12)	2550	1287	
9,173.00	Berger/Walker (Psychology)(6/1/12 - 9/30/12)	2474	1288	
2,019.00	Kallio/Morgan (Psych. WSUV)(1/1/12-5/31/12)	5810	1275	Undergraduate Student Grants
2,019.00	Fitzgibbon/Morgan (Psych. WSUV)(1/1/12-5/31/12)	5810	1276	
5,330.00	Restis/McLean (Animal Sciences)(5/1/12 - 8/31/12)	3031	1282	
5,330.00	McBride/Craft (Psychology)(5/1/12 - 8/31/12)	2474	1283	
5,330.00	Smith/Walker (Psychology)(5/1/12 - 8/31/12)	2474	1284	
50,000.00	Beauchaine Start-Up (Psych.) 9/2/11-12/31/13 (2 X 25K)	2474	1274	Start-Up Funds
26,250.00	Magnan Start-Up	5810	1286	
11,700.00	Kapas/Sorg (Sleep Center/VCAPP)(3/12/12 - 12/31/12)	2550	1281	Equipment Grant
$347,610.00	**Total for Fiscal Year 2012**			

* The amount awarded is listed. The amount actually expended may be less.

Amount*	7/1/2012 - 6/30/2013	Budget	Project	
30,000.00	McLean (Animal Sciences)(7/1/12 - 12/31/13)	3031	1289	
24,134.00	Bumpus (Human Development)(6/18/12 - 12/31/12)	2144	1292	Pilot grants
26,972.00	Dyck/Skaer (Psychology WSUS)(5/30/13 - 11/30/14)	5701	1303	
10,699.00	Mehalick/Morgan (Psych. WSUV)(7/1/12 - 12/31/12)	5810	1290	
12,227.00	Zhang/Hill (Chemistry)(7/1/12 - 12/31/12)	2452	1291	Graduate Student
10,699.00	Roulette/Hagen (Anthro. WSUV)(7/1/12 - 12/31/12)	5810	1293	Grants
7,993.00	Haas/Craft (Psych.)(3/4/13 - 9/30/13)	2474	1296	
2,019.00	Taff/Morgan (Psych. WSUV)(1/1/13 - 5/31/12)	5810	1294	
2,019.00	McGinnis/Walker (Psych.)(1/1/13 - 5/31/12)	2474	1295	
5,330.00	Campion/Morgan (Psych. WSUV)(4/16/13 - 8/31/13)	5810	1297	Undergraduate
5,330.00	Corboy/Jansen (IPN)(4/16/13 - 8/31/13)	2550	1298	Student Grants
5,330.00	Ohrt/Sorg (IPN WSUV)(4/16/13 - 8/31/13)	5811	1299	
4,080.00	Cervenka/Craft (Psych.)(6/1/13 - 5/31/14)	2474	1301	
$146,832.00	**Total for Fiscal Year 2013**			

* The amount awarded is listed. The amount actually expended may be less.

Amount*	7/1/2013 - 6/30/2014	Budget	Project	
30,000.00	Appleyard (IPN)(6/21/13 - 12/31/14)	2550	1305	Pilot grants
22,500.00	Walker (Psych.)(1/1/14 - 6/30/15)	2474	1311	
24,434.00	Sorg (IPN WSUV)(2/21/14 - 9/30/15)	5811	1313	
10,009.00	Cooper (Human Dev.)(5/5/14 - 11/30/15)	4143	1320	
10,698.00	Mamey/Burns (Psych.)(7/1/13 - 12/31/13)	2474	1302	Graduate Student Grants
10,609.00	Bender/VanDongen (Sleep)(7/1/13 - 12/31/13)	5702	1304	
7,270.00	Sawaqdeh/O'Connell/Marcus (Psych.)(10/17/13 - 8/31/14)	2474	1308	
12,382.00	Page/Appleyard (IPN)(1/1/14 - 5/31/14)	2550	1311	
8,616.00	Nguyen/Roberts (WWAMI)(1/7/14 - 8/31/14)	5750	1312	
10,566.00	Slaker/Sorg (IPN WSUV)(4/1/14 - 9/30/14)	5811	1314	
7,553.00	Kissler/Walker (Psych.)(4/1/14 - 9/30/14)	2474	1315	
4,904.00	Norris/Marcus (Psych.)(5/16/14 - 9/30/14)	2474	1321	
4,040.00	Male Ervik/Skaer (Pharm. Prac.)(8/1/13 - 5/31/14)	2958	1306	Undergraduate Student Grants
4,040.00	Nwude/Skaer (Pharm. Prac.)(8/1/13 - 5/31/14)	2958	1307	
2,010.00	Wescom/Morgan (Psych. WSUV)(12/10/13 - 5/31/14)	5810	1310	
6,388.00	Nicoara/Quock (Psych)(4/1/14 - 8/31/14)	2474	1316	
50,000.00	Fuchs Start-Up (IPN) 12/6/13 - 6/30/16) 25K X 2	2550	1309	Start-Up Funds
50,000.00	Rossi Start-Up (IPN) 12/6/13 - 6/30/16) 25K X 2	2550	1317	
$276,019.00	**Total for Fiscal Year 2014**			

* The amount awarded is listed. The amount actually expended may be less.

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**		

* The amount awarded is listed. The amount actually expended may be less.

START-UP DETAILS
(Entire History)

Faculty	Amount*	Year	Department
Craft	$50,000	1993	Psychology
Jerrells	50,000	1997	Pharmaceutical Sciences
Quock	50,000	1998	Pharmaceutical Sciences
Ouimette	17,000	2001	Psychology
Dong	100,000	2006	Veterinary and Comparative Anatomy, Pharmacology, and Physiology (VCAPP)
Walker	100,000	2008	Psychology
Beauchaine	50,000	2011	Psychology (Note: Dr. Beauchaine left WSU in 2013. He returned all but $2,075.44 of the start-up funds.)
Magnan	26,250	2012	Psychology (WSU – Vancouver)
Fuchs Lokensgard	50,000	2013	Integrative Physiology and Neuroscience (formerly VCAPP)
Rossi	50,000	2014	Integrative Physiology and Neuroscience (formerly VCAPP)
Total	**$543,250.00**		
Average	**$54,325**		

* The amount awarded is listed. The amount actually expended may be less.

Alcohol and Drug Abuse Research Program Seminars
July 2011 to June 2014

Date	Name	Affiliation	Title
2011 – 9/16	Paul Kenny	Department of Molecular Therapeutics, *Scripps Institute (Florida Campus)*	"Nicotinic Receptor Signaling in the Habenulo-Interpeduncular Tract Regulates Nicotine Intake"
2011 – 10/28	Rita Fuchs	Department of Psychology, *University of North Carolina*	"Drug Context-Induced Relapse to Cocaine Seeking: an Interplay of Memory, Impulsive Decision Making, and Motivation"
2011 – 11/9	Oliver Schlüter	European Neuroscience Institute, *Gottingen University Medical School and Max-Planck Society*	"DLG-MAGUKs: A Diverse Family of Signaling Scaffolds of Synaptic Plasticity and Neuronal Excitability"
2011 – 12/1	Andrey Ryabinin	Behavioral Neuroscience, *Oregon Health & Science University*	"Neurocircuitry and Social Aspects of Alcohol Abuse: Novel Findings with Stress Peptides and Prairie Voles"
2012 – 3/23	Bryan Yamamoto	Department of Neurosciences, *University of Toledo*	"Stressed Out on Methamphetamine: Biogenic Amines and Beyond"
2012 – 4/27	William Carlezon	Program in Neuroscience *Harvard Medical School*	"CREB and Kappa-Opioid Receptors in the Study and Treatment of Substance Abuse and Depressive Disorders"
2012 – 5/4	Colleen McClung	Center for Neuroscience, *University of Pittsburgh*	"Circadian Genes, Rhythms and Psychiatric Disease"

Date	Name	Affiliation	Title
2012 – 5/9	Gregory Bagby	Department of Physiology, *Louisiana State University Health Sciences Center*	"Impact of Alcohol Consumption on HIV Disease"
2012 – 9/14	Cristina Alberini	Center for Neural Science, New York University	"Molecular Mechanisms Underlying Long-term Memory Formation"
2012 – 11/16	Rita Fuchs	Department of Psychology *University of North Carolina*	"Drug Context-Induced Relapse to Cocaine Seeking: Interplay of Memory, Impulsive Decision Making, and Motivation"
2013 – 3/1	Todd Thiele	Department of Psychology, *University of North Carolina*	"Overlapping Neuropeptide Modulation of Binge Alcohol Drinking and Eating Disorders: Can we Kill Two Birds with One Stone"
2013 – 9/5	Stephen Pruett	Department of Basic Sciences *Mississippi State University*	"A Block at the Toll Gate: Effects of Alcohol on Innate Immunity"
2013 – 9/17	Yavin Shaham	Behavioral Neuroscience Branch *National Institute on Drug Abuse*	"Neurobiology of Relapse to Drug Seeking"
2014 – 2/7	Michael Bruchas	Division of Biology and Biomedical Sciences, *Washington University in St. Louis*	"Dissection of GPCR Signaling and Neural Circuits in Stress Behavior"
2014 – 3/7	Matthew Hill	Hotchkiss Brain Institute *University of Calgary*	"Endocannabinoid Signaling as a Molecular Signal Linking Stress and Neuroinflammation"
2014 – 4/25	Annie Lang	Department of Telecommunications, *Indiana University*	"Processing Substance Cues and Prevention Messages: Individual Differences in Biological Responses and Motivated Cognition"

Pilot and Graduate Student Grant Abstracts

Grants Awarded during FY 2012

Cues Associated with Kappa-Opioid Receptor-Induced Negative Affective States Promote Excessive Alcohol Self-Administration in Rats. ***Psychology, Anthony Berger, Graduate Student. Mentor: Brendan Walker ($9,173).***

Activation of kappa-opioid receptors (KOR) is associated with the production of negative affective states as well as escalated consumption of alcohol. Research has shown that activation of KORs can be paired with neutral stimuli and that following such pairings, the stimuli induce a negative affective state when presented alone. However, no research has been conducted to examine the effects of cues previously associated with KOR activation on alcohol self-administration. Elucidating the connection between cues reflective of negative affective states and alcohol consumption is of particular importance in order to understand the factors underlying relapse to drugs of abuse such as alcohol. This study seeks to examine the underlying neurobiology of cued negative affective states and how a neutral cue associated with a negative affective state is capable of influencing operant alcohol self-administration.

The Effects of Inhibitor Binding and Substrate Analogs on Glycosylated Sites of the Neuronal Dopamine Transporters. ***Chemistry. Veronica Chiu, Graduate Student. Mentor: James Schenk ($24,066).***

Dopamine (DA) is a catecholamine neurotransmitter synthesized in presynaptic terminals of the brain and plays a role in reward, reinforcement, and motivation pathways; it also contributes to effects caused by many drugs of abuse. The dopamine transporter (DAT) is a single gene product which exhibits different states of glycosylation in different areas of the brain. It acts in the dopaminergic neurotransmission pathways by removing DA from the synaptic space, thereby regulating DA binding to DA receptors. Glycosylation plays an important role in the DAT because only glycosylated DAT is functional. Some literature has shown that the striatum and nucleus accumbens have the same DAT protein sequence but exhibit different glycosylation patterns. In addition, preliminary results from our laboratory show that removal of the carbohydrate components on DAT decreases the rate of DA uptake and that cocaine binds to glycosylated DAT. Based on preliminary data, this study will determine if the binding of cocaine, mazindol, bupropion, methamphetamine (METH), tyramine, and 4-ethylcatechol involve glycosylated regions on the DAT in striatum and nucleus accumbens.

Analysis and Modeling of the Effects of Dopamine Transporters in Cl- Regulation. ***Mathematics and Science (WSU-Vancouver), Alexander Dimitrov, Assistant Professor ($28,782).***

The combined physiological and computational studies outlined in this proposal will elucidate the mechanisms of Cl- homeostasis in DA neurons, provide new insight into the mechanisms of psychostimulant action on the DA system, and ultimately lead to a better understanding of the cellular processes underlying psychostimulant addiction. The main organizational goal of this proposal is to establish a new collaborative effort between the groups of Dr. Ingram and Dr. Dimitrov (a new faculty in Mathematics) at WSU-Vancouver in order to clarify effects of DAT-mediated chloride currents on neuronal excitability. Dr. Ingram will use simultaneous electrophysiological recordings and fluorescence imaging of internal Cl- concentration to monitor DAT function over the entire cell. Dr. Dimitrov will contribute his expertise in biomedical signal processing and neural modeling to relate the optical signals to biophysical quantities and prepare models for expressing more quantitative hypotheses. Specific Aim I in this proposal is for Dr. Dimitrov to develop and adapt quantitative methods for advanced signal processing, which will allow for a translation between the observed fluorescent signal and Cl- concentration of interest. As illustrated later, the fluorescent signal does not provide a direct indication of Cl- concentration and dynamics. We will use general tools from Systems Identification theory to achieve these goals. In Specific Aim II, we will extend the class of models to include more biophysically realistic models of the studies' structures. These will be applied in two ways. As with the general Systems Identification tools, the biophysical models will be used for systems identification and model-based filtering. They will also be refined and used to make inferences about how the mechanistic functioning of the DAT and supporting structures (ion channels and proteins) change DA neuron excitability.

Dysregulation of Sleep, Activity, and Temperature Rhythms following Alcohol is Mediated by Corticotrophin-Releasing Factor (CRF). ***Veterinary and Comparative Anatomy, Pharmacology, and Physiology, Heiko Jansen, Associate Professor, and Steve Simasko, Professor ($29,014).***

Disturbed sleep is a frequent complaint of alcoholics and shift workers. Indeed, shiftwork is associated with increased rates of alcohol use, with many shiftworkers using alcohol as a sleep aid. Additionally, the severity of sleep disturbances is related to the propensity of abstinent alcoholics to relapse. Why chronic alcohol use causes disturbances in sleep and why the severity of disturbed sleep is predictive of relapse is unknown. Our working hypothesis is that disturbed sleep caused by chronic alcohol results from altered timing of the diurnal activity/temperature rhythms (desynchrony) leading to disturbances in the CRF system of the brain. We have gathered preliminary data confirming alterations in patterns of general activity and body temperature as a result of chronic moderate-level alcohol exposure (10 weeks). We propose to follow up these studies with a protocol that produces a higher alcohol intake achieved by giving alcohol in a liquid diet and thereby

producing even more dramatic disturbances of daily rhythms. We will test a mechanistic hypothesis that the disturbances in sleep/circadian timing that occur as a result of chronic alcohol result from alterations in CRF by using a CRF antagonist in behavioral experiments and by measuring changes in circulating corticosterone. Finally, we will directly examine the relationship between our activity/body temperature measurements and sleep by performing high-resolution simultaneous analysis of all three parameters to determine if chronic alcohol changes the relationship between these parameters as is suggested by the literature. Completion of these experiments will not only advance our understanding of alcohol-induced behavioral pathologies, but will also provide us with the necessary preliminary data (alcohol exposure model and suggested biochemical mechanism) that will enable us to successfully compete for extramural funding. Drs. Jansen and Simasko are ideally suited for these studies as they have extensive experience with circadian studies (Jansen) and sleep monitoring following alcohol exposure (Simasko) using rats as an animal model.

Effects of Human-Animal Interactions on Affect and Empathy of Adolescents in Substance Abuse Treatment. ***Animal Sciences, Lindsay Madden, Graduate Student. Mentors: Ruth Newberry and Sarah Tragesser ($8,997).***

Drug addiction is a major public health problem associated with numerous societal and financial consequences. Adolescents are at elevated risk of developing drug addiction and, if left untreated, the addiction may last a lifetime. Ensuring that adolescent drug abusing individuals complete substance abuse treatment is critical for increasing the likelihood of sobriety, thereby reducing these profound consequences. However, individuals with substance use disorders often have impairments in affect (i.e., mood; internal feeling state) and empathy (emotional response to the emotion of another) that may increase treatment drop-out rate and reduce the chance for a successful treatment outcome. Interaction with companion animals can provide important psychological and physiological benefits for human health and offers a novel route to improving treatment outcomes. Currently, adolescents in inpatient substance abuse treatment programs are unlikely to have opportunities to interact with animals. Our objective is to investigate the effectiveness of a human-animal interaction activity program, specifically involving dogs from an animal shelter, in improving affect and empathy of adolescent substance abuse patients. We hypothesize that adolescents in inpatient substance abuse treatment will express greater empathy and an improvement in affect when participating in an experimental human-animal interaction activity program when compared to control "treatment-as-is" therapy (i.e., standard substance abuse treatment). Using a mixed between- and within-subjects repeated measures crossover design, the effects of the human-animal interaction activity program on the adolescents' affective and empathetic states will be evaluated using a series of self-report questionnaires. Scores of subjects in the human-animal interaction program will be compared with those of subjects in the control group. Within-subjects

comparisons will also be made between pre- and post-treatment questionnaire scores. Expected outcomes of this summer project include demonstration of the feasibility of implementing a human-animal interaction activity program for adolescent substance abuse patients specifically involving shelter dogs, validation of methodology in this context, and generation of pilot data indicating immediate beneficial effects on affective and empathetic states. If human-animal interactions are found to induce immediate, positive changes in affect and empathy, this study will point to a novel and innovative clinical approach to adolescent substance abuse treatment to be pursued through applications for extramural funding.

Contribution of the Periaqueductal Gray to Morphine Withdrawal. ***Department of Psychology (WSU-Vancouver), Mike Morgan, Professor ($16,344).***

Opioid withdrawal is a serious medical problem and a leading cause of continued drug use. Although a number of brain structures have been identified that appear to contribute to opioid withdrawal symptoms, the neural basis for withdrawal is poorly understood. A number of studies indicate that the periaqueductal gray (PAG) contributes to somatic aspects of withdrawal. The objective of the current proposal is to test the hypothesis that the PAG contributes to the psychological aspects of withdrawal. This hypothesis will be tested by measuring withdrawal using a conditioned place aversion procedure. Rats will be given repeated microinjections of morphine into the PAG and then placed on one side of a conditioning chamber immediately after microinjection of the opioid antagonist naloxone into the PAG. Rats will be returned to the conditioning box 24 hours later to determine whether naloxone caused an aversion. If successful, this study will link PAG neurons to morphine withdrawal and provide the basis for subsequent studies examining the mu-opioid receptor signaling responsible for naloxone-precipitated withdrawal.

The Role of Ghrelin in Methamphetamine-Induced Arousal and Reward. ***Eva Szentirmai, Assistant Professor, and Levente Kapas, Associate Professor ($30,000).***

Methamphetamine has strong reinforcing/rewarding effects, properties that are related to the addictive nature of the drug. It also elicits behavioral activation, increased alertness, and arousal, effects that often trigger and maintain initial drug use. The molecular substrates underpinning these actions of methamphetamine are not fully understood. The central hypothesis of this pilot grant application is that ghrelin signaling is a key component in circuits involved in the reinforcing and arousal-stimulating effects of methamphetamine. The following evidence supports our hypothesis. Ghrelin signaling is an integral part of the central arousal and food intake regulatory mechanisms. Ghrelin also modulates the activity of the mesolimbic system by stimulating neuronal activity and synapse formation of the dopaminergic cells in the ventral tegmental area and by enhancing dopamine turnover in the nucleus accumbens. The mesolimbic dopaminergic pathway is activated by rewarding stimuli, such as food, and by addictive psychoactive drugs, such as

cocaine, amphetamines, and alcohol. Recently it was shown that ghrelin plays a role in alcohol-, cocaine- and amphetamine-induced reward mechanisms. Locomotor stimulation and accumbal dopamine release after alcohol, cocaine, or methamphetamine administration are abolished in mice lacking functional ghrelin receptors. We will test our hypothesis by pursuing the following specific aims: 1) Determine the rewarding and reinforcing potentials of methamphetamine in ghrelin receptor knockout (KO) mice by using a conditioned place preference test and the drug self-administration model, 2) Determine the effects of methamphetamine on sleep, activity and body temperature in ghrelin receptor KO mice. Psychoactive stimulants, such as methamphetamine, have high potential for abuse and addiction by activating reward circuits in the brain. The proposed experiments are innovative because they have the potential to identify a novel mechanism underlying the development of drug abuse and addiction. A better understanding of natural brain reward systems will enhance our understanding of the neural cause of addiction. The present pilot grant application has the potential to provide data that will place us in a strong position to seek expanded National Institute of Health (NIH) funding at the R01 level.

Borderline Personality Disorder Features and Risk for Prescription Opioid Use Disorders in a Pain Patient Sample. ***Psychology (WSU – Tri Cities), Sarah Tragesser, Assistant Professor ($29,995).***

Despite the evidence on the association between personality disorders (PDs) and substance use disorders, an understanding of how PDs relate to risk for opioid use disorders (OUDs) among chronic pain patients is lacking. My long-term goal is to investigate the association between Borderline Personality Disorder (BPD) and risk for prescription opioid abuse and dependence among individuals with chronic pain complaints. The overall objective of this application is to examine the role of the personality features emotion dysregulation and impulsivity in the relationship between BPD features and risk for prescription OUDs among individuals being treated for chronic pain complaints. My central hypothesis is that emotion dysregulation and impulsivity account for the association between BPD features and risk for OUDs in pain patient samples. Self-report questionnaires will be used to address the following specific aims: (1) Identify the role of emotion dysregulation in the association between BPD features and risk for OUDs; (2) Identify the role of impulsivity in the association between BPD features and risk for OUDs. Aim 1 will test the hypothesis that emotion dysregulation accounts for greater pain severity and emotional reactions to pain, which confer greater risk for dependence on opioid pain medications. Aim 2 will test the hypothesis that impulsivity is directly associated with risk for OUDs, as well as indirectly through its association with treatment noncompliance behaviors that may prolong or exacerbate pain conditions. Results will provide pilot data for extramural funding to investigate these ideas using longitudinal designs among larger samples. These findings will contribute to an understanding of how personality features confer risk for prescription OUDs among individuals being treated for pain complaints, explaining the

association between PD features and risk and providing implications for prevention and treatment of both pain and OUDs in pain treatment settings.

Stem Cell Gene Therapy for HIV/AIDs Patients with Alcohol Use Disorders. ***Pharmaceutical Sciences, Grant Trobridge, Assistant Professor ($30,000).***

Individuals with alcohol use disorders are more likely than the general public to contract HIV, and HIV-positive individuals are more likely to have serious problems with alcohol use. Highly active antiretroviral therapy (HAART) has led to marked improvements in immunologic and virologic outcomes and quality of life for HIV infected patients. However, the optimal benefits of HAART rely on the patient rigorously adhering to a defined schedule of a cocktail of anti-retroviral drugs, and non-adherence to HAART therapy in patients with alcohol use disorders limits its efficacy. Here we propose research to expand and improve an alternative approach to HIV treatment, hematopoietic stem cell (HSC) gene therapy. In this approach, uninfected stem cells are removed from an HIV infected patient, a gene or combination of genes that inhibit HIV replication are introduced into these stem cells, then the stem cells are re-introduced (transplanted) into the patient where they repopulate the infected individual and restore their immune system. A major advantage of this approach is that transplantation has the potential to protect the individual for life, without the need for continued HAART treatment. Thus HSC gene therapy for HIV/AIDS may be particularly advantageous for patients with alcohol disorders, who are at risk for AIDS progression due to non-adherence to a HAART drug schedule. Here we propose to develop more effective and safer anti-HIV vectors for AIDS gene therapy and to study the effect of chronic alcohol use on the efficacy of HSC gene therapy using a powerful mouse model that allows for transplantation of human stem cells. The proposed research has the potential to improve therapeutic options for HIV/AIDS patients with alcohol use disorders.

Cellular Adaptations to Sleep Deprivation and Cocaine Exposure in CB1 Receptor Expressing Neurons of the Nucleus Accumbens. ***Veterinary and Comparative Anatomy, Pharmacology and Physiology, Brad Winters, Graduate Student. Mentor: Yan Dong ($25,892)***

Sleep disruption is a significant co-morbidity in almost all psychiatric disorders, including drug addiction, depression, schizophrenia, and anxiety [1-6]. In drug addiction, sleep disruptions are not merely coincidental phenomena, but may also aggravate the development and maintenance of the addictive state [7-9]. Our long-term research goal is to uncover cellular adaptations mediating the interaction between sleep disruption and cocaine addiction. As a first step to attain this goal, the objective of this proposal is to determine the effects of sleep deprivation (SD) and cocaine exposure on nucleus accumbens (NAc) neurons, then to examine the influence of SD on cocaine-induced cellular alterations. The NAc is part of the mesocorticolimbic dopamine system and key to emotional gating and processing of rewarding stimuli [10, 11]. Synaptic and intrinsic membrane plasticity in the NAc that

results in dysregulation of NAc function is heavily implicated in production of the addicted state [12-15]. The NAc has a role in sleep regulation [16], as does the larger dopamine system [17]. The dramatic reduction in sleep associated with psychostimulants, including cocaine and amphetamine, is partially mediated by increases in dopamine [17]. Sleep loss results in decreased motivation and emotional dysregulation [18-21]. Since dysregulation of emotional processing is evident in cocaine addiction and SD, we hypothesize that the NAc is one point where these two will overlap. Thus, characterization of the effects of SD and cocaine exposure on NAc neurons will provide insight into the common cellular basis underlying the interaction between sleep disruption and cocaine addiction. Cannabinoid receptor 1 (CB1) is enriched in the mesocorticolimbic system [22-27], and the cannabinoid system is implicated in many general neurobiological aspects of addiction, such as drug-related cue association and reinstatement of self administration [28-32]. Consolidation of CB1-mediated learning in the mesolimbic reward pathway is proposed to be a common factor in development of the addicted state for multiple drugs of abuse including psychostimulants [28, 30]. Cocaine exposure disrupts CB1-mediated synaptic plasticity within the NAc shell [33]. Also, CB1 signaling can modulate sleep timing and duration [34-36]. Thus, modulation of synaptic and membrane properties of CB1-expressing neurons in the NAc may be one of the common substrates through which SD and cocaine exposure achieve cellular interaction. I will examine the effects of cocaine exposure and SD on CB1-expressing neurons of the NAc.

Drug Abuse Violations in Communities: Community Newspapers as a Macro-Level Source of Social Control. ***Murrow College of Communication, Masahiro Yamamoto, Graduate Student. Mentor: Doug Hindman ($7,369).***

A doctoral student in the Edward R. Murrow College of Communication proposes a project designed to investigate the role of community newspapers in explaining community-level variations in drug abuse violations. Despite a rich body of work in health communication, few studies to date have directly linked local mass media with variations in arrests for drug offenses across communities. The current project derived from a long tradition of research on community journalism will assess the direct and indirect effects of social control that stems from community newspapers. First, community newspapers are posited to directly affect drug abuse violations by reinforcing the normative culture in pursuit of safe and healthy communities. Second, the shared values of residents in support of social welfare derived from community newspapers are posited to increase civic engagement and proactive policing, which in turn account for community-level variations in drug abuse violations. To test this theoretical model, this project will construct a national sample of U.S. counties. The overall purpose is to examine the role of community newspapers in regulating drug offenses and developing healthy environments.

Grants Awarded during FY 2013

Parent-Student Communication and Alcohol Use and Misuse Across the Transition to College. ***Human Development. Matthew F. Bumpus, Associate Professor, Sarah Ullrich-French, Assistant Professor ($24,134).***

Some evidence exists suggesting that parents can play an important role in influencing the alcohol-related behaviors of their college-bound offspring, but this literature is plagued by conceptual and methodological problems. Here we propose a short-term longitudinal study investigating the associations among parent-adolescent communication (i.e., parental monitoring, parent-adolescent communication about alcohol, parental knowledge, adolescent disclosure) and alcohol use and consequences across the transition to college. We seek to recruit a sample of 300 mother-student dyads, who will each complete questionnaires in the summer prior to attending college and then again during the first and second semesters of the student's freshman year. We are requesting funds for participant incentives and research assistant expenses.

Multiple Family Groups, Mindfulness, and the Management of Chronic Pain and High Risk Opiate Use. ***Department of Psychology, College of Pharmacy, and College of Nursing. Dennis Dyck (PI), Tracy Skaer (Co-PI), J.P. Garofalo, Donelle Howell, Celestina Barbosa-Leiker ($26,972).***

Chronic pain is a significant public health problem in the U.S. Increasing numbers of chronic pain patients are treated with long-term opioid therapy. Many of these patients contend with chronic pain as well as the risk of developing an opioid addiction. The impacts of chronic pain on family members are often as life-altering as those of the person living with the pain. Family members often suffer along with the pain patient, developing their own dysfunctional symptoms and coping strategies [1]. Over time, the pain may become the central organizing feature of the family [2]. This treatment development study will test the feasibility, acceptability and preliminary efficacy of an MFG-Mindfulness intervention for patients and their spousal caregivers. Results from this pilot study will be an important first step in advancing treatment options for individuals with chronic pain and prescription opioid misuse.

Sex Differences in Antinociception Produced by Cannabidiol (CBD) delta-9-Tetrahydrocannabinol (THC) Combinations. ***Psychology. Aaron Haas, Graduate student. Mentor: Rebecca Craft ($7,993).***

Previous research has found that men and women experience pain differently, both in severity and duration. Furthermore, women have been found to be more sensitive than men to the analgesic effects of opioid pain medications. Though effective for relatively short-term analgesia, the chronic use of opioid pain medications has been found to produce adverse effects. As such, analgesia research has begun examining the use of cannabinoids, mainly THC and THC-like substances, for treating chronic pain.

Unfortunately, the psychotropic properties of THC have inhibited its use clinically. Recently, cannabinoid research has broadened to the study of CBD, which has been found to have anti-psychotropic, anti-inflammatory, and antinociceptive properties, particularly when administered alongside THC. In clinical studies, Sativex®, a 1:1 THC:CBD drug, has been found to be effective at reducing chronic pain without the psychotropic effects of THC alone. Although sex differences in the antinociceptive effects of THC have been demonstrated, no studies have been conducted examining sex differences associated with CBD alone or the potential sex differences associated with combined THC:CBD administration. The proposed study will test the hypothesis that females are more sensitive than males to the antinociceptive effects of THC and CBD administered alone and in combination, using an animal model of chronic pain. This study will determine some effects of CBD in females for the first time and provide further preclinical insight into the antinociceptive potential of cannabinoids across the sexes.

Investigation of Cellular Mechanisms Regulating Alcohol Disruption of Spermatogonial Stem Cell Activity. *Animal Sciences, Derek McLean, Associate Professor ($30,000).*

Alcohol (ethanol) exposure can have a severe impact on multiple aspects of cell survival and differentiation during development. It is well known that even a single exposure to ethanol has neurotoxic effects on the developing brain, leading to cell death and long-term consequences. One route of ethanol toxicity in cells is through mitochondrial damage. Ethanol causes changes in mitochondrial structure and function by decreasing respiratory rates, increasing production of reactive oxygen species (ROS), and altering enzymatic activity. Mitochondrial function also regulates stem cell fate by controlling the energetic balance required for stem cell proliferation and differentiation. The goal of this proposal is to determine how ethanol toxicity disrupts the activity of spermatogonial stem cells (SSCs) by investigating the role of mitochondrial damage following ethanol treatment. We have demonstrated that a single *in vivo* exposure of ethanol in pre-pubertal mice results in disruption of SSC activity, resulting in fewer SSCs in the testes when the animals reach puberty. This means we disrupted formation and/or proliferation of the SSC population. In addition, we found that the single exposure to ethanol caused significant apoptosis of differentiating germ cells in the testis and long-term changes in the expression of genes associated with SSC homeostasis. Thus, we know ethanol disrupts SSC function; our next step is to determine the cellular mechanism(s) causing this disruption. The hypothesis of this proposal is that ethanol damages SSC mitochondria so self-renewal and production of differentiating progeny is compromised. To test this hypothesis, we will complete the following aim: Determine if ethanol treatment of cultured SSCs causes mitochondrial damage resulting in fewer SSCs and evaluate mitochondrial morphology in ethanol-treated cultured SSCs and of undifferentiated germ cells after *in vivo* ethanol treatment. Completion of these experiments will provide us valuable preliminary data for our long-term

goal of determining the cellular mechanisms regulating ethanol damage to SSCs. The overall objective is to develop a focused research project with sufficient preliminary data to prepare a proposal for two NIH Program Announcements to study biological processes involving the cellular organelles and cellular stress responses in alcohol-induced tissue injury outlined in detail in section XII. The proposed project is innovative because it contributes to our development of a stem cell model to investigate ethanol-induced tissue injury at a cellular level. The results will contribute to our understanding of stem cell biology and potential negative regulators of fertility.

Analysis of a Clinically Relevant Model of Morphine Antinociception and Tolerance during Chronic Inflammatory Pain in the Rat.
Department of Psychology, Washington State University, Vancouver. Melissa Mehalick, Graduate Student. Mentor: Mike Morgan ($10,699).

Preclinical studies of chronic inflammatory pain typically employ pain evoked response assays that primarily measure responses to noxious stimuli rather than innate pain behaviors. Therefore, results from these studies do not provide the most accurate translational insight into pharmacological treatments for chronic pain patients. Additionally, preclinical studies mainly use male animals as subjects, even though chronic pain in humans is often more common and problematic for women (Manson, 2010; Wijnhoven et al., 2006; Leveille et al., 2005; Fillingim et al., 2009; Dominick et al., 2003). Several studies have measured pain-suppressed behaviors, such as locomotor activity and feeding, in rats and mice with chronic pain conditions to more closely mimic human pain behavior (Stevenson et al., 2011; Stevenson et al., 2009; Stevenson et al., 2006; Miller et al., 2011). The proposed study extends this approach by examining morphine antinociception and tolerance to suppressed locomotion as a result of Freund's Complete Adjuvant (CFA)-induced inflammatory chronic pain in both male and female rats. Locomotor activity will be measured continuously in the rat's home cage before and after administration of CFA. It is hypothesized that the presence of chronic inflammatory pain will suppress locomotor activity. Although acute administration of morphine is known to suppress locomotion, in this paradigm the antinociceptive effect of morphine is expected to restore activity. Repeated systemic injections of morphine (3.2 or 5.6 mg/kg) should induce tolerance as indicated by an inability of morphine to alleviate pain-suppressed locomotion. Additionally, traditional nociceptive tests such as the von Frey and Hargreaves tests will be used to validate the use of pain suppressed behaviors. These data will provide a translational basis for future studies examining the mechanisms for opioid antinociception and tolerance.

Do Nicotine and THC Consumption Reduce the Risk of Helminth Reinfection in Central African Foragers? ***Department of Anthropology. Casey Roulette, Graduate Student. Mentor: Ed Hagen ($10,699).***

The proposed project is an important part of a pilot study, partially funded by a prior grant from the Alcohol and Drug Abuse Research Program, that is testing an evolutionary theory of substance use. Many non-human animals appear to consume toxic plants to defend themselves against pathogens. Because most drugs of abuse, such as nicotine, are plant toxins or their close chemical analogs, it is possible that some human consumption of these substances is (unconsciously) motivated by their medicinal properties. We have been testing this hypothesis with a population of Central African forest foragers from 2008-present. Specifically, if high levels of tobacco and cannabis use in this population are motivated, in part, by high levels of intestinal helminth (worm) infection, then treating these infections with a commercial anthelmintic should reduce smoking, a hypothesis we are testing with a randomized control trial (RCT) study design. Using a longitudinal design, we are also testing whether high levels of smoking by uninfected individuals protects against future infections. The proposed research will complete the longitudinal study. Specifically, 356 assays of 178 saliva and urine samples from the year-long longitudinal study will be completed, followed by statistical analyses and write-up as preliminary data for extramural funding opportunities, as well as submission for publication.

The Analysis of Neuronal Metabolomes from Cocaine Abusing Rats by ESI-IM-TOFMS. ***Chemistry. Xing (Nancy) Zhang, Graduate Student. Mentor: Herb Hill ($12,227).***

The large amount of information contained in metabolomics complements data obtained from genomics, transcriptomics and proteomics – adding a final piece to the biochemical approach for the study of a biological system. The study of metabolomics involves the identities, quantization and fluxes of hundreds of thousands of metabolites, which show wide variations in chemical and physical properties. In the field of drug addiction, although extensive work has been done in neurobiology and animal models, metabolomes associated with drug addiction have not been sufficiently investigated. There are significant changes in brain metabolomes due to cocaine abuse, but the details are unknown. Elucidation of those changes will definitely uncover fundamental biochemical information on drug addiction. In this project, an analytical technique called electrospray ion mobility time of flight mass spectrometry (ESI-IM-TOFMS) is employed, and this technique allows efficient and sensitive analysis of all metabolites in one single analysis. After data acquisition from ESI-IM-TOFMS, global metabolic analysis by principle component analysis and further metabolic identification will be done. Hence, we will generate new metabolic insights into the biomolecular mechanisms of drug addiction.

Grants Awarded during FY 2014

Role of Catecholamine Neurons in the Solitary Tract Nucleus in Opioid Dependence and Reward*. Integrative Physiology and Neuroscience. Suzanne Appleyard, Assistant Professor, and Mingyan Zhu, Research Assistant Professor ($30,000).*

Physiological behaviors, such as drug reward and withdrawal, are complex phenomena that only occur in the context of a living animal with an intact nervous system. Moreover, these phenomena include interactions between different areas of the nervous system. Therefore, most aspects of these phenomena cannot currently be studied in tissue culture or by computer simulation. The mouse species was chosen because it is the only mammal for which there is a transgenic animal available in which NTS-CA neurons are labeled with EGFP. This model is invaluable to the proposed studies as it makes identification of the NTS-CA neurons possible in a live slice. In addition, mice have been used previously for many of the basic discoveries concerning drug abuse, and many mouse models are available. Therefore, using mice as our animal model will allow us to use these other lines of mice in the future to pursue different avenues of research that arise from these studies. The Principal Investigator has extensive experience with handling of mice as well as the analysis of mice using many different techniques including electrophysiology, neuroanatomy and behavior.

Sleep Disturbance & Smoking Relapse. *Sleep and Performance Research Center. Amy Bender, Graduate Student. Mentors: Matt Layton, John Roll, and Hans Van Dongen ($10,609).*

Of the forty-five million American adults who smoke cigarettes, approximately 50% attempt to quit each year. Only 6% successfully abstain from cigarettes for longer than six months. Given the adverse health consequences of continued smoking, identifying better, more reliable predictors for smoking relapse is needed in order to target treatments and improve cessation rates. Several studies have found a link between self-reported sleep disturbances and an increased risk for smoking relapse. However, the unreliability of subjective sleep reports and mixed results regarding types of sleep disturbance make it difficult to pinpoint which aspects of sleep physiology are related to and may underlie the risk of relapse. This project aims to clarify this issue through the use of polysomnography, the gold standard of objective sleep measurement. We hypothesize that compared to individuals who successfully quit smoking, those who relapse will have less total sleep time and more fragmented sleep before quitting and especially during the nights following the quitting attempt. Subjects in the study will be healthy smokers wanting to quit, with no co-occurring medical conditions, free from drugs, and aged 22-40 years (to control for sleep confounds associated with natural aging and/or poor health). Smoking status will be assessed objectively throughout the experiment using a carbon monoxide detector and salivary cotinine samples for later quantitative analysis. Depending on whether and when subjects relapse, sleep will be recorded in the laboratory up to three consecutive

nights – the night before and the two nights after smoking cessation. This study will yield the first data relating objective measures of sleep disturbance to relapsing in smokers and will provide preliminary data for an NIH R01 grant application to study bidirectional relationships between sleep disturbance and drug addiction.

Sustainability of a Youth Substance Use Prevention Program. ***Human Development. Brittany Cooper, Assistant Professor ($10,009).***

Strengthening Families Program (SFP), a nationally recognized evidence-based family skills training program for youth ages 10-14 and their parents, is one of the leading adolescent substance abuse prevention programs in the country and has been widely disseminated by WSU Extension and community partners across the state of Washington with over 500 programs implemented over the past 10 years (Cantu, Hill & Becker, 2010; Foxcroft, Ireland, Lister-Sharp, Lowe, & Breen, 2003). The program has demonstrated consistent positive impacts on youth behavior problems, delinquency, and alcohol and drug abuse in numerous clinical trials (Spoth, Redmond, & Lepper, 1999; Spoth, Reyes, Redmond, & Shin, 1999); however, many questions remain about how best to support the long-term sustainability of SFP in the real world. Few empirical studies have examined program sustainability in a systematic way, and those that have typically focus on simple, linear associations between predictors and sustainability (Stirman et al., 2012). The present project aims to move this work forward by gaining a more in-depth, multifaceted picture of the sustainability of SFP at 16 program sites across Washington State which have shown differential success at long-term sustainability. Making use of existing connections between WSU Extension and these communities, I will collect both quantitative and qualitative information from the site coordinator and lead program facilitator about the community, organizational, and program factors associated with sustainability. As the adoption and spread of evidence-based programs increases, providing the technical assistance and support needed to successfully promote sustainability becomes even more critical. The proposed pilot study represents the first step towards developing a federal grant proposal aimed at the development and evaluation of empirically-based tools, strategies, and technical assistance for promoting the sustainability of public health substance use prevention programs in real-world contexts.

Negative Affective Cue-Induced Impulsive-like Behavior: Role of Kappa-Opioid Receptors. ***Department of Psychology. Jessica Kissler, Graduate Student. Mentor: Brendan Walker ($7,553).***

Little research has examined the role of the dynorphin / kappa-opioid receptor system (DYN / KOR) in impulsive behavior. The DYN / KOR system is known to be dysregulated in alcohol dependence, making this system clinically relevant in regulating impulsive behavior and relapse to alcohol and substance use. Data from our laboratory demonstrates that KOR agonists can induce an impulsive phenotype and that cues associated with KOR agonist-induced negative affective-like states can drive escalated alcohol self-administration. This study will investigate the role of cues associated with

negative affective-like states (i.e., KOR agonist infusions) in modulating impulsive-like responding on the stop-signal reaction time (SSRT) task and delay-discounting (DD) task.

Assessing Parallel Development of Co-Morbid Substance Use in Adolescents with ADH. ***Department of Psychology. Mary Rose Mamey, Graduate Student. Mentors: Len Burns and Sterling McPherson ($10,698).***

This application seeks funding from the WSU ADARP program to start a new line of investigation within the WSU addiction research community focused on adolescent substance use disorders (SUD) with co-occurring attention deficit hyperactivity disorder (ADHD). The use of advanced statistical and psychometric analyses has not yet been fully integrated into the SUD and ADHD literature, thus creating an area that requires exploration to evaluate effectively combined treatment approaches for these two disorders. Furthermore, data collected through many SUD clinical trials (via the National Drug Abuse Treatment Clinical Trials Network) are rarely analyzed beyond the initial purpose of the design, limiting the potential of such elaborate, time-consuming, and expensive datasets. Upon funding, this application will take unique advantage of a broad skill set maintained by the research team, including: 1) expertise in advanced biostatistical methods, 2) expertise in common, co-occurring mental health conditions among adolescents with substance use disorders (e.g., ADHD), and 3) direct clinical application of the research findings obtained from the proposed investigations. Our long-term goal for this project is to better understand the longitudinal relationship between substance use and ADHD symptoms in adolescents diagnosed with an SUD and co-morbid ADHD in order to improve public health and inform future treatment protocol design. With the availability of preexisting longitudinal clinical trial data, we hope to implement the more advanced statistical and psychometric methods in order to understand the relationship between SUD and ADHD, assess the effectiveness of treatment using novel methodology not previously explored, and allow for the replication of this process in order for others to pursue their own exploration using similar techniques. Because SUD clinical trials are perhaps the most important modality for producing externally valid treatments to the research/clinician community in order to improve public health, it is essential to maximize analytic accuracy.

Evaluation of Prevalence of Tobacco Use and Its Influence on Inpatient Rehabilitation Outcomes. ***WWAMI Medical Education Program. Michael Nguyen, Medical Student. Mentor: Kenneth Roberts ($8,616).***

Tobacco use is a main cause of preventable mortality in the United States and a leading contributor to morbidity as well. People with physical disabilities use tobacco at higher rates than their able bodied peers, yet little is known about the effects of smoking on health in this population compared to that of the able bodied, smoking population. There is considerable variability in the rates of tobacco use in the population of people with

physical disabilities, and even those who do not smoke may be at increased risk for exposure to second-hand smoke from family members and caregivers. One uniquely susceptible sub-population is people who have survived a stroke. Even though tobacco use is a major, modifiable, stroke risk factor, the impact of smoking on clinical outcomes following stroke remains poorly investigated. Because tobacco use is a modifiable risk factor, promoting tobacco cessation for these individuals is a critical public health goal. Determining the prevalence and impact on patient outcomes is a critical starting point. In the healthcare continuum, acute medical in-patient rehabilitation is an ideal starting point for investigating the prevalence and impact on outcomes in this population. The purpose of this project is to: 1) establish rates of tobacco use among inpatients receiving medical rehabilitation services for conditions including stroke, traumatic brain injury, spinal cord injury, amputation, major trauma, and cardiac events; 2) assess the rate of formal smoking cessation efforts instituted in this setting; and 3) determine the correlation between tobacco use and rehabilitation outcomes, including length of stay and degree of functional independence at discharge. We propose two hypotheses: 1) that the rate of tobacco use among inpatients with physical disabilities will exceed the recommended Healthy People 2020 objective, as well as national and state rates for the able bodied population; and 2) that tobacco use will be associated with longer length of stay and poorer functional outcomes compared to matched non-smokers, controlling for age distribution and gender in both smoker and non-smoker groups. This study will yield preliminary data about tobacco use among inpatients receiving rehabilitation services to inform future extramurally funded intervention projects that aim to test smoking cessation interventions in this population.

Patterns and Correlates of Substance Use Among Sexual Minority College Students*. Alyssa Norris, Graduate Student. Mentor: David Marcus ($4,904).*

Substance use is widespread on college campuses. Rates of alcohol consumption are higher for college students than for their same-age noncollege peers; as many as 80% of college students drink alcohol with 40-50% being classified as heavy drinkers (NIAAA, 2013; O'Malley & Johnston, 2002). Substance use is associated with death, assault, sexual abuse, personal injury, academic problems/drop-out, and poor mental health and suicidality (NIAAA, 2013). A continuing challenge for substance abuse researchers is to build an understanding of who is likely to experience negative outcomes from their substance use. Lesbian, gay, and bisexual (LGB) individuals not only demonstrate higher rates of substance use disorders (e.g., Green & Feinstein, 2012; McCabe et al., 2003), but they are also at higher risk for physical and sexual assault (Rothman et al., 2011), academic problems (e.g., Kosciw et al., 2009), and a range of deleterious mental health outcomes, including suicidality and self-harm, depression, and anxiety disorders (King et al., 2008; Mays & Cochran, 2001). Most researchers have examined substance use as yet another outcome of identifying as LGB, but it is possible that substance use is one pathway that

confers greater risk for subsequent outcomes (e.g., drop-out, poor mental health) among LGB students than their heterosexual peers. Using national (N = 534,661) as well as WSU-specific data (N = 5540 students) collected through the American College Health Association's National College Health Assessment, this project aims to build a greater understanding of the relationships among minority status, campus climate and discrimination, substance use, and related mental health outcomes.

Role of Catecholamine Neurons in the Solitary Tract Nucleus in Chronic Nicotine Exposure and Cessation*. Department of Integrative Physiology and Neuroscience. Stephen Page, Graduate Student. Mentor: Suzanne Appleyard ($12,382).*

Nicotine is well known as an addictive and dependence-forming drug. Tolerance to nicotine develops with chronic tobacco use, and long-term smokers report serious physiological side effects associated with withdrawal from the drug. Due to the negative effects of smoking cessation, including sudden weight gain and anxiety, nicotine addicts are often unsuccessful at quitting. A little understood aspect of nicotine dependence is the involvement of catecholamine neurons located in the nucleus of the solitary tract (NTS-CA). The NTS acts as an integration site for a number of visceral sensory inputs, and it projects to a variety of CNS sites – some of which are involved in both the rewarding aspect of nicotine and the stress/anxiety responses associated with withdrawal. We have shown in electrophysiological experiments that nicotine excites NTS-CA neurons, both directly and indirectly by activating glutamate inputs, through activation of nicotinic acetylcholine receptors (nAChRs) located on both CA cell bodies and afferent terminals of the vagus nerve. Our *long-term goal* is to understand the role of NTS-CA neurons in drug abuse and withdrawal and in the adaptive changes that occur during chronic exposure. We plan to submit a pre-doctoral NRSA to fund research that addresses 1) the mechanisms by which NTS-CA neurons undergo changes in activity during chronic nicotine exposure and 2) the role of endogenous cholinergic transmission in NTS-mediated adaptation to nicotine. The viability of the proposed research depends on our ability to measure a change in the electrophysiological properties of NTS-CA neurons. Hence, the overall objective of this proposal is to determine whether the electrical properties of NTS-CA neurons, and their response to nicotine administration, are altered during both chronic nicotine exposure and spontaneous withdrawal. We are prepared to address the above questions with the use of mouse horizontal brain slice preparations by electrophysiological techniques. Our approach provides precise measurements of neuronal responses to acute nicotine application onto NTS-CA neurons. This system allows us to study the mechanism(s) by which CA cell responses are altered in animals that were chronically treated with nicotine or in those that received chronic exposure to nicotine and were then acutely deprived of it. The contribution of the proposed study is expected to be significant because an understanding of the neural mechanisms which underlie nicotine addiction and withdrawal is required for the development of more targeted pharmacological treatment options.

Predicting Substance Use and Risky Sexual Behavior: Psychopathic Personality Traits and Urgency. ***Department of Psychology. Abere Sawaqdeh and Debra O'Connell, Graduate Students. Mentor: David Marcus ($7,270).***

Two out of every five college students are considered heavy drinkers and 20% of college students are current users of illicit drugs (O'Malley & Johnston, 2002; Substance Abuse and Mental Health Services Administration, 2011). While substance use can lead to a number of detrimental outcomes, including injury or death, one of the most frequent correlates is risky sexual behavior (RSB). Predicting these types of behaviors is necessary for developing practical interventions. Both psychopathic personality traits and urgency (i.e., the tendency to engage in rash behaviors when experiencing extreme emotion) have been linked to substance use and RSB; however, the majority of these studies have been cross-sectional and suffer other methodological deficiencies. Furthermore, no study has assessed these personality characteristics simultaneously. In our proposed study, we plan to conduct a three week interval-contingent ecological momentary assessment where approximately 100 students will provide daily reports of their substance use, RSB and mood. Baseline assessments will gauge the aforementioned personality traits in order to construct predictive models of substance use and RSB. Our hope is to provide an innovative and ecologically valid picture of why certain students engage in these potentially harmful behaviors while others do not.

RNA Interference to Investigate the Role of Perineuronal Nets in Cocaine-Seeking Behavior. Integrative Physiology and Neuroscience. ***Megan Slaker, Graduate Student. Mentor: Barbara Sorg ($10,566).***

Perineuronal nets (PNNs) are unique aggregations of the extracellular matrix (ECM) that are found primarily around a subset of fast-spiking, parvalbumin-containing GABAergic interneurons. PNNs have been implicated in the loss of plasticity within the cortex that results in limited learning. Removal of PNNs reinstates learning dependent plasticity in adult animals within the visual cortex, hippocampus, amygdala, and medial prefrontal cortex (mPFC). We have recently found that removal of PNNs within the mPFC impairs consolidation and reconsolidation of cocaine-associated memories in a cocaine-induced conditioned place preference (CPP) task. Most studies, including our own, use chondroitinase-ABC (Ch-ABC) as a pharmacological manipulation to degrade components of the PNN. However, this method produces a global disruption of the so-called "loose" ECM that is present throughout the brain, which confounds interpretation of the results. This proposal seeks to use a different molecular technique, small interfering RNA (siRNA), to specifically target and knockdown one critical component of the PNN. The component we have chosen to target is cartilage link protein-1 (Crtl-1) because it is located exclusively within PNNs and is essential for the proper formation of PNNs. The first goal is to determine the time course for the intensity of PNNs to decrease following administration of a Crtl-1 siRNA within the mPFC. The second goal is to administer a Crtl-1 siRNA within the

mPFC prior to training rats on a CPP task. This approach will allow us to target specifically PNNs rather than both PNNs and the rest of the loose ECM. This will allow us to determine more specifically the role of PNNs in cocaine-seeking behavior. Two alternative methods that are also proposed are a) an adeno-associated virus (AAV) encoding a small hairpin RNA specific to Crtl-1 and b) a designer receptor exclusively activated by designer drugs (DREADDs) to specifically activate or inhibit only those neurons surrounded by PNNs within the mPFC.

Adenosine: Linking Cocaine Addiction to Sleep Abnormalities.
Integrative Physiology and Neuroscience. Barbara Sorg, Professor (PI), James Krueger, Regents Professor (Co-I), Jonathan Wisor, Associate Professor (Co-I) ($24,434).

Disrupted sleep in cocaine addicts is consistently reported, and this disruption worsens over the course of abstinence. Our long-term goal is to determine whether disrupted sleep during cocaine withdrawal increases the susceptibility to relapse and, conversely, whether normalizing sleep in cocaine addicts suppresses relapse or renders addiction treatments more effective. This proposed project in rats represents a critical step toward developing a comprehensive, multi-disciplinary program at WSU that will focus on sleep, circadian rhythms, and addiction in animals with Drs. Jim Krueger, Jonathan Wisor, and Heiko Jansen. Future studies will focus on human studies with Drs. John Roll, Matt Layton, and Hans Van Dongen at WSU Spokane and the Sleep and Performance Research Center. The studies described here are the first to integrate the research strengths of WSU faculty in sleep, circadian rhythms, and addiction.

We hypothesize that withdrawal during cocaine abstinence alters sleep and that this abnormality in part drives relapse behavior in a vicious cycle. We further hypothesize that the mechanism for disruptive effects of cocaine on sleep occurs through alterations in adenosine regulation. Remarkably, no studies have bridged the gap between disrupted sleep in cocaine-abstinent addicts by examining the mechanisms by which sleep is disrupted during withdrawal. There are many short-term effects of cocaine exposure; however, long-term withdrawal leads to enduring molecular changes that are most relevant to relapse occurring over long abstinence periods in human cocaine addicts. It is over this longer withdrawal period that disrupted sleep is observed and during which we propose to identify mechanisms underlying this disrupted sleep. Our preliminary data indicate that daily long-access (6 hr) to cocaine self-administration during the second half of the active cycle, essentially over the same phase as cocaine, is most often taken by humans and overrides the ability of light to entrain daily rhythms. This finding indicates that cocaine self-administration usurps normal daily rhythms, readjusting them to follow the time of cocaine exposure rather than the time of light exposure, and implicates alterations in both circadian and sleep regulation. Surprisingly, no studies to our knowledge have tracked sleep patterns in rats after cocaine self-administration. A prime candidate molecule that links sleep and addiction is adenosine. Here we will identify cocaine withdrawal-induced changes in a key adenosine receptor, the A2A receptor

(A2AR), which is known to critically modulate both cocaine reward and sleep via its effects on dopamine and glutamate systems. In turn, we will determine how modifying activity of A2ARs at two times of day will contribute to cocaine reward and sleep.

Rats will be trained to self-administer saline (control) or cocaine for 6 hr, and sleep recordings will be conducted during the entire course of self-administration and also over a 3 wk withdrawal period from cocaine. We will also collect brain samples (nucleus accumbens core and shell regions, dorsal striatum, and hypothalamus) two times of day to assess the diurnal pattern of A2AR mRNA expression. To define the link between cocaine-seeking behavior and sleep, A2ARs will be targeted to manipulate sleep and cocaine-seeking behavior. Establishing a mechanistic link between sleep and cocaine-seeking behavior lies at the core of future studies in humans to establish a causal connection between abnormal sleep and relapse to cocaine.

Alcohol Dependence-Induced Working Memory Deficits: Role of Dysregulated Dynorphin/Kappa-Opioid Receptors. ***Department of Psychology. Brendan Walker, Associate Professor ($22,500).***

Alcohol abuse and dependence is a chronic relapsing disorder characterized by continued alcohol use despite numerous adverse consequences. Impaired working memory and severe negative affective states in alcoholics are devastating symptoms of alcohol dependence that promote excessive alcohol consumption and contribute to treatment failure. As such, there is a considerable need to develop therapeutics that address various symptoms during acute and protracted withdrawal for the alcohol-dependent population. The principal investigator's long-term goal is to identify effective therapeutic targets for the treatment of alcohol abuse and dependence. The objective of this application is to understand alterations in the dynorphin/kappa-opioid receptor (DYN/KOR) system and the resulting changes in KOR-mediated signaling pathways in the medial prefrontal cortex (mPFC) following chronic alcohol exposure that lead to working memory deficits. The central hypothesis is that chronic alcohol exposure upregulates the DYN/KOR system in the mPFC of alcohol-dependent populations through a presynaptic KOR-mediated increase in extracellular signal-regulated kinases (ERK) signaling that reduces GABA release to produce working memory impairments. The rationale is that the present study will identify the mPFC DYN/KOR system as a novel target to alleviate working memory deficits commonly observed in alcoholics and will enable the development of effective pharmacotherapies to treat alcohol dependence. Two specific aims will be pursued in order to accomplish the objective of this study. Specific Aim 1 will evaluate the effect of chronic alcohol exposure on working memory-related performance and the impact of mPFC KOR blockade on alcohol dependence-induced working memory impairments. Specific Aim 2 will evaluate DYN A peptide expression and KOR-mediated ERK signaling in mPFC presynaptic GABAergic terminals of alcohol-dependent rats. Collectively, the present study will characterize neuroadaptations in the DYN/KOR system and underlying mechanisms within the mPFC which contribute to working memory impairment in alcohol dependence. Targeting the DYN/KOR system is a novel approach that could

help to treat alcohol abuse and dependence by treating symptoms (e.g., impaired working memory) that are currently unaddressed both conceptually and practically. The results of proposed studies will have a substantial positive impact, as currently there are no medications available to treat the cognitive impairment that contributes to reduced treatment compliance and increased chance of relapse to harmful alcohol consumption.