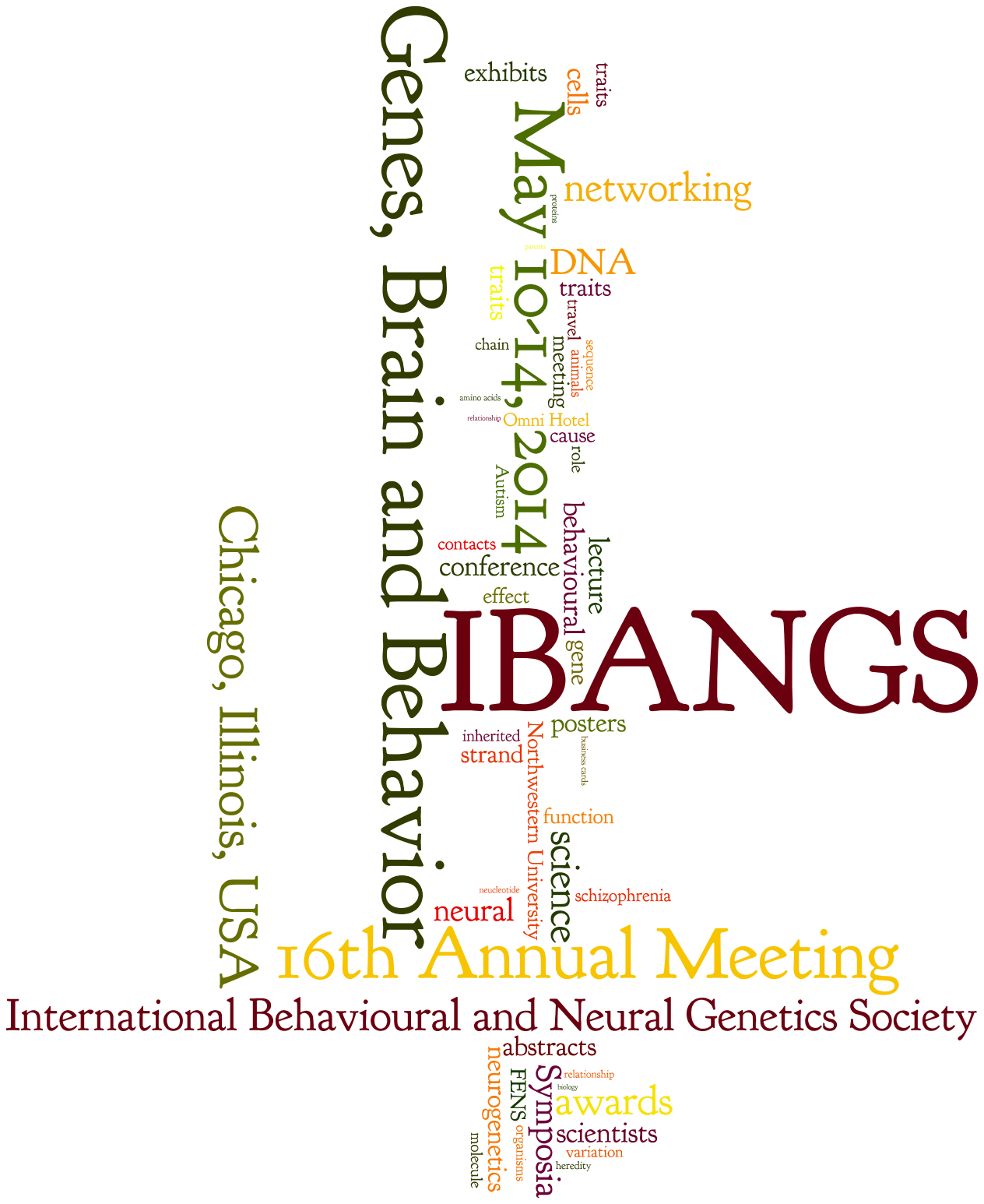
Genes, Brain and Behavior
May 10-14, 2014
Chicago, Illinois, USA
IBANGS
16th Annual Meeting
International Behavioural and Neural Genetics Society
exhibits
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proteins
parents
DNA
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Symposia
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variation
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molecule

Genes, Brain, and Behavior 2014

16th Annual Meeting of the International Behavioural and Neural Genetics Society

May 10 – 13, 2014

Chicago, Illinois
USA

Save the Dates!

Genes, Brain and Behavior 2015

Uppsala, Sweden
May 20-22, 2015
Local Host: Lina Emilsson

Local Hosts and Organizing Committee:

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Eva Redei, Co-Chair
Clarissa Parker
Mark Rutledge-Gorman
Amy Lasek
Julia Chester
Justin Rhodes

Program Committee:

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Leo Schalkwyk
Lina Emilsson
Wim Crusio
Mary-Anne Enoch
Igor Ponomarev
Abraham Palmer

IBANGS Central Office:

Marianne Van Wagner, Executive Coordinator
Alison Watson, MBA

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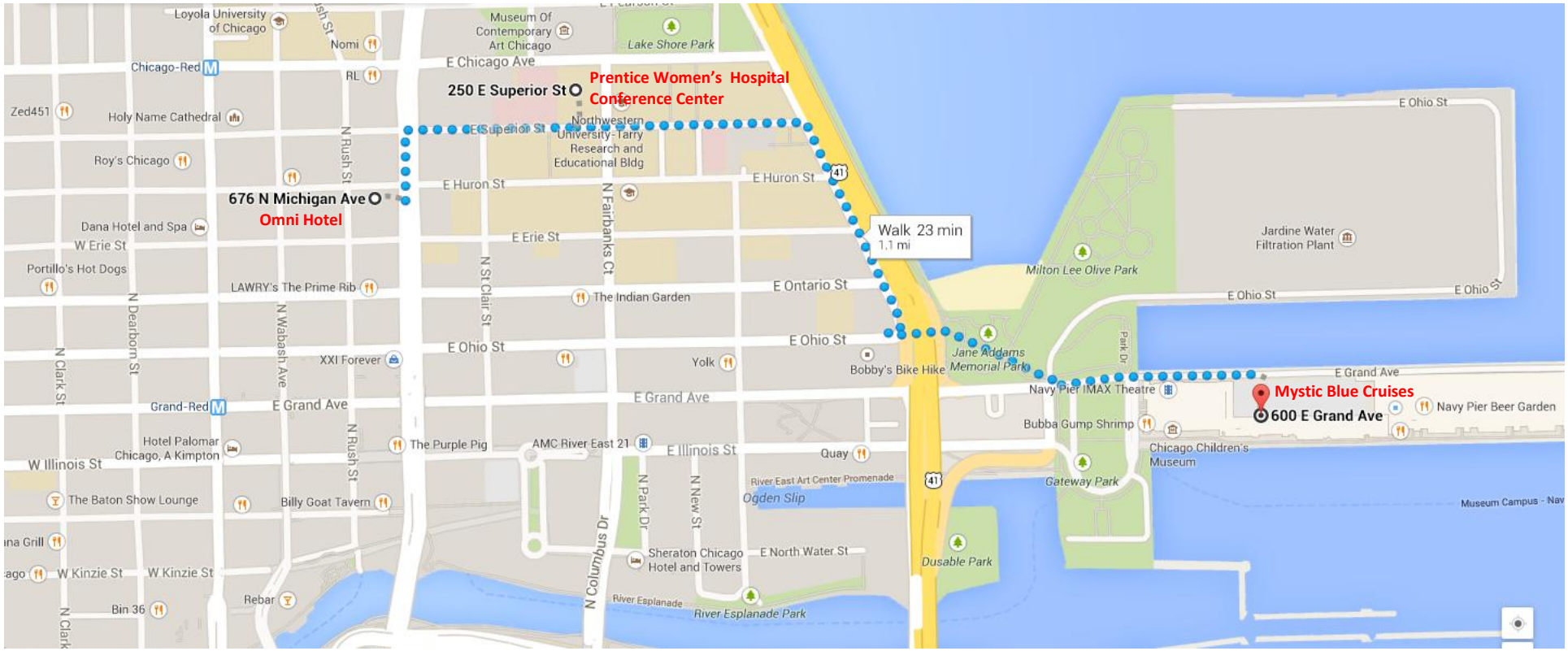
Reston, Virginia, USA 20190
http://cleversysinc.com/
(703) 787-6946

Applicant's Name	Affiliation	Country
Graduate Students		
Barkley-Levenson Amanda	Oregon Health & Science Univ	USA
Cousin Margot	Mayo Graduate School	USA
Eastwood Emily	Oregon Health & Science Univ	USA
Fritz Brandon	Indiana Univ-Purdue Univ Indianapolis	USA
Gileta Alexander	Univ of Chicago	USA
Goldberg Lisa	Boston Univ	USA
Gonzales Natalia	Univ of Chicago	USA
Harkness John	Oregon Health & Science Univ	USA
Kasten Chelsea	Indiana Univ-Purdue Univ Indianapolis	USA
King Christopher	State Univ of New York at Buffalo	USA
Krug Lisa	Cold Spring Harbor Laboratory	USA
Krug Randall	Mayo Graduate School	USA
Lee Han	Mayo Graduate School	USA
McMurray Katherine Johnston	Univ of Chicago	USA
Mehta Neha	Northwestern Univ	USA
Melroy Whitney	Univ of Colorado	USA
Mustroph Martina	Univ of Illinois at Urbana-Champaign	USA
O'Tousa David	Indiana Univ-Purdue Univ Indianapolis	USA
Rieger Michael	Washington Univ - St Louis	USA
Schoenrock Sarah Adams	Univ of North Carolina-Chapel Hill	USA
St Pierre Celine	Univ of Chicago	USA
Sungur Özge	Philipps-University of Marburg	Germany
Tunc-Ozcan Elif	Northwestern Univ	USA
Vadnie Chelsea	Mayo Graduate School	USA
Weera Marcus	Purdue University	USA
Yazdani Neema	Boston Univ	USA
Postdocs		
Darlington Todd	Univ of Utah	USA
Dickson Price	The Jackson Laboratory (JAX)	USA
Distler Margaret	Univ of Chicago	USA
Fenckova Michaela	Radboud Univ, Nijmegen	Netherlands
Klyuchnikova Maria	Severtsov Institute of Ecology and Evolution	Russia
Linsenbardt David	Indiana Univ-Purdue Univ Indianapolis	USA
Maloney Susan	Washington Univ - St Louis	USA
Montgomery Karieen	Baylor Univ	USA
Sittig Laura	Univ of Chicago	USA
Junior Faculty		
Balodis Iris	Yale Univ	USA
Bichler Zoë	National Neuroscience Institute	Singapore
Chen Gang	Nanjing Univ	China
Clark Karl	Mayo Graduate School	USA
Greenwood Ben	Univ of Colorado	USA
Kamens Helen	Penn State Univ	USA
Kliethermes Christopher	Drake Univ	USA
Parker Clarissa	Middlebury College	USA
Seggio Joseph	Bridgewater State Univ	USA

IBANGS Meeting Map



Omni Chicago Hotel

676 North Michigan Avenue
Chicago, Illinois 60611
Phone: (312) 944-6664, Fax: (312) 266-3015

Mystic Blue Cruises

600 E. Grand Avenue
Chicago, Illinois 60611
Phone: (312) 595-7437

Prentice Women's Hospital

250 East Superior, 3rd Floor, Conference Center, Room L, Chicago, Illinois 60611

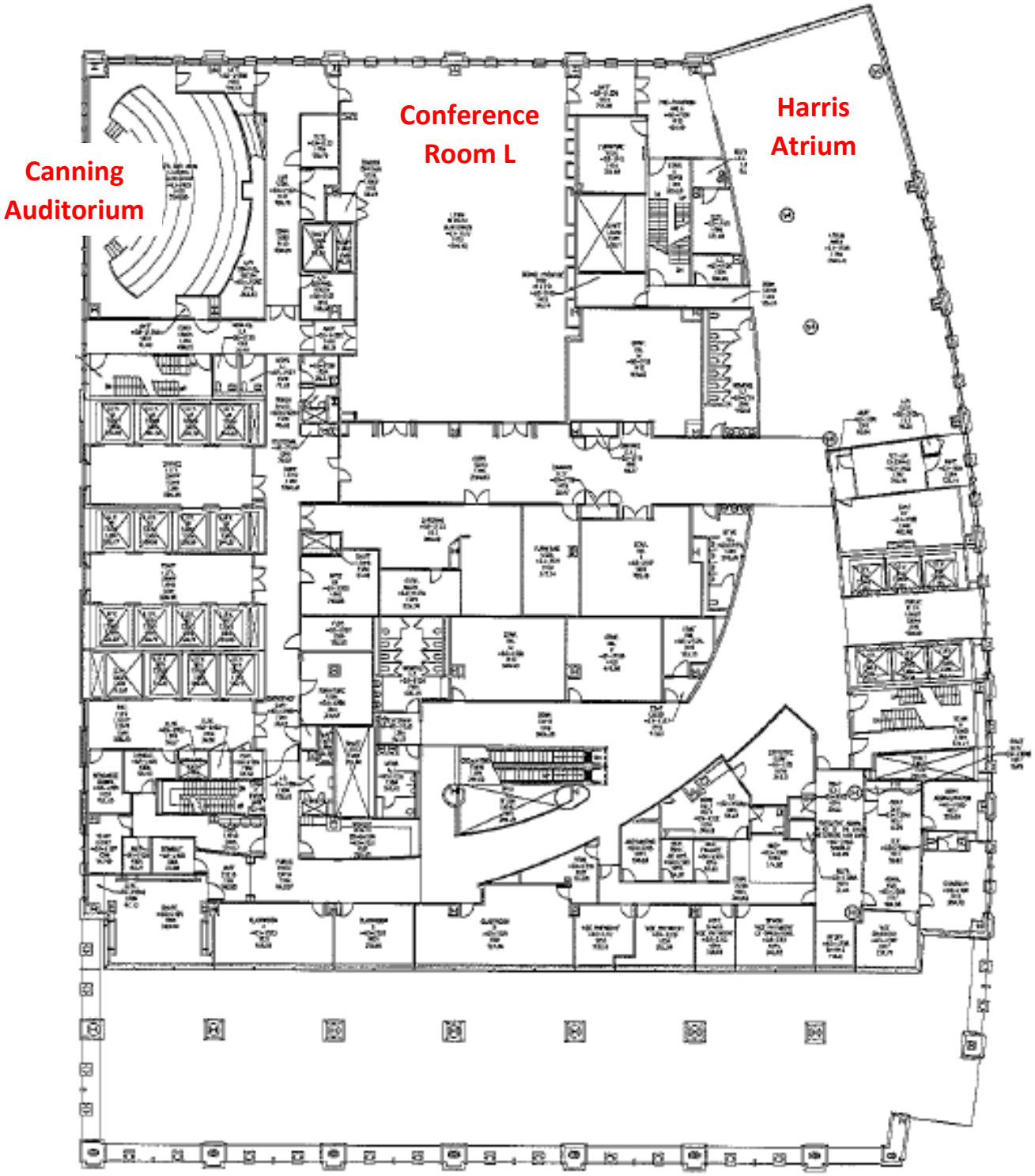
Airport Transportation

MIDWAY: Take a taxi from the taxi line, or the 55 CTA bus to campus. Midway is 25 minutes by car/taxi and 50 minutes by public transportation.

O'HARE: Take a taxi from the taxi line, or the Blue CTA train line to downtown Chicago, and transfer to the 6, X28, or 2 bus on State Street.

Prentice Women's Hospital

Floor Plan



The University of Chicago Committee on Genetics, Genomics & Systems Biology presents:

Annual Symposium

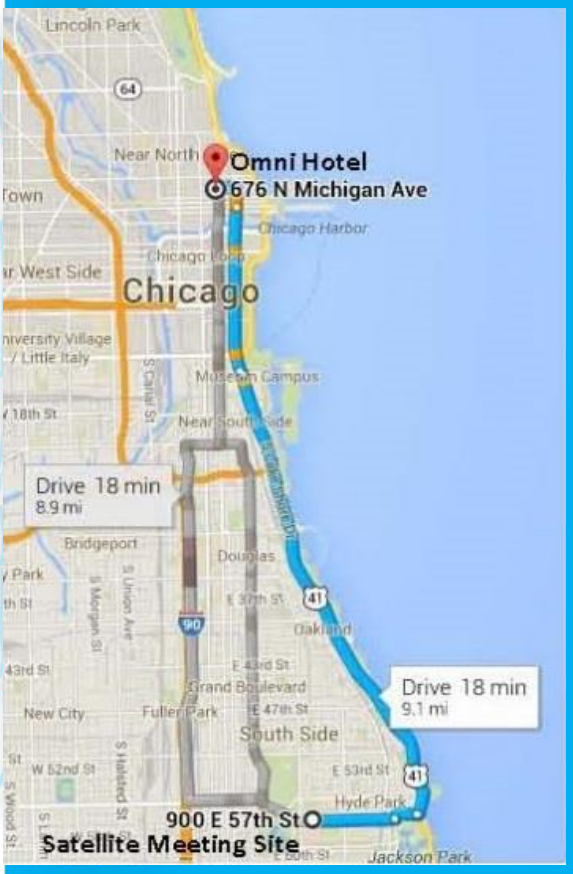
Using quantitative genetics to elucidate the mechanisms of psychiatric health and disease

LAUREN WEISS, PhD
University of California, San Francisco
"New Angles in the Genetic Architecture of Autism"

JONATHAN SEBAT, PhD
University Of California, San Diego
"From CNVs to Whole Genome Sequencing in Psychiatric Disease"

BENJAMIN NEALE, PhD
Broad Institute
"How persistence succeeded in the GWAS of schizophrenia"

LOUIS J. PTÁČEK, MD
Howard Hughes Medical Institute
University of California, San Francisco
"Novel insights into circadian function and sleep through studies in humans"



Friday, May 9, 2014

1:00 p.m. – 5:00 p.m.

Knapp Center for Biomedical Discovery (KCBD)
Auditorium, Room 1103
900 East 57th Street, Chicago, IL 60637

For information and assistance contact Sue Levison at 773.702.2464

This special symposium will precede the 16th Annual IBANGS Meeting: Genes, Brain & Behavior (www.ibangs.org).

Omni Chicago Restaurant List - 2014

Restaurant/Cuisine Type	Private Dining	Price Range	Address	Phone #	Miles from hotel
	$ = $1 - $10		**$$$ = $31 - $50**		
	$$ = $11 - $30		**$$$$ = $51+**		
Breakfast					
Corner Bakery	n/a	$	676 N. St. Clair	312-266-2570	0.3
Eggsperience	n/a	$$	35 W. Ontario	312-870-9773	0.3
Einstein Bros Bagel	n/a	$	109 E. Pearson	312-943-9888	0.3
Oak Tree Restaurant	☑	$$	900 N. Michigan 6th Floor	312-751-1988	0.4
Original Pancake House	n/a	$	22 East Bellevue	312-642-7917	0.5
Panera Bread	n/a	$	635 N. Fairbanks	312-274-3955	0.5
Sunny Side Up Café	n/a	$$	42 E. Superior	312-930-4242	0.2
Tempo	n/a	$$	6 E. Chestnut Street	312-644-1500	0.4
West Egg Café	n/a	$$	620 N. Fairbanks	312-280-8366	0.5
Yolk	n/a	$$	747 N. Wells or 355 E. Ohio	312-787-2227	0.5
American (Contemporary)					
Bandera	n/a	$$	535 N. Michigan Ave	312-644-3524	0.4
Cheesecake Factory	n/a	$$	875 N. Michigan Ave	312-337-1101	0.3
Epic Lounge	☑	$$$$	112 W. Hubbard	312-222-4940	0.7
Girl & The Goat	☑	$$$	809 W. Randolph	312-492-6262	1.8
Graham Elliott	☑	$$$$	217 W. Huron St.	312-624-9975	0.5
Grand Lux Café	n/a	$$	600 N. Michigan Ave.	312-276-2500	0.3
Hubbard Inn	☑	$$$	110 W. Hubbard St.	312-222-1331	0.7
MK	☑	$$$$	868 N. Franklin St.	312-482-9179	0.8
Purple Pig	n/a	$$	500 N. Michigan Ave.	312-464-1744	0.3
RL (Ralph Lauren Restaurant and Café)	n/a	$$$	115 E. Chicago Ave.	312-475-1100	0.2
Sepia	☑	$$$	123 N. Jefferson St.	312-441-1920	1.9
Signature Room - 95th Floor of John Hancock Building	☑	$$$$	875 N. Michigan Ave.	312-787-9596	0.3
Table 52	☑	$$$	52 W. Elm St.	312-212-1112	0.7
Tavern at the Park	☑	$$$	130 E. Randolph St.	312-552-0070	0.8
Tavern on Rush	☑	$$$	1031 N. Rush St.	312-664-9600	0.6
Tortoise Club	☑	$$$	350 N. State St.	312-755-1700	0.5
Chinese/Pan Asian					
Big Bowl	n/a	$$	60 E. Ohio St.	312-951-1888	0.3
Moto	☑	$$$$	945 W. Fulton Market	312-491-0058	1.5
P.F. Chang's	n/a	$$	530 N. Wabash Ave.	312-828-9977	0.3
Shanghai Terrace	☑	$$$	108 E. Superior St.	312-573-6744	0.1
Sunda	☑	$$$	110 W. Illinois St.	312-644-0500	0.6
Lounge/Bar					
American Junkie	☑	$$$	15 W. Illinois St.	312-239-0995	0.5
Bijans Bistro	☑	$$	663 N. State St.	312-202-1904	0.2
The Gage	☑	$$$	24 S. Michigan Ave.	312-372-4243	1
Howl at the Moon	☑	$$	26 W. Hubbard St.	312-863-7427	0.6
Jake Melnick's	☑	$$	41 E. Superior St.	312-266-0400	0.1
The Kerryman	☑	$$$	661 N. Clark St.	312-335-8121	0.3
PJ Clarkes	☑	$$$	302 E. Illinois St.	312-670-7500	0.5
Pops for Champagne	☑	$$$	601 N. State St.	312-266-7677	0.3
Public House	☑	$$	400 N. State St	312-265-1240	0.6
The Publican	☑	$$$	837 W. Fulton Market	312-733-9555	1.9
Rockit Bar and Grill	☑	$$$	22 W. Hubbard St.	312-645-6000	0.5
Theory	☑	$$	9 W. Hubbard St.	312-644-0004	0.5
Three Dots and a Dash	☑	$$	435 N. Clark St.	312-610-4220	0.7
Timothy O'Tooles	☑	$$	622 Fairbanks Ct.	312-642-0700	0.4
Untitled	☑	$$$	111 W. Kinzie St.	312-880-1511	0.7

Restaurant/Cuisine Type	Private Dining	Price Range	Address	Phone #	Miles from hotel
Brazilian					
Brazzaz	☑	$$$	539 N. Dearborn St.	312-595-9000	0.4
Fogo De Chao	☑	$$$	661 N. LaSalle St.	312-932-9330	0.4
Texas de Brazil	☑	$$$	51 E. Ohio St.	312-670-1006	0.2
Zed 451	☑	$$$	739 N. Clark St.	312-266-6691	0.5
French					
Bistronomic	☑	$$$	840 N. Wabash Ave.	312-266-3383	0.3
Blackbird	☑	$$$$	619 W. Randolph St.	312-715-0708	1.8
Café Des Architectes	☑	$$$	20 E. Chestnut St.	312-324-4000	0.3
Everest	☑	$$$$	440 S. LaSalle St.	312-663-8920	1.6
Le Colonial	☑	$$$	937 N. Rush St.	312-255-0088	0.4
Les Nomades	☑	$$$$	222 E. Ontario St.	312-649-9010	0.6
NoMI - French, Japanese	☑	$$$$	800 N. Fairbanks Ct.	312-595-0800	0.2
Paris Club	☑	$$$	59 W. Hubbard St.	312-595-0800	0.6
Pierrot Gourmet	n/a	$$	108 E. Superior St.	312-573-6749	0.1
Greek					
Athena	☑	$$	212 S. Halsted St.	312-655-0000	2.9
Greek Islands	☑	$$	200 S. Halsted St.	312-782-9855	2.9
Parthenon	☑	$$	314 S. Halsted St.	312-726-2407	2.3
Indian					
Gaylord	n/a	$$	100 E. Walton St.	312-664-1700	0.5
Indian Garden	☑	$$	247 E. Ontario St.	312-280-4910	0.5
India House	☑	$$	59 W. Grand Ave.	312-645-9500	0.5
Vermilion - Indian, Latin American, South American	☑	$$$$	10 W. Hubbard St.	312-527-4255	0.5
Italian					
Bar Toma	☑	$$	110 E. Pearson St.	312-266-3110	0.2
Caliterra Restaurant	☑	$$$	633 N. St. Clair St.	312-274-4444	0.3
Carmine's	☑	$$$	1043 N. Rush St.	312-988-7676	0.6
Coco Pazzo	☑	$$$	300 W. Hubbard St.	312-836-0900	0.9
Coco Pazzo Café	☑	$$	636 N. St. Clair St.	312-664-2777	0.4
Francesca's on Chestnut	☑	$$	200 E. Chestnut St.	312-482-8800	0.4
Maggiano's	☑	$$	516 N. Clark St.	312-644-7700	0.6
Phil Stefani's 437 Rush	☑	$$$	437 N. Rush St.	312-222-0101	0.6
Piccolo Sogno	☑	$$$	464 N. Halsted St.	312-421-0077	1.4
Prosecco	☑	$$$	710 N. Wells St.	312-951-9500	0.5
Quartino's	☑	$$	626 N. State St.	312-329-2500	0.2
Rosebud on Rush	☑	$$$	720 N. Rush St.	312-266-6444	0.1
RPM	☑	$$$	52 W. Illinois St.	312-222-1888	0.5
Spiaggia	☑	$$$$	980 N. Michigan Ave.	312-280-2750	0.4
Volare	☑	$$	201 E. Grand Ave.	312-410-9900	0.5
Japanese					
Japonais	☑	$$$	600 W. Chicago Ave.	312-822-9600	1
Kamehachi	☑	$$	240 E. Ontario St.	312-587-0600	0.5
Niu	☑	$$	332 E. Illinois St.	312-527-2888	0.5
Oysy	n/a	$$	50 E. Grand Ave.	312-670-6750	0.2
Roka Akor	☑	$$$$	111 W. Illinois St.	312-477-7652	0.6
Ron of Japan	☑	$$$	230 E. Ontario St.	312-644-6500	0.5
Sushi Samba Rio	☑	$$$	504 N. Wells St.	312-595-2300	0.7
Mediterranean					
Naha - Mediterranean, Cali Fusion	☑	$$$$	500 N. Clark St.	312-321-6242	0.6
Middle Eastern					
Alhambra - Moroccan	☑	$$$	1240 W. Randolph St.	312-666-9555	1.8
Sayat Nova - Armenian, Mediterranean	n/a	$$	157 E. Ohio St.	312-644-9159	0.3

Restaurant/Cuisine Type	Private Dining	Price Range	Address	Phone #	Miles from hotel
Pizza					
Gino's East	☑	$$	162 E. Superior St.	312-266-3337	0.1
Giordano's	☑	$$	730 N. Rush St.	312-951-0747	0.1
Lou Malnati's	☑	$$	1120 N. State St.	312-725-7777	0.6
Pizzeria Due	n/a	$$	619 N. Wabash Ave.	312-943-2400	0.2
Pizzeria Uno	n/a	$$	29 E. Ohio St.	312-321-1000	0.2
Spanish/Mexican					
Adobo Grill	☑	$$	1610 N. Wells St.	312-266-7999	1.6
Carnivale	☑	$$$	702 W. Fulton St.	312-580-5005	1.7
Café Iberico	☑	$$	739 N. LaSalle Blvd.	312-573-1510	0.4
Cantina Laredo	☑	$$	508 N. State St.	312-955-0014	0.4
Frontera Grill	☑	$$$	445 N. Clark St.	312-661-1434	0.4
Mercadito	☑	$$$	108 W. Kinzie St.	312-329-9555	0.8
Mercat a la Planxa	☑	$$$	638 S. Michigan Ave.	312-765-0524	1.6
Nacional 27	☑	$$$	325 W. Huron St.	312-664-2727	0.6
Salpicon	☑	$$$	1252 N. Wells St.	312-988-7811	1.2
Tavernita	☑	$$$	151 W. Erie St.	312-274-1111	0.4
Topolobampo	☑	$$$	445 N. Clark St.	312-661-1434	0.6
Xoco	☑	$$	449 N. Clark St.	312-334-3688	0.6
Seafood					
Devon Seafood Grill	☑	$$	39 E. Chicago Ave.	312-440-8660	0.2
GT Fish and Oyster	☑	$$$	531 N Wells St.	312-929-3501	0.7
Hugo's Frog Bar & Fish House	☑	$$$	1024 N. Rush St.	312-640-0999	0.5
Joe's Seafood Prime Steak & Snow Crab	☑	$$$$	60 E. Grand Ave.	312-379-5636	0.4
L2O	☑	$$$$	2300 N. Lincoln Park West	773-868-0002	2.5
McCormick & Schmick's	☑	$$	41 E. Chestnut St.	312-397-9500	0.2
Riva Navy Pier - Phil Stefanis	☑	$$$	700 E. Grand Ave.	312-644-7482	1.5
Roy's Hawaiian Fusion	☑	$$$	720 N. State St.	312-787-7599	0.2
Steak					
Capital Grille	☑	$$$$	633 N. St. Clair St.	312-337-9400	0.3
Chicago Chop House	☑	$$$	60 W. Ontario St.	312-787-7100	0.4
Chicago Cut	☑	$$$$	300 N. Lasalle St.	312-521-5100	0.8
David Burke's Primehouse	☑	$$$$	616 N. Rush St.	312-660-6000	0.3
Ditka's	☑	$$$	100 E. Chestnut Ave.	312-587-8989	0.3
Erie Café	☑	$$$	536 W. Erie St.	312-266-2300	0.9
Fleming's	☑	$$$	25 E. Ohio St.	312-329-9463	0.2
Gene and Georgetti	☑	$$$	500 N. Franklin St.	312-527-3718	0.8
Gibson's	☑	$$$	1028 N. Rush St.	312-266-8999	0.5
Harry Caray's Italian	☑	$$$	33 W. Kinzie St.	312-828-0966	0.6
Keefer's	☑	$$$$	20 W. Kinzie St.	312-467-9525	0.6
Lawry's Prime Rib	☑	$$$	100 E. Ontario St.	312-787-5000	0.3
Mastro's	☑	$$$$	520 N. Dearborn St.	312-521-5100	0.5
Michael Jordan's	☑	$$$$	505 N Michigan Ave.	312-321-8823	0.2
Morton's (Original)	☑	$$$$	1050 N. State St.	312-266-4820	0.6
Morton's	☑	$$$$	65 E. Wacker Pl.	312-201-0410	0.8
Rosebud Steak House	☑	$$$	192 E. Walton St.	312-397-1000	0.1
Ruth's Chris	☑	$$$	431 N. Dearborn St.	312-321-2725	0.6
Saloon	☑	$$$	200 E. Chestnut St.	312-280-5454	0.4
Shula's	☑	$$$$	301 E. North Water St.	312-670-0788	0.5
Smith & Wolensky	☑	$$$$	318 N. State St.	312-670-9900	0.6
Sullivan's	☑	$$$$	415 N. Dearborn St.	312-527-3510	0.6
Wildfire	☑	$$	159 W. Erie St.	312-787-9000	0.5
Upscale - 2013 AAA 5 Diamond Awarded					
Alinea - New American (4 Consecutive Years)	☑	$$$$	1723 N. Halsted St.	312-867-0110	2
Arun's - Thai (8 Consecutive Years)	☑	$$$$	4156 N. Kedzie Ave.	773-539-1909	7.2
Everest - French (14 Consecutive Years)	☑	$$$$	440 S. LaSalle St.	312-663-8920	1.6
Tru - American (10 Consecutive Years)	☑	$$$$	676 N. Saint Clair St.	312-202-0001	0.3

Friday 09-May-14

18:00 **Opening Reception**
Omni Chicago Hotel - Picasso Ballroom

13:00 **Satellite Meeting**
Knapp Center for Biomedical Discovery

Saturday 10-May-14

7:00 **Breakfast**
Harris Family Atrium

8:30 **Outstanding Travel Awardees**
Barkley-Levenson
Mustroph
Clark
Sittig
Chair: Rutledge-Gorman Conf Rm L

10:00 **Coffee Break**
Harris Family Atrium

10:30 **Symposium I**
Conference Room L
"Behavioral, neural and genetic studies of compulsive eating in model organisms and humans"
Chair: Bryant

12:30 **Lunch**
Harris Family Atrium

13:30 **Symposium II**
Conference Room L
From junk to fame: the roles of transposable elements and non-coding RNAs in brain health and disease"
Chair: Reilly and Ponomarev

15:30 **Coffee Break**
Harris Family Atrium

16:00 **Distinguished Scientist Award Lecture**
Marla Sokolowski, PhD
Conference Room L

17:00 **Conclusion of Day 1**

Sunday 11-May-14

7:00 **Breakfast**
Harris Family Atrium

9:00 **Presidential Lecture**
Laura Jean Bierut, MD
Conference Room L

10:00 **Coffee Break**
Harris Family Atrium

10:30 **Symposium III**
Conference Room L
"Mechanisms underlying habituation across species - highly diverse, yet highly conserved?"
Chair: Schmid

12:30 **Lunch**
Harris Family Atrium

13:30 **Symposium IV**
Conference Room L
"Genes, brain, and exercise"
Chair: Ehringer

15:30 **Poster Session**
Harris Family Atrium

18:00 **Executive Committee Meeting**
Omni Chicago Hotel - Van Gogh meeting room, 3rd floor

20:00 **Conclusion of Day 2**

Monday 12-May-14

7:00 **Breakfast**
Harris Family Atrium

9:00 **Keynote Lecture**
Antonello Bonci, MD
Conference Room L

10:00 **Coffee Break**
Harris Family Atrium

10:30 **Symposium V**
Conference Room L
"Genetic and neurobiological networks implicated in social communication"
Chair: Dougherty

12:30 **Lunch**
Harris Family Atrium

13:30 **Selected Talk Session I**
Chair: Pollock Conference Room L
Rothenfluh
Parker
Shorter
Cummings
Delprato
Han

15:30 **Coffee Break**
Harris Family Atrium

16:00 **Young Investigator Lecture**
Camron Bryant, PhD
Conference Room L

17:00 **General Business Meeting**
Conference Room L

18:30 **Dinner Cruise**
Mystic Blue Cruises

22:00 **Conclusion of Day 3**

Tuesday 13-May-14

7:00 **Breakfast**
Harris Family Atrium

8:00 **Selected Talk Session II**
Chair: Boehm Canning Auditorium
Kamens
Krug
Eastwood
Mulligan

9:30 **Symposium VI**
Canning Auditorium
"Workshop on the use of advanced mouse populations"
Chair: Chesler

11:30 **Meeting Adjourned**

Friday, May 9

6:00-7:00 **Opening Reception** – *Omni Chicago Hotel, Picasso Ballroom*

Saturday, May 10

7:00-8:30 **Breakfast** – *Harris Family Atrium*

8:30-10:00 **Outstanding Travel Awardees** – Conference Room L
Chair: Mark Rutledge-Gorman, Oregon Health & Science University, USA

A. M. Barkley-Levenson - Oregon Health & Science University, USA, and Portland Alcohol Research Center, VA Medical Center, USA. *Genotypic- and sex-differences in anxiety-like behavior and anxiolytic response to alcohol in High Drinking in the Dark mice*.

Karl J. Clark - Mayo Addiction Research Center, Mayo Clinic., Rochester, Minnesota, USA. *Developing zebrafish methodology to model genetic and environmental modifiers of the vertebrate stress response system (SRS)*.

M. L. Mustroph - University of Illinois at Urbana-Champaign, USA. *New neurons are not necessary for exercise to abolish conditioned place preference for cocaine*.

Laura J. Sittig – University of Chicago, Chicago, Illinois, USA. *Genetic susceptibility to comorbid psychiatric phenotypes in a panel of mice deficient for the human type 2 diabetes gene TCF7L2*.

10:00-10:30 **Coffee Break** – Harris Family Atrium

Saturday, May 10 ***continued***

10:30-12:30 **Symposium I** – Conference Room L
Behavioral, neural and genetic studies of compulsive eating in model organisms and humans
Chair: Camron D. Bryant, Boston University School of Medicine, USA

- 10:30 Animal models of eating disorders: What we've learned and what's next. Nicole M. Avena, University of Florida-Gainesville, USA
- 11:00 Lateral hypothalamic circuits that regulate feeding and reward. Garret D. Stuber, University of North Carolina-Chapel Hill, USA
- 11:30 Generalized reward processing and inhibitory control in obese individuals with and without binge eating disorder. Iris M. Balodis, Yale University, USA
- 12:00 Genetics of eating disorders: Are cross disorder insights valuable for classification? Cynthia M. Bulik, University of North Carolina-Chapel Hill, USA

12:30-1:30 **Lunch** – Harris Family Atrium

1:30-3:30 **Symposium II** – Conference Room L
From junk to fame: The roles of transposable elements and non-coding RNAs in brain health and disease
Chair: Matthew Reilly, NIAAA and Igor Ponomarev, University of Texas at Austin

- 1:30 L1 retrotransposition in the nervous system. Alysson Muotri, University of California San Diego, USA
- 2:00 Intersection of RNA editing with gene expression and silencing: Implications for disease. Robert Reenan, Brown University, USA
- 2:30 The transposon storm hypothesis of neurodegeneration. Lisa Krug, Cold Spring Harbor Lab, USA
- 3:00 Transcriptional regulation of transposable elements in alcohol models. Igor Ponomarev, The University of Texas at Austin, USA

3:30-4:00 **Coffee Break** – Harris Family Atrium

4:00-5:00 **Distinguished Scientist Award Lecture** – Conference Room L
Marla Sokolowski, PhD, Professor of Ecology & Evolutionary Biology, University of Toronto, Canada. *Gene-environment interplay and behavior*.

Sunday, May 11

7:00-9:00 **Breakfast** – *Harris Family Atrium*

9:00-10:00 **Presidential Lecture** – Conference Room L
Laura Jean Bierut, MD, Professor of Psychiatry, Washington University School of Medicine, St. Louis, USA. *How Genetic Risk for Nicotine Dependence Translates into Successful Smoking Cessation*

10:00-10:30 **Coffee Break** – Harris Family Atrium

10:30-12:30 **Symposium III** – Conference Room L
Mechanisms underlying habituation across species - highly diverse, yet highly conserved?
Chair: Susanne Schmid, University of Western Ontario, Canada

- 10:30 High throughput phenotypic profiling leads to insights into mechanisms of habituation in C. elegans. Cathy Rankin, University of British Columbia, Canada
- 11:00 Using high-throughput light-off jump reflex habituation to understand learning deficits in Drosophila models of Intellectual Disability. Michaela Fenckova, University of Nijmegen, Netherlands
- 11:30 Forward genetic screen reveals a role for the pregnancy associated plasma protein-a gene in habituation learning. Marc Wolman, University of Wisconsin-Madison, USA
- 12:00 Synaptic mechanism underlying habituation of startle in rodents. Susanne Schmid, University of Western Ontario, Canada

12:30-1:30 **Lunch** – Harris Family Atrium

Sunday, May 11 ***continued***

1:30-3:30 **Symposium IV** – Conference Room L
Genes, brain, and exercise
Chair: Marissa Ehringer, University of Colorado, USA

1:30 The temporal effects of exericse on hippocampus-dependent memory in the rat: Multiple roles of BDNF. Áine M. Kelly, Trinity College, Ireland

2:00 Voluntary exercise reduces voluntary consumption of ethanol in mice: identification of candidate genes through striatal gene expression profiling. Todd M. Darlington, University of Colorado-Boulder, USA

2:30 Plasticity in the central serotonergic system contributes to exercise-induced stress resistance. Benjamin Greenwood, University of Colorado-Boulder, USA

3:00 Translating the effects of exercise on recognition memory: Dependence on age and genotype. David J. Bucci, Dartmouth College, USA

3:30-6:00 **Poster Session** – Harris Family Atrium

6:00-8:00 **Executive Committee Meeting** – Omni Chicago Hotel
Van Gogh Meeting Room, 3rd Floor

Monday, May 12

7:00-9:00 **Breakfast** – *Harris Family Atrium*

9:00-10:00 **Keynote Lecture** – Conference Room L
Antonello Bonci, MD, Scientific Director, National Institute on Drug Abuse, Baltimore, Maryland, USA. *Optogenetic approaches to understanding synaptic plasticity and substance use disorders.*

10:00-10:30 **Coffee Break** – Harris Family Atrium

10:30-12:30 **Symposium V** – Conference Room L
Genetic and neurobiological networks implicated in social communication
Chair: Joseph Dougherty, Washington University School of Medicine St. Louis, Missouri, USA

10:30 A mouse model for communication deficits. Joseph D. Dougherty, Washington University School of Medicine, USA
11:00 Insect models for social behavioral plasticity. Yehuda Ben-Shahar, Washington University-St. Louis, USA
11:30 A songbird model for social effects on sensory learning. Sarah E London, University of Chicago, USA
12:00 Genetics of interactive social behavior in silver foxes (Vulpes vulpes). Anna V. Kukekova, University of Illinois at Urbana-Champaign, USA

12:30-1:30 **Lunch** – Harris Family Atrium

Monday, May 12 ***continued***

1:30-3:30 **Selected Talk Session I** – Conference Room L
Chair: Jonathan Pollack, NIDA

1) Rsu1 acts downstream of integrin to regulate Rac1 activity and ethanol consumption in drosophila and humans. Adrian Rothenfluh, Department of Psychiatry, Program in Neuroscience, UT Southwestern Medical Center at Dallas, USA
2) Genome-wide mapping of complex psychiatric traits in commercially available outbred mice. Clarissa Parker, Department of Psychology, Program in Neuroscience, Middlebury College, USA
3) Understanding epistasis and gene networks in complex traits: An analysis of the genetic architecture of aggression in a model system. John R. Shorter, Genetics Program in Department of Biological Sciences, NCSU, USA
4) (Synaptic) Plasticity of the mate choice mind: a neuro-comparative approach to female preference across mate choice and coercive poeciliid fishes. Molly Cummings, Department of Integrative Biology, University of Texas at Austin, USA
5) The genetic architecture of the hippocampus and spatial learning. Anna Delprato, Institut de Neuroscience Cognitive et Intégrative d'Aquitaine (INCIA), University of Bordeaux and CNRS, Bordeaux (Talence), France
6) D2 dopamine receptor in brain development and behavioral plasticity. Kyung-An Han, Department of Biological Sciences, BBRC Neuroscience/Metabolic Disorders, University of Texas at El Paso, USA

3:30-4:00 **Coffee Break** – Harris Family Atrium

4:00-5:00 **Young Investigator Lecture** – Conference Room L
Cameron Bryant, PhD, Boston University School of Medicine, USA
Genes, brain and addiction traits: Moving from discovery toward validation and mechanism.

5:00-6:00 **General Business Meeting** – Conference Room L

6:30-10:00 **Dinner Cruise**
Mystic Blue Cruises

Tuesday, May 13

7:00-8:00 **Breakfast** – *Harris Family Atrium*

8:00-9:30 **Selected Talk Session II** – Canning Auditorium
Chair: Stephen Boehm, Indiana University – Purdue University Indianapolis, USA

1) Rare variants in the CHRNA6/CHRNB3 gene region are associated with dependence vulnerability. Helen M. Kamens, Department of Biobehavioral Health, Penn State University, USA
2) A transgenic zebrafish model for monitoring glucocorticoid receptor activity. Randall Krug, Mayo Clinic Department of Biochemistry and Molecular Biology, Rochester, USA
3) Finer mapping of a QTL for methamphetamine intake in high and low methamphetamine drinking mice. Emily Eastwood, Department of Behavioral Neuroscience and Methamphetamine Abuse Research Center, Oregon Health & Science University, USA
4) Cloning QTLs the easy way: Leveraging a reduced complexity cross between C57BL/6J substrains. Megan K. Mulligan, The University of Tennessee Health Science Center, Memphis, USA

9:30-11:30 **Symposium VI** – Canning Auditorium
Workshop on the use of advanced mouse populations
Chair: Elissa Chesler, The Jackson Laboratory, USA

9:30 Overview. Systems genetic analysis of brain and behavior in the Diversity Outcross population. Elissa Chesler (Chair), The Jackson Laboratory, USA
10:00 Genetic and Genomic Analysis in the Diversity Outcross. Gary Churchill (Moderator), The Jackson Laboratory, USA
10:30 Behavioral phenotyping in mouse genetic populations Lisa Tarantino (Moderator), University of North Carolina-Chapel Hill, USA
11:00 Phenotyping strategies in large-scale mouse experimentation John Crabbe (Moderator), VA Medical Center-Portland, USA

11:30 Meeting Adjourned

Poster #1

The effects of larval ethanol exposure on type-2 photic phase shifting stimuli in *period* mutants of *Drosophila melanogaster*

DN Amaral, GC Nash, NF Nascimento, KN Carlson, DM Pyne, JA Seggio

The effects of light, drugs, and other stimuli on the circadian rhythm are identified through studies investigating the period of free-running rhythm or phase responses to light pulses. In such studies, altering the phase or period of the free-running rhythm is thought to reflect the underlying circadian pacemaker. Recent investigations have shown that larval-ethanol treatment can alter the period and *period* gene transcription of adult *Drosophila period* mutants, even after ethanol exposure has ceased. This study aims to uncover the effects of larval-ethanol exposure on the photic phase responses in *period* mutant fruit flies. *Drosophila period* mutant larvae were raised on food laced with either water or 10%-ethanol and upon eclosion were placed into activity monitors in LD for three days. On the last day of LD, light pulses at ZT 14 and ZT 21 were administered using an Aschoff Type-2 protocol. It was found that both *perS* and *perL* have increased phase delaying responses to light pulses at ZT 14 compared to wild-type *CS*. Additionally, while both *perS* and *CS* responded with normal sized phase advances to light pulses at ZT 21, *perL* showed shifts of approximately 10-hours, most likely due to their extremely long rhythm. Although ethanol causes changes in the period of the rhythm, it appears that larval-ethanol produces no changes in the responses to light pulses. These results indicate that developmental ethanol affects the period and phase differently in *Drosophila*, and that there are species differences in how ethanol affects the phase between flies and rodents.

Department of Biological Sciences, Bridgewater State University, Bridgewater, Massachusetts, USA

Animal Models of Eating Disorders: What We've Learned and What's Next

N. M. Avena

In recent years, several animal models have been developed to study patterns of disordered eating in an effort to better understand the conditions and characteristics that may increase risk for or protect against their development, assess their effects, as well as identify effective intervention techniques. Binge eating, which is characteristic of both bulimia nervosa and the more recently recognized binge eating disorder, has been modeled using a number of behavioral paradigms that suggest a role for variables such as palatable food, limited access, and stress in the development of this behavior. Further, models of binge eating have provided evidence that animals that regularly binge eat palatable food exhibit behavioral and neurochemical symptoms that mimic those more commonly seen within the context of drug addiction. In addition to this line of work, several groups, including our laboratory, have been studying anorexia nervosa with an animal model characterized by undereating and excessive exercise. This talk will include a discussion of noteworthy findings that have resulted from the use of laboratory animal models of eating disorders, as well as suggestions for future research that may better bridge the gap between animal models and clinical reality.

Columbia University, New York Obesity Research Center, USA

Funding support: NIH DA03123

Generalized reward processing and inhibitory control in obese individuals with and without binge eating disorder.

Iris M. Balodis[1], Carlos M. Grilo[1,4], Nathan D. Molina[1], Hedy Kober[1], Patrick D. Worhunsky[1], Marney A. White[1], Michael C. Stevens[1,2], Godfrey D. Pearlson[1,2,3], Rajita Sinha[1,4,5], Marc N. Potenza[1,2,5]

An important step in obesity research involves identifying neurobiological underpinnings of non-food reward processing and cognitive control unique to specific subgroups of overweight individuals. This talk will focus on neuroimaging findings during cognitive control and reward processing tasks in obese individuals with binge eating disorder
(BED), without BED and lean comparison (LC) participants. These findings show diminished activity in the BED group in the inferior frontal gyrus (IFG) and insula during cognitive control, relative to the non-BED and LC groups. Reward processing in the BED group also shows diminished recruitment of ventral striatal areas relative to obese individuals without BED. This diminished recruitment was further related to treatment outcome in the BED group. These findings suggest that heterogeneity exists amongst obese individuals with respect to the neural correlates of cognitive control and reward processing. These findings will further be discussed in the context of current knowledge of the neurobiology of reward processing. Examining reward processing across disorders of impulse control provides additional insight into a neurobiological framework that might best conceptualize each disorder. These findings have implications in clarifying the etiology of this disorder and developing effective therapies.

[1]Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, USA
[2]Institute of Living/Hartford Hospital & Olin Neuropsychiatry Research Center, Hartford, Connecticut, USA
[3]Department of Neurobiology, Yale University School of Medicine, New Haven, Connecticut, USA
[4]Department of Psychology, Yale University School of Medicine, New Haven, Connecticut, USA
[5]Child Study Center, Yale University School of Medicine, New Haven, Connecticut, USA

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Genotypic- and sex-differences in anxiety-like behavior and anxiolytic response to alcohol in High Drinking in the Dark mice

AM Barkley-Levenson[1,2] , JC Crabbe[1,2]

The High Drinking in the Dark (HDID) mice are selectively bred for high blood alcohol concentrations (BACs) following limited access alcohol drinking. These mice readily drink to intoxicating BACs in a short time and represent a genetic model of risk for binge-like drinking. In humans, alcohol abuse and anxiety disorders are highly comorbid. In the present study, we sought to determine whether a relationship exists between propensity to binge drink and basal anxiety and ethanol-induced anxiolysis in our mouse model of drinking to intoxication. Alcohol-naïve male and female mice from the first HDID replicate line (HDID-1) and heterogeneous controls (HS) were tested for anxiety-like behavior on the elevated zero maze following injection with saline, 0.5, 1.0, or 1.5 g/kg alcohol. Anxiety variables consisted of the percent open arm time (OAT) and the number of open arm entries (OAE), and line crossings were used as a measure of general locomotor activity. Alcohol dose-dependently reduced anxiety-like behavior and increased locomotor activity. HDID-1 mice had more OAT and made more OAE than HS mice, and female mice spent significantly more time in the open arms than male mice. These findings suggest that HDID-1 mice may have generally lower levels of anxiety than HS mice regardless of alcohol dose, and that female mice of both genotypes are less anxious than males. Thus, altered sensitivity to alcohol-induced anxiolysis does not appear to be a correlated response to HDID selection and instead decreased anxiety-like behavior may be more closely related to the high drinking phenotype.

[1]Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, Oregon, USA
[2]Portland Alcohol Research Center, VA Medical Center, Portland, Oregon, USA

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Insect models for social behavioral plasticity

Yehuda Ben-Shahar[1]

The Ben-Shahar laboratory takes advantage of the rich behavioral repertoires of insects to develop a better understanding of how individual animals perceive and process signals from their social environment. We use a powerful combination of the strength of Fruit Fly (*Drosophila melanogaster*) genetics and neurobiology with the obligatory social life style of the European Honey Bee (*Apis mellifera*). By using state-of-the-art genetic, genomic, neurophysiological, and molecular tools we ask which signals, and their cognate cellular and molecular receptors, are playing a role in determining how an individual animal will process and respond adaptively to changes in its social environment. Our current efforts focus on two highly informative behavioral paradigms. The first is mating behavior in the fruit fly. The second is the age-dependent division of labor among honey bee workers. Both behaviors are well described, robust, have strong genetic components, and are amenable to experimental manipulations. The presented work will demonstrate some of our recent findings related to pheromonal social communication and the possible roles of non-coding RNAs in the social behavioral plasticity.

[1]Washington University in St. Louis, St. Louis, Missouri, USA

Poster #2

Longitudinal study of a mouse model for Parkinson Disease

Zoë Bichler[1,4], Nurul Dini Abdul Rahim[1], Sally Qianying Dong[1], Li Zeng[2,4], and Eng King Tan[3,4]

Parkinson Disease (PD) is one of the most common neurodegenerative diseases. Patients develop motor symptoms as well as several non-motor dysfunctions including psychiatric disorders, cognitive decline, sensorial deficits, poor social skills, sleep disorders and constipation. The highest risk factor of PD identified to date in both autosomal dominant familial and sporadic PD is genetic mutations of the Leucine-Rich Repeat Kinase 2 (LRRK2) gene, R1441G being among the most described site of pathogenic LRRK2 substitutions.

To better understand the pathogenesis of PD and the relationship between motor and non-motor features, we have characterized the onset of specific symptoms with age on LRRK2(R1441G) mice, a BAC transgenic mouse model overexpressing the R1441G mutation of the LRRK2 gene. We have previously shown that transgenic mice displayed early gastrointestinal disorders and motor deficits at late stages compared to their non-transgenic littermates (Bichler et al., 2013, PLOS One). Here we asked whether chemical and stress factors would exacerbate such phenotypes. Brain samples have also been analyzed to characterize common neurotransmitters profiles at different ages in these mice. To summarize, we will draw a sequential map of the appearance of behavioral and neuropathological phenotypes that correlate with serious motor disabilities displayed by these mice and discuss these results considering the clinical data available from PD patients.

[1]Behavioral Neuroscience Lab, National Neuroscience Institute, Singapore
[2]Neural Stem Cells Research Lab, National Neuroscience Institute, Singapore
[3]Department of Neurology, National Neuroscience Institute, Singapore
[4]Duke-NUS Graduate Medical School, NBD Program, Singapore.

Funding support: Singhealth Research Foundation, Singapore Millennium Foundation and National Medical Research Council, Singapore.

How Genetic Risk for Nicotine Dependence Translates into Successful Smoking Cessation

Laura Jean Bierut, MD

Smoking is the greatest cause of preventable mortality, contributing annually to over 400,000 deaths in the U.S. and 5 million deaths worldwide. Genome-wide association studies, a powerful genetic discovery tool, highlight heaviness of smoking as associated with the non-synonymous variant, rs16969968. This variant in the gene encoding the α5 nicotinic receptor subunit (*CHRNA5*) is strongly associated with cigarettes per day in meta-analyses including over 73,000 subjects ($p=5.57 \times 10^{-72}$). Further analyses demonstrate at least two distinct signals in this region contribute to smoking behavior, and functional studies suggest two different biological mechanisms: changed protein structure and altered mRNA expression.

A critical next step is to determine whether this genetic variation influences smoking cessation. We find delayed smoking cessation in those with these high-risk genetic variants. This same locus is also the strongest genetic contributor to the risk of developing lung cancer and chronic obstructive pulmonary disease. This genetic risk for lung cancer and other smoking related diseases is driven by smoking more cigarettes, inhaling more deeply, and quitting much later.

The ultimate public health significance of understanding biological underpinnings of smoking behaviors comes from translating this knowledge into improved treatment. Those with these high-risk genetic variants have difficulty quitting, and importantly, this genetic risk can be ameliorated by pharmacologic treatment. This work exemplifies precision medicine: using genetic information to differentiate people who likely respond to pharmacologic treatment from those who receive little benefit. This work represents the important translation of genetic discoveries for nicotine dependence into smoking cessation and improved health.

Washington University School of Medicine, St Louis, Missouri, USA

Support: NIDA, NCI, and NIAAA

Optogenetic approaches to understanding synaptic plasticity and substance use disorders

A. Bonci

The ventral tegmental area (VTA), nucleus accumbens (NAC) and prefrontal cortex (PFC) are all part of the limbic system and play a fundamental role in motivation, reward- and drug-dependent behaviors. A few years ago, my laboratory has shown that drugs of abuse such as cocaine can produce long-term synaptic plasticity and that the duration of such plasticity is dependent upon the modality of drug or reward administration. By applying a multidisciplinary approach that includes electrophysiology, optogenetics and behavioral procedures, my laboratory has produced a series of studies aimed at defining the pathways that control and modulate reward and drug-dependent behaviors. During my presentation, I will present the latest data on the cellular mechanisms and pathways that underlie reward substance use disorders.

National Institute on Drug Abuse, Baltimore, Maryland, USA

Poster #3

Retrotransposon activation in TDP-43-mediated neurodegeneration

R Borges[1,2], L Krug[1,3], N Chatterjee[1], W Donovan[1,3], A Julien[1,4], Y Jin[1], L Prazak[1], M Hammell[1], J Dubnau[1].

Retrotransposons are inherited virus like repetitive elements capable of replicating and re-inserting into *de novo* locations within the genome. Retrotransposition has been largely studied in germline where new insertions produce heritable genetic variants. However, increasing evidence suggests transposable elements are also capable of mobilizing in somatic tissue, including the brain. We have previously shown that some LINE-like and LTR retrotransposons are active in the *Drosophila* brain during aging, leading to accumulation of *de novo* mutations in neurons. We demonstrated that genetically activating LINE-like and gypsy transposons results in accelerated effects of aging on neurophysiological decline. Previous work from our group has also revealed that TDP-43, a protein that is a central player in neurodegenerative diseases, normally binds to retrotransposon sequences. Such binding is lost in tissue from frontotemporal lobar degeneration (FTLD) patients, leading to the hypothesis that retrotransposon activation might be observed with TDP-43-mediated neurodegeneration. Currently, we are searching for signatures of retrotransposon sequences in post-mortem brain tissue from FTLD patients. We are also using a *Drosophila* model in which TDP-43 pathology is driven to test this transposon storm hypothesis of neurodegeneration. This manipulation of TDP-43 leads to activation of gypsy transposon expression. TDP-43 pathology in glial cells shows more dramatic gypsy expression than manipulation solely in neurons. This is accompanied by apoptotic cell death, locomotion defects, and we are currently quantifying the accumulation of double strand breaks. Our findings have implications for the mechanisms of neurodegeneration seen in amyotrophic lateral sclerosis and frontotemporal dementia, where TDP-43 pathology is central.

[1]Cold Spring Harbor Laboratory, 1 Bungtown Road, Cold Spring Harbor, New York, USA
[2]The Undergraduate Program on Genomic Sciences of the National Autonomous University of Mexico, Mexico
[3]Watson School of Biological Sciences, Cold Spring Harbor Laboratory, [4]Magistère de Génétique Graduate Program at Université Paris Diderot, Sorbonne Paris Cité, France

Genes, brain and addiction traits: Moving from discovery toward validation and mechanism

Camron D. Bryant, Ph.D.

Genetic and genomic approaches toward the biological mechanisms of behavior provide an unfiltered lens through which novel discoveries can be gleaned. My interest in addiction neurobiology led me pursue a quantitative trait locus (QTL) mapping approach in mice to gain insight into the molecular mechanisms of heritable traits associated with addiction. As a launching point, I focused on genetic mapping of the locomotor stimulant properties of drugs of abuse – a behavior that shares neurobiological mechanisms with reinforcement. QTL, pharmacological, and molecular genetic analysis of casein kinase 1-epsilon (*Csnk1e*) revealed a significant role in locomotor sensitivity to psychostimulants and opioids. In my laboratory, we translated these findings to the conditioned rewarding properties of drugs of abuse and are currently using transcriptome analysis to identify the molecular pathways responsible for *Csnk1e* regulation of drug reward. In a second research area, I previously fine mapped a QTL for methamphetamine sensitivity containing only two protein coding genes (*Hnrnph1* and *Rufy1*). We have since conducted transcriptome, pathway, and network analysis of the striatum in congenic mice capturing this QTL which has provided new leads into the neural mechanisms that bridge genetic variation with behavior. We are using designer endonucleases to rapidly target *Hnrnph1* and *Rufy1* and recently generated our first knockout founders for behavioral validation of these candidate genes. Finally, in a new line of research, we are applying a genetic mapping approach toward understanding the neurobiology of food “addiction” in a novel behavioral model combining binge eating with conditioned reward for palatable food.

Laboratory of Addiction Genetics, Department of Pharmacology and Experimental Therapeutics and Psychiatry, Boston University School of Medicine, USA

FUNDING: R00DA029635, T32GM008541, Burroughs Wellcome Fund Transformative Training Program in Addiction Science (TTPAS)

Translating the effects of exercise on recognition memory: dependence on age and genotype

DJ Bucci[1], ME Hopkins[1], and AM Robinson[1]

It is well established that physical exercise improves hippocampal-dependent learning and memory and increases hippocampal neurogenesis and BDNF levels. However, comparatively less is known about the effects of exercise on other forms of learning and memory that are supported by structures outside the hippocampus. It is also unknown if the effects of exercise are age-dependent, or relatedly, if exercising during pregnancy impacts cognition in the offspring. To investigate these questions, we tested the effects of voluntary on object recognition memory. In rats, 4 weeks of access to a running wheel enhanced recognition memory, an effect that was correlated with BDNF expression in perirhinal cortex. The effect was independent of the effects of exercise on anxiety or locomotor activity. Moreover, we found that exercising during adolescence had more dramatic and persistent effects compared to exercising during adulthood. We also found that wheel running during pregnancy enhanced recognition memory in adult offspring. Translating these studies to humans, we demonstrated that 4 weeks of regular exercise similarly improved object memory in young adults. In contrast, a single bout of exercise did not affect object recognition memory in humans. The effect of regular exercise was entirely dependent on BDNF genotype in that object recognition memory was enhanced exclusively in participants who were homozygous for the BDNF Val allele. By comparison, those with a methionine substitution did not exhibit enhanced recognition memory. Together these findings demonstrate that regular exercise has age and genotype-dependent effects on object recognition memory in humans and laboratory rodents.

[1]Department of Psychological and Brain Sciences, Dartmouth College, Hanover, New Hampshire, USA

Funding source: R01MH082893

Genetics of Eating Disorders: GWAS and Cross Disorder Insights Into Comorbidity

Cynthia M. Bulik, PhD

Anorexia nervosa (AN) is a complex and heritable eating disorder characterized by the maintenance of dangerously low body weight. Two subtypes, restricting—marked by decreased energy consumption and increased energy expenditure—and binge-eating/purging—marked by the presence of both low weight and binge eating or purging exist. Both represent extremes of dysregulated appetite and weight. Two small genome-wide association studies (GWAS) of AN have been conducted, neither of which has yielded genome-wide significant findings, as would be expected by sample size. A mega analysis is underway to be followed by cross-disorder analyses with other phenotypes present in the Psychiatric Genomics Consortium (i.e., obsessive-compulsive disorder, major depression, alcohol and drug dependence, major depression, autism, attention-deficit hyperactivity disorder, schizophrenia, bipolar disorder, and post-traumatic stress disorder). With the increasing availability of large GWAS genotyped samples of many psychiatric disorders, we are well positioned to apply molecular genetic approaches to explain clinical comorbidity. Such analyses, including genome-wide complex trait analysis (GCTA) enable the calculation of bivariate SNP heritabilities and determination of genetic correlations between disorders. Based on observed comorbidities, for both subtypes of AN, relevant comparisons include obsessive-compulsive disorder, major depression, and autism, and for the binge-purge subtype of AN and for bulimia nervosa, the overlap with substance use disorders is of particular relevance given observed comorbidity. Such genetic approaches may directly inform controversies in the field regarding the biological appropriateness of classifying some eating disorders as addictions. This talk will present up-to-date findings and analyses on the horizon relevant to the genetics of eating disorders.

University of North Carolina at Chapel Hill, USA

Poster #4

A genome-wide association analysis by assessing epistasis and the influence of comorbid substance dependence identifies novel susceptibility genes and SNPs for alcoholism

Ruyan Wu[1,2], Baomei Xia[1,2], Wenda Xu[1,2], Jun Zhu[3] and Gang Chen[1,2]

Alcohol dependence is a complex disease involving polygenes and their interactions with environment. Current GWAS have only identified very few susceptible SNPs or genes and heritability is missed. By using a genetic model including epistasis and environment interactions, we analyzed alcohol dependence genetic risk factors from 3838 alcoholics with or without comorbid substance-use disorders and non-dependent subjects in the Study of Alcohol Addiction: Genetics and Addiction. From our analysis, the heritability of alcohol dependence is estimated as 33.7%, comparable to the estimation of 50% based on family and twin studies, with strong dominance related effects. Eleven SNPs yielded high significant association, with 3 reported previously, ADH1C, KCNB2, and SNP RS1363605, supporting the overall validity of the model. We also found 2 novel risk genes, Alox15B and FLYWCH1, and 6 novel SNPs including RS7616413. FLYWCH1 interacts with LOC101929265, a gene for noncoding RNA, showing an additive-dominance epistasis effect in European American. The dominance effect of Alox15B was masked by nicotine dependence. Alox15B also interacts with RS1363605, showing an additive-additive epistasis effect in African American. RS7616413, located near PTPRG, interacts with ANGPT1 encoding a protein tyrosine phosphatase (PTP), under the influence of Marijuana, nicotine, opiate or cocaine dependence. Additionally, PTPRT alone showed a dominance effect, supporting an important role of PTP signaling in alcohol dependence. These findings indicated the full genetic model substantially improved the detection of heritability and individual risk SNPs. Moreover, we demonstrated genetic risks for alcohol dependence are impacted by substance dependence, suggesting some common underlying mechanisms.

[1]Center for Translational Systems Biology and Neuroscience
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Funding Support: JiangSu Innovation & Entrepreneurship Talents Plan

Developing zebrafish methodology to model genetic and environmental modifiers of the vertebrate stress response system (SRS).

Tanya L. Poshusta, Randall G. Krug II, Han B. Lee, Tammy. M. Greenwood, Nicole J. Boczek, Samantha L. Gardner, Makayla R. Berg, Courtnee Heyduk, David P. Argue, and Karl J. Clark

Stress-induced changes in brain function and physiology contribute to many complex disorders, including neuropsychiatric disorders—a major cause of disability in the world. Both genetic heritability and environmental factors contribute to the progression of neuropsychiatric disorders, such as major depressive, generalized anxiety, and substance use disorder. These complex multisystem disorders require whole animal models for effective study. The zebrafish (Danio rerio) is an ideal animal model for discovery of genetic modifiers of the vertebrate-conserved SRS. We observed that larval zebrafish temporarily increase locomotion following exposure to a hyperosmotic stressor. This behavior correlates with acute changes in cortisol production. Importantly, mutation of the CRH receptor (crhr1), ACTH receptor (mc2r), or the glucocorticoid receptor (nr3c1) blocks locomotor stimulation. In addition to the behavioral assay that measures rapid, “non-genomic” effects of cortisol signaling, we have developed a transgenic reporter that produces a short half-life green fluorescent protein in response to “genomic” activity of the glucocorticoid receptor (see Randall G. Krug II et al.).

We are using a combination of our newly developed assays, fish lines, and genome engineering technology to investigate the vertebrate SRS. Using a library of random gene-break transposon mutants, we are identifying genetic loci that modify the vertebrate SRS. Using custom nucleases and exogenous ligands, we are investigating the role of endocannabinoid signaling in normal SRS functioning (see Randall G. Krug II et al.). More recently, we are investigating the interaction of the microbiome and the stress response system (see Han B. Lee et al.).

Department of Biochemistry and Molecular Biology and the Mayo Addiction Research Center, Mayo Clinic., Rochester, Minnesota, USA

Funding Support: DA032194 and Mayo Foundation

Poster #5

Ethanol and nicotine interaction in zebrafish

M. A. Cousin, A. R. Wiinamaki, D. P. Argue, K. J. Clark, S. C. Ekker, E. W. Klee

Excessive alcohol consumption and cigarette smoking place tremendous burdens on US society. Tobacco-related disease is a leading cause of death of alcoholics due to the overwhelming incidence of comorbid use, but little is known on how to address the specific needs of the individual with alcohol use disorder and comorbid tobacco dependence. We have previously shown genetic and pharmacotherapeutic modifiers of nicotine-induced locomotor activation have largely distinct effects on ethanol-induced locomotion. We are now exploring the interaction of nicotine and ethanol on larval zebrafish locomotion.

Exposure of nicotine 1.5 hours prior to ethanol exposure significantly potentiated the locomotor response to ethanol when locomotion had returned to baseline levels. Nicotine administration 20 minutes following ethanol administration alters the nicotine response in larval zebrafish; the initial locomotion induced by nicotine is consistent with nicotine-only response, but the duration is shorter. These data suggest that prior exposure to nicotine enhances the rewarding response of ethanol, but that ethanol may blunt the duration of nicotine reward. Currently, we are determining the temporal and dosing parameters for these altered responses and looking to profile similar responses in adult zebrafish. We are also evaluating the pharmacotherapeutic and genetic modifiers for impact on these interactions.

These results indicate overlapping, yet partially distinct mechanistic underpinnings of the locomotor responses to ethanol and nicotine in zebrafish. The interaction of these stimuli may explain, in part, the overwhelming coincident smoking habits of alcohol-dependent individuals. Elucidating genetic loci and medications that modulate this interaction may lead to genetically-informed personalized treatment strategies.

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The genetic architecture of the hippocampus and spatial learning

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Hippocampal morphometry and spatial learning were studied in 53 genetically characterized isogenic BXD mouse strains in order to understand the genetic bases of variation and covariation of these traits. For the morphometrical analyses, data were collected on seven hippocampal subregions in CA3 and CA4. For the spatial learning task, mice were tested for their ability to learn a standard 8 arm radial maze task.

A combination of experimental, neuroinformatic, and systems genetics methods were used to analyze the data. Results indicate that hippocampal morphometry varies widely among the BXD strains tested. Significant effects of strain and sex, and sex-by-strain interactions were observed for many of the hippocampal and spatial-learning variables.

Quantitative Trait Loci (QTLs) were identified for morphometry-related traits: intra- and infrapyramidal mossy fibers, stratum radiatum, and stratum pyramidale, and for the spatial learning trait, total errors. Common QTLs for hippocampal anatomy and spatial learning were not found in this study.

Based on database query and published literature, corresponding gene lists were screened and narrowed depending on the presence of sequence variants, hippocampal expression, presence of expression QTLs, and functional association.

Several genes that may potentially influence the traits under study were identified. The candidate genes and interaction networks have biological themes in signal transduction, cell adhesion/migration, cell cycle regulation, transcriptional regulation, and neuronal development.

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(Synaptic) Plasticity of the mate choice mind: a neuro-comparative approach to female preference across mate choice and coercive poeciliid fishes

M. E. Cummings[1], M. Schumer[2], S. Wang[1], M. E. Ramsey[1]

Understanding whether species-level variation in reproductively isolating behavior is plastic or canalized is critical to understanding evolutionary change. Our investigations of female preference behavior in different species of freshwater poeciliid fishes with diverse mating systems (female mate choice or male coercion) suggests that the neuromolecular processes governing female response represent a shared molecular pathway linked to synaptic plasticity that is differentially engaged by male phenotype. Both microarray and RNASeq analyses with different species (*Xiphophorus nigrensis, Poecilia latipinna)* demonstrate that short term exposure to mate choice conditions (30 min) triggers dramatic changes in gene expression in the female brain with genes differentially regulated by mate preference behavior enriched for neurological processes, including synaptic plasticity. Whole brain expression of preference-synaptic plasticity associated genes (*neuroserpin*, *neuroligin-3*) exhibit positive correlations with preference behavior in female choice taxa, *X. nigrensis and P. latipinna;* whereas this relationship is reversed in *Gambusia affinis*, a mate coercive poeciliid with no courting males. We explored whether species-level differences in female behavioral and brain molecular responses represent 'canalized' or 'plastic' traits by exposing female *G. affinis* to heterospecific (*P. latipinna*) coercive and courting males. We find positive correlations between preference-synaptic plasticity gene expression and female preference strength during exposure to courting heterospecific males, but a reversed pattern following exposure to coercive heterospecific males. This suggests that the neuromolecular processes associated with female preference behavior are plastic and responsive to different male phenotypes (courting or coercive) rather than a canalized response linked to mating system.

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Voluntary exercise reduces voluntary consumption of ethanol in mice: identification of candidate genes through striatal gene expression profiling

Todd M. Darlington, Riley D. McCarthy, Ryan J. Cox, Jill Miyamoto-Ditmon, and Marissa A. Ehringer

The behavioral interaction known as hedonic substitution has been observed and replicated, and again we show mice decrease ethanol consumption and preference when given access to a running wheel. However, the despite attempts at identifying the underlying neurobiological mechanism, this remains unknown. To identify candidate genes and pathways involved in hedonic substitution, we quantitatively sequenced mRNA from the striatum of female C57BL/6J mice. There were four groups of mice, control, access to two-bottle choice ethanol, access to a running wheel, and access to both two-bottle choice ethanol and a running wheel. We identified many differentially expressed genes, including several in ethanol preference quantitative trait loci that are differentially expressed in response to running. Furthermore, we conducted Weighted Gene Co-expression Network Analysis and identified putative exercise responsive gene networks, with one network implicating a role for glial cells. We identify roles for potassium channel genes as well as other candidate genes, *Ttr, Stx1b*, and *Oprm1* in regulating hedonic substitution. Because many of the genes and functional groups have been previously identified in studies of initial sensitivity to ethanol, we proposed that exercise may induce a change in sensitivity, which affects ethanol consumption; however, we were unable to confirm this with a test of Loss of Righting Reflex due to ethanol. Furthermore, these results provide a rich resource for studies involving transcriptional changes in gene networks in response to ethanol consumption and wheel running.

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Poster #6

Identifying rare variants for suicide risk through a combined pedigree and phenotype approach.

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Completed suicide is a complex disease, with evidence for genetic risk independent of other risk factors including psychiatric disorders. Since 1996, over 3,000 DNA samples from suicide decedents have been collected through the Utah Medical Examiner. In addition, over 12,000 suicides were identified through examination of death certificates back to 1904. By linking this data with the Utah Population Database, we have identified multiple pedigrees with increased risk for suicide. Certain conditions may increase risk of suicide, including asthma. Of the pedigrees at increased risk for suicide, we identified three pedigrees also at significantly increased risk for asthma. Five suicide decedents from each pedigree were genotyped. An additional 3 decedents with diagnosed asthma, 3 decedents with 1st degree relatives with asthma, and 7 decedents with 2nd degree relatives were genotyped. A further 444 suicide decedents were genotyped as non-asthma controls. Genotyping was done using the Infinium HumanExome BeadChip (v1.0). For analysis, we used an extension of Variant Annotation, Analysis, and Search Tool (VAAST v2.0.1); a probabilistic disease-gene finder that uses variant and amino acid substitution frequency to calculate disease burden of each gene. The Phenotype Driven Variant Ontological Re-ranking tool (Phevor) then re-ranked our VAAST results in context of the phenotype. Using the phenotypes of asthma and depression Phevor traverses biomedical ontologies and identified genes with similar biological properties to those known to result in these phenotypes. Our top associated genes are TYW3, CRYZ, TUBD1, PANK2, P2RX3, SPAST, DCTN1, HTR1A, SGCE, and BDNF. Our results demonstrate the power of combining pedigree and phenotype to identify rare variants associated with disease.

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Poster #7

Novelty-related traits predict intravenous cocaine self-administration in Diversity Outbred mice

Price E. Dickson[1], Juliet Ndukum[1], Troy Wilcox[1], James Clark[1], Brittany Roy[1], Lifeng Zhang[2], Yun Li[2], Da-Ting Lin[2], Elissa J. Chesler[1]

Preference for and reaction to novelty are strongly associated with addiction disorders in humans. However, the genetic variants and molecular mechanisms underlying these phenomena are largely unknown. Although the relationship between novelty- and addiction-related traits has been observed in experimental animals, the majority of these studies have been conducted in mouse and rat populations with limited genetic variation and precision. Thus, the extent to which novelty-related traits predict addiction-related traits through a common biological mechanism is largely unknown. We examined the relationship between multiple novelty- and addiction-related traits in diversity outbred (DO) mice, a recently developed high-resolution genetic mapping population possessing high allelic and phenotypic diversity. DO mice of both sexes were tested on open field exploration, hole board exploration, and novelty preference followed by intravenous cocaine self-administration (IVSA). Mice that acquired cocaine IVSA did so rapidly, and this was especially true in males. Some mice failed to reach commonly used acquisition criteria. These mice nevertheless exhibited a preference for the active lever. Novelty-related behaviors were positively associated with cocaine IVSA, and multivariate analysis of the associations among novelty- and addiction-related traits revealed a large degree of shared variance (45%). The variation and co-variation among these phenotypes indicates that the relationship between novelty- and addiction-related traits is amenable to genetic dissection in DO mice. The high genetic precision and phenotypic diversity in the DO will facilitate discovery of the biological mechanisms which drive the behavioral predisposition to develop addiction disorders.

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Poster #8

Glyoxalase 1 and its substrate, methylglyoxal, regulate seizure phenotypes

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Epilepsy is characterized by a predisposition toward seizures. While numerous anti-epileptic drugs are available, they are not effective in all patients and can have adverse side effects. The identification of novel mechanisms underlying epilepsy may identify new therapeutic targets. In our previous work, we identified methylglyoxal (MG) as an endogenous agonist of the γ-aminobutyric acid-A ($GABA_A$) receptor. Because the $GABA_A$ receptor is a known mediator of seizures and a target of some anti-epileptic drugs, we predicted that MG may augment seizure phenotypes. Therefore, we investigated the role of MG and its catabolic enzyme, glyoxalase 1 (GLO1), in seizures.

First, we pre-treated mice with MG before seizure induction with picrotoxin or pilocarpine. Pre-treatment with MG attenuated pharmacologically-induced seizures at both the behavioral and EEG levels. We then investigated GLO1's role in seizures. Pharmacological inhibition of GLO1 increased MG concentration in vivo and attenuated seizures. Next, we explored the genetic relationship between *Glo1* expression and seizures. Among C57BL/6J × DBA/2J recombinant inbred mice with differential *Glo1* expression, lines with high *Glo1* expression had increased seizure susceptibility. Lastly, we investigated a causal role for Glo1 in seizure susceptibility by inducing seizures in transgenic mice that overexpressed *Glo1*. Transgenic mice displayed reduced MG concentration in the brain and increased seizure severity.

Our findings suggested that MG is an endogenous regulator of seizures. Accordingly, inhibition of GLO1 attenuates seizures, poising this as a novel therapeutic approach for the treatment of epilepsy. Finally, *Glo1* may be a genetic determinant of epilepsy risk.

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A mouse model for early communication deficits

J. D. Dougherty

Mice are known to produce ultrasonic vocalizations (USVs) in response to a variety of social situations, including pup-dam separation, juvenile play, and adult courtship, and assessment of vocal behavior has become a common component of behavioral phenotyping batteries for mouse models of autism. Our laboratory utilized a unique strategy to identify candidate genes for the association testing in autism by leveraging tanscriptomic data specifically profiling disease-relevant cell types from the mouse brain. Common and rare variant analyses of these genes in humans suggested variants in Celf6, an RNA binding protein highly expressed in neuromodulatory cells, may contribute to disease risk, spurring our development of a Celf6-/- mouse model. Our Celf6 mutant mice show profound deficits in the amount of pup vocal communication, in spite of normal capacity for vocal production and otherwise normal social interactions. These data suggest that specific genetic circuits regulate the motivational component of vocal communication in mouse pups, independent of social drive and motor capability. We are now using these mutants in conjunction with both conditional genetic strategies and high throughput approaches to map the neurobiological and genetic circuits regulating this component of vocal communication.

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Finer mapping of a QTL for methamphetamine intake in high and low methamphetamine drinking mice

E. C. Eastwood[1], H. Baba[1], T. J. Phillips[1,2]

Selective breeding from an originating population of F2 intercrossed mice from the C57BL6/J (B6) and DBA/2J (D2) inbred strains, was used to produce two replicate sets of mouse lines that consume higher (MAHDR) or lower (MALDR) amounts of methamphetamine (MA) in an 18-h two-bottle choice MA drinking (MADR) procedure. Quantitative trait locus (QTL) analysis identified a QTL in both sets of lines on proximal mouse chromosome (Chr) 10, with a 2-LOD support interval of up to 40 Mb that accounts for > 50% of the genetic variance in MA intake. D2 alleles in this region account for higher MADR values, consistent with previous data showing that D2 mice consume more MA than B6 mice. To narrow the identified QTL interval, two congenic strains of mice were used. These mice have a small segment of B6 Chr 10 that has been introgressed onto the D2 background genome. The congenic strain mice were tested for MA intake, along with the D2 background strain. The congenic strain with a Chr 10 B6 segment covering the 0-7.72 Mb interval did not differ in MA intake from the D2 background strain. However, the congenic strain with a Chr 10 B6 segment from 0-20.4 Mb consumed less MA compared to D2 background strain mice. These results reduce the QTL region from a 40 Mb interval to an approximately 12.68 Mb region on Chr 10. Further fine mapping will be necessary to further reduce the QTL interval to a tractable number of genes for further consideration.

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Poster #9

Global expression of glutamatergic genes in healthy human brain; altered expression in the human hippocampus after chronic exposure to alcohol or cocaine

M. A. Enoch, A. Rosser, Z. Zhou, D. C. Mash, Q. Yuan, D. Goldman

Much of what is known about gene expression in brain has been derived from rodents. The purpose of this study was to identify global patterns of glutamatergic gene expression in healthy adult brain before determining the effects of chronic alcohol and cocaine exposure on gene expression in the hippocampus.

RNA-Seq data from 'BrainSpan' was obtained across 16 brain regions from nine control adults. We derived RNA-Seq data from postmortem hippocampus from eight alcoholics, eight cocaine addicts and eight controls. Analyses of the 28 genes encoding glutamate ionotropic (AMPA, kainate, NMDA) and metabotropic receptor subunits, together with glutamate transporters were undertaken.

The expression of each gene was fairly consistent across the brain with the exception of the cerebellum, the thalamic mediodorsal nucleus and the striatum. Five factors accounted for 80% of the variance in global gene expression. Seven genes with high cerebellar expression loaded onto one factor (20% variance). The alcoholics showed FDR corrected ($p<0.05$) up-regulation of three genes relative to controls and cocaine addicts: *GRIA4* (encoding GluA4), *GRIK3* (GluR7) and *GRM4* (mGluR4). Expression of both *GRM3* (mGluR3) and *GRIN2D* (GluN2D) was up-regulated in alcoholics and down-regulated in cocaine addicts relative to controls. The strongest finding ($p = 0.008$) was for *GRIN2B* (encoding GluN2B), that was up-regulated in both alcoholics and cocaine addicts.

At least in the hippocampus, the effect of chronic alcohol use is largely to up-regulate glutamatergic genes. It is possible that the NMDA GluN2B receptor subunit might be implicated in a common pathway to addiction.

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Using high-throughput light-off jump reflex habituation to understand learning deficits in *Drosophila* models of Intellectual Disability

M. Fenckova[1], B Nijhof[1], L Asztalos[2], Z Asztalos[2], A Schenck[1]

Impaired cognition is the central feature of human Intellectual Disability (ID), a genetically and clinically highly heterogeneous group of disorders. Up to date, mutations in more than 500 genes are known to cause ID ("ID genes"). A number of them have already been shown to work in common molecular pathways, but paucity of functional data is hampering identification of such key cognition-regulating modules.

Our aim is to systematically describe the role of ID genes in neuronal function and cognition, define molecular modules through similar phenotypes and identify common targets for therapeutic intervention. To investigate the function of the large number of ID genes in learning, we use *Drosophila* as a model and a high-throughput light-off jump reflex habituation paradigm, where the startle jump response to repeated light-off stimulus gradually wanes. We have performed a systematic panneuronal RNA interference-mediated screen targeting *Drosophila* ID gene orthologs and identified a number of habituation mutants that are simultaneously being investigated for synaptic morphology. Our future goals are to map the light-off jump habituation circuit and dissect the cellular and molecular mechanisms that lead to impaired habituation in our ID *Drosophila* models.

Established *Drosophila* habituation models allow to test for genetic interactions between known and with novel candidate ID genes. Interacting genes/proteins act in common cognitive processes and can potentially be targeted by common treatment strategies. As a first step towards drug testing, our group focused on a group of chromatin-remodeling genes implicated in ID and has recruited a drug library that will be tested.

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Poster #10

Cocaine locomotor sensitivity and sensitization in mice selectively bred for high and low alcohol preference drinking

Brandon M. Fritz, Michel Companion, Stephen L. Boehm II

Human and animal research has indicated a significant degree of overlap in abuse potential for alcohol and cocaine. Estimates of ~60-84% of human cocaine abusers meet lifetime alcohol use disorder (AUD) criteria. In addition, prior cocaine exposure can increase sensitivity to ethanol in rodents. As evidenced by these findings, there appear to be common neural elements affected by both substances. Given the significant genetic component of AUD susceptibility, we evaluated whether or not a *genetic predisposition* for excessive alcohol intake would translate to enhanced neurobehavioral sensitivity to cocaine in alcohol-naive mice. High and Low Alcohol-Preferring mice from the second replicate of selection (HAP2 and LAP2) have been selectively-bred for high or low alcohol preference in a 2-bottle choice test for 10% ethanol or water. HAP2 mice currently consume in excess of ~20 g/kg/day whereas LAP2 mice consume < 2 g/kg/day. Naïve HAP2 and LAP2 male and female mice (PND 65-120) were injected with saline and placed in Accuscan VersaMax acrtivity monitors on days 1-2 to habituate animals to the procedure. On days 3-11, mice were injected every other day with cocaine (10mg/kg; i.p.), saline, or saline until day 11 when they received an acute injection of cocaine. Preliminary results suggest that while the lines may not differ in acute cocaine sensitivity, HAP2 mice may develop robust sensitization to this dose of cocaine whereas LAP2 mice exhibit no such effect. Future work will address the influence of Pavlovian conditioning in this response as well as cross-sensitization to ethanol.

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Poster #11

Ventral striatum reactivity and coping strategies indirectly link a *PDYN* haplotype to alcohol use

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The kappa-opioid system plays a critical role in the encoding of stress and the rewarding properties of alcohol, reflecting its abundant expression in the paraventricular nucleus and striatum, respectively; as such, it is well situated to mediate alcohol consumption in the context of stressful life circumstances and psychopathology. A functional haplotype in the gene that codes for the kappa-opioid ligand precursor prodynorphin (*PDYN*) (rs2235749, rs910079, rs910080) has been associated with altered prodynorphin mRNA levels in the ventral striatum and substance use disorders. Furthermore, genetic variation across *PDYN* has been linked to differential propensities to drink in negative emotional states.

Genetic and neuroimaging data were available from 672 participants who completed the Duke Neurogenetics Study, an ongoing protocol assessing a wide range of behavioral and biological phenotypes among young adult volunteers. We tested a moderated mediation pathway model in which an interaction between this *PDYN* Haplotype and early life adversity predicted reward-related ventral striatal reactivity, which predicted substance-related coping strategies and alcohol use.

PDYN haplotype indirectly predicted alcohol use via early life stress moderational effects on reward-related ventral striatal reactivity and alcohol-related coping strategies (95% Boot-strapped CI for effect size: [0.001, 0.008]).

The results of this study suggest that this *PDYN* haplotype indirectly effects alcohol use through its effects on ventral striatal reactivity to reward and alcohol-related coping strategies in the context of stress exposure. It will be important for future research to replicate the described model and experimentally manipulate prodynorphin levels in non-human animals.

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Poster #12

Genome-wide association study of incentive salience in outbred rats

A. F. Gileta, S. Gopalakrishnan[1], S. B. Flagel[2], T. E. Robinson[3], A. A. Palmer[1,4]

Incentive salience is the motivational value attributed to a reward-predicting stimulus. Stimuli that acquire incentive salience become intrinsically desirable and can trigger drug-seeking and/or craving. Pavlovian sign-tracking (or autoshaping), a quantitative trait shown to be both highly heritable and variable in outbred rat populations, has been successfully utilized as a measure of the incentive salience attributed to a stimulus. As the primary issue in addiction treatment is the tendency of addict to relapse, an occurrence that is due in part to exposure to drug-associated stimuli, we believe it is important to understand the genetic basis underlying the attribution of incentive salience. We will perform the first large-scale genome-wide association study (GWAS) for this trait on a sample of approximately 3,000 outbred Sprague-Dawley (SD) rats that have been phenotyped for sign-tracking through a behavioral paradigm called the Pavlovian Conditioned Approach (PCA). To obtain genotypes for the 3,000 rats, we will utilize genotype-by-sequencing (GBS), a reduced-representation sequencing approach being optimized for rats in our lab. Due to the extensive population structure observed in SD rat populations, analysis will be done using a mixed model with a random effects term containing relatedness matrices based on the SNP genotypes. This study will provide us with insights into the molecular mechanisms underlying the attribution of incentive salience and may have important implications for future drug-abuse research.

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Poster #13

A role for casein kinase 1-epsilon in the motivational properties of opioids

Lisa R. Goldberg[1,2], Stacey L. Kirkpatrick[1,2], and Camron D. Bryant[1]

Recent genetic and pharmacological studies indicate that Casein kinase-1 (CK1) contributes to the behavioral properties of diverse drug classes, including psychostimulants, opioids, and ethanol. We previously found that selective pharmacological inhibition of casein kinase-1 epsilon (Csnk1e) enhanced the locomotor stimulant properties of the selective mu opioid receptor agonist fentanyl, indicating a negative regulatory role for Csnk1e in drug-induced behavioral responses. Here, we tested the hypothesis that *Csnk1e* negatively regulates the motivational properties of fentanyl. Using the conditioned place preference (CPP) assay, 24 hours post-assessment of initial preference for the drug-paired side on Day 1, mice received fentanyl (0-0.2 mg/kg, i.p.) on Days 2 and 4 and were confined to the drug-paired side, and saline (i.p.) on Days 3 and 5 and were confined to the other side. On Day 8, mice were assessed for fentanyl CPP (Day 8-Day 1). *Csnk1e* knockout mice showed a leftward shift in the inverted u-shaped curve for opioid reward, exhibiting enhanced reward at lower doses (0.05 mg/kg, i.p.) and significantly decreased reward at higher doses (0.2 mg/kg, i.p.). No differences were observed in fentanyl analgesia in the 52.5°C hot plate assay (0-0.4 mg/kg, i.p.), implicating a neural mechanism selective for dopaminergic reward circuitry. To gain further insight into the neural mechanism, we are testing the hypothesis that *Csnk1e* knockout mice show differential DARPP-32 signaling in response to fentanyl. Finally, we are using an unbiased transcriptome approach (mRNA sequencing) to generate novel hypotheses regarding the molecular mechanism that mediates Csnk1e-mediated inhibition of opioid reward.

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Poster #14

Genome-wide association study of behavior in an advanced intercross line of mice

N. M. Gonzales[1], S. Gopalakrishnan[1], A. A. Palmer[1,2].

Mice are powerful tools for studying the mammalian brain and the genetic basis of behavior. We are conducting a powerful systems genetics analysis of conditioned place preference (CPP) for methamphetamine in a LG/J x SM/J advanced intercross line (AIL) of mice. The CPP paradigm has been widely used to study the motivational effects of drugs of abuse in rodents. We are using a cutting-edge genotyping-by-sequencing (GBS) strategy to obtain genotypes for mapping quantitative trait loci (QTLs) in 1,000 individuals. For a subset of these mice we will also measure gene expression in the brain; this data will be used to identify QTLs that regulate gene expression (eQTLs). Integrating genotype, phenotype and gene expression data is a powerful approach that will accelerate the process of gene identification and provide insight into the biological mechanisms influencing the development of drug abuse. Here we present preliminary phenotype and genotype data from ~500 individuals from generations $F_{50\text{-}52}$ of the LG/J x SM/J AIL.

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Plasticity in the central serotonergic system contributes to exercise-induced stress resistance

Benjamin Greenwood and Monika Fleshner

Exercise increases resistance against the development of stress-related psychiatric disorders such as anxiety, depression, and drug abuse, but underlying mechanisms remain unresolved. Rats exposed to an uncontrollable stressor display behaviors resembling human stress-related disorders, including social avoidance, exaggerated fear, cognitive inflexibility, and potentiated rewarding effects of abusive drugs. These behavioral consequences of uncontrollable stress are sensitive to physical activity status; whereby rats allowed access to running wheels for several weeks prior to stressor exposure are protected against stress-induced behaviors. We have demonstrated that exercise-induced neuroplastic changes in the central serotonergic system could contribute to exercise-induced stress resistance. Affymetrix microarray analysis on laser-captured serotonergic dorsal raphe nucleus (DRN) neurons reveals that gene expression within the DRN is sensitive to physical activity status. Moreover, *in situ* hybridization and behavioral pharmacological studies implicate a role for specific serotonergic targets, both within the DRN (5-HT_{1A} autoreceptor) and in DRN projection sites (5-HT_{2C} receptor), in exercise-induced stress resistance. Results of these studies could provide insight into the signals by which the experience of exercise is communicated to the brain to result in stress resistance, as well as inform the optimal design of exercise programs in order to maximize the benefits to mental health.

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Poster #15

Identification of a network of microRNAs that have a significant role in hippocampal morphology and hippocampal-related behaviors

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Genetic differences in a wide range of behaviors or responses to environmental stimuli have been reported which have implications for a variety of psychiatric illnesses and maladies. To understand the cause of these genetic differences requires the identification of differentially expressed molecular networks. Recently it has been recognized that microRNAs (miR), defined as short, non-coding RNAs, are important regulators of expression by modifying either translation or post-translational processing. In the current study, we examine global changes in miR expression in the hippocampus and use bioinformatics analyses to assess the role of these miRs in mediating genetic differences in a range of phenotypes. Expression was evaluated in a hippocampal dataset that includes data from adult male and female mice from the C57BL/6J, DBA/2J, D2B6F1s and over 60 BXD strains. Bioinformatic analyses was conducted using tools found at www.genenetwork.org. From this analysis, we identified a cohort of microRNAs that have strongly correlated expression and are highly related in principal components analysis. Interestingly, this cohort of miRs all map to a region on chromosome 6 showing that there is a gene within this location that modulates expression of all of these miRs. The PCA shows significant correlation with a number of hippocampal-related phenotypes including several related to neurogenesis and cell number, and behavioral phenotypes including latency to reach the platform in the Morris water maze and several measures in prepulse inhibition. Thus, we have identified a network of related microRNAs that have a significant role in hippocampal morphology and hippocampal-related behaviors.

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D2 Dopamine Receptor in Brain Development and Behavioral Plasticity

P. R. Sabandal, J. Burciaga, I. Mercado, J. M. Sabandal, and K-A. Han

Dysregulated dopamine functions are implicated in the pathogenesis of schizophrenia. Schizophrenia is also linked to increased incidences of substance abuse and addiction. These observations suggest that abnormal dopamine activity may serve as a common neurobiological basis that predisposes people comorbid for schizophrenia and drug use disorders. The goal of this study is to investigate the mechanism by which abnormal dopamine activity leads to this comorbidity by focusing on dopamine D2 receptors. In *Drosophila*, there are three major D2 receptor isoforms dD2R-606, dD2R-506, and dD2R-461, which may correspond to three D2 receptor subtypes in mammals. We examined the flies with loss of function or overexpression of dD2R isoforms, and found a wide range of morphological phenotypes especially in the mushroom bodies, the brain structure crucial for associative learning and memory. Notably, penetrance and expressivity of the mushroom body phenotypes vary with different dD2R isoforms. When tested for behavioral characteristics, *dd2r* mutants exhibited decreased basal locomotor activity and abnormal ethanol-induced disinhibition. We are currently exploring the stage (i.e. developmental, physiological or both) that dD2R function is critical for the mushroom body morphology and behaviors. The outcome of this study may provide important insights into the pathogenic mechanisms of schizophrenia and addiction. This work was supported by the NIMHD and NIAAA grants.

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Poster #16

Matters of a mechanism mediating mouse methamphetamine-induced malaise

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Selectively bred Methamphetamine High Drinking (MAHDR) line mice are sensitive to rewarding effects of MA, but insensitive to MA-induced conditioned taste aversion. The opposite has been shown in Methamphetamine Low Drinking (MALDR) line mice. However, these mouse lines do not differ in sensitivity to ethanol-induced conditioned taste aversion. We previously found that MALDR, but not MAHDR, mice exhibit a profound hypothermic response to 4 mg/kg MA. High sensitivity to MA-induce hypothermia may contribute to the high sensitivity to MA-induced taste aversion in MALDR mice. To examine this further, we tested MAHDR and MALDR line mice for hypothermic response to lower doses of MA (1 and 2 mg/kg), doses used in previous conditioned taste aversion studies. We also examined ethanol-induced hypothermic responses to 2 and 4 g/kg ethanol, and predicted that the lines would not differ. MALDR, but not MAHDR, mice became hypothermic at multiple time points out to 180 minutes post injection of 1 and 2 mg/kg MA. MAHDR and MALDR mice showed equal hypothermic responses to 2 and 4 g/kg ethanol. Thus, sensitivity to MA-induced hypothermia appears to be mechanistically distinct from sensitivity to ethanol-induced hypothermia. Furthermore, conditioned taste aversion results for MA and ethanol correspond with the hypothermic effects of these drugs in the MAHDR and MALDR lines. These data suggest that differential sensitivity to MA-induced hypothermia may be one MA effect that contributes to differences in MA-induced conditioned taste aversion and MA intake in the MALDR and MAHDR lines.

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Poster #17

Value of integrative analysis across multiple behavioral tasks for models of Alzheimer amyloidosis

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Mouse models of neurodegeneration manifest compromised behavior across multiple domains, and develop relevant to disease pathology of central nervous system. Clinical evaluation of patients encompasses multiple behavioral domains, however the initial characterization of a mouse model is often done in one testing paradigm. Although, the best phenotypic characterization should be achieved in several complementary tests, the lack of correlation between similar paradigms, and considerable within and between subject variability cloud analyses and conclusions regarding alignment between a model and a disease. The use of multiple tests addressing complementary behavioral systems is pivotal in pre-clinical studies evaluating therapeutics in mouse models. We used 3 behavioral paradigms focusing on: (1) conditioned fear memory, (2) orientation to a proximate visual cue in water maze test, and (3) species-specific propensity to burrow and build a nest in order to phenotype transgenic mice modeling Alzheimer's disease amyloidosis, and relate the results to developing brain amyloid pathology. We show that the distribution of scores from individual tests is not always associated with amyloid pathology and might lead to false negative results in experiments using smaller sample sizes of mice. In contrast, an integrative analysis of the results from multiple tests is feasible and yields reliable characterization of changes in multiple behavioral systems, which is associated with the amyloid brain pathology. In conclusion, using tests targeting multiple behavioral systems, and integration of results obtained from complementary tests in the final analysis might refine translational applicability of a model used for "diagnosis" of drug efficacy in pre-clinical studies.

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Rare variants in the CHRNA6/CHRNB3 gene region are associated with dependence vulnerability

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Common SNPs in nicotinic acetylcholine receptor genes (*CHRN* genes) have been associated with nicotine, alcohol and cocaine phenotypes, but the influence of rare genetic variants is less characterized. The goal of this project was to identify novel rare variants in *CHRN* genes in the Center for Antisocial Drug Dependence (CADD) and Genetics of Antisocial Drug Dependence (GADD) samples and to determine if rare variants are associated with drug use vulnerability. Two hundred samples representing the tails of the phenotypic distribution of dependence vulnerability were selected for sequencing. DNA was sent to Centrillion Bioscience for custom target capture of all 16 *CHRN* genes (*CHRNA1-7, 9,10, CHRNB1-4, CHRND, CHRNG, CHRNE*) and sequencing on an Illumina Hi-Seq. Sequencing reads were aligned to the human reference sequence using the burrows-wheeler aligner prior to variant calling with the genome analysis tool kit (GATK). Rare variants (minor allele frequency < 0.05) were analyzed with two statistical packages (SKAT-O and C-alpha) that examine the distribution of rare variants among cases and controls. The region containing the *CHRNA6/CHRNB3* gene cluster was significantly associated with disease status using both SKAT-O and C-alpha (p's < 0.05). Variant annotation tools provided evidence of two novel variants in the coding region of *CHRNB3*, while none were found in *CHRNA6*. Sequencing of family members provided evidence that these were not *de novo* mutations, but rather inherited mutations not previously identified in existing databases. These data support a role for rare genetic variants in *CHRN* genes in drug behaviors.

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Poster #18

Enantioselective effects of baclofen on ethanol intake in High Alcohol Preferring Line 1 mice

C. R. Kasten[1], S. L, Boehm II[1, 2]

High Alcohol Preferring (HAP) mice, selectively bred for intake of 10% ethanol, represent a viable model of chronic ethanol intake that is useful for screening alcohol use disorder (AUD) treatments. One widely researched AUD treatment is the $GABA_B$ agonist baclofen. Preclinically, baclofen has been shown to reduce and increase ethanol consumption. Seventy-two HAP1 mice (41F, 31M) were given 16 days of 24-hour access to 10% ethanol and distilled water. On Day 15, all mice received a saline injection. On Day 16, all mice received an injection of 1, 3, 10, or 30 mg/kg S(-)- or 10 mg/kg R(+)-baclofen. Both injections took place at the beginning of the dark cycle. Intake was recorded at 1, 2, and 3 hours post injection. Day 16 intakes were compared to Day 15 intakes. The experiment was repeated in the same animals using 0.32% saccharin and distilled water following a two week water washout period. Males and females were used to analyze sex differences; however sex was not a significant factor in the overall analysis. A Time*Day*Dose ANOVA on ethanol intake revealed a Dose*Day interaction, with the 10 mg/kg R(+)-baclofen dose reducing total 3 hour ethanol drinking and the 10 mg/kg S(-)- dose increasing drinking compared to the saline day (p's < .05). Saccharin consumption showed no Day*Dose interaction (p < .05). There was no omnibus Time*Day*Dose interaction for ethanol or saccharin. These results highlight the enantioselective effects of baclofen while supporting the use of HAP1 mice as a model of chronic ethanol intake.

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Poster #19

Genetic dissection of the zebrafish brain by the Gal4-UAS method

Koichi Kawakami, Lal Pradeep, and Mari Itoh

We have developed *Tol2*-transposon mediated genetic methods in zebrafish, including transgensis, gene trapping, enhancer trapping and the Gal4FF-UAS system. By employing these methods, we have performed large-scale genetic screens, and, to date, generated more than 1,000 transgenic lines that expressed Gal4FF, a synthetic Gal4 transcription activator, in specific cells, tissues, and organs. Our transgenic fish resource has been valuable for the study of developmental biology and neuroscience.

Here we aim to explore the neural circuitry in the brain that controls complex behaviors, such as learning and memory, by applying these methods and resources. First, we analyzed 350 Gal4FF fish from our collection and identified 77 lines that showed strong and restricted Gal4FF expression in the adult brain. We analyzed these expression patterns by making serial coronal sections, and constructed a database named “ZeBrain” containing these data. Second, we developed a system to analyze active avoidance conditioning. Wild type zebrafish could learn active avoidance response when light (CS) and electric shock (US) was coupled. Finally we crossed transgenic fish that expressed Gal4FF in restricted regions of the brain with a UAS-neurotoxin fish, and analyzed behaviors of the double transgenic fish. We found that, when neuronal activity of the dorsomedial telencephalon was inhibited, the leaning ability was reduced. Thus, the dorsomedial telencephalon plays an important role for emotional learning, and may be a functional equivalence of mammalian amygdala. We propose that our approach is powerful to study functional neural circuits that regulate complex vertebrate behaviors.

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The temporal effects of exercise on hippocampus-dependent memory in the rat: multiple roles of BDNF

S. M. McCreddin, R. G. Bechara, Á. M. Kelly

The cognitive-enhancing effects of exercise have been widely-investigated and are consistently correlated with increased expression of the neurotrophin brain-derived neurotrophic factor (BDNF) in the hippocampus and with increased neurogenesis in this brain region. However, the mechanisms underlying these effects of exercise are not well understood and consequently, the therapeutic applicability of exercise regimens or the development of pharmacomimetics of exercise for improving and maintaining cognitive function has been limited. The magnitude of the exercise-induced effects and their persistence are likely to depend on the duration and intensity of exercise training. We have assessed the effects of exercise protocols of different durations on object recognition and object displacement memory in the rat. Our data indicate that single bouts of exercise are sufficient to enhance performance of these learning and memory tasks and that these improvements are concomitant with activation of BDNF-stimulated signalling pathways. Moreover, these changes are mimicked by intracerebroventricular or intravenous administration of BDNF. The effects also appear to be linked with task acquisition rather than consolidation or recall. In contrast, the longer-term effects of exercise may enhance learning in a neurogenesis-dependent manner that may also require increased expression of BDNF.

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Poster #20

A forward genetic mouse model of compulsive eating: Implications for human GWAS of eating disorder traits

Stacey L. Kirkpatrick[1], Amanda Bolgioni[1], Megan K. Mulligan[3], Pietro Cottone[2], Camron D. Bryant[1]

Eating disorders are among the most lethal neuropsychiatric conditions and exhibit a lifetime prevalence of 1 to 3%. Eating disorders are heritable; however the responsible genetic factors have not been identified. Mammalian model organisms offer a powerful approach to studying the genetic and biological basis of behavioral symptoms that define eating disorders, including binge eating. We developed a model of compulsive-like binge eating using a conditioned place preference (CPP) procedure whereby outbred CFW mice exhibited a nine-fold escalation in palatable food (PF) consumption that was accompanied by PF-CPP. Strikingly, the progressive escalation in food consumption coincided with an escalating, nearly perfect correlation with PF-CPP ($r = 0.95$), thus assigning increasing motivational value behind each binge episode. The C57BL/6NJ (B6NJ) inbred strain also showed robust binge eating that was accompanied by PF-CPP; however, the closely related C57BL/6J substrain (B6J) did not show any binge eating nor PF-CPP. Preliminary studies in B6J x B6NJ-F_1 mice indicate a dominant mode of inheritance for binge eating and PF-CPP. We are currently generating F_2 progeny (target sample size = 250 mice) for this Reduced Complexity Cross (RCC) and will use quantitative trait locus mapping to identify candidate genes mediating compulsive eating. There are only 10,000 putative variants segregating in the RCC compared to 40,000,000 in the Collaborative Cross and Diversity Outbred mice – this nearly complete lack of genetic diversity makes gene identification a tractable goal and could inform translational genetic studies and novel pharmacotherapeutic development in humans.

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Poster #21

Transcriptional changes in zebrafish following chronic exposure to nicotine and ethanol

M. A. Cousin, S. C. Ekker, E. W. Klee

In the 50 years since the US Surgeon General's report on Smoking and Health, public health initiatives have driven a decrease in smoking rates and ~30% increase in life expectancy. Despite these advances, cigarette-smoking rates in the US have plateaued over the last decade and smoking remains the highest cause of preventable death and excess health care costs in the US. Exacerbating this health-care crisis is the link between nicotine and ethanol use. Smokers consume twice as much alcohol as non-smokers, and >70% of alcoholics smoke. Tobacco-related disease is also a leading cause of death among patients with alcohol use disorder. Improved understanding of the genetic factors influencing nicotine, ethanol, and nicotine-ethanol interaction responses may ultimately drive improved treatment options for patients suffering from these substance use disorders.

In this study, we profiled the transcriptional changes in neural-enriched zebrafish tissue following chronic nicotine, ethanol, and combined nicotine and ethanol exposure. Biological triplicates were analyzed using RNAseq with an average of 120 million reads per sample. DESeq computed differential expression was generated against water-treated controls and pathway enrichment computed using WebGestalt.

Preliminary data identified statistically significant differentially expressed genes in each subgroup, including enrichment for genes in the circadian rhythm pathway. The results are supported by observations in rodent models linking the circadian rhythm genes to addiction reward response and dopamine regulation, following chronic ethanol and cocaine exposure. Further investigation of this pathway may lead to novel pharmacotherapeutic targets and improve the treatment of nicotine and ethanol substance use disorders.

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Poster #22

Evolutionary conservation of the locomotor stimulant response to ethanol among arthropods

Christopher L. Kliethermes

While the sedative action of ethanol can be described in part by mechanisms common to other sedatives and anesthetics, ethanol's low-dose stimulant effect is more enigmatic, being variously described as reflective of the disinhibitory, anxiolytic, euphoric, or reinforcing effects of ethanol. The fruit fly *Drosophila melanogaster* shows an ethanol-induced stimulant response similar to that seen in vertebrates, yet as a species, it diverged from the vertebrate lineage approximately 280 million years ago, implying that any conserved ethanol-sensitive circuitry must be evolutionarily ancient in origin. The current experiments tested the generality of the stimulant response across multiple arthropod lineages, including a panel of 13 fruit fly species and a phylogenetically diverse panel of arthropod species from several classes and multiple orders. Of the fruit fly species tested, 10 showed a clear stimulant response to ethanol, with *D pseudoobscura* showing the highest degree of stimulation. Two species, *D yakuba* and *D willistoni*, failed to show a stimulant response. The responses among the other arthropods were variable, with no stimulation seen in *T domestica* (firebrats), *T confusum* (flour beetles), or *P Laevis* (woodlouse), but strong responses seen in the other insect species, as well as in an arachnid and a diplopod. Given the phylogenetic and ecological diversity of the species which showed a response, these results are consistent with a recent suggestion of functional conservation between arthropod and vertebrate locomotor-generating circuitry. The comparative approach used in these studies strengthens the assertion that studies of fly ethanol-related behaviors can be used to identify evolutionarily conserved mechanisms of ethanol's actions.

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Poster #23

Genetic control of specific anosmia to androstenone in a mouse model

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Specific anosmia (inability to smell or very low olfactory sensitivity) to the sex boar pheromone androstenone affects about 50% of adult humans (Amoore, 1977; Labows, Wysocki, 1984). A functional role for this phenomenon remains unclear, though putative involvement of androstenone in human chemical communication is under consideration. An animal model for specific anosmia to androstenone was developed using inbred strains of mice CBA/J and NZB/BlNJ. CBA/J mice detected androstenone at a concentration 2000-fold lower than NZB/BlNJ mice did (Voznessenskaya et al., 1995). We measured androstenone thresholds in F1 and F2 hybrids between the NZB/BlNJ and CBA/J strains using a training procedure with food reinforcement. The observed segregation of androstenone threshold phenotypes in F2 hybrids allowed us to perform chromosomal linkage analysis. DNA purified from tail biopsies of the F2 mice was used for a genome-wide scan with 98 microsatellite and 41 single nucleotide polymorphism markers. An association analysis performed using R/QTL software (Broman et al, 2003) revealed suggestive linkages for androstenone thresholds to mouse chromosomes 2, 12 and 17, and a significant male sex-specific linkage to chromosome 10. Genes located within the QTL intervals were investigated to find candidates that are either olfactory receptor genes or are implicated in genetic control of olfactory sensitivity to androstenone in humans (Keller et al, 2007, Knaapila et al, 2012). The locus on the chromosome 12 appears to be orthologues in mouse and human. Overall, our findings demonstrate value of using the mouse model to understand mechanisms of specific anosmia to androstenone.

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Poster #24

An interaction of *GABRA2* genotype and recent drinking modifies subjective responses to alcohol.

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How a person feels when intoxicated is likely to influence continued alcohol drinking and subsequent risk of alcohol abuse. In the present study, we tested how subjective perceptions were influenced by genes (family history of alcoholism and GABRA2 receptor genotype) and experience (recent drinking history and the results of a laboratory alcohol or placebo challenge). 103 non-dependent drinkers, aged 21-27, participated in within-subjects, single-blind, randomized-order, 2-session, crossover design. One session was an intravenous alcohol "clamp" (during which breath alcohol concentration was held steady at 60 mg/dl for 3 hours), and in the other only saline was infused. Subjective perceptions of intoxication, enjoyment, stimulation, relaxation, anxiety, tiredness and estimated number of drinks were acquired before the infusion, and during the first and final 45 minutes of the clamp. An index of acute adaptation to alcohol was calculated for each subjective perception, the n principal component analysis of the ensemble was used to weight and sum the indices for each subject into a single aggregate measure. ANCOVA revealed significant associations of gender (p=0.05), recent drinking history (p=0.04), *GABRA2* genotype (rs279858; p=0.05), and the recent drinking history x genotype interaction (p=0.01) with acute adaptation of the subjective responses to alcohol. For carriers of the CC risk genotype, higher recent drinking was associated with persistent sensitivity to pleasant effects of alcohol (absence of acute tolerance); this may represent a mechanism predisposing to abuse and dependence.

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The transposon storm hypothesis of neurodegeneration

Lisa Krug and Joshua Dubnau

Retrotransposons are inherited virus like repetitive elements that are capable of replicating and re-inserting into *de novo*locations within the genome. As a whole, retrotransposon sequences contribute a vast fraction of the genome, up to 30% in flies and even higher in humans. To date, retrotransposition has been largely studied in germline where new insertions produce heritable genetic variants. But transposons also are capable of mobilizing in somatic tissue. In two recent publications, we demonstrated that some LINE-like and LTR retrotransposons become aggressively active with age, leading to accumulation of de novo mutations in neurons. We also demonstrated that genetically activating LINE-like and gypsy transposons results in accelerated effects of aging on neurophysiological decline. This leads to rapid age-dependent memory impairment, defects in locomotion, and ultimately to shortened lifespan. We also discovered evidence that links this transposon storm to the neurodegenerative effects seen with TDP-43 pathology in mammals, including humans. More recently, we have tested this hypothesis using a Drosophila model of TDP-43 neurodegeneration. We will show evidence that TDP-43 pathology in glial cells causes activation of retrotransposons, leading to accumulation of DNA damage and ultimately apoptotic cell death. Our findings have implications for the mechanisms of neurodegeneration seen in amyotrophic lateral sclerosis and frontotemporal dementia, where TDP-43 pathology is central.

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A transgenic zebrafish model for monitoring glucocorticoid receptor activity

R. G. Krug II, T. L. Poshusta, K. J. Skuster, M. R. Berg, S. L. Gardner, K. J. Clark

Gene regulation resulting from glucocorticoid receptor and glucocorticoid response element sequence interactions is a hallmark feature of the vertebrate stress response. Imbalances in stress response signaling have been linked to socio-economically crippling neuropsychiatric disorders, and thus *in vivo* models are needed to help understand disease progression and management. Therefore, we developed a transgenic zebrafish reporter line with six glucocorticoid response element sequences used to promote expression of a short half-life green fluorescent protein (GFP) following glucocorticoid receptor activation. To characterize the ability of the reporter line to model glucocorticoid receptor signaling, transgenic larvae were either treated with exogenous glucocorticoid receptor ligands, or exposed to stressors including drugs of abuse or hyperosmotic conditions. The changes in GFP expression relative to control fish were assessed using both qRT-PCR and high-resolution imaging. Herein, we show that chronic and acute glucocorticoid treatment causes transgene activation in numerous tissues including the brain, and provides a single cell resolution in the effected regions.

The specificity of these responses is demonstrated using the partial agonist mifepristone and mutation of the glucocorticoid receptor with transcription activator-like effector nucleases. Importantly, the reporter line also modeled the dynamics of endogenous stress response signaling, including the increased production of the glucocorticoid cortisol following exposure to stress and fluctuations of basal cortisol concentrations with the circadian rhythm. Collectively, these results characterize our newly developed reporter line for elucidating modifiers of stress response signaling, which may provide insights to the neuronal mechanisms underlying neuropsychiatric disorders.

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Genetics of interactive social behavior in silver foxes (*Vulpes vulpes*).

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Interactive behaviors are comprised of many traits that are displayed or not displayed during the social interaction. To understand the mechanisms implicated in individual's differences in behavioral responses we are studying specific strains of the silver fox (*Vulpes vulpes*). Foxes from the tame strain are friendly and playful towards humans, paralleling the sociability of canine puppies, whereas foxes from the aggressive strain are defensive and exhibit aggression to humans. To identify the genetic basis of these behaviors fox crossbred pedigrees have been established. Fox behavior was tested in a structured four-stage test and scored from video records using 98 behavioral observations describing fox location in the cage, body postures, sounds, and other traits. Principle component (PC) analysis was used to reconstruct behaviors expressed during the individual test stages and in the course of the whole test. Several genetic loci were identified repeatedly by mapping PCs and individual traits, while other identified loci were associated only with specific PCs or individual traits. Significantly, several PCs from individual test stages were mapped to different regions in the genome, further supporting the underlying genetic complexity of the tame and aggressive patterns. In combination with genome sequencing and transcriptome analysis these data may provide novel insight into the regulation of interactive social behaviors in foxes and other mammals including humans.

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Poster #25

ALK in the ventral tegmental area regulates binge ethanol consumption and dopamine receptor sensitivity in mice.

A. W. Lasek[1], H. Chen[1], C. You[2], M. S. Brodie[2]

ALK is a receptor tyrosine kinase expressed in the nervous system that we previously found to regulate behavioral responses to ethanol in mice. To further characterize the ability of ALK to regulate ethanol consumption, we treated mice systemically with the ALK inhibitor, TAE684, and tested them for binge drinking using the drinking in the dark (DID) protocol. Mice treated with TAE684 drank less ethanol than controls, indicating that ALK activity in adult mice promotes binge drinking. Since the ventral tegmental area (VTA) is a key brain region involved in the rewarding and reinforcing effects of ethanol, we examined whether *Alk* expression in the VTA might be important for ethanol consumption. A lentiviral-delivered short hairpin RNA (shRNA) targeting *Alk* or a non-targeting control shRNA was delivered into the VTA. Mice expressing *Alk* shRNA in the VTA drank less ethanol in the DID test compared to mice expressing a control shRNA. We characterized the expression of ALK in the VTA using immunohistochemistry and found that ALK is expressed on dopamine neurons, suggesting that ALK might regulate the firing properties of these neurons. Extracellular recordings of putative dopaminergic (pDA) neurons in VTA slices treated with TAE684 showed that there was no difference in the ability of dopamine to inhibit firing of pDA neurons. However, TAE684 prevented the desensitization of pDA neuron firing after prolonged exposure to moderate concentrations of dopamine. Together, these data suggest that ALK activity in the VTA regulates binge ethanol consumption and desensitization of dopamine receptors.

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Poster #26

A zebrafish model to characterize host stress response and gut microbiota interaction

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It is increasingly clear that gut microbiota interact with the neuroendocrine and immune system to modulate the host's responses to environmental stressors. Disruption of gut microbiota results in altered anxious behaviors and brain chemistry in mice and zebrafish. When we derived germ-free (GF) larval zebrafish, the GF fish showed increased stress responsiveness compared to zebrafish with normal gut flora in hyperosmotic (100 mM NaCl) and physical (shaking) stress assays—demonstrating that the microbiota modulates host stress responses. It is largely unknown what host genes are the cognate partners of the gut microbiota responsible for these behavioral and physiological changes. We are developing a zebrafish model to characterize these host factors that modulate the gut microbiota with a focus on stress responses. We will investigate microbial compositional changes that occur in mutant backgrounds with or without acute stressors. We are currently analyzing changes in microbial compositions in wildtype zebrafish after exposure to acute stressors. Next, we will perform the 16S rRNA sequencing with mutant zebrafish strains that we have generated in the lab. Using custom nucleases, we have knocked out il6 and nod2. These genes are involved in immune stress responses (e.g. inflammatory bowel disease). Comparing the microbial compositions of these mutant fish to those of wildtype fish under stress or non-stress conditions will increase our understanding on how host genes modulate the gut microbiota in the context of stress responses. Moreover, we are developing a forward genetic screen to identify host factors that modulate bacterial colonization.

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Poster #27

Alcohol Preferring 'P' Rats Display Greater Discounting of Sucrose Pellets and Lack Prospective Memory-like Behavioral Responding

David N. Linsenbardt, Michael P. Smoker, Brandon G. Oberlin, & Christopher C. Lapish

Individuals that are family history positive for an alcohol use disorder (AUD) as well as rodents selectively bred for excessive drinking tend to exhibit a impulsive behavioral phenotype, which suggests that these traits are regulated by similar genes. However, common measures used to assess impulsivity often do not assess whether distinct memory-related processes are involved in mediating these genetically-regulated deficits in decision making. The primary goal of this work was to determine the involvement of prospective memory in genetically-mediated impulsive behavior. Alcohol-preferring (P) rats and heterogeneous Wistar rats were used in a delay discounting task to assess differences in the tendency to favor small immediate rewards at the expense of larger delayed rewards. Wistar rats were less impulsive and more likely to make a reward choice on the same lever used to initiate a trial (regardless of reward lever), suggesting that Wistar rats choice behavior was planned prior to the start of each trial. These data provide additional support that similar genes regulate impulsivity and vulnerability to alcohol intake, and suggest that this effect may be mediated in part by genetic differences in ability and/or use of prospective memory.

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A songbird model for social effects on sensory learning

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The social environment is key in shaping appropriate communication styles for animals such as humans and songbirds who learn their specific vocal patterning. Much like humans, all male zebra finches hatch with the potential to learn conspecific song from a "tutor" and learn to sing during a restricted developmental sensitive period. As part of our goal to identify neurogenomic mechanisms that limit and promote the ability to learn from the social environment, we measure and manipulate patterns of genomic activation in the context of tutor experience to test the effects on song copying. We have used this strategy to identify the avian equivalent of the auditory cortex as a primary locus for tutor song memorization. We showed that experience-dependent genomic regulation emerges across the developmental song learning period; this has functional implications as ERK-mediated genomic activation specifically during tutor experience is essential for song learning. Analysis of predicted position weight matrices suggested that steroids may coordinately regulate a subset of these genes, and others have shown that steroids can be rapidly synthesized within the auditory forebrain. We therefore hypothesized that tutoring may trigger steroid synthesis that alters gene expression and song learning fidelity. Our preliminary evidence to support this hypothesis suggests that we can identify specific neural mechanisms by which transient developmental social experience can have long-term consequences for complex learned behavior.

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Poster #28

Competing mechanisms for the influence of Lhx9 on sleep and wakefulness.

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Orexin-expressing neurons play a role in the sleep and wakefulness cycle and an absence of these cells causes narcolepsy in humans and animal models. We previously demonstrated the transcription factor LIM homeobox 9 (Lhx9) is enriched in orexinergic neurons and global deletion of Lhx9 in the mouse produces hypersomnolence with an increase in NREM sleep and a corresponding decrease in wakefulness. Lhx9 knockout ($Lhx9^{-/-}$) mice also exhibit a 30% decrease in orexin-expressing neurons and lack gonad development. In the current study, we sought to clarify the mechanism by which the absence of Lhx9 alters sleep and wakefulness patterns testing two alternative hypotheses. First, to understand the influence of gonadal hormones in our model, we compared behaviors of castrated wild-type and $Lhx9^{-/-}$ mice with and without hormone replacement. The lack of gonads influences sleep and wakefulness levels but does not account for the entire $Lhx9^{-/-}$ phenotype, as castrated males do not fully recapitulate the mutant phenotype. Furthermore, hormone replacement did not restore $Lhx9^{-/-}$ sleep and wakefulness levels or alter the orexin-expressing cell numbers. To determine if sleep is disturbed through the orexinergic system, we generated Lhx9 and orexin peptide double knockout mice and are comparing sleep and wakefulness levels to that of single knockout and wild-type mice. Our results suggest that neither loss of gonads nor partial loss of orexin-expressing neurons is completely responsible for the sleep phenotype of our mutant model. Finally, to generate alterative hypotheses for molecular mechanism of the sleep alteration, we evaluated gene expression changes following Lhx9 deletion by microarray data analysis.

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Poster #29

Glo1 and methylglyoxal modulate anxiety- and depression-like behavior in mice

K. M. J. McMurray[1] and A. A. Palmer[2]

GLO1 is a ubiquitous cellular enzyme responsible for detoxifying methylglyoxal (MG), a byproduct of glycolysis. We previously showed that overexpression of *Glo1* reduced MG concentrations and increased anxiety-like behavior, whereas IP injections of MG reduced anxiety-like behavior. We further showed that MG is a competitive partial agonist at GABA-A receptors, which likely explains GLO1's effects on anxiety-like behavior.

To determine the neuroanatomical regions associated with *Glo1* and MG modulation of anxiety-like behavior, we bred transgenic mice with a floxed-stop codon upstream from human *Glo1* to various CRE driver lines which resulted in tissue specific overexpression of *Glo1 (*C57BL/6J background). Limiting overexpression of *Glo1* to neurons or forebrain was sufficient to increase anxiety-like behavior in the open field test (OFT). We also assessed C57BL/6J mice in the OFT after bilateral microinjection of MG directly into the basal-lateral amygdala (BLA), a region shown to regulate anxiety-like behavior. Direct injection of MG into the BLA reduced anxiety-like behavior in the OFT.

As anxiety and depression are highly comorbid, we investigated the effects of both pharmacological and genetic inhibition of GLO1 on depression-like behavior in mice. We found that inhibition of GLO1 reduced depression-like behavior across multiple behavioral assays and in multiple strains. While antidepressants are commonly used to treat anxiety, anxiolytics that act at GABA-A receptors are not commonly used to treat depression and fail to reduce depression-like behavior in mouse models. Our studies suggest GLO1 inhibition offers a unique mechanism for the treatment of both anxiety and depression.

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Poster #30

Prolonged psychological stress exaggerates behavioral and molecular traits of a genetic rat model of depression

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Major depressive disorder (MDD) is a highly prevalent and devastating disorder. Its etiology is thought to involve genetic susceptibility and environmental stress. While the biological underpinnings of these two causes are molecularly distinct, they may interact to increase vulnerability to MDD. The Wistar Kyoto More Immobile (WMI) rat strain is a genetic model of depression. Throughout 32 generations, the WMIs have shown consistently greater despair-like behavior in the forced swim test (FST) than their genetically close control strain, the Wistar Kyoto Less Immobile (WLI). Here we sought to determine the behavioral and molecular effects of prolonged stress on this genetic model of depression. Adult males of both strains underwent an initial FST followed by two weeks of daily two-hour restraint stress, and finally a follow-up FST. Higher floating scores indicate greater despair-like behavior in the FST. While the WMIs maintained higher floating scores than the WLIs from baseline ($p=.01$) to the follow-up ($p<.05$) testing, both strains showed a similar percent increase in floating behavior in the FST (WMI: 357% increase, WLI: 316% increase). Since floating increased in parallel in both strains after stress, the genetic and environmental (stress) contributions to depression-like behavior seem to be additive. Transcript levels of previously identified MDD biomarkers were either similarly altered by stress in both strains, or changed strain-specifically in both the blood and hippocampus of these animals. Thus, the pathways by which stress induces greater despair-like behavior may differ between a control strain and a genetic model of MDD.

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Poster #31

Examination of the involvement of cholinergic-associated genes in nicotine behaviors in European and African Americans

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Upon chronic exposure to nicotine, nicotinic acetylcholine receptors (nAChRs) undergo upregulation of receptor numbers (Schwartz & Kellar 1983; Marks 1983; Benwell 1988). However, this response is not due to an increase in mRNA of nAChR genes (Marks 1992). Various theories to explain this phenomenon include increased receptor trafficking (Darsow 2005), decreased nAChR subunit degradation (Rezvani 2007, 2009), increased nAChR subunit maturation and folding (Harkness & Millar 2002; Nashmi 2003; Sallette 2005), and increased translation and 2nd messenger signaling (Gopalakrishnan 1997). Through manual curation of primary literature and in discussion with experts in the nAChR field, we have developed a list of 96 gene products known to interact with nAChRs that may promote increased surface expression.

Using Joint Association of Genetic Variants (Lips & Kooyman, submitted), a gene-based test was run on several GWAS data sets to test the hypothesis that these genes are associated with nicotine dependence (ND) and cigarettes smoked per day (CPD). P-values for each gene were combined across studies using the weighted Z-score method (Whitlock 2005). Preliminary results revealed associations between *CHRNA9* and *CAMK2A* with ND in European Americans at combined $p < 0.05$, as well as suggestive associations between *ERBB4* and *CHRNA9* with ND and CPD in African Americans. These findings were analyzed also using an independent statistical test in PLINK (Purcell 2007). This work highlights the value of collaboration between neuroscience experts and statistical geneticists to identify and characterize novel genetic associations.

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Poster #32

The role of genetic background on exercise-induced neurogenesis and memory performance in the adult male mouse

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Adult hippocampal neurogenesis in the dentate gyrus is robustly stimulated by aerobic exercise, and new neurons have been hypothesized to facilitate learning and memory. Genetic differences in exercise-induced neurogenesis were recently reported for 12 inbred strains. However, the extent to which learning and memory is facilitated in these strains from exercise is not known. Therefore, the goal of this study was to compare effects of exercise on neurogenesis in five strains, C57BL/6J, 129S1/SvImJ, B6129SF1/J, DBA/2J, and B6D2F1/J, as well as evaluate behavioral performance on the rotarod and plus water maze. Male mice were given injections (i.p.) of 5-bromo-2'-deoxyuridine (BrdU) for the first 10 days to label dividing cells. After 30 days of exercise or sedentary conditions, mice were tested on the plus water maze and rotarod at 9 weeks of age. B6129SF1/J and DBA/2J mice ran significantly more than 129S1/SvImJ mice, and C57BL/6J and B6D2F1/J ran intermediate distances. Strain differences in levels of neurogenesis and behavioral performance were observed as expected. However, all mice displayed a similar increase in neurogenesis in response to exercise and exercise improved water maze performance in all strains to a similar degree. On the other hand, only the DBA/2J mice displayed improved performance on the rotarod from exercise. Taken together, these results demonstrate that despite different levels of baseline neurogenesis and memory performance in these mouse strains, all strains can equally increase neurogenesis and improve memory performance through aerobic exercise.

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Poster #33

The effects of cadherin 13 (*Cdh13*) gene deletion on measures of behavioral regulation and Pavlovian conditioning in rats.

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Genome-wide association studies have suggested that cadherin 13 (*Cdh13*) gene variants are associated with attention deficit hyperactivity disorder, methamphetamine dependence, smoking, alcoholism, and the subjective response to amphetamine. To determine the role of CDH13 in attention and addiction-related traits in rats, we tested littermates that were homozygous or heterozygous for the *Cdh13* gene deletion and wild type controls in several behavioral paradigms, including a reaction time (RT) task, sensory reinforcement (SR), operant responding for saccharin, Pavlovian conditioned approach (PCA), and cocaine-induced conditioned place preference (CPP). For the RT task, in which a rat must maintain sustained attention to a visual stimulus to obtain saccharin reinforcers, we found that knockout rats were slower to acquire the task but had no deficits in response withholding or stimulus control after they acquired the task. There were also no genotype differences in responding for a light stimulus in the SR task or for saccharin. In the PCA task, in which rats are presented with a lever that predicts the delivery of a food pellet, we found similar lever-directed (sign-tracking) and food-cup directed (goal-tracking) responses in all three genotypes. In the CPP task, cocaine and saline were paired different tactile floor cues on alternating days. When presented with both cues, wild-type and heterozygous rats displayed more preference for the cocaine paired floor than knockouts. These results suggest that *Cdh13* deletion does not result in an ADHD-like phenotype, but that CDH13 is involved in the formation of cue-drug associations.

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Poster #34

Cortical-hippocampal interactions in visual memory processing

K. S. Montgomery[1] and D. Ji[1,2]

During a new experience, multisensory components are processed by the cortex and indexed by the hippocampus (HP), resulting in a memory trace. During memory recall, hippocampal neurons communicate back to the cortex and reactivate indexed neurons, leading to reinstatement of the sensory memory. Although this theory is popular, it has not been fully tested. Recent studies have focused on the involvement of neocortex in memory, and although not much is known about the neural representations that support visual memories in vivo, the secondary visual cortex (V2) has been implicated in memory consolidation. We hypothesize that V2 is involved in the long term consolidation of visual components of HP-dependent spatial memories. We propose a neocortical-hippocampal model for memory consolidation in which neuronal activity in V2 is related to the consolidation of object memory representation during the establishment of a HP-dependent memory trace. Our model predicts that during memory retrieval of the memory trace, V2 cells will be reactivated. Here, V2 and HP activities are evaluated simultaneously by multielectrode recordings in freely moving rats. Preliminary results show that a population of V2 cells responds to the presence of an object in a familiar spatial environment, while others may respond to a particular location independent of 3-dimensional cues in the context. Results from this proposal will shed light on how HP and visual cortical circuits interact to mediate consolidation of visual-spatial memories.

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Cloning QTLs the easy way: Leveraging a reduced complexity cross between C57BL/6J substrains

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We generated a reduced complexity cross (RCC) with low genomic diversity but moderate phenotypic diversity using C57BL/6J (J) and C57BL/6NJ (N) as progenitors of an F2 intercross. Separated since the 1950s, J and N show marked differences for a large number of traits. Substrains differ at ~ 15,000 SNPs and ~50 genes segregate damaging coding variants, including *Nnt*, *Cyfip2*, *Crb1*, *Pmch*, *Adcy5*, and *Nlrp12* (Simon et al., 2013; PMID 23902802). To identify causal variants controlling trait variation we phenotyped the RCC for traits shown to differ between parental substrains—alcohol preference, anxiety, motor coordination, activity in a novel environment, acoustic startle, PPI, pain sensitivity, glucose and insulin tolerance, and organ weight. We designed custom Fluidigm genotyping assays with 96 markers spaced ~30 Mb. Even with a modest number of RCC F2 progeny (*n* = 182), we detected suggestive and significant QTLs and confirmed that deletions in *Nnt* (*J allele*) alter glucose metabolism. Using a reverse genetic approach we show that none of our traits are modulated by a missense mutation in *Cyfip2* (*N allele*) that modulates response to cocaine and methamphetamine (Kumar et al., 2013; PMID 24357318). As expected, candidate genomic intervals are large (~10 cM) but this is counterbalanced by the extremely low density of segregating sequence variants in the RCC. Reduction of genetic complexity greatly simplifies candidate gene discovery. The addition of novel phenotypic differences between substrains and gene and protein expression profiles is expected to further enhance the JxN RCC as a genetic resource.

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L1 retrotransposition in the nervous system

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LINE-1 (L1) retrotransposons are active elements in the genome capable of mobilization in neuronal precursor cells, resulting in a mosaic brain (Muotri et al, 2005). Upon mobilization, L1 insertions can alter gene expression, resulting in a genetic heterogenic population of neurons. However, the physiological consequence of somatic L1 retrotransposition is unknown. Mutations on the methyl-CpG-binding protein 2 (MeCP2) gene cause Rett Syndrome (RTT), a severe X-linked neurodevelopmental. Few studies, however, were able to correlate *MeCP2* mutations to specific symptoms or severity of RTT. In fact, the spectrum of neurological abnormalities associated with MeCP2 dysfunction extends beyond RTT, including Angelman-like syndrome and autism. We show that MeCP2 is a negative regulator of L1 expression in the brain (Muotri et al, 2010). Based on this, we postulate that the phenotypic heterogeneity in RTT could be, at least in part, due to variable neuronal pattern of L1 activity in the brain. These data identify retroelements as potentially important somatic components of neuropsychiatric diseases that are consistent with genetic, environmental, and neurodevelopmental aspects of the disease process observed in schizophrenia, RTT, autism and others similar complex syndromes with unknown origins and diverse expression. The validation of this hypothesis may open new possibilities for therapeutic interventions for L1-related neurodevelopmental diseases.

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New neurons are not necessary for exercise to abolish conditioned place preference for cocaine

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Recent evidence suggests wheel running can abolish conditioned place preference (CPP) for cocaine in mice. Running significantly increases the number of new neurons in the hippocampus, and new neurons have been hypothesized to enhance plasticity and behavioral flexibility. Therefore, we tested the hypothesis that increased neurogenesis was necessary for exercise to abolish cocaine CPP. Male nestin thymidine kinase transgenic mice were conditioned with cocaine, then housed with or without running wheels for 28 days. Half the animals were fed valganciclovir in their chow to induce apoptosis in newly divided neurons and the other half were fed standard chow. The first 10 days mice received daily injections of BrdU to label dividing cells. Levels of running were similar in animals fed valganciclovir or normal chow. Valganciclovir significantly reduced number of BrdU+ NeuN+ cells in the dentate gyrus of both sedentary and runners. However, even though valganciclovir-fed runners displayed similar levels of neurogenesis as sedentary normal-fed controls, they displayed the same abolishment of CPP as runners with intact neurogenesis. Results demonstrate that new neurons are not necessary for running to abolish CPP in mice.

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Poster #35

The effects of combined lithium and ethanol treatment on the behavioral circadian activity rhythm

N. F. Nascimento, K. N. Carlson, D. N. Amaral, G. C. Nash, D. M. Pyne, J. A. Seggio

Lithium has been traditionally used to treat Bipolar disorder among other psychiatric disorders that have been linked to disruptions in the circadian rhythm. Numerous studies have shown that lithium treatment produces period lengthening and amplifies expression of *per2*. Conversely, ethanol drinking has been shown to produce period shortening and reductions in *per2* expression. In addition, ethanol drinking also blunts the phase-shifting effects of light pulses. All B6 mice were placed into DD for 3-weeks with water only; after the initial 3-weeks, mice were given one of four drinking solutions: water, 10 mM LiCL, 10%-ethanol, or a combination of lithium and ethanol, and were allowed additional 3-weeks in DD. In addition, light pulses at ZT 15 and ZT 21 were conducted to determine if lithium can prevent ethanol's blunting of photic phase responses. As expected, lithium significantly increased the period, while alcohol produced a small but non-significant decrease in the period. When combined ethanol/lithium solution was given, it produced similar free-running periods to control mice. Additionally, ethanol produced reductions in photic phase shifting, but when lithium was given with ethanol, the combined effect produced phase shifts similar to water controls. The combined lithium/ethanol group drank significantly less fluid than the lithium, ethanol, and water groups, indicating that lithium treatment can be used as a mechanism for decreased ethanol intake, and thus, reducing the effects of both drugs on the circadian clock. These results may also indicate that lithium and ethanol may be affecting the same clock mechanisms and having opposite effects.

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Poster #36

Selection for High Alcohol Preference increases motivated operant responding during reinforced, but not during non-reinforced conditions

D. S. O'Tousa and N. J. Grahame

High-Alcohol Preferring replicate 2 (HAP2) mice have been selectively bred to volitionally consume high quantities of 10% alcohol (v/v) solution, and reach blood ethanol concentrations of nearly 150 mg/dl during 24-hour free-choice drinking. Low-Alcohol Preferring (LAP2) mice do not volitionally consume 10% alcohol. Operant behavior using a palatable reinforcer had not been previously characterized. Water-deprived HAP2 and LAP2 mice were trained to lever-press to obtain a reinforcer of 1% banana flavoring (v/v) solution on a fixed-ratio 1 (FR1) schedule, in which every lever press allows reinforcer access. Once operant behavior was acquired, reinforcement schedule was amended to variable-interval (VI): 3 days of VI30, in which a reinforcer was available on average every 30 seconds, followed by 12 days of VI60. All preceding sessions were 45-min. 15-min probe sessions were interspersed during which the reinforcer was not available (i.e., extinction conditions). For these tests, mice were divided into water-deprived and non-water-deprived groups to assess differential motivational states. Results indicated that throughout operant training, HAP2 mice demonstrated higher levels of reinforcer seeking and general activity than LAP 2 mice, assessed by active and inactive lever presses, respectively. HAP2 mice also showed higher ingestive behavior, assessed by volume of reinforcer consumed. During extinction tests, active lever presses between lines did not differ, though within each line water-deprived mice responded at markedly higher levels. This experiment suggests that selection for alcohol preference in rodents affects seeking, general activity, and ingestive behavior, but not motivation in the absence of reinforcement.

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Poster #37

Synaptic TRAP: High-throughput identification of mRNA from synapses *in vivo*

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Subcellular localized translation restricts protein synthesis and function to a specific location in the cell. In neurons, local translation at the synapse is hypothesized to be the foundation to learning and memory. Dysregulated synaptic translation is associated with many intellectual disorders; however, there is no consensus on which mRNAs are translated at the synapse or how this changes with disease or across different classes of neurons. The Translating Ribosome Affinity Purification (TRAP) method allows for easy isolation of specific cell type mRNA by immunoprecipitation of an eGFP-tagged ribosomal protein (eGFP-L10a) driven by a cell specific promoter, or in all neurons using a transgenic mouse line with a SNAP25 promoter. Here, I am developing a Synaptic-TRAP method to identify synaptic mRNAs by combining classical biochemical fractionation of synaptoneurosomes with TRAP. Through this method we are able to isolate cell specific synaptic mRNA *in vivo* and analyze it in a high throughput method. Our hope is that this method will permit us to better understand the underlying mechanisms for neurogenetic disorders associated with dysregulation of synaptic translation.

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Genome-wide mapping of complex psychiatric traits in commercially available outbred mice

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Understanding the genetic basis of behavior remains a major challenge. We used commercially available outbred mice to demonstrate the benefits of outbred populations for investigating the genetic basis of complex behavioral traits. We have taken advantage of an extant outbred population, the CFW stock, that has been maintained at Charles River Laboratories for over 100 generations using an outbred breeding scheme. Following protocols we have developed in previous work, we phenotyped ~1200 male CFW mice for a range of behavioral traits, including methamphetamine sensitivity, conditioned fear, and prepulse inhibition. We developed a novel genotyping pipeline based on the "genotype-by-sequencing" approach to generate high-density SNP data (~100,000 SNPs) across the genome in 1161 mice. We assessed LD decay to substantiate a main motivation for using the CFW mouse stock—namely, the ability to map QTLs at a higher resolution than more commonly used mouse populations. We show "decay of LD" is faster than comparable outbred mouse populations. We are also using these data to perform a genome-wide association study for each trait. We have obtained strong support for QTLs for several complex traits within narrow chromosomal intervals. In addition, we have performed RNASeq on three brain regions (prefrontal cortex, hippocampus, and striatum) for ~300 mice, which allows us to co-map regions associated with variation in both behavior and gene expression. Our results demonstrate that the outbred mice offer a good balance of power and resolution to better elucidate genes underlying complex behavioral traits.

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Transcriptional regulation of transposable elements in alcohol models

Igor Ponomarev

There is emerging evidence for the role of genomic transposable elements (TEs) in regulation of brain functions. TEs are normally silenced by epigenetic mechanisms, including DNA methylation and modifications of histone tails, but can be expressed when the epigenetic silencing is released. We investigated regulation of TEs in various alcohol models using the DNA microarrays. We first used the RepeatMasker program to align 50-base probes of various Illumina microarray platforms to genomic TEs and found that over 3,500 probes from the Human HT-12 platform and over 2,000 probes from the Mouse WG-6 platform could be mapped to one of four classes of TEs. We next compared TE expression levels in postmortem human brains between 15 controls and 17 alcoholic cases. A large number of probes mapped to LTR-containing and human-specific LINE-1 TEs were up-regulated in alcoholic brains. This up-regulation was associated with less DNA methylation at the regulatory regions of these TEs, suggesting that alcohol abuse results in global DNA hypomethylation. Parallel studies determined differential expression of various classes of TEs in a mouse genetic model of binge drinking and after chronic self-administration of alcohol in mice, suggesting some similar mechanisms of epigenetic regulation of TEs in different alcohol models. Common downstream effects of TE activation may include neuroinflammation, DNA damage and apoptosis.

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High Throughput Phenotypic Profiling leads to Insights into Mechanisms of Habituation in *C. elegans*

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Habituation is a fundamental form of learning highly conserved phylogeny. Although habituation is considered the simplest form of learning, until recently almost nothing was known about the cellular mechanisms of habituation. In the years that my lab has studied habituation in *C. elegans* we have developed an understanding of tap habituation and the neural circuit mediating this behavior. We are now focusing on the genes underlying this learning using a novel high-throughput behavioral analysis system, the multi worm tracker. With this system we examined 508 known nervous system gene mutations and identified a large number of habituation mutants. Detailed analyses of habituation phenotypes revealed four genetically independent features of habituation: rate of habituation and final habituated level for response probability, rate of habituation and final level of habituation for response magnitude. Analysis of genes for these features led to the hypotheses that final level of response probability involves a ubiquitin mediated process, and final level of response magnitude is mediated by a kinase pathway that includes PKC and MAP kinases. We have also been genetically analyzing habituation of behaviors elicited by photoactivation of two sensory neurons in the head of the worm. We have found that this habituation is also made up of different subcomponents that show different patterns/kinetics of habituation.

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Intersection of RNA editing with gene expression and silencing: Implications for disease

Robert Reenan

RNA editing by adenosine deaminase acting on RNA (ADAR) enzymes modifies structured RNAs. ADAR genes themselves, as well as the editing status of their targets, are implicated in human disease. Such editing involves the chemical conversion of adenosine-to-inosine (A-to-I) and occurs in two modes: specific, usually affecting only one or several adenosines in short duplex regions of messenger RNA; or promiscuous, involving up to 40% of adenosine residues in long perfect dsRNA. Both modes redirect the destiny of RNA molecules informationally, as inosine is interpreted by cellular machines as guanosine. Our most recent data indicates that ADAR activity dramatically remodels endogenous long dsRNAs, in opposition to the processing of those precursors into small interfering RNAs. As many such long duplex RNAs serve to prime the silencing mechanism for endogenous transposable elements (TEs), ADAR activity in the nervous system serves as a mechanism to interdict normal silencing in neurons.

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Poster #38

Comparison of common classification schemes for analysis of adult mouse mating song in behavioral context

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Mouse ultrasonic vocalization, which can be elicited under social contexts, is regularly used to evaluate mouse models of psychiatric disorder, such as autism. Higher order features of vocalization, including classification of vocalized calls into subtypes, is often performed, but it is not clear how to evaluate various analytic models. The current investigation aims to evaluate differences between methods in analysis of C57Bl6/J mice. Thirty singly-housed, sexually naive C57Bl6/J males were tested with presentation of unfamiliar females on two days, during their dark cycle. Analysis of recorded vocalization was performed using several commonly employed classification schemes. Males were highly correlated between test days with respect to numbers of observed calls (Pearson`s R = 0.82, $p = 5x10^{-10}$) and while numbers of calls increased significantly when presented females were in estrus ($p = 0.04$) as expected, it appears that performance on first day of testing was a better predictor of performance on second day of testing regardless of estrus state. This indicates that males may be 'identifiable' by their pattern of vocalization. Comparison of classification schemes will test whether call types can uniquely identify animals between test days, and it will test whether schemes are equally able to demonstrate non-random patterns of sequence. Furthermore, analysis of synchronized video will further explore the relationship of vocalization to observed behavior. We hope this work will provide information useful to the standardization of vocalization analysis.

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Rsu1 acts downstream of integrin to regulate Rac1 activity and ethanol consumption in *drosophila* and humans

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Millions of people abuse alcohol, but little is understood about the molecular causes. We report the first gene to affect ethanol consumption in flies and humans. Ras suppressor 1 (Rsu1) is required in adult *Drosophila* brains for normal sensitivity to ethanol-induced sedation, and acts upstream of Rac1 and downstream of integrin to regulate the actin cytoskeleton. In an ethanol preference assay, loss of Rsu1 causes immediate heightened preference. In contrast, flies specifically lacking Rsu1 in the mushroom bodies show normal initial preference, but then fail to acquire ethanol preference like normal flies do. In adolescent humans, a genetic *RSU1* variant is associated with increased brain activation in the ventral striatum during reward anticipation and with decreased spatial working memory. It also associates with increased drinking in girls. This suggests a conserved role for integrin/Rsu1/Rac1/actin signaling in modulating behavioral plasticity, including ethanol consumption across phyla.

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Poster #39

Behavioral responses to ethanol are regulated by the LIM only protein LMO3

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The LIM-only protein LMO3 is a transcriptional regulator that has primarily been characterized for its developmentally-regulated expression in the brain and role in neuroblastoma. We previously determined that Lmo3 expression in the brains of transgenic mice expressing a short hairpin RNA (shRNA) targeting Lmo3 is significantly correlated with ethanol-induced loss-of-righting reflex (LORR) and 2-bottle choice ethanol consumption. To further characterize the role of Lmo3 in behavioral responses to ethanol, we tested Lmo3 knockout (Lmo3KO) mice for several behaviors. Lmo3KO mice showed significantly increased LORR sedation time at doses of 3.2 and 3.6 g/kg ethanol, similar to previous findings with the Lmo3 shRNA transgenic mice. In contrast, we observed no genotype effect in 2-bottle choice ethanol consumption, whereas results with shRNA transgenic mice suggested a positive correlation between Lmo3 expression and consumption. Interestingly, in a model of binge drinking (drinking-in-the-dark, DID), Lmo3KO mice consumed significantly more ethanol than wild-types. To understand where Lmo3 might function to regulate these behaviors, we examined the expression of ß-galactosidase (ß-gal) in the Lmo3KO mice (which contain an insertion of the ß-gal gene under the control of the Lmo3 promoter). Strong ß-gal activity was evident in several regions that have been implicated in alcohol use disorders (i.e., nucleus accumbens, ventral tegmental area, amygdala). In addition, Lmo3 expression in the nucleus accumbens of male wild-type mice was significantly negatively correlated with ethanol consumed in the DID test. These data suggest that Lmo3 might act in the nucleus accumbens to inhibit binge drinking behavior.

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Synaptic mechanism underlying habituation of startle in rodents

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Synaptic mechanisms underlying habituation have been studied in different organisms. It has been proposed that homosynaptic depression within the primary sensorimotor pathway mediates the attenuation of behavioural response upon repeated activation in *Aplysia*. The mechanism responsible for homosynaptic depression has never been fully resolved, but is presumably located at the presynaptic terminal of sensory neurons synapses on motor outputs, and to be calcium-dependent. We use the rodent startle pathway as a model to study short-term habituation of acoustic startle. Combining behavioural pharmacology, genetic approaches and electrophysiology in acute brain slices, we have identified a form of synaptic depression at sensorimotor synapses in the brainstem of rats that are likely to mediate habituation. Paralleling findings in *Aplysia*, this synaptic depression is located presynaptically and calcium dependent. We started to examine genes that have been identified in invertebrates for their role in both habituation and synaptic depression in rodents. The high conductance voltage – and calcium activated potassium channel (BK channel), encoded by the gene slo-1, has been reported to mediate habituation of startle-like responses in *C. elegans* and in *drosophila*. Accordingly, we showed that mice lacking functional slo-1 show disruptions in short-term but not long-term habituation of startle or habituation of motivated behaviours. We currently test whether blocking BK channels pharmacologically disrupts habituation/synaptic depression.

While there might be an abundance of different molecular pathways underlying habituation, depending on type of behavior, modality, and time course of stimulation, our data indicate that slo-1 mediated short-term habituation of startle is highly conserved across species.

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Poster #40

Effects of maternal diet during the perinatal period on anxiety and depressive-like behavior in mice

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Nutritional deficiencies during the perinatal period have been linked to increased risk for development of psychiatric disorders in the human population and have been modeled in rodents and result in behavioral changes. The mechanism in both humans and animal models is believed to be epigenetic changes that alter gene expression.

We designed an experiment to examine the effects of maternal dietary deficiencies on different genetic backgrounds to study alterations in behavior and gene expression in mice. We are utilizing a disjoint reciprocal diallel using 16 Collaborative Cross (CC) mouse lines crossed to produce recombinant inbred intercross (RIX) mice. Females from each line are exposed to one of four diets (vitamin D and protein deficient, methyl enriched and control) prior to mating and throughout gestation and weaning. Adult female offspring are tested in a battery of behavioral assays to measure stress response, anxiety- and depressive-like behaviors. Whole brain gene expression is also assessed using RNA-Seq.

Comparison of behavior and gene expression within reciprocals and across CC-RIX lines exposed to *in utero* dietary deficiencies will reveal genetic, diet, parent-of-origin and diet-specific parent-of-origin effects. These data will provide us with a set candidate genes that interact with diet during development to change behavior in adult offspring.

Thus far, we have screened 105 CC-RIX offspring and identified significant strain, parent-of-origin, diet and diet-specific parent-of-origin effects on behavior.

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Poster #41

The effects of ethanol vapor on alcohol dehydrogenase, ethanol sensitivity, and activity patterns in *period* mutants of *Drosophila melanogaster*

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Drosophila melanogaster is a widely used model organism to study the effects of ethanol intoxication and tolerance, because of their natural exposure to ethanol. Previous reports using ethanol vapor have shown that high-concentration ethanol-vapor produces sedation, while low ethanol vapor produces increases in locomotion and alcohol dehydrogenase (ADH) activity. While studies have been conducted showing how ethanol vapor differently affects wild-type flies and flies genetically altered for differing ethanol sensitivity, no studies have examined the effects of ethanol vapor on tolerance and other ethanol related factors in circadian rhythm mutants. Even in *Drosophila*, there is a connection between ethanol consumption and alteration in the biological clock, as larval ethanol exposure produces changes in the free-running rhythm and *per* locus transcription levels in a dose dependent manner. This investigation seeks to determine if differences are present for ADH enzyme levels, ethanol sensitivity, and activity levels when exposed to moderate ethanol vapor among *Canton-S* (*CS*) and the *period* mutants (*perS*, *perL*, and *per0*) of *Drosophila*. Even without the presence of ethanol, *perL* and per0 have lower ADH enzyme levels than both *perS* and *CS* and show greater intolerance to ethanol. While all genotypes showed decreases in activity levels when exposed to ethanol vapor, *perL* showed decreased entrainment percentage to a 12:12 Light:Dark (LD) cycle. In conclusion, it appears that *perL* and *per0* are more sensitive to the effects of ethanol exposure, when compared to *perS* and *CS*. These results indicate there may be a connection between circadian clock function and ADH levels.

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Poster #42

Wheel-running attenuates weight gain and blood glucose levels in a type-2 diabetic mouse model

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Type-2 diabetes is a chronic disease that affects the pancreatic islets and alters insulin release and/or function. Some type-2 diabetics exhibit insulin resistance, which leads to decreased insulin function, hyperinsulinemia, and hyperglycemia. Insulin is secreted in a circadian pattern from the pancreas, and a functional biological clock is necessary for proper insulin release. Studies have also shown that diabetes affects the transcription of *period*, *clock*, and *bmal1*, genes which regulate the circadian rhythm. As there is a relationship between circadian rhythms and diabetes, this study investigated the circadian activity rhythm and diabetic symptoms in a type-2 diabetic mouse model, TALLYHO/Jng (TH). Male TH mice mimic human diabetes symptoms such as hyperglycemia, hyperinsulinemia, obesity, and enlargement of pancreatic islets at 10-weeks of age. While there are no differences in the circadian activity rhythms of TH mice, when compared to B6 controls, TH mice showed decreased wheel-running activity than B6 mice. TH mice with access to a running wheel showed attenuated body mass and blood glucose levels, when compared to previous studies where TH mice did not have access to running wheels, even after access to running-wheels have ended. These results indicate that early-access wheel-running may provide a mechanism to prevent future weight gain and high blood glucose levels in older less-active individuals. Future studies will be conducted to determine if circadian stressors would exacerbate the diabetic symptoms of TH mice and if wheel-running can prevent other diabetes symptoms (impaired glucose tolerance, plasma cholesterol and triglyeride levels, and hyperinsulinemia) due to stress.

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Understanding epistasis and gene networks in complex traits: An analysis of the genetic architecture of aggression in a model system

John R. Shorter, Charlene Couch, Robert Anholt, Trudy F. C. Mackay

Most animals display aggressive behavior to secure food resources, protect against predators and facilitate access to mating partners. Among social animals, appropriately balanced aggressive behavior gives rise to a stable social organization by creating and maintaining dominance hierarchies. Inappropriate or excessive aggression has detrimental consequences for a society. Aggressive behavior is genetically complex, influenced by many genes as well as interactions with the environment. However, the genetic pathways affecting variation in aggressive behavior are evolutionarily conserved, enabling general inferences to be drawn from genetic analysis using a model system. We investigated the natural genetic variation of aggression using the *Drosopihla melanogaster* Genetic Reference Panel (DGRP), a collection of 205 inbred lines with fully sequenced genomes. We performed a genome wide association study (GWAS) and identified 74 genetic variants associated with variation in aggression. Additionally, we performed an independent experiment to replicate causal candidate variants by creating an outbred population from lines representing the extremes of the DGRP. We measured aggressive behavior of 3,000 individuals across 7 generations from this outbred population and performed extreme quantitative trait mapping, which identified several genes in common with the GWAS in the DGRP. We also tested these gene candidates by using RNAi knockdown to reduce gene expression. We identified several previously known genes involved in aggression as well as several more with no previous known associations with aggression.

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Poster #43

Dysregulated neuroendocrine system is associated with hyperphagia-mediated obesity in ADAR2-Tg mice

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Obesity has become a major health issue in the USA. Our studies indicate that alterations in the neuroendocrine system and RNA changes in the hypothalamus play a key role in hyperphagia-mediated obesity that bears similarities with the Prader Willi Syndrome (PWS)-like phenotype, suggesting that a previously unknown ADAR2-mediated pathway may be involved in PWS.

ADAR2 is a double stranded RNA binding protein that modifies adenosine residues in duplex RNAs. The double stranded RNA binding domain of ADAR2 is distinct from its enzyme activity domain. Due to binding and editing properties of ADAR2, double stranded RNA-mediated gene silencing is affected by competing for duplex RNAs. We have generated two strains of ADAR2 transgenic mice (ADAR2-Tg) on a normal B6D2F1 background, under the control of the cytomegalovirus (CMV) promoter that ectopically express either the deaminase functional ratADAR2 transgene (rADAR2DF-Tg) or the deaminase deficient (rADAR2DDTg) transgene. Both rADAR2 transgenes have functional double stranded RNA binding domains. Surprisingly, both strains of ADAR2-Tg mice suffer from chronic overeating and morbid obesity.

Recent studies of hormonal, pharmacological, and RNA editing and expression changes from the hypothalamus of ADAR2-Tg mice lead us to hypothesize that ADAR2-Tg mice represent a PWS-like model. Furthermore, RNA-Seq, RNA editing and expression analyses from the hypothalamus of both strains of ADAR2-Tg mice show distinct RNA expression changes from the chromosome 7 region, which contains genes involved in PWS. Altogether the results suggest ADAR2 may play a key role in PWS syndrome.

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Genetic susceptibility to comorbid psychiatric phenotypes in a panel of mice deficient for the human type 2 diabetes gene *TCF7L2*.

Laura J. Sittig, Camila M. Barrios Camacho, Peter Carbonetto, Marcelo Nobrega and Abraham A. Palmer

Anxiety, depression, and schizophrenia are more prevalent among patients with type 2 diabetes suggesting shared genetic contributions to metabolic dysfunction and psychiatric disease. In humans, *TCF7L2* remains the best replicated finding from genome-wide association studies for type 2 diabetes across multiple ethnicities. *TCF7L2* has also been linked to schizophrenia in several reports and alters behavior in mice. It is very likely that gene-gene interactions (epistasis) explains some of the variability and comorbidity in both diseases, but interacting alleles remain difficult to identify in human genetic data. We used mice with a null allele of *Tcf7l2* to investigate 1) the dual effects of *TCF7L2* on psychiatric behavior and diabetes-related traits; and 2) genetic modifiers of risk and resilience to the effects of mutations in *Tcf7l2*. We bred B6$^{Tcf7l2+/-}$ males to females from 30 inbred mouse strains, creating a test population of F1 hybrid offspring. We tested approximately 20 mice/strain, balanced across sex and *Tcf7l2* genotype (+/+ or +/-), for body weight, fasting and baseline glucose levels, open field test, prepulse inhibition, and forced swim test. We found a main effect of *Tcf7l2* mutation on blood glucose levels, body weight, anxiety in the open field test, and sensorimotor gating deficits in prepulse inhibition. We also identified strain x genotype interactions indicating that these inbred strains segregate alleles that modify the phenotypes of *Tcf7l2* haploinsufficiency. This novel and tractable approach may allow us to identify specific genes/alleles that epistatically modulate the effects of mutations in *Tcf7l2*.

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Gene-environment interplay and behaviour

M. B. Sokolowski

My lab is interested in how DNA variation predisposes organisms to be more or less affected by their experiences (gene-environment interactions), how our experience gets embedded in our biology (epigenetics) and finally how DNA variation interacts with epigenetic processes to affect behavior. Experiential affects, like developmental ones, can occur on different time scales. For example nutritional and social adversity or enrichment can occur throughout the lives of organisms, in early life with enduring effects on later life stages, or acutely over a matter of minutes or hours. To address these issues we take a genetic perspective using mostly *Drosophila melanogaster* but also rats and humans and consider both candidate single genes and candidate pathways. This approach provides interesting opportunities and challenges because many genes and pathways that modulate behavior have multiple functions (pleiotropy) and do themselves exhibit plastic responses to experience.

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Poster #44

Genetic mapping of anxiety-like traits in an advanced intercross line (AIL) of mice

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Anxiety is a complex neurobehavioral trait with a heritable genetic basis in both humans and mice. We are exploring the relationship between anxiety-like behavior and natural genetic variation in ~750 mice. Mice are powerful tools for studying the etiology of mammalian behavior. Previously, our lab used a highly recombinant LG/J x SM/J advanced intercross line (AIL) of mice to map quantitative trait loci (QTLs) associated with anxiety responses in the Open Field test (OFT). The OFT measures locomotor activity in a controlled environment and has been widely used to model anxiety-like behavior in rodents. We will replicate these results as well as identify novel loci by combining cutting-edge technologies with more recent generations of this population. The AIL have accumulated many additional recombination events since the original study, which allows for more precise mapping of causal regions. We are also utilizing an innovative genotyping-by-sequencing (GBS) strategy to obtain genotypes and a recently-developed software package (R/QTLRel) to perform statistical analyses. Here we present preliminary phenotype and genotype data from generations F_{39-43} of the LG/J x SM/J AIL.

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The inhibitory circuit architecture of the lateral hypothalamus orchestrates feeding

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The growing prevalence of overeating disorders is a key contributor to the worldwide obesity epidemic. Dysfunction of particular neural circuits may trigger deviations from adaptive feeding behaviors. The lateral hypothalamus (LH) is a crucial neural substrate for motivated behavior including feeding, but the precise functional neurocircuitry that controls LH neuronal activity to engage feeding has not been defined. I will discuss our recently published findings that demonstrate that inhibitory synaptic inputs from the extended amygdala preferentially innervate and suppress the activity of LH glutamatergic neurons to control food intake. In addition, I will present unpublished data that show how LH GABAergic neurons encode aspects of food consumption. These findings help explain how dysregulated activity at a number of unique nodes can result in a cascading failure within a defined brain network to produce maladaptive feeding.

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Poster #45

What happens in the long run? a developmental perspective on autism-like social communication deficits and aberrant cognitive phenotypes in mice lacking the post-synaptic scaffolding protein *SHANK1*

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Autism spectrum disorders (ASD) are a class of neurodevelopmental disorders characterized by persistent social communication deficits across multiple contexts, together with repetitive patterns of behavior. Among the most promising ASD candidate genes is the *SHANK* gene family, including *SHANK1*. To study the contribution of *SHANK1* mutations to ASD symptoms throughout development, *Shank1*+/+, *Shank1*+/-, and *Shank1*-/- mice were compared in behavioral assays developed to detect social communication deficits and aberrant cognitive phenotypes as pups, juveniles, and adults. When assessing isolation-induced ultrasonic vocalizations as a measure for communication during early development, call rate exhibited the typical inverted U-shaped developmental pattern in all genotypes. However, *Shank1*-/- pups were found to be developmentally delayed and characterized by a less prominent inverted U-shaped call emission pattern, reflecting an overall reduction in ultrasonic calling. Preliminary data further indicate reduced call rates in *Shank1*-/- pups across various social contexts, including the exposure to maternal odors and odors from a stranger adult male. As juveniles, social approach and recognition were evident irrespective of genotype. In contrast, object recognition was affected by the *Shank1* deletion, with *Shank1*-/- mice being severely impaired, not showing a preference for the novel object. In adulthood, *Shank1*-/- males and controls displayed normal social approach, but impaired social recognition. Object recognition was additionally impaired in adult *Shank1*-/- males. Conversely, adult Shank1-/- females exhibited deficits in social recognition only. In summary, the present findings indicate that *Shank1* deletions lead to communication deficits and an aberrant cognitive phenotype, together with age- and sex-dependent effects on social behavior.

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Poster #46

Primary hippocampal cell culture to study consequences of prenatal alcohol exposure on insulin pathway genes

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Fetal Alcohol Spectrum Disorder (FASD) encompasses a continuum of disabilities caused by prenatal alcohol exposure (PEE). Hippocampus-based cognitive deficits are among the most debilitating consequences of PEE. Currently, no treatment is available for FASD. Development of novel drug targets often relies on *in vitro* studies, which are limited in FASD research. Primary hippocampal cell culture could aid in finding compounds that reverse PEE-induced molecular changes. The goal of this study was to compare the effects of PEE on transcript levels of insulin pathway genes, known to be involved in learning and memory, in the hippocampus *in vivo* and *in vitro*. We used our established animal model of FASD. Pregnant rat dams were fed control and ethanol containing diets from gestational day (GD) 8 to 20. On GD21, fetal hippocampi were dissected for transcript analysis. For the in vitro study, hippocampi were cultured from embryonic day 18 to 21, when RNA was isolated. Transcript level changes of, insulin-like growth factor 2 (*Igf2),* Igf2 receptor (*Igf2r*), insulin receptor (*Insr*) and ras-guanine nucleotide releasing factor 1 (*Rasgrf1*) in response to PEE in the primary hippocampal cell culture were similar to those found in GD21 fetal hippocampus. Furthermore, allele-specific expression of *Igf2* was preserved even after three days in culture, suggesting that processes by which PEE affects genetic imprinting in the brain can be studied in culture. Accordingly, primary hippocampal culture could be useful to develop and characterize interventions to reverse PEE-induced hippocampal dysregulation.

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Poster #47

Activation of Neurotensin Receptor Type 1 in the Nucleus Accumbens Attenuates Locomotor Activity

Chelsea Vadnie [1,2], David Hinton [1,2], Sun Choi [2], YuBin Choi[2], Christina Ruby[2,5], Alfredo Oliveros[2], Miguel L. Prieto [3,4], Jun Hyun Park[2], Doo-Sup Choi [1,2,3]

Neurotensin (NT) has been implicated in alcohol addiction, schizophrenia and movement disorders. NT-induced hypolocomotion may occur by inhibition of dopamine D2 receptors (D2R) through a receptor-receptor interaction with type 1 NT receptor (NTS1), which is a compounding factor to develop medication targeting the NTergic system. The brain region- and receptor subtype-specific mechanisms underlying NT-induced hypolocomotion are unclear. We investigated the effect of systemic and brain region-specific NTS1 activation on locomotion using a blood brain barrier permeable, selective NTS1 agonist PD149163. Systemic administration of PD149163 attenuated locomotor activity of mice in a novel environment as well as in their homecage. Subsequently, we examined whether PD149163 blocks dopamine receptor-mediated hyperactivity. Pretreatment with 0.1 mg/kg and 0.05 mg/kg of PD149163 inhibited D2R agonist bromocriptine (8 mg/kg)-mediated hyperactivity. However, only 0.1 mg/kg of PD149163 prevented D1R agonist SKF81297 (8 mg/kg)-induced hyperlocomotion. Since the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC) have been implicated in the behavioral effects of NT, we examined whether microinjection of PD149163 into these regions reduces locomotion. Microinjection of PD149163 (2 pmol) into the NAc, but not the mPFC suppressed locomotion. Lastly, PD149163 reduced glycogen synthase kinase-3 (GSK-3) signaling in the NAc. Inhibition of D2R and potential downstream Akt/GSK-3 signaling are associated with reduced movement. Thus, our results provide a novel role for NAc NTS1 in suppressing movement through inhibition of D2R-mediated Akt/GSK-3 signaling. Our study will be helpful to identify pharmacological factors and a therapeutic window for NTS1-targeted therapies for alcohol addiction, schizophrenia and movement disorders.

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Poster #48

Reward-related responses to nicotine, alcohol, and their co-administration in mice selectively-bred for high or low alcohol preference.

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Alcohol and nicotine addiction are highly co-morbid and studies have shown that addiction to these drugs may share a common genetic basis. Here, we investigated neural and behavioral reward-related responses to alcohol, nicotine, and their co-administration in mice selectively bred for high (HAP) or low (LAP) alcohol preference. We hypothesized that (1) nicotine would induce greater reward-related responses in HAP2 compared to LAP2 mice and (2) nicotine would increase the reward-related responses of alcohol in HAP2 but not LAP2 mice. We tested these hypotheses with two sets of experiments. In experiment 1, we investigated reward-related responses of HAP2 and LAP2 mice to nicotine using conditioned place preference (CPP) and patch clamp recordings of ventral tegmental area (VTA) dopaminergic (DAergic) neurons. In experiment 2, we investigated the reward-related responses of HAP2 and LAP2 mice to nicotine and alcohol co-administration using CPP and c-Fos immunohistochemistry of VTA DAergic neurons. In experiment 1, we found that nicotine induced place preference in HAP2 mice and place aversion in LAP2 mice. We also found greater nicotine-induced inward current deflections in VTA DAergic neurons of HAP2 compared to LAP2 mice. In experiment 2, nicotine co-administration with alcohol did not enhance alcohol-induced CPP in either line. Additional replications of this study are currently underway. These data suggest that genetic predisposition toward high alcohol preference may be related to greater sensitivity to nicotine's rewarding effects.

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Poster #49

Monitoring choice behavior of mice using reward size- and taste-based delay discounting tasks in the IntelliCage

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Delay discounting tasks (DDTs) assess impulsive choice (cognitive impulsivity) with comparable outcomes in humans and animals by letting subjects choose between an immediate but small reward and a larger but delayed reward. Existing DDTs for mice require social isolation and food or water deprivation. Our aim was to develop a DDT for the IntelliCage, a fully automated cage where mice can be group-housed but singly tested and where no prior deprivation is needed.

We first implemented DDT based on the choice between an immediate water reward and a saccharin reward available at increasing delays (0-15s). Testing of C57BL/6 mice produced the expected hyperbolic discounting function. However, functions of other strains were biased by a reduced preference for saccharin. This bias was minimized in DDT variants based on choices between water and sucrose or between short and long access time to water. We further tested mice with hippocampal or cortex lesions in the water-saccharin DDT. The discounting functions of these mice were unexpectedly shifted towards longer delays. However, in an aversively motivated variant of the task, using a choice between quinine and water, their discounting curves were normal, indicating that the lesions are probably associated with poorly controlled responses to reward rather than increased delay tolerance.

Together, our results indicate that delay discounting in mice can be tested in a social environment and without prior stressful deprivation. The combination of appetitive, aversive and size rewarded DDT permits to dissociate changes of delay resistance from altered response to reward.

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Forward genetic screen reveals a role for the pregnancy associated plasma protein-a gene in habituation learning

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The nervous system continuously integrates sensory information with previous experiences to select an appropriate behavioral response. A fundamental form of this integration process is habituation; a simple form of non-associative learning that is conserved from *Aplysia* and *C. elegans* to mammals. Habituation is defined as response suppression to repeated, irrelevant stimuli. Unbiased, large-scale systematic approaches in invertebrate organisms have yielded great insight into the genetic regulation of behavior, however for many reasons, this approach has been difficult to recapitulate in mammalian vertebrate organisms. Larval zebrafish show a remarkable capacity for behavioral plasticity, including habituation, and provide a promising model system to which we can apply the design of invertebrate behavior based screens to reveal the genetic mechanisms critical for cognitive function in vertebrates. Using zebrafish larvae, we performed the first genetic screen for vertebrate learning mutants and identified 18 mutants with reduced habituation. Whole genome sequencing of a subset of mutants identified a premature stop codon in the vertebrate specific *pregnancy associated plasma protein-a (papp-a)* gene. PAPP-A has been shown to enhance insulin-like growth factor (IGF) availability, and while IGF-receptor signaling plays roles in neural circuit assembly, synaptic plasticity and memory formation, the precise roles of *papp-a* in the nervous system and how it regulates habituation are unknown. Thus, *papp-a* provides a unique entry point to decipher the neural circuits underlying vertebrate habituation.

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Poster #50

Transcriptome analysis of a congenic mouse line demonstrating decreased methamphetamine sensitivity

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We previously utilized interval-specific congenic lines derived from C57BL/6J (B6) and DBA/2J
(D2) alleles to fine map a quantitative trait locus (QTL) influencing methamphetamine (MA)- induced locomotor activity. We identified a 0.23 MB critical interval on chromosome 11 containing only two protein coding genes, *Rufy1* and *Hnrnph1*. Notably, *Rufy1* contains three missense SNPs and *Hnrnph1* contains 1 SNP near the 5' UTR. We are currently generating null mutant lines for both genes using transcription activator-like nucleases (TALENs) to determine the quantitative trait gene(s) that influence MA sensitivity. In an effort to identify the molecular mechanisms that bridge genetic variation with behavior, we conducted transcriptome analysis via mRNA sequencing (RNA-seq) in a B6.D2 congenic line (chr.11: 50-60 Mb) that captures the QTL. There was an overrepresentation of *cis*-regulated, differentially expressed genes within the congenic interval (4 out of 92 differentially expressed genes; FDR < 0.05) and widespread genomic regulation on all autosomes. Using Ingenuity Pathway Analysis (IPA), the top canonical pathways were "glutamate receptor signaling" and "GalphaQ signaling," while our top gene networks were "Behavior, Nervous System Development and Function, Tissue Morphology" and "Behavior, Neurological Disease, Cell-to-Cell Signaling and Interaction." In both networks, brainderived neurotrophic factor (*Bdnf*) was a central, down-regulated gene ($p = 2.3 \times 10\text{-}5$). Future studies will be designed to test the hypothesis that the decreased MA-induced locomotor activity is caused by several convergent mechanisms, including both a deficit in the development and sustanence of dopaminergic neurons as well as a decrease in glutamate and adrenergic transmission and signaling in response to MA.

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Poster #51

Natural Antisense Transcripts Regulate the Neuronal Stress Response and Excitability in *Drosophila melanogaster*

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Neurons regulate ionic fluxes across their plasma membrane to maintain their excitable properties under varying environmental conditions. However, the mechanisms that regulate ion channels abundance remain poorly understood. Here we show that *pickpocket 29*(*ppk29*), a gene that encodes a *Drosophila* degenerin/epithelial sodium channel (DEG/ENaC), regulates neuronal excitability via a protein-independent mechanism. We demonstrate that the mRNA 3'UTR of *ppk29* affects neuronal firing rates and associated heat-induced seizures by acting as a natural antisense transcript (NAT) that regulates the neuronal mRNA levels of seizure (*sei*), the Drosophila homolog of the human *Ether-à-go-go* Related Gene (hERG) potassium channel. We find that the regulatory impact of *ppk29* mRNA on *sei* is independent of the sodium channel it encodes. Thus, our studies reveal a novel mRNA dependent mechanism for the regulation of neuronal excitability that is independent of protein-coding capacity.

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