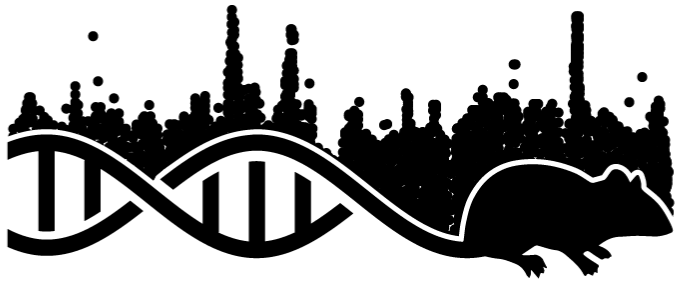
NIDA Center for GWAS in Outbred Rats

Abraham Palmer

Department of Psychiatry

University of California San Diego



Genes and Addiction

NIDA Center for GWAS in Outbred Rats

Genes and Addiction
NIDA Center for GWAS in Outbred Rats

News

- Updates related to COVID19
- Dr. Suzanne Mitchell has been featured in the "Mentors receive as much as they give" article by blogs.OSHU.edu
- Drs. de Guglielmo and Kallupi's work on HS rats has been featured in multiple national media
- PNAS has accepted Dr. Guglielmo's article about oxycodone-addicted HS rats
- Bonnie Lin joined Palmer Lab as a data analyst
- Palmer lab is hiring!

Palmer Lab

DRS. ABRAHAM PALMER AND SANDRA SANCHEZ ROIGE'S ARTICLE ACCEPTED FOR PUBLICATION IN NATURE NEUROSCIENCE April 17, 2020

Drs. Abraham Palmer, Amelie Baud, and Oksana Polesskaya and Apurva Chitre's Article Accepted for Publication in EBioMedicine April 15, 2020

DRS. ABRAHAM PALMER AND

There are few effective therapies to treat drug abuse and dependence, despite the urgent need to develop more effective treatments. A major impediment to the development of such treatments is our extremely limited understanding of the biological basis of drug abuse. While human genome-wide association studies (GWAS) have begun to elucidate genes that influence various traits relevant to drug abuse, they are still unable to attribute more than a small fraction of the heritable variance to specific genes. **NIDA center for genetic studies of drug abuse in outbred rats (P50DA037844)** was created in 2014 to perform GWAS on numerous behavioral traits that have well-established relevance to drug abuse using outbred rats. The Center was successfully renewed in 2019. We expect to discover new genes that can influence drug abuse-related behaviors in rats, therefore improving our understanding of genetic susceptibility to drug abuse in humans. Our results will help to identify new opportunities to treat psychiatric disorders, including addiction.

Why rats? The use of rats is critical because many of the phenotypes we study were developed using rats and difficult or impossible to adapt for mice. We utilize a unique rat population: the N/NIH heterogeneous stock (**HS**), which is derived from 8 fully sequenced inbred rat strains and has been maintained as an outbred population for 90+ generations. This population is designed to resolve quantitative trait loci (**QTL**) to regions that are small enough to permit identification of specific genes. The colony is maintained by Dr. Leah Solberg Woods, Wake Forest University (Breeding Core).

What behaviors do we study? We have carefully selected a range of behavioral

Events

6th Annual Retreat for the NIDA Center for GWAS in HS Rats
11/01/20 San Diego, CA, UCSD campus, Biomedical Research Facility BRF2

5th Annual Retreat for the NIDA center for GWAS in outbred rats
06/12/19 UCSD campus, Biomedical Research Facility

17th Annual Meeting of the Complex Trait Community
06/09/19 University of California San Diego

NIDA Genetics Consortium Meeting
06/16/18

Fourth Annual Retreat for the P50 Center
06/15/18

See all events

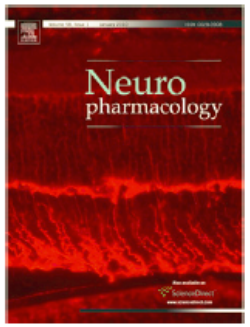
Links and Resources

Neuropharmacology 76 (2014) 250–258

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

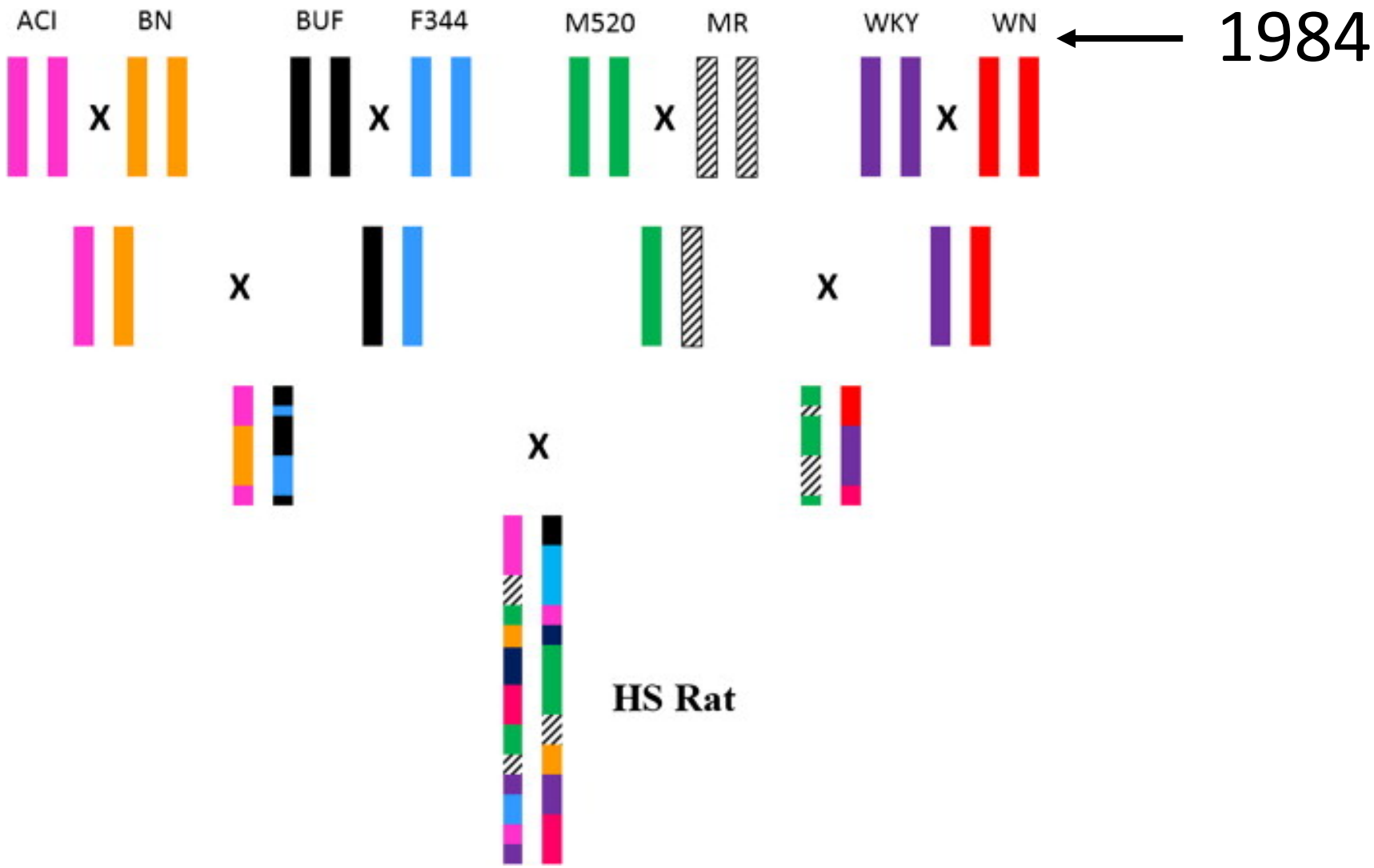


Invited review

Rats are the smart choice: Rationale for a renewed focus on rats in behavioral genetics

Clarissa C. Parker [a], Hao Chen [b], Shelly B. Flagel [c], Aron M. Geurts [d], Jerry B. Richards [e], Terry E. Robinson [f], Leah C. Solberg Woods [g], Abraham A. Palmer [a, h, *]

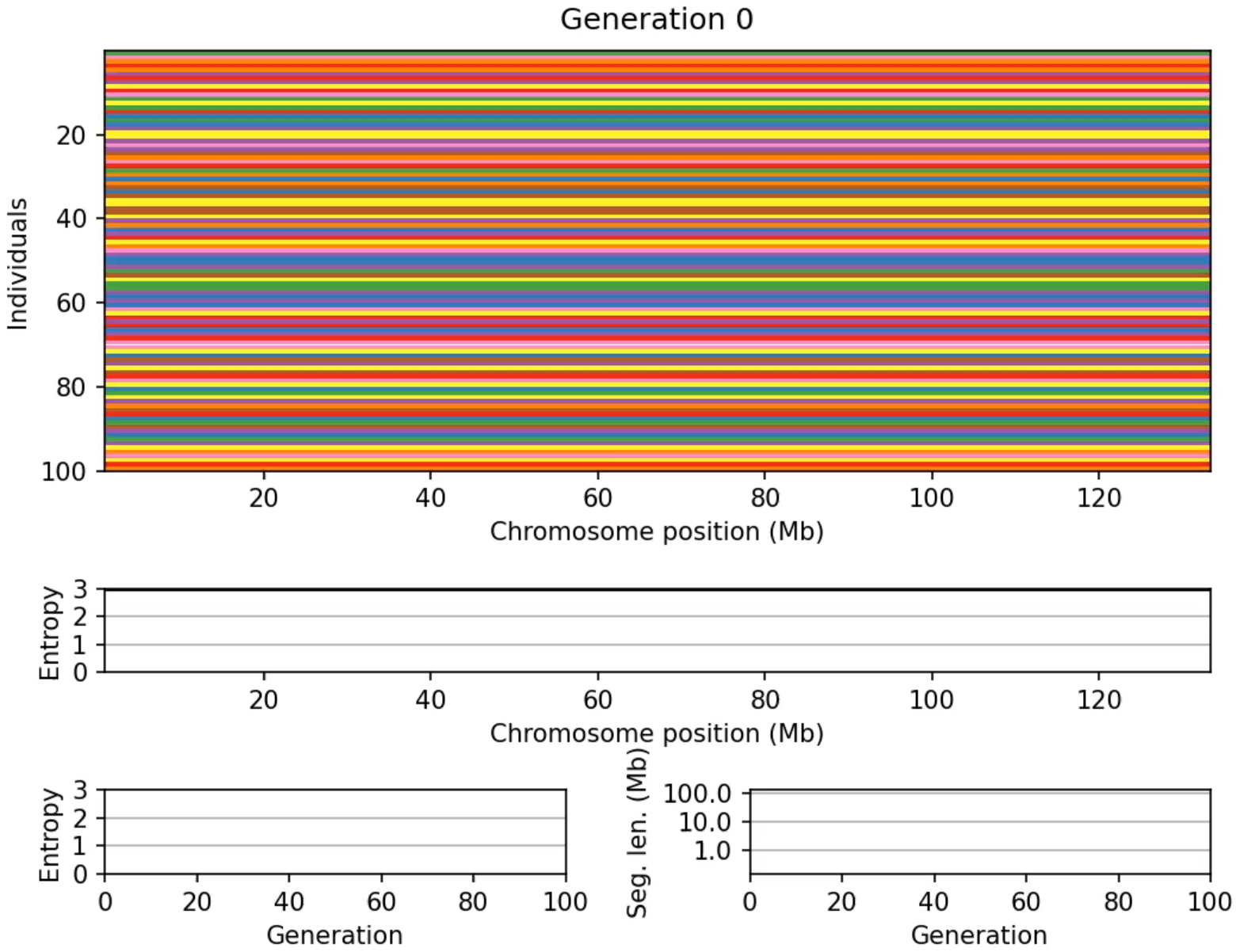
N/NIH Heterogeneous stock (HS) rats



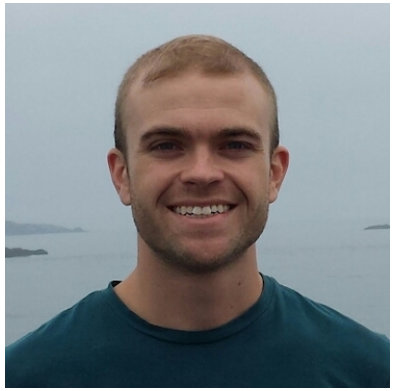
Leah Solberg Woods

Currently at generation 94

- 1984: Colony initiated and maintained at NIH
  - 60 breeder pairs, random mating
- 2003: colony transferred to Northwestern University (Dr. Eva Redei)
  - 25 breeder pairs
- 2006: colony transferred to Medical College of Wisconsin (MCW; Dr. Solberg Woods)
  - 46 breeder pairs, circular mating (minimizes inbreeding and controls genetic drift)
  - 2014: increase to 64 breeder pairs, use mating program to mate distantly related pairs
- 2016: colony transferred to Wake Forest School of Medicine (WFSM; Dr. Solberg Woods)
  - 40 breeder pairs, mating program to mate distantly related pairs
  - 2019: increase to 92 breeder pairs, mating program to mate distantly related pairs
- 2020: embryo cryopreservation at RRRC (2,876 zygotes from 75 breeding pairs)



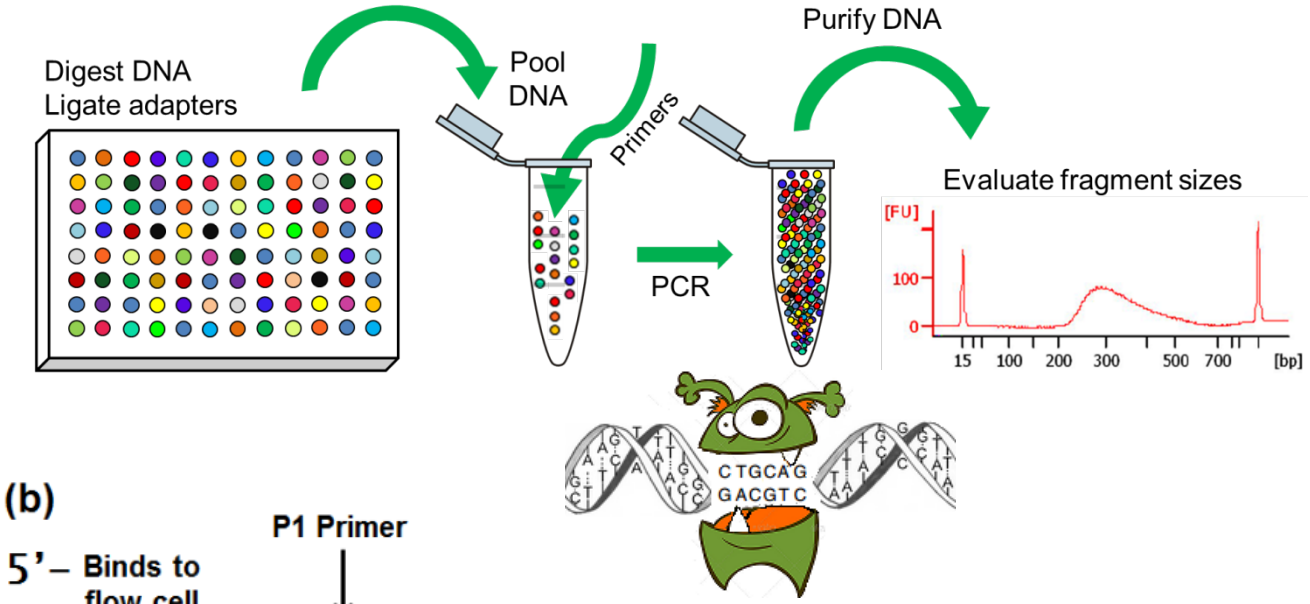
Rotational breeding, assuming 50 breeding pairs/generation

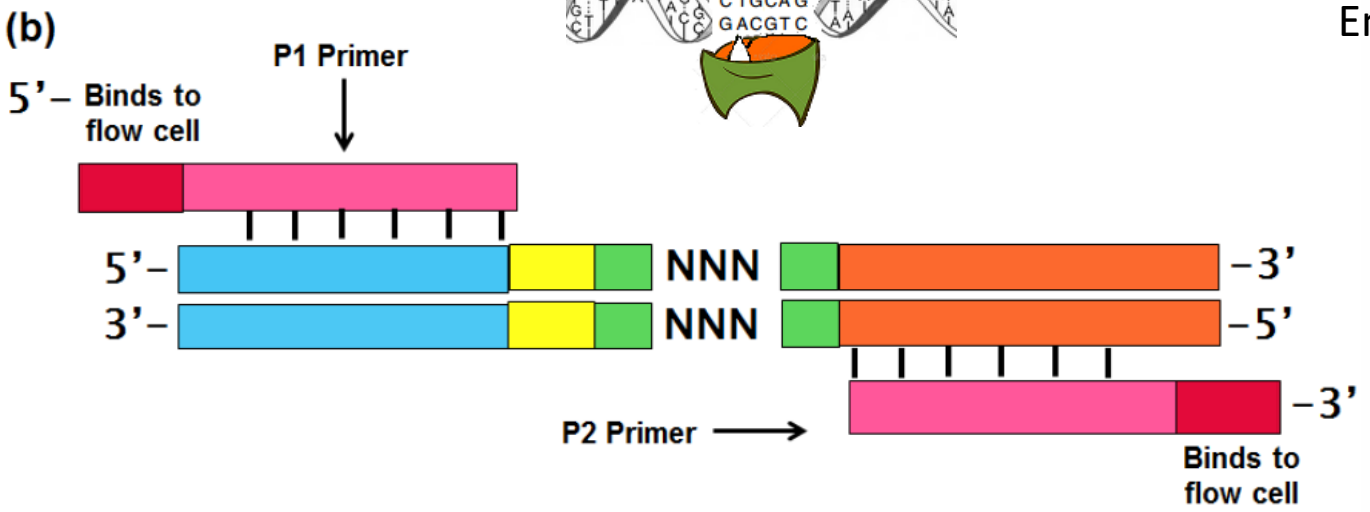


Dan Munro

- Unlike other species, there is no inexpensive microarray for genotyping rats
  - One limitation of microarrays is that they are specific for a given population
  - Also, the design and unit cost of microarrays is relatively high
- Since about 2012, of our mouse and rat work genotyping has relied of sequencing based methods, followed by imputation
- Until recently, we have relied on genotyping by sequencing (GBS) which is adapted from plant genetics
- We have now transitioned to low-pass whole genome sequencing
  - ~0.25x coverage is sufficient
  - Imputation using STITCH or Beagle->Impute2
  - Overtime this will provide us with deep coverage of the existing HS haplotypes, which may differ from available HS founder samples

Genotype by sequencing (GBS)





Natalia Gonzales

Oksana Polesskaya

Shyam Gopalakrishnan

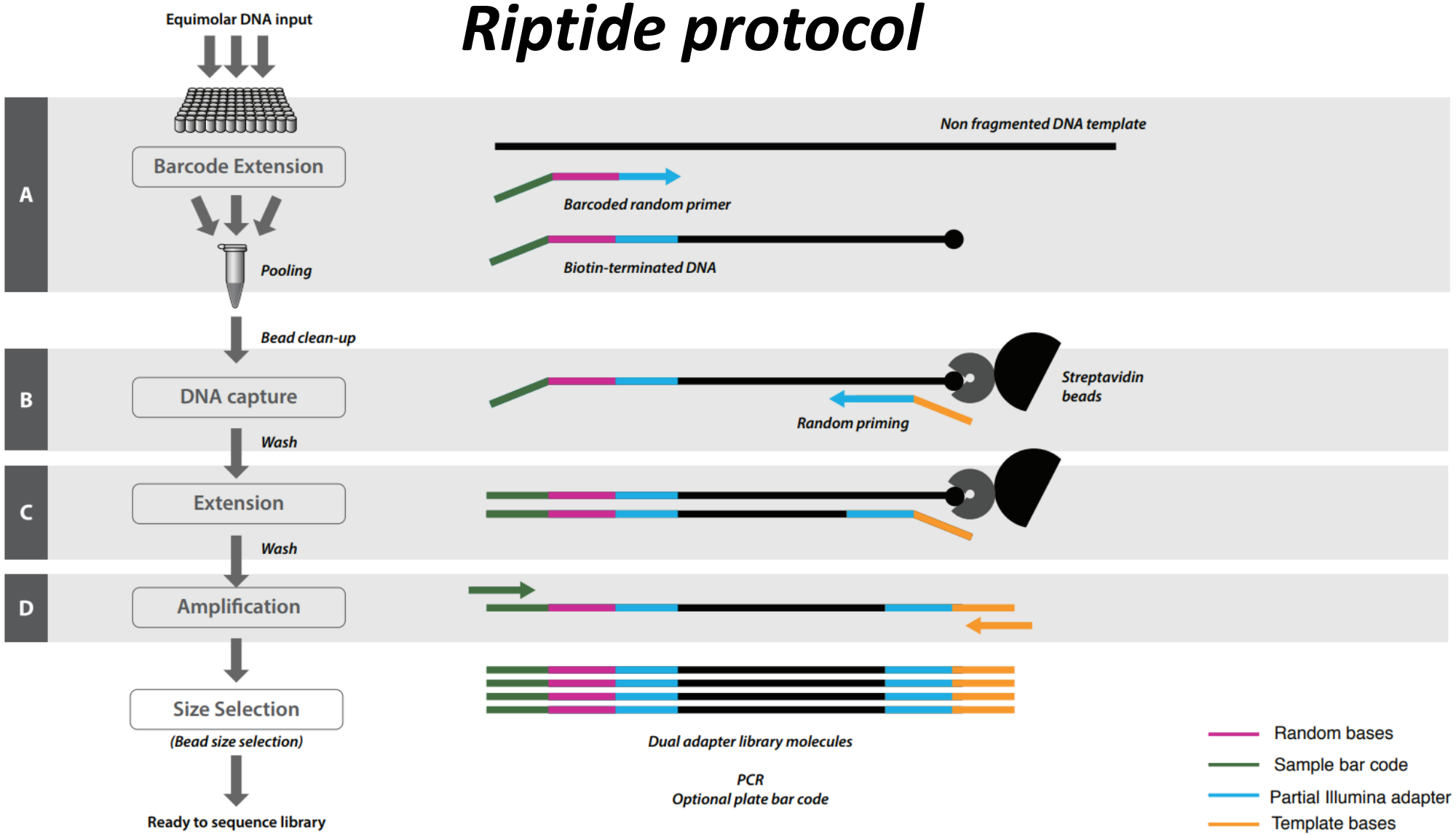
Emmanuel Aryee

Jianjn Gao

Alex Gileta

Hannah Bimschlager

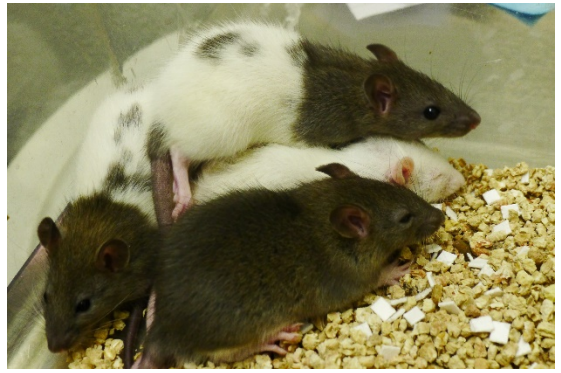
Riptide protocol



Now transitioning to the new rat genome mRatBN7!

Center goals

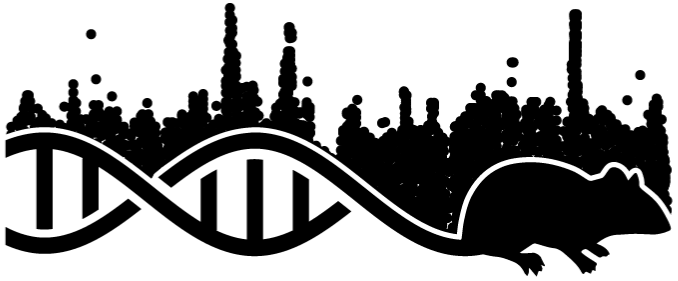
- Use quantitative genetics to identify genes that influence a constellation of psychologically complex behavioral traits that are associated with drug abuse
  1. Rats not mice
  2. Outbred HS rats
  3. Next gen sequencing to genotype
  4. Behavioral domain experts
  5. Very large sample sizes
  6. Multi-omic data integration
  7. Analysis pipeline to produce “reports”
- Please visit www.ratgenes.org for more information!



Genes and Addiction
NIDA Center for GWAS in Outbred Rats

Center for GWAS in outbred rats

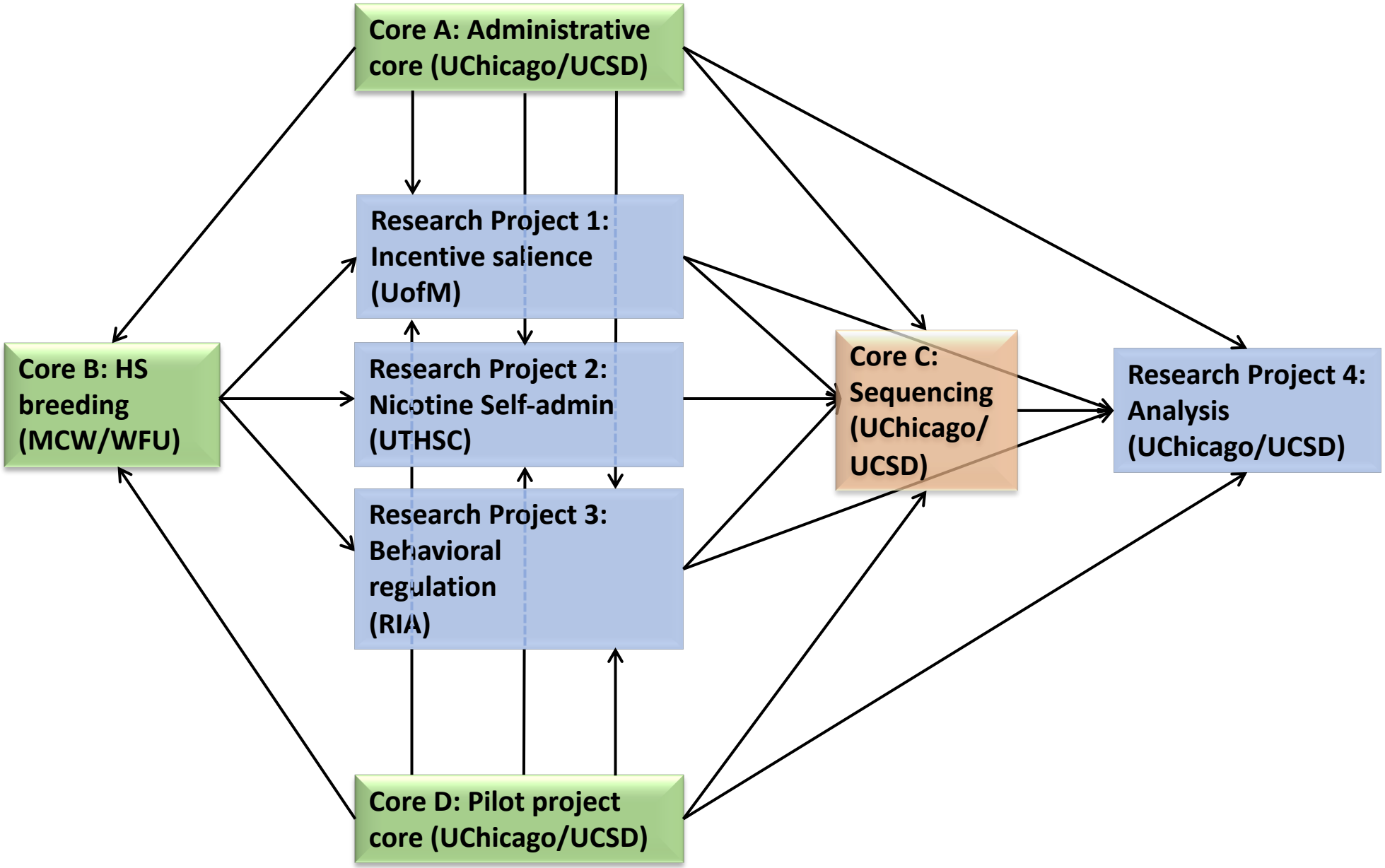
- The key elements of the center
  - Production of HS rats
  - Phenotyping of HS rats
  - Genotyping of HS rats
  - Analysis of genotype and phenotype data



Genes and Addiction

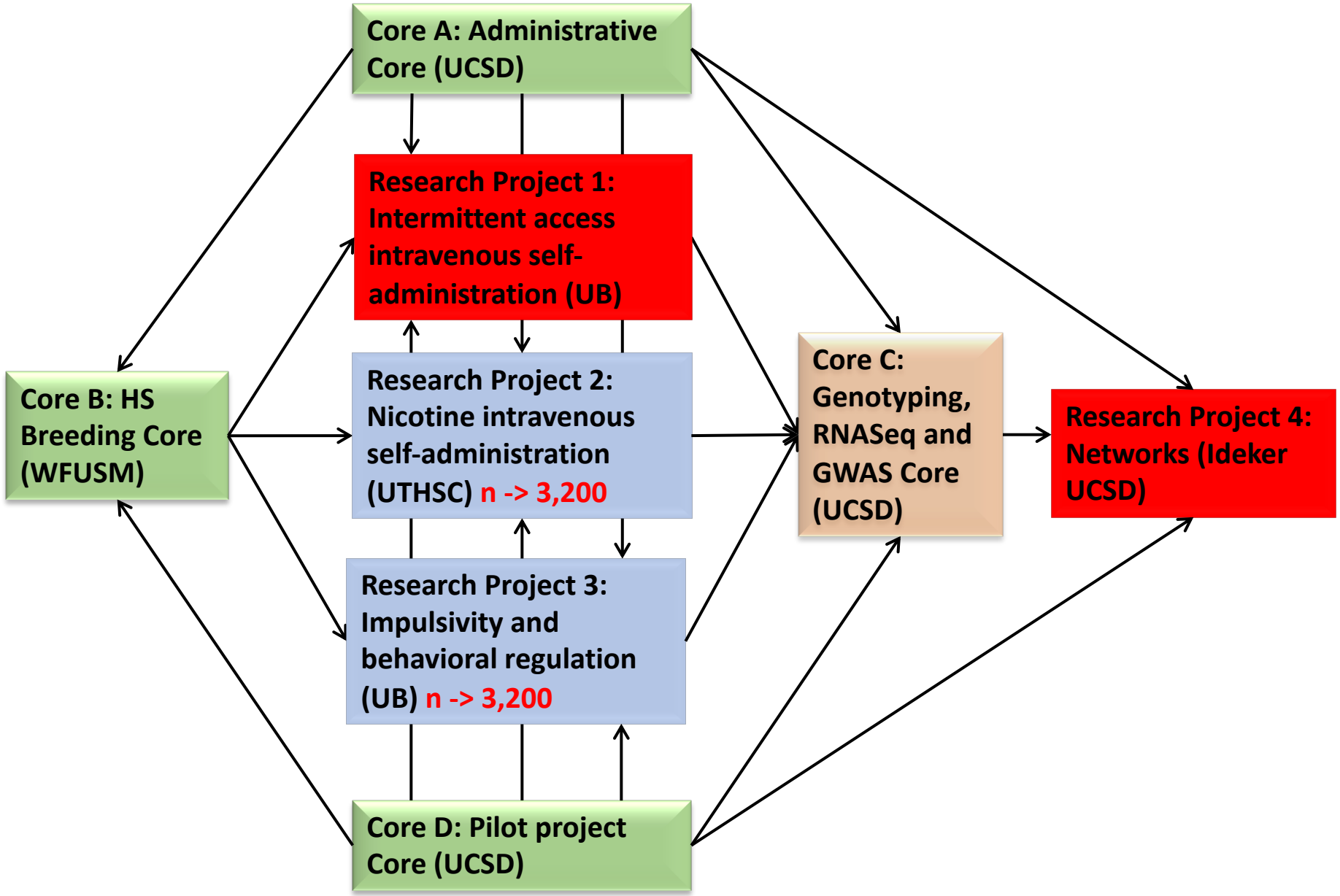
NIDA Center for GWAS in Outbred Rats

Initial Funding Period: 2014-2019



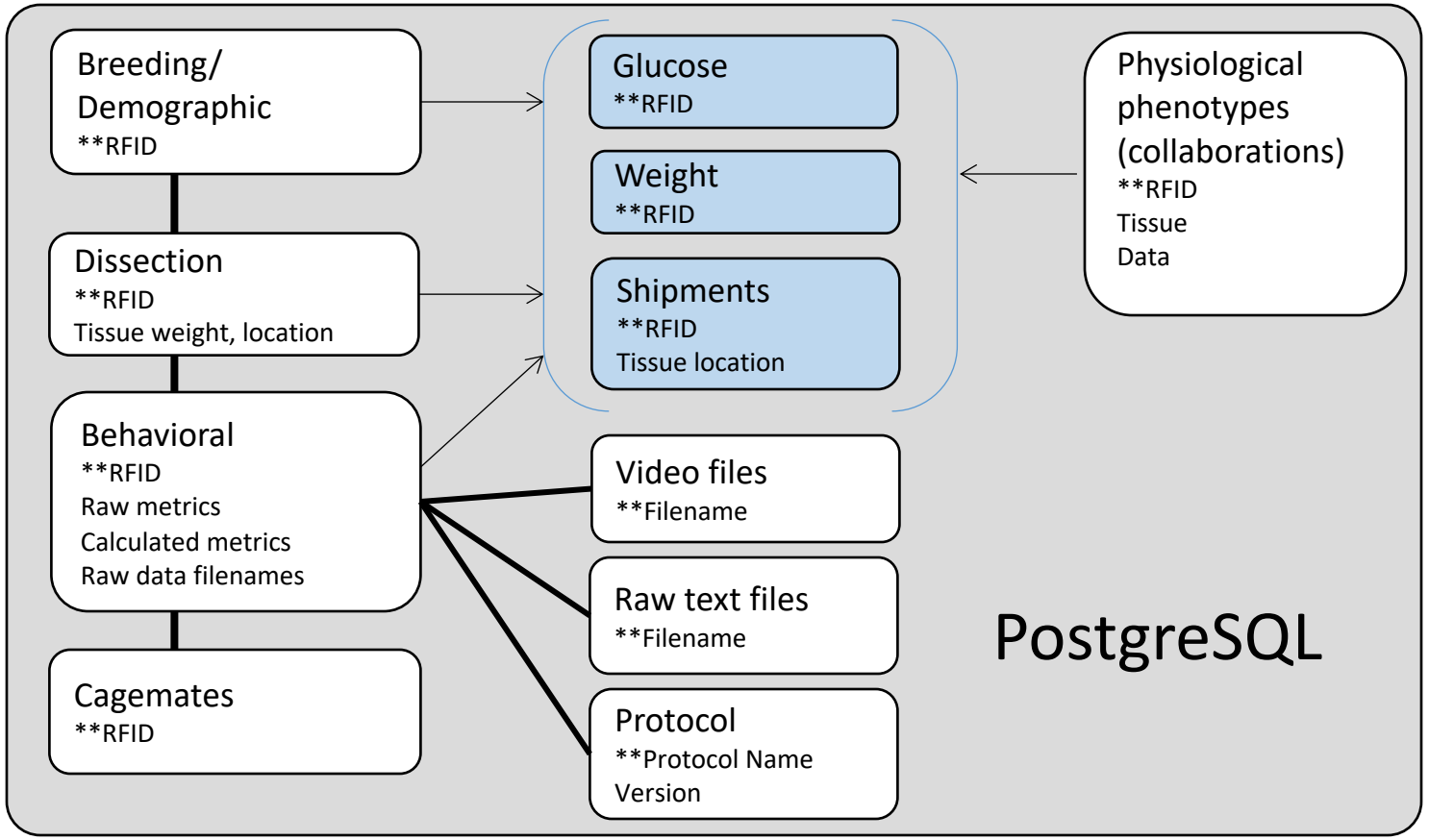
Research Project 1	Research Project 2	Research Project 3
University of Michigan	University of Tennessee Health Center	University at Buffalo
PIs: Terry Robinson, Shelly Flagel	**PI:** Hao Chen	**PIs:** Jerry Richards, Paul Meyer
Pavlovian conditioned approach Conditional reinforcement Novelty seeking Cocaine contextual conditioning	Open field Novel object Elevated Plus Maze Marble burying Social interaction Socially acquired nicotine self-administration Gene expression in 5 brain regions: n=88 per region	Locomotor activity Light reinforcement Reaction time Delay discounting Pavlovian conditioned approach Conditional reinforcement Novelty seeking Cocaine cue preference

Renewal Period: 2019-2024



Research Project 1	Research Project 2	Research Project 3
University at Buffalo	University of Tennessee Health Center	University at Buffalo
PIs: Paul Meyer	**PI:** Hao Chen	**PIs:** David Dietz (PI), Keita Ishiwari (coI), Paul Meyer (coI), Suzanne Mitchell (coI)
Intermittent access cocaine self administration Gene expression in 3 brain regions following either intermittent or extended access cocaine	Open field Novel object Elevated Plus Maze Marble burying Social interaction Socially acquired nicotine self-administration Gene expression in 5 brain regions for eQTL	Locomotor activity Light reinforcement Reaction time Delay discounting Pavlovian conditioned approach Conditional reinforcement Novelty seeking Cocaine cue preference

Database



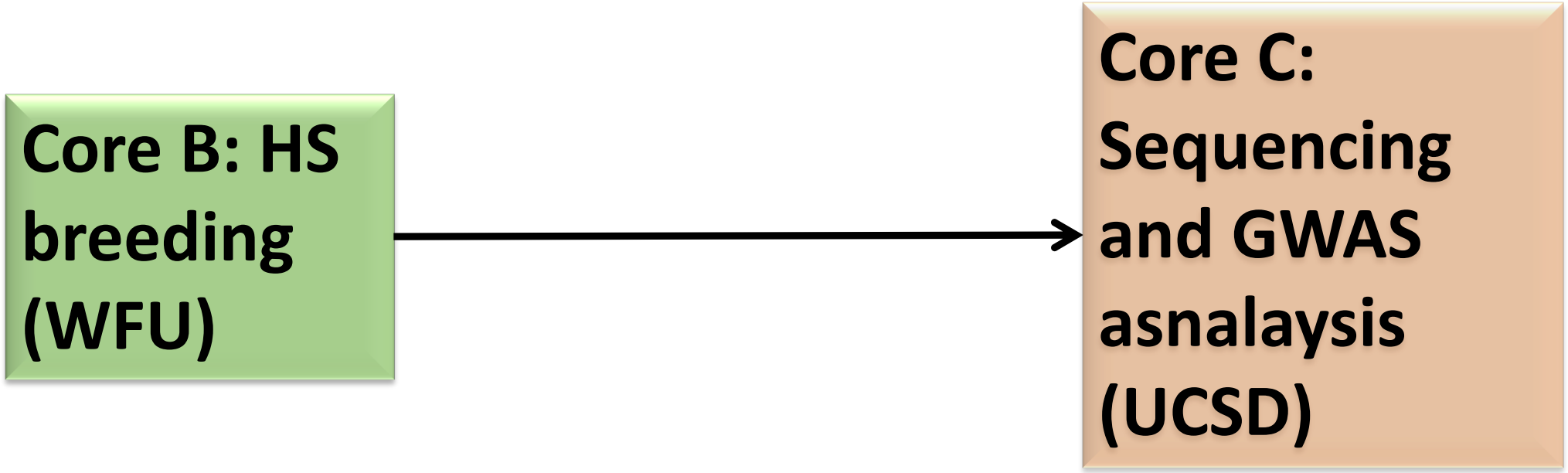
Apurva Chitre

Bonnie Lim

Denghui Chen

Genes and Addiction
NIDA Center for GWAS in Outbred Rats

Numerous U01s and other grants have benefitted from two key cores in this center



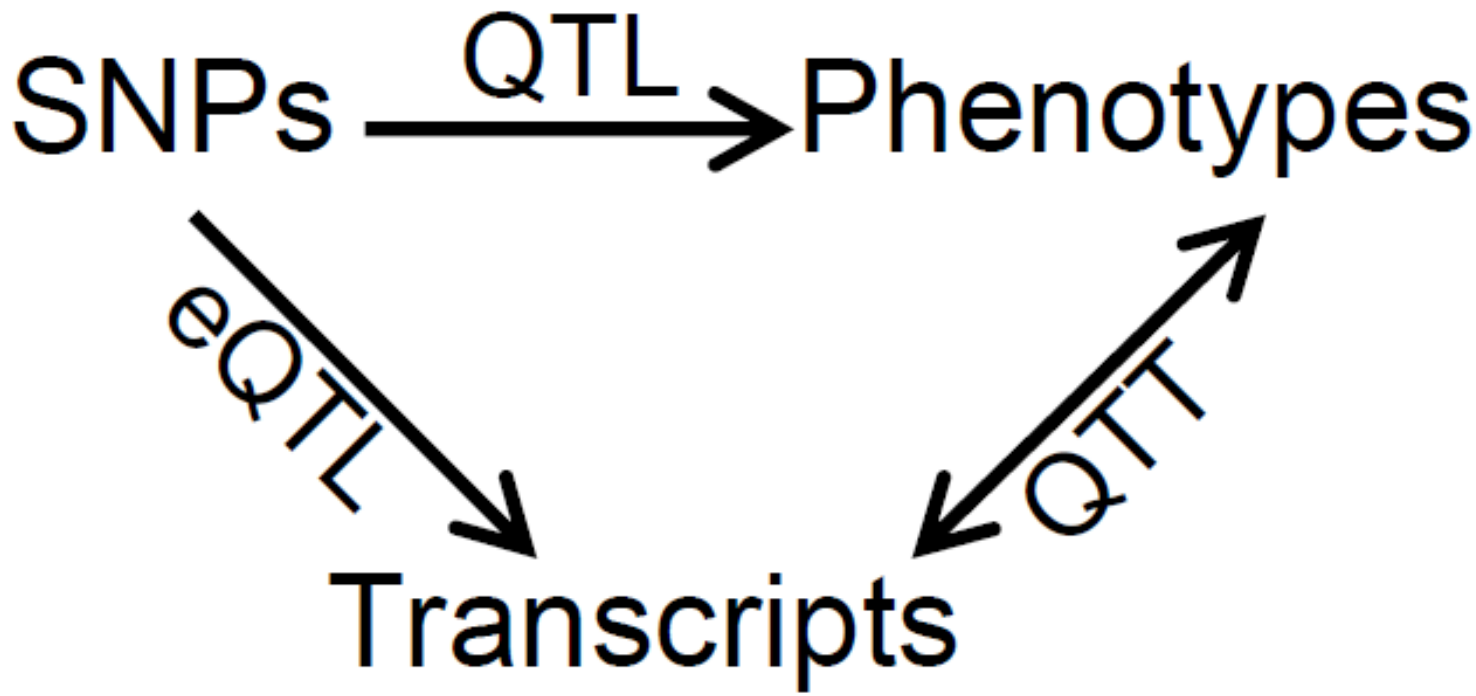
Physiological collaborations

	Collaborator	Institution	Area of Interest	Tissue	Grant
1	Arimantas Lionikas	University of Aberdeen, UK	muscle-tendon-bone	hind limb	None
2	Diethard Tautz	Max Planck Institute, Germany	evolution	heads	None
3	Cheryl Ackert-Bicknell Douglas Adams	University of Colorado, Denver	musculoskeletal research	carcass, limbs	Funded R01
4	Leah Solberg-Woods Kevin Regner	Wake Forest University, US Medical College of Wisconsin	type 2 diabetes	serum, fat, liver, muscle	Funded State of Wisconsin Grant
5	Amelie Baud, John Cryan, Rob Knight	UCSD, University College Cork, Ireland	microbiome	cecum, fecal material	Funded pilot from CMI
6	Matthew Dean	University of South California, US	evolutionary biology	baculum	None
7	Amelie Baud	EMBL-EBI, UK	indirect genetic effects	cage mates info	None
8	Mohit Jain	UC San Diego, US	metabolomics	serum, brain	None
9	Francesca Telese	UC San Diego, US	epigenetics	brain tissue	Funded U01
10	Derek Daniels	University at Buffalo, US	feeding behaviors	food and water consumptions	None
11	Monica Jablonski	University of Tennessee, US	retinal biology	eyes	Funded R01
12	Chris Vulpe	University of Florida, US	copper and iron metab	liver, serum	None
13	Michael R. Garrett	University of Mississippi, US	Renal physiology	kidney	R01 being resubmitted
14	Joe Nadeau	University of Maine	noise/signal structure	phenotypic data	None

Spin-off grants (funded)

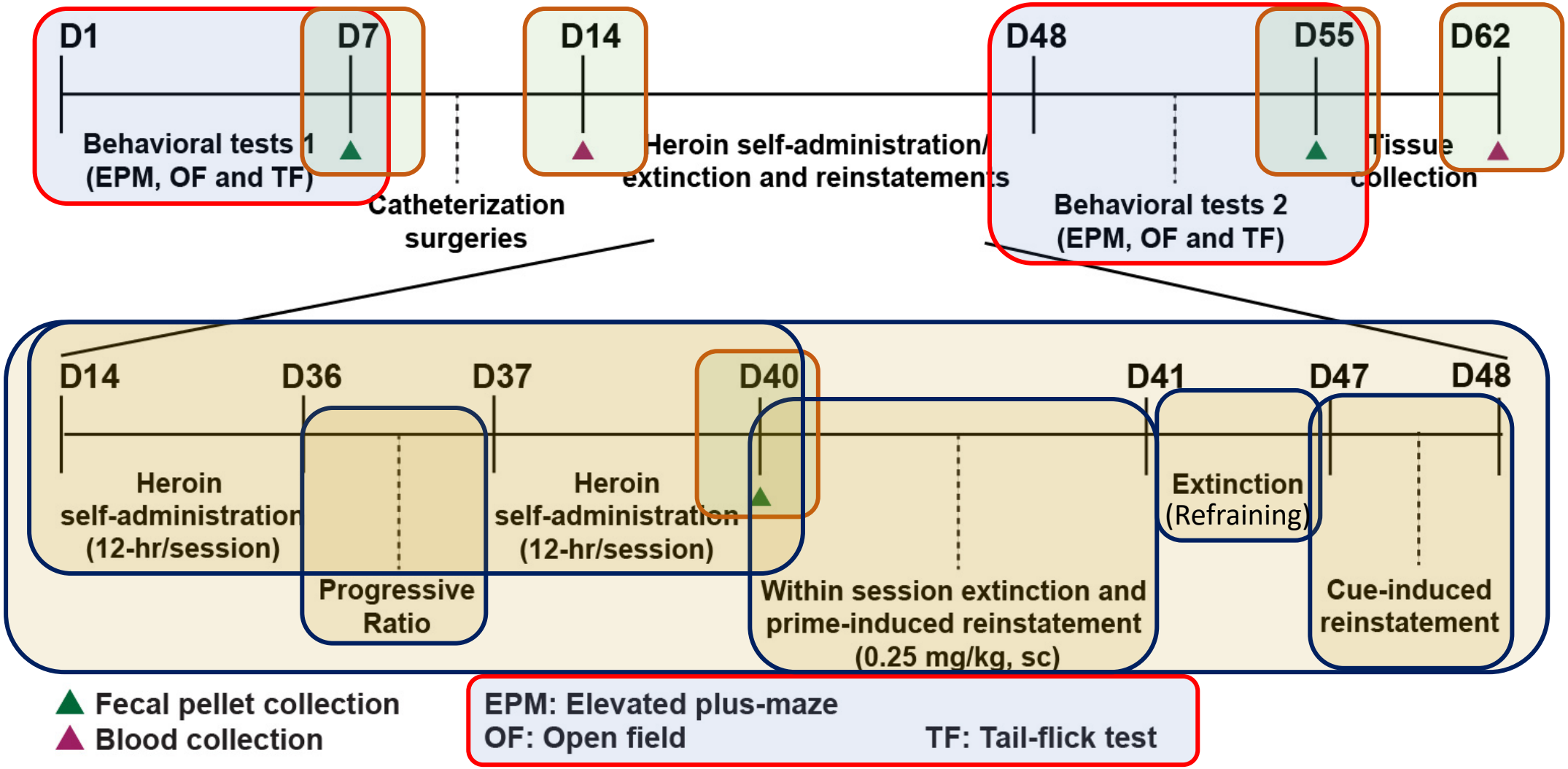
	Investigators	Grant #	Title	Funded by
1	Shelly Flagel	R01 DA038599	*Dynamic Control of Cue-Driven Behavior Via the Paraventricular Thalamic Nucleus*	NIDA
2	Paul Meyer	R01 AA024112	*Nicotine amplification of behavioral and neural responses to alcohol cues.*	NIAAA
4	Douglas Adams	R01 AR070879	*Identification of Genes Regulating Bone Matrix Composition and Quality*	NIAMS
3	Leah Solberg-Woods & Kevin Regner (MPI)	Awarded	*Genetic Mapping and Gene Identification in Acute Kidney Injury Using Outbred Rats*	HWE/MCW
5	Oksana Polesskaya & Amelie Baud	Awarded	*Genetics of microbiome in HS rats*	CMI/UCSD
6	Huda Akil & Jun Li	U01 DA043098	*Genetics of Novelty seeking and Propensity for Drug Abuse in Outbred Rats*	NIDA
7	Olivier George & Abraham Palmer (MPI)	U01 DA043799	*Identification of Genetic Variants that Contribute to Compulsive Cocaine Intake in Rats*	NIDA
8	Olivier George & Abraham Palmer (MPI)	U01 DA044451	*Use of Next-Gen Sequencing to Identify Genetic Variants that Influence Compulsive Oxycodone Intake in Outbred Rats*	NIDA
9	Thomas Jhou	U01 DA044468	*Genomic analysis of avoidance learning in addiction*	NIDA
10	Suzanne Mitchell & Bob Hitzemann (MPI)	U01 DA046077	*Identification of genetic features of delay discounting using a heterogeneous stock rat model*	NIDA
11	Monica Jablonski	R01 EY021200	*Genetic Modulation of Glaucoma*	NEI
12	Peter Kalivas, et al	U01 DA45300	*The Genetic Basis of Opioid Dependence Vulnerability in a Rodent Model*	NIDA
13	Francesca Telese	U01 DA050239	*Single-Cell Resolution Analysis of Chromatin Accessibility and Gene Expression Changes in a Model Of Drug Addiction*	NIDA

Project	Tissue	# samples
P50 DA037844 (Chen, Palmer)	nucleus accumbens core	88
P50 DA037844 (Chen, Palmer)	lateral habenula	88
P50 DA037844 (Chen, Palmer)	orbitofrontal cortex	88
P50 DA037844 (Chen, Palmer)	infralimbic cortex	88
P50 DA037844 (Chen, Palmer)	prelimbic cortex	88
P50 DA037844 (Chen, Palmer)	posterior ventral tegmental area	100
P50 DA037844 (Chen, Palmer)	medial habenula	100
P50 DA037844 (Chen, Palmer)	ventral hippocampus	100
P50 DA037844 (Chen, Palmer)	insular cortex	100
P50 DA037844 (Chen, Palmer)	lateral hypothalamus	100
U01 DA050239 (Telese)	nucleus accumbens	100
R01 EY021200 (Jablonsky)	Eye	50
P50 DA037844 (Chen, Telese, Palmer)	Half brain (sagittal)	350
U01DA046077 (Mitchell, Hitzemann)	Basolateral amygdala	200
U01DA046077 (Mitchell, Hitzemann)	Prelimbic cortex	200
U01DA044468 (Jhou)	rostromedial tegmental nucleus	80
U01DA044468 (Jhou)	rostromedial tegmental nucleus	80
U01DA044468 (Jhou)	rostromedial tegmental nucleus	80
U01DA044468 (Jhou)	rostromedial tegmental nucleus	80

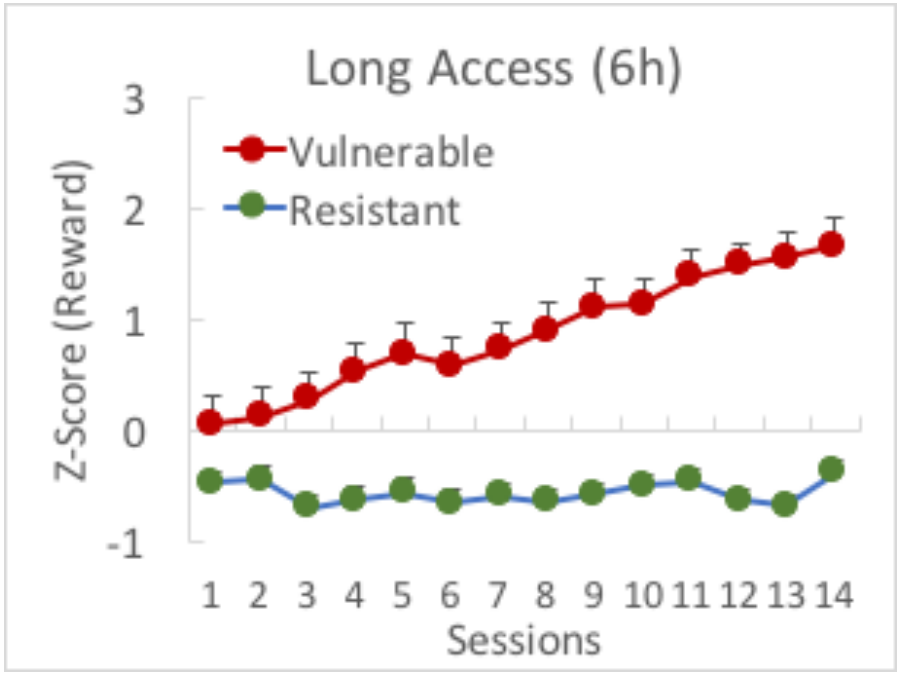

SNPs
QTL
Phenotypes
eQTL
QTT
Transcripts

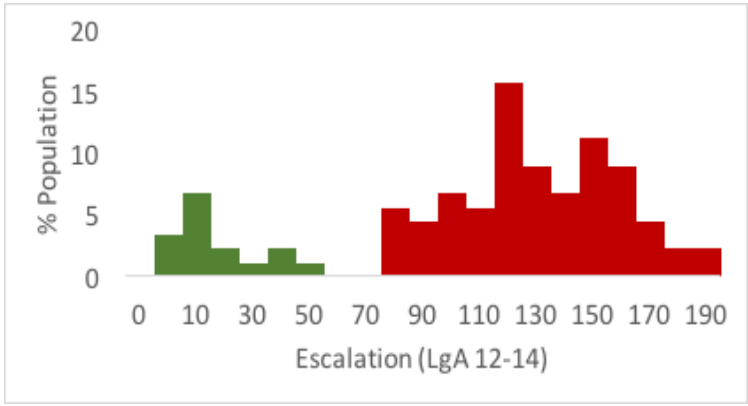
The Genetic Basis of Opioid Dependence Vulnerability in a Rodent Model (U01DA045300; Kalivas)

The team



Identification of Genetic Variants that Contribute to Compulsive Cocaine Intake in Rats (U01DA043799; George)

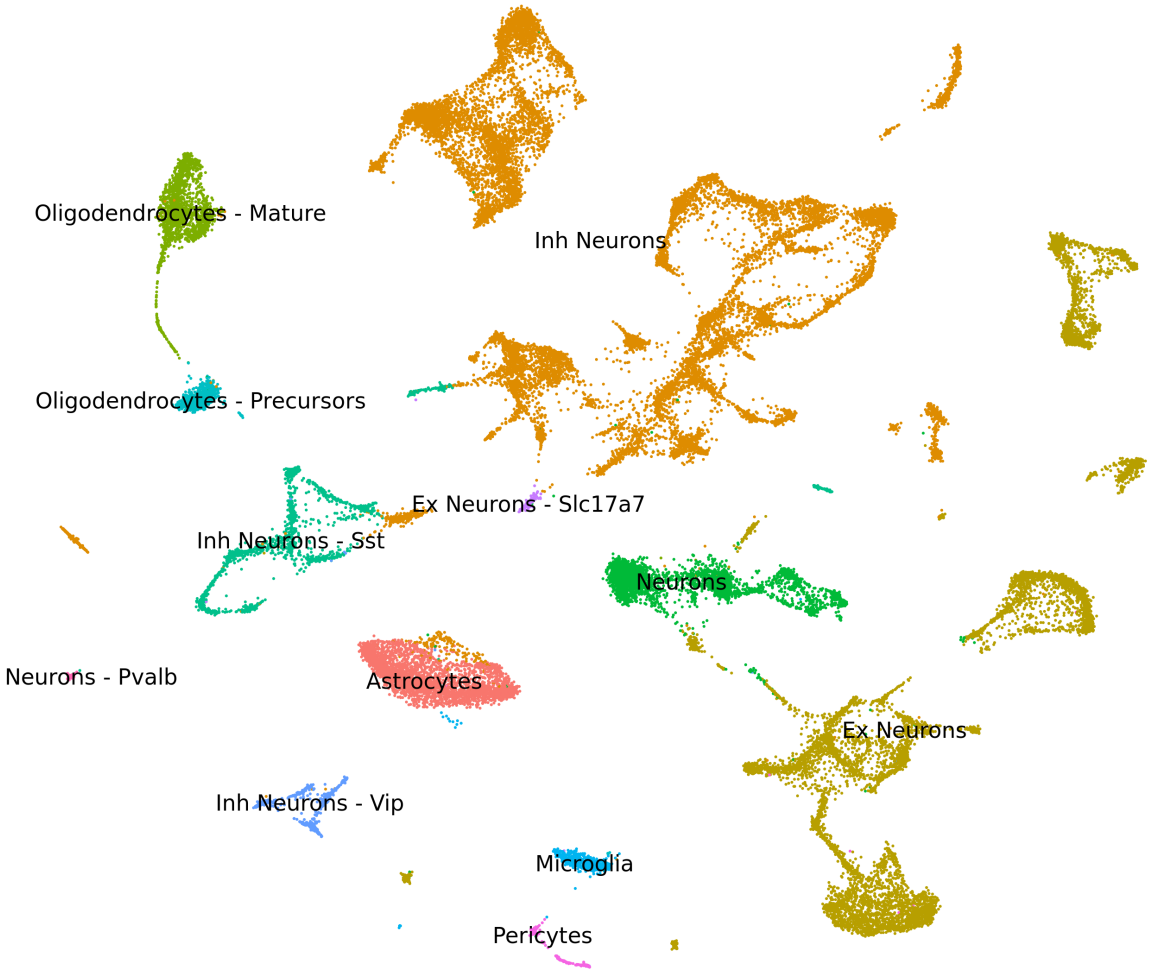




Olivier George

Giordano De Guglielmo

Single-Cell Resolution Analysis of Chromatin Accessibility and Gene Expression Changes in a Model Of Drug Addiction (U01DA050239)



- Astrocytes
- Inh Neurons
- Ex Neurons
- Oligodendrocytes - Mature
- Neurons
- Inh Neurons - Sst
- Oligodendrocytes - Precursors
- Microglia
- Inh Neurons - Vip
- Ex Neurons - Slc17a7
- Pericytes
- Inh Neurons - Pvalb

Francesca Telese

Jessica Zhou

Graham McVicker

Arya Massarat

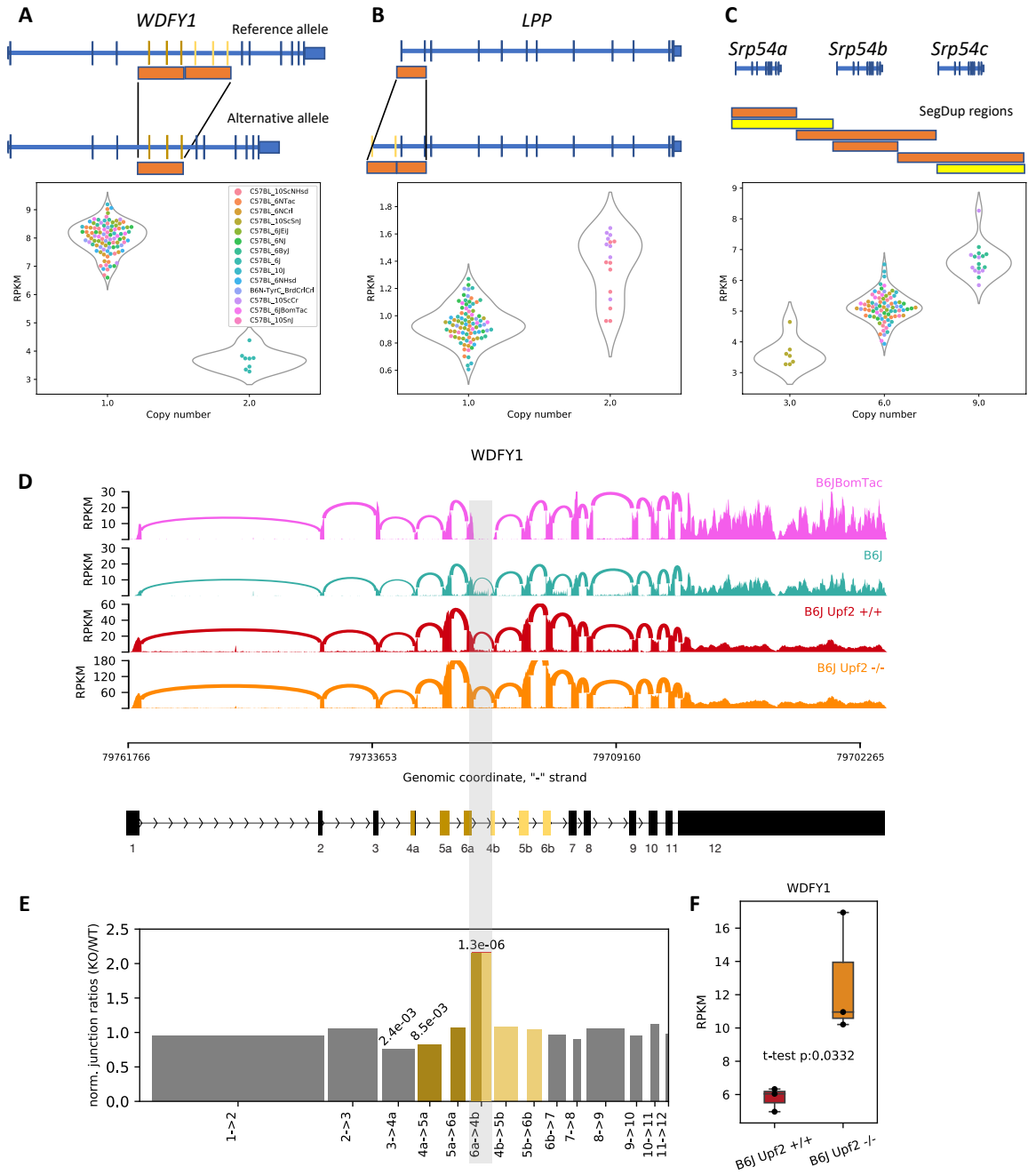
Characterization of Tandem Repeat and Structural Variants Contributing to Addictive Behaviors in Mice and Rats (U01DA051234)

Jonathan Sebat

Melissa Gymrek

Mikhail Maksimov

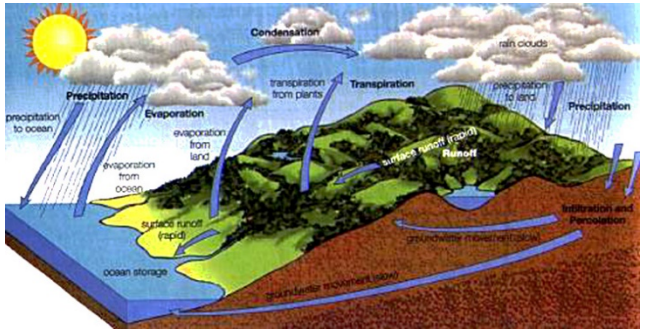
Milad Mortazavi



	Cohort	Number to be studied	Data sources	Currently funded NIDA U01 and related grants (see Letters of support (LOS) and Dr. Palmer's existing roles)
Inbred mice	BXD	155 (see LOS from Williams)	Illumina pe150 35x available, this grant will generate PacBio	U01DA041632; Gene variants for nicotine withdrawal deficits in learning (Thomas Gould, see LOS) LOS from Rob Williams also included
	HMDP	85 (HMDP is n= 114 but 29 are also in BXD RIs; Ghazalpour, et al 2012)	This grant will generate PacBio and Illumina for the subset for which it is not already available	U01DA044399; Computational methods for identification of genetic factors affecting the response to drug abuse (Gary Peltz, see LOS) U01DA041602; Genetic pathways for impulsivity and drug reinforcement: DNA and transcriptome variation in mice (Desmond Smith, see LOS) LOS from Jake Lusis also included
Outbred mice	DO (HS-CC)	96 for which RNASeq data are available (see LOS)	This grant will generate PacBio and Illumina	P50DA039841; Center for systems neurogenetics of addiction (Elissa Chesler, see LOS, Dr. Palmer is a member of the external advisory board (EAB)) U01DA041579; Genetic risk for methamphetamine abuse (Tamara Richards, see LOS) U01DA043809; Genetic control of addiction by host and microbiome (George Weinstock, see LOS) LOS from Gary Churchill & Steve Munger also included
Inbred rats	HRDP	96 (These are the 96 that make up the HRDP, see LOS from Dwinell)	Illumina provided by Dwinell (see LOS), this grant will generate PacBio.	R24OD024617; Hybrid rat diversity program (Melinda Dwinell, see LOS, Palmer is on the EAB) R24AA013162; The heritable transcriptome and alcoholism (Boris Tabakoff & Laura Saba, see LOS, Palmer is on EAB) P30DA044223; Center of excellence in transcriptomics, systems genetics and the addictome (Robert Williams and Laura Saba, see LOS, Palmer is on EAB) U01DA047638; System genetics of menthol and nicotine addiction (Hao Chen, see LOS) LOS from Jun Li also included
Outbred rats	HS (N/NIH)	88 (These will be the same rats for which Dr. Palmer's P50 center generated RNASeq from	This grant will generate Illumina and PacBio.	P50DA037844; Center for genetic studies of drug abuse in outbred rats (Abraham Palmer in the PI) U01DA043799; Identification of genetic variants that contribute to compulsive cocaine intake (Olivier George, Palmer is MPI) U01DA044451; Use of next-gen sequencing to identify genetic variants that influence compulsive oxycodone intake in outbred rats (Olivier George, Palmer is CoI)

AllofUS-rats

The Ecosystem



Core B: HS breeding (WFU)

Research Project 1: Incentive salience (U Michigan)

Research Project 2: Nicotine Self-admin (UTHSC)

Research Project 3: Behavioral regulation (RIA)

U01: Compulsive Cocaine Intake (George, Palmer UCSD)

U01 Compulsive Oxycodone Intake (George, Palmer UCSD)

U01 Avoidance learning in addiction (Jhou MUSC)

U01 Heroine Self Administration (Kalivas et al, MUSC)

U01 Delay discounting (Mitchell, Hitzemann OHSU)

Core C: Sequencing (UCSD)

Research Project 4: Analysis (UCSD)

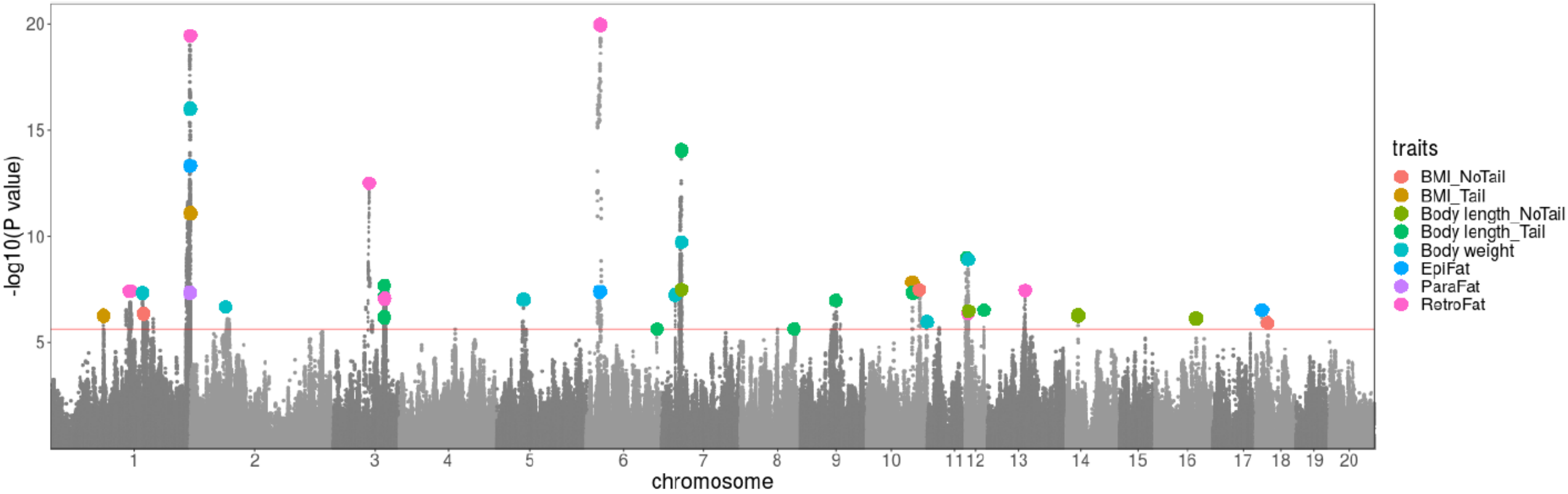
U01 SV and TRs in mice and rats (Palmer, Sebat and Gymrek UCSD)

U01 Single Cell RNASeq in Oxycodone Exposed rats (Telese, UCSD)

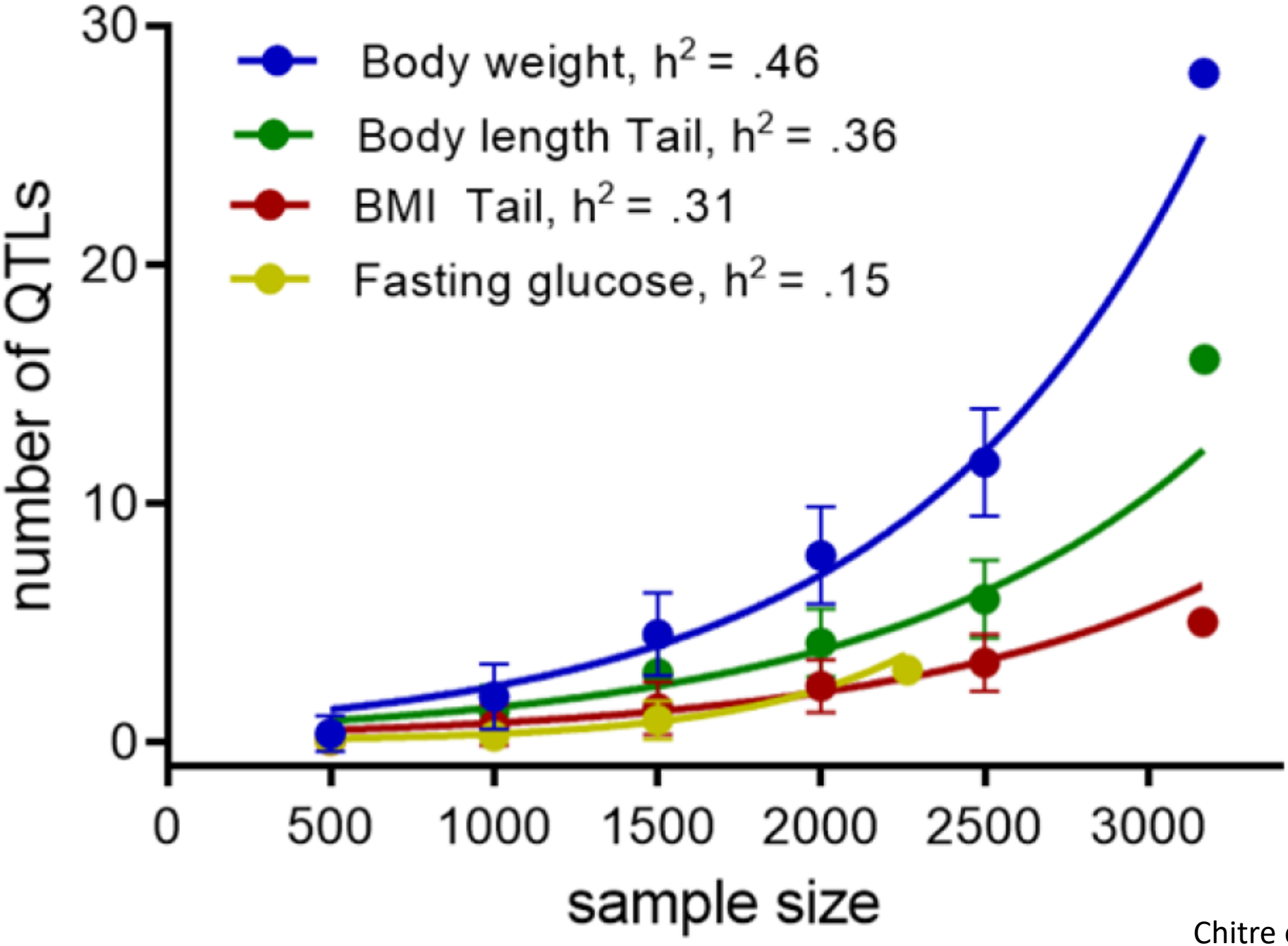
Total sample size from all funded grants 15,696 HS rats

A few quick stories

GWAS for body weight (n=3,184; h^2= 0.46)



Chitre et al, Obesity, 2020



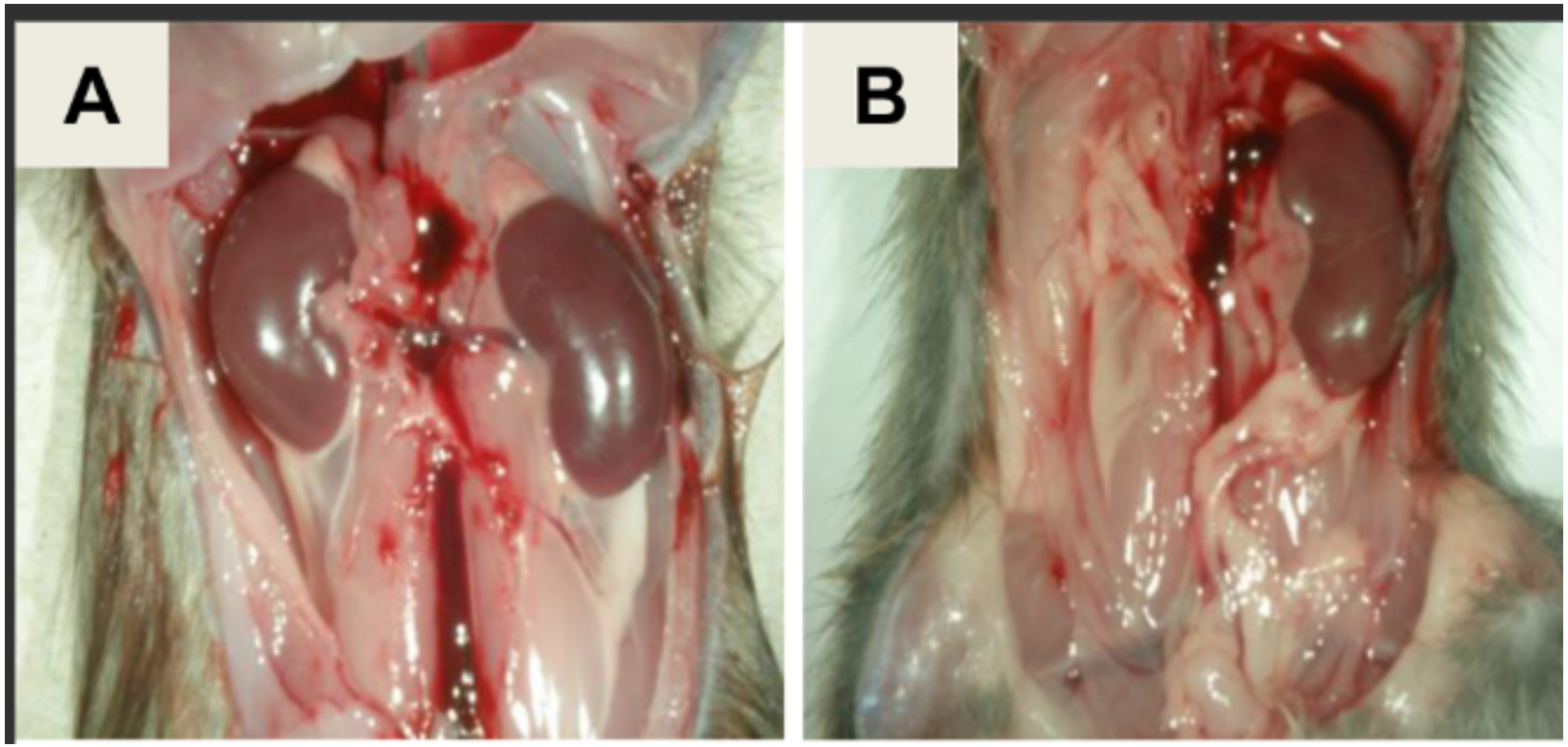
Chitre et al, unpublished

The mystery of the missing kidney…

Michael Garrett

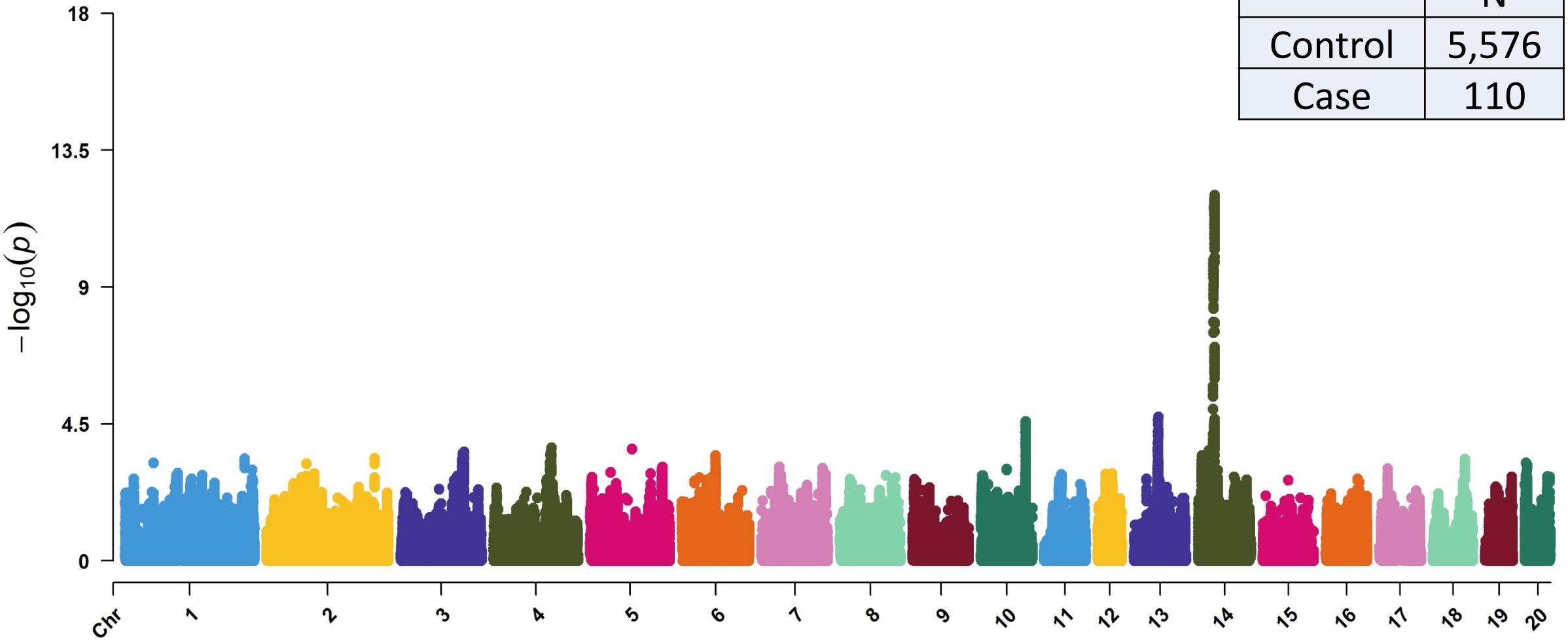
Joel David Leal Gutierrez

Leah Solberg Woods



The mystery of the missing kidney…

	N
Control	5,576
Case	110



Microbiome studies

- Center for Microbiome Innovation at UCSD is one of the largest in the world
  - We have collected Cecum from all P50 rats
  - We received a substantial pilot award from the CMI and additional support from Rob Knight himself
- we will soon have microbiome (16S) from ~4,800 rats and metabolome in a subset of about 1,100 samples
- Questions:
  - How does genotype influence microbiome?
  - Does microbiome correlated with behavioral and physiological phenotypes?
  - Does microbiome correlate with gut metabolome?
  - What is the best way to summarize 16S reads into traits for analysis?
- Social genetic effects:
  - Does the genotype of social partners influence the phenotype of their cagemates?
  - If so, might shared microbiome mediate some of these effects?

Reports

file:///C:/Users/Abraham%20Palmer/Downloads/elevated_plus_maze.html