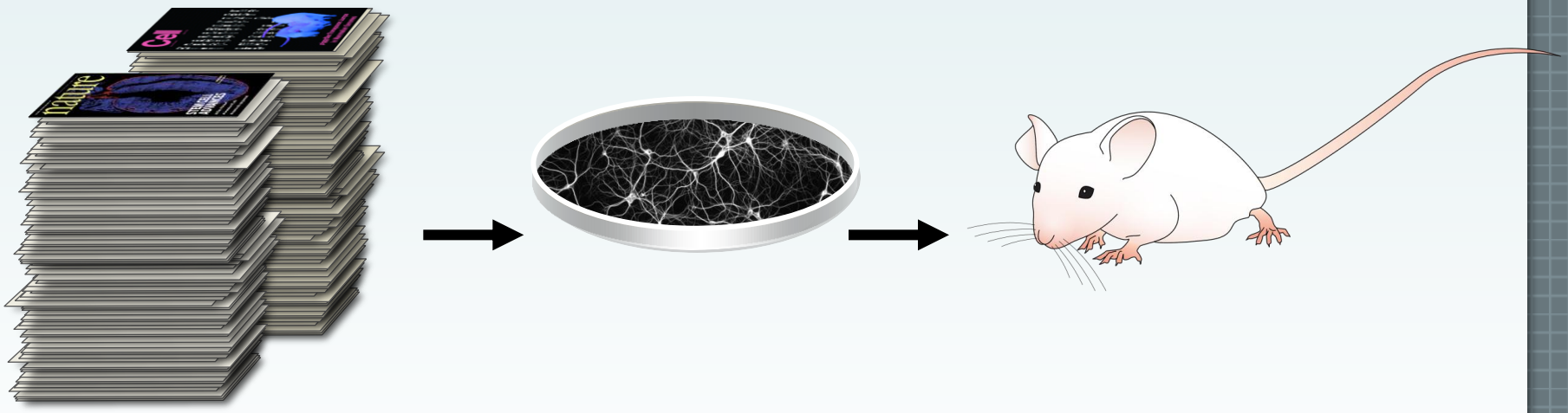
Drug discovery by high-content screening in the mouse brain

Pavel Osten

Preclinical drug discovery pipeline



1) target identification 2) tests *in vitro* 3) tests in animals

Tests in animals

are designed to model:

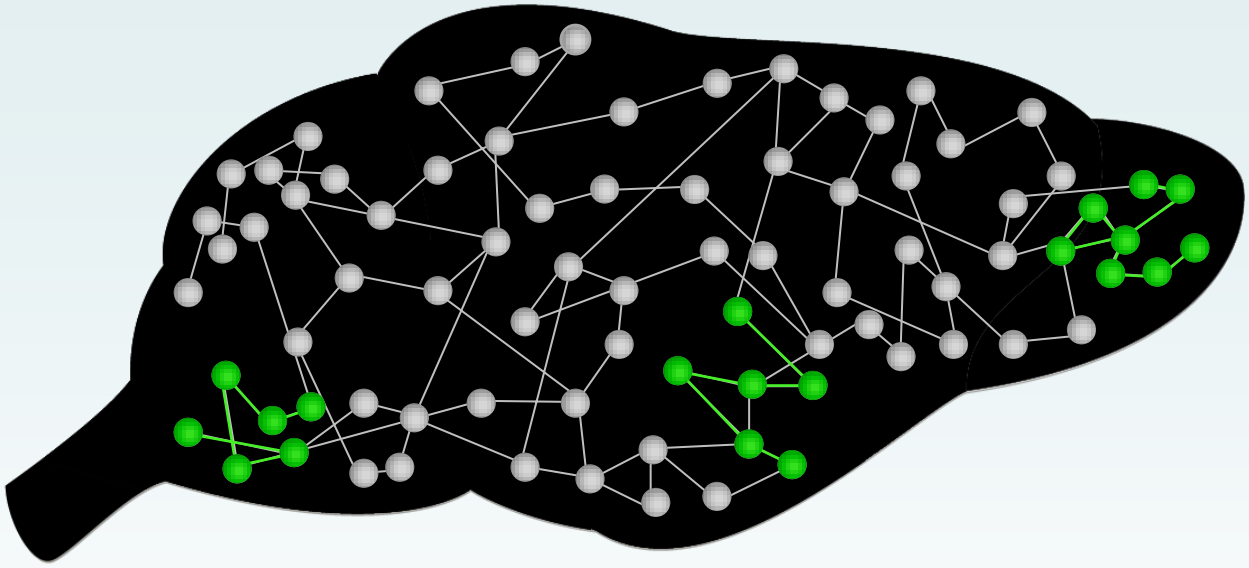
- the mechanism of the disorder (*construct validity*)
- the manifestation of the disorder (*face validity*)
- known drug response (*predictive validity*)

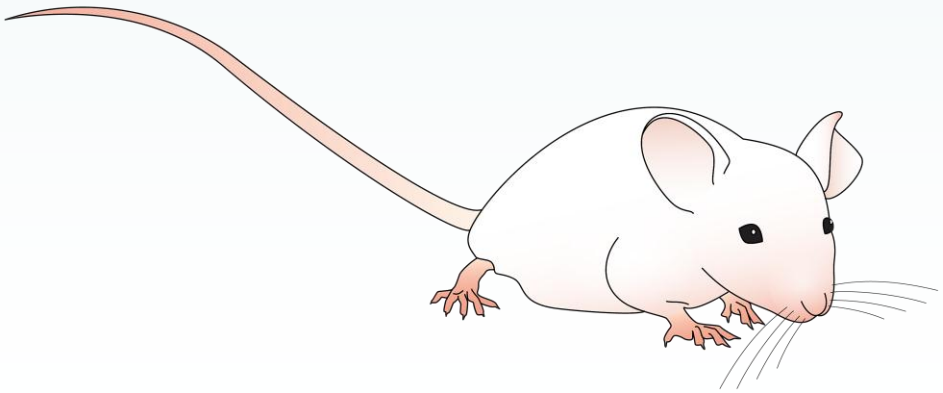
The most important is predictive validity

a drug used successfully in the clinics needs to show a quantifiable effect in the animal model

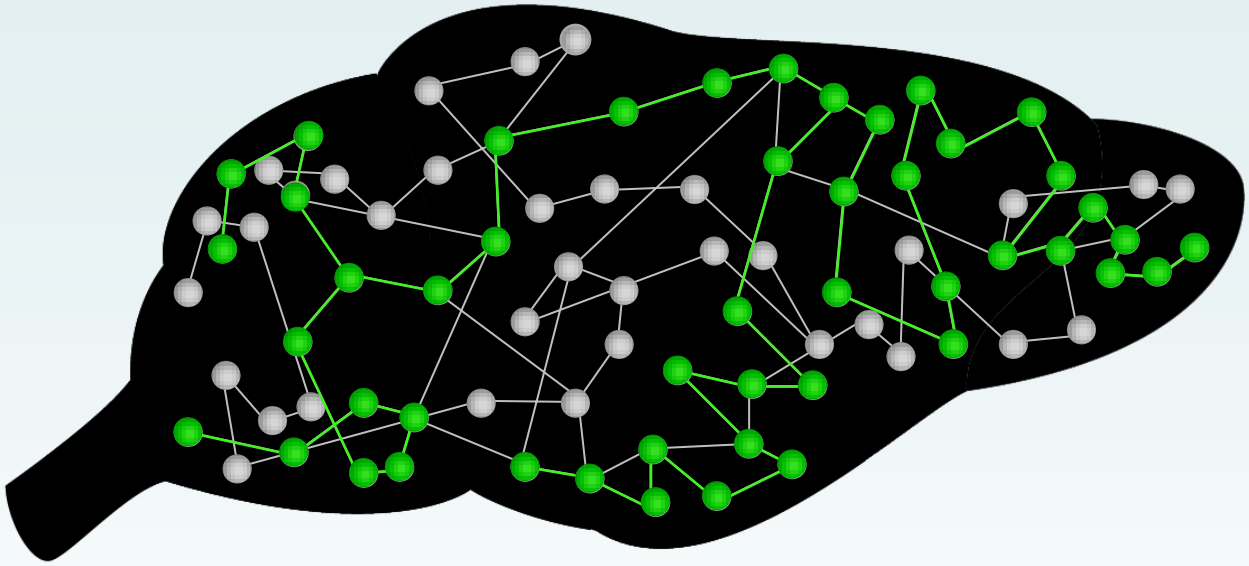
- such effect could be used to compare new drugs and predict their clinical effects
- but the therapeutic effects in animal models are unreliable due to low construct and face validity

Reporter Mouse

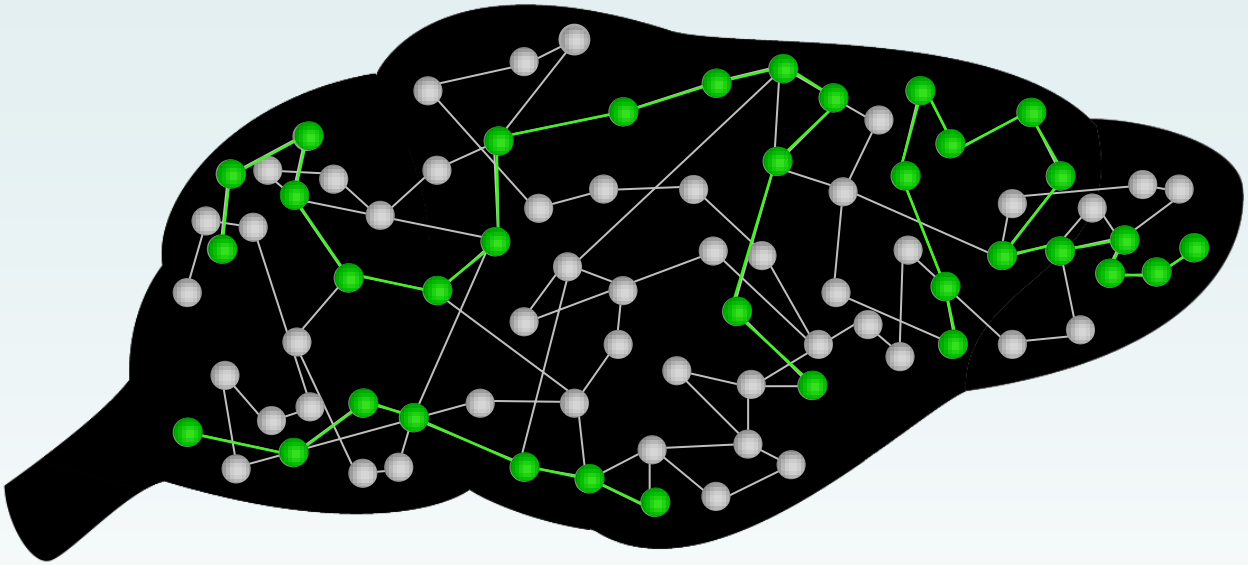




Social interaction

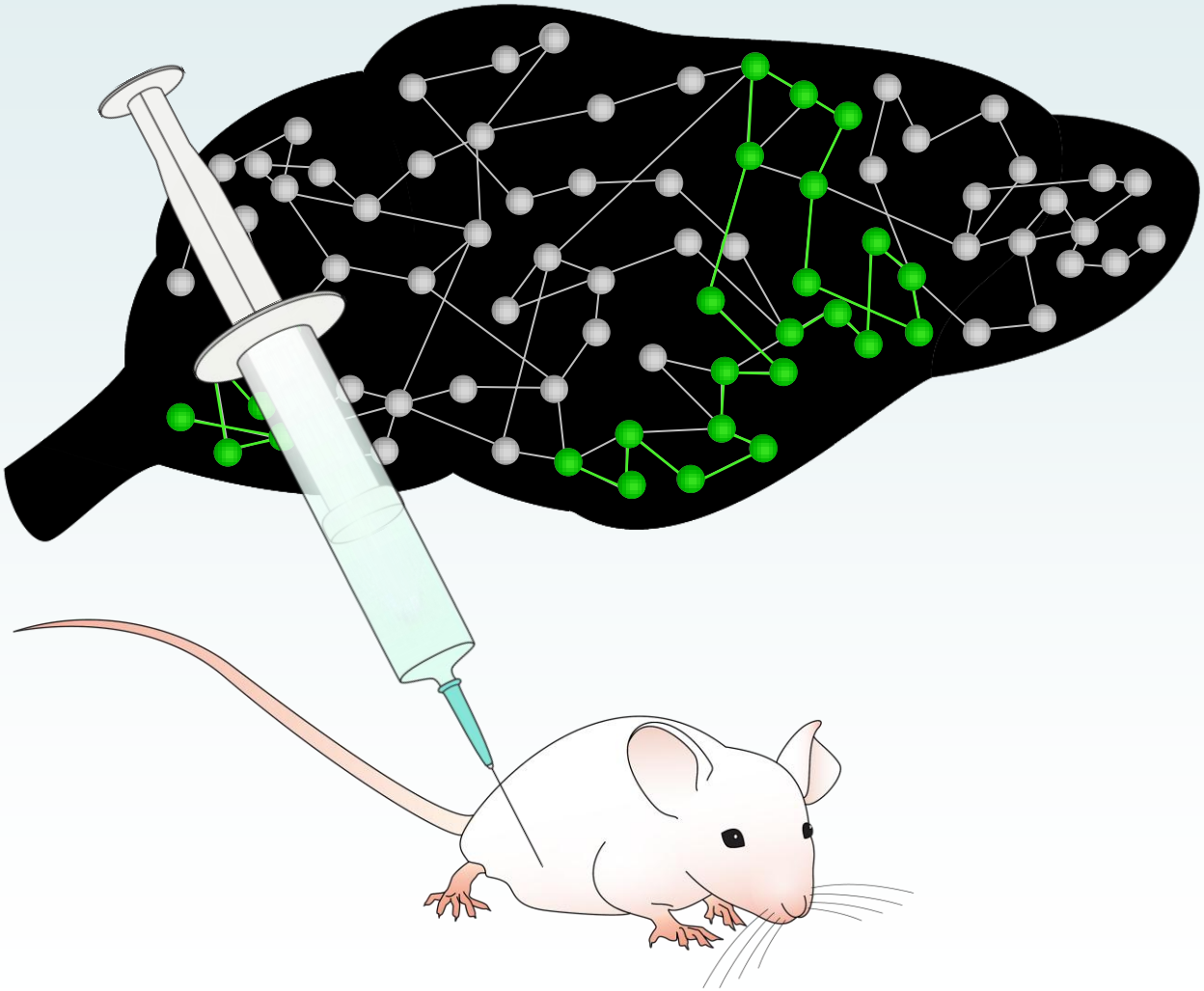


Exploration



Social interaction

Compound #1



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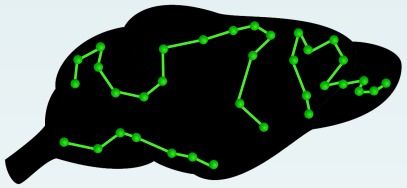

Exploration

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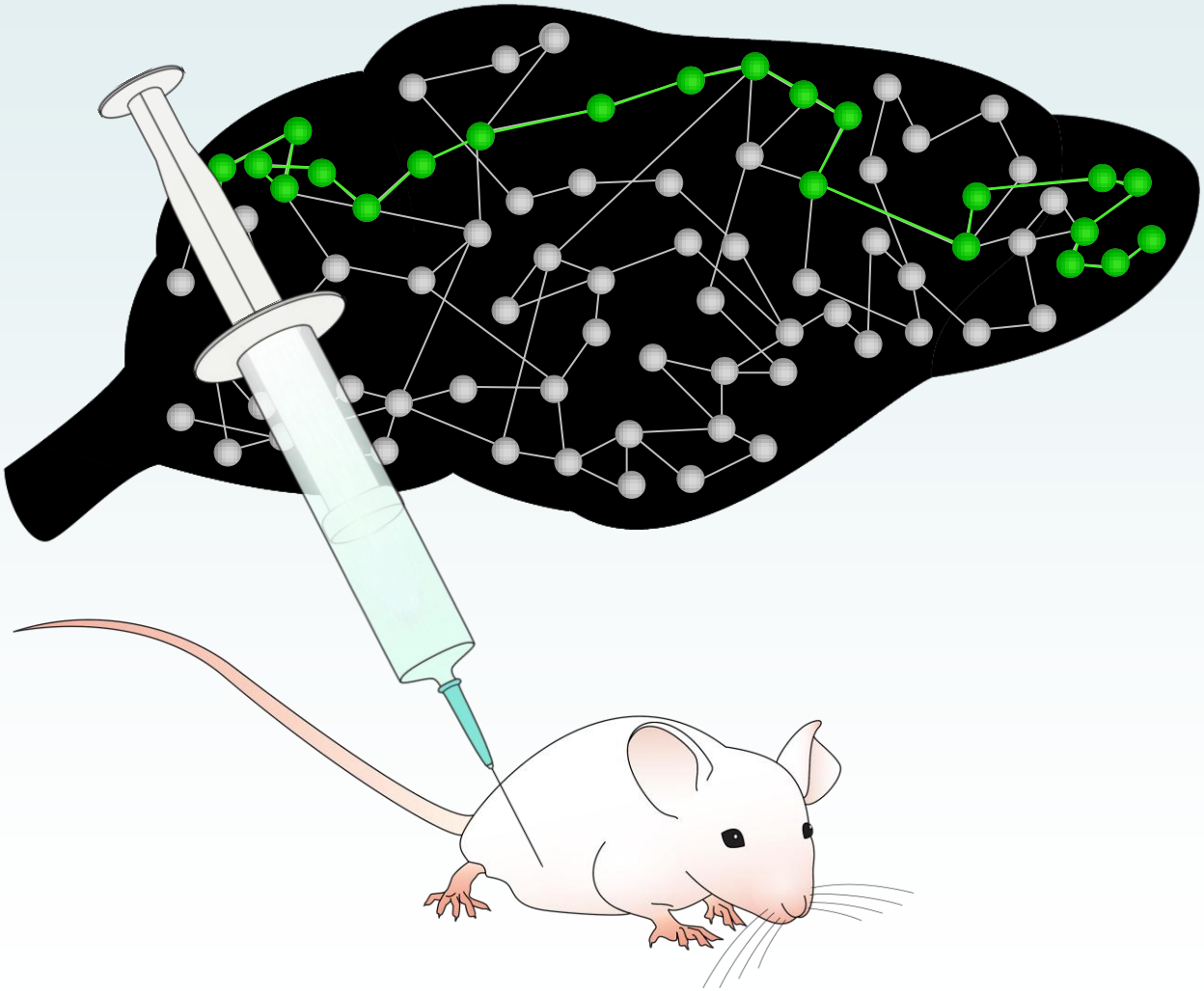

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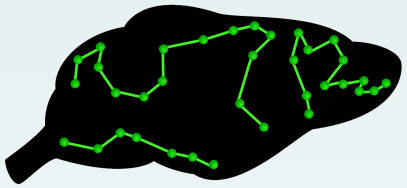

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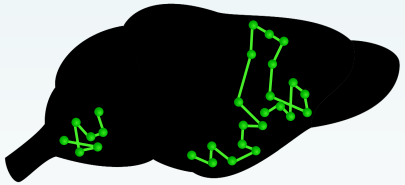
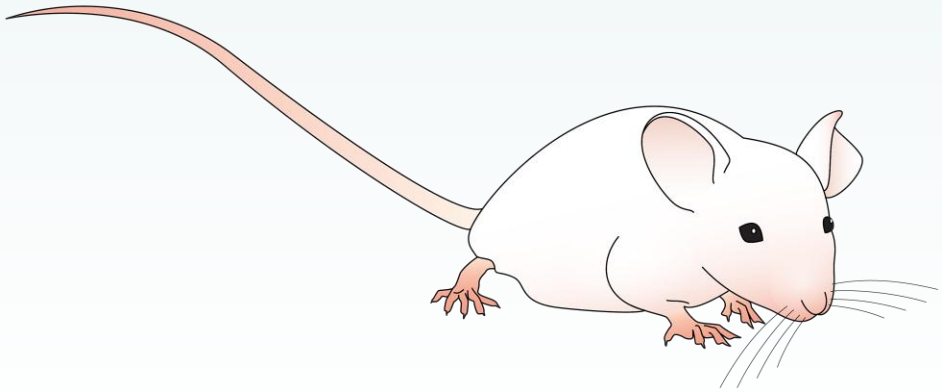


Compound #1

Brain activity patterns

- underlie and define specific behaviors
- represent fingerprint-like signatures of drug-evoked brain activation



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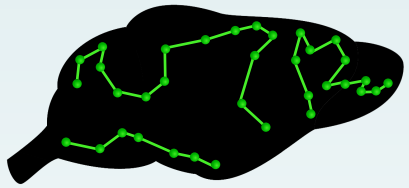

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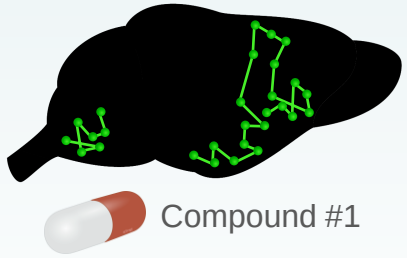
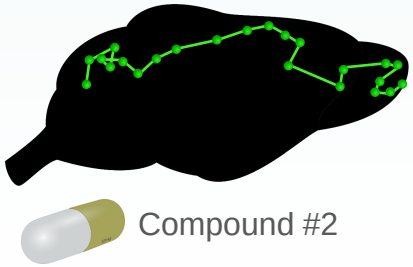
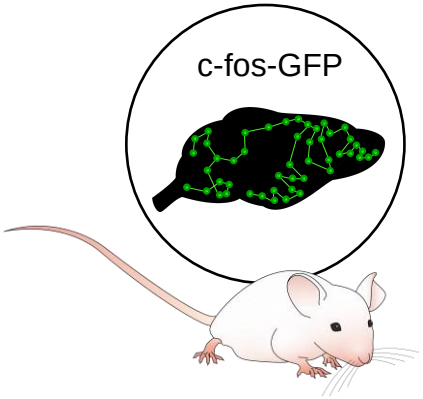


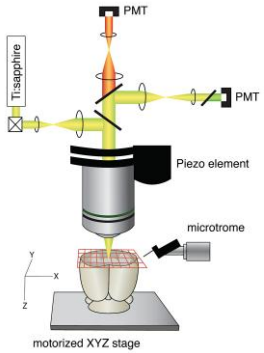
Compound #1

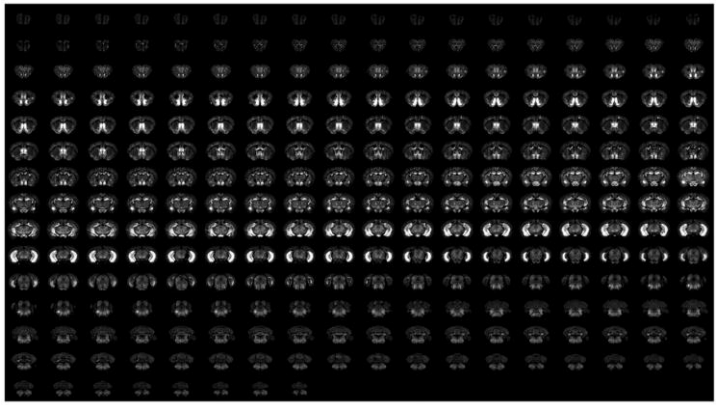


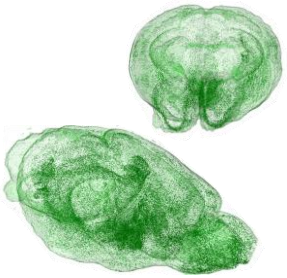
Compound #2

Predictive validity based on mouse brain activity



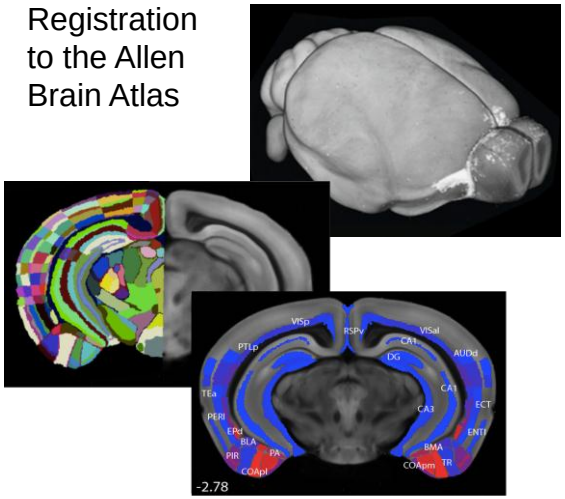




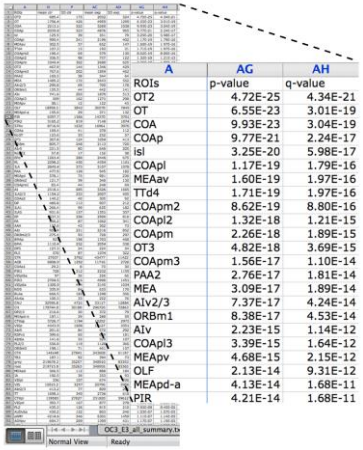


Brain activation → Automated imaging → Whole brain dataset → Whole brain c-fos data

Registration to the Allen Brain Atlas

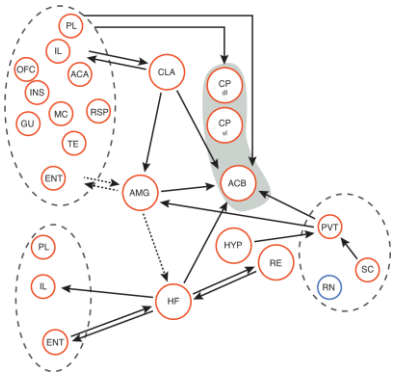


→ Statistical data analysis →



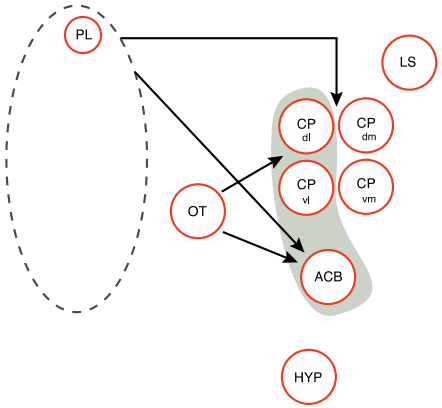
	A	AG	AH
	ROIs	p-value	q-value
	OT2	4.72E-25	4.34E-21
	OT	6.55E-23	3.01E-19
	COA	9.93E-23	3.04E-19
	COAp	9.77E-21	2.24E-17
	isl	3.25E-20	5.98E-17
	COApl	1.17E-19	1.79E-16
	MEAav	1.60E-19	1.97E-16
	TTd4	1.71E-19	1.97E-16
	COApm2	8.62E-19	8.80E-16
	COApl2	1.32E-18	1.21E-15
	COApm	2.26E-18	1.89E-15
	OT3	4.82E-18	3.69E-15
	COApm3	1.56E-17	1.10E-14
	PAA2	2.76E-17	1.81E-14
	MEA	3.09E-17	1.89E-14
	AIv2/3	7.37E-17	4.24E-14
	ORBm1	8.38E-17	4.53E-14
	AIv	2.23E-15	1.14E-12
	COApl3	3.39E-15	1.64E-12
	MEApv	4.68E-15	2.15E-12
	OLF	2.13E-14	9.31E-12
	MEApd-a	4.13E-14	1.68E-11
	PIR	4.21E-14	1.68E-11

→ Brain circuit-level data interpretation

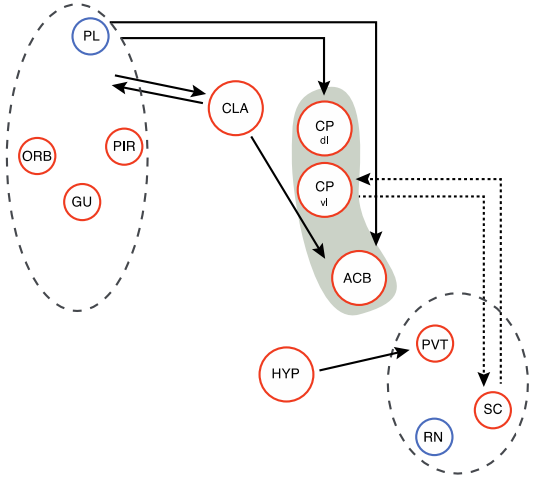


Mouse brain “pharmacomaps” of 3 antipsychotics

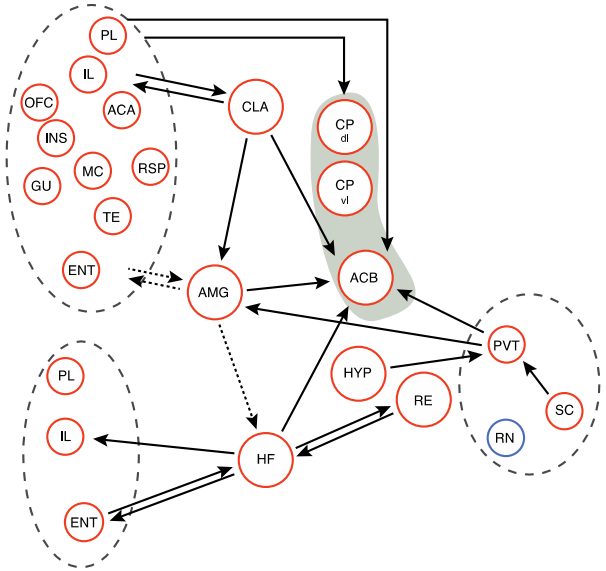
Haloperidol



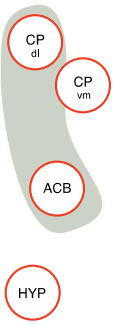
Risperidone



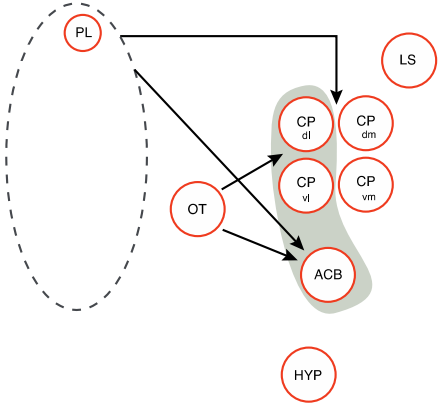
Aripiprazole (Abilify)



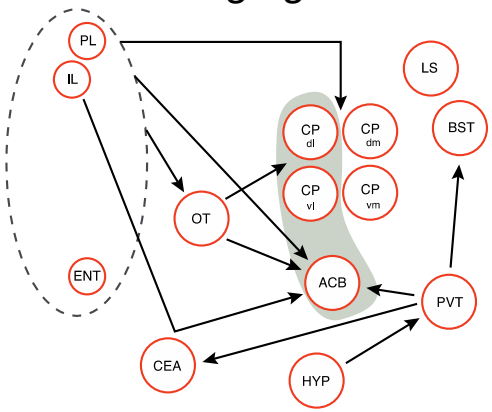
Haloperidol: 0.05



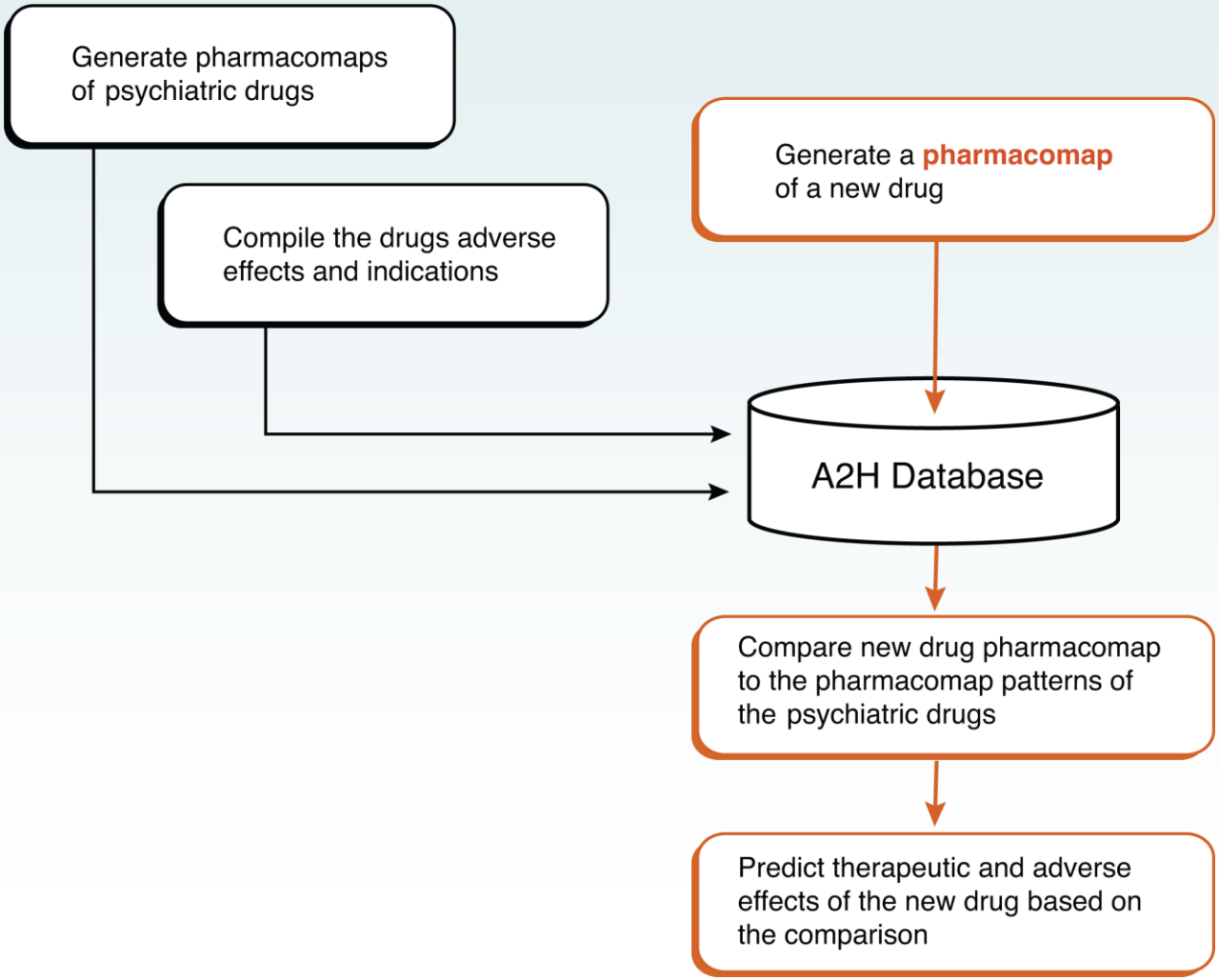
0.25



1.0 mg/kg



Pharmacomap comparisons for predictive validity



Fast-track SBIR grant

Title: Improving animal-to-human predictability in clinical trials for mental disorders

proposal to generate pharmacomaps for 61 mental health medication (each at 3 doses)

year 1: $350K (start January 2013)

year 2-4: $600K per year

total: $2.15mn

Business Plan

1. Contract Research Organization:

    - providing an improved predictability between preclinical animal data and outcome of clinical trials

2. Drug Discovery

    - partnership with medicinal chemistry company

Patent application “A Drug Screening Method and Uses Thereof” (No.: 61/558,877; Jones Day, New York, NY)

- a method of predicting the therapeutic effect or toxicity effect of a test compound
  - a database of template pharmacomaps
  - methods to correlate template pharmacomaps and human clinical effects and side-effects
  - methods to predict human clinical effects and side-effects based on template and test pharmacomaps
  - a database of abnormal brain activity maps in genetic and other mouse models of human brain disorders
  - methods to identify treatments based on correcting abnormal brain activity maps in genetic mouse models

Current projects based on small scale pharmacomap comparisons

Otsuka:
Aripiprazole (Abilify) vs. Brexpiprazole comparison

Abilify 2011 US revenue = $2.76bn

Roche:
RO5510629 - identified as an antipsychotic drug by behavioral screening (SmartCube®; Psychogenics, Inc.)

Lilly UK:
2 compounds - LSN, SKF

(total revenue about $600K)

Options

1. Slow growth - revenue ~$1mn / per machine
   - risk of letting others to compete

1. Rapid growth - gain large share of drug screening market for CNS and other drugs

1. Exit - sale to large pharma (or CRO)

1. Drug discovery - begin to screen own drugs and license compounds

People

Founders	Pavel Osten, CSHL
	Sebastian Seung, MIT
CSO	Lolahon Kadiri
Lab technician	Michael Castelli
Comp. scientist	Kannan Umadevi Venkataraju
Comp. intern	Cheng Qian, SUNY SBU

Consultants

Kathleen Rockland, MIT, CSHL (neuroanatomy)

Kith Pradhan, CSHL (statistics)