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
Compound #1

Social interaction

Exploration
Compound #1

Social interaction

Exploration

Compound #1
Brain activity patterns

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

Brain circuit-level data interpretation
Mouse brain “pharmacomaps” of 3 antipsychotics

- **Haloperidol**: 0.05
- **Risperidone**: 0.25
- **Aripiprazole (Abilify)**: 1.0 mg/kg
Pharmacomap comparisons for predictive validity

Generate pharmacomaps of psychiatric drugs

Compile the drugs adverse effects and indications

Generate a pharmacomap of a new drug

A2H Database

Compare new drug pharmacomap to the pharmacomap patterns of the psychiatric drugs

Predict therapeutic and adverse effects of the new drug based on the comparison
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

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Founders</td>
<td>Pavel Osten</td>
<td>CSHL</td>
</tr>
<tr>
<td></td>
<td>Sebastian Seung</td>
<td>MIT</td>
</tr>
<tr>
<td>CSO</td>
<td>Lolahon Kadiri</td>
<td></td>
</tr>
<tr>
<td>Lab technician</td>
<td>Michael Castelli</td>
<td></td>
</tr>
<tr>
<td>Comp. scientist</td>
<td>Kannan Umadevi Venkataraju</td>
<td></td>
</tr>
<tr>
<td>Comp. intern</td>
<td>Cheng Qian, SUNY SBU</td>
<td></td>
</tr>
<tr>
<td>Consultants</td>
<td>Kathleen Rockland, MIT, CSHL (neuroanatomy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kith Pradhan, CSHL (statistics)</td>
<td></td>
</tr>
</tbody>
</table>