NEUROTRANSLATIONAL DRUG DISCOVERY PROGRAM

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BSi NeuroTranslational Drug Discovery Program

- How We Got Started
- Our Mission
- Our Staff and Capabilities
- First 20 Months at JHU
- Future Plans
HOW did the Johns Hopkins NeuroTranslational Drug Discovery Program get started?
In 2006, Jack Griffin published “Research in neurological diseases: Lost in translation?”

Nature Clinical Practice Neurology (2006) 2, 59

- Pharma increasingly reluctant to invest in early stage projects, especially in risky areas such as CNS
- Biotech sector is struggling with limited capitalization
- Academia has tried to conduct Translational Research but has suffered from:
  - Lack of integrated staff and facilities dedicated to drug discovery
  - Lack of a drug discovery expertise
  - Lack of team focus
In 2007, JHU Initiated the Brain Science Institute (BSi) with Jack Griffin as Director

- BSi started with a philanthropic gift of >$100M from an anonymous donor

- Mission of BSi
  - Solve fundamental questions about brain development and function and to use these insights to understand the mechanisms of brain disease
  - *Aide in the translation of these basic science discoveries into small molecule therapeutics*
In 2010, BSi Initiated NeuroTranslational Drug Discovery Program

- Integrated staff with industry-experience
  - Medicinal Chemistry
  - Assay Development
  - Animal Pharmacology/Tox
  - Drug Metabolism / Pharmacokinetics
  - Business Development

- Working collaboratively with ~450 JHU brain scientists to translate discoveries into small molecule therapeutics

- Goal is to ultimately partner technologies with PHARMA or spin-out new ventures
Who are the staff?
What are their capabilities?
BSi NeuroTranslational Drug Discovery
Scientific Staff
under leadership of BSi Director Jeffery Rothstein, MD, PhD

- Barbara Slusher, Director
- Angie Rubin, Administrator
- Camilo Rojas, Assay Devel
- Takashi Tsukamoto, Med Chemistry
- Krystyna Wozniak, Pharm/Tox
- *Michelle Rudek, Drug Metabolism And PK CORE
- Aditya Polsani, Business Dev

25 STAFF: 14 staff scientists; 9 post docs/student interns, administrator, bus dev and licensing associate

Plan to grow an additional 50% in 2012-13
NeuroTranslational Drug Discovery

Staff

Capabilities

- **Medicinal Chemistry**
  Design, synthesis, purification, characterization, and scale-up of small molecules
  HPLC, Mass Spec, NMR

- **Biochemistry / Assay Development**
  High throughput screening assay development
  Receptor pharmacology, Enzyme kinetics and mechanisms, Cell culture

- **Drug Metabolism and Pharmacokinetics**
  Bioananalysis
  Microsomal stability, Protein binding, Caco2, CYP screening, Rodent PK

- **Animal Pharmacology/Toxicology**
  Preclinical rodent toxicology
  Animal models of peripheral neuropathy, schizophrenia, neuropathic pain, multiple sclerosis

- **Business Development and Licensing**
  Alliance management with PHARMA/Biotech, Investors
  Liaison between Research Administration, Technology Transfer, and General Counsel
Our First 20 Months at JHU
First 20 Months at JHU

1. Built collaboration network at JHU
2. Initiated drug discovery projects
3. Sustained our funding
4. Started training and education courses
5. Partnered our programs
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Built Awareness of Druggable Targets at Johns Hopkins

- Held individual meetings with 97 faculty interested in brain sciences

- **School of Medicine, Public Health, Homewood, KKI**
  Anesthesiology, Biology, Comparative Medicine, Neurology, Neurosurgery, Neuroscience, Ophthalmology, Psychiatry, Medicine, Mind Brain Institute, Pharmacology, Oncology, Immunology, Radiology

- **Purpose**
  Become aware of possible drug discovery projects on campus
  Assemble a database of faculty research to be used with PHARMA interested in collaborations with JHU
Initiated Twenty Collaborations

- Synthesizing “tool compounds”
  - Pin-1 inhibitor (P Worley); Wyeth BACE inhibitor (J Griffin); Rapamycin derivative (G Ming); Sutent analogs (D Zack); MrgX agonists and antagonist (X Dong); curcumin derivatives (T Dawson); lactosylceramide synthase inhibitor (S Chatterjee); mGIR1 PAM (R Huganir); GLS1 inhibitor (C Dang; G Riggins); Petidomimetic BACE inhibitors (P Wong); Biotinylated glutaminase inhibitor (C Dang); DMT inhibitor (Sumner); 4-Hydroxytamoxifen (Caterina)

- Conducting drug metabolism and pharmacokinetics studies
  - Ethoxyquin (A Hoke)
  - RR-DPT (A Sawa)
  - Cyclo GRGDSP (T Nguyen)
  - NAC / NACA (P Campochiaro)

- Aiding in assay development
  - MCT1 / gliogenesis (J Rothstein)
  - Mechanoreceptors (X Dong)
  - Neurite outgrowth (A Hoke)
  - Retinal ganglion cell survival (D Zack)
  - Glutamate release (J Bressler)
  - MrgX agonist/antagonist (X Dong)
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Established 4 Integrated Drug Discovery Projects

- **D-Amino Acid Oxidase (DAAO) Inhibitors for Schizophrenia**
  Collaboration with Akira Sawa (Psychiatry) and Michaela Gallagher (Psychology)

- **Glutaminase Inhibitors for Cancer and Neurodegeneration**
  Collaboration with Chi Dang (Medicine), Greg Riggins (Neurosurgery), Christine Zink (Comparative Medicine), Peter Calabresi (Neurology), Jeff Rothstein (Neurology), Walter Kauffman (KKI)

- **MrgX1 Ligands for Pain / Pruritis**
  Collaboration with Xinzhong Dong (Neuroscience)

- **GCPII inhibitor for Peripheral Neuropathy**
  Collaboration with Mohamed Farah (Neurology), Adam Kaplin (Psychiatry)
Initiated 3 Exploratory Drug Discovery Projects

- **System Xct- Inhibitors for Brain cancer**
  Collaboration with Dr. Greg Riggins (Neurosurgery)

- **MCT inhibitors/activators for Cancer/Neurodegeneration**
  Collaboration with Jeff Rothstein (Neurology)

- **Protein Kinase inhibition for Retinal Disorders**
  Collaboration with Dr. Don Zack (Ophthalmology)
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Sustaining Funding

Submitted 22 grant applications
13 AWARDED: ~$4M

1. R01 Development of DAAO inhibitors for Schizophrenia
2. Eisai Development of Biomarkers to Support GCPII Clinical Studies
3. R21 Design of Novel Glutaminase Inhibitors for Brain Cancer
4. NeuroAIDS grant Characterization of glutaminase in SIV model
5. R03 High throughput Assay to identify novel glutaminase inhibitors
6. MJ Fox Foundation, LRRK ligands for neuroimaging (C Ross/D Wong)
7. Eisai, Direct comparison of the neuropathy inducing effects of eribulin vs paclitaxel, ixabepilone
8. Eisai, Evaluation of Eribulin in animals with a pre-existing neuropathy
9. Helsinn HealthCare, Pharmacological interaction between 5HT3/NK1 receptors
10. MD biotechnology grant, Synthesis and characterization of Neuronascent’s NNI-351 for Down Syndrome
11. Helsinn Healthcare, Netupitant receptor pharmacology
13. R01 supplemental grant, Development of a HTS assay for MCT1
# Sustaining Funding

9 UNDER REVIEW: ~$3.8M

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<tbody>
<tr>
<td>1.</td>
<td>R01 Design of GCPII Inhibitors for Chemotherapy-induced Neuropathy</td>
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<td>2.</td>
<td>R21 GCPII inhibition to Enhance Cognition in Multiple Sclerosis</td>
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<td>3.</td>
<td>ACS postdoctoral training grant</td>
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<td>4.</td>
<td>R21 Assay development for small molecule system xCT- inhibitors</td>
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<td>5.</td>
<td>U01 in collaboration with Justin MacArthur/Dan Hanly, Clinical Coordinating Center for the Network of Excellence in Neuroscience Clinical Trials (NEXT - CCC)</td>
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<td>6.</td>
<td>U01 in collaboration with Don Zack, Development of novel Sutent analogs for retinal disorders</td>
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<td>7.</td>
<td>BSi grant in collaboration with D Wong, Development of CB1 imaging agents for pain</td>
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<td>8.</td>
<td>R25 Neurotherapeutics Drug Discovery Course to taught throughout US submitted in collaboration with Harvard, Norhtwestern, UCSD</td>
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<td>9.</td>
<td>Miles for Hope, High throughput Screening for novel System xCT- for brain cancer</td>
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4. **Started training and education courses**
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Contributing to JHU’s Educational Mission by Teaching/Training Drug Discovery

- Drug Discovery Course for graduate students
- Drug Discovery & Development Workshop for post doc fellows
- NeuroTranslational conference co-organized with Carey Business School
- Initiated Entrepreneurs' “Boot Camp” and “Vine-and-Venture” seminar series on the Biotech start-up
- Drug Discovery Training program: post docs, undergrad, HS students
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Hosted Number of Companies/Investors to Explore R&D Partnerships

- Abbott
- Lundbeck
- Merck
- GSK
- Eisai
- Johnson & Johnson
- Biogen Idec
- Druid BioVentures
- Helsinn Healthcare
- Red Abbey
- HIG Ventures
- NEA

**Biogen Idec:**
- Master R&D Collaboration
- Funded 6 research projects
- Joint Steering Committee

**Johnson & Johnson:**
- Master R&D / License Collaboration
- Translational Fellows
- Fund research re: novel diseases biology/targets
- Joint Steering Committee
- Evaluating multiple projects currently
Eisai Enters Licensing Agreement on GCPII Inhibitors With Johns Hopkins Brain Science Institute

**STATUS**

- Active GCPII drug discovery efforts at JHU
- Joint Eisai / JHU steering committee
- Identify clinical candidate compound to license to Eisai for clinical development
Spun Out a New Company to Develop Second Drug Discovery Program

Press Release  May 24, 2011  09:00 ET
Cerecor, Inc
Appoints Management Team and Board of Directors; Plans for a $30 Million Series

STATUS

- Co-founded by Sol Snyder, Barb Slusher, Isaac Blech, Blake Paterson
- Cerecor licensing proprietary DAAO inhibitors from BSi for clinical development
Future Activities
Submitted an R25 to teach a National NeuroTranslational Course with 3 Other Academic Centers

- Collaboration with UC Davis, Harvard, Northwestern, Johns Hopkins

- “Training in NeuroTherapeutics Discovery and Development for Academic Scientists”

- Drug Discovery Short Course to be taught over 5 years
  - Didactic lectures
  - Personal drug discovery project support
  - 2-yr mentoring
  - Pharma internship
JHU-Eisai High Throughput Screening Agreement

- JHU identifies new brain targets and develops screening assays

- Eisai screens their internal drug library collection and share “hits” with JHU

- JHU conducts medicinal chemistry/drug discovery and identify new clinical candidate compounds

- Eisai licenses the clinical candidates and provide JHU with milestone payments and royalties

- True “WIN-WIN”
  - JHU: access to a large diverse library
  - Eisai: access to novel targets

PHARMA – ACADEMIA partnerships
SUMMARY

- Established a CNS-focused Drug Discovery Program with industry seasoned staff
- Initiated a large number of collaborations with JHU faculty
- Supplemented our philanthropic funding with Pharma, NIH, Disease Foundations grants
- Established new drug discovery courses/training on campus
- Partnered one program with PHARMA and spun out another program into a new company