How to do Translational Neurology and Drug Discovery in Academia?

Barbara Slusher, PhD, MAS
Professor, Neurology, Psychiatry, and Neuroscience
Director, Johns Hopkins Drug Discovery

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Topics to Cover

- What it takes to discover and develop a new drug? *Quiz*

- Changing Ecosystem of Drug Discovery
  what has changed?

- What’s unique about doing drug discovery in academia?

- Example of an academic drug discovery center and an academic/Pharma collaborative project
Drug Discovery and Development

**QUIZ**

- Average **TIME** from discovery to market new drug?
- Average **COST** to discover and market new drug?
- Average **SUCCESS RATE**?

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**Drug Discovery and Development**

- Average **TIME** from discovery to market new drug?
  - **15-20 YEARS**
- Average **COST** to discover and market new drug?
  - **$1-2 BILLION**
- Average **SUCCESS RATE**?
  - **< 2%**
Costs are $264 M per drug approved

<table>
<thead>
<tr>
<th>Phase of Discovery/Development</th>
<th>Average cost ($ M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target to Drug Screening Hit</td>
<td>1</td>
</tr>
<tr>
<td>Screening Hit to Lead</td>
<td>2.5</td>
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<tr>
<td>Lead to Clinical Candidate</td>
<td>10</td>
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<tr>
<td>Candidate to IND filing</td>
<td>5</td>
</tr>
<tr>
<td>Phase 1</td>
<td>15</td>
</tr>
<tr>
<td>Phase 2</td>
<td>40</td>
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<tr>
<td>Phase 3</td>
<td>150</td>
</tr>
<tr>
<td>NDA filing / Launch</td>
<td>40</td>
</tr>
<tr>
<td>Market</td>
<td>264</td>
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But not all projects succeed and there is a cost of attrition

<table>
<thead>
<tr>
<th>Phase</th>
<th>Average cost per project ($ M)</th>
<th>Average success rate</th>
<th># projects per launch</th>
<th>Cumulative cost of phase per launch ($ M)</th>
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<tbody>
<tr>
<td>Target to Hit</td>
<td>1</td>
<td>80%</td>
<td>64</td>
<td>64</td>
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<tr>
<td>Hit to Lead</td>
<td>2.5</td>
<td>75%</td>
<td>51</td>
<td>129</td>
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<tr>
<td>Lead to Candidate</td>
<td>10</td>
<td>85%</td>
<td>39</td>
<td>386</td>
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<tr>
<td>Candidate to IND</td>
<td>5</td>
<td>69%</td>
<td>33</td>
<td>164</td>
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<tr>
<td>Phase 1</td>
<td>15</td>
<td>54%</td>
<td>23</td>
<td>339</td>
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<tr>
<td>Phase 2</td>
<td>40</td>
<td>18%*</td>
<td>12</td>
<td>488</td>
</tr>
<tr>
<td>Phase 3</td>
<td>150</td>
<td>50%*</td>
<td>2.2</td>
<td>330</td>
</tr>
<tr>
<td>NDA / Launch</td>
<td>40</td>
<td>91%</td>
<td>1.1</td>
<td>44</td>
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<tr>
<td>Market</td>
<td>264</td>
<td></td>
<td>1</td>
<td><strong>$1,943</strong></td>
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</table>

Data from Nat. Rev. Drug Discovery 9, 203 (2010)
*Updated for Phase 2 and 3 from J. Arrowsmith at Nat. Rev. Drug Discovery (2011)
**What takes so long?**

Drug Discovery

![Diagram showing the stages of drug discovery and development](image)

**Drug Development**

- **Drug Discovery**
  - Preclinical
    - 100's compounds
    - 3 - 6 years
  - Clinical Trials
    - Phase 1
      - 20-100
      - 6 - 7 years
    - Phase 2
      - 100-500
      - 6 - 7 years
    - Phase 3
      - 1,000-5,000
      - 6 - 7 years
- FDA Review
  - 0.5 - 2 years
- Large-scale MFG
  - ONF FDA
  - Approved Drug

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**Why do we fail so often?**

Lessons learned from the fate of AstraZeneca’s drug pipeline

*Nature Reviews Drug Discovery Vol 13 pg 419, June 2014*

**Pfizer**: “in the majority of efficacy failures, it was not possible to conclude if the mechanism had been adequately engaged”. More PK/PD, exposure, PET, biomarkers, functional pharmacology needed

*Drug Discovery Today Vol 17, No9/10 May 2012*
What does it mean for you?

Cost of making the drug
Cost to discover and develop the drug
Cost to discover and develop the failed drugs

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  what has changed?

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- Example of an academic drug discovery center and an academic/Pharma collaborative project
Pharma: Business Model Under Challenge

Approved drugs per $1B spent is 50-fold worse than 30 yrs ago

- $130B of patented sales to face generics by 2016 (57% of 2010 US sales)
- >50K jobs lost / reduced internal research efforts

Pharma: Dramatic decline in number of CNS programs past 5 years

<table>
<thead>
<tr>
<th>CNS Programs in Pharma</th>
<th>2009 vs 2014</th>
<th></th>
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<tbody>
<tr>
<td>Abbott/AbbVie</td>
<td>17 ➔ 10</td>
<td></td>
<td></td>
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<tr>
<td>AstraZeneca</td>
<td>21 ➔ 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>12 ➔ 2</td>
<td></td>
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<tr>
<td>Glaxo SmithKline</td>
<td>40 ➔ 14</td>
<td></td>
<td></td>
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<tr>
<td>Johnson &amp; Johnson</td>
<td>18 ➔ 17</td>
<td></td>
<td></td>
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<tr>
<td>Lilly</td>
<td>16 ➔ 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Merck/Schering-Plough</td>
<td>32 ➔ 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novartis</td>
<td>14 ➔ 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfizer/Wyeth</td>
<td>46 ➔ 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roche/Genentech</td>
<td>22 ➔ 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanofi/Genzyme</td>
<td>29 ➔ 12</td>
<td></td>
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</table>

Choi et al., Neuron 84:554–563 (Nov. 5, 2014)

Includes discovery, preclinical, and clinical drug development programs
Pharma: Rise of Open Innovation

Closed Innovation
20th century
Secretive, intramural

Open Innovation
21st century
Porous, world is our lab

NIH: increasing efforts in drug discovery and translation

- NIH Roadmap; Translational Research
  - Clinical and Translational Science Awards (CTSA)
  - Molecular Libraries Program
  - Rapid Access to Interventional Development (RAID)
  - Cures Acceleration Network (CAN)

- National Center for Advancing Translational Sciences (NCATS)
  - Catalyze public-private translational research
  - Repurposing Drugs
  - Rare Disease Therapeutics
  - Re-engineering Translational Sciences

- Although NIH 2014 budget is flat, NCATS increased by 14%

"Initiatives designed to transform the Nation’s medical research capabilities and improve the translation of research into practice"
**Acadia: Drug Discovery Centers in 1990**

*Approx. 6 centers; Based upon Academic Drug Discovery Consortium (ADDC) Membership*

**Acadia: Drug Discovery Centers in 2002**

*Approx. 17 centers; Based upon Academic Drug Discovery Consortium (ADDC) Membership*
Acadia: Drug Discovery Centers in 2014

*Approx. 100 centers; Based upon Academic Drug Discovery Consortium (ADDC) Membership, Molecular Libraries Program, and CTSA catalog

Academic-Industrial Partnerships On the Rise
Not just 1:1 Partnerships
broad alliances, new programs

- **Pfizer** (Johnson & Johnson) embedding into academic space
  - State-of-the-art laboratories and incubators in Boston, CA, NY, Texas

- **MERCK** - to bring academic ideas to pre-clinical proof of concept
  - $90 million; led by P Schultz; close to UCSD, Scripps, Salk Institute

- Abbott, BMS, GSK, Janssen, Sanofi, Pfizer, AstraZeneca, and Lilly
  - made 58 of their abandoned clinical compounds available to academics through NCATS
  - Discovering New Therapeutic Uses for Existing Molecules Pilot Program

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Survey Results: Academia and Pharma have distinct strengths

Survey of 78 US drug discovery centers


Academic Drug Discovery

ADVANTAGES

- **Academia has long-term focus**
  Unparalleled depth of knowledge on specific diseases/targets

- **Climate of creativity / innovation**
  Could lead to diversified drug discovery approaches

- **Less time/market pressures**
  Freedom to tackle complex, risky problems, orphan and 3rd world diseases

- **Enhanced clinical interactions**
  Many team members are physician-scientists who treat patients in field of interest

- **Access to new biology, tools, animal models**

CHALLENGES

- **Funding**
  Reliance on grants with long cycle times, philanthropy, partnerships

- **Reward System**
  Independent scientist, not team orientation
  Hypothesis-driven research, not product development
  Timely publications which can compromise patent strategy

- **Chemical libraries**
  Less diverse and proprietary

- **Unrealistic expectations/lack of expertise**
### Academic Drug Discovery

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### Topics to Cover

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- **Changing Ecosystem of Drug Discovery**
  - What has changed?
- **What’s unique about doing drug discovery in academia?**
- **Example of an academic drug discovery center and collaborative project with Pharma**
**Johns Hopkins’ Brain Science Institute (BSi)**

Started from a philanthropic pledge $100M from an anonymous donor

**Mission of BSi**
- Solve fundamental **BASIC SCIENCE** questions about brain development/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

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**Drug discovery team from Pharma moved to Brain Science Institute in 2010**

- MGI Pharma (Baltimore) acquired for $3.8B by Eisai
- Team of drug discovery scientists left Eisai and joined Bsi
  - Medicinal Chemists, Drug Metabolism, Pharmacokinetics, Assay Developers, Screening, Animal Pharmacology, Toxicology

**NEW JOB:** Work collaboratively with faculty to translate Hopkins’ brain discoveries into clinical therapeutics
Drug Discovery Capabilities

- ~20 STAFF
- Average of 15 years PHARMA experience drug discovery

Johns Hopkins Drug Discovery

first 5 years….

- Support translational activities on campus
- Training and education
- Commercialization
- Secured external funding
- Founded Academic Drug Discovery Consortium
- Collaborative drug discovery
Provided translational services to >90 faculty (2010-2014)

- 39 Support Letters for Translational Grants (~$30M)
- 48 Tool Compounds Synthesized
- 31 Drug Metabolism and Pharmacokinetic Studies Conducted
- 41 Aided with Assay Development

Contribute to educational mission

- 2 New JH Graduate Courses in Drug Discovery
  Basics of Drug Discovery
  Case Studies in Drug Discovery

- Post Doctoral
  Drug Discovery Workshop
  Drug Discovery & Development / Pharma R&D

- 3 Drug Discovery Conferences
  NeuroTranslational Conference
  World Health Summit with Carey Business School
  Drug Discovery in Academia

- 5-yr NIH Drug Development Course
Obtained external funding and executed Pharma collaborations

- Applied for 49 drug discovery grants/contracts
- 32 awarded totaling >$14M ($10 direct; $4M indirect)

Multiple sources of funding

- NIH
- Disease Foundations
- Pharma

Collaborative with faculty

- Internal BSI
- In Collaboration with JHU Faculty

Founded New Baltimore Company

- Co-founded by JHU faculty Sol Snyder/Barb Slusher
- Sol Bauer (Celgene) Chairman of the Board
- Raised $65M in financing
Founded an international consortium

- Drug Discovery Education
- Foster Academia/Pharma partnerships
- Enhance collaboration between university drug discovery centers
- Advocacy to NCATs

In first 2 years, >115 academic centers and 1200 members joined the consortium

ADDC in the News...

Universities Stepping Up Efforts To Discover Drugs

Bringing together the academic drug discovery community

The newly formed Academic Drug Discovery Consortium (ADDC) aims to support the growing number of university centers engaged in drug discovery that have emerged in response to recent changes in the drug discovery ecosystem.
5 collaborative drug discovery programs

*SCHIZOPHRENIA

D-Amino Acid Oxidase (DAAO) Inhibitors
Drs. Sowa

INFLAMMATORY BOWEL DISEASE

GCPII inhibitors
Drs. Weinberger, Li, Kaplin, Rahn

* PAIN / ITCH

MrgX1 Agonist/ Antagonists
Drs. Xinzhong Dong and Yun Guan

* CANCER / IMMUNOLOGY

Glutaminase Inhibitors / Glutamine Analogs
Drs. Le, Hanes, Powell, Raabe, Zink, Griffin, Raabe

* BRAIN CANCER / EPILEPSY

System xc− Inhibitors
Drs. Riggins, Calabresi, Powell

Academic/Pharma Collaborative Drug Discovery

System xc− Inhibitor Project
**System \( x_c^- \) cystine/glutamate antiporter (SLC7A11)**

- Cellular uptake of cystine to maintain glutathione
- Non-vesicular glutamate release

Constitutive expression in CNS (astrocytes, microglia, immature cortical neurons) and immune cells (macrophages, thymus, spleen)

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**System \( x_c^- \) is Upregulated in Disease**

**CANCER CELLS**

- **Brain Cancer**
  - J Neurosci 1999, 19, 10767
  - Cancer Res 1999 59: 4383-4391
  - J Neurosci 2005, 25 (31), 7101-7110
  - Nat Med 2008, 14, 629
  - J Cell Physiol 2008 215:593-602
  - J Neurochem 2008 105(2):287
  - J Neurochem 2009 110(1) 182-193
  - Ann Anat 2010, 192, 309
  - Amino Acids 2011, 42(1) 231-246
  - Nat Med 2011, 17, 1195–119
  - Neurosurgery 2013 72(1) 33-41
  - Cell Death and Disease 2015 6

- **Other cancers**
  - Triple negative breast cancer
    - Cancer Cell 2013 14:24(4):450-65
  - Hepatocellular carcinoma
    - Oncol Rep 2013 29(2) 68509

**CNS**

- **NeuroAIDs**
  - Invest Ophthalm Vis Sci 2004 45(9) 3906;
  - Neurosci Lett 2010, 485, 233

- **Multiple Sclerosis**
  - J. Neuroinflammation 2011, 8, 63

- **ALS**
  - Brain. 2015 Jan;138(Pt 1):53-68

- **Alzheimer’s Disease**
  - J. Neurosci. 2006, 26, 3345

- **Parkinson’s Disease**
  - FASEB J, 2011, 25, 1359

- **Epilepsy**
  - Antioxid Redox Signal 2014 20:2907-22
GLIOMA

upregulated system $x_c$; down regulated Glu transport

RESULT

$\text{GLU release} \downarrow \text{GLU uptake} = \text{HIGH EXTRACELLULAR GLUTAMATE}$

- SEIZURES
- EXCITOOTOXIC DEATH TO SURROUNDING TISSUE

System $x_c$- inhibitors decrease tumor volume, block edema, and prolong survival

Survival (%)

$tumor\ volume$ (Sulfasalazine)

$perifocal\ edema$ (S-4CPG)

$survival$ (S-4CPG)

Nat Med 2008, 14, 629; Chung et al, J Neurosci 2005
System $x_c$- siRNA blocks edema, peritumoral neurodegeneration and prolongs survival

Confidential

Nat Med 2008, 14, 629

System $x_c$- inhibitor blocks tumor associated glutamate release and seizures in mice

Glutamate release by primary brain tumors induces epileptic activity

Susan C. Buckingham, Susan L. Campbell, Brian R. Haas, Vedrana Montana, Stefanie Robel, Toyin Ogunrimes & Harald Sontheimer

Nat Med 2014 17, 1269–1274
High system $x_c^-$ expression associated with high glutamate, seizures, and poor prognosis in patients with glioma

Patients with reduced xCT expression live 9 mo. longer. Tumor xCT expression correlates with peritumoral glutamate release

Why has system $x_c^-$ received little attention as a therapeutic target?

1. Blockade of system $x_c^-$ has been thought to deplete cells of glutathione and induce oxidative stress
   - Two different strains of mice lacking system $x_c^-$ were reported to be healthy and fertile, no enhanced oxidative stress
   - Neither siRNAs against system $x_c^-$ nor system $x_c^-$ inhibitors have shown any major side effects

2. No good inhibitors to assess therapeutic utility
No Potent, Selective, Drug like $x_C$ Inhibitors Available

**Sulfasalazine** ($IC_{50}= 30uM$)
Extensively metabolized by azoreductases to sulfapyridine/salicylate
*(Br J Clin Pharmacol 1982, 13, 523)*

**S-4CPG** ($IC_{50}= 15uM$)
Non selective: also group I mGluR
*(J Neurosci 1994, 14, 3370)*

* Presence of carboxylates hinder brain penetration

Our attempts to optimize Sulfasalazine failed

- Increase metabolic stability (diazo to alkyne)
- Carboxylate necessary
- Truncated analogs not potent
- Potency remained poor

DISCONTINUED EFFORT
Our attempts to optimize 4-SCPG failed

- Carboxylate and amine groups essential for activity
- Analogs lost potency

DISCONTINUED EFFORT

Established High Throughput Screening (HTS) assay for $x_C^-$

Fluorescence assay using STTG1 astrocytoma cells

- Assay in 384-well format
- Z’ ~ 0.5 – 0.7 / good reproducibility
  red: controls; green: totals
Executed High Throughput Screening Agreement with Pharma

- JHU shares target and validated HTS assay
- Eisai screens their drug library against JHU targets
- JHU conducts drug discovery on "hit" compounds and develops clinical candidate
- Eisai licenses the clinical candidate for commercialization

"WIN-WIN"

JHU: access to a large diverse drug library

PHARMA: access to novel targets

How Collaborative Drug Discovery works

6mo
- Disclosure of Target
- Selection of Target
- HTS assay development/optimization

12mo
- HTS of Eisai-library compounds
- HTS-hits confirmation/2nd screening

6mo
- HTS hit

12-24 mo
- JHU-led Research
- Collabo Research

Lead Series

12-24 mo
- Candidate Selection
Lead series xCT inhibitors recently identified

Orally available / brain penetrable

Exploring therapeutic utility

Epilepsy – NINDS ASP / Dr Kehne
Glioma – Dr. Riggins
NeuroAIDS – Dr. Volsky
Multiple Sclerosis – Dr. Rahn/Calabresi
Neuroinflammation – Dr. Rojas

Summary

✓ What it takes to discover and develop a new drug?
  costly, long timelines, risky, multi-disciplinary (team sport)

✓ Changing Ecosystem of Drug Discovery
  • Pharma under challenge; decreased internal discovery; open innovation
  • Academia/NIH are increasing efforts in drug translation
  • Academic-Industry partnerships on the rise

✓ What's unique about academic drug discovery?
  longer term focus, less market pressures, more innovation/creativity/flexibility,
  clinical interaction, newer biology models

✓ Example of an academic drug discovery center and project
  Hopkins Bsi Drug Discovery / xCT collaborative relationship with JHU/Eisai