Drug Discovery & Development

Neal G. Simon, Ph.D.
Professor
Dept of Biological Sciences
Lehigh University

September 27, 2019
CNS Disorders

- More than 1 billion people worldwide suffer from diseases of the central nervous system (CNS).

- One in five Americans currently takes at least one psychiatric drug and mental disorders are recognized worldwide.

- In the United States and European Union, the economic burden of CNS diseases—including direct medical costs, direct nonmedical costs, and costs of informal (family) care—is estimated at more than $2 trillion, a number expected to triple to $6 trillion by 2030.
Serendipity or Good Science: Building Opportunity

Hoffman

Osterloh
Mood Disorders: Medial Prefrontal Network & Amygdala

Price & Drevets (2010)
Outline

I. Time & Risk

II. The R&D Landscape: Cost

III. Innovation and Transformation

IV. Designing Drug Development Trials: Alzheimer’s Disease
1. Time and Risk
Drug Development Process: The Path to New Medicines

Figure 2: The Drug & Therapy Development Pipeline

- **Basic Research**
  - Funding: Largely Public
  - Example: NIH, DoD
  - Variable

- **Translational Research**
  - Funding: Mix of Government & Private
  - Underfunded Area
  - 1-6 years

- **Clinical Development**
  - Funding: Largely Industry & For-Profit
  - FDA Oversight
  - 5-10 years

- **FDA Review & Approval**
  - 1-2 years

**Clinical Trials**
- Phase 1
- Phase 2
- Phase 3

Source: Parkinson's Action Network
Biopharmaceutical Drug Development: Attrition

Drug Discovery
- 10,000 Compounds
- 5 years

Pre-Clinical
- 250 Compounds
- 1.5 years

Clinical Trials
- 5 Compounds
- 6 years
  - Phase I: 20-100 Volunteers
  - Phase II: 100-500 Volunteers
  - Phase III: 1000-5000 Volunteers

FDA Review
- NDA Submitted
- 2 years

Large Scale Manufacturing/Phase IV
- 1 FDA Approved Drug
- 2 years

Approvals from Phase 1 by Disease Area

Likelihood of Approval from Phase I

- Hematology: 26.1%
- Infectious disease: 19.1%
- Ophthalmology: 17.1%
- Other: 16.3%
- Metabolic: 15.3%
- Allergy: 15.1%
- Endocrine: 14.7%
- Respiratory: 13.2%
- Urology: 12.8%
- Autoimmune: 11.4%
- All Indications: 11.1%
- Neurology: 9.6%
- Cardiovascular: 8.4%
- Psychiatry: 6.6%
- Oncology: 6.2%
- Other: 5.1%

Thomas et al (2016) BIO.
II. The Research & Development Landscape
Cost Drivers

- Increased clinical trial complexity
- Larger clinical trial sizes
- Greater focus on targeting chronic and degenerative diseases
- Higher failure rates for drugs tested in earlier phase clinical studies

R&D Cost Model per New Medical Entity

### TABLE 1: Domestic R&D and R&D Abroad,* PhRMA Member Companies: 1980–2018

(dollar figures in millions)

<table>
<thead>
<tr>
<th>Year</th>
<th>Domestic R&amp;D</th>
<th>Annual Percentage Change</th>
<th>R&amp;D Abroad*</th>
<th>Annual Percentage Change</th>
<th>Total R&amp;D</th>
<th>Annual Percentage Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>$62,219.7</td>
<td>11.6%</td>
<td>$17,383.1</td>
<td>11.1%</td>
<td>$79,602.8</td>
<td>11.5%</td>
</tr>
<tr>
<td>2017</td>
<td>$55,755.0</td>
<td>6.4%</td>
<td>$15,644.4</td>
<td>19.2%</td>
<td>$71,399.4</td>
<td>8.9%</td>
</tr>
<tr>
<td>2016</td>
<td>$52,418.2</td>
<td>9.0%</td>
<td>$13,120.1</td>
<td>13.8%</td>
<td>$65,538.3</td>
<td>9.9%</td>
</tr>
<tr>
<td>2015</td>
<td>$48,110.5</td>
<td>18.1%</td>
<td>$11,531.9</td>
<td>-7.9%</td>
<td>$59,642.4</td>
<td>12.0%</td>
</tr>
<tr>
<td>2014</td>
<td>$40,737.3</td>
<td>0.8%</td>
<td>$12,515.9</td>
<td>11.6%</td>
<td>$53,253.2</td>
<td>3.2%</td>
</tr>
<tr>
<td>2013</td>
<td>$40,396.0</td>
<td>7.7%</td>
<td>$11,217.6</td>
<td>-7.1%</td>
<td>$51,613.6</td>
<td>4.1%</td>
</tr>
<tr>
<td>2012</td>
<td>$37,510.2</td>
<td>3.1%</td>
<td>$12,077.4</td>
<td>-1.6%</td>
<td>$49,587.6</td>
<td>1.9%</td>
</tr>
<tr>
<td>2011</td>
<td>$36,373.6</td>
<td>-10.6%</td>
<td>$12,271.4</td>
<td>22.4%</td>
<td>$48,645.0</td>
<td>-4.1%</td>
</tr>
<tr>
<td>2010</td>
<td>$40,688.1</td>
<td>15.1%</td>
<td>$10,021.7</td>
<td>-9.6%</td>
<td>$50,709.8</td>
<td>9.2%</td>
</tr>
<tr>
<td>2009</td>
<td>$35,356.0</td>
<td>-0.6%</td>
<td>$11,085.6</td>
<td>-6.1%</td>
<td>$46,441.6</td>
<td>-2.0%</td>
</tr>
</tbody>
</table>

* R&D Abroad includes expenditures outside the United States by U.S.-owned PhRMA member companies, and R&D conducted abroad by the U.S. divisions of foreign-owned PhRMA member companies. R&D performed abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded. Domestic R&D, however, includes R&D expenditures within the United States by all PhRMA member member companies.
Private & Public R&D Spending: Is There a Partnership

- National Institutes of Health: $33 billion
- PhRMA Member Companies: $79 billion
U.S. FDA drug approvals

NUMBER OF APPROVALS

Source: U.S. Food and Drug Administration
III. Innovation and Transformation
Innovation and Transformation Models

Hu et al (2007)
Schumaker et al, 2016

Challenges:
- Higher burden for approval and reimbursement of NMEs
- Complex research for new drug targets
- Poorly predictive animal models
- Complexity of clinical trials
- Lower risk tolerance of regulators and society
- Licensing, co-development, or joint venture negotiations
- Strategic changes
- Commercials demands
- Decreasing number of research-based pharmaceutical companies

Results:

- High capitalized costs for R&D
- Low NME output
- Reduced R&D efficiency of research-based pharmaceutical companies

Consequences:
- Create growth options by M&As
- Reduce R&D costs by cost-efficient outsourcing
- Widen the competence field by collaborating with universities and biotechnology/pharmaceutical companies
- Increase the technology base by licensing drug candidates in all phases of R&D
- Strengthen the innovation potential by venture capital investments
- Broaden the knowledge base by using the crowd
<table>
<thead>
<tr>
<th>Year</th>
<th>Drug Name</th>
<th>Brand Names</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>Fluvoxamine</td>
<td>(Luvox; Solvay)</td>
<td>SSRI</td>
</tr>
<tr>
<td>1987</td>
<td>Fluoxetine</td>
<td>(Prozac; Lilly)</td>
<td>SSRI</td>
</tr>
<tr>
<td>1992</td>
<td>Sertraline</td>
<td>(Zoloft; Pfizer)</td>
<td>SSRI/NRI</td>
</tr>
<tr>
<td>1993</td>
<td>Venlafaxine</td>
<td>(Effexor; Wyeth)</td>
<td>SSRI/NRI</td>
</tr>
<tr>
<td>1996</td>
<td>Bupropion</td>
<td>(Wellbutrin; Wyeth)</td>
<td>SNRI/DRI</td>
</tr>
<tr>
<td>2002</td>
<td>Escitalopram</td>
<td>(Lexapro; Forrest)</td>
<td>SSRI</td>
</tr>
<tr>
<td>2004</td>
<td>Duloxetine</td>
<td>(Cymbalta; Lilly)</td>
<td>SSRI/NRI</td>
</tr>
<tr>
<td>2008</td>
<td>Devenlafaxine</td>
<td>(Pristiq; Wyeth/Pfizer)</td>
<td>SNRI</td>
</tr>
<tr>
<td>2011</td>
<td>Vilazidone</td>
<td>(Vybrid; Forest Labs)</td>
<td>SSRI/5HT1a</td>
</tr>
</tbody>
</table>
IV. Designing Drug Development Trials: Alzheimer’s Disease
Alzheimer’s Disease

- An estimated 5.7 million Americans have Alzheimer's Disease
- 6th leading cause of death in the United States
- $232 billion: the direct costs of care in the United States in 2017
- In 2050: 14 million people will have AD
- In 2050: $1.1 trillion in direct costs (2018 dollars)

Desperate need for Treatment
Alzheimer’s Disease: Symptoms

- Memory loss that disrupts daily life
- Challenges in planning or problem solving
- Difficulty completing familiar tasks
- Confusion with time or place
- Trouble with visual images and spatial relationships
- New problems with words when speaking or writing
- Mood and personality changes
The Alzheimer’s Brain: Gross Anatomical Changes

- The cortex shrivels up, damaging areas involved in thinking, planning and remembering.

- Shrinkage is especially severe in the hippocampus, an area of the cortex that plays a key role in formation of new memories.

- Ventricles (fluid-filled spaces within the brain) grow larger.

[Image of healthy brain vs. advanced Alzheimer's brain with highlighted areas of brain changes]

alz.org / braintour
The Alzheimer’s Brain: Microscopic Changes

- Alzheimer’s tissue has many fewer nerve cells and synapses than a healthy brain.

- PLAQUES, abnormal clusters of protein fragments, build up between nerve cells.

- Dead and dying nerve cells contain TANGLES, which are made up of twisted strands of another protein.
146 Total Unsuccessful Drugs | 4 Total Approved Medicines
Bateman et al (2012)  
Clinical and Biomarker Changes in Dominantly Inherited Alzheimer’s Disease

- Autosomal dominant AD
- 128 patients
- Baseline clinical and cognitive assessments, brain imaging, and cerebrospinal fluid (CSF) and blood tests
- Participant’s age at baseline assessment and the parent’s age at the onset of symptoms of Alzheimer’s disease to calculate the estimated years from expected symptom onset
- Autosomal dominant Alzheimer’s disease was associated with a series of pathophysiological changes over decades in CSF biochemical markers of Alzheimer’s disease, brain amyloid deposition, and brain metabolism as well as progressive cognitive impairment

Bateman et al., 2012
Precuneus:

- Episodic memory, visual-spatial abilities, and motor activity coordination strategies. Self perception, consciousness, and the executive and working memory.

- At rest it has the highest metabolic rates, consuming more glucose than any other cortex.

- Part of Default Mode Network.
### PUTATIVE BIOMARKERS I

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated Years from Expected Symptom Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-25</td>
</tr>
<tr>
<td><strong>Aβ deposition in the precuneus (SUVR ratio)</strong> $\dagger\dagger$</td>
<td></td>
</tr>
<tr>
<td>Noncarriers</td>
<td>0.69</td>
</tr>
<tr>
<td>Carriers</td>
<td>0.71</td>
</tr>
<tr>
<td>Difference</td>
<td>0.02±0.28</td>
</tr>
<tr>
<td><strong>Glucose metabolism in the precuneus (SUVR ratio)</strong> $\ddagger\ddagger$</td>
<td></td>
</tr>
<tr>
<td>Noncarriers</td>
<td>2.06</td>
</tr>
<tr>
<td>Carriers</td>
<td>2.16</td>
</tr>
<tr>
<td>Difference</td>
<td>0.10±0.16</td>
</tr>
<tr>
<td><strong>Total hippocampal volume (mm$^3$)</strong></td>
<td></td>
</tr>
<tr>
<td>Noncarriers</td>
<td>8999</td>
</tr>
<tr>
<td>Carriers</td>
<td>8767</td>
</tr>
<tr>
<td>Difference</td>
<td>-232±675</td>
</tr>
</tbody>
</table>

$\dagger\dagger$ Deposition of amyloid-beta (Aβ) in the precuneus was measured by positron-emission tomography (PET) with the use of Pittsburgh compound B (PIB). A higher SUVR indicates greater binding of PIB to fibrillar amyloid.

$\ddagger\ddagger$ Glucose metabolism in the precuneus was measured by PET with the use of fluorodeoxyglucose. A lower SUVR indicates lower metabolism.

$\ddagger$ $P<0.01$  
$\dagger$ $P<0.05$  
$\dagger\dagger$ $P<0.001$
Scores on the CDR-SOB range from 0 (cognitive normality) to 18 (maximal cognitive impairment).‡ P<0.01. § P<0.001. ¶ Scores on the Mini–Mental State Examination (MMSE) range from 0 (severe impairment) to 30 (no impairment). A score higher than 27 is considered normal. Scores on the Logical Memory subtest of the Wechsler Memory Scale–Revised range from 0 (no recall) to 25 (complete recall). ** P<0.05.
Brain scans show evidence of Alzheimer’s disease 20 years before symptoms arise (far left), 10 years before (middle), and after the onset of symptoms (right). Beta amyloid, a protein associated with the disease, is more visible in people who develop the disease (top row) than in those who don’t. The more color in the scan, the more beta amyloid is present in the brain.

Bateman et al (2012)
Serendipity or Good Science: Building Opportunity

Hoffman

Osterloh
Thank you for your time and attention