Translating Science into Innovation in Healthcare

Better Drugs and Vaccine – The existing model

Briggs W. Morrison, M.D.
AstraZeneca
Agenda

- The Existing Model
- The Economics of the Innovative Biopharmaceutical Industry
- The Innovation Challenge
Agenda

- The Existing Model
- The Economics of the Innovative Biopharmaceutical Industry
- The Innovation Challenge
The Existing Model

1. Identifying the Target
2. Inventing the Molecule
3. Characterizing the biologic properties of the molecule
The Existing Model

1. Identifying the Target
2. Inventing the Molecule
   - Most Difficult: Inventing the next important medicine to prevent or treat one or more human diseases
3. Characterizing the biologic properties of the molecule
The Existing Model

1. Identifying the Target

2. Inventing the Molecule
   - **Most Difficult**: Inventing the next important medicine to prevent or treat one or more human diseases

3. Characterizing the biologic properties of the molecule
   - **Second Most Difficult**: Figuring out if you have done #2
## The Existing Model

<table>
<thead>
<tr>
<th>Time</th>
<th>8-15 years</th>
</tr>
</thead>
</table>
| Risk   | - Small molecule – 40+ candidates to get 1 medicine  
|        | - Large molecule – 9+ candidates to get 1 medicine |
| Cost   | - It is expensive –$1B (out of pocket) to develop a single medicine (over $2B in capitalized costs) |
| Volume | - Only 20-30 new medicines are approved annually and only a subset of these are truly innovative |
Characterizing a molecule

**HIV Protease**
Characterizing a molecule

![Pie Chart showing distribution of protein categories.](image)

- Isomerases: 94; 0.5%
- Receptors: 1076; 6.3%
- Storage proteins: 15; 0.1%
- Structural proteins: 280; 1.6%
- Surfactants: 15; 0.1%
- Cell junction proteins: 67; 0.4%
- Chaperones: 130; 0.8%
- Transcription factors: 2067; 12.0%
- Phosphatases: 230; 1.3%
- Membrane traffic proteins: 321; 1.9%
- Transfer/carrier proteins: 248; 1.4%
- Hydrolases: 454; 2.6%
- Defense/immunity proteins: 107; 0.6%
- Calcium-binding proteins: 63; 0.4%
- Viral proteins: 7; 0.0%
- Extracellular matrix proteins: 72; 0.4%
- Proteases: 476; 2.8%
- Cytoskeletal proteins: 441; 2.6%
- Transporters: 1098; 6.4%
- Transmembrane receptor regulatory/adaptor proteins: 84; 0.5%
- Transferases: 1512; 8.8%
- Oxidoreductases: 550; 3.2%
- Lyases: 104; 0.6%
- Cell adhesion molecules: 93; 0.5%
- Ligases: 260; 1.5%
- Nucleic acid binding: 1466; 8.5%
- Signaling molecules: 961; 5.6%
- Enzyme modulators: 857; 5.0%

PANTHER Pie Chart at the PANTHER Classification System homepage. Retrieved May 25, 2011

Briggs W. Morrison, MD / October 27, 2012
Characterizing a molecule

CYP 3A4, 2D6, 2C8, 2C9, 2C19, 1A2, 2E1, 2B6, 2A6.

Pgp, hERG, BCRP, BSEP, OATP1B1, OATB1B3, UGT1A1, UGT2B4, UGT2B7, UGT2B17, OAT1, OAT3

- Toxicology
- Efficacy
- Metabolism
- Carcinogenicity
- Genotoxicity
- Mitochondrial toxicity

Briggs W. Morrison, MD / October 27, 2012
Characterizing a molecule

Antibodies

Growth hormone

Insulin

Briggs W. Morrison, MD / October 27, 2012
Characterizing a molecule

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Regulatory Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictive computer models</td>
<td>Pharmacokinetics</td>
<td>Safety</td>
<td>Safety</td>
<td>Regulatory submissions per country</td>
</tr>
<tr>
<td>Animal models</td>
<td>Pharmacodynamics</td>
<td>Efficacy</td>
<td>Efficacy vs Standard of Care</td>
<td>Regulator interaction</td>
</tr>
<tr>
<td>ADME</td>
<td>Safety</td>
<td>Initial demonstration of benefit in humans</td>
<td>Significant characterization of Benefit:Risk</td>
<td>Labeling</td>
</tr>
<tr>
<td>GLP Toxicology</td>
<td>Efficacy?</td>
<td>Dose refinement</td>
<td>Dose(s) confirmation</td>
<td>Post marketing commitments</td>
</tr>
<tr>
<td>Manufacturing scale-up</td>
<td>1 to 3 years</td>
<td>2a vs 2b</td>
<td>2 to 5 years</td>
<td>1 – 2 years</td>
</tr>
<tr>
<td>Investigational New Drug (IND)</td>
<td>~50% success rate</td>
<td>Active control?</td>
<td>~70% success rate</td>
<td>~ 90% success rate</td>
</tr>
<tr>
<td>6 -13 months</td>
<td></td>
<td>1.5 to 3.5 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Phase 1: 1 to 3 years
- Phase 2: 1.5 to 3.5 years
- Phase 3: 2 to 5 years

~50% success rate

~70% success rate

~90% success rate
Characterizing a molecule

Three Pillars:

1. **Exposure at target site of action**
2. **Binding to pharmacologic target**
3. **Expression of downstream pharmacology**

<table>
<thead>
<tr>
<th>Pillar 1 and 2</th>
<th>Pillar 1, 2, 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total = 12</td>
<td>Total = 14</td>
</tr>
<tr>
<td>• 5 tested mechanism</td>
<td>• All 14 tested mechanism</td>
</tr>
<tr>
<td>• 2 advanced to Phase 3</td>
<td>• 12 achieved POC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>None or Partial Pillars</th>
<th>Pillar 2 and 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 12</td>
<td>Total = 6</td>
</tr>
<tr>
<td>• 12 failed to tested mechanism</td>
<td>• 5 tested mechanism</td>
</tr>
<tr>
<td>• All failed in Phase 2</td>
<td>• No Phase 3 starts</td>
</tr>
</tbody>
</table>

A doctor’s decision

What is the right therapeutic plan for the patient who is sitting before me?

- What are the options?
- What are the benefits and risks of each option?
- Is the available data applicable to my patient?
### Factors Affecting Benefit-Risk

<table>
<thead>
<tr>
<th>Intrinsic</th>
<th>Extrinsic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetics</td>
<td>Exogenous consumables</td>
</tr>
<tr>
<td>● Drug Metabolism</td>
<td>● Food</td>
</tr>
<tr>
<td>● Immune response</td>
<td>● Con meds</td>
</tr>
<tr>
<td>● Disease genetics (eg – tumor)</td>
<td>● Tobacco</td>
</tr>
<tr>
<td>Age</td>
<td>● Alcohol</td>
</tr>
<tr>
<td>Race</td>
<td>● Compliance</td>
</tr>
<tr>
<td>Organ function</td>
<td>● Medical Practice</td>
</tr>
<tr>
<td>Body Mass</td>
<td>● Cultural Practices</td>
</tr>
<tr>
<td></td>
<td>● Disease Definition</td>
</tr>
</tbody>
</table>
Characterizing a molecule

Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization.

Cumulative Kaplan–Meier Estimates of Key Study End Points in Patients under the Age of 75 Years during 30 Months of Follow-up.

Characterizing a molecule

Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy

Kaplan–Meier Estimates of Primary and Secondary End Points in the Intention-to-Treat Population

Agenda

- The Existing Model
- The Economics of the Innovative Biopharmaceutical Industry
- The Innovation Challenge
Success rates and Economics

Cost of success = $3.2BB

Cost of failure = $5.2BB

Economics

Cost of Failure (target to market)

- cost to get 88 molecules (that will fail) to Phase 1 = $1.58 BB
- cost to fail 88 molecules in Phase 1 = $1.32 BB
- Cost to fail 36 molecules in Phase 2 = $1.44 BB
- Cost to fail 5 molecules in Phase 3 = $0.75 BB
- Cost to fail 1 molecule in registration = $40 MM

Total = $5.2 BB

Cost of Success (target to market)

- cost to succeed 12 molecules

Total = $3.2 BB

Cost per New Drug

~ $700MM


*$18MM preclinical; $15MM Phase 1; $40MM Phase 2, $150MM Phase 3; $40MM registration

Briggs W. Morrison, MD / October 27, 2012
Economics

**Cost of Failure (target to market)**

- Cost to get 88 molecules (that will fail) to Phase 1 = $1.58 BB
- Cost to fail 88 molecules in Phase 1 = $1.32 BB
- Cost to fail 36 molecules in Phase 2 = $1.44 BB
- Cost to fail 5 molecules in Phase 3 = $1.50 BB
- Cost to fail 1 molecule in registration = $40 MM

Total = $5.9 BB

**Cost of Success (target to market)**

- Cost to succeed 12 molecules

Total = $5.0 BB

**Cost per New Drug**

- ~ $900MM


*$18MM preclinical; $15MM Phase 1; $40MM Phase 2; $300MM Phase 3; $40MM registration

Briggs W. Morrison, MD / October 27, 2012
Economics

Success rate by type of molecule

2002-06
- Large molecule: 22% (N=174)
- Small molecule: 7% (N=1818)

2006-10
- Large molecule: 12% (N=479)
- Small molecule: 2% (N=1807)

2007-11
- Large molecule: 10%

Source: PBF
Return on Investment

\[ \text{Return on Investment} = \frac{\text{Gain from Investment} - \text{Cost of Investment}}{\text{Cost of Investment}} \]
Agenda

- The Existing Model
- The Economics of the Innovative Biopharmaceutical Industry
- The Innovation Challenge
### Innovation challenges in the current model

<table>
<thead>
<tr>
<th>Productivity</th>
<th>Regulatory</th>
<th>Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Breakthrough science focused on precise unmet medical need.</td>
<td><img src="cpi.png" alt="CPI Logo" /> <img src="sentinel.png" alt="Sentinel Initiative Logo" /></td>
<td><img src="pcori.png" alt="PCORI Logo" /> <img src="nhs.png" alt="NHS Logo" /> <img src="cms.png" alt="CMS Logo" /> <img src="iqwig.png" alt="IQWiG Logo" /></td>
</tr>
<tr>
<td>• Fail less – and much earlier</td>
<td><img src="fda.png" alt="FDA Logo" /></td>
<td><img src="ema.png" alt="European Medicines Agency Logo" /></td>
</tr>
<tr>
<td></td>
<td><img src="sfda.png" alt="SFDA Logo" /></td>
<td><img src="sfda.png" alt="State Food and Drug Administration, P.R. China Logo" /></td>
</tr>
</tbody>
</table>
Discussion