innovation and intellectual property in drug discovery

Dr Tony Wood
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outline

- the cost and complexity of innovation in drug discovery
- attrition its relationship to disease and the need to drive molecular diversity
- the role of IP from a researchers perspective
- collaboration and open source research
R&D process summary

**Figure 11: The R&D Process: Long, Complex, and Costly**

- **Drug Discovery:**
  - Pre-Discovery: 5,000–10,000 Compounds
  - 3–6 Years

- **Preclinical Phase:**
  - IND Submitted
  - 250

- **Clinical Trials:**
  - Phase 1: 20–100
  - Phase 2: 100–500
  - Phase 3: 1,000–5,000
  - 6–7 Years

- **FDA Review:**
  - ½–2 Years

- **Large-Scale Manufacturing:**
  - NOA Submitted

**Discover the right target**

**Invent the right molecule**

*Source: PhRMA Industry Profile, 2009*
costs are increasing

FIGURE 13: Cost to Develop One New Drug

R&D expenditure

pharmaceutical and other industries spend as percentage of annual revenues

<table>
<thead>
<tr>
<th>Industry</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical R&amp;D</td>
<td>17.5</td>
</tr>
<tr>
<td>Computer Software &amp; Services</td>
<td>10.5</td>
</tr>
<tr>
<td>Electrical &amp; Electronics</td>
<td>8.4</td>
</tr>
<tr>
<td>Office Equipment &amp; Services</td>
<td>7.8</td>
</tr>
<tr>
<td>Telecommunications</td>
<td>5.3</td>
</tr>
<tr>
<td>Leisure Time Products</td>
<td>4.7</td>
</tr>
<tr>
<td>Automotive</td>
<td>3.9</td>
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<tr>
<td>Aerospace &amp; Defense</td>
<td>3.8</td>
</tr>
<tr>
<td>Metals &amp; Mining</td>
<td>1.2</td>
</tr>
<tr>
<td>Paper &amp; Forest Products</td>
<td>0.73</td>
</tr>
<tr>
<td>All Industries</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Source: PhRMA, 2006, based on data from PhRMA Annual Survey and Standard & Poor's Compustat, a division of McGraw-Hill
better medicines can reduce healthcare costs

**AIDS Deaths per 100,000 Population**

**Monthly Health Spending for AIDS Patients**

HIV Mortality Declined Dramatically After Introduction of First “Expensive” Antiretrovirals...

...While Monthly Costs for AIDS Patients Decreased by 16% After HAART Introduced

key decisions in drug discovery

- discover the right biological target
- invent the right molecule
two examples from HIV

a new approach

CCR5Δ32

- <1.5% no HIV infection
- <20% delayed progression (2 years average)
- ca.80% normal progression

improved response to therapy
high throughput screening

- essential tool for hit identification
- 1 million compounds tested to find a starting place
X-ray crystallography

100 μm
structure based design

UK-453061/K103N RT complex
ArCN contacts to F227 & W229

Capravirine/wt RT complex
ArCl contacts to Y188 & W229
IP supports investment

- Hit identification and lead compound optimisation are technologically demanding and capital and resource intensive.
- IP is essential to encourage investment in technology and drive speed through competition.
- Knowledge and experience are key and lead to advancement of scientific best practice through patents and publication.
many approaches are needed to overcome attrition

attrition is disease agnostic

Can the pharmaceutical industry reduce attrition rates? Ismail Kola and John Landis NATURE REVIEWS, DRUG DISCOVERY, VOLUME 3, 2004, 711
IP drives new compound diversity

CCR5 antagonists

- maraviroc (Pfizer, launched)
- vicrivioc (SP, PhII)
- TAK 652 (Takeda, PhII)
- aplaviroc (Ono, discontinued)

DPPIV inhibitors

- sitagliptin (Merck, launched)
- vildagliptin (Novartis, launched)
- gosogliptin (Pfizer, PhIII)
- alogliptin (Takeda, pre-registration)
R&D funding sources

![Bar chart showing R&D spending over years from 1996 to 2005, comparing industry sponsored and government sponsored sources.]

Source: Thomson CenterWatch, 2004; NIH, 2004; PhRMA Industry Profile, 2004; Goldman Sachs, 2003
Development of the 21 Drugs with "Highest Therapeutic Value" Introduced Between 1965 and 1992

- Key Enabling Discovery
- Synthesis of Compound

The average lag between the “key enabling discovery” and the introduction of the drug was 24 years.

WHO-TDR/ Pfizer collaboration

identifying novel lead compounds for tropical diseases while building scientific capacity for less developed countries

Pfizer:
PGRD Sandwich, UK
PAH Kalamazoo, MI USA

Antiprotozoal Screening:
STI, Basel – Reto Brun, Marcel Kaiser
U of Washington – Frederick Buckner
LMPH, U of Antwerp – Louis Maes

Anthelminthic Screening:
TBRI, Egypt – Fouad Yousef
NPI MR – Simon Townson
LSHTM – Quentin Bickle

New Molecular Target (GSK-3 from T. brucei)
U. Of Washington – Wesley Van Voorhis
lead compound discovery activities

Pfizer selected compound files

Protozoan Targets
P. falciparum, T. cruzi, L. donovani, T. brucei

Helminth Targets
O. linealis, S. mansoni

screening – identify actives

leverage Pfizer compound file
re-synthesize where necessary

titrated compounds for potency
test for cellular toxicity

potent, selective in vitro hits

exploits knowledge, skills, and resources of all partners
other achievements

- WHO-TDR Chemistry Fellow Chitalu Musonda moved to Ithemba Pharma, S. Africa in July 2008

- two manuscripts published

- three new WHO-TDR Fellows recruited
  - Stephen Barasa (Chemistry Fellow, August 2008)
  - Silvere Ngouela (Chemistry Fellow, September 2009)
  - Richard Oduor (Biology Fellow, February 2009)

- T. brucei GSK-3 screen enabled through agreement with U. of Washington and recruitment of Biology Fellow

- pharmacologically active file (BIOPRINT) screened
MMV/ Pfizer collaboration

**Medicines for Malaria Venture (MMV):** not for profit organisation with mission to promote R&D of new anti-malarial drugs

- Pfizer compound library made available to MMV to screen for compounds having anti-malarial potential

- screening to be carried out at Eskitis Institute for Cell and Molecular Therapies, Griffith University, Brisbane, Australia

- upon completion of screening, Pfizer and MMV to determine which compounds are suitable for progression into potential drugs
neglected disease portfolio

Portfolios are fragmented across players – even in key diseases

- Development costs will mean need for PDP and government contributions
- Herrling - Fund for R&D in Neglected Diseases (FRIND)

Source: Paul L Herrling, Global Forum Update on Research for Health, Vol 5, 152
summary

- R&D is long, complex, and costly
- IP is essential to ensure investment in technology and drive diversity and speed
- collaboration to make better use of combined resources is a potential solution
- understanding the transition between pre-competitive and competitive activities will be critical to future success