THE CHANGING FACE OF DRUG DISCOVERY

New Approaches, New Skills and New Technologies

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Global R&D expenditure, development times, global pharmaceutical sales and new molecular entity output 2001-2011

*The development time data point for 2011 includes data from 2010 and 2011 only

Source: CMR International & IMS Health
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Limitations of the current, reductionist drug discovery paradigm
The failure of genomics?

Drugs for bad bugs: confronting the challenges of antibacterial discovery

David J. Payne, Michael N. Gwynn, David J. Holmes and David L. Pompliano

Abstract | The sequencing of the first complete bacterial genome in 1995 heralded a new era of hope for antibacterial drug discoverers, who now had the tools to search entire genomes for new antibacterial targets. Several companies, including GlaxoSmithKline, moved back into the antibacterials area and embraced a genomics-derived, target-based approach to screen for new classes of drugs with novel modes of action. Here, we share our experience of evaluating more than 300 genes and 70 high-throughput screening campaigns over a period of 7 years, and look at what we learned and how that has influenced GlaxoSmithKline's antibacterials strategy going forward.


- Biology-dominated targets selection had no impact on producing anti-bacterial development candidates.
- Single essential target approach
Lessons for the drug hunter

• What drug discovery is learning from system biology & large-scale functional genomics
  – Redundancy
  – Degeneracy
  – Robustness
  – Synthetic behaviour
    • (lethality, sickness, rescue)
  – Disease networks

Consequences of deletions:

- Lethality (Giaever et al., 2002)
- Growth defect in rich medium (Deutschbauer et al., 2005)
- Growth defect in this study
- No phenotype in this study

Edelman & Gally, PNAS(2001), 98(24), 13763-8
Hopkins A, Nature Chemical Biology (2008), 4(11), 682-690

Chan et al, Nature (2008), 452, 429-435
Polypharmacology as one of the productivity solutions
The Myth of the Selective Drug?

Polypharmacology of psychoactive drugs


PDSP Ki database at US National Institute of Mental Health Psychoactive Drug Screening Program
Promiscuity of kinase inhibitors in cancer therapy

Sutent, SU11248 (approved treatment for renal cell carcinoma) binds to 79 protein kinase $K_d < 10 \text{mM}$

Promiscuity & cLogP

2000 compounds tested against 200 targets


This relationships supports the philosophy of fragment screening

Drug strategies against multiple targets?

Drug Combination

Cleavable Conjugate

Conjugate

Overlapping Pharmacophore

Highly Integrated Pharmacophore

Increase in MW and structural complexity

Increase in degree of overlap between pharmacophores, P1 and P2

Future of Pharma?
Profitless Growth for Biotech

The revenues of publicly held biotech companies have grown dramatically but their profits have hovered close to zero. Excluding Amgen, the largest and most profitable firm, the industry has been consistently in the red. Its losses would be even greater if private companies were included in the data pool.

Revenue and operating income before depreciation ($ billions 2004)

- All public companies
- All public companies except Amgen
- All public companies except Amgen

1980

2004

$0

$35.8

$25.2

$2.5

($2.1)

Gary Pisano, Can science be a business? Lessons from Biotech., HBR, 10, 2006
Biotech Has Produced No Breakthrough in R&D Productivity

As the graph below indicates, the average R&D cost per new drug launched by biotech firms is not significantly different from the average cost per new drug launched by major pharmaceutical companies.

The sample of biotech companies includes all publicly held companies that tried to develop new drugs. The sample of pharmaceutical companies includes the top 20 companies in the world according to their R&D spending. The drugs do not include line extensions, reformulations, or approvals for new uses. Every annual data point represents the cumulative R&D expenditures from 1985 through the given year divided by the cumulative number of drugs launched during the same period. The first four and last four years of data were adjusted to account for the lag between R&D spending and the resultant output. Credit for a jointly developed new drug was divided equally between the biotech firm and its partner, the established pharmaceutical company.

Gary Pisano, Can science be a business? Lessons from Biotech., HBR, 10, 2006
Comparative advantages

Big Pharma
- Capital
- Huge Physical Corporate Compound File
- Large-scale Proprietary Databases
- Med Chem expertise
- Drug Hunting know-how
- Development expertise
- Large Portfolio
- IP, legal strengths

Biotechs/Universities
- Energetic, entrepreneurial staff
- Strong links to Academia
- Biological/Disease expertise
- Fluid funding
- Focused projects
- Fluid skills base
- Fast to react to new opportunities

Advantages

Disadvantages
- Relatively fixed budgets
- Relatively fixed skills base
- Can be slow to react to new opportunities

- Risky portfolio
- Lack of infrastructure
- Lack of scalable business processes
- Lack of access to compound file
- Limited informatics
- Lack of drug hunting experience
“The future.. for the major pharmaceutical companies is a role analogous to publishers: the providers of marketing, finance, selection and co-ordination skills.”

— John Kay
Professor of Economics, Oxford & LSE

“When you discovery something novel the medical imperative is to come up with a good use for it”

Paul Janssen
Janssen's successful chemo-centric learning strategy
Systematic Searching for Evidence

“Show me all the diseases associated with PDE5 from scientific literature”

PDE5 has 40 synonyms

(PDE5 or phosphodiesterase 5 or phosphodiesterase V or phosphodiesterase (PDE) 5 or phosphodiesterase (PDE) V or pde V or PDE-5 or PDE V or PDE 5 or phosphodiesterase-5 or phosphodiesterase 5A or HSPDE5A or PDE5A or phosphodiesterase-5A or PDE(5) or PDE(5A) or phosphodiesterase (PDE) 5A or PDE 5A or PDE-5A or UK-092,480 or viagra or sildenafil or IBMX or 3-isobutyl-1-methylxanthine or zaprinast or tadalafil or vardenafil or SKF-96231 or YC-1 or DMPPO or UK-83405 or Sch-51866 or UK-343664 or WIN-65579 or GF-248 or T-1032 or SR-265579 or KF-31327 or OPC-35564)

There are about 12 million articles in Medline

12 million abstracts from 32,000 separate journals.
4 billion words

There’s ~ 6000 curated diseases

Here’s just one:

(ASTHMA or asthmatic or Acute severe asthma or Astmaticus or Excercise induced Asthma or mild intermittent asthma or mild persistant Asthma or moderate persisitant Asthma or Severe persistant Asthma or chronic persistant Asthma or extrinsic Asthma or intrinsic Asthma or aspirin-sensitive asthmatics or Aspirin induced Asthma or occupational asthma or Atopy or allergic asthma)

Statistic co-occurrence and Natural Language Processing used to identify evidence with high confidence

Hopkins et al., US Patent No. US2005060305
“In the last analysis the popular proof of science is technology”
Society and Technological Change, Rudi Volti

• Commonalities of Science and Technology
  – Both share rational thought processes
  – Mathematics fundamental to both
  – Both based on the acquiring knowledge
  – Both advance through cumulative development of knowledge and data

• Different motivations:
  – *Science-* Is it true? *Technology-* Will it work?

• We assume technological developments linearly follow scientific advances
  – However Technology often emerged without scientific knowledge and Scientific advance sometimes depends on prior Technological advances
Lessons for Innovation from other industries

“Not only are the market applications for disruptive technologies unknown at the time of their development, they are unknowable.”

– Clayton Christensen, The Innovator’s Dilemma

• Markets for disruptive technologies are discovered together in a dialogue between inventors and users

• Plans for disruptive innovation must be for learning and discovery rather than execution
Dr. Christopher Lipinski
Scientific Advisor to Melior Discovery, Exton PA.
Drivers for discovery changes

• Chemistry, 65% successful predictivity
  • rules and filters, eg. phys chem, structural
  • ADME predictivity worsens outside of RO5 space
• Safety, 50% successful predictivity
• Efficacy, 10% successful predictivity

• Tackle efficacy using academic collaborations
  • systems biology still too new to save us
  • target quality is most likely from rich biology
Attrition rates by phase

Figure 1 | Trends in attrition rates of drug development projects. Data are for projects started between 1990 and 2004 in the United States, Europe and Japan. Source: analysis of the Pharmaceutical Industry Database (BOX 1).

Target-based drug discovery:
....the real picture
Has drug discovery gone wrong?

• Prevailing mantra: identify a mechanism and discover a selective ligand for a single target
• Counter responses:
• Improve target validation, academic collaboration
• Spread financial risk – collaborations, outsourcing
• Phenotypic screening
• Drug repurposing
• Multi targeted drug discovery
Drugs Under Active Development involved in Multiple Programs

Within Integrity there are over 20,000 active preclinical drug programs. Here we have taken a sample set of 1000 active preclinical drug programs.

Note – this includes all those with anything active in 10 or over programs, hence the apparent increase.

Source: Thomson Reuters Integrity℠
Academic versus corporate patents

Data and graph courtesy of Kurt Zielenbach, Chemical Abstracts Service
Top 15 Therapeutic Areas by Patenting Activity 2012

Source: Thomson Reuters Integrity℠ patent information
Top 15 Therapeutic Areas by Active Preclinical Drug Products

### Total no. of Drugs under Active Development

1. Cancer, ovary
2. Cancer, pancreas
3. Psoriasis
4. Pain
5. Multiple myeloma
6. Infection, HIV
7. Asthma
8. Rheumatoid arthritis
9. Dementia, Alzheimer’s type
10. Cancer, prostate
11. Cancer, breast
12. Diabetes type 2
13. Cancer, lung (non-small cell) (NSCLC)
14. Cancer, solid tumor
15. Cancer

Source: Thomson Reuters Integrity℠
The usual attrition question

• We had a drug-like compound that was potent and selective against our target with good preclinical PK and PD.
• The PK and PD translation to man was good.
• Our compound failed in the clinic for lack of efficacy.
• WHY?
Changing the attrition question

• Mechanistic screening for a selective drug should fail 90% of the time
• Screening diverse compounds is the worst way to discover a drug (0% success)
• No drug is ever truly selective

Questions should be:
• Why do a few drugs succeed clinically?
• What is so special about these drugs?
Indicators of a successful drug (1)

• Drug does not affect the disease process but affects the set point of a normal process
  — Hypertension
  — Ulcers / GERD
  — BPH

• Drug exerts an effect in normal animals & man

• Do not need to understand details of the disease process

• Often found through phenotypic screens
Indicators of a successful drug (2)

• Drugs displays poly-pharmacology
• By luck the combination of mechanisms works
• By luck the side effects are tolerable
• Hypercholesterolemia eg. statins
• Baychol withdrawn due to rhabdomyolysis
• Cancer eg. kinase inhibitors eg. sorafenib
• CNS diseases eg. virtually all useful CNS drugs
• “Better lucky than smart”
The majority of small-molecule first-in-class NMEs that were discovered between 1999 and 2008 were first discovered using phenotypic assays (FIG. 2): 28 of the first-in-class NMEs came from phenotypic screening approaches, compared with 17 from target-based approaches.

Repurposed diabetes drug

Lyn kinase activator
new mechanism, one of 264 mechanism possibilities
The Key Therapeutic Areas by no. of Associated Targets

- Infection, Bacterial: 218
- Obesity: 264
- Infection, HIV: 107
- Asthma: 327
- Rheumatoid arthritis: 300
- Dementia, Alzheimers: 299
- Cancer, Breast: 247
- Cancer, Prostate: 231
- Cancer, Lung: 223
- Diabetes, Type 2: 190

Source: Thomson Reuters Integrity℠
Total of Drugs in Phase One compared to Biologics in Phase One

Trendline demonstrates large increase in drugs in phase one

Source: Thomson Reuters Integrity™
Percentage of Biologics in Phase One compared to Total Drugs in Phase One

Trendline demonstrates that the percentage of Biologics in the total is increasing slowly

Source: Thomson Reuters Integrity SM
Future of drug discovery

• More drug approvals but smaller markets
• Increase in pre-competitive initiatives
• More risk sharing
• More collaborations, academic and biotech
• Equilibrium in domestic job erosion
• Big 3 diseases - cancer, alzheimers & obesity
• Fragmentation in disease diagnosis
• Polypharmacology, phenotypic screening, drug repurposing
QUESTIONS

To ask a question please click on the ‘Ask a Question’ tab above.
A unique knowledge solution integrating biology, chemistry and pharmacology data to empower drug discovery and development activities.