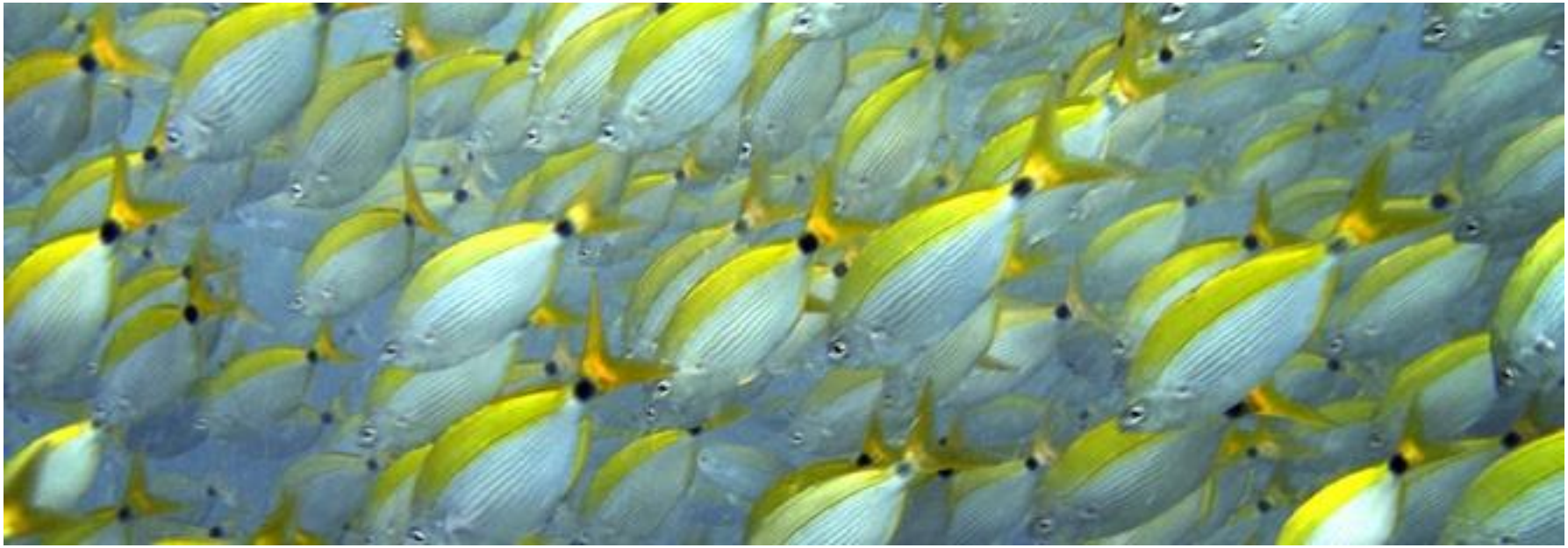

THE CHANGING FACE OF DRUG DISCOVERY

New Approaches, New Skills and New Technologies

Professor Andrew L. Hopkins DPhil FRSC FSB
Prof. of Medicinal Informatics & SULSA Research Prof. of Translational Biology. University of Dundee

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Product Manager at Thomson Reuters

THOMSON REUTERS

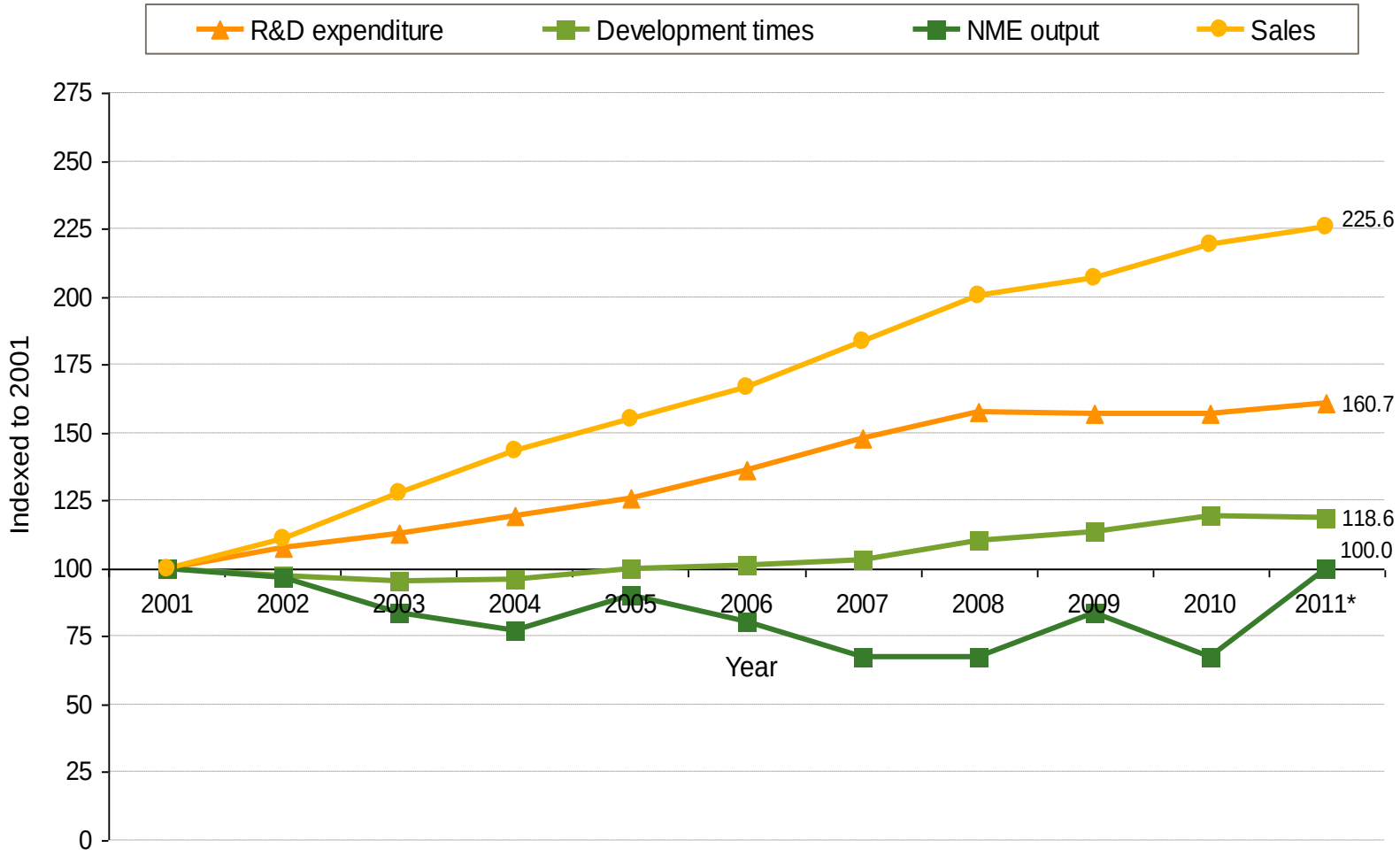
Dr Nicola Marlin

Product Manager at Thomson Reuters

CONTENT

- Industry overview
- Drivers for discovery changes
  - Limitations of the current paradigm
  - Lessons for the drug hunter
  - Attrition and successful drugs
  - The future of Pharma
  - The future of Drug Discovery
- Question and answer session

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

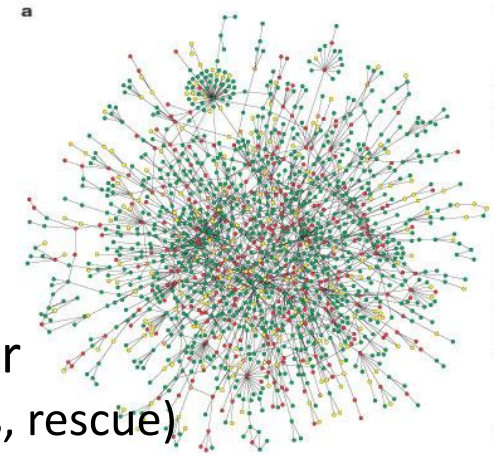
Abstract | The sequencing of the first complete bacterial genome in 1995 heralded a new era of hope for antibacterial drug discoverers, who now had the tools to search entire genomes for new antibacterial targets. Several companies, including GlaxoSmithKline, moved back into the antibacterials area and 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.

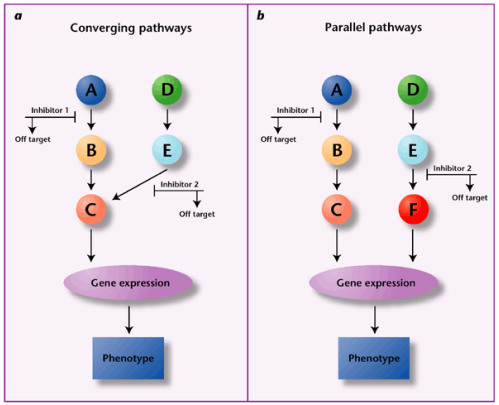
Payne, DJ et al., Nature Reviews Drug Disc. (2007) 6(1), 29-40

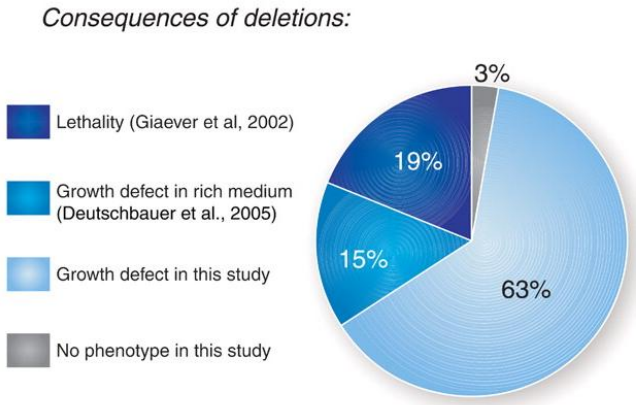
- Biology-dominated targets selection had no impact on producing anti-bacterial development candidates.
- Single essential target approach

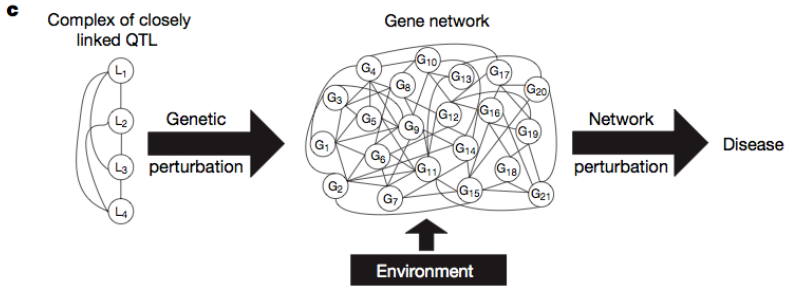
Lessons for the drug hunter

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









Chan et al, Nature (2008), 452, 429-435

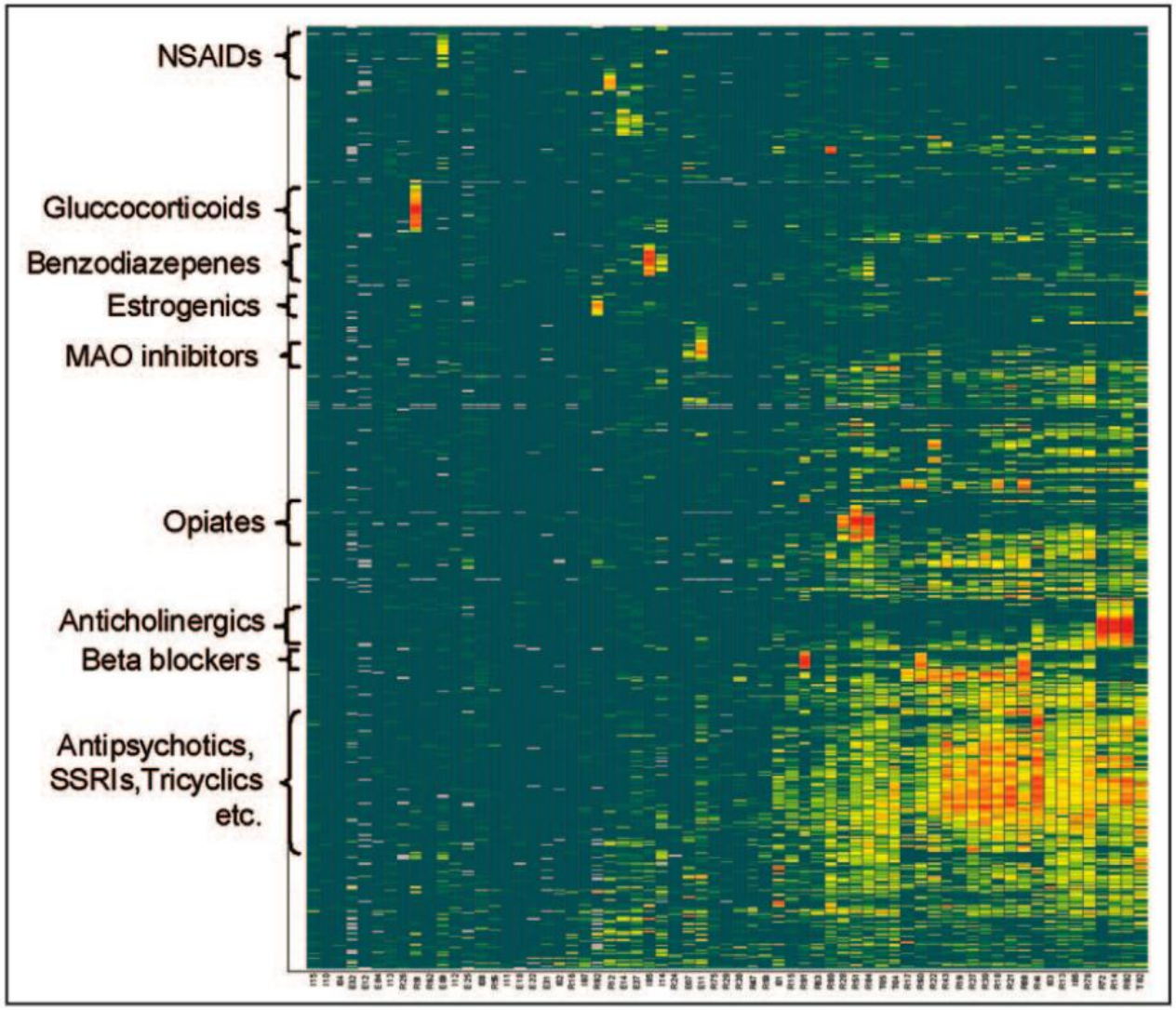
Hillenmeyer et al, Science, (2008), 320(5874),362-5

Edelman & Gally, PNAS(2001), 98(24), 13763-8

Hopkins A, Nature Chemical Biology (2008), 4(11), 682-690

Polypharmacology
as one of the productivity solutions

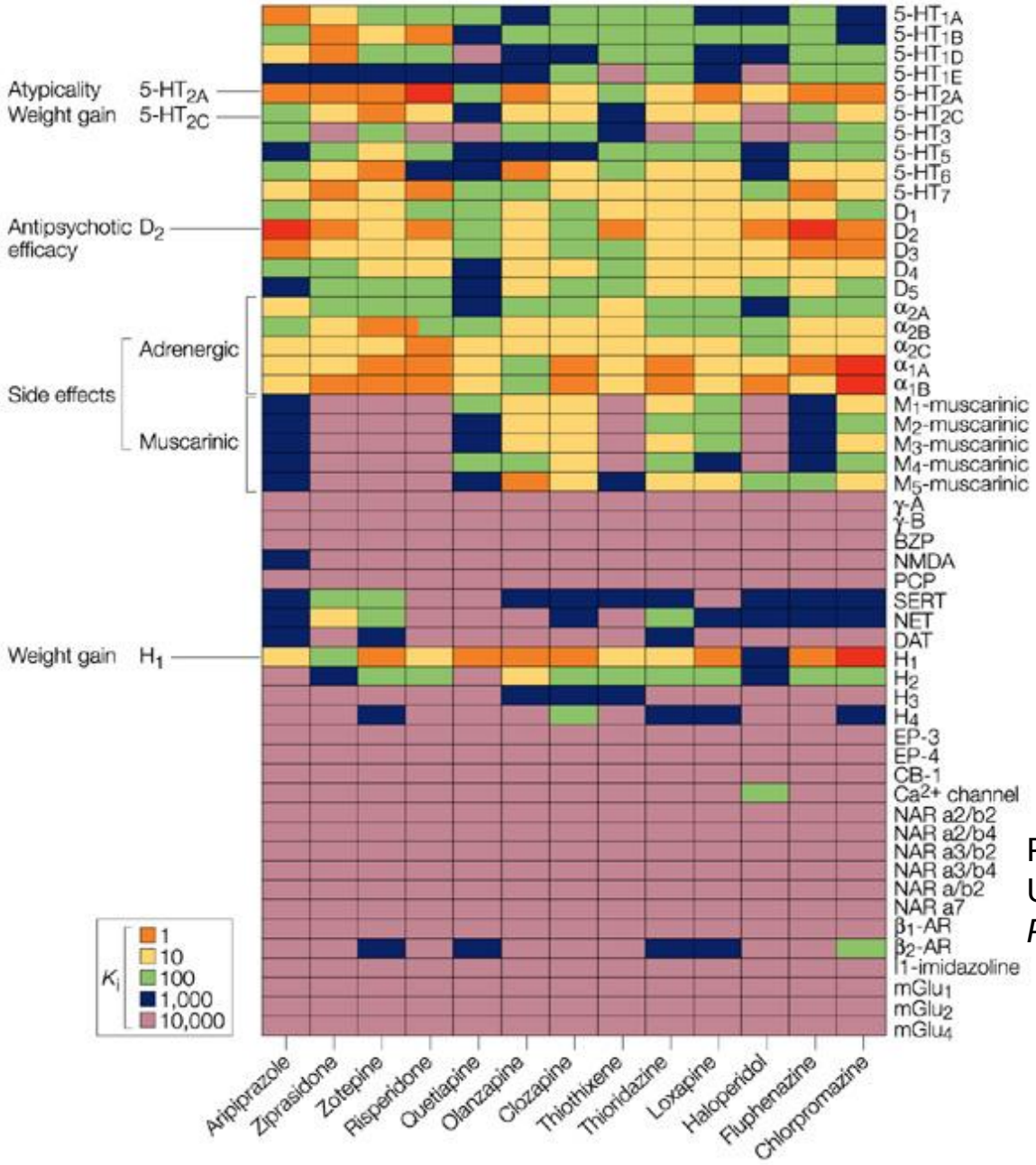
The Myth of the Selective Drug?



Cerep
Bioprint Screens
2000 drugs
x 200 assay

Hopkins et al, Curr Op Struct Biol (2006), 16, 127-136

Polypharmacology of psychoactive drugs



PDSP Ki database at
US *National Institute of Mental Health Psychoactive Drug Screening Program*

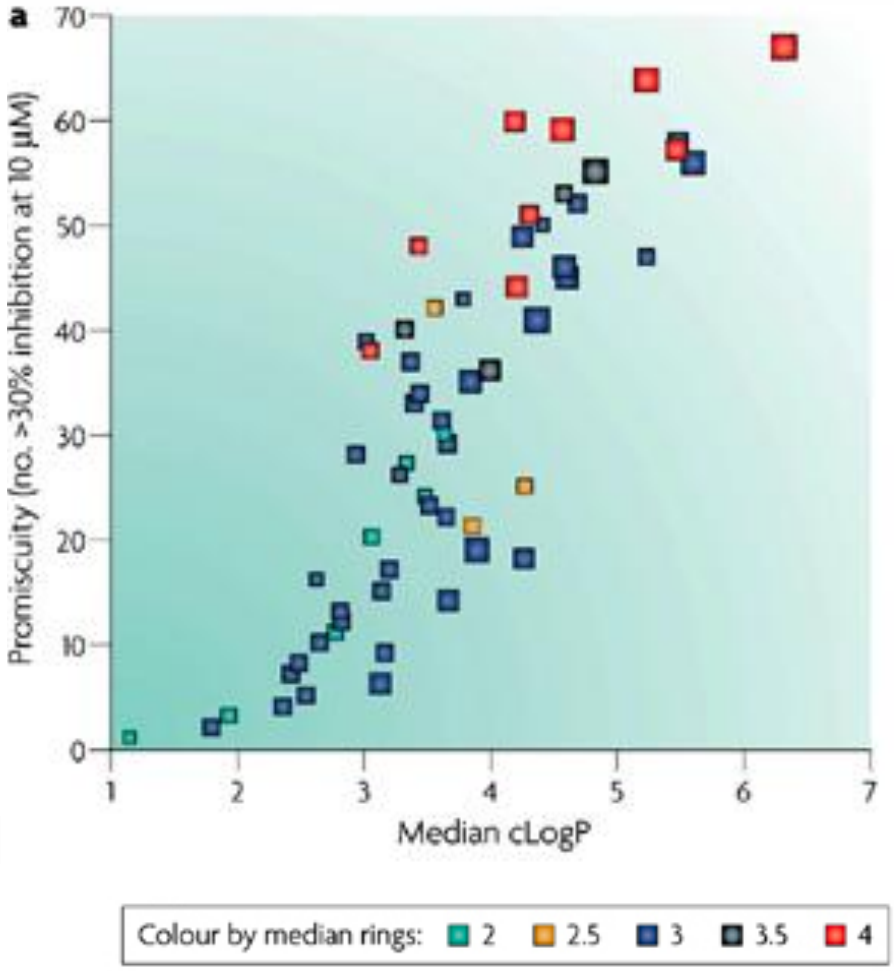
Roth, B. *et al.*, *Nature Reviews Drug Discovery 3, 353-359 (April 2004)*

Promiscuity of kinase inhibitors in cancer therapy

Sutent, SU11248 (approved treatment for renal cell carcinoma) binds to **79** protein kinase K_d < 10mM

Fabian MA et al, *Nature Biotechnology 23, 329 - 336 (2005)*

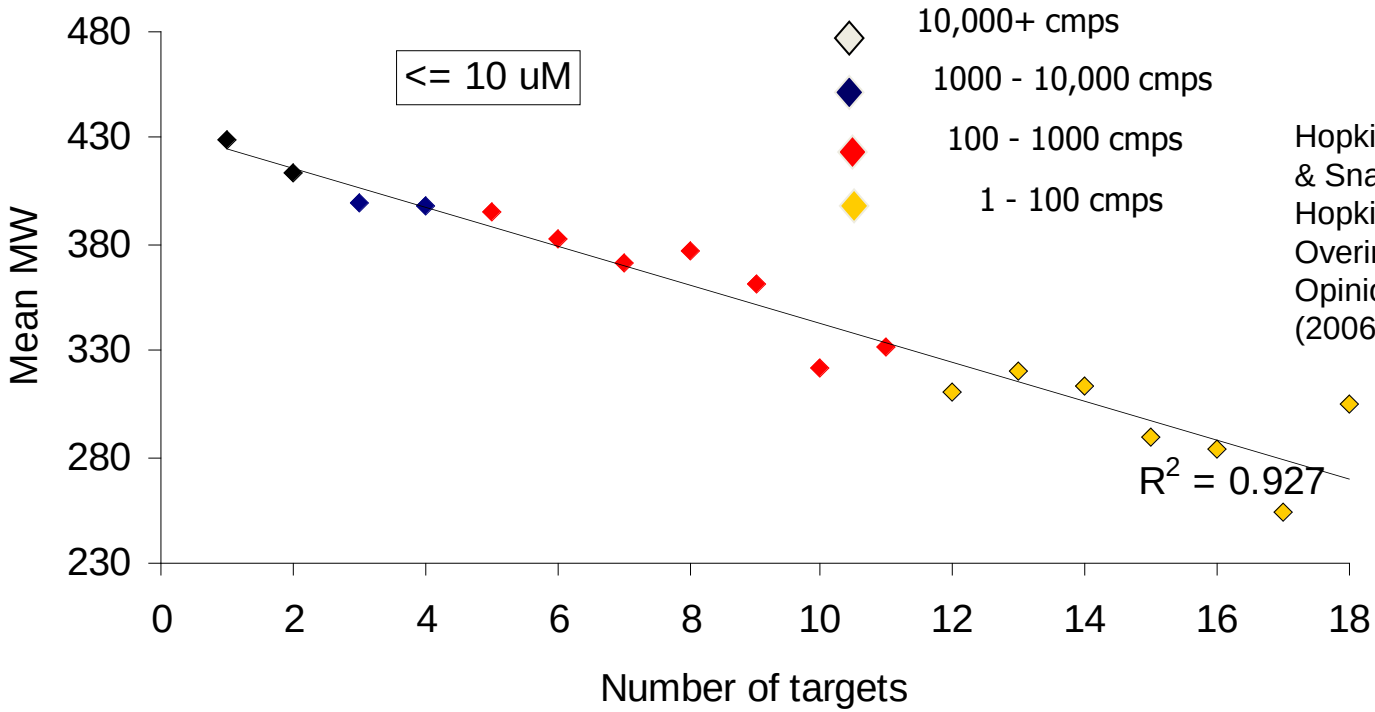
Promiscuity & cLogP



2000 compounds tested against 200 targets

Leeson, PD and Springthrope, B.
Nature Reviews Drug Discovery (2007) **6,** 881-89

Complexity and Promiscuity



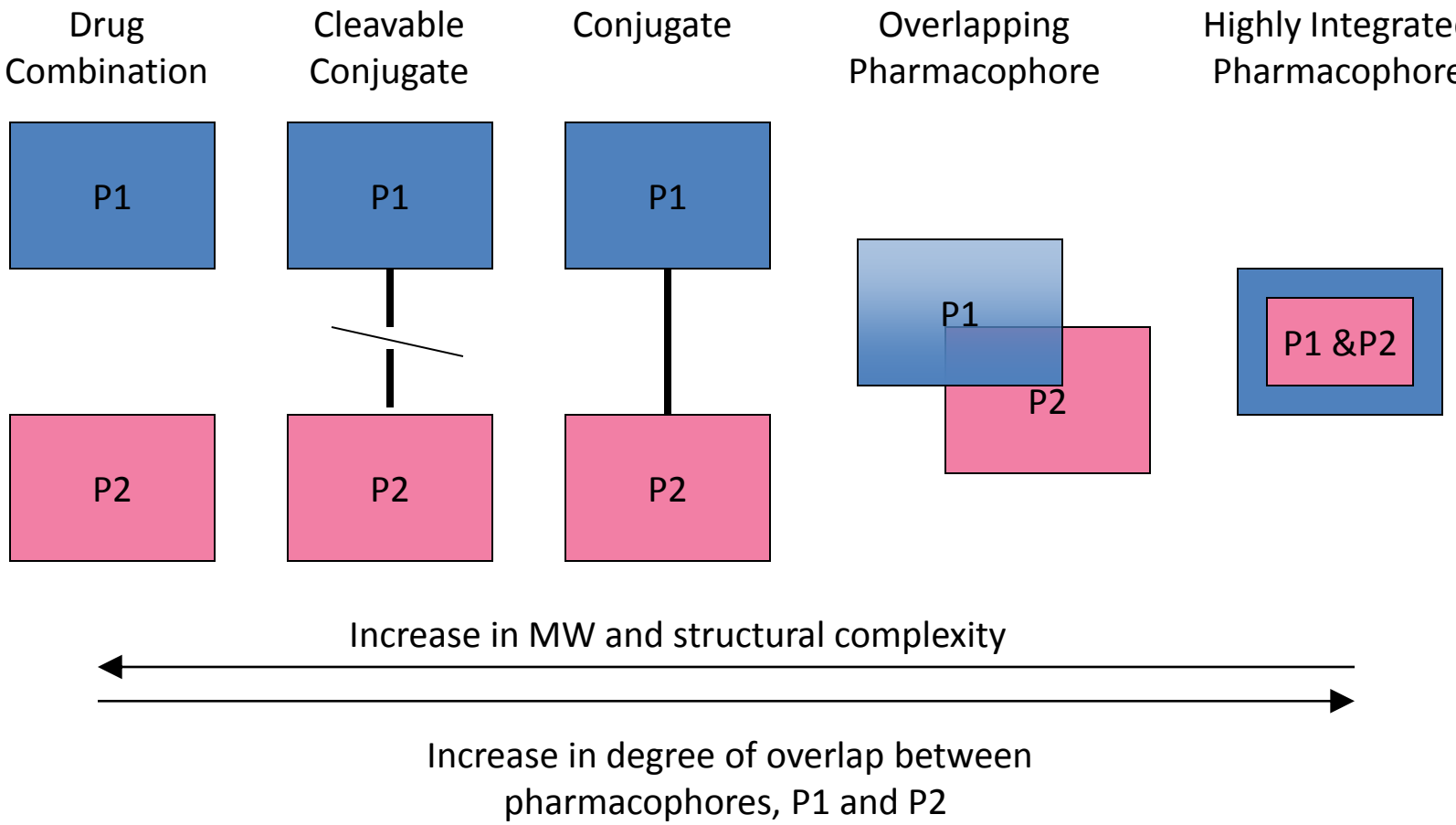
Hopkins, Groom, Barker & Snarey taken from Hopkins, Mason & Overington, Curr Opinion Struct Biol (2006), 16, 127-136

Feature Position	1	2	3	4	5	6	7	8	9
Receptor features	-	-	+	-	+	-	-	+	-
Ligand mode 1	+	+	-						
Ligand mode 2						+	+	-	
(reverse mode 3)					-	+	+		
(end wrap mode 4)	+							-	+

This relationships supports the philosophy of fragment screening

Hann, Leach & Harper, Molecular Complexity and Its Impact on the Probability of Finding Leads for Drug Discovery. JCICS, 41(3): 856-864 (2001)

Drug strategies against multiple targets?



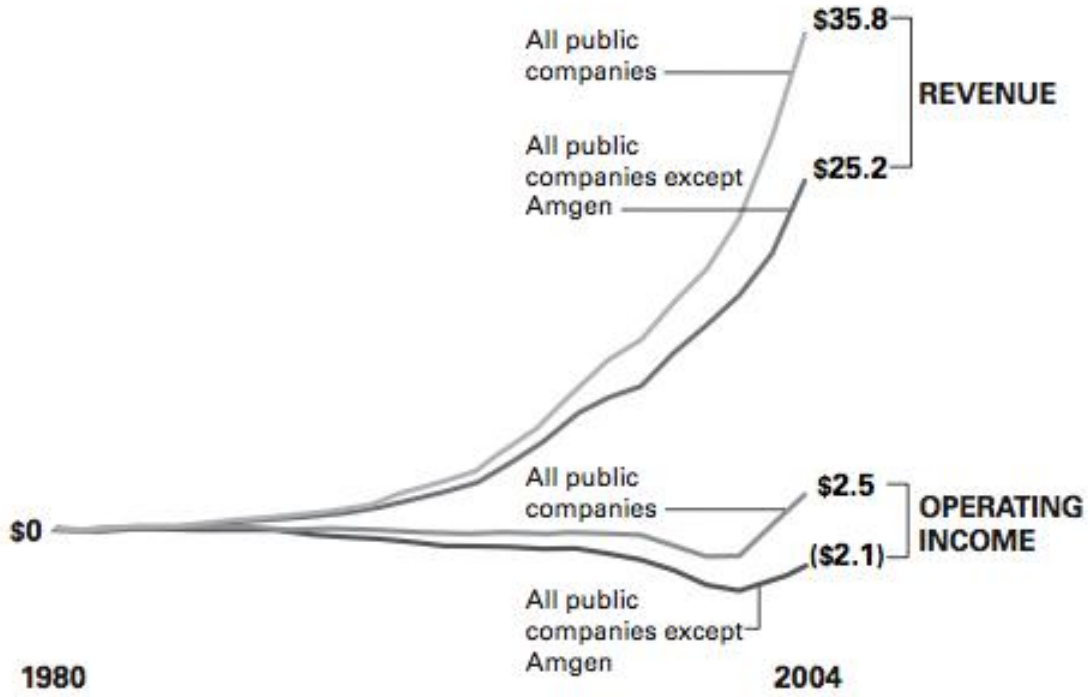
Morphy, Kay & Rankovic, Drug Discov Today, (2004) 9, August, 641-651

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.

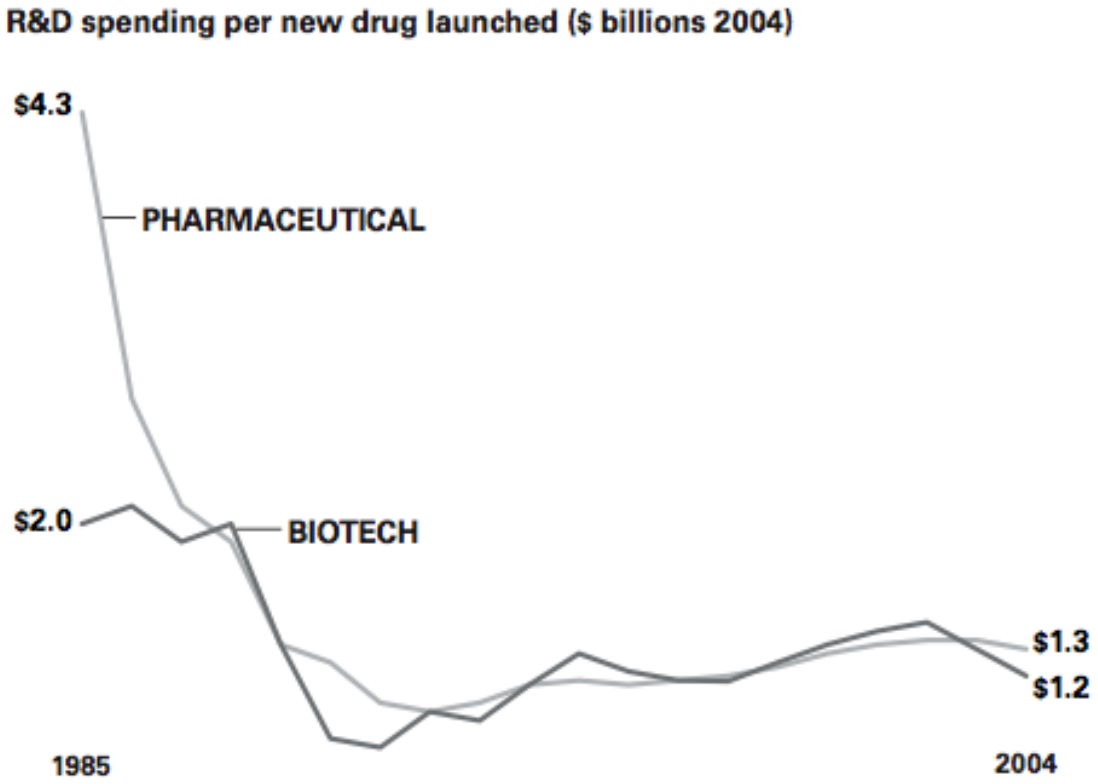
Revenue and operating income before depreciation ($ billions 2004)



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	Biotechs/Universities
Advantages	• Capital • Huge Physical Corporate Compound File • Large-scale Proprietary Databases • Med Chem expertise • Drug Hunting know-how • Development expertise • Large Portfolio • IP, legal strengths	Energetic, entrepreneurial staff Strong links to Academia Biological/Disease expertise Fluid funding Focused projects Fluid skills base Fast to react to new opportunities
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."

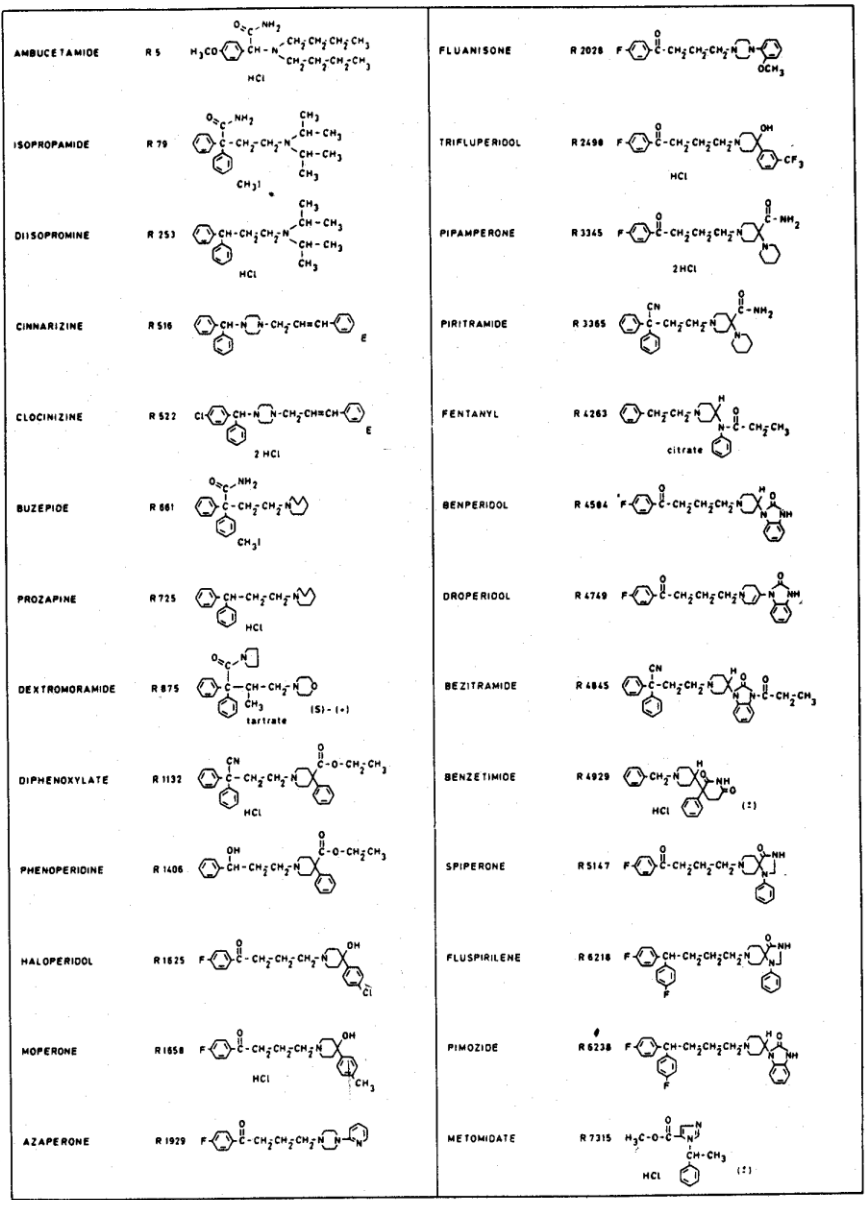
– John Kay
Professor of Economics, Oxford & LSE

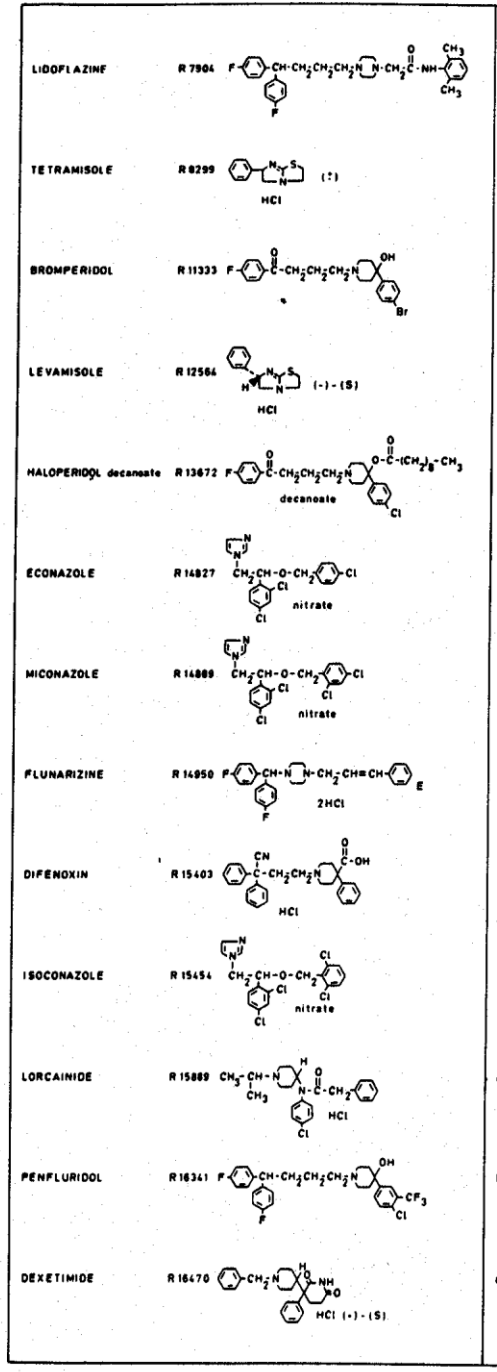
Changes in Market Structure, in *Consolidation and Competition in the Pharmaceutical Industry*, Office of Health Economics, London (2000) Ed. Hannah Kettler

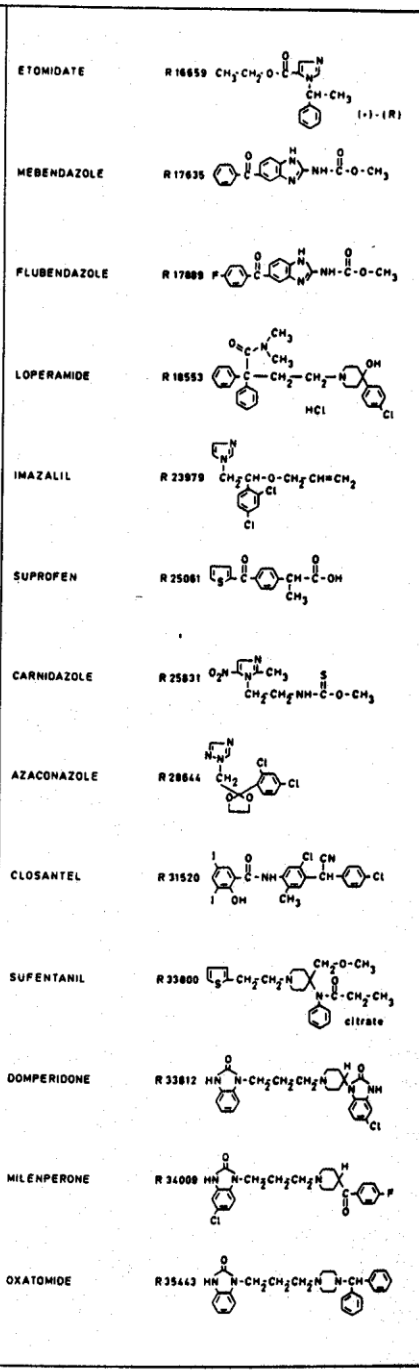
“When you discovery something novel the medical imperative is to come up with a good use for it”

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)

X

There are about 12 million articles in Medline

National Library of Medicine NLM

12 million abstracts from 32,000 separate journals.

4 billion words

X

There's ~ 6000 curated diseases

Here's just one:

(ASTHMA or asthmatic or Acute severe asthma or Asthmaticus 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

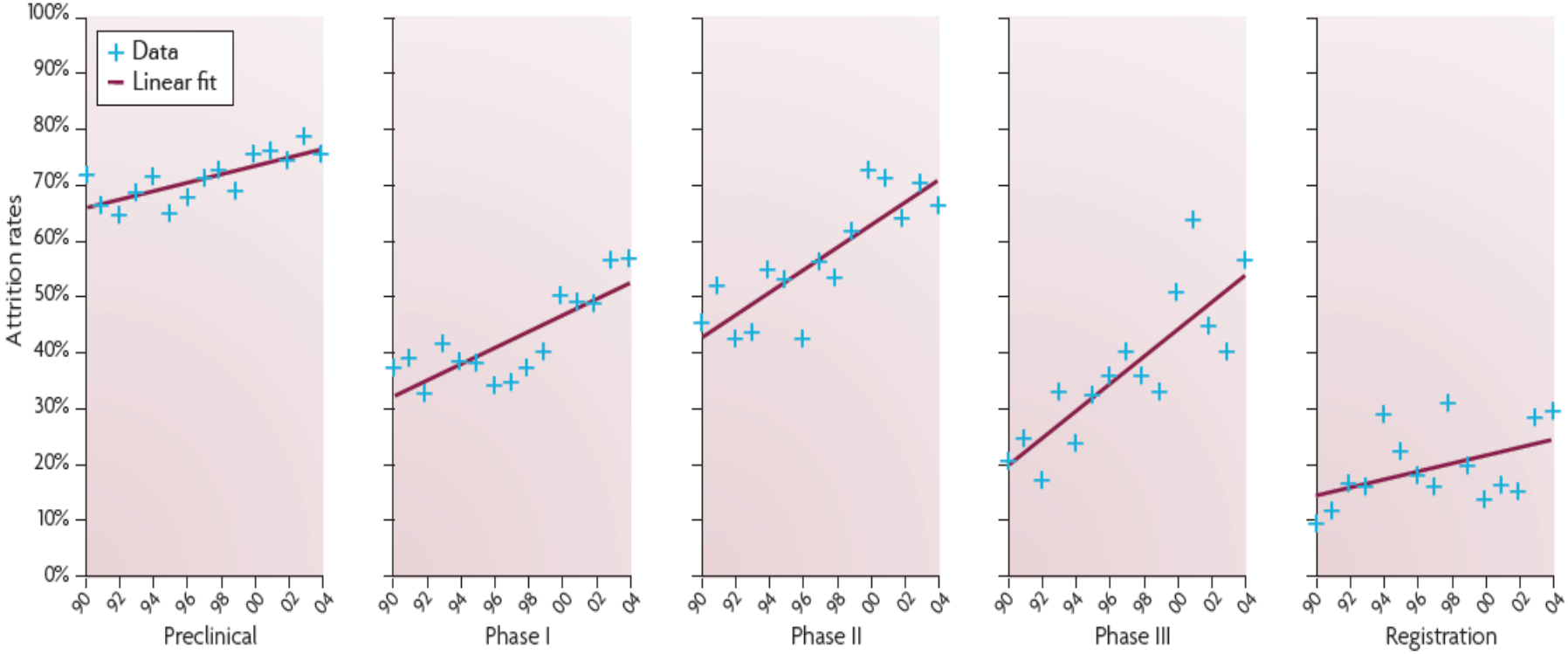
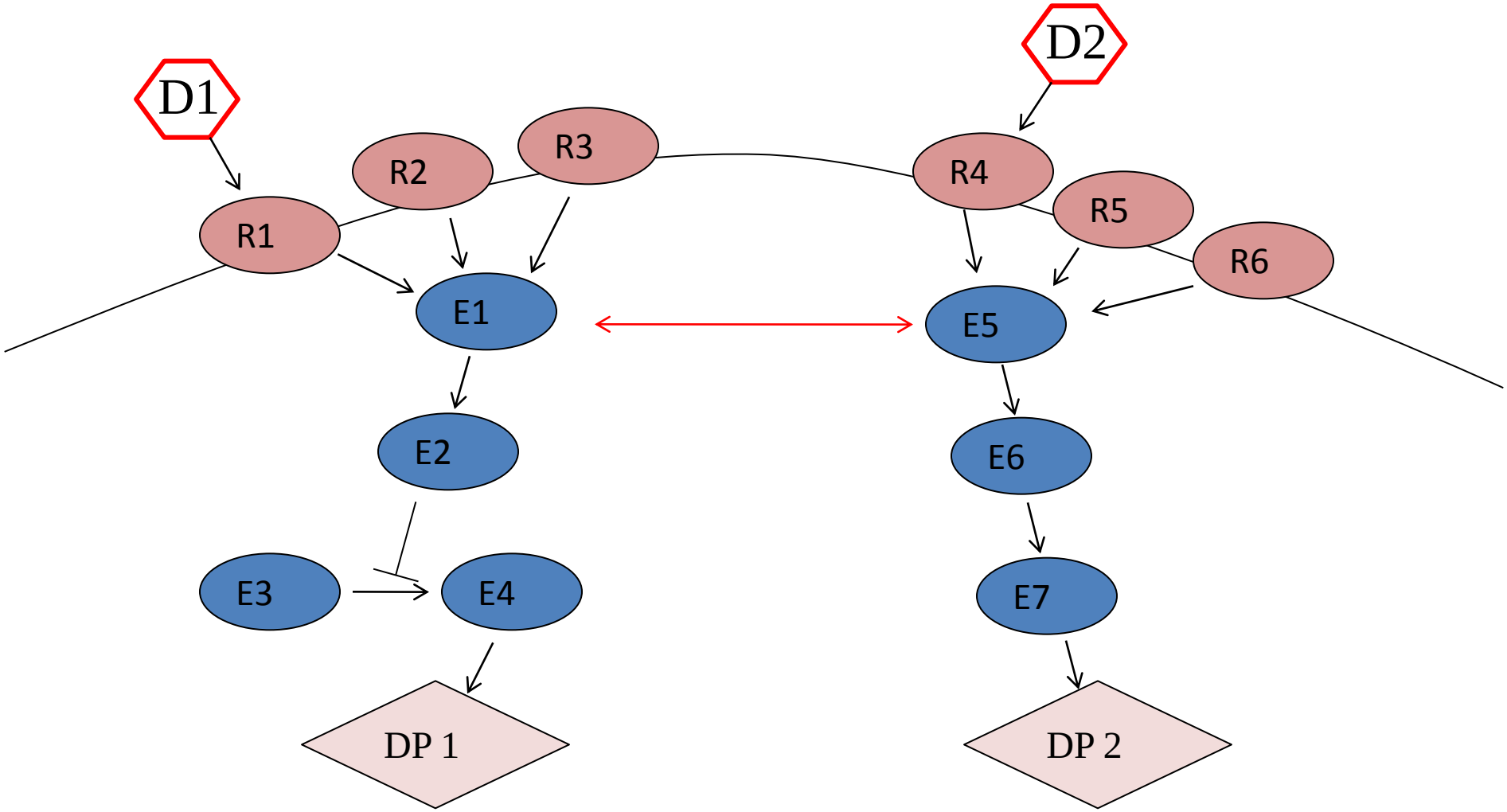


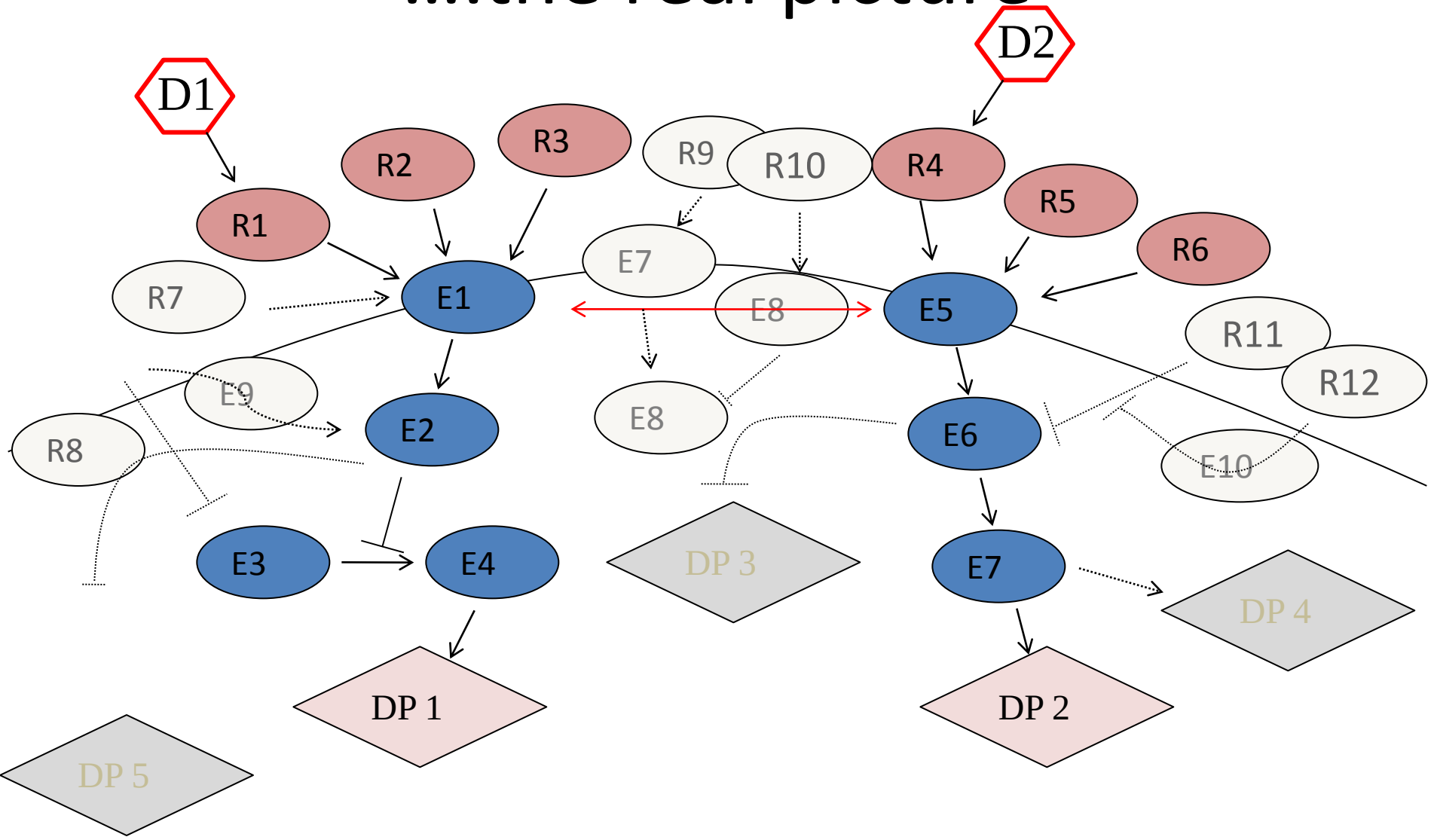
Figure 1 | **Trends in attrition rates of drug development projects.** Data are for projects started between 1990 and 2004 in the United States, Europe and Japan. Source: analysis of the Pharmaceutical Industry Database (BOX 1).

The Productivity Crisis in Pharmaceutical R&D, *Fabio Pammolli, Laura Magazzini and Massimo Riccaboni, Nature Reviews Drug Discovery 2011 (10) 428-438.*

Target-based drug discovery:



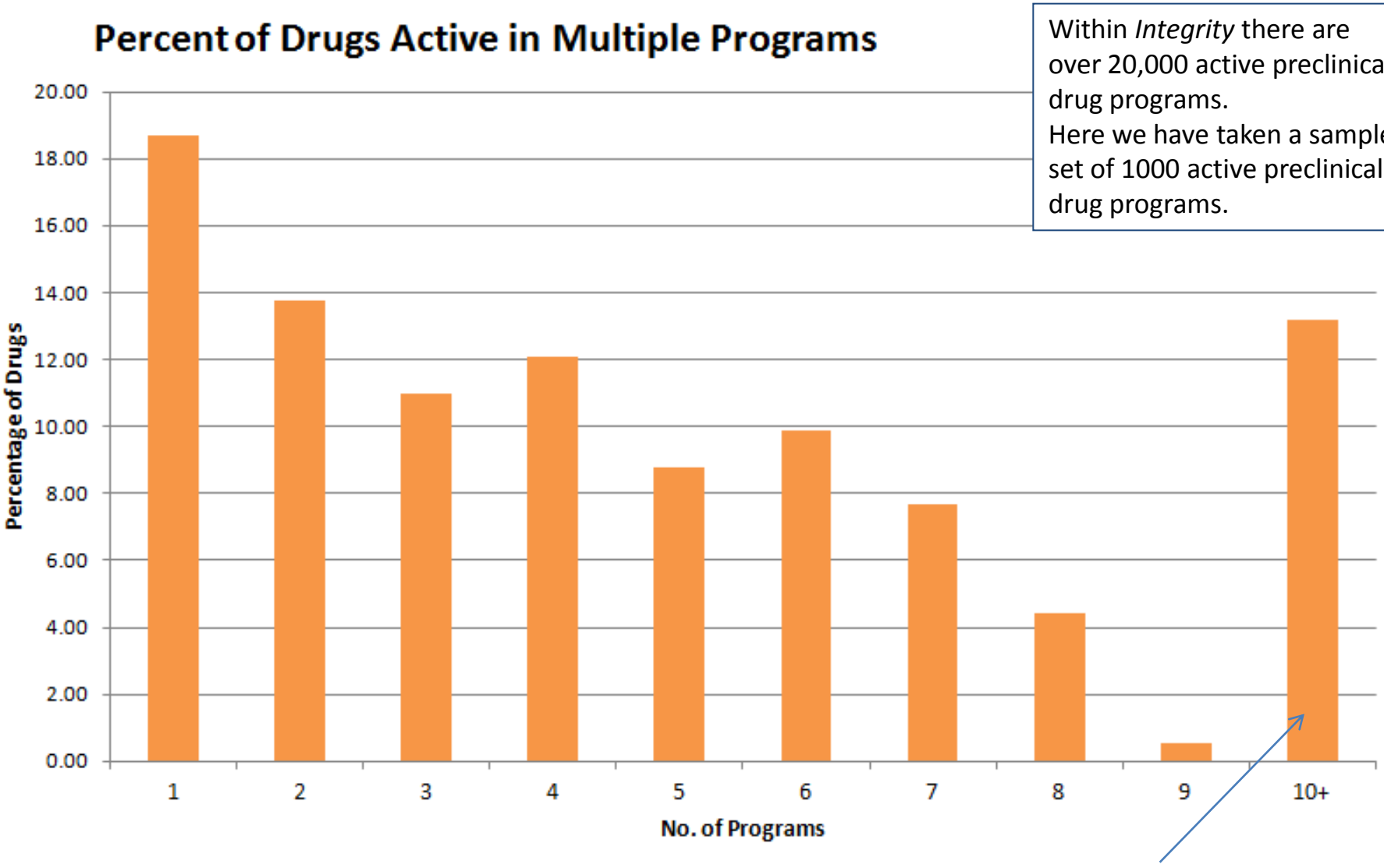
….the real picture



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

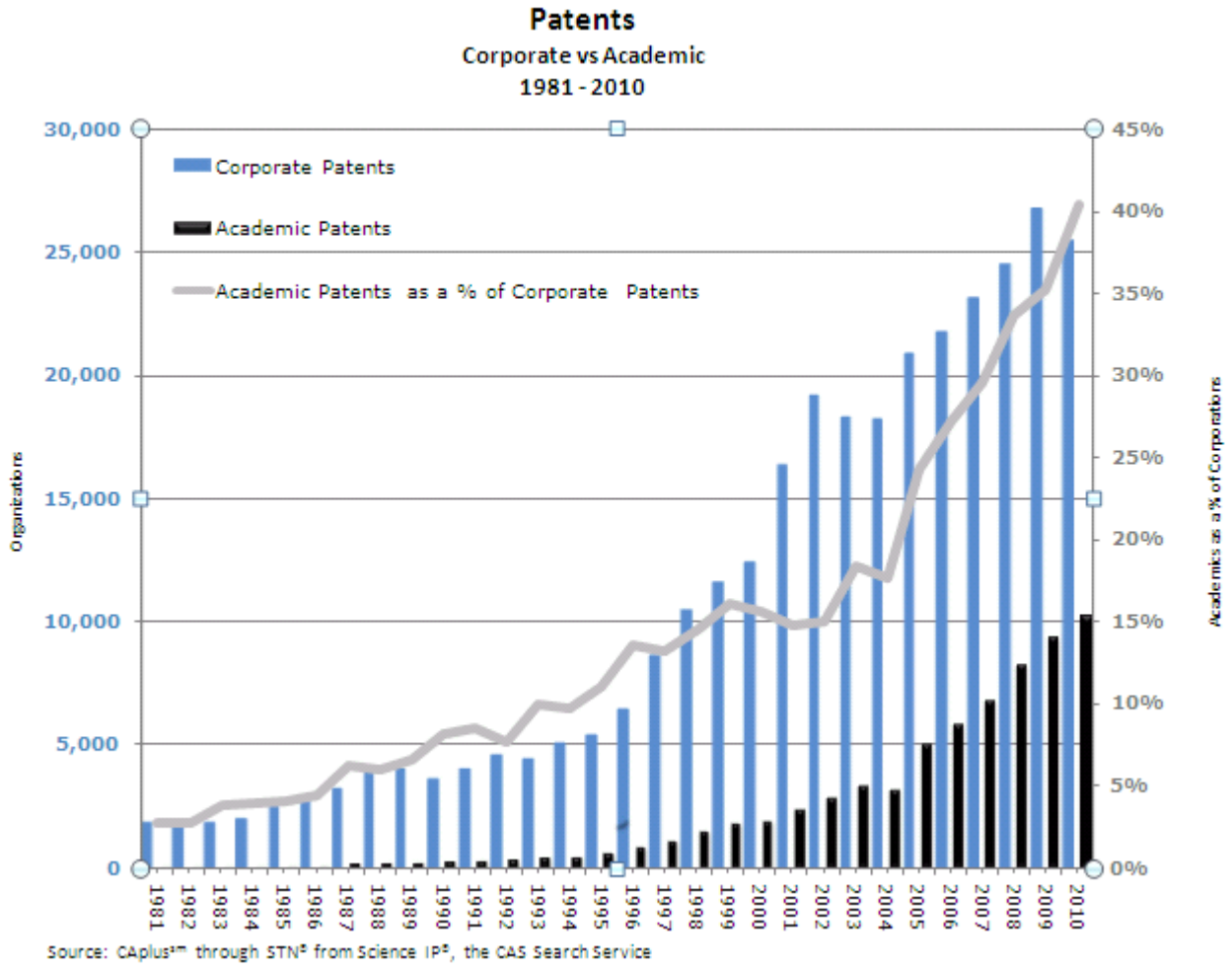


Within *Integrity* there are over 20,000 active preclinical drug programs.
Here we have taken a sample set of 1000 active preclinical drug programs.

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

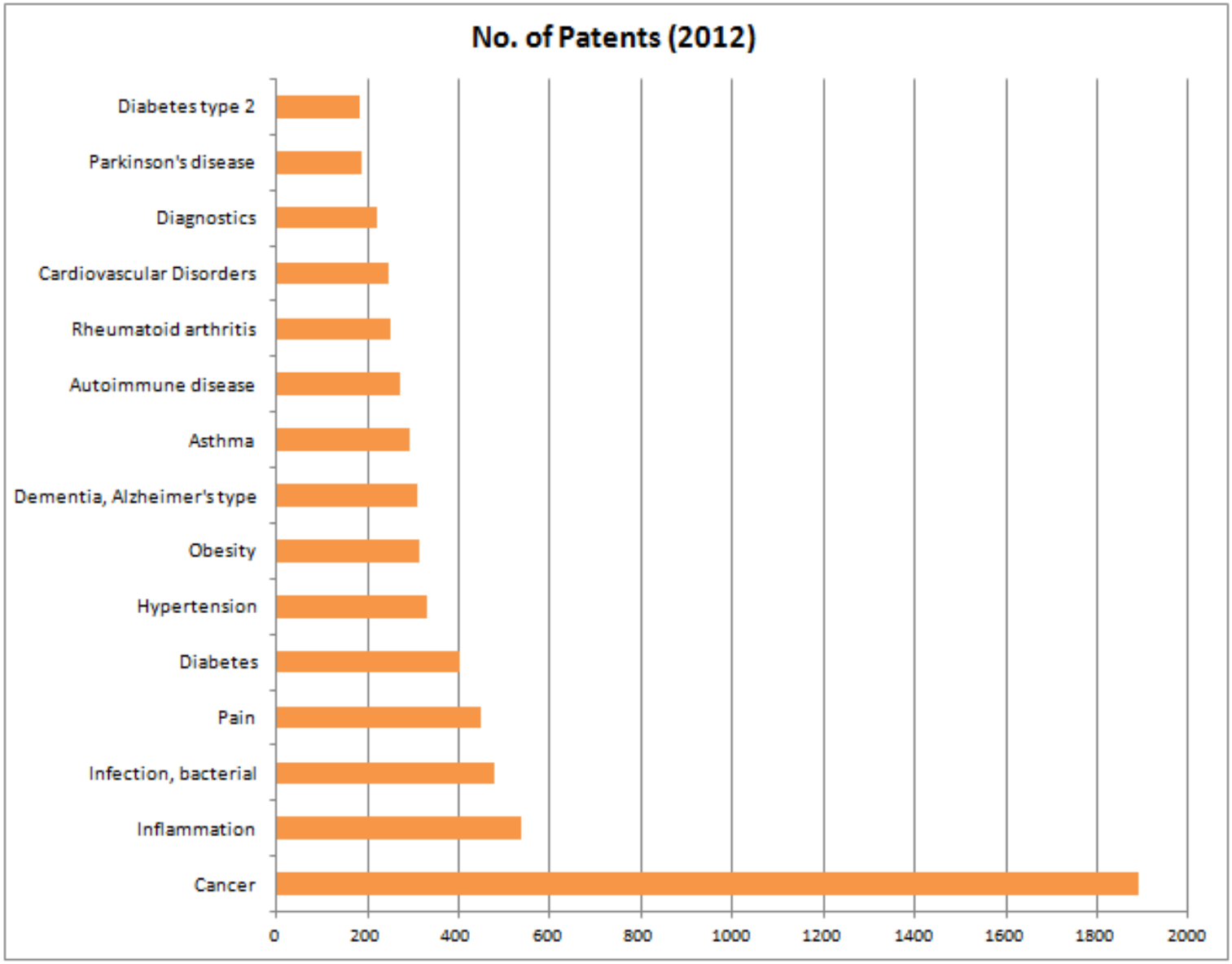
Source: Thomson Reuters *Integrity*℠

Academic versus corporate patents



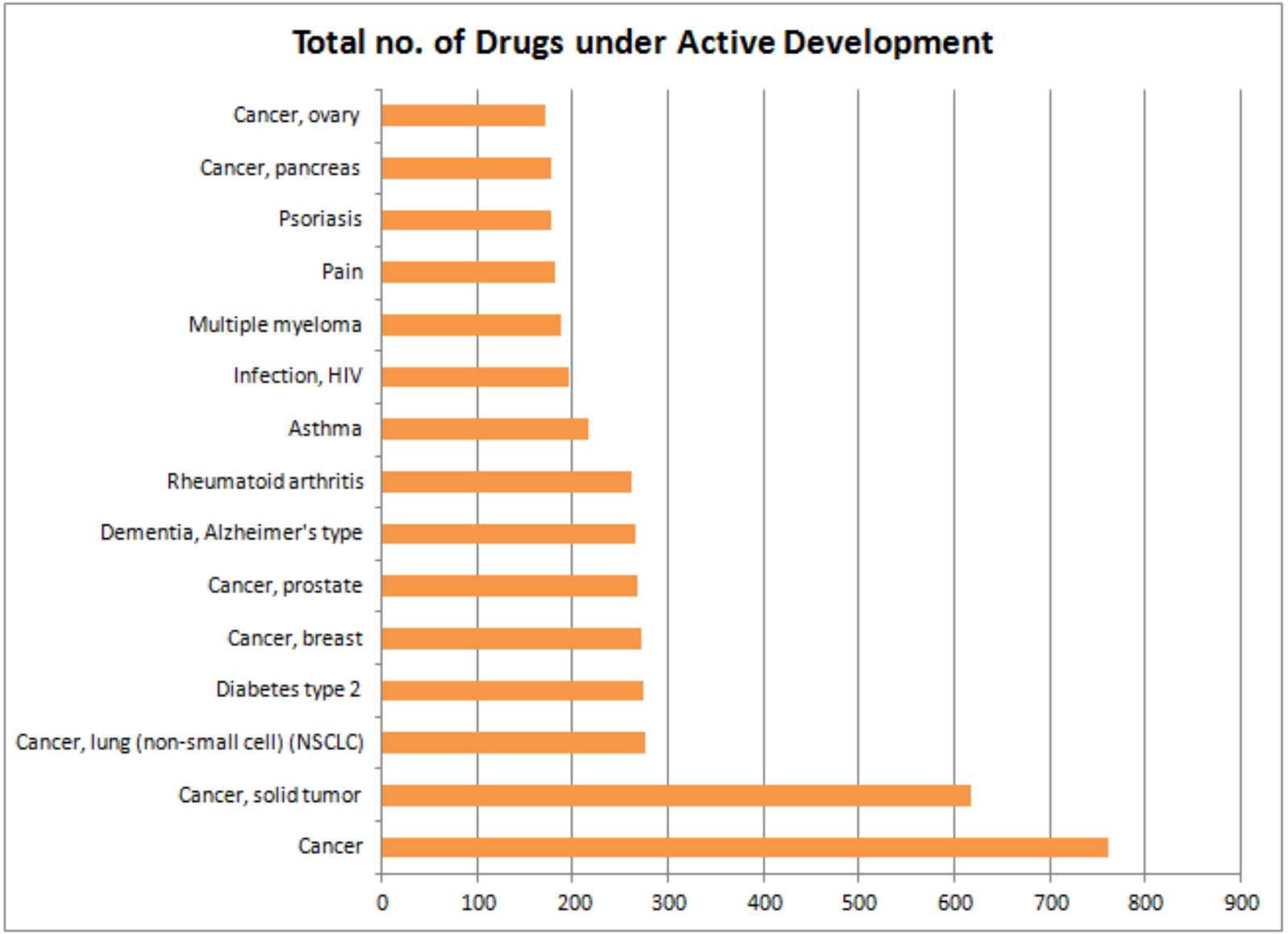
Data and graph courtesy of Kurt Zielenbach, Chemical Abstracts Service

Top 15 Therapeutic Areas by Patenting Activity 2012



Source: Thomson Reuters *Integrity*℠ patent information

Top 15 Therapeutic Areas by Active Preclinical Drug Products



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
- Hypercholesteremia 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”

Phenotypic screening advantage

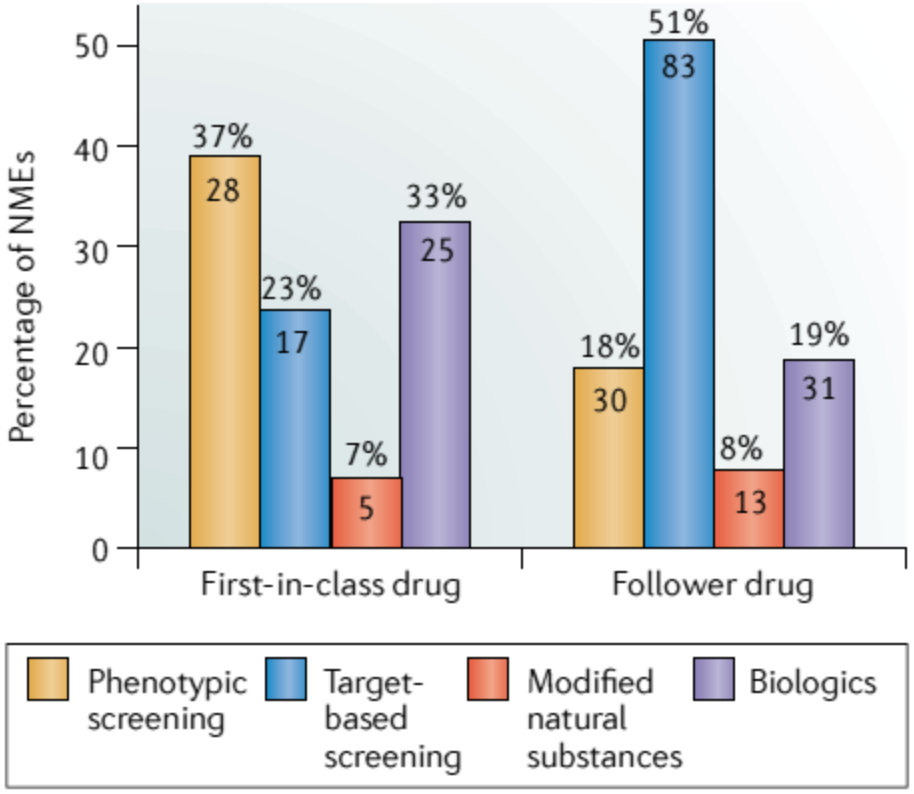
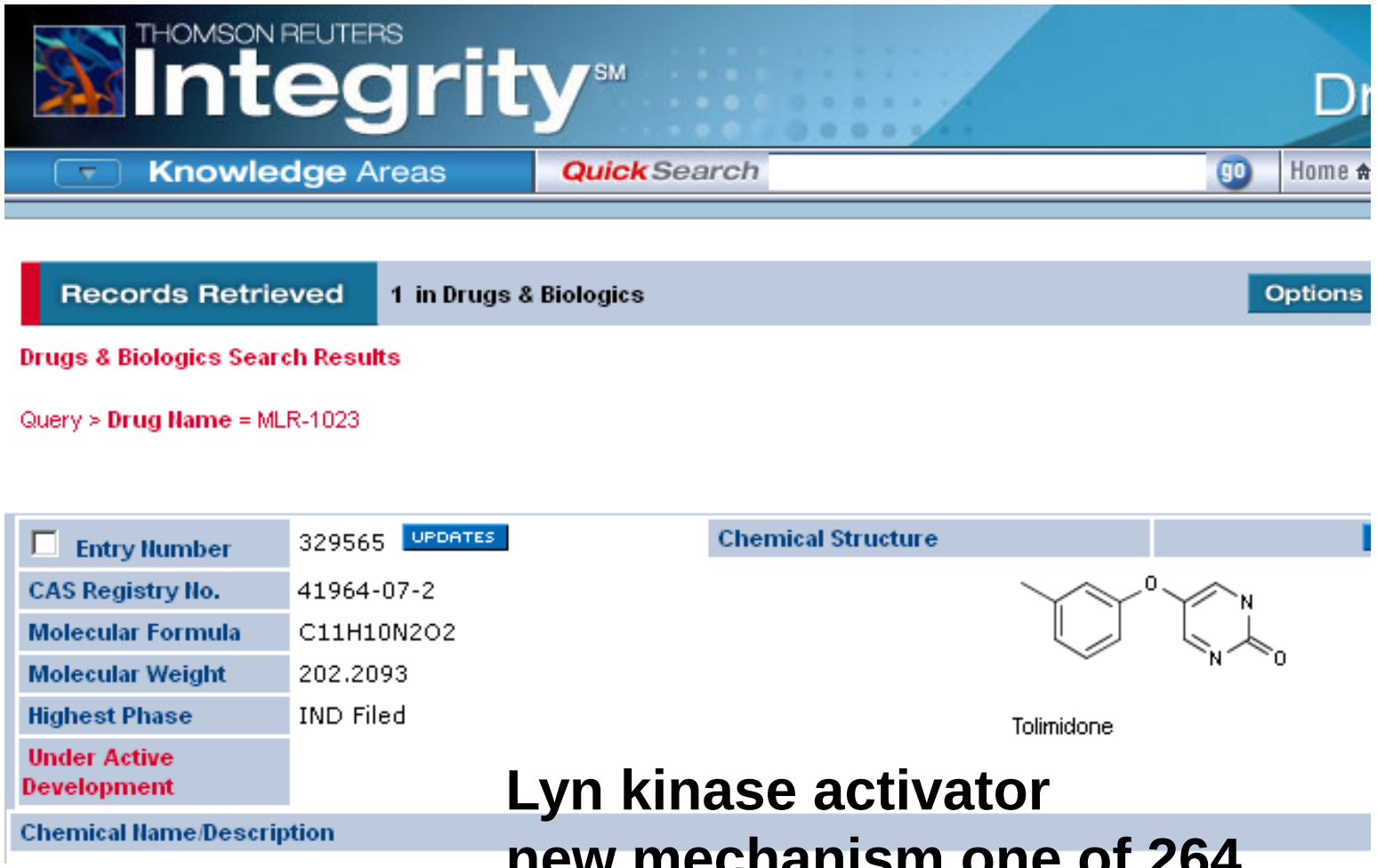


Figure 2 | **The distribution of new drugs discovered between 1999 and 2008, according to the discovery strategy.** The graph illustrates the number of new molecular

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.

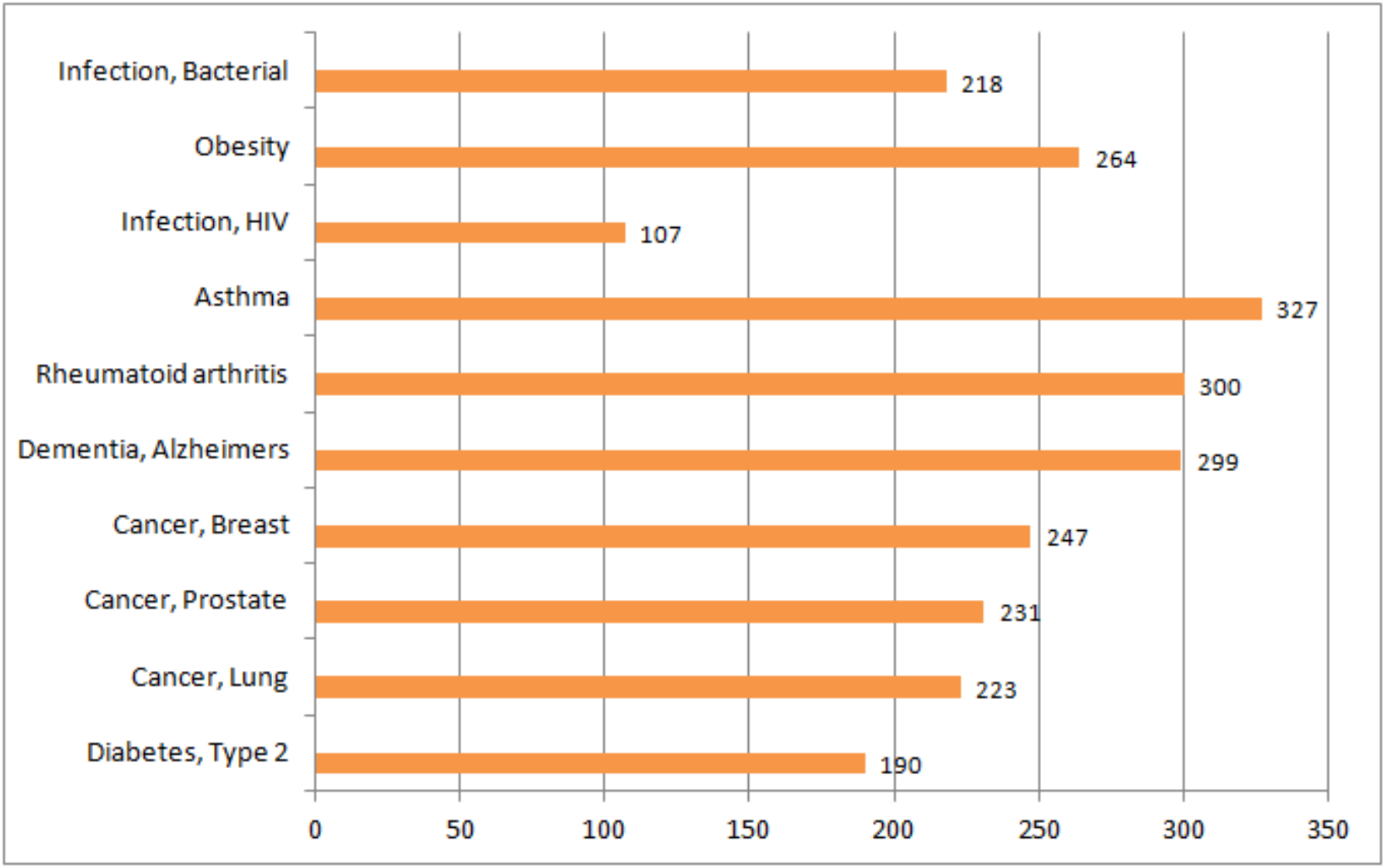
How were new medicines discovered? *David C. Swinney and Jason Anthony Nature Reviews Drug Discovery 2011 (10) 507-519.*

Repurposed diabetes drug



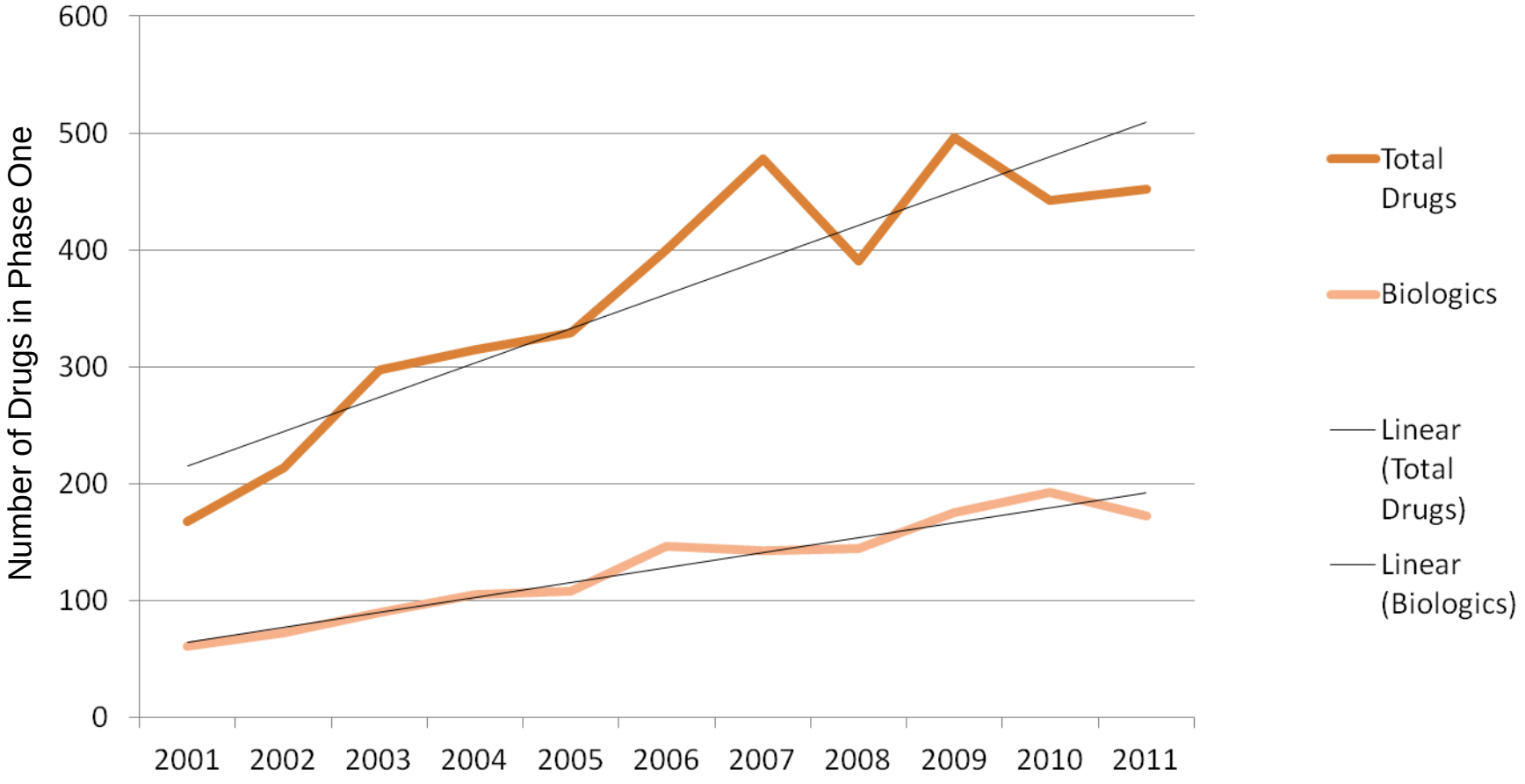
Lyn kinase activator
new mechanism,one of 264 mechanism possibilities

The Key Therapeutic Areas by no. of Associated Targets



Source: Thomson Reuters *Integrity*℠

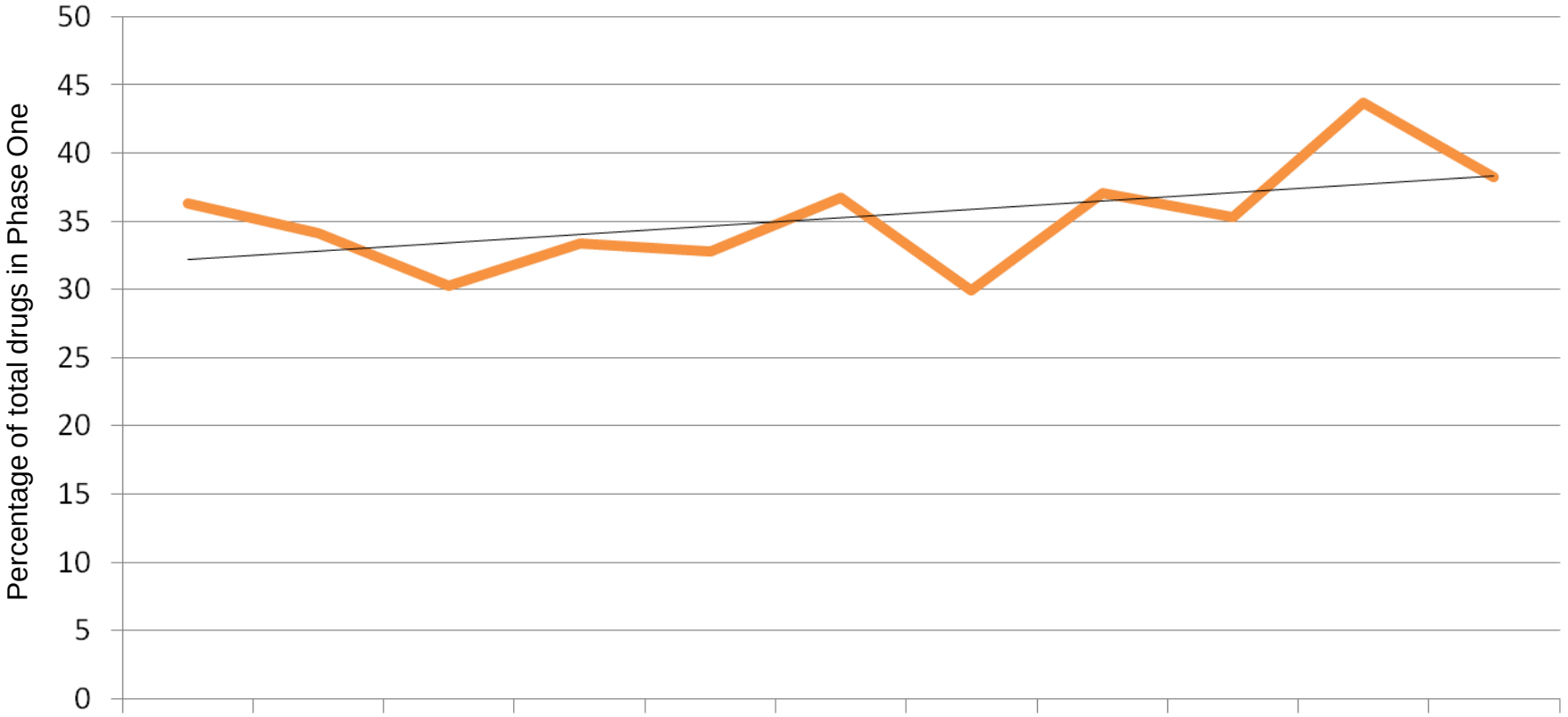
Total of Drugs in Phase One compared to Biologics in Phase One



Trendline demonstrates large increase in drugs in phase one

Source: Thomson Reuters *Integrity* SM

Percentage of Biologics in Phase One compared to Total Drugs in Phase One



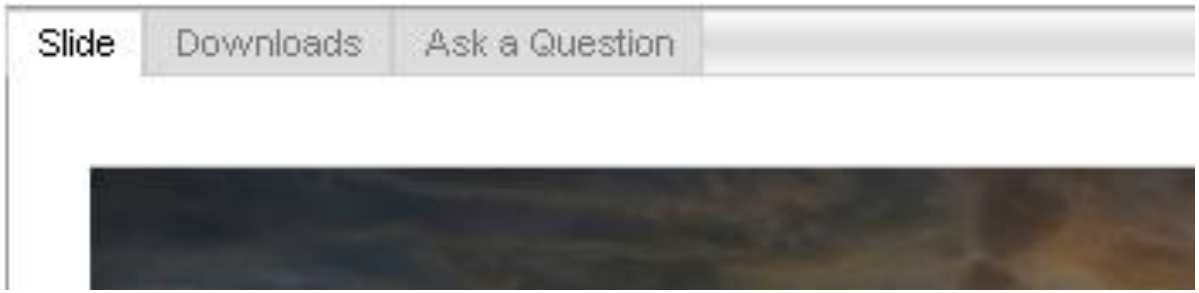
Trendline demonstrates that the percentage of Biologics in the total is increasing slowly

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.

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