US National Academies, OECD, Royal Society
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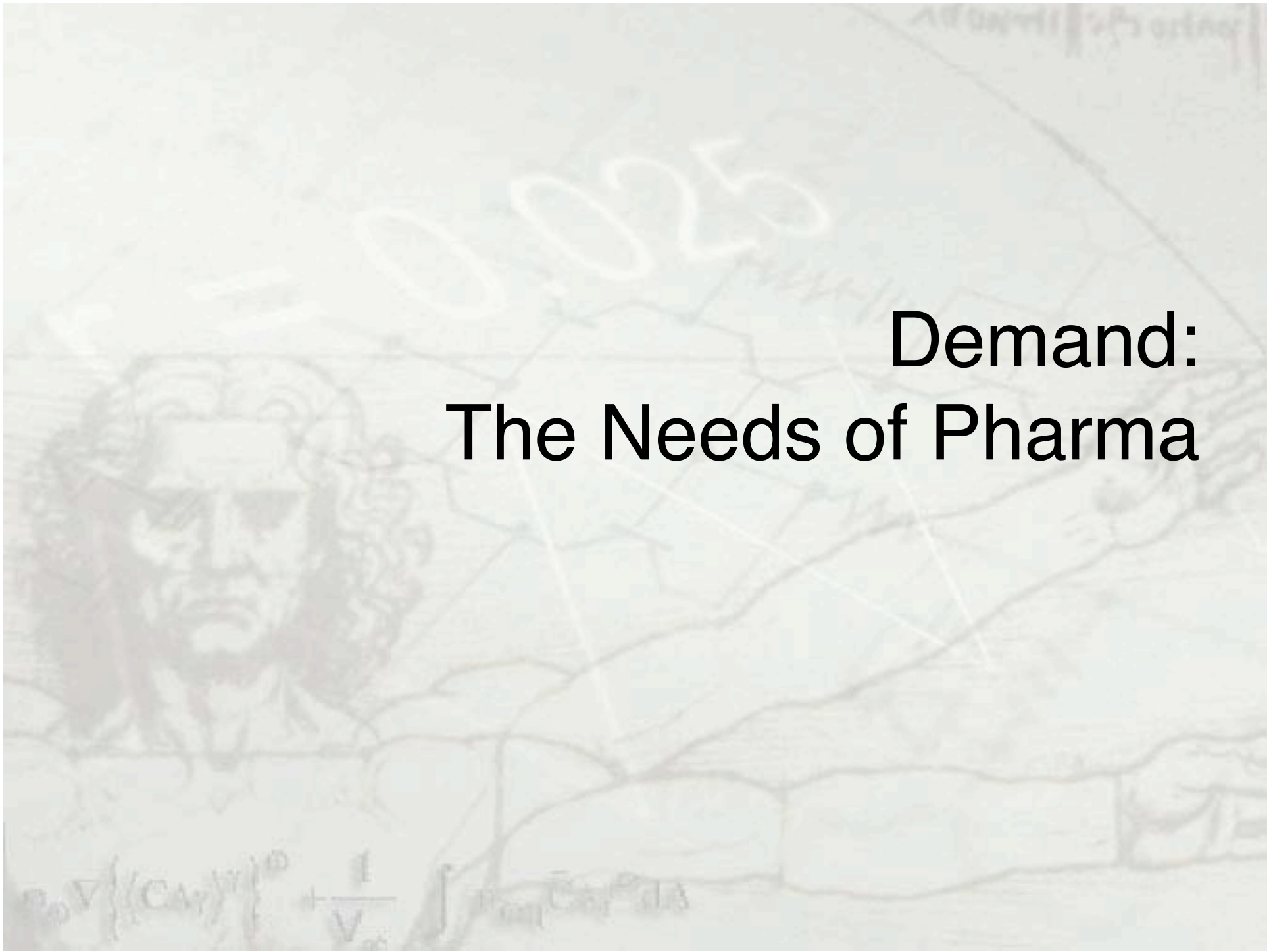
Opportunities and Challenges in The Emerging Field of Synthetic Biology: *Health & Medicine*

A view from the pharmaceutical sector

Adriano Henney

Vision for SynBio
(RAEng Report)

- 5,10 and 25 year horizons
- Improving/ reproducing natural therapies (artemisinin),
- Biosensors
- Optimisation of biopharmaceutical production
- Personalised therapy, reduced toxicity and side effects



Demand:
The Needs of Pharma

Harvard Business Review
www.hbr.org

To save themselves, pharmaceutical companies will have to break up their giant R&D organizations, overhaul core processes, and put passionate scientists back in charge.

Rebuilding the R&D Engine in Big Pharma

by Jean-Pierre Garnier

Historically, the pharmaceutical industry has been a leader in financial performance and value creation. In recent years, however, its stock-market record has raised doubts about the sustainability of that history along with fundamental questions about the industry's health. From December 2000 to February 2008 the top 15 companies in the industry lost roughly $850 billion in shareholder value, and the price of their shares fell from 32 times earnings, on average, to 13.

COMMENTARY

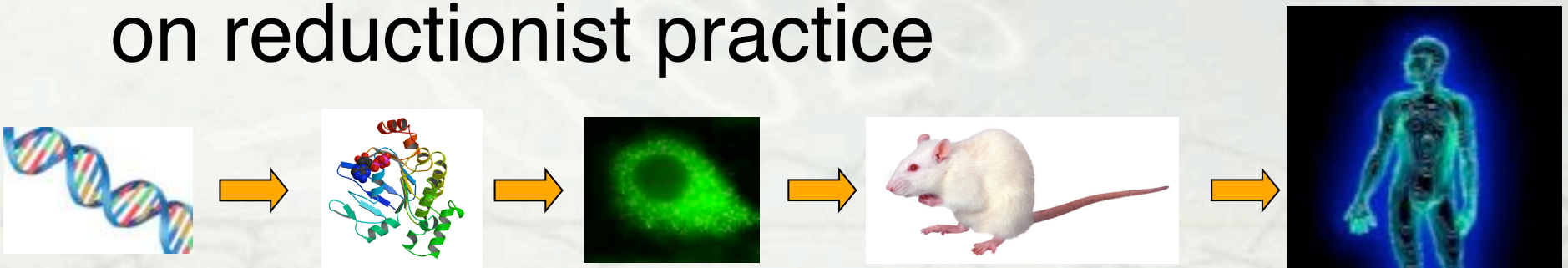
The impact of systems approaches on biological problems in drug discovery

Leroy Hood & Roger M Perlmutter

"The pharmaceutical industry **will lose nearly $80 billion in revenue by 2008** due to patent expiration, and the current drug pipeline will only replace a small fraction of this value. **Existing approaches to drug discovery are failing to keep up with the demands** of an industry that experienced 11% average growth per year for more than 30 years."

Nature Biotechnology (2004) **22** (10): 1215-1217

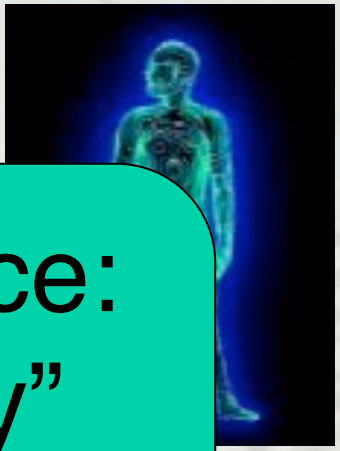
The drug discovery pipeline is built on reductionist practice



Data

- “Omics” technologies generate a large amount of data, but information ≠ knowledge
- Reductionist approaches only address individual components of a bigger, complex system
- Animal models tend to be poor representations of human disease
- Cannot understand or predict how the wider system will behave → unanticipated effects seen in man

The drug discovery pipeline is built on reductionist practice



Need step change in science: Move from a "guess & pray" mentality to adopt "predict & test" strategies

- "
in
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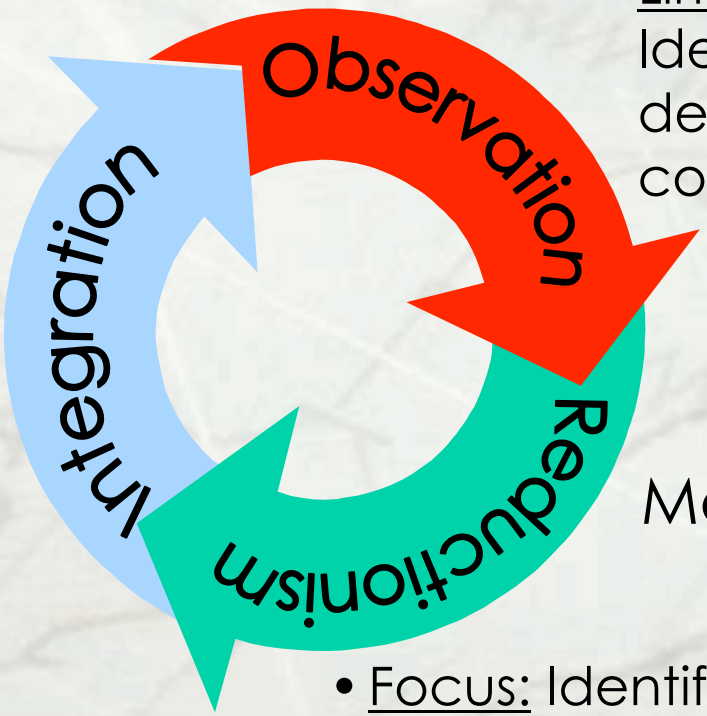
21st Century Physiology

- Focus: Organ function &metabolism
- Limitation: Identification & definition of cellular components



Systems Biology
2000 ->

- Focus: Convergence & Integration of previously separate areas of science
- Limitation: Quality, and consistency of quantitative data; computational infrastructure & tools

Molecular Biology
1950 ->

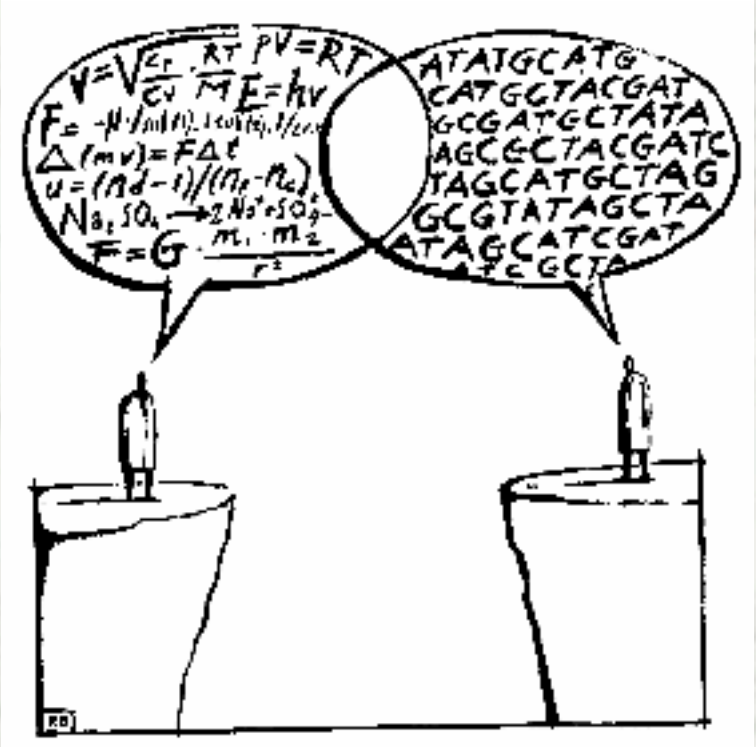
- Focus: Identification of individual components of systems & study of function
- Limitation: Inability to explain how interactions -> phenotype

SynBio: Drug discovery & development

- Current success in area of metabolic engineering- artemisinin
- Extension to target complex physiology needs understanding of system dynamics
  - System responses to interventions
- SynBio and SysBio are tightly linked in context of human biology and medicine

Industry Hurdles & Challenges

- Building evidence of potential utility
  - Credible & reproducible data relevant to pharmacology & medicine
- Natural resistance & caution to adoption of new technologies/ ideas
  - Post genome effect
- Skills
  - Maths for biology & *vice versa*
  - Biology with an engineering perspective
  - Multidisciplinary thinking



Hurdles & Challenges 2

- Key developments in Synthetic & Systems Biology will largely be driven out of academia & biotechs
- Application of the academic learning to meet the challenges of improving health and tackling disease needs to be driven by pharma & biotechs
- Industry & Academia have to find ways of working together if we are to succeed:
  - Significant economic and regulatory constraint for the industry, when the appetite for exploring unproven technologies is likely to be low
  - Must find optimal mechanisms to overcome this hurdle
  - Examples of JV/ PPPs in place.. IMI, MMV etc

COMMENTARY

The impact of systems approaches on biological problems in drug discovery

Leroy Hood & Roger M Perlmutter

"**It remains to be seen how industry will exploit this novel opportunity.** Will in house efforts bolstered by academic partnerships permit implementation of systems approaches in the traditional pharmaceutical houses, or will powerful and effective new systems-biology companies emerge to capture the front end of the drug discovery market?

In our view, **systems biology will inevitably change the rules that govern the selection and development of new therapeutics** and will catalyze the **development of personalized, predictive and preventive medicine** in the next decade. The fascinating question is: **who will lead this extraordinary change process? "**

Nature Biotechnology (2004) **22** (10): 1215-1217

nature Vol 455|9 October 2008

COMMENTARY

A network solution

With the right plan, systems biology can empower drug discovery, say **Adriano Henney** and **Giulio Superti-Furga**. Field leaders have contributed and now the authors want to hear from you.

Systems biology focuses on interactions within and between the mechanisms that combine to give rise to the function and behaviour of a biological system. To some it is the logical and inevitable next-level understanding that will propel drug discovery from empiricism to mechanism-based rational design. Countless column inches in the scientific press hail systems approaches as the latest weapon to tackle the major challenges of modern medicine. But to others, it is an ill-defined pile-up of '-omics' approaches that in terms of usefulness for drug discovery represents the culmination of all delusions. So it is not a suprise that the pharmaceutical industry remains unconvinced, fearing parallels with the genomics hype and considering the approaches currently impractical.

and often semi-quantitative data that are hard to integrate into biological models. Additionally, there are multiple gaps in the data stream linking experiment to clinical outcome. For the field to advance effectively, we need to find new ways to create a reliable data pipeline that is compatible with the needs of systems biology. This pipeline can only be achieved realistically by the establishment of a consortium to set appropriate standards, quality-control metrics and processes on behalf of the community. How best to achieve such standardization procedures remains to be seen, but as soon as they are established, initial efforts should focus on closing the data gaps and on acquiring multiple data types on a limited number of standard models and samples. Lastly, it is of paramount importance to concentrate on the creation of necessary

response to combination therapies[6].

Although they are already being used extensively post-hoc in an explanatory mode to rationalize specific outcomes, these models and approaches have not yet been integrated routinely as tools in early drug discovery. Concentrating on the development and refinement of these approaches, and finding opportunities to apply them in areas, such as solid tumours and inflammation, in which other methods have proven inefficient, would help to build confidence in the ability of systems-based approaches to make predictions. We think that this step represents a good

EMBO reports

science & society

Who will take up the gauntlet?

Challenges and opportunities for systems biology and drug discovery

Adriano M. Henney

In 2002, the Editorial that accompanied the launch of *Nature Reviews Drug Discovery* stated that "[d]espite all the excitement that accompanies each wave of technical innovation, from protein structure determination to proteomics, and from combinatorial chemistry to e-clinical trials, the fundamental truth is that pharmaceuti-

During the past 10 years, the cost of bringing a single new drug to market has escalated hugely to somewhere in the region of US$1 billion; however, the success in doing so has approximately halved compared with the early 1990s, and the time taken has doubled to ~12 years, although efforts are succeeding in reducing

…[system biology's] potential impact on interpreting the complexity of physiological systems that underpin the development of new medicines still needs to be tested

Concluding points

- There is no alternative to adopting systems approaches to interpret physiological complexity
- Gathering evidence of utility for human health is imperative to demonstrate impact (SysBio & SynBio)
- Loads of effort/ funding- little coordination (SysBio… SynBio?)
- Is true potential and benefit to human health failing to be realised because of lack of readiness to study application in an industrial setting? (SysBio less so for SynBio?)
- SysBio = 21st C Physiology
- SynBio = Bioengineering?