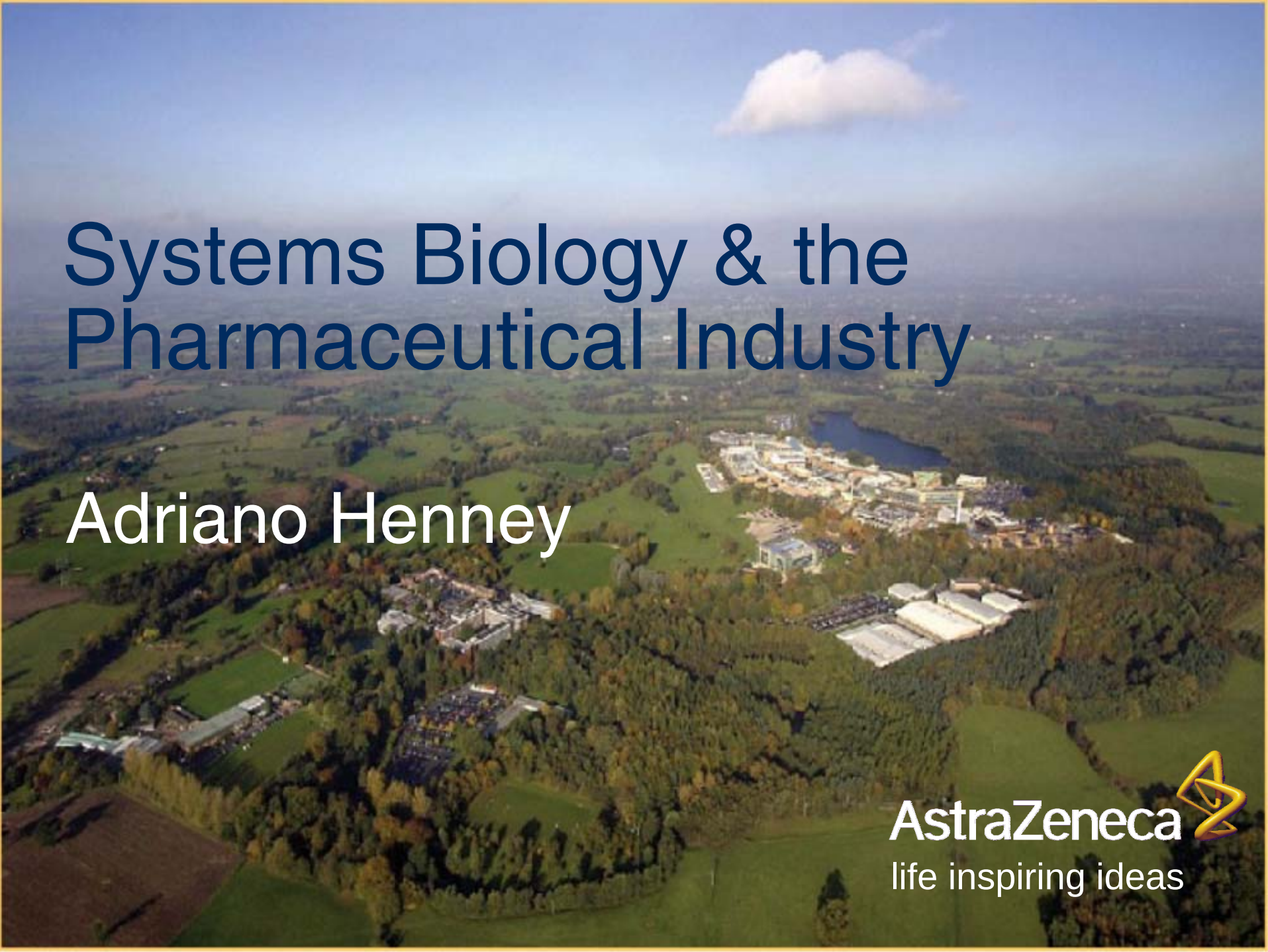
Systems Biology & the Pharmaceutical Industry

Adriano Henney



AstraZeneca

life inspiring ideas

Drug Discovery
What is disease?

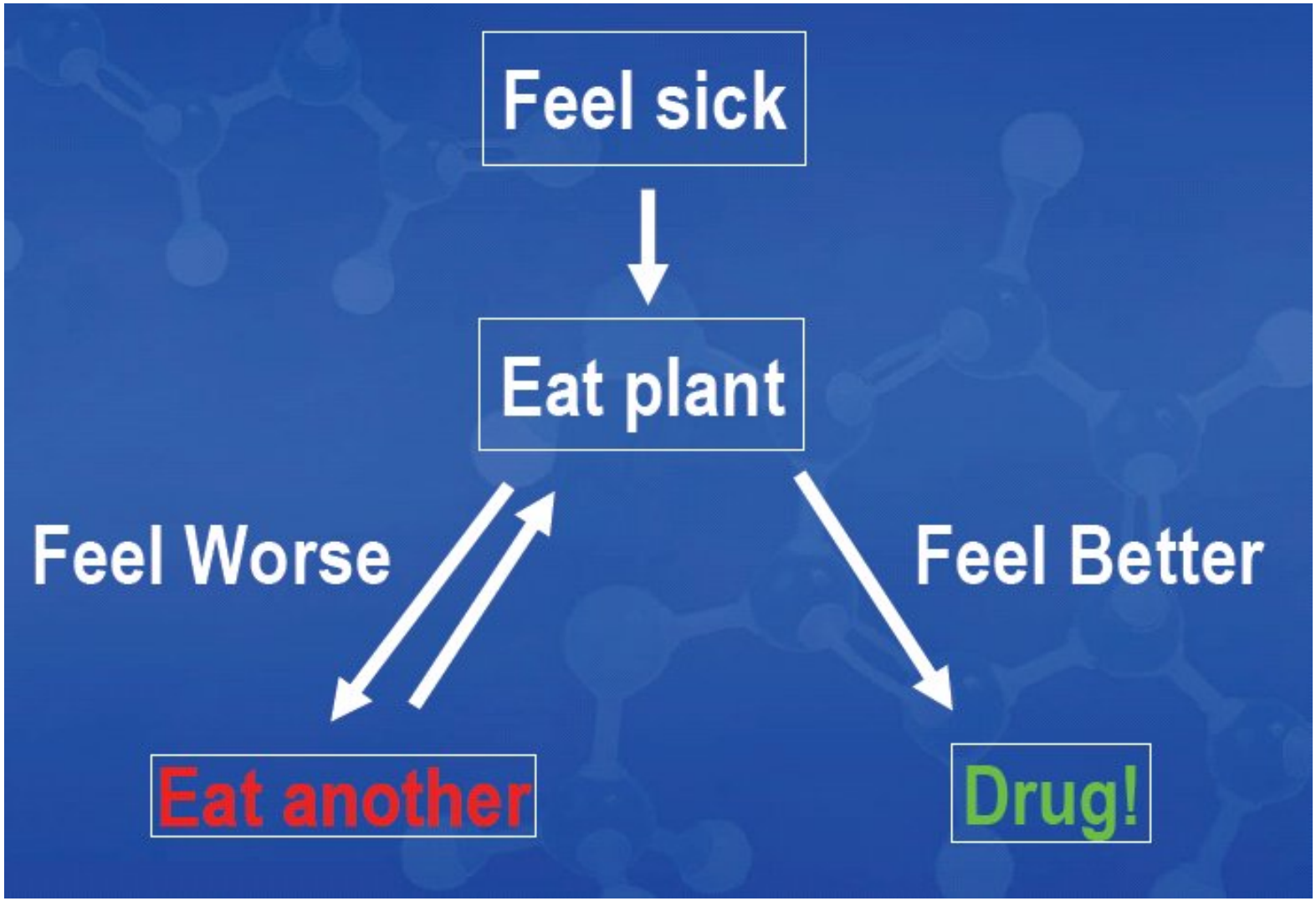
- A condition which alters or interferes with the normal state of an organism and is usually characterised by the abnormal functioning of one or more of the organism's systems, parts or organs

- Diseases can be complex but the basic cause can often be traced to an infectious agent such as a bacterium or virus or to the over- or under-activity of a key cellular process or control mechanism

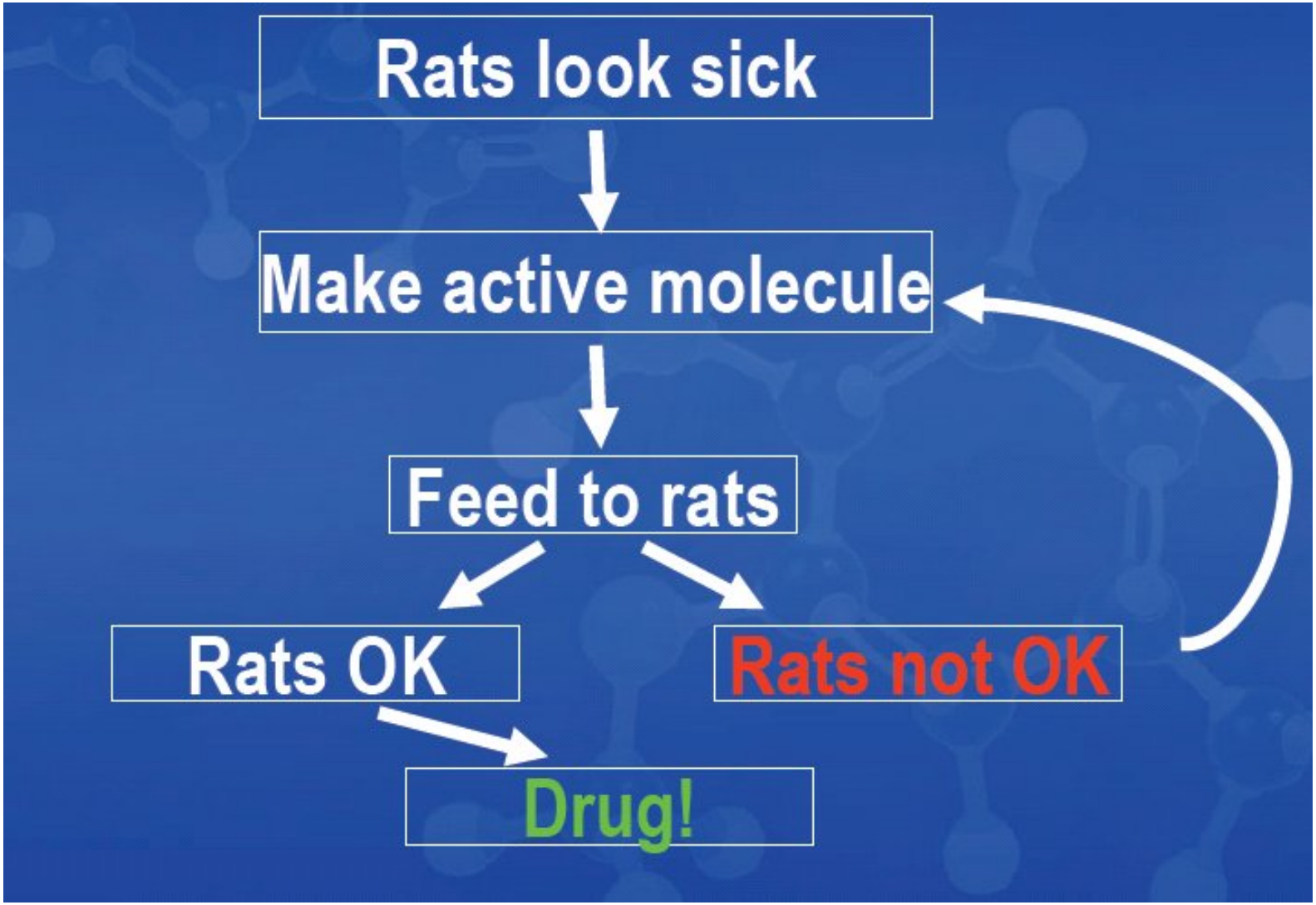
Drug Discovery
Pharmaceutical drugs – what are they?

Chemical compounds (small molecules or “biologicals”) that either inhibit or stimulate targeted biological mechanisms involved in disease processes and which have pharmaceutical properties consistent with allowing productive access to the target in the disease situation

Drug Discovery in the Early Days



Drug Discovery: Golden Age



Drug Discovery: 21st Century

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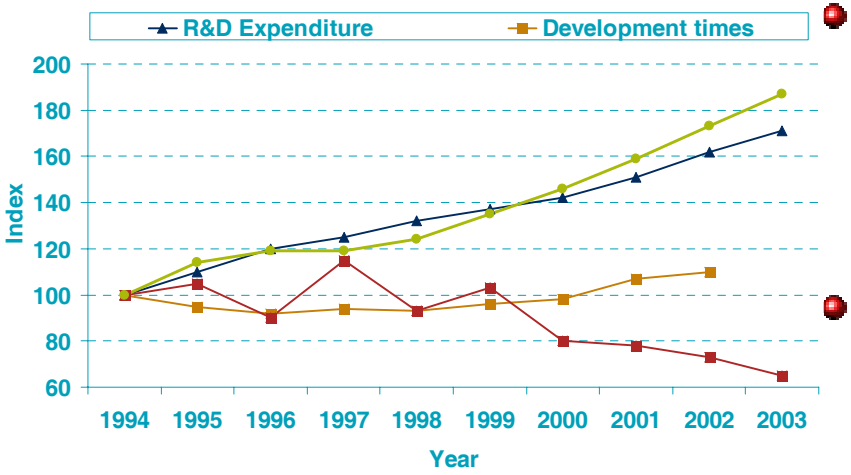
The Genome Revolution: Hope & Expectation

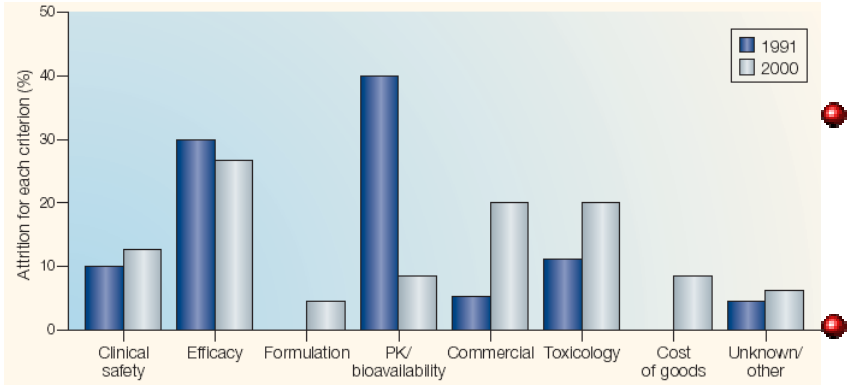
- Huge advances in genetics, molecular & cellular biology and supporting technologies
- Acquisition of highly detailed molecular information in high quantity and quickly
  - Ability to define disease at the molecular level, with expectation that this would increase understanding
  - Hope that this would deliver novel therapies quickly

Drug Discovery and Development in the 21st Century

Data

Pharma Challenges





- Rising cost of R&D but not paralleled by increased number of NME approvals
- Increased risk due to increased difficulty of developing innovative molecular targets
- Continued attrition due to tox and lack of efficacy
- Regulatory environment more challenging: risk/benefit ratio increasingly difficult to achieve

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R&D Process

Compounds Screened

Discovery (2 - 10 yrs) — 5,000 – 10,000

Preclinical — 250

PI — 5

PII

PIII

File for Registration — 1

-10 -5 0 5 10 15

10 – 12 years to bring product to market

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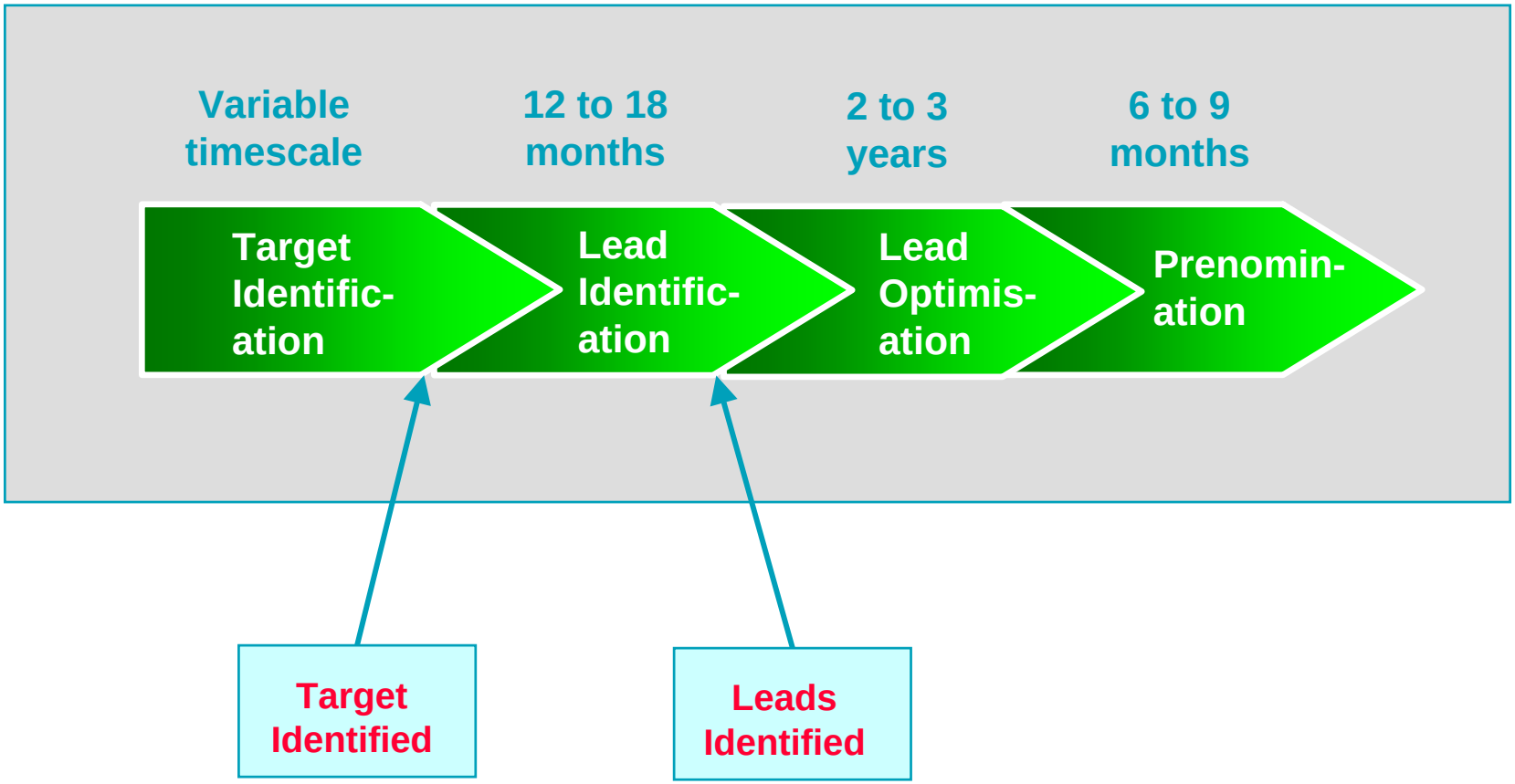
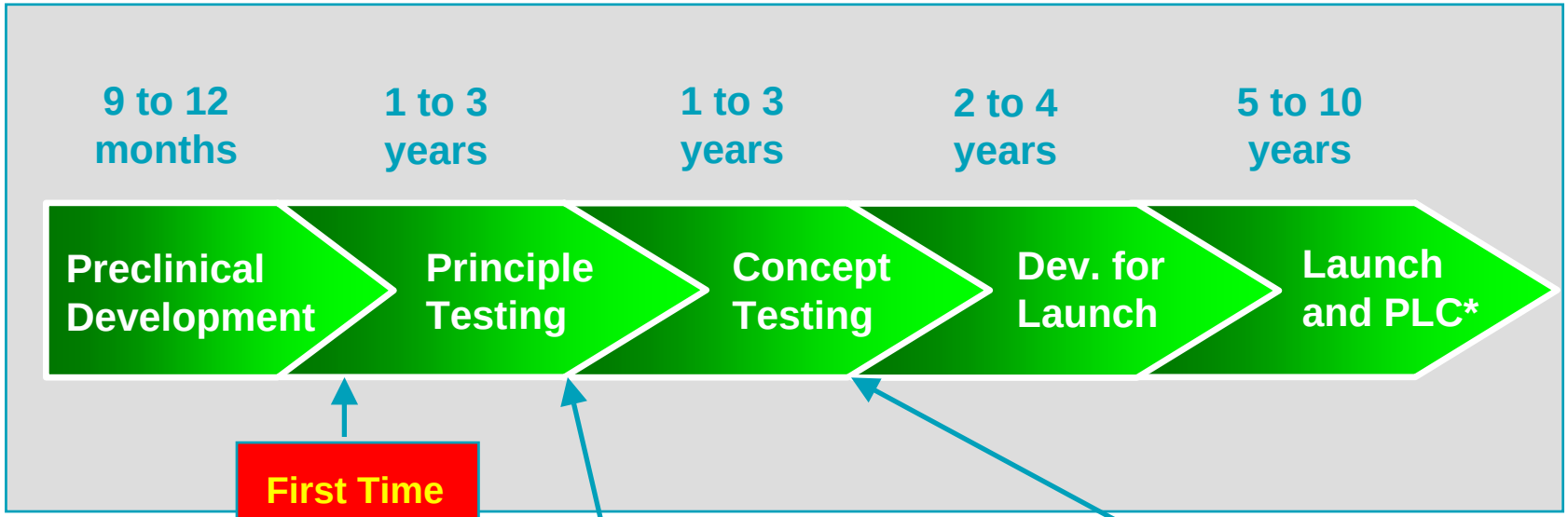
Drug Discovery
Discovery-led activities: the early stages



Drug Discovery
Development-led activities: the later stages



Studies in healthy volunteers or patients using biomarkers or in patients using a surrogate or clinical endpoint

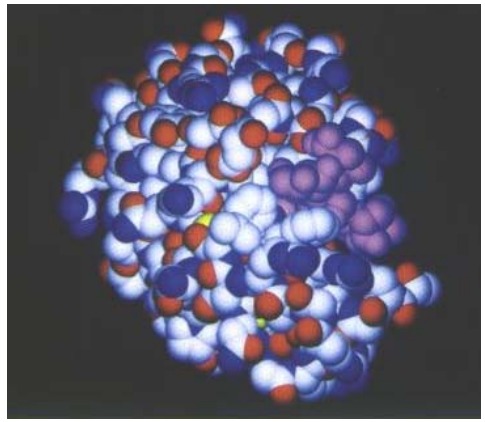
Proof of Principle

Demonstration of efficacy and safety in the target patient group

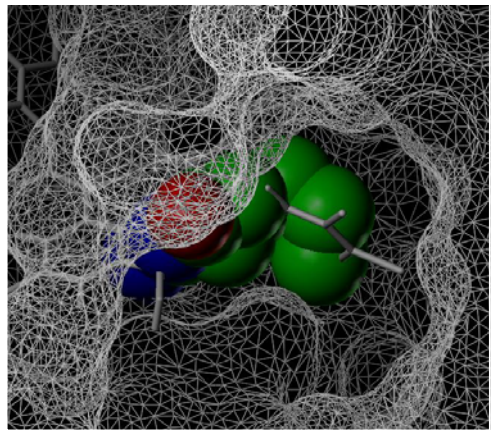
Proof of Concept

Target Identification Phase

Goal:
Identify a target whose modulation could provide clinical benefit in a relevant disease



- **Most targets are proteins**
  - Large biomolecules with a biological function



- **Most drugs are small compounds**
  - Interact physically with target
  - Alter biological function of target

Target Identification → Hit Identification → Lead Identification → Lead Optimisation → CD Nomination

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Drug Discovery
Strategies for target identification

- Biological understanding
  - Study of diseases in whole organisms
    - Clinical sciences
    - In vivo animal studies
- Molecular approaches
  - Driven by advances in molecular biology

Target Identification
Biological Understanding

- Based on good biological intelligence – understanding biological systems and how they work
- Traditionally the main target discovery strategy
- Remains important for diseases in which the relevant phenotype can only be detected at the whole organism level, e.g.
    - Atherosclerosis
    - Obesity
    - Heart failure
    - Neurodegenerative disorders
    - Hypertension
    - Behavioural disorders

Target Identification
Molecular approaches

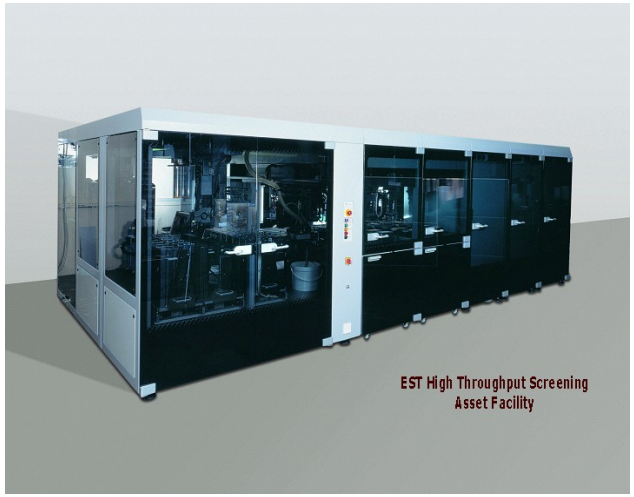
Driven by technologies that attempt to correlate molecular changes with human disease:

- Gene expression: genomics
- Protein expression: proteomics
- Genetic variation: genetic association
  - Absence or mutation of a particular gene can result in serious disease or risk of contracting a disease
    - e.g. Apolipoprotein E – cardiovascular disease
    - BRCA 1 and 2 – breast and ovarian cancer

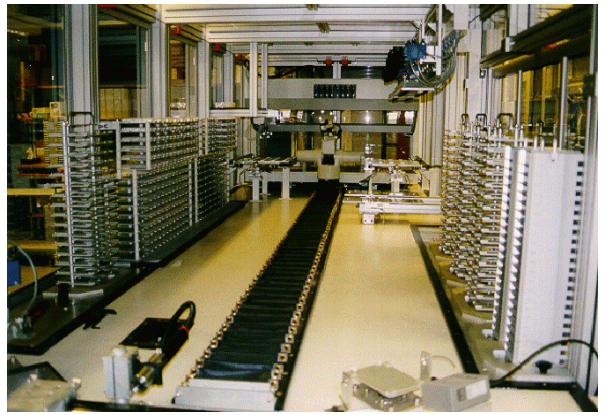
Hit Identification Phase

Goal:
Identify compounds that act at the target and produce the desired biological effects

Develop a High Throughput Screen (HTS)



•Screen large compound libraries: 50'000 – 1'000'000



Target Identification → **Hit Identification** → Lead Identification → Lead Optimisation → CD Nomination

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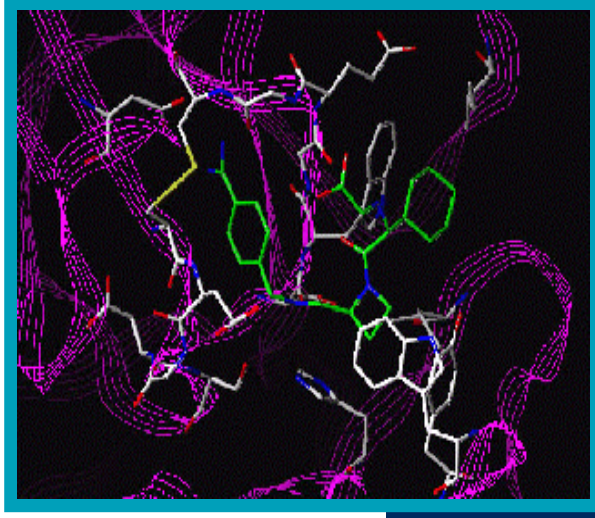
Lead Identification Phase



Goal:
Identify several structurally distinct chemical series that produce the desired pharmacological effects, have acceptable drug like properties and are patentable.

- Develop Structure Activity Relationship (SAR) with respect to
  - Potency
  - Selectivity – what other targets are affected?
  - Drug Metabolism and Pharmacokinetics (DMPK)
- Apply knowledge of target protein structure to chemical design

Target Identification → Hit Identification → **Lead Identification** → Lead Optimisation → CD Nomination

Drug Discovery
Lead Optimisation

The application of medicinal chemistry to produce optimised analogues of a lead series to deliver one or more Candidate Drugs (CDs)

Lead Optimization Phase

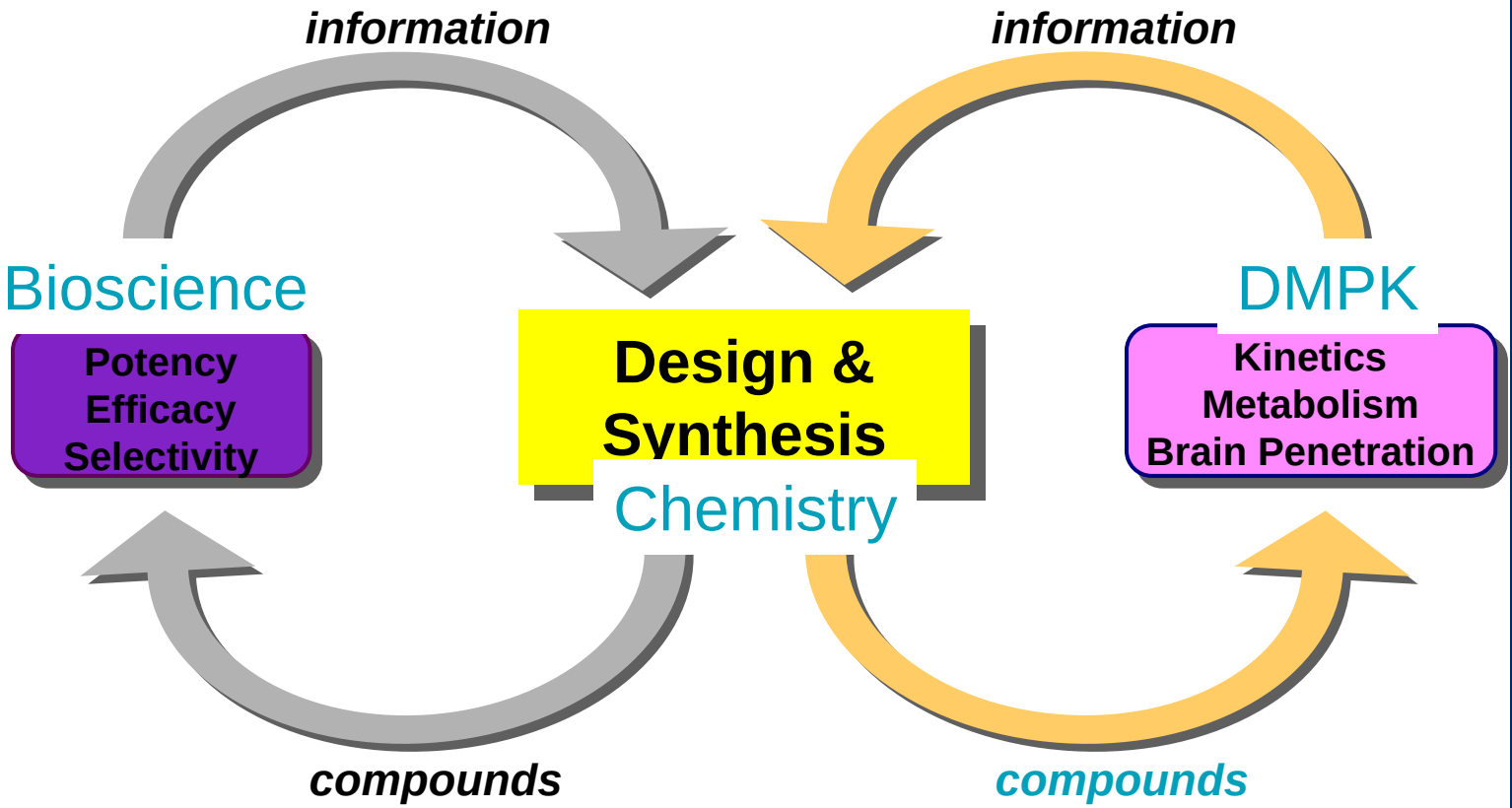
Goal:
Identify 2-4 compounds that meet the CDTP

- Optimise lead compounds with respect to
  - Potency
  - Selectivity
  - DMPK
  - Effects in disease
  - Model safety
- Scale up chemistry
- Define Clinical strategy: markers of drug action and disease effect.

Aims of Lead Optimisation

- Achieve in vivo efficacy in a disease and/or pharmacodynamic model, predictive of human disease, using a dose and dosing schedule consistent with the proposed clinical use in humans
- Manage target-related toxicity and minimise off-target toxicity based on predicted human levels of drug when dosing according to the proposed clinical schedule in human subjects
- If all of the desired properties are delivered, then the next step is to plan the track into human dosing for Proof-of-Principle and then Proof-of-Concept studies

Two Optimisation Cycles Needed



Complementary, synchronous & equally important

One project specific, the other generic

Lead Optimization

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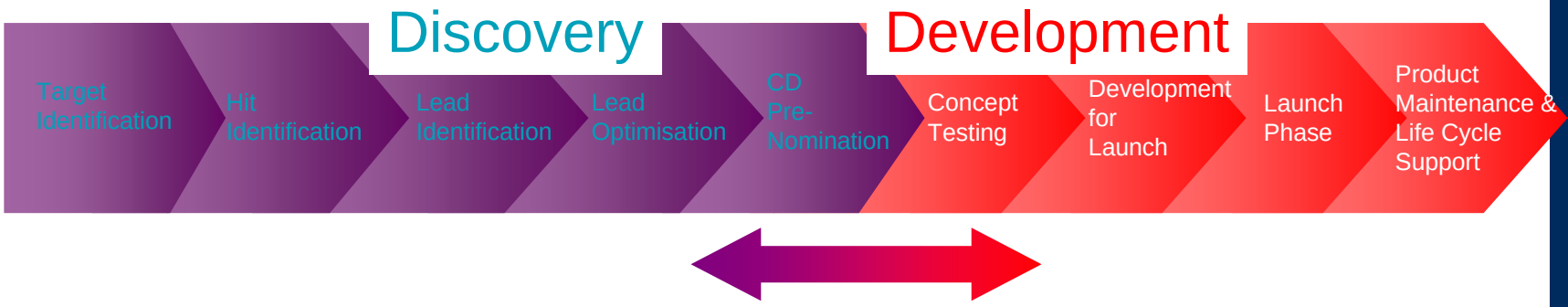
Moving from Candidate Drug to Proof of Principle

- Discovery Medicine is critical
  - Integration of pre-clinical and clinical data
  - Patient data will drive target validation
  - Development of biomarkers that facilitate early “stop/ go” decisions in phase II
- Involves close collaboration with Development partners



TG4

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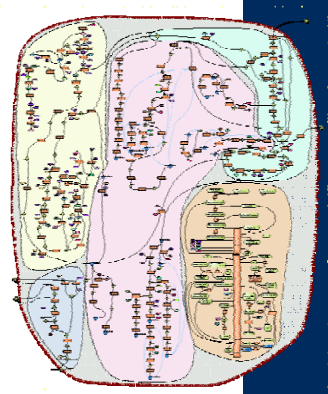
Discovery Medicine

Integrating patient and pre-clinical information



- **Mechanism:** new targets from human tissues, validation – early data in man

- **Model:** Translational disease models: animals ⟷ man

- **Marker:** Predictive response: Efficacy, safety, Appropriate patient populations

Clinical benefit > side effects

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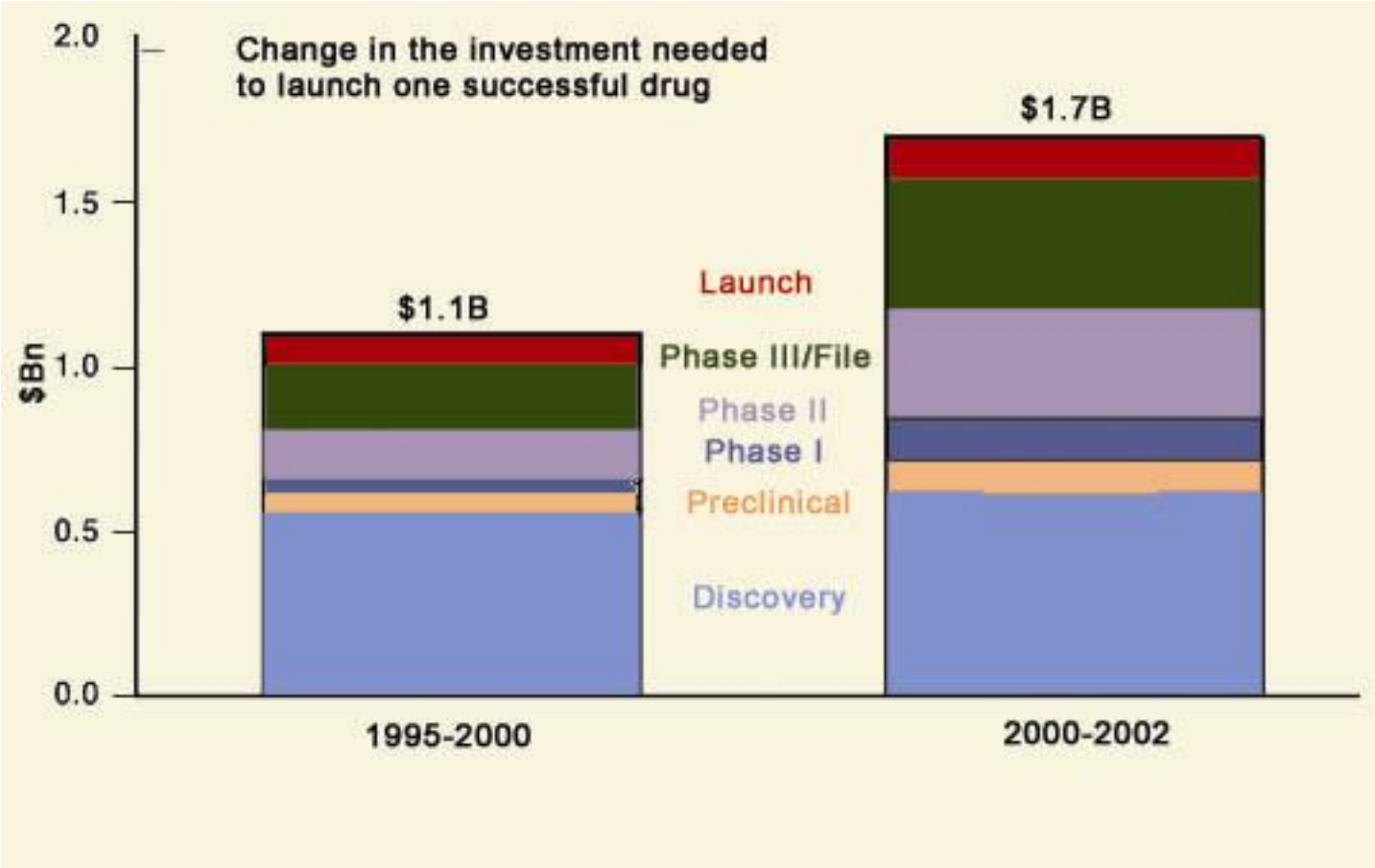
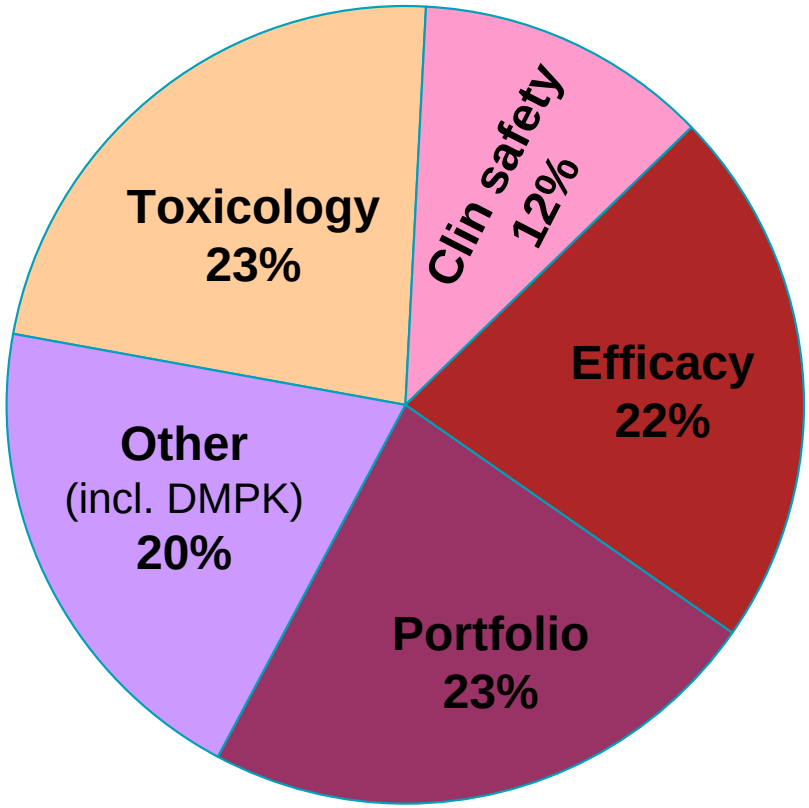
Pharmaceutical R&D Costs



Only 7% of candidate drugs become products: Reasons for failure



The Consequences

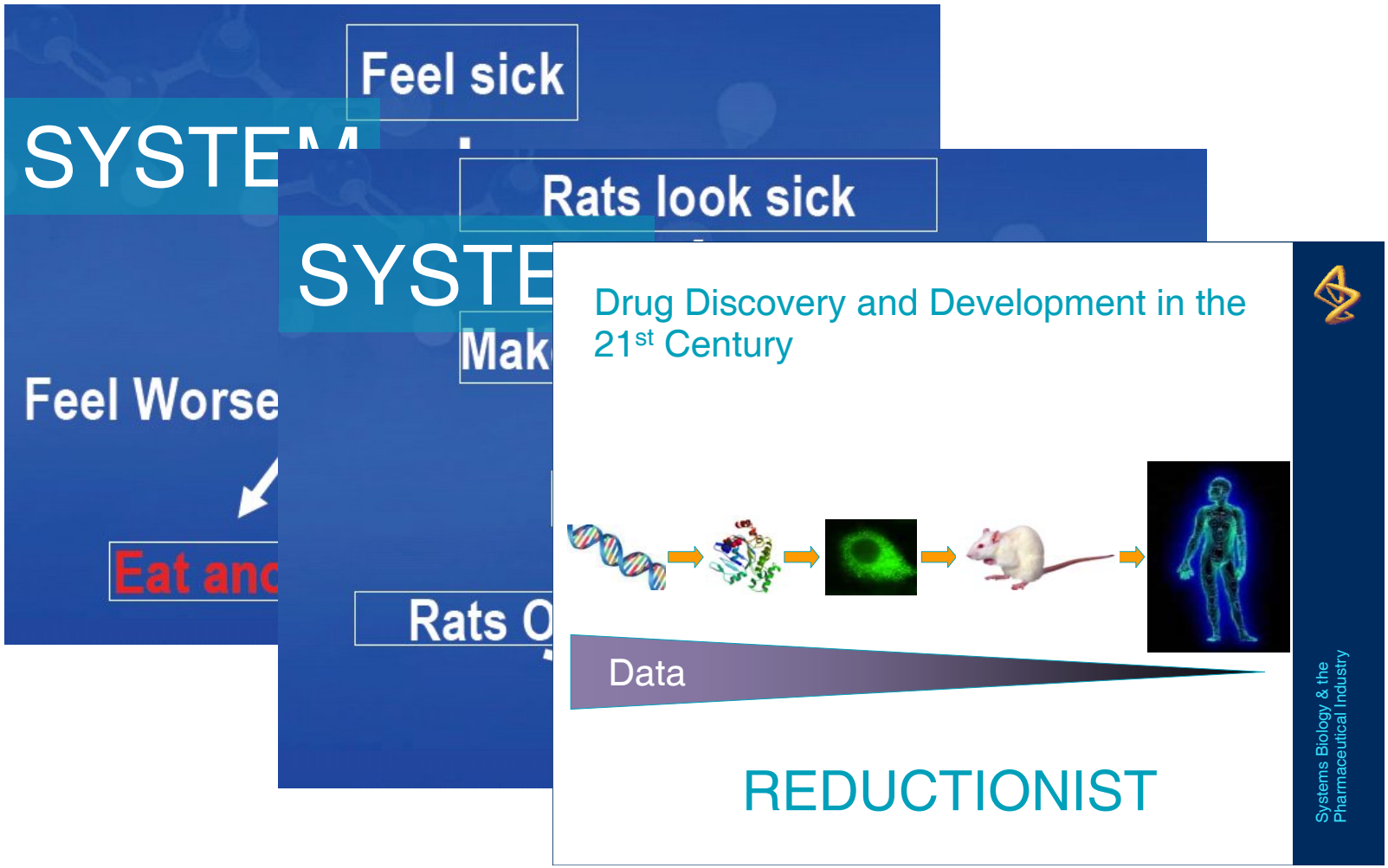
- Fiercely competitive market
- Technologies -> high throughput screening strategies using 100,000's of compounds and biological assays relevant to disease mechanism
- Refinement of compound structure & activity to enhance benefit and reduce potential for side effects
- Increasing speed and volume through pipeline
- BUT: Significantly increased output from Discovery into Development not mirrored by increased success in development

The Consequences

- Fiercely competitive market
- Tech… …egies using… …says relev…
- Refi… enha… …ects
- Incre…
- BUT: …ery into Development not mirrored by increased success in development

Question:
Is turning the handle faster and pushing more compounds through the pipeline using the current approach alone likely to be an effective solution?

The Evolution of Drug Discovery



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Post-Genome Issues

- Genetics & Molecular Biology have provided very detailed information on single entities associated with or linked to complex diseases
- Reductionist approach identifies single components and, possibly, their function, but
  - Only parts of a complex system
  - No information on cellular/ system interactions
- *"....putting together rather than taking apart, integration rather than reduction..."* Dennis Noble: "The Music of Life" OUP 2006

Henri Poincaré

(1854- 1912)

“Science is built up of facts, as a house is with stones. But a collection of facts is no more a science than a heap of stones is a house.”