Target Selection and Validation:
A More Strategic and Collaborative Approach

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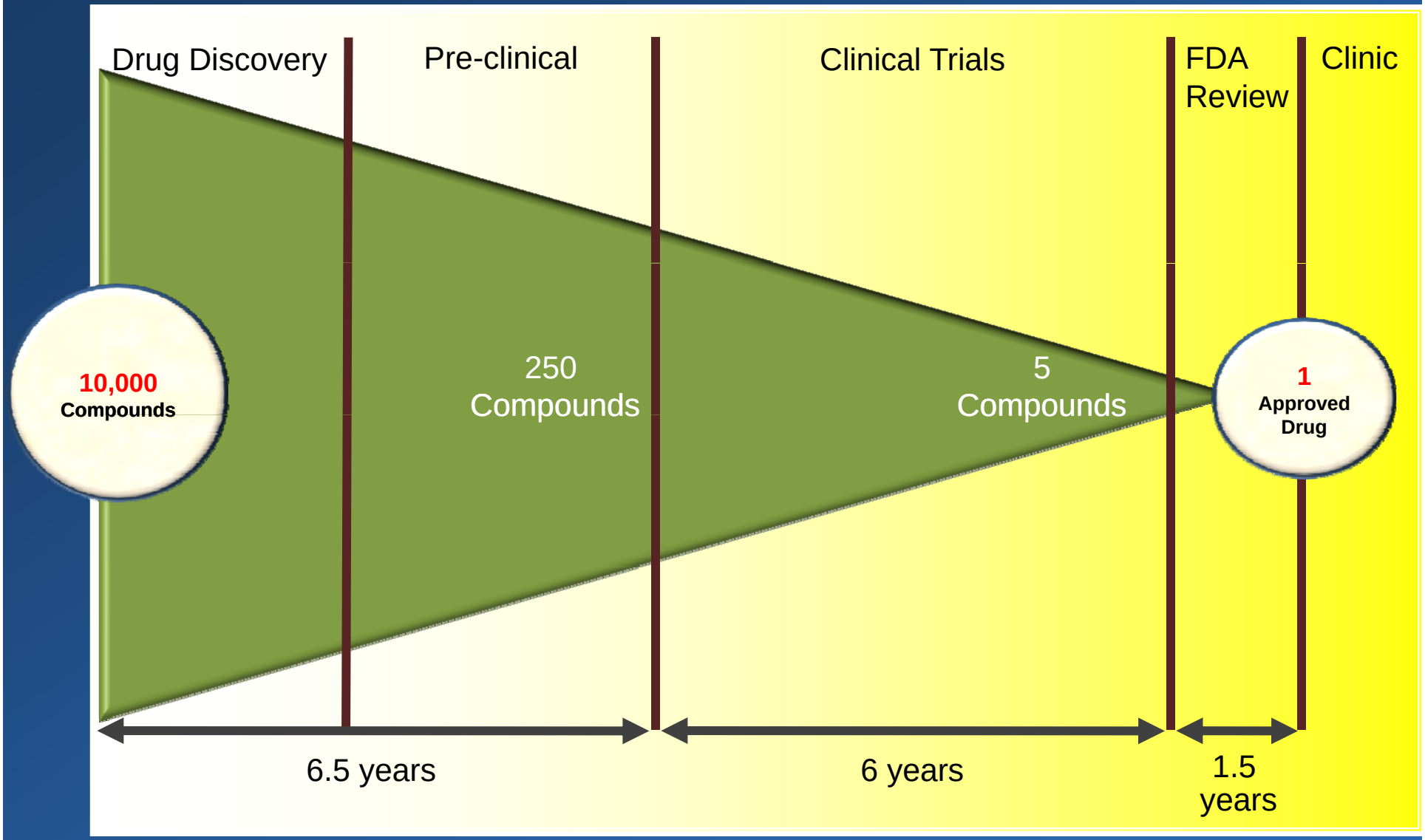
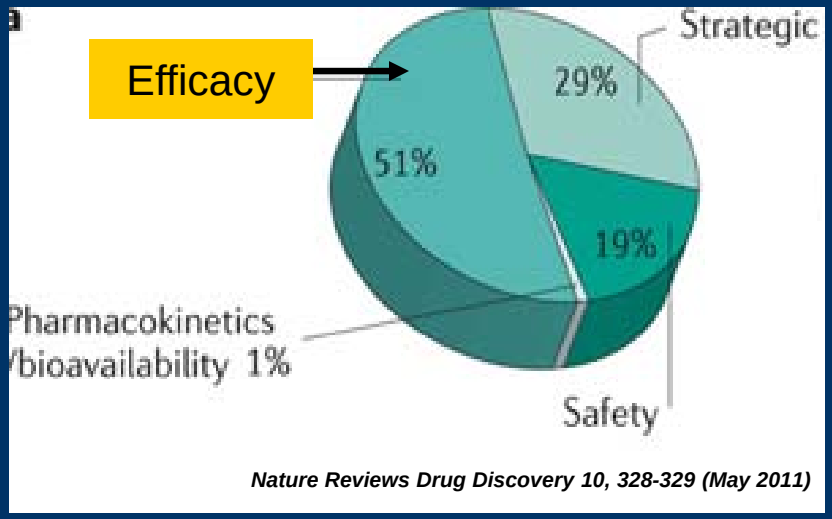
Advisory Committee to the Director

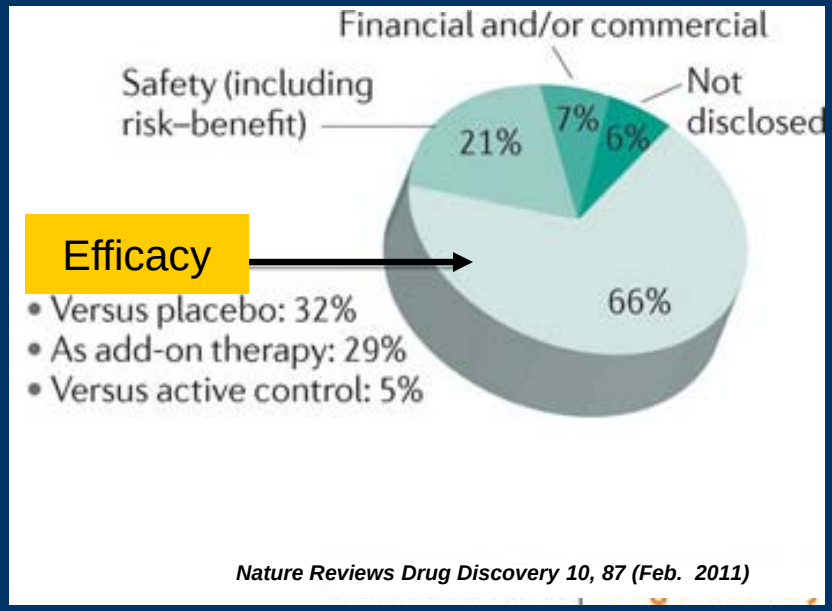
Development of New Therapeutics



High attrition rate of late-stage drug development points to the need for better target validation

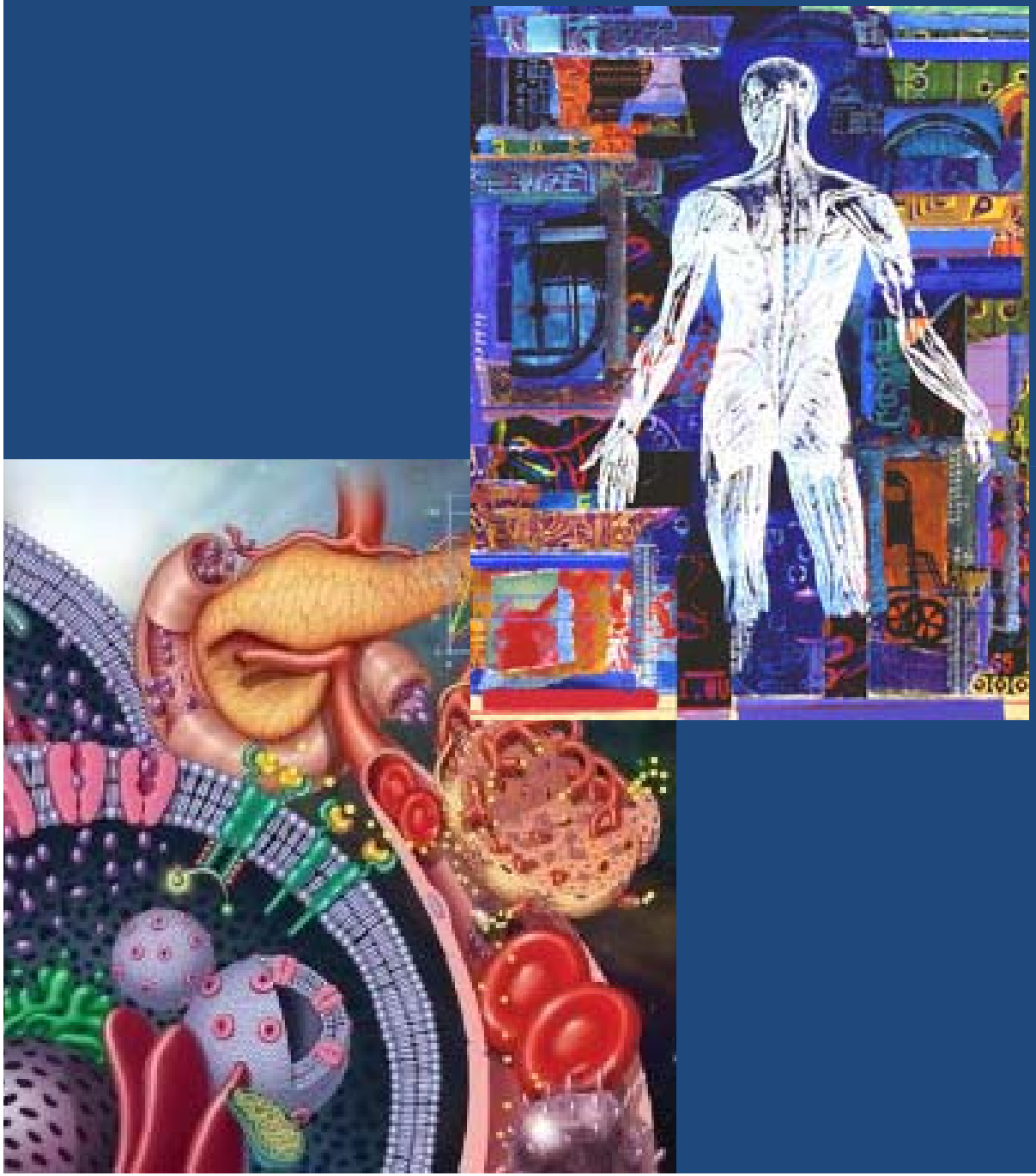


Nature Reviews Drug Discovery 10, 328-329 (May 2011)



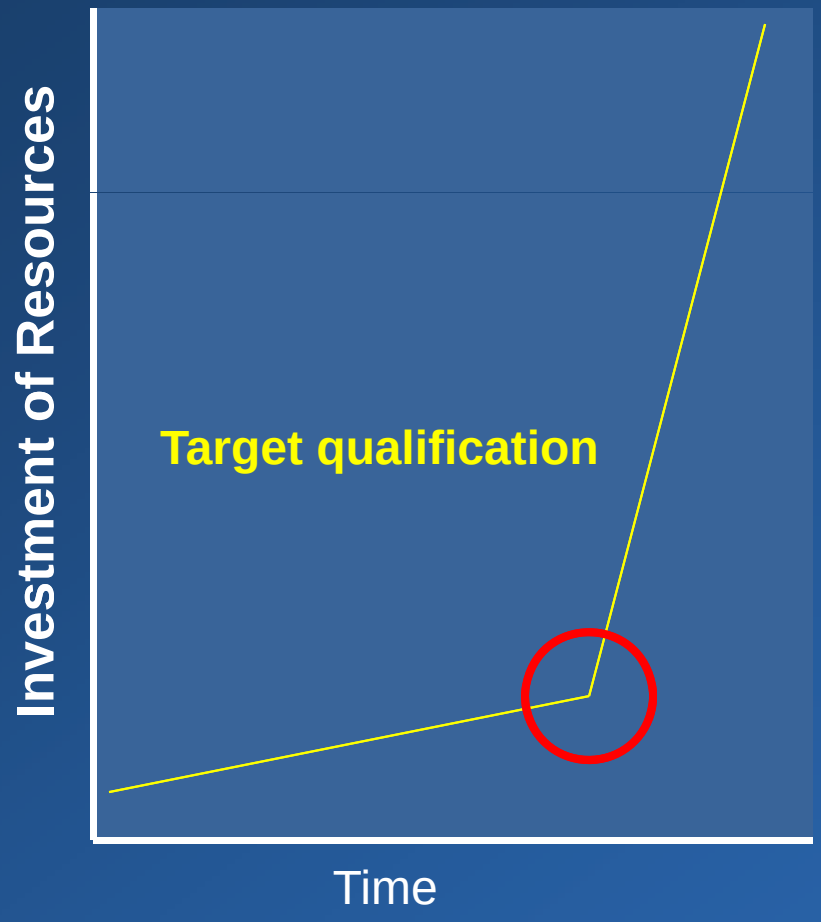
Nature Reviews Drug Discovery 10, 87 (Feb. 2011)

- **Phase II failures (2008-2010):**
  - **51% due to lack of efficacy**
- **Phase III and submission failures (2007-2010):**
  - **66% due to lack of efficacy**



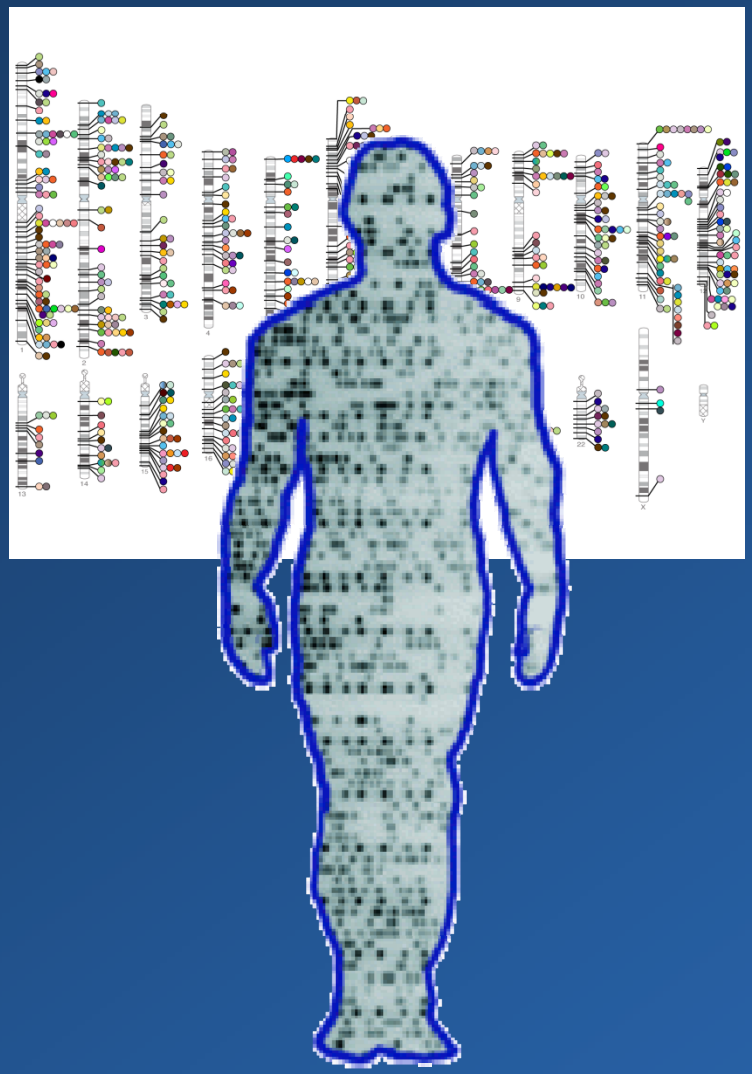
- **Needed:**
- **Full understanding of the target's role in normal physiology and disease pathogenesis**

Taking Another Look at Criteria for Target "Qualification"



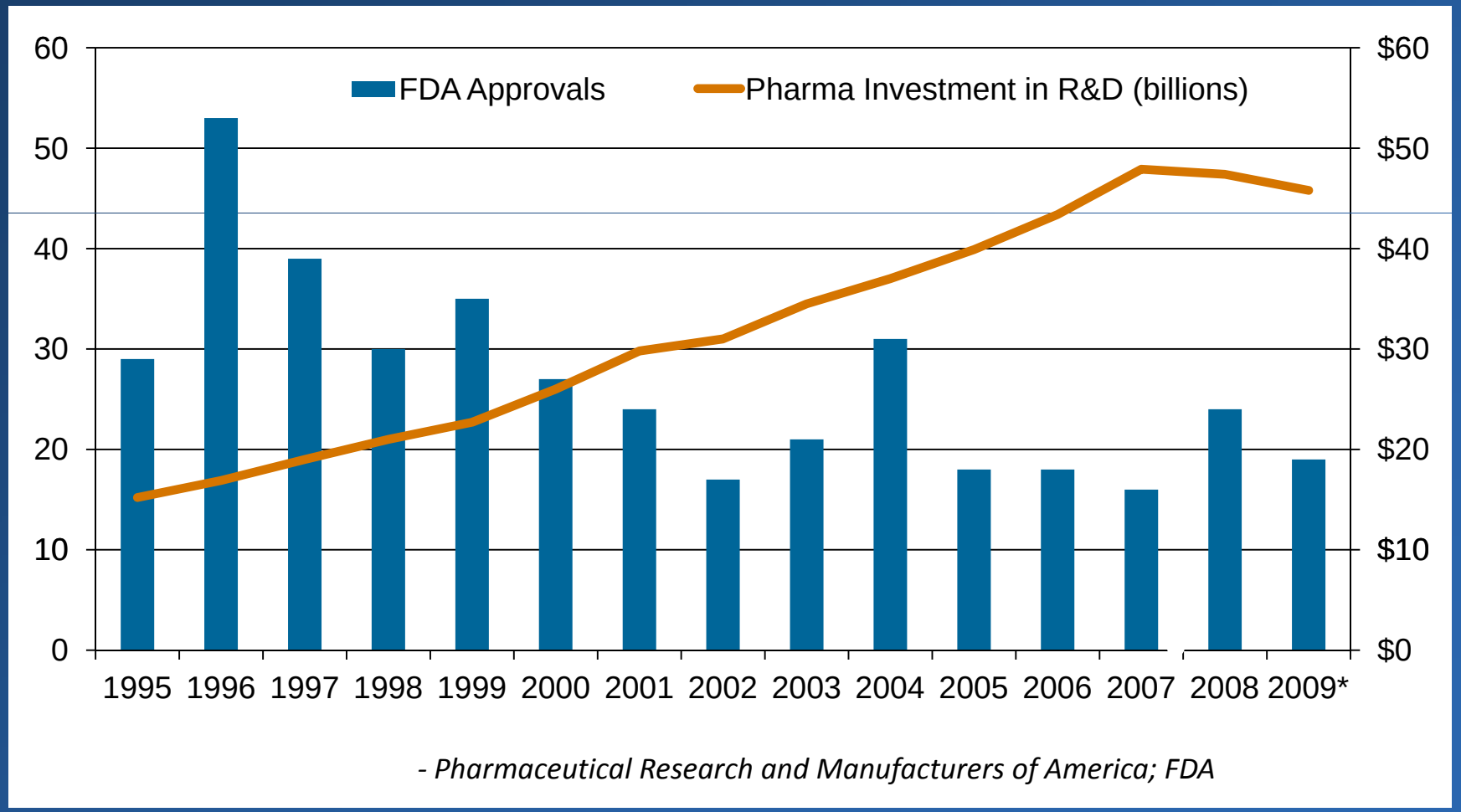
- **Industry is taking a much closer look at the criteria for qualifying a potential target prior to investment of critical resources in drug development**

An Abundance of Potential Targets



- **Generating a significant inventory of potential targets for new diagnostics and therapeutics:**
  - **Human genome sequence studies**
  - **Large genome wide association studies coupled with meticulous clinical phenotyping**
  - **Microbial genome sequence studies**

Despite Greater Investments in R&D by Pharma, Number of New Drug Approvals Has Declined



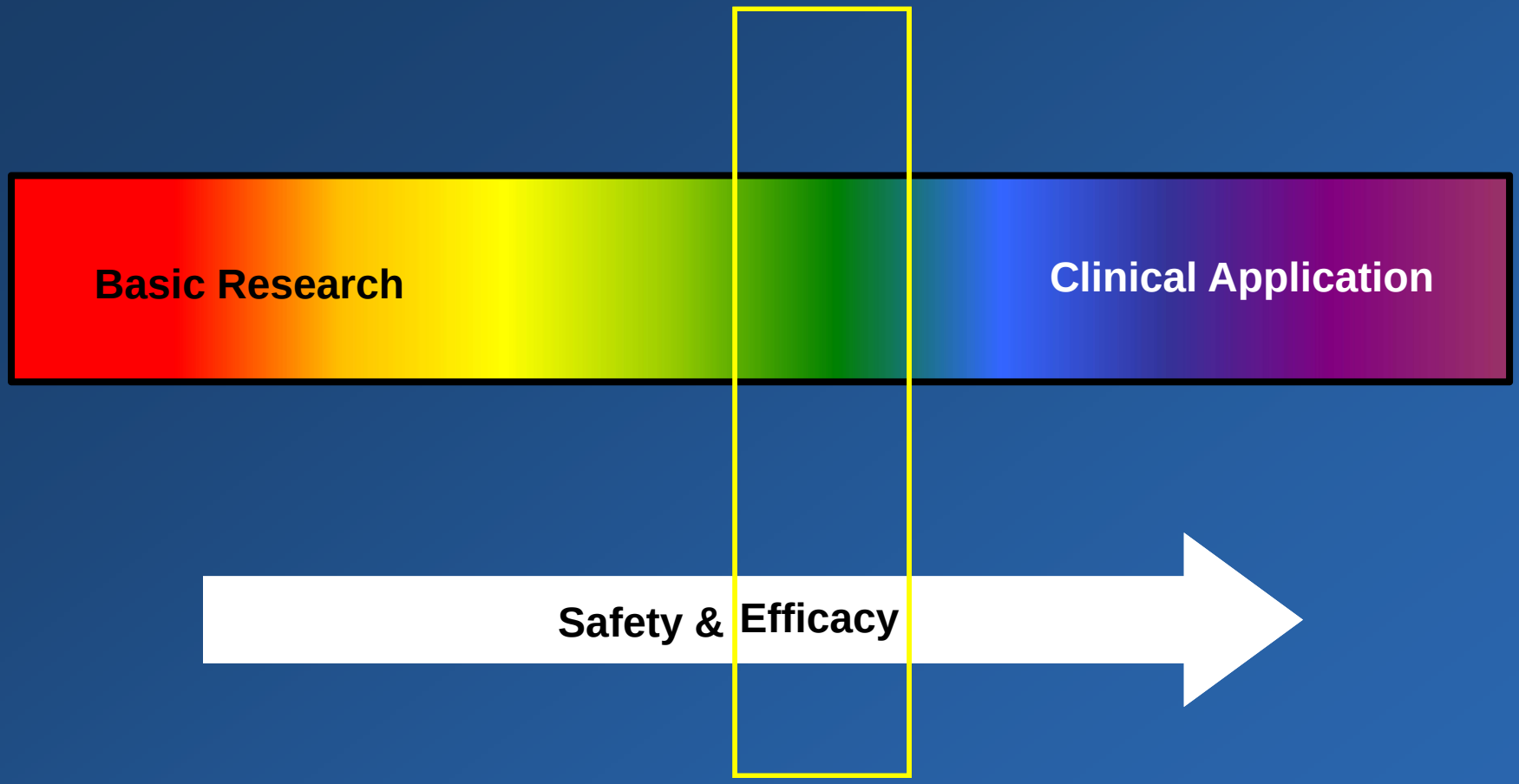
- Pharmaceutical Research and Manufacturers of America; FDA

Missing: Innovation

- **Rate of innovation in novel target drugs has remained stable over the last 30 years**
- **Majority of new drugs approved between 1982-2010 target previously exploited structures encoded by the human genome**

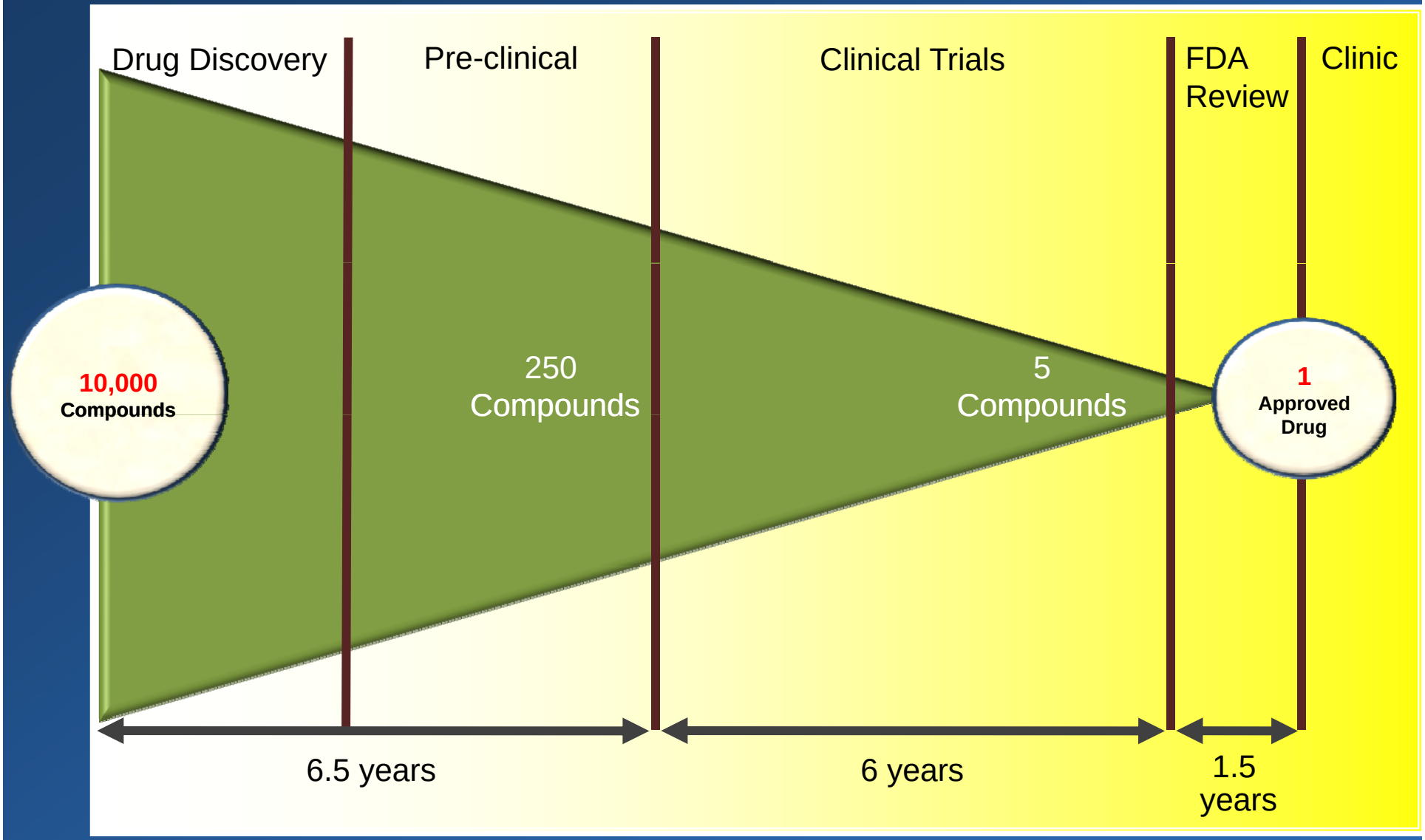
Nature Reviews Drug Discovery 10, 579-590 (August 2011)

Upstream Focus on Target Validation

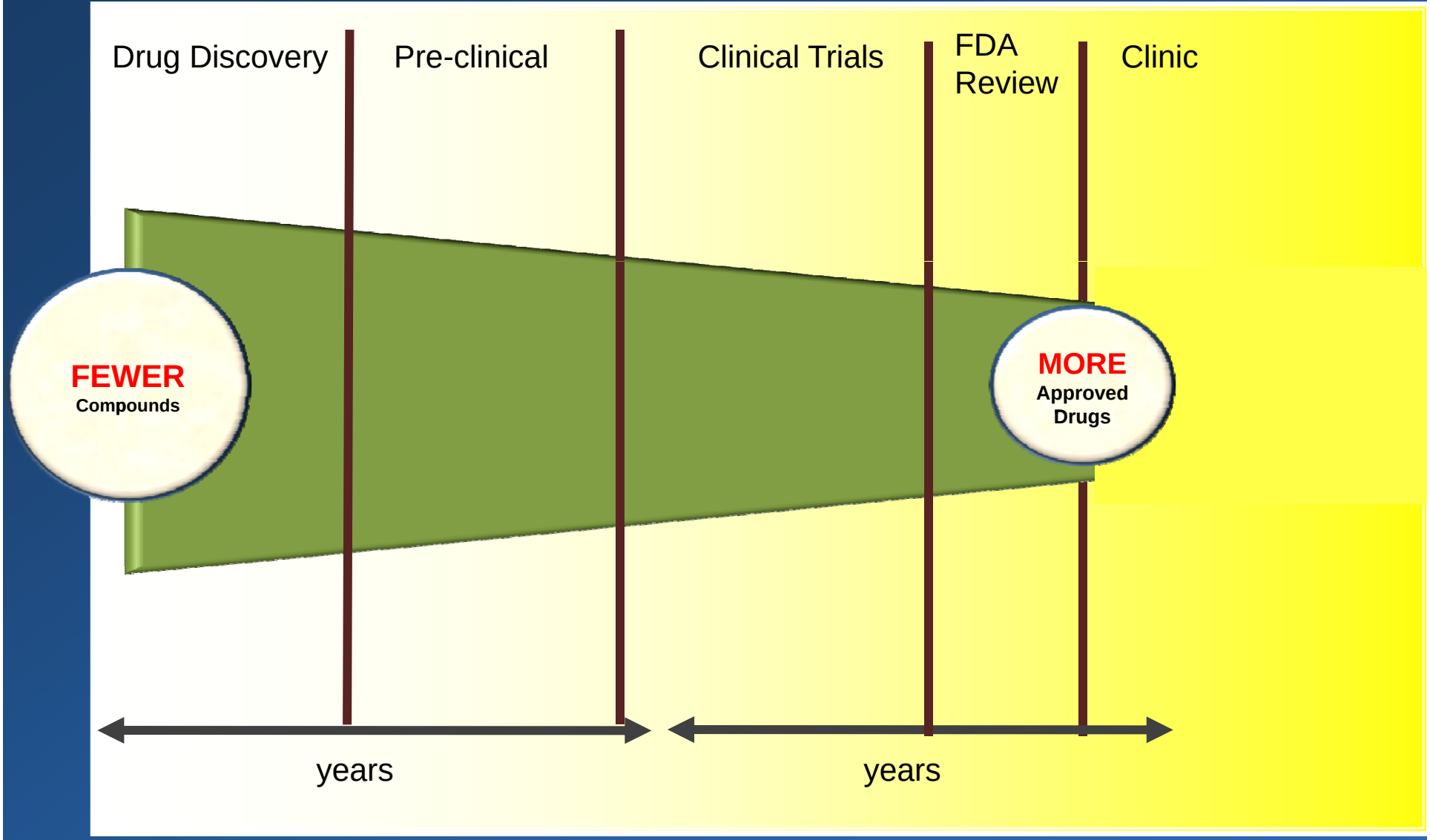


Need new methods, approaches, tools, and technologies to undertake validation in a more efficient and predictable fashion

Development of New Therapeutics



Vision: Development of New Therapeutics with Well Qualified Targets



Challenges

- Insufficient understanding of biologic networks
- Incomplete understanding of the biology of drug-target interaction
- Lack of efficient and accurate ways to determine clinical relevance
- Need to integrate of massive amounts of sequence and phenotype data from public and private sector sources

Select, Relevant NIH Programs

- Whole exome and whole genome sequencing
- The Cancer Genome Atlas (TCGA)
- Genotype-Tissue Expression Resource (GTEx) Pilot Program
- ENCODE and Epigenomics Programs
- RNAi Screening
- Library of Integrated Network-based Cellular Signatures (LINCS)
- iPSCs to model disease phenotypes
- Knockout Mouse Project (KOMP)
- The Brain Atlas
- The Biomarkers Consortium

NIH Sequencing Projects: Current Inventory

- **Opportunity to strategically mine genome and exome sequencing projects for target validation**
  - **192 projects in 16 Institutes and Centers**
  - **Involve ~68,000 subjects**
  - **31% include some whole genome sequencing**
  - **38% intramural from seven ICs (NCI, NEI, NHGRI, NIAID, NICHD, NIDCR, NINDS)**
  - **30 projects (16%) have $\geq$ 10% samples of non-European ancestry; 55% of projects unspecified**

JOINT NIH–INDUSTRY TARGET VALIDATION WORKSHOP

NATIONAL INSTITUTES OF HEALTH
BUILDING 31, C WING • CONFERENCE ROOM 10
NOVEMBER 3–4, 2011

Workshop Participants

- Leaders and experts from:
  - Industry
  - Academia
  - Government

Workshop Focus

- **Development of a collective understanding of the landscape of the target validation through review of:**
  - **Current industry target validation process**
  - **Illuminating case studies examining**
    - **Biological relevance of the target to clinical condition**
    - **Mechanism of action of the target**
    - **Druggable attributes**
    - **Potential therapeutic agents**
    - **Lessons learned**
      - **Successful examples illustrated importance of confirming mechanisms of action and biological relevance**

Gene- and Phenotype-Directed Target Validation: Selected Examples

Target	Abbreviation (Gene)	Disease/ Condition	Initial Id	Characteristics	Development
Voltage Gated Sodium Channel 1.7	$Na_v1.7$ (SCN9A)	Pain, Pain Disorders	Phenotype	Known - MOA, LoF/GoF	Preclinical Lead
Renal Outer Medullary K^+ Channel	ROMK (KCNJ1)	Hypertension, Congestive Heart Failure	Phenotype	Known – MOA, LoF/GoF, SNP	Preclinical Lead
Isocitrate Dehydrogenase 1	IDH1 (IDH1)	Secondary Glioblastoma Multiforme	Exome Sequencing	Known – LoF/GoF	Preclinical Lead
Proprotein Convertase Subtilisin Kexin Type 9	PCSK9 (PCSK9)	Hypercholesterolemia	Phenotype	Known – MOA, LoF/GoF	Preclinical Lead, Clinical Trials,
p38 Mitogen-Activated Protein Kinase	P38 MAPK (several isoforms)	Rheumatoid Arthritis, Crohn's Disease, Disorders involving CNS	Biochemical	Biochemical Evidence	Preclinical Lead, Clinical Trials

Workshop Focus (continued)

- Ways to optimize the target validation process
  - Brief overview of relevant resources including an inventory of NIH exome and genome sequencing projects
  - Breakout groups
    - Sequencing
    - Gene expression/epigenomics
    - Networks/perturbagens
    - Multi-cell systems

Moving Forward

- **Develop more accurate processes and techniques to identify the most promising targets and to predict which targets are likely to be biologically relevant and tractable**
  - **Take advantage of advances in sequencing, perturbagens, humanized tissue models, epidemiology, and systems biology**
- **Capitalize more fully on large scale genome wide association studies and phenotyping efforts to verify clinical relevance of potential targets**
- **Develop analytic platforms to store, harmonize, and analyze data from multiple sources**
- **Create a precompetitive shared space or "biology knowledge commons"**

Outcomes and Next Steps: Stand Up the Target Validation Consortium

- Launch four workstreams:
  - Genotype2Phenotype
  - Phenotype2Genotype
  - Information Commons for Biological Function
    - Workshop in Boston
  - Cancer Information Commons
    - NCI Workshop
- Further develop the consortium
  - Mission, shared values, value proposition for stakeholders
  - High level governance
  - Explicit goals and milestones
  - Funding

“The odds of hitting your target go up dramatically when you aim at it.”

-- *Anonymous*