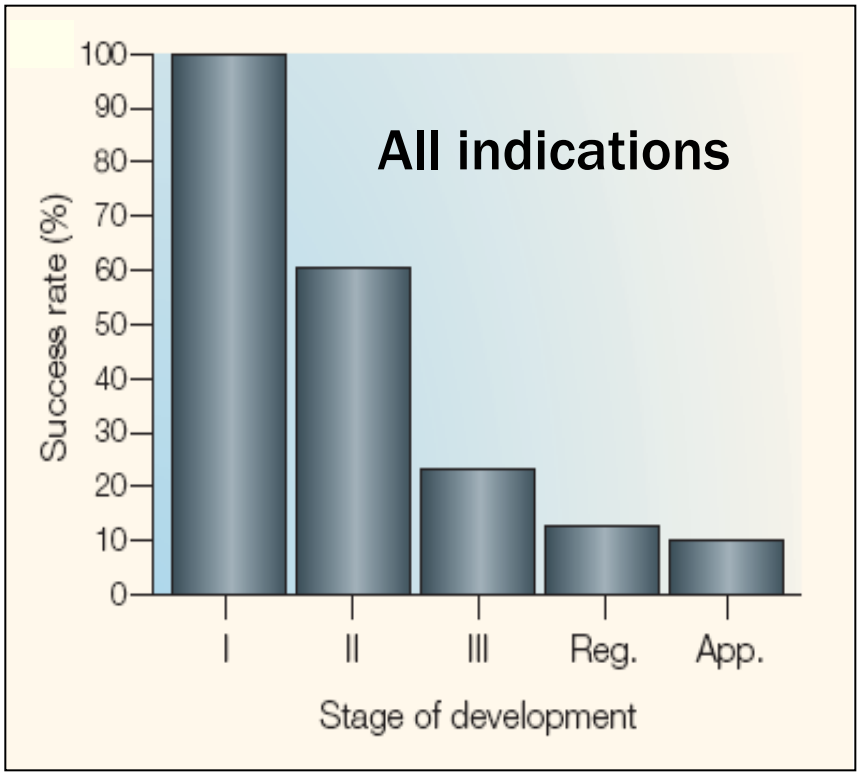
IOM Workshop: The Role of Clinical Studies For Pets with Naturally Occurring Tumors in Translational Cancer Research

The Problem

- Cancer drug attrition rates are significantly higher than in other therapeutic areas
  - 5% success rate compared to 20% success rate in cardiovascular drug development
- Has led to many attempts to improve outcomes

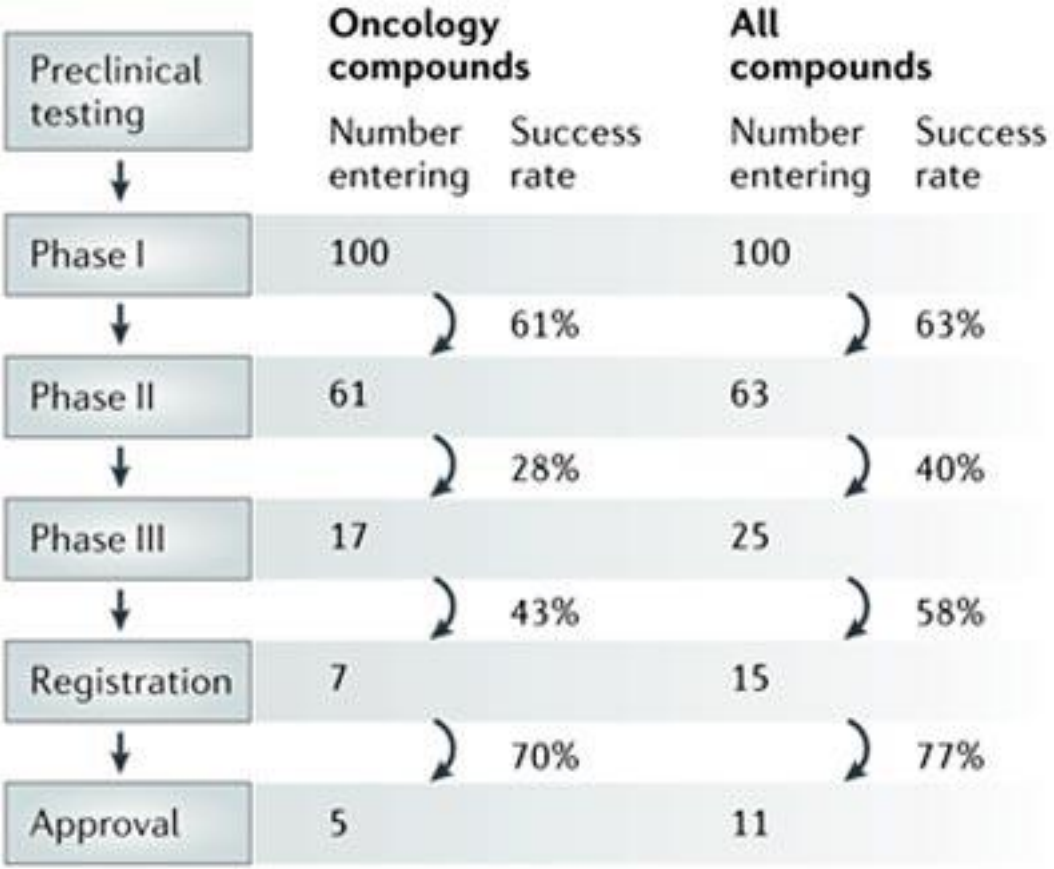
Most Drugs Fail in Late Stages of Development, Particularly in Oncology



Rates of success for compounds entering first-in-man that progress to subsequent phase trials

- 70% of oncology drugs that enter Phase 2 fail to enter Phase 3
- **59% of oncology drugs that enter Phase 3 fail**
- Late stage failure leads to enormous risk
- Failure is more often due to lack of efficacy than to toxicity

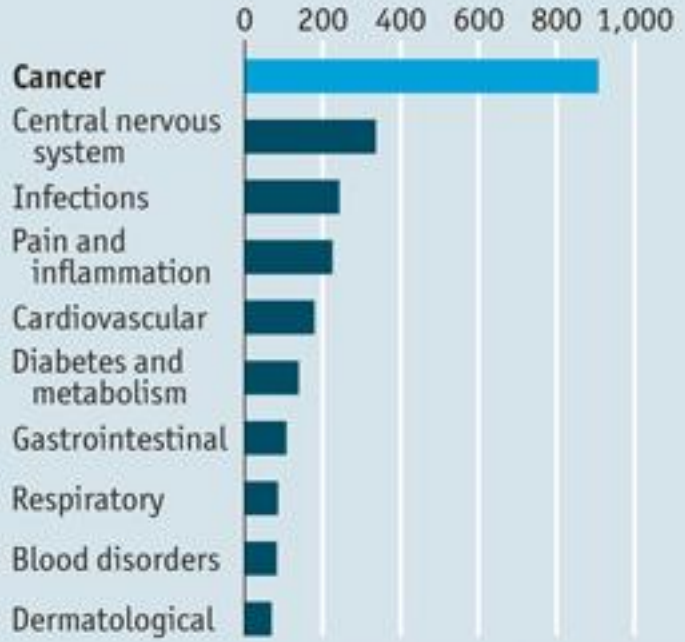
Kola & Landis; Nature Reviews Drug Discovery 2004



Nature Reviews | Drug Discovery

The big C

Drugs in development*, 2010



Source: Medco, *R&D Directions*

*Top ten therapeutic areas for the world's big pharmaceutical firms, includes drugs in Phase I, II, III or awaiting FDA approval

CROSSING THE VALLEY OF DEATH

A chasm has opened up between biomedical researchers and the patients who need their discoveries. **Declan Butler** asks how the ground shifted and whether the US National Institutes of Health can bridge the gap.

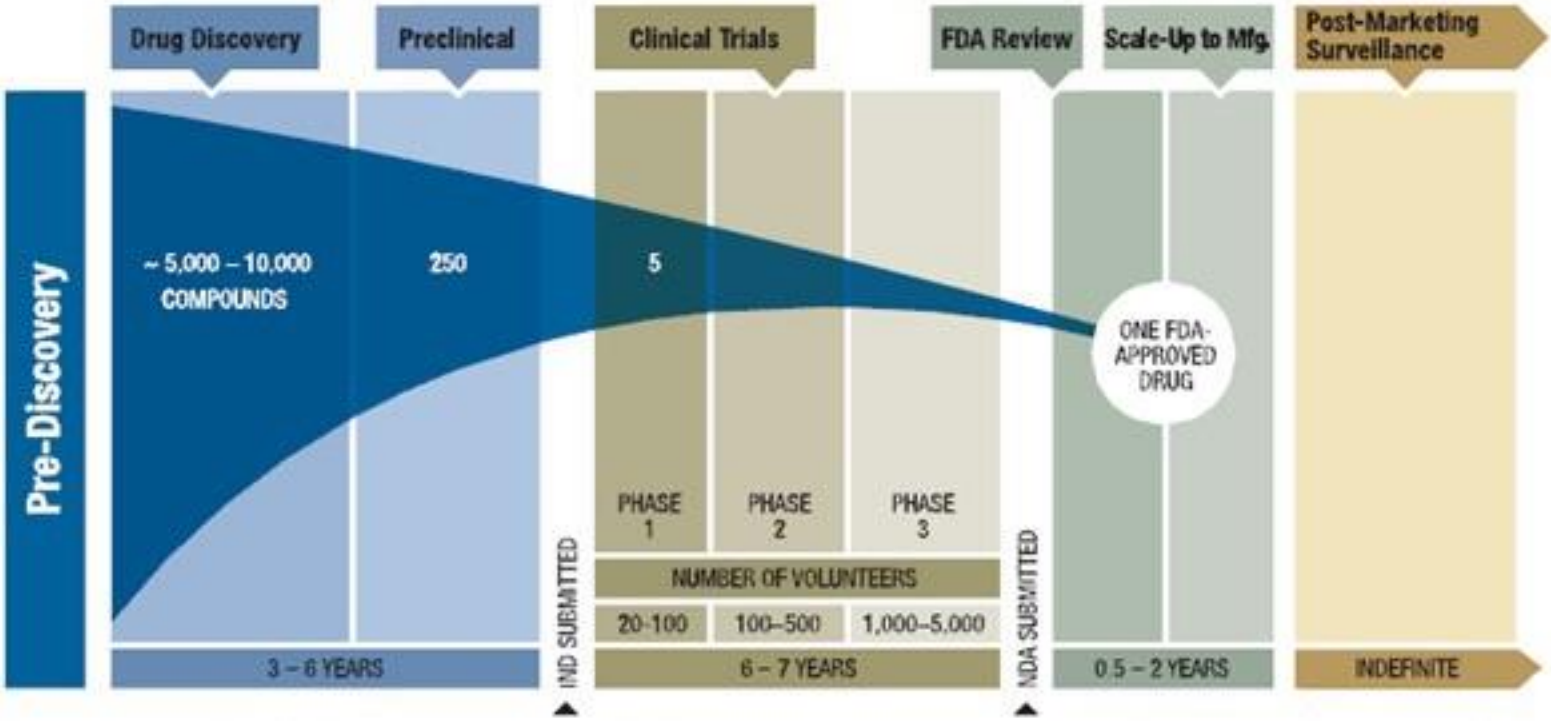
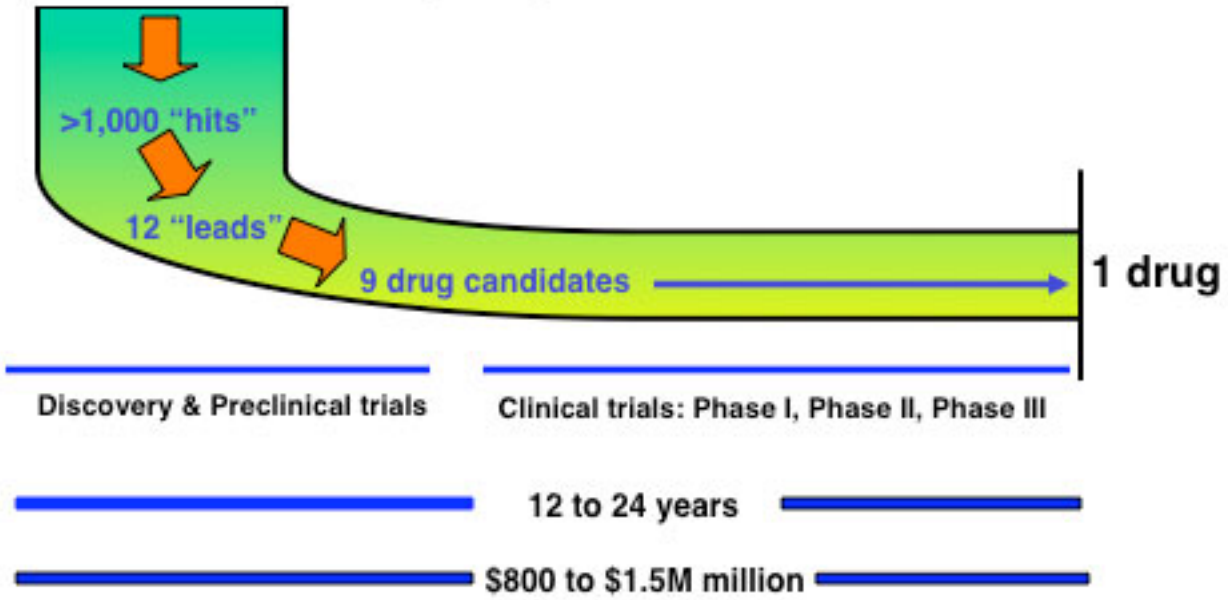
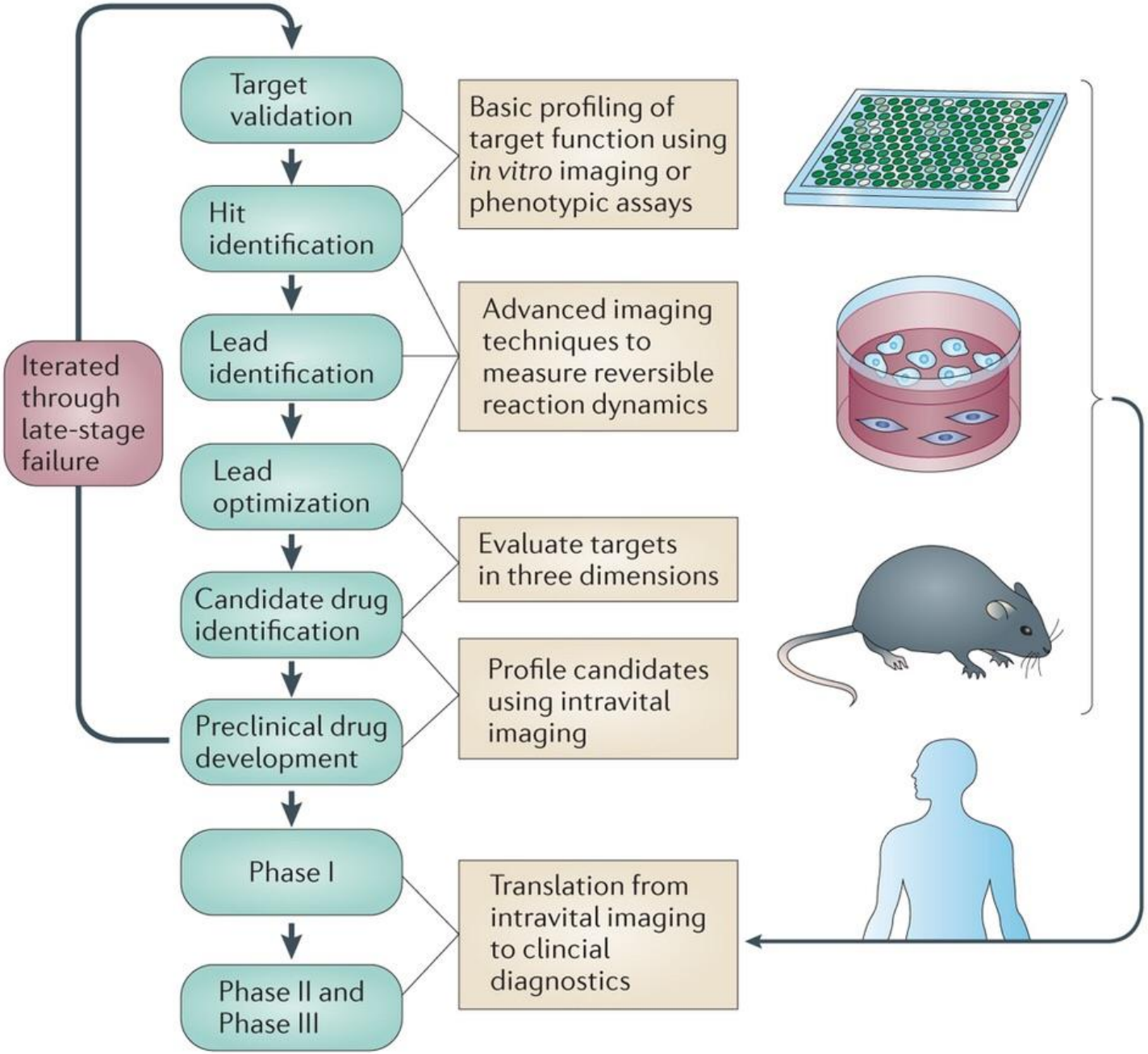


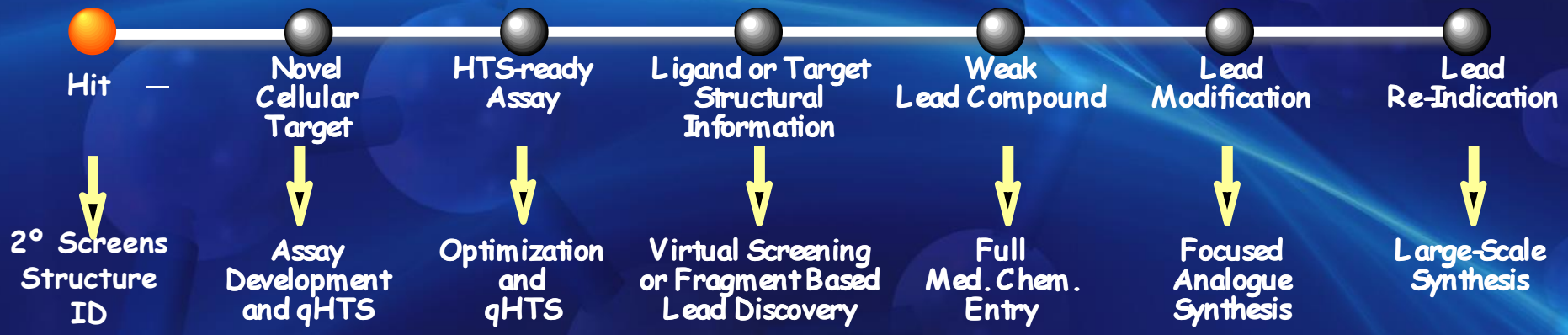
Figure 7: The Protracted Process of Drug Development. Once a candidate drug(s) has been identified (see the blue panels in this figure and **Figure 6**), the company or companies developing them must get permission to test them in humans. This is done by filing an investigational new drug application (IND) with the FDA. A successful IND allows the candidate drug(s) to be tested in patients in clinical trials (olive Phase 1, 2, and 3 rectangles). Clinical trials are multi-year assessments of the safety and efficacy of drugs, requiring increasing numbers of patients in subsequent phases; see **SIDEBAR on Molecularly Informed Clinical Trials**. If a compound is successful in treating a given cancer, the company then files for a new drug application (NDA), at which time the FDA will review the application and either approve or reject the drug based on the results of the clinical trials; in some cases, the FDA will require further testing before approval can be granted (green FDA review rectangles). If the drug is granted approval, a market authorization is given, and the company can begin marketing and selling the drug (green FDA review rectangles), once they have produced enough of the drug to meet patient demand (green scale-up rectangle). Once a drug is on the market, physicians and patients are encouraged to report any adverse reactions so that they can be tracked by the FDA and further investigation may be required; this is the post-marketing surveillance period, also known as pharmacovigilance (gold post-marketing surveillance rectangle). Adapted from pharma.org.

50,000 - 5,000,000 compounds are
often screened to find a single drug



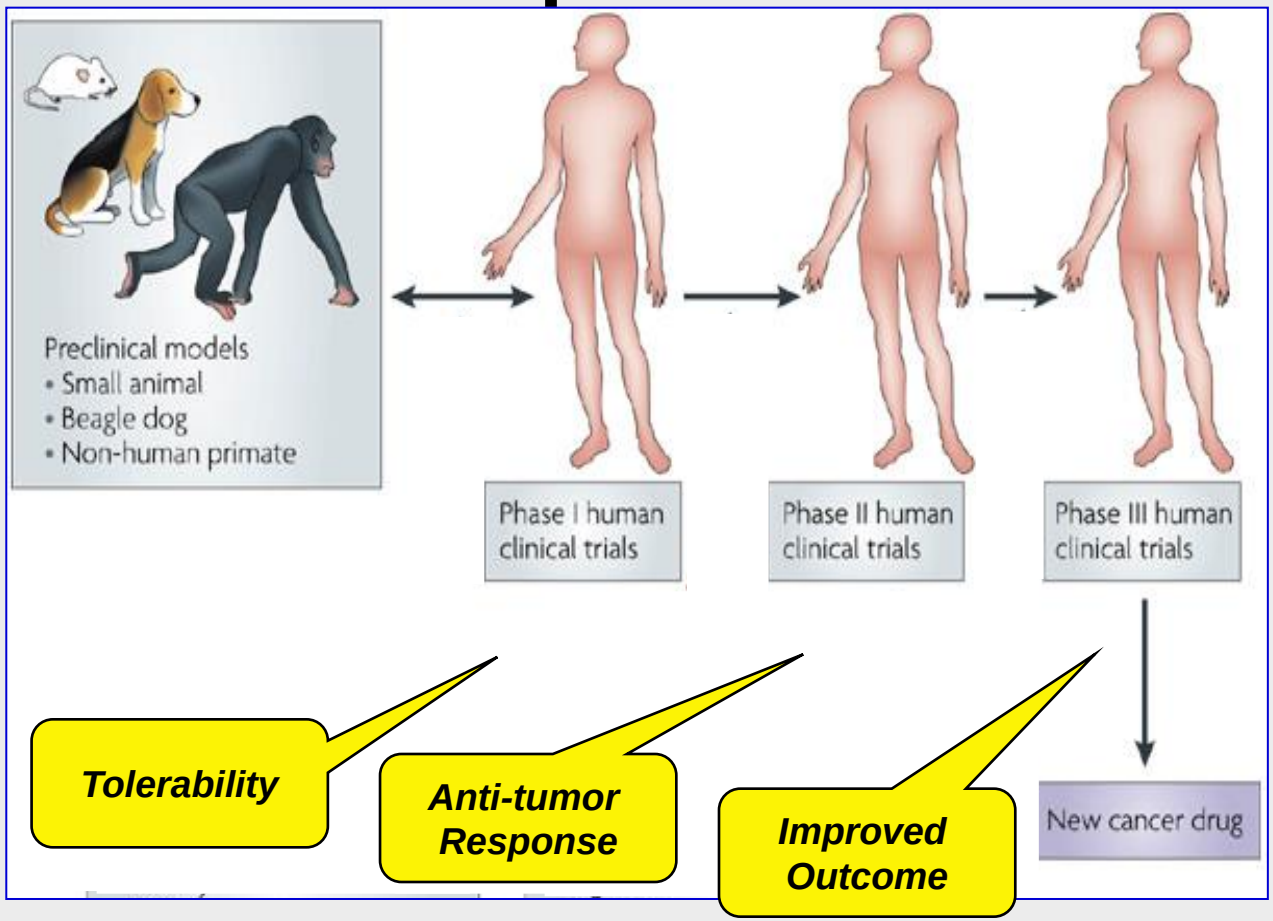

Target validation
Hit identification
Lead identification
Lead optimization
Candidate drug identification
Preclinical drug development
Phase I
Phase II and Phase III
Iterated through late-stage failure
Basic profiling of target function using *in vitro* imaging or phenotypic assays
Advanced imaging techniques to measure reversible reaction dynamics
Evaluate targets in three dimensions
Profile candidates using intravital imaging
Translation from intravital imaging to clincial diagnostics

Multiple Entry Points into the NExT/CBC Discovery/Development Pipeline



- ✓ Transgenic and PDX Animal Model Development
- ✓ PD Endpoint Validation
- ✓ Small Animal Imaging Center
- ✓ Clinical Biomarker Assay Development and Validation
- ✓ Clinical Grade Genomics Assays

The Conventional Cancer Drug Development Path



What is the reason for the high attrition rate for oncology drugs?

- ***Cancer is a complex problem***
- ***Preclinical models are not predictive***
- ***Pathway is linear and largely ignores opportunties to be informed***

Comparative Oncology

TO PROVIDE OPPORTUNITIES TO INCLUDE NATURALLY OCCURRING CANCER MODELS IN THE STUDY OF CANCER BIOLOGY AND THERAPY

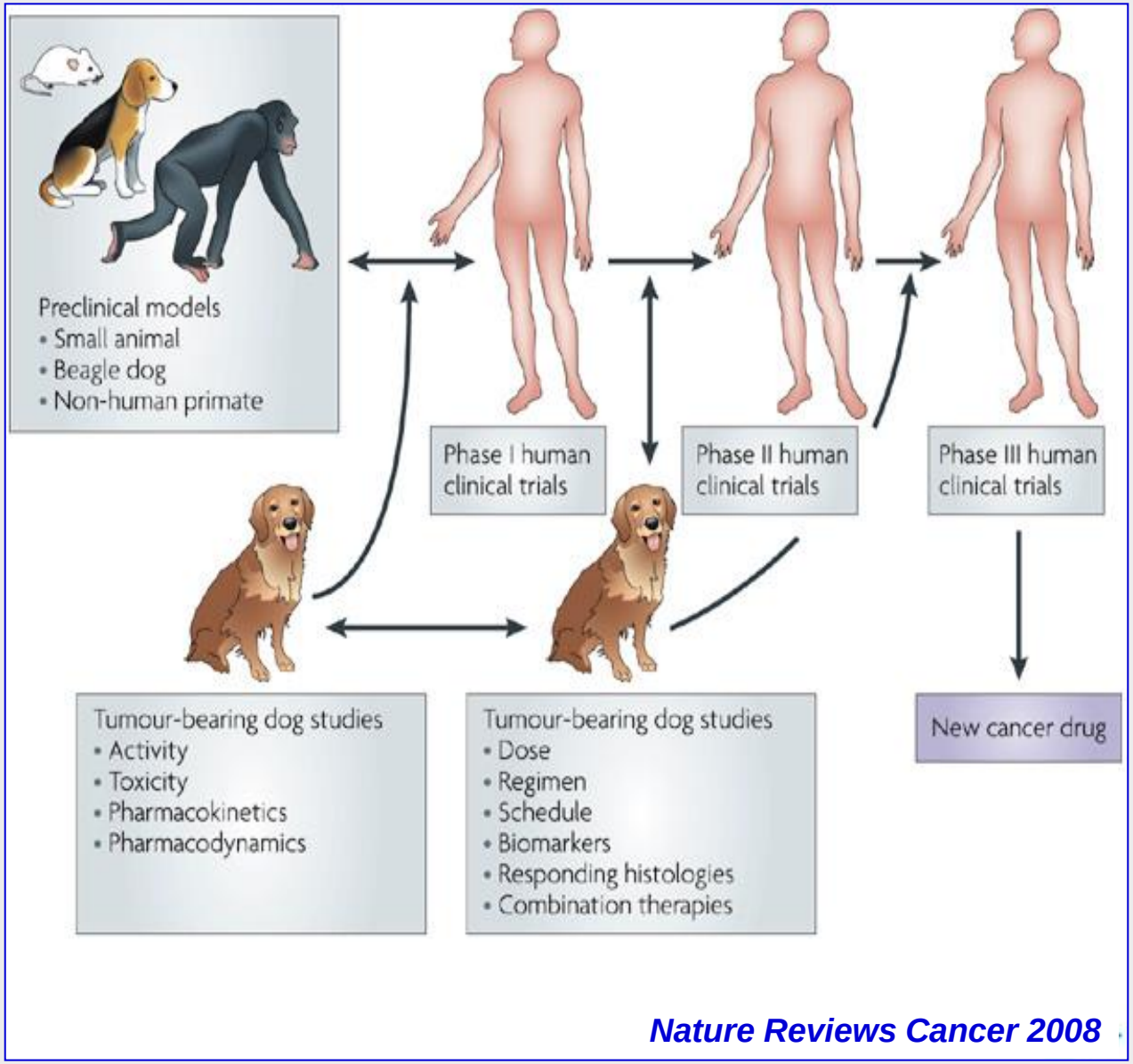
Cancer IN Companion Animals

- **72 Million Companion Dogs in the US**
- **Approximately 1 million pet dogs diagnosed with cancer each year**
- **Pet owners seek advanced care for their pets**

Companion Animal Cancer Models

- **Large outbred animals**
- **Strong genetic similarities to humans**
- **Naturally occurring cancers**
- **Immune competant and syngeneic**
- **Relevant tumor histology/genetics**
- **Relevant response chemotherapy**
- **No “Gold Standards”**
- **Compressed progression times**
- **Tumor heterogeneity**
- **Recurrence/Resistance**
- **Metastasis biology**

A Comparative and Integrated Approach to Cancer Drug Development



Nature Reviews Cancer 2008

Bridging the "Valley of Death"

http://activerain.com/states/NV/cities/Las%20Vegas/communities/Hoover%20Dam