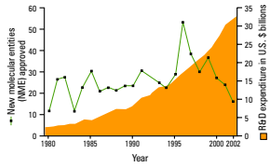
Reinventing Drug Development at the National Cancer Institute

SUCCESS STORY

The Issue: The Number of New Drugs Reaching the Market Is in Decline

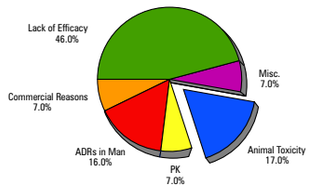
According to a 2003 PhRMA annual membership survey, although research and development (R&D) expenditures have risen steadily since 1980, the number of new drug approvals (NDAs) has dropped.

New Molecular Entities Compared with R&D Expenditure, 1980–2002



What are the main reasons that the development of potential drugs has stopped?

Reasons for Termination of Development of NCEs



Reference: *Nature Reviews Drug Discovery* 2:566–580(2003).

NCI Goal

Increase the number of new anticancer interventions available to the patient.

DTP Goal

Increase the number of new, targeted anticancer therapeutics reaching clinical trials.

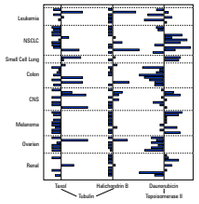
The Current Model at DTP

Discovery

Primary* In Vitro *Screen

- 60 human tumor cell lines from 9 disease types exposed to drug for 48 hours over a 5-dose range. The pattern of sensitivity and resistance may give an indication of molecular mechanism of action.
- Cost: ~ $100 per compound.
- History: > 87,000 compounds screened in 15 years.
- Our experience: Low cost can indicate molecular target, but no correlation to human response.

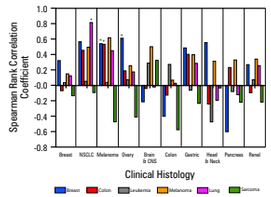
Agents with Similar Mechanisms Have Similar Mean Graphs



In Vivo *Models*

- *Hollow fiber (HF) assay*: Introduced in 1995 as a selection tool for xenograft testing.
- Cost: ~ $1,000 per compound.
- Our experience: Useful in determining which compounds to select for xenograft testing. Compounds with high total scores are more likely to be active in xenograft studies (20% activity rate for high scores vs. 3% activity rate for low scores).
- *Human tumor xenografts*: End point is effect on growth rate of tumor, with regression and tumor-free animals with no toxicity the goal.
- Correlation to human clinical response: For 39 clinical agents for which phase II and animal model data were available, only non-small cell lung (NSCL) xenografts were predictive of clinical activity in the same histology.
- Cost: $3,000 per compound per model.
- Newer models: Orthotopic, transgenics, knockout/knockin, bioluminescence—no data on correlations.
- Our experience: No correlation by disease type; small correlation if compound active in multiple tumor models. Cost is minimal but so is correlation to clinical response.

Xenograft Histology



*Statistically significant correlation
Source: Johnson et al, *Brit J Cancer*, 84(10):1424–1431, 2001.

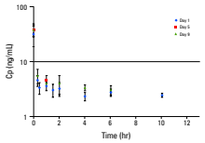
Development

PK study showing rapid distribution phase followed by a long terminal phase.

Current Pharmacology Study Design:

- Typical costs for pharmacokinetic (PK) and pharmacodynamic (PD) studies include:
  - Method development.
  - *In vitro* drug plasma stability studies.
  - Protein binding studies.
  - Pharmacokinetic studies in three species.
- Total: $150,000 to $235,000 for each (PK, PD).
- Our experience: Only 7% of drug failures are due to PK problems, *but* these studies are very expensive. PK/PD studies have not been connected to the concentration and duration of drug in human fluid/tissue required to affect the molecular target.

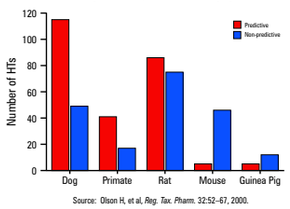
Dog–0.04 mg/kg/dose (1 hour infusion)



How Well Do Our Animal Models Predict Human Drug Toxicity?

Current Toxicology Study Design

Human Toxicity Prediction/Non-Prediction by Species



Source: Olson H, et al, *Reg. Tox. Pharm.* 32:52–67, 2000.

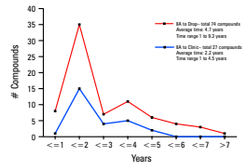
- Typical costs for toxicology studies: > $1 million.
- Our experience:
  - Safe starting doses predicted ≥ 98% of the time. MTDs are reasonably well predicted (82%).
  - Studies are very costly; dose-limiting toxicities are well predicted for bone marrow and gastrointestinal toxicities, but other toxicities are not as well predicted.
- Other costs/studies include analyses, formulation, and bulk production.
- Total DTP costs (acquisition to IND-tox): $1,000,000 to $6,000,000 per drug.

Between 1990 and 2002, DTP selected 101 small molecules for development, 27 of which were promoted to NCI-sponsored clinical trials. The rest were dropped from the program.

Reasons to Adopt the PK/PD Paradigm

Efficacy considerations—failures; toxicity considerations—lack of predictability; and desire for target-relevant drugs.

Preclinical Drug Development— 1990 to Present for 101 Development Candidates



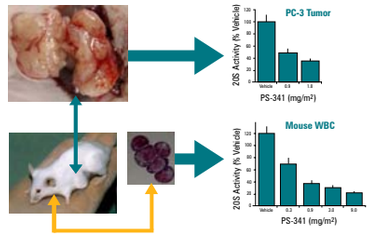
Efficacy Studies

- Use cell line assay for potential target information.
- Incorporate microarray studies.
- Determine effective doses in molecular target-based assays.
- Determine drug concentration and duration requirements *in vitro* and in animal models—target effective dose (TED), biomarkers.

PK and PD Studies

Collect tissues, blood samples, and serum—analysis based on targets and surrogate biomarkers.

Velcade®: 20S Inhibition



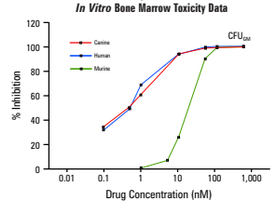
Toxicity Studies

Use *in vitro* toxicity assays to:

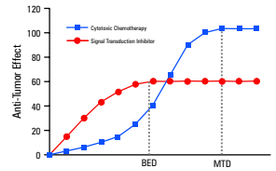
- Determine IC90 in CFU-GM assay for mouse vs. human and canine.
- Determine MTDs in animals.
- Calculate projected human MTD using *in vitro* and *in vivo* data

Base dose escalation on target effect rather than toxic effect.

9-Amino [20S] Camptothecin (NSC 603071): *In Vitro* Bone Marrow Toxicity Data



BED Versus MTD



Source: Johnston, SRD, *Lancet Oncol*, 2:18–26, 2001

Cost: $100,000 per drug vs. $1,000,000 per drug

Clinical Dose Basis for Limited PK/PD Phase 0 Studies

Scale dosing scheme to the drug concentration that produces an effect on PD/biomarker at minimal effective dose (MED) in the most sensitive species.

Overall goal is to provide initial rationale and guiding principles for further agent development based on studies in humans (rather than xenografts).

Conclusion

Adoption of the PK/PD development paradigm will decrease time and financial commitment and will bring about the rapid translation of new, targeted anti-cancer therapeutics that reach clinical trials.

Developmental Therapeutics Program of the National Cancer Institute

TURNING MOLECULES INTO medicines FOR THE public health