Drug Discovery Toxicology: 
*From Target Assessment to Translational Biomarkers*

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What Do You Think It Takes to Make a Prescription Drug?
**Presentation Overview**

- Candidate drug discovery, target engagement, and preclinical efficacy
- Drug target validation and lead generation
- Preclinical testing and Investigational New Drug (IND) application filing
- Clinical trials (Phases 1, 2, and 3)
- New Drug Application (NDA) filing
- NDA review/decision on approval
- Phase 4 clinical studies


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**On Average, How Many Years Does It Take to Generate Sufficient Research Data to Support Approval of a Prescription Drug?**
The Importance of Preclinical Safety Testing

- The estimated cost for developing a new drug is ~$2.6 billion
- Preclinical safety studies constitute ~15% of total drug development costs
- Clinical trials constitute ~30% of total drug development costs
- Approximately 70% of all discovery compounds do not become drugs due to early identification of preclinical safety findings
- The approval rate for candidate drugs entering clinical development is <12%
- The importance of preclinical safety testing is to decrease discovery research efforts for toxic compounds that are unlikely to become drugs

[Link to source: https://www.agozmed.com/2014/12/a-tough-road-cost-to-develop-one-new-drug-is-26-billion-approval-rate-for-drugs-entering-clinical-devel.html]
During the Initial Discovery Phase, How Many Steps Do Chemists Often Perform in Efforts to Discover a Candidate Prescription Drug?

Drug Discovery, Target Engagement, and Preclinical Efficacy

The drug discovery and target validation processes are intended to demonstrate potential correlations between preclinical and clinical readouts:

- Demonstrating drug-like properties (Target Engagement)
- Preclinical data (e.g., efficacy biomarker profiles) should inform backup compound selections

What Emerging Technology Do You Believe May Be Used to Help Validate a Candidate Prescription Drug?
Lead Candidate Drug Generation

The identification of a “lead compound” to progress toward preclinical safety testing includes:

• **In vitro assays** and **in vivo studies** aid the prioritization of compounds to identify a “lead compound” to progress toward preclinical safety testing

• **Predict compound-induced toxicologic risks to humans using in vitro, in vivo, and/or in silico models**


**Case Example—In Vitro Assay: Receptor Selectivity for Ibrutinib**

**Ibrutinib**

- Bruton’s Tyrosine Kinase (BTK) inhibitor
- Used to treat B cell malignancies
- Hits several other kinases at clinically and toxicologically relevant levels

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<th>Median Cmax (unbound)</th>
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What Do You Think It Takes to Ensure a Candidate Drug Is Safe for Humans?

Preclinical Safety Testing

1. Determination of the potential for general toxicity
   - Identification of target organs of toxicity
   - Delayed effects
   - Reversibility of effects
   - Probability of occurrence
   - Identification of appropriate parameters to monitor in the clinic

2. Characterization of the nature of the adverse effects
   - Cellular, biochemical, molecular

3. Determination of the potential for specialized toxicity
   - Reproductive and developmental
   - Ocular
   - Cardiogenic
   - Other "other" (e.g., immunotoxic, behavioral toxicity, neurotoxic)

4. Selection of appropriate doses for clinical trial
   - Initial starting dose
   - Dose escalation scheme

5. Assessment of risk versus benefit in relation to clinical indication
   - Normal volunteers
   - Patients
   - Identify 'at risk' populations

Preclinical Safety Testing

Preclinical Safety Study Design Considerations

- Species selection:
  - Typically default to rat and dog
- Dosing formulation testing
- Dose level testing:
  - At high enough exposure in good laboratory practice (GLP) studies to support Phase 1 clinical trial
- Study duration:
  - 5–14 days
- Clinical endpoints:
  - Clinical observations, body weights, and food consumption
- Pathology endpoints:
  - Clinical, routine, and molecular pathology

What Is Your Perceived Definition of a Translatable Safety Biomarker?
Translatable Safety Biomarkers

- TV: On-target related TOX
- LO: Expected potential TOX
- LLO: Unexpected TOX during single/repeated dosing
- FIH: Adverse drug reactions during clinical development
- PoC: Safety biomarkers for compound selection and mechanistic understanding
- Phase II/III: Candidate translational safety biomarker analysis to enable early prediction of ADRs, mechanistic understanding in issue solving, and patient selection

Investigational New Drug (IND) Application Filing

- **US FDA/CDER has 30 days to assess safety per the IND application**
  - No comments or minor → proceed with Phase I trial
  - Phone call or letter → clinical hold

  - **Why?**
    - Duration of toxicology studies (in two species) insufficient to support proposed clinical duration
    - Doses/exposures not high sufficient enough in toxicology studies
    - NOAEL not established in toxicology studies

- C<sub>max</sub>: peak concentration
- AUC: area under the curve
- Time: time to peak concentration
List a Toxicity That Would Cause Regulatory Authorities to Enforce a "Clinical Hold" (aka Delay or Suspend Ongoing Research) for a Candidate Drug Trial in Humans.
Clinical Trial Holds: Partial or Complete

The reason for a clinical hold is concern for the safety of clinical trial participants.

- **Partial Clinical Hold**
  - Drug Delivery Device–Related Issues
    - When a gene therapy (e.g., brain) delivery device poses risk to humans

- **Complete Clinical Hold**
  - Developmental or Reproductive Toxicology
    - When a candidate drug is intended to treat a life-threatening disease or condition affecting both genders
Case Example: Candidate Drug-Induced Testicular Toxicity

- Candidate drug-induced testicular toxicity can lead to a clinical hold or very restrictive clinical enrollment and/or robust monitoring


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Questions?