Toxicology in Drug Discovery and Development

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General Outline: Toxicology in Drug Discovery and Development

Overview of toxicology in drug discovery and development
- Toxicology as a critical component of success in drug discovery and development
- Differences in discovery and development
- Toxicology paradigm from nonclinical to clinical sciences

The 3 Rs: right target, right compound, right clinical plan
- Toxicology contributions to critical decisions: case examples

Attributes and interests for toxicologists in drug discovery and development
- Diversity of targets, modalities, issues, and approaches
Drug Failures Inform Paradigms for Success

- **Discovery:** > Thousands; Biologics typically lower
- **Nonclinical Research:** Hundreds
- **Clinical Research:** Few
- **DRUG:** 1

- **Target:** 28%
- **Strategy:** 19%
- **Fate:** 9%
- **Safety:** 44%
Toxicology in Drug Discovery and Development

The Traditional View

Drug Safety Evaluation: Candidate Progression

- **Candidate Discovery and Optimization**
  - IND Toxicology \( \leq 30 \) Day Rodent and Nonrodent

- **Clinical Trials**
  - Phase 1
  - Phase 2
  - Phase 3

- **Approval and Launch**
  - ≤ 30 Day Rodent and Nonrodent
  - Small Population (NHV) Dose Range, PK, Safety
  - Largest Population; Establish Clinical Dose, Efficacy, and Long-Term Safety
  - Small Population (Disease) Efficacy, Safety, Dose Confirmed Proof of Concept

- Compound Identified
Toxicology in Drug Discovery and Development

The Toxicology View

<table>
<thead>
<tr>
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GLPs: ensure reliable generation and verification of all data to establish data integrity

- Genetic Toxicology
- Safety Pharmacology
- Chronic Toxicology (6–9 months)
- Carcinogenicity Studies
- Reproductive Toxicology Studies (Fertility and Teratology) conducted before including women (child-bearing potential)

Variety of tools to optimize compounds and prevent "predictable" failure (Non-GLP)

Must meet Good Laboratory Practices (GLP) requirements

Validation
Statistical Analysis
# Toxicology in Drug Discovery and Development

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**Investigational New Drug Application (IND)**
Provides documentation that it is reasonable to proceed with human exposure: starting dose, dose escalation, hazard identification, potential side effects, monitoring, managing.

**New Drug Application (NDA); Biologics License Application (BLA)**
Formal request for approval: ALL documentation that tells the “full story” of the drug
Clinical results are paramount, labeling proposed, patient information, safety, directions for use.
Comparing Toxicology in Drug Discovery and Development

**Discovery Toxicology**
- Target validation including liabilities
- Work with very early compounds: high attrition
- Program-specific questions
- Compound optimization
  - Is toxicity from the compound or the target?
  - Mechanisms and models to screen
  - Understand clinical use and estimate safety
  - Integrate fate, toxicity, dose regimen

**Drug Safety Evaluation**
- Work with compounds advanced from Discovery
  - Regulated (GLP) studies required for definitive safety evaluation
  - Longer dosing periods
  - Human exposure and response informs study needs and design
  - Understand clinical plans
    - Dosing regimen
    - Benefit/risk
  - Advance tools for evaluating mechanisms of toxicity
Three Key Decisions in Drug Discovery and Development

1. Choose the right target
2. Choose the right compound
3. Design the right clinical development program
Choose the Right Target

• Tumor Necrosis Factor α (TNFα)
  • Important mediator of inflammation (rheumatoid arthritis, inflammatory bowel disease, etc.)
  • Activated by TNFα Converting Enzyme (TACE)

• Target Inhibition of TACE to reduce TNFα and reduce inflammation

• TACE inhibitors caused inflammation (liver)
What Would You Do?

• Is the TACE inhibitor directly toxic to liver cells?
• Is the TACE inhibitor metabolized to something that was toxic?
• Is this toxicity unique to rat?
TACE: Not the Right Target

- Inactive enantiomer was *not* hepatotoxic
- Mechanism of Inhibition causes toxicity
  - Uncleaved, membrane-bound TNF is biologically active

<table>
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<tr>
<th>proTNFα</th>
<th>TNF 1–76</th>
<th>TNF 77–233</th>
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<tr>
<td>26 kD</td>
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<td>TNFα 17 kD</td>
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- Highlights hypothesis testing and collaboration with chemists
Animal Models May Not Predict Human Response

Sphingosine-1-Phosphate Receptor-1 Agonist: Modulate Lymphocyte Trafficking
5 S1P Receptors (1-5); S1P3 agonism reduces HR in nonclinical species

S1P1/S1P3 Agonist in Rats

Selective S1P1 Agonist in Rats

Significant, comparable bradycardia in humans
Human Inducible Pluripotent Stem Cell-Derived Cardiomyocytes

Rat Telemetry Evaluation
No effect at > 2 μM

Bradycardia seen clinically at < 1 nM
Choose the Right Compound

- Eliquis (Inhibitor of Coagulation Factor Xa)
- Finding the right compound: Optimization
  - Highly selective, reversible
  - Orally bioavailable, high blood levels
  - No effect on platelet aggregation
  - Toxicity limited to anti-coagulation
- Advance the right compound into clinical trials
  - 1, 3, 6, month, lifetime, reproductive toxicology, carcinogenicity
  - Precedent to Eliquis failed in chronic studies
  - Support paradigm for clinical dose selection

Highlights the time required to advance from discovery to development when successful
Develop the Right Clinical Program

- No-Observed-Effect Level (NOEL) or No-Observed-Adverse-Effect Level (NOAEL)
  - NOEL: Highest dose/exposure showing no unexpected effect
  - NOAEL: Highest dose/exposure showing no “biologically important” increases in frequency or severity of an effect

- **Margin of Safety** = Exposure at NOAEL ÷ Exposure for Efficacy

- **EXAMPLES**
  - Eliquis is dosed twice daily: reduces maximal blood levels and minimizes bleeding risk
  - Dosing schedule for immunotherapies (antibodies) based on exposure, residence time, and toxicity
Toxicology in Drug Discovery and Development: Recipe for Success

**Toxicologists integrate**
- Physiology, biochemistry, molecular biology, chemistry, pathology, comparative biology

**Toxicologists apply**
- Hypothesis testing, exposure relationships, risk assessment, new/best methods

**Toxicologists advance**
- Problem-solving, mechanisms of effect, risk management or mitigation

The Birth of Science
Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy.

Paracelsus must have been thinking about drug discovery and development!

(1493–1541)