Introduction to Drug Safety Toxicology

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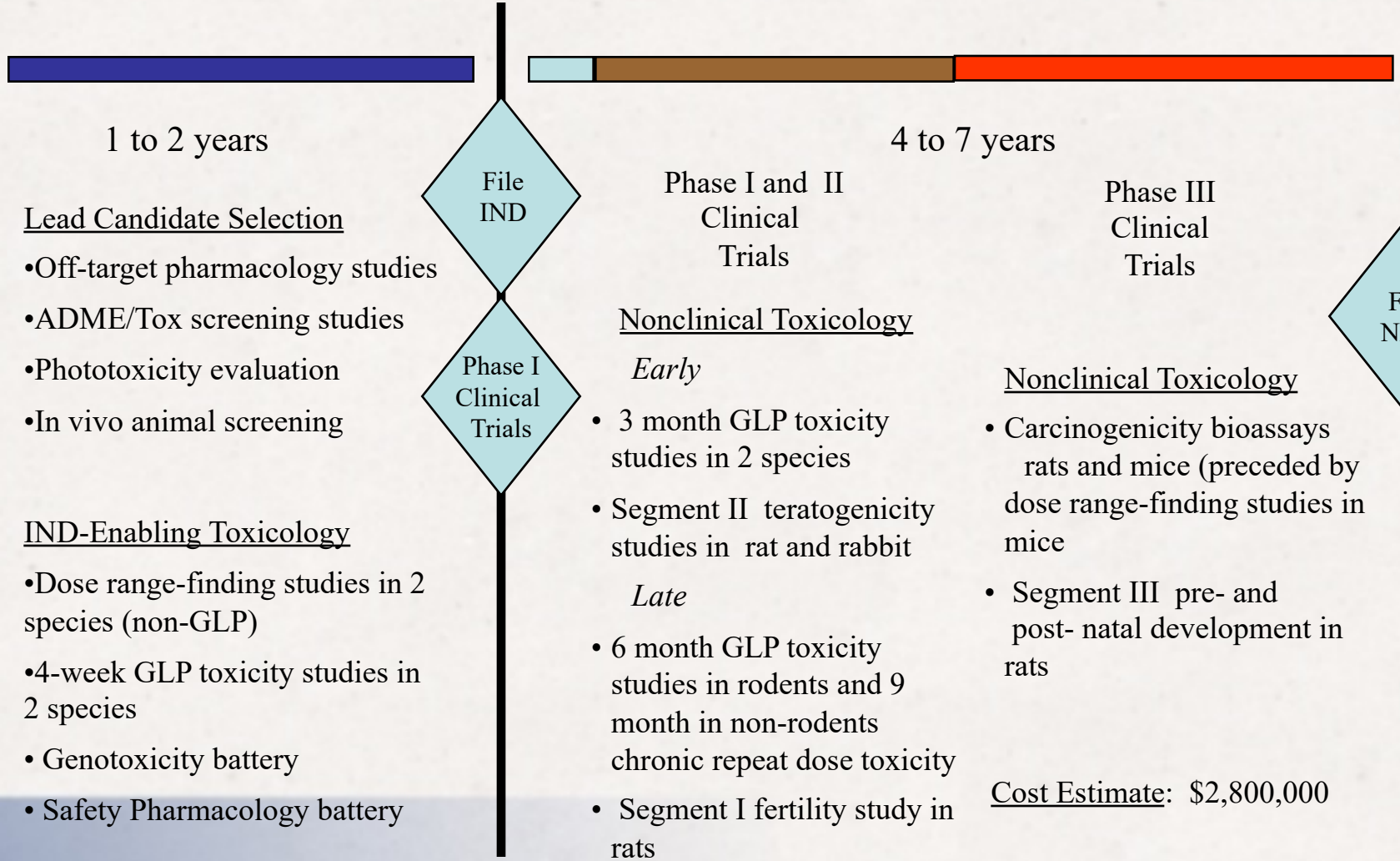
“Turning Your Research Into A Therapeutic

What You Should Think About and When"

Development of New Drug



Early Screening – Lead Candidate Selection

- Off-target pharmacology
  - Screening for inhibition of multiple targets; i.e. transporters, ion channels, neurotransmitters
- ADME screening
  - CYP-P450 inhibition, protein binding, microsomal stability, reactive intermediates
- In vitro toxicology
  - hERG inhibition and phototoxicity; may consider Ames mutagenicity screening
- In vivo toxicology
  - Target organ screening, bioavailability, initial dose selection

IND-Enabling Toxicology Studies

- Dose range-finding non-GLP toxicology studies
  - Generally, 2 species
  - Set doses for definitive GLP toxicology studies
- 4-week GLP toxicology studies
  - Generally, in 2 species
- ICH S2 Genotoxicity battery
  - Requirement depends upon indication and molecule
- ICH S7 Safety pharmacology battery
  - Requirement depends upon indication and molecule
- ICH S10 Phototoxicity
  - Tiers defined

To Progress or Not to Progress?

- Its hard to hear, but the goal shouldn't be to advance your drug, the goal should be to kill the development of a drug with liabilities BEFORE you spend a lot of money

- Define your No Go/ Go Decision before you get your study results

Preclinical In Vivo Toxicology and PK

- Goals:
  - Identify/characterize target organ toxicities
  - Maximum Tolerated Dose (MTD), No Observable Effect Level (NOEL) & Lowest Observable Effect Level (LOEL)
  - Assess time to toxicity and reversibility of effects
  - At what blood levels (tissue levels) are toxicities observed
  - Do systemic exposures vary with number of doses?

- Characterize toxicity profile in animals and not humans!

What You Intend to do in the Clinic Drives Preclinical Development

- Preclinical Toxicology and PK
  - Determine appropriate species dependent on drug/biologic
  - Treatment duration and regimen determines what the toxicology program looks like
    - How often and how long?
  - Treatment indication determines what toxicology program looks like
    - Genotoxicity, reproductive toxicology
  - Route and excipients

To sum, studies are not conducted in a vacuum

What You Intend to do in the Clinic Drives Preclinical Development

Table 1: Examples of Treatment Schedules for Anticancer Pharmaceuticals to Support Initial Clinical Trials

Clinical Schedule	Examples of Nonclinical Treatment Schedule[1,2,3,4]
Once every 3-4 weeks	Single dose
Daily for 5 days every 3 weeks	Daily for 5 days
Daily for 5-7 days, alternating weeks	Daily for 5-7 days, alternating weeks (2-dose cycles)
Once a week for 3 weeks, 1 week off	Once a week for 3 weeks
Two or three times a week	Two or three times a week for 4 weeks
Daily	Daily for 4 weeks
Weekly	Once a week for 4-5 doses

Development team needs define the clinical project

ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

- Type, timing and flexibility can differ from nonclinical studies for other pharmaceuticals
  - Phototoxicity studies outline in S10 generally still required
  - Stand-alone Safety Pharmacology battery called for in ICH S7 are not required
  - Reproductive toxicology may include only one species and be conducted later in the program
  - Genetic Toxicology battery outlined in ICH S2 not required to conduct clinical trials
- First in man dose calculation differs from standard 1/10 of the NOEL in most sensitive species
  - Start dose 1/10 the Severely Toxic Dose (STD) in 10% of rodents in GLP toxicology
  - Start dose 1/6 the Highest Non-Severely Toxic Dose (HNSTD) in non-rodents

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/estimating-maximum-safe-starting-dose-initial-clinical-trials-therapeutics-adult-healthy-volunteers

Repeated Dose Toxicology Studies - Species

- Use the most relevant species
- Studies usually conducted in two species (rodent and non-rodent)
  - Rat is primary rodent species, mice used less frequently
  - Dogs are the primary choice for small drug molecules and seem to be the preferred species, at least by FDA

  - Monkeys are commonly used as the non-rodent species (and sometimes as the only species) for biological products
  - Additional non-rodent species used less frequently include rabbits and pigs

Dose Range-Finding Studies

- Potential duration
  - Single dose, 5 days, 7 days, 10 days, 14 days
- Single dose LD50 studies
  - LD50 determination of pharmaceuticals has been abandoned. In its place, the maximum tolerated dose level should be determined.
- Protocol Elements
  - Single dose study in rodents may include necropsies at Day 3 and Day 14
  - Repeated dose studies in rodents may use a wide range of dose levels and dose groups
  - Non-rodent study may be first a single dose, dose escalation study to determine MTD, followed by repeated doses

Repeated Dose GLP Toxicology Studies – Protocol Elements

- Control and low, mid, and high dose drug treatment groups
- Parameters evaluated will be clinical observations, body weight, food consumption, ophthalmological exams, clinical pathology, organ weights and histopathology
- Non-rodent species will also include ECGs (and consider other safety pharmacology assessments; i.e. respiratory, behavior)
- Studies will usually include systemic exposures/pharmacokinetics as recommended in ICH S3 (don't forget bioanalytical costs, formulation validation)
- Include reversibility groups in at least control and high dose
- Additional elements are study specific; i.e. anti-drug antibody analyses with biologics, cytokines with certain drug classes, IHC staining

Summary

- Toxicology studies are conducted to assist the clinical development team conducting your clinical trial by defining what can go wrong and at what dose and is the effect reversible
- The goal of toxicology testing is NOT to show the drug is safe (you don't select all dose levels to show no toxicity). Rather you have to show toxicities to be able to predict what might happen in the clinic
- Toxicology studies are not research studies. We generally don't explain why, we just describe what….

Appendix

ICH Safety Guidances

International Conference on Harmonsation (ICH)
www.ich.org

S1 Topic: Carcinogenicity

S2 Topic: Genotoxicity

S3 Topic: Toxicokinetics and tissue distribution

S4 Topic: Duration of chronic toxicity testing

S5 Topic: Reproductive toxicity testing

S6 Topic: Safety assessment of biotechnology derived drugs

S7 Topic: Safety pharmacology evaluation

S8 Topic: Immunotoxicity testing

S9 Topic: Nonclinical evaluation of anticancer drugs

S10 Topic: Photosafety

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