IS IT SAFE?

Toxicology in Therapeutic Development
A development platform advancing life-saving therapies from university labs through human proof of concept

1. **Unique Sourcing Capability**
   - Leverage existing relationships with tech transfer offices and scientists
   - On the ground engagement enhances visibility in local ecosystems

2. **Operational Model Drives Success**
   - Strong development team with track record of multiple INDs and NDAs working across platform of biotech programs
   - Team has complementary skill sets including toxicology, medicinal chemistry, CMC, and regulatory
   - Capital efficient through use of CROs and CDMOs

**Goals:**
- Advance life-saving therapies to meet patients’ needs
- Valuable US-based partner for researchers and universities
- Build companies locally to help develop local biotech ecosystems

**Multipronged outreach strategy to build relationship with universities and local ecosystems**

**Venture Partners**
- Strategic key hires in target geographies to “walk the halls” of the universities and stay close to principal investigators (PI’s)
- Plan regular touchpoints with tech transfer
- Provide active feedback to academics to encourage ongoing engagement

**Internship Programs**
- Internship program (launched already at several universities) designed to expose PhD students to the “business side” of biotech VC
- Strengthens relationship with PI’s and tech transfer

**Partnership Model**
- Include the PIs as core members of the team (CSOs/advisors) at our portfolio companies
- Build companies locally to help the local biotech ecosystem and ensure strong ties to both PI and university partner
- Hire locally whenever possible for additional team members for operating cos
- Include local funds in our syndicates whenever possible
Overview

Toxicology

Toxicology in Therapeutic Development
IT DEPENDS
Define Toxicology

The study of the **adverse** effects of chemical, physical or biological agents on living organisms and the ecosystem, INCLUDING the prevention and amelioration of such adverse effects
Dose Response

Dose vs. Response Graph with a Halloween theme.
Impact of Toxicology Results

Serious, non-reversible, non-monitorable, narrow safety margin, occurs in both tox species, steep dose response, mechanism not understood, not linked to pharmacology, not seen with competitor products.

Not serious, reversible, monitorable in man, occurs in only one tox species, explanation for species specificity, shallow dose response, large safety margin, mechanism understood and not relevant to man, extension of pharmacology, seen with all competitor products.

Usually Work in this Space
The 3 Rs

- **Reduction**
  - Reduce the number of animals used to achieve scientific goal

- **Refinement**
  - Improve the methods and procedures used in animal experimentation

- **Replacement**
  - Substitute non-animal systems or lower species for living animals or higher species
What is Nonclinical Development?

• Risk assessment based on interdisciplinary data set
  • Pharmacology
  • Pharmacokinetics
  • Toxicology
  • Pathology

• Extrapolate from animals to humans

• Define Safety Margin for Patients

• Important to differentiate Test Article effects from other findings
What

- Identify organs, tissues, cell types exhibiting altered function or damage
- Characterize Test Article-related changes
- Correlate findings with exposure (Dose-Response)
- Indicate pathway-related versus off-target findings
- Recovery/reversibility
- ADME of Test Article
- What is the worst that can happen?
Nonclinical Study Design

Standard Package
- 2 Species
  - Rodent: 10/sex/dose
  - Nonrodent (dog, non-human primate): 3-4/sex/dose
- 3 Dose Groups plus Control
- Escalating Dose to Maximum Tolerated Dose
- Duration
  - 2-4 weeks; 3 month; 6-9 month; 2 year (rodent only)
Regulatory Requirements
Basic Tenets of Toxicology Testing

General assumptions
  • Animal models will predict human efficacy and safety/toxicity
  • High doses will maximize model sensitivity to detect effects
$55M How Well Do Animals Predict Humans?


The ability of animal studies to detect serious post marketing adverse events is limited

Target organ toxicities in studies conducted to support first time in man dosing: An analysis across species and therapy areas

First dose of potential new medicines to humans: how animals help

Peter Greaves, Andrew Williams & Malcolm Eve

About the authors
Concordance of Animal & Human Toxicities

- International Life Sciences Institute (ILSI) workshop (Survey)
  - 150 compounds, 221 human toxicities; 12 companies

- 71% of the time, target organ toxicity seen in humans occurred in one or more animal models
- Dogs tend to be slightly more in line with predicting human toxicity than rodents

- 94% of toxicities were detected in the 1-month studies
- Highest concordance: Hematological, GI, Cardiovascular (Least = Cutaneous)

# Differences Between Animals & Humans

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Animals</th>
<th>Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Large Groups</td>
<td>Individual</td>
</tr>
<tr>
<td>Age</td>
<td>Young Adult</td>
<td>All ages</td>
</tr>
<tr>
<td>State of health</td>
<td>Healthy</td>
<td>Usually sick</td>
</tr>
<tr>
<td>Genetic background</td>
<td>Homogeneous</td>
<td>Heterogeneous</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Doses</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnitude</td>
<td>Therapeutic to toxic</td>
<td>Therapeutic</td>
</tr>
<tr>
<td>Schedule</td>
<td>Usually once daily</td>
<td>Therapeutic optimum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Circumstances</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Housing, Nutrition</td>
<td>Uniform, optimal</td>
<td>Variable</td>
</tr>
<tr>
<td>Concomitant therapy</td>
<td>Never</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic procedures</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal contact</td>
<td>None</td>
<td>Intensive</td>
</tr>
<tr>
<td>Physical exam</td>
<td>Limited</td>
<td>Extensive</td>
</tr>
<tr>
<td>Clinical lab</td>
<td>Limited, standardized</td>
<td>Individualized</td>
</tr>
<tr>
<td>Timing</td>
<td>Predetermined</td>
<td>Individualized</td>
</tr>
<tr>
<td>Autopsy/Histopathology</td>
<td>Always / Extensive</td>
<td>Exceptional</td>
</tr>
</tbody>
</table>
# Common (Human) Reactions to Drugs

<table>
<thead>
<tr>
<th>Predictable from Animal Studies</th>
<th>NOT Predictable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>Nausea</td>
</tr>
<tr>
<td>Sedation</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Nervousness</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Heartburn</td>
</tr>
<tr>
<td>Weakness</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Nasal Dryness of nasopharynx</td>
<td>Headache</td>
</tr>
<tr>
<td>Stiffness</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
</tr>
</tbody>
</table>

When

- Contingent upon clinical plan
- Follow regulatory (e.g. ICH) guidelines
- Strategic Development Considerations
- Outcome of previous studies
Characterize dose-response for pharmacologic effect

Characterize dose-response for target organ toxicities

MOS = Margin of Safety
Toxicology Based Risk Assessments

• No fixed rules or recipe books!
• Need to consider a number of inter-related questions, answers to which either increase or decrease level of concern
• Nature of lesion, reversibility, monitorability and safety margin most important features
• Extremes are relatively straight-forward, but seldom in this position
• Understanding mechanism of toxicity very valuable if in a ‘grey’ area
• No substitute for inter-disciplinary discussion and experience
Species Selection

Pharmacologically Relevant?

- rat
- dog
- rabbit
- hamster
- pigs
- guinea pig
- mouse
- Nonhuman primate
Route of Exposure

• Same as human

• Main routes - oral, intravenous

• Other routes - inhalation, ocular, dermal, intrathecal, intra-articular, diet
Dose Levels

- **Vehicle Control**
- **Low dose**
  - NO toxic effect
  - Multiple of efficacious dose level
- **Mid dose**
  - show dose-dependent toxicity
- **High dose**
  - Identify target organs of toxicity, maximum tolerated dose (MTD), or maximum feasible dosage (MFD)
Integration of Data

• Reams of data
• Establish potential relevance to humans and clinical situation
• Recognize limitations of species differences, sex differences, in vitro data, sample size, variability of human race
• Is it safe enough for humans?
• Focus on educating Regulatory Agency
Why Wasn’t That Seen in Nonclinical Studies?

- Animal toxicity = human toxicity
  - Compound may not be active in certain species
  - Relative homogenous animal population versus a heterogenous human population (diet, genetic makeup, metabolism, etc)

- Numbers game - Statistics

- Tightly controlled dosing in animals (mg/kg) versus humans
  - Same doses given to humans over a range of weight

- In vitro data = in vivo results

- ♂ = ♀
  - Exposure and/or sensitivity

- Rats = dogs = primates...
  - COX2 inhibitors are contraindicated in dogs
    - Ibuprofen metabolizes slowly, reaches toxic levels, causes liver and kidney failure
  - Metabolism Example: species fails to convert pro-drug to active moiety
Continuous Evaluation

$1.5 Billion

Average cost of development

$2.6 Billion


Tufts Center for the Study of Drug Development, 2014
99% Failure Rate
What does an NDA/BLA look like?
# Sample Small Molecule IND Timeline

<table>
<thead>
<tr>
<th>ID</th>
<th>Task Name</th>
<th>Start</th>
<th>Finish</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Exploratory Analyses</td>
<td>Mon 5/1/07</td>
<td>Mon 5/10/07</td>
<td>1 day</td>
</tr>
<tr>
<td>2</td>
<td>IMPK Studies</td>
<td>Thu 3/2/07</td>
<td>Mon 3/16/07</td>
<td>83 days</td>
</tr>
<tr>
<td>3</td>
<td>Cross Species Metabolite Profiling</td>
<td>Tue 5/1/07</td>
<td>Mon 5/7/07</td>
<td>1.5 days</td>
</tr>
<tr>
<td>4</td>
<td>Cytokine Induction (in-house)</td>
<td>Wed 5/1/07</td>
<td>Wed 5/7/07</td>
<td>1 mon</td>
</tr>
<tr>
<td>5</td>
<td>PK/PD Induction</td>
<td>Tue 5/2/07</td>
<td>Mon 5/8/07</td>
<td>2 mon</td>
</tr>
<tr>
<td>6</td>
<td>PK/PD Studies</td>
<td>Mon 5/7/07</td>
<td>Mon 5/8/07</td>
<td>1 mon</td>
</tr>
<tr>
<td>7</td>
<td>R&amp;D Transition</td>
<td>Mon 5/8/07</td>
<td>Mon 5/9/07</td>
<td>1 mon</td>
</tr>
<tr>
<td>8</td>
<td>Tox Studies</td>
<td>Mon 5/9/07</td>
<td>Mon 5/10/07</td>
<td>1 mon</td>
</tr>
<tr>
<td>9</td>
<td>BIA Candidate Analyses</td>
<td>Mon 5/10/07</td>
<td>Fri 5/11/07</td>
<td>1 day</td>
</tr>
<tr>
<td>10</td>
<td>IMPK Studies</td>
<td>Mon 5/11/07</td>
<td>Fri 5/11/07</td>
<td>1 day</td>
</tr>
<tr>
<td>11</td>
<td>Assay Transfer/Validation (in-house)</td>
<td>Mon 5/15/07</td>
<td>Fri 5/17/07</td>
<td>3 mon</td>
</tr>
<tr>
<td>12</td>
<td>Assay Transfer/Validation (dog)</td>
<td>Fri 5/17/07</td>
<td>Fri 5/17/07</td>
<td>1 mon</td>
</tr>
<tr>
<td>13</td>
<td>Assay Transfer/Validation (dog)</td>
<td>Fri 5/17/07</td>
<td>Fri 5/17/07</td>
<td>1 mon</td>
</tr>
<tr>
<td>14</td>
<td>Tox Studies</td>
<td>Mon 5/21/07</td>
<td>Fri 5/24/07</td>
<td>3 mon</td>
</tr>
<tr>
<td>15</td>
<td>15-l day Repeat in Dog</td>
<td>Mon 5/24/07</td>
<td>Fri 5/24/07</td>
<td>3 mon</td>
</tr>
<tr>
<td>16</td>
<td>15-l day Repeat in Dog</td>
<td>Fri 5/24/07</td>
<td>Fri 5/24/07</td>
<td>3 mon</td>
</tr>
<tr>
<td>17</td>
<td>15-l day Repeat in Rat</td>
<td>Mon 5/24/07</td>
<td>Fri 5/24/07</td>
<td>3 mon</td>
</tr>
<tr>
<td>18</td>
<td>15-l day Repeat in Rat</td>
<td>Fri 5/24/07</td>
<td>Fri 5/24/07</td>
<td>3 mon</td>
</tr>
<tr>
<td>19</td>
<td>15-l day Repeat in Rat</td>
<td>Mon 5/24/07</td>
<td>Fri 5/24/07</td>
<td>3 mon</td>
</tr>
<tr>
<td>20</td>
<td>15-l day Repeat in Rat</td>
<td>Fri 5/24/07</td>
<td>Fri 5/24/07</td>
<td>3 mon</td>
</tr>
</tbody>
</table>

## 12-18 Months

- Assay Transfer/Validation (dog)
- Transfer/Validation
- Protein Binding
- CYP/450 reaction phenotyping
- 15-l day Repeat dose in Dog
- 15-l day Repeat dose in Rat
- 16-20 weeks in Dog
- 20-24 weeks in Rat
- 30-35 weeks in Rat
- 30-35 weeks in Rat
- 30-35 weeks in Rat
- 30-35 weeks in Rat
- 30-35 weeks in Rat
<table>
<thead>
<tr>
<th>Function</th>
<th>$ Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPK</td>
<td>$400,000</td>
</tr>
<tr>
<td>Bioassay</td>
<td>$440,000</td>
</tr>
<tr>
<td>CMC (CRDMO)</td>
<td>$6,507,000</td>
</tr>
<tr>
<td>QA</td>
<td>$250,000</td>
</tr>
<tr>
<td>TOX (CRO)</td>
<td>$1,900,000</td>
</tr>
<tr>
<td>Reg Ops, Affairs</td>
<td>$150,000</td>
</tr>
<tr>
<td>Clin Ops, Medical (Phase 1 Normal Healthy)</td>
<td>$2,970,000</td>
</tr>
<tr>
<td><strong>TOTAL (~18 mo)</strong></td>
<td><strong>$ 12,617,000</strong></td>
</tr>
</tbody>
</table>
Determine NOAELs (mg/kg) in tox studies

Animal NOAEL to HED justified based on mg/kg or other?

Convert animal NOAELs to HED based on BSA mg/m^2

MRSD = HED/SF

HED mg/kg = NOAEL (mg/kg) or other

Select appropriate (most sens) species

“Consider lower dose based on other factors, i.e., PAD”

Choose Safety Factor

Default SF = 10

Clinical Dose Selection
Other Considerations (e.g. Safety Factor)
Clinical Dose Selection
MABEL and NOAEL Approaches

Dose or Exposure

- Biologic Activity
- Therapeutic Range
- Unacceptable Tox or Exaggerated Pcol

Effect

- MABEL
- ED (hi)
- NOAEL

Margin of Safety
Dose Escalation
Adverse Effect

A biochemical, morphological, or physiological change (in response to a stimulus, in this case test article) that either singly or in combination causes concern for the health and/or survival or significantly compromises the performance of the test animal.
An effect is less likely to be adverse if...

- there is no alteration in general function
- it is an adaptive response
- it is transient
- the severity is limited, below thresholds of concern, or within the accepted range of normal variation for that species.
- the effect is isolated or independent
- the effect is not a precursor that is part of an accepted continuum of change that is known to progress with time to an established adverse effect
## 1-Month Rat Study

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>0</th>
<th>0.1</th>
<th>1</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>N=10/sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Clinical observations – mostly reversible</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft feces*</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rough haircoat*</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Body weight (% change vs control) Wk 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>--</td>
<td>↑6</td>
<td>↓4</td>
</tr>
<tr>
<td>Clinical pathology (change relative to control) – all reversible</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered electrolytes</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>↑ ALT</td>
<td>N/A</td>
<td>N/A</td>
<td>--</td>
<td>√</td>
</tr>
<tr>
<td>↑ AST</td>
<td>N/A</td>
<td>N/A</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>↑ Total cytochrome P450</td>
<td>N/A</td>
<td>N/A</td>
<td>--</td>
<td>√</td>
</tr>
<tr>
<td>Morphologic pathology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach: necrosis &amp; atrophy</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Liver: Hepatocellular vacuolation</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Liver: Hepatocellular necrosis</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Heart: Myocardial necrosis</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

* # of rats affected    N/A = Not Applicable    -- = No important changes    NR = Not Reversible
# 1-Month Rat Study

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>0 (Control)</th>
<th>0.1</th>
<th>1</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=10/sex</td>
<td>M F</td>
<td>M F</td>
<td>M F</td>
<td>M F</td>
</tr>
<tr>
<td>Mortality*</td>
<td>0 0</td>
<td>0 1</td>
<td>0 0</td>
<td>0 0</td>
</tr>
</tbody>
</table>

### Clinical observations – mostly reversible

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>F</th>
<th>M</th>
<th>F</th>
<th>M</th>
<th>F</th>
<th>M</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft feces*</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Rough haircoat*</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

### Body weight (% change vs control) Wk 12

<table>
<thead>
<tr>
<th></th>
<th>N/A</th>
<th>N/A</th>
<th>↑6</th>
<th>↓4</th>
<th>↑10</th>
<th>↑15</th>
</tr>
</thead>
</table>

### Clinical pathology (change relative to control) – all reversible

<table>
<thead>
<tr>
<th></th>
<th>--</th>
<th>--</th>
<th>--</th>
<th>--</th>
<th>√</th>
<th>√</th>
<th>√</th>
<th>√</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered electrolytes</td>
<td>N/A</td>
<td>N/A</td>
<td>--</td>
<td>--</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>↑ ALT</td>
<td>N/A</td>
<td>N/A</td>
<td>--</td>
<td>--</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>↑ AST</td>
<td>N/A</td>
<td>N/A</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>↑ Total cytochrome P450</td>
<td>N/A</td>
<td>N/A</td>
<td>--</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

### Morphologic pathology – NR = Not Reversible

<table>
<thead>
<tr>
<th></th>
<th>--</th>
<th>--</th>
<th>--</th>
<th>--</th>
<th>√ NR</th>
<th>√ NR</th>
<th>√ NR</th>
<th>√ NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach: necrosis &amp; atrophy</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Liver: Hepatocellular vacuolation</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Liver: Hepatocellular necrosis</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>√</td>
</tr>
<tr>
<td>Heart: Myocardial necrosis</td>
<td>--</td>
<td>10</td>
<td>10x</td>
<td>10</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**NOAEL**

```
√
```
Overall Conclusions

Make it **better**

Make it **safer**

Make it **predictable**
Clear as a Donut Hole?