Preclinical Designs/Efficacy Models Supporting Proof of Concept Studies

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Disclosures:

The author is an employee of DUCK FLATS Pharma, LLC.
Learning Objectives:

1. Identify challenges in the transition from animal models to clinical development.

2. Understand how drug type (chemical, biologic) and immunological differences between animals and humans impact drug development programs.

3. Evaluate how previous successes and failures can be utilized to improve future drug development programs.
Overview

Most drugs that enter clinical development fail due to:

• Lack of efficacy – 56%\textsuperscript{1}  
  (Phase 2 to Submission, 2011-2012)

• Safety - 28%\textsuperscript{1}  
  (Phase 2 to Submission, 2011-2012)
Overview

Failure rates (provided for areas where a failure reason is given) are particularly high in the areas of oncology and central nervous system (CNS).

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Failure Rate$^{1,2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>29.5%</td>
</tr>
<tr>
<td>Central Nervous System (CNS)</td>
<td>14%*</td>
</tr>
<tr>
<td>Infectious Disease</td>
<td>9.5%</td>
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<tr>
<td>Musculoskeletal</td>
<td>8.5%</td>
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<tr>
<td>Cardiovascular</td>
<td>8.5%</td>
</tr>
<tr>
<td>Other</td>
<td>30%</td>
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</tbody>
</table>

* Rates provided for areas where a failure reason is reported. Almost half of CNS failures excluded due to non-disclosure of reason.
Considerations and Challenges

• Animal models versus human response
  o Toxicity
  o Innate and adaptive immunity
  o Predictability

• Drug Development
  o New chemical entity versus biologic versus approved compound

• Estimation of First-in-Human (FIH) dose
Considerations and Challenges

• Adequate study designs

• Demonstration of efficacy versus placebo or marketed drug
  o Due to variability of placebo effects, some treatments may fail to prove drug superiority over placebo even though their total effects are of clinical relevance\(^3\)
Considerations and Challenges

Animal Models and Selection

• Species-specific toxicity
  o Liver metabolism in animals very different from humans
  o Immunogenicity may prevent proper study in animals

• Assessment of efficacy, PK, and safety in the same model may not be possible

• Animal models
  o Rodent versus non-rodent models
  o Model is not well-validated
Considerations and Challenges

Chemical Entities versus Biologics
(Small versus Large Molecule)

- Target and species specificity
- More complex CMC processing needed to optimize effectiveness of biologics
- Oral vs. parenteral route (examples: IV, IM, SC, IT)
  - Impacts drug absorption and bioavailability: Distribution of biologics via SC administration into tissues is generally slower compared to IV or oral administration.
Considerations and Challenges

Chemical entities versus Biologics (continued)

- Differences in metabolism/catabolism\(^7\)
  - Metabolites may be active in chemical entities
  - Biologics may be catabolized to amino acids or peptides

- Toxicity from biologics typically due to exaggerated pharmacology\(^8\)

- Potential for formation of anti-drug antibodies (ADAs) for biologics
  - Can result in decreased drug efficacy\(^9,10\)
Considerations and Challenges

Innate and adaptive immunity differences between animals and humans such as: 11,12

- Leukocyte subsets - monocytes, mast cells, CD4+ cells
- Cytokines and cytokine receptors
- Ig isotypes in allergic response
  - Both IgE and IgG1 in mice
  - IgE only in humans
- Significant bronchus-associated lymphoid tissue in mice
Preclinical Testing

- *In vitro* experiments
- *In vivo* experiments
- Wide-range of study drug doses
- Preliminary efficacy, toxicity, and pharmacokinetic, and metabolism data
- Basis for decision whether to further develop a drug candidate
Estimation of FIH Dose

No observed adverse effect level (NOAEL)
- Highest dose tested in animal species that does not produce a significant increase in adverse events versus a control group; toxicology studies

Pharmacologically Active Dose (PAD)
- Starting exposure expected to have pharmacological activity
- Position on exposure-response curve justified by risk-benefit considerations
Estimation of FIH Dose

Minimum Anticipated Biological Effect Level (MABEL)
• Estimate exposure associated with minimal pharmacological activity
• Usually apply additional safety factor to give a No-Effect Level

Highest Non-Severely Toxic Dose (HNSTD)
• Applications in cancer patients
Proof of Concept Studies

• Generally Phase 1B/2A
• Provide preliminary evidence of efficacy and safety
  o Translation into a beneficial therapeutic effect
• Utilize placebo or a comparator treatment
• Small population to limit potential drug exposure risks
• Biomarkers/surrogate markers to bridge gap between animal/human and determine efficacy endpoint
• Inform the decision whether to proceed into full drug development
Phase 2 Studies – Potential Issues

- Inadequate design
  - Number of studies
  - Sample size – must consider patient heterogeneity

- Choice of endpoints
  - Provide limited or misleading information on drug efficacy

- Improper execution
  - Good Clinical Practice (GCP) failures – can lead to poor quality data
Implementation After Phase 2

Poor implementation of programs at this stage leads to Phase 3 study failures.

- Current failure rate for Phase 3 studies is about 45%\textsuperscript{13}
- Majority of failures due to efficacy\textsuperscript{14}
- Overall, failure rate at the pivotal development stage (Phase 3) could be reduced by more adequate Phase 2 designs and dose-ranging studies
Efficacy and Safety Models

The following areas of drug development will be discussed to provide examples of how animal models translated to human studies:

• Cardiovascular
  o Arrhythmia

• Central Nervous System (CNS)
  o Inflammatory Disease - Multiple Sclerosis
  o Pain Management

• Oncology
Cardiovascular (Arrhythmia)

Anti-arrhythmic drugs generally affect cardiac arrhythmias by modulating conduction velocity, or effective refractory period, or both.

Drug classification based on electropharmacologic and electrophysiological properties.

Different animal models needed based on arrhythmia type (supraventricular and ventricular) and drug action; choice of model important to determine best clinical results.
Cardiovascular (Arrhythmia)

Supraventricular tachycardia\(^{15,16}\)
Animal models closely resemble clinical features of patients

- \textit{In vitro:} Microelectrode studies on isolated rabbit heart preparations provided insight into arrhythmia mechanisms on a cellular level
  - However, this model \textbf{does not} mimic AV-nodal re-entrant tachycardia in humans

- \textit{In vitro and in vivo:} Canine models used for atrial flutter [right atrial crush, acetylcholine infusion and rapid pacing (isolated blood perfused heart), aconitine or delphinine application to right atrium (anesthetized dogs)]
Cardiovascular (Arrhythmia)

Ventricular arrhythmias\textsuperscript{15,16}

More difficult to align animal models to human patients

- \textit{In vivo and in vitro}: Porcine models for ventricular fibrillation (pacing electrode through right cephalic vein to right ventricle, induction by 60-hz alternating current in isolated right ventricle)

- \textit{In vivo}: Mongrel dog models for sudden cardiac death (electrical stimulation performed after induction of anterior myocardial infarction by occlusion/perfusion on left anterior coronary artery)
Cardiovascular (Arrhythmia)

Case Study: Sotalol
(Approved and marketed in the US and Europe)

- Class II (beta-adrenoreceptor antagonist) properties

and

- Class III (Potassium-channel blocker) properties
  - Prolongs the plateau phase of the cardiac action potential in the isolated myocyte, as well as in isolated tissue preparations of ventricular or atrial muscle
Cardiovascular (Arrhythmia)

Case Study: Sotalol

- Previous studies usually performed in anaesthetized animals
  - Can produce bradycardia and prolong QT interval in most species

- Dogs typically used in safety pharmacology studies but differences in PK and drug metabolism compared to humans

- Non-human primates may be better model to determine the dose- and plasma-response effects of sotalol
Cardiovascular (Arrhythmia)

Case Study: Sotalol

Findings of study conducted in non-anaesthetized cynomolgus monkeys:\textsuperscript{17}

- Decreased heart rate
- Prolonged RR, PR, QT and corrected QT intervals
- Little or no effects on the QRS complex, arterial pressure, or body temperature
Cardiovascular (Arrhythmia)

Case Study: Sotalol

The cardiovascular effects in monkeys occurred in a similar pattern and to a comparable degree as those reported in human studies.

Study demonstrated the validity of utilizing conscious telemetry-instrumented non-human primates for the cardiovascular safety pharmacology assessment of drugs prior to FIH testing.\(^{17}\)
CNS (Inflammatory Disease)

Relative to the human response, mice are highly resilient to inflammatory challenge.

For example, the lethal dose of endotoxin is 5–25 mg/kg for most strains of mice, whereas in humans, a dose that is 1 million-fold less (30 ng/kg) has been reported to cause shock.¹⁸
CNS (Inflammatory Disease)

Murine Model versus Human Model

- In humans, acute inflammatory stresses from different etiologies result in highly similar genomic responses regardless of genetic make-up
- Poor correlation in individual murine model responses to acute inflammatory stresses compared to human and other mice models
CNS (Inflammatory Disease)

Multiple Sclerosis
• Chronic inflammatory disease of central nervous system
• Appears to have a large autoimmune component
• Areas of inflammation and demyelination
  o CD4+ T-helper cells reactive to myelin
    ▪ Produce proinflammatory cytokines [ex: interferon-gamma (IFN-\(\gamma\)), osteopontin (OPN) and tumor necrosis factor-a (TNF-a)]
    ▪ Known to have a leading role in MS
CNS (Inflammatory Disease)

Multiple Sclerosis Case Study 1: IFN-γ Studies

Experimental autoimmune encephalomyelitis (EAE) mimics the demyelination seen in central and peripheral nerves in MS; widely-used model for this disease.

- Preclinical studies: IFN-γ protective in EAE as neutralizing Abs exacerbate disease, potentially by blocking induction/activation of suppressor activity

- Clinical trials: Treatment with IFN-γ was found to exacerbate disease
CNS (Inflammatory Disease)

Multiple Sclerosis Case Study 2: Integrin Studies\textsuperscript{11,20}

- Preclinical (mice) studies: Blocking VLA-4 (\(\alpha_4\beta_1\) integrin)-VCAM-1 interaction may help in MS

- Clinical trials: Demonstrated successfully in human trials

These examples highlight how caution is required when extrapolating results from mouse studies to the clinic, but suggest that mouse models can successfully predict some therapies for human disease.
CNS (Pain Management)

• Currently, more than 1.5 billion people worldwide suffer from chronic pain of varying degrees\textsuperscript{21}

• Neuropathic pain, which is the most difficult to medically treat, affects approximately 3\% to 4.5\% of the global population\textsuperscript{21}

• Demand for better management and therapies for both chronic and acute pain expected to rise with increased age of the population
CNS (Pain Management)

N-type calcium channels have been recognized as crucial targets in controlling pain because of their key role in transmitting pain through the spinal nerves to the brain.
Case Study: Ziconotide
(Approved and marketed in the US and Europe)

- Synthetic equivalent of a naturally occurring conopeptide found in the piscivorous marine snail, Conus magus
- Non-narcotic analgesic drug; acts by blocking N-type calcium channels
- Available as an intrathecal injection to treat chronic pain
CNS (Pain Management)

Case Study: Ziconotide

• Binds to N-type voltage-sensitive calcium channels (NVSCCs) [Cav2.2] located on the primary nociceptive (A-δ and C) afferent nerves in the superficial layers of the dorsal horn in the spinal cord\textsuperscript{22}

• Produces potent antinociceptive effects reducing release of pronociceptive neurotransmitters in dorsal horn in the spinal cord\textsuperscript{23}
  ○ Inhibits pain signal transmission
Case Study: Ziconotide

Non-clinical studies conducted in several different animal models:²²

- Toxicology (acute and subchronic) in rats, dogs, and monkeys
- Reproductive toxicity in rats and rabbits
- *In vivo/in vitro* mutagenic and carcinogenic evaluations
- Immunogenicity in mice, rats, and guinea pigs
- Intraspinal granuloma formation in dogs
CNS (Pain Management)

Case Study: Ziconotide

Indication 1 - Chronic/Neuropathic Pain\textsuperscript{22,23}

- Animal models - Potent antinociceptive profile

- Clinical studies
  - Severe pain (due to cancer or AIDS): Moderate to complete pain relief
  - Severe chronic pain (mostly neuropathic): Significant pain relief; decreased consumption of opioids
CNS (Pain Management)

Case Study: Ziconotide

Indication 2: Post-Operative Pain$^{22,23}$

- Rat incisional model: Demonstration of more potent and longer activity than morphine

- Clinical study: Significant pain relief at both low and high doses; decreased consumption of morphine
Oncology

The average rate of successful translation from animal models to clinical cancer trials is less than 8%.\textsuperscript{24}
Oncology

Translation failures due to:

• Complexity of human carcinogenesis process, physiology, and progression

• Genetic, molecular and physiological limitations

• Animal Models
  o While there is some uniformity, best-practice standards do not exist; experiments do not always include the appropriate species

• Negative data/findings often unpublished for oncology (and other drug development areas)
Oncology

Case Study: TGN1412

TGN1412 was described as an immunomodulatory humanized agonistic anti-CD28 monoclonal antibody developed for the treatment of certain cancers with immunological etiology.
Oncology

Case Study: TGN1412 Preclinical Studies

• *In vitro* evaluation in human and non-human cells (rodent and primate)

• *In vivo* studies in cynomolgus and rhesus monkeys (CD28 receptors affinity for TGN1412 similar to humans)

• Repeat-dose administration in cynomolgus and rhesus monkeys

• Toxicology studies in relevant species using rat anti-CD28 antibody jj316 or TGN1112 (Ig variant of TGN1412)
Oncology

Case Study: TGN1412 Dose Calculation

- Safe dose calculated from non-human primate model was considered of suitable relevance for calculation of FIH dose
  - TGN1412 showed specificity toward CD28 receptor expressed on human and non-human primate T cells

- Prior tests in cynomolgus and rhesus monkeys had demonstrated a dose of 50 mg/kg (administered for four consecutive weeks) to be safe
Oncology

Case Study: TGN1412 Dose Calculation

• Based on the repeat-dose toxicity studies in cynomolgus monkeys, NOAEL was considered to be 50 mg/kg per week for not less than four consecutive weeks.

• A dose of 0.1 mg/kg was decided to be administered to healthy volunteers based on:
  o FDA guidelines
  o Minimal Anticipated Biological Effect Level (MABEL)
  o Safety Criteria for the safe first dose
Oncology

Case Study: TGN1412 Phase 1 Clinical Study (2006)

Clinical study was conducted in six volunteers.

After the very first infusion of a dose:

- All six volunteers faced life-threatening conditions involving multi-organ failure resulting from rapid release of cytokines by activated T cells

This was despite the fact that multiple pre-clinical studies had shown that this drug, (given at much higher doses in animals), was safe.
Oncology

Case Study: TGN1412 What happened and Why?²⁵

• Interpretation of preclinical (primate) studies
  o Low-level cytokine release in primate studies should have prompted more caution in clinical trial

• Insufficient in vitro human studies performed
  o Important that human material is as close as possible to the target tissue

• Choice of starting dose
  o Prediction of risk and dose range from animal studies not always reliable (even from non-human primates)
In Summary:
Transition from animal models to human studies

• Choice of animal model(s)
  o Best fit to potential human response

• Correct dose(s)/dosing range/biomarker(s)
  o Minimize toxicity and efficacy issues

• Adequate Proof of Concept/Phase 2 study design
  o Critical in lessening Phase 3 failures

• Recognition that certain diseases (such as cancer) are harder to treat due to nature of disease
  o Requires more vigilant interpretation of animal data
References:


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