Quantitative Pharmacology in a Translational Research Environment

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Outline

• Translational Research
• Opportunity for Academic Medical Research
  – Alignment with the FDA Critical Path
• The CTSA
  – Quantitative Pharmacology Integration
• The CHOP / UPenn CTSA
  – Case Study - IPCP Award: NK1r antagonists in the treatment of HIV

Translational Research

A discipline that encompasses:

• Basic science studies which define the biological effects of therapeutics in humans
• Investigations in humans which define the biology of disease and provide the scientific foundation for development of new or improved therapies for human disease
• Non-human or non-clinical studies conducted with the intent to advance therapies to the clinic or to develop principles for application of therapeutics to human disease
• Any clinical trial of a therapy that was initiated based on above with any endpoint including toxicity and/or efficacy.
• Appropriate product development for clinical use in various stages of investigational clinical trial.
Translational Research

• “... better referred to as "reality-driven" research underlining the concept that direct human observation may direct to the study of hypotheses relevant to human reality.”

• “Three major obstacles to effective translational medicine.
  1. The challenge of translating basic science discoveries into clinical studies.
  2. The translation of clinical studies into medical practice and health care policy.
  3. The available standard therapies for most common diseases are less efficacious than they are believed by the Public to be and significant funds are allocated to maintain this "placebo" effect through standard care. Proportionately, very little is spent to identify truly effective therapies.”

Mankoff SP, Brander C, Ferrone S, Marincola FM
Lost in Translation: Obstacles to Translational Medicine, JTM, 2006

Translational Research

"The heart of translational research resides in Phase I trials where novel treatments are tested for feasibility and toxicity in preparation for a Phase II trial in which therapeutic effectiveness is tested. In the wake of a potential "breakthrough" in the lab, the Phase I trial offers great temptation to test what could be a pioneering therapeutic effect and learn from the novel concepts derived from clinical experience that could be shared with those bench scientists who originally conceived the treatment.”

Marincola, FM
Translational Medicine: A two-way road, JTM, 2006

Scope of Research Effort: Diagnosis to Treatment

Reliant on integration of medical informatics with molecular technologies (genomics and proteomics)
Translational Research
Workflow Proposal

Necessity of integrated data solutions

Mapping molecular correlates to molecular pathways in order to identify disease mechanisms
Translational Research
The End Product . . .
Clinical and molecular diagnostic tests to predict patient prognosis

The Opportunity for Academic Medical Centers
STRUCTURAL REFORM IN ACADEMIC MEDICAL CENTERS: THE SCENE IN BIG PHARMA
- Substantial resources, focused mission
- Division of talent - high end basic research with weaker clinical research expertise
- No primary access to patients, but resources for scale and proprietary compounds
- Physical and intellectual segregation of basic and human pharmacology
- Secular pressures to move to phase 3 at expense of dose finding and mechanistic

The Opportunity for Academic Medical Centers
STRUCTURAL REFORM IN ACADEMIC MEDICAL CENTERS: THE SCENE IN AMCs
- Talented physician scientists in one focal location
- Access to patients
- Resource limited; no incentives for herding the cats
- Poor infrastructure for scale, unfocussed mission and consequent delay in process
- Often poorly educated in pharmacology
The Opportunity for Academic Medical Centers

**ITMAT OBJECTIVES**

- To integrate infrastructural and educational resources relevant to translational research
- To increase the number of investigators skilled in translational research
- To identify and reduce the barriers which they face

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CTSA

**A THREAT AND A PROMISE**

**THE CLINICAL AND TRANSLATIONAL SCIENCE AWARD**

- Bid for up to $6M/yr incremental total costs – fund 3-6 from ~36
- Increment comes from closing GCRCs
- Heavily reliant on institutional investment
- Joint proposal from Penn, CHOP, WI and USP – 9 / 12 schools from Penn
- Programmatic consideration for 4.5 months, then structure, then budget

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CTSA

Kinetics, Modeling and Simulation (KMAS) Core. This new core will provide crucial infrastructure to the growing translational effort at the partner institutions. Jeffrey S. Barrett, Ph.D. of CHOP and Ian Blair, Ph.D. will co-direct the core. The core will (a) aid in the development of drug assays; (b) promote and assist in the performance of tracer kinetic studies; (c) develop novel approaches to kinetic data analysis; (d) provide pharmacokinetic (PK), PK-pharmacodynamic (PD), and tracer kinetic modeling; and (e) develop educational modules in pharmacokinetics and tracer kinetics to populate the educational initiatives pursued within the CTSA.
The Pharmacometric Training Unit will provide educational and training resources to support the translational research conducted under the auspices of the CTSA. It will also provide an outlet for the great demand for education in this area of research and promote additional collaborations with the drug industry. It will be co-directed by Dr. Barrett and Dr. Boston. Drs. Barrett and Boston will co-develop a module on tracer kinetics, pharmacokinetics, and compartmental and pharmacometric modeling to be offered as a core requirement in a Translational Therapeutics track in the MTR and electively as a stand-alone course or a component in other degree courses administered via ITMAT and the CCEB in support of the CTSA. The initial foray into this arena will be a two-semester course on Kinetic and Pharmacometric Approaches to Translational Research. We also plan a broader track in the Masters in Translational Research Program to be called Translational Therapeutics.

Recently, the American College of Clinical Pharmacology (ACCP) provided an online training resource to promote independent investigation into the science of pharmacometrics. As described elsewhere in the proposal, both the FDA and GSK (as an initial, but not exclusive industry partner) are collaborating with educational initiatives in the broad area of Translational Therapeutics with ITMAT. GSK and FDA staff will participate, both as faculty participants and as sites for rotation sites for CTSA students. Furthermore, BioAdvance will facilitate regionalization of access to this program, as to other CTSA-supported innovative educational initiatives.
Case Study
IPCP Award: NK1r antagonists in the treatment of HIV

Overall goal of Integrated Preclinical/Clinical Program (IPCP) is to identify a neurokinin-1 receptor (substance P preferring receptor) antagonist that is:

1. Active as an anti-HIV agent through interaction with chemokine/cytokine receptors (Project 1);
2. Specific for chemokine and G-protein coupled receptors (Project 2);
3. Safe for use in SIV-infected non-human primates and provides proof of concept related to antiviral, immunomodulatory, and neurobehavioral effects (Project 3); and,
4. Safe in HIV-infected humans and provides positive immunomodulatory effects, in particular through innate immunity and natural killer cells (Project 4).

Case Study
IPCP Award: NK1r antagonists in the treatment of HIV

A key component of this IPCP is the linkage between the translational science coupled with modeling and simulation techniques to aid in . . .

1. Ranking of various preclinical candidates,
2. Criteria for advancement to animal pharmacologic testing (proof-of-principle / proof-of-mechanism),
3. Evaluation of drug properties which constitute suitable criteria for advancement to human testing, and
4. Specific experimental and study design features which will permit specific, hypothesis-driven evaluation of the clinical utility of neurokinin-1 receptor antagonism as a treatment modality in patients infected with HIV-1.
NK1 Receptor Antagonism
M&S Drivers: Target Drug Exposure

Empirical Dose Calculation

\[
\text{Dose}_{\text{target}} = \frac{24 \text{hr} \cdot \text{CL}}{V \cdot F}
\]

Required information:
- PK parameters
  - CL
  - V
  - F
- Target concentrations
  - BC to C_{\text{efficacy}}

NK1 Receptor Antagonism
Defining Target Exposure for Aprepitant

Preclinical data support single agent activity and demonstration of synergistic effects when given in combination with clinically relevant agents (including HAART agents).

Aprepitant inhibits HIV-1 infection of MDM by down regulating CCR5 expression.
NK1 Receptor Antagonism
M&S Drivers – Preliminary Data

Allometric modeling with aprepitant
• Interpolation of monkey PK for SIV dosing strategy
• Human Phase 1B dose selection

Table 1. Interspecies Pharmacokinetic Data with Aprepitant

<table>
<thead>
<tr>
<th>Species</th>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>CL (mL/min/kg)</td>
<td>2.6 ± 2.5</td>
<td>Huskey et al., Drug Metab Disposit, 1999</td>
</tr>
<tr>
<td></td>
<td>Vdss (L/kg)</td>
<td>3.8 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td>CL (mL/min/kg)</td>
<td>0.0 ± 0.2</td>
<td>Huskey et al., Drug Metab Disposit, 1999</td>
</tr>
<tr>
<td></td>
<td>Vdss (L/kg)</td>
<td>0.9 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Ferret</td>
<td>CL (mL/min/kg)</td>
<td>1.5 ± 0.1</td>
<td>Huskey et al., Drug Metab Disposit, 2003</td>
</tr>
<tr>
<td></td>
<td>Vdss (L/kg)</td>
<td>1.3 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>AUC0-24h (ng*h/mL)</td>
<td>19455</td>
<td>Aprepitant NDA (21-549)</td>
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**NK1 Receptor Antagonism**

**Compound Progression**

**PK/PD in SIV**
- Define target profile and ITW in the cynomologous monkey
- Scale doses to obtain human equivalent exposures

**PK/PD in HIV**
- Project exposure-response profile in HIV-1 infected patients
- Simulate Phase 1B exposure-response
- Conduct trial
- Evaluate Pop-PK/PD in patients
- Simulate Phase 1B Proof-of-concept trial outcomes

**COMPOUND SCREENING / SELECTION / RANKING**
- Create mol file for chemical structures under consideration
- Model NK1 and immunomodulatory activity (Projects 1 and 2)
- Project criteria for advancement based on “druggability”
- Conduct tox and pharmacology studies on viable candidates
References


