Quantitative Pharmacology in a Translational Research Environment

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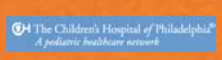


Outline

- 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.

Mario Sznol, *J Translational Medicine* Editorial Board

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

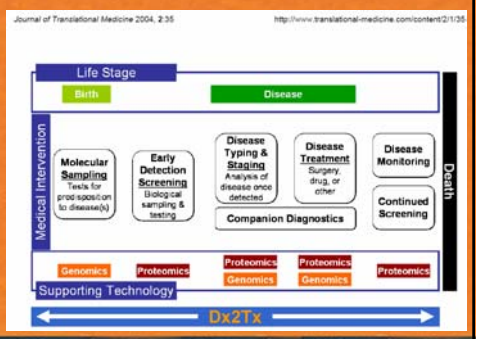
"The heart of translational research resides in Phase I trials where novel treatments are tested for feasibility and toxicity in preparation for a Phase II trial in which therapeutic effectiveness is tested. In the wake of a potential "breakthrough" in the lab, the Phase I trial offers great temptation 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

Translational Research

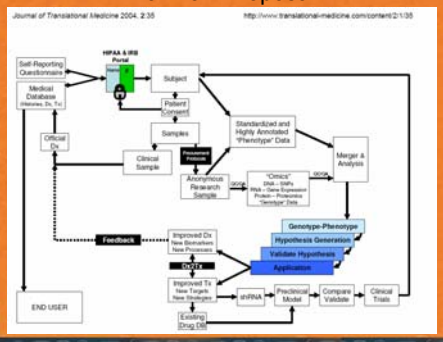
Scope of Research Effort: Diagnosis to Treatment

Reliant on integration of medical informatics with molecular technologies (genomics and proteomics)



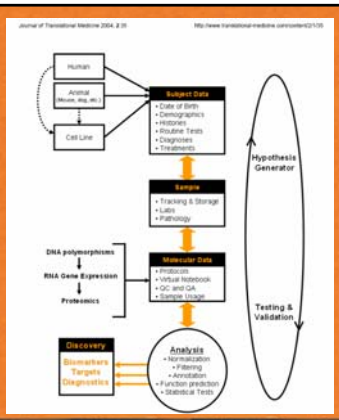
Translational Research

Workflow Proposal



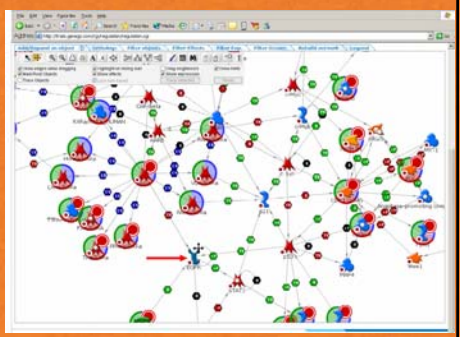
Translational Research

Necessity of integrated data solutions



Translational Research

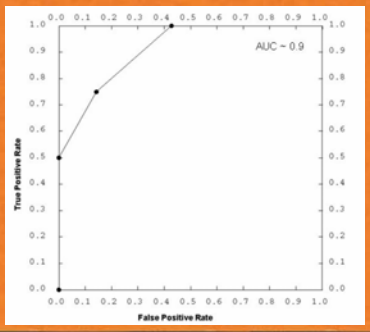
Mapping molecular correlates to molecular pathways in order to identify disease mechanisms



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

www.itmat.upenn.edu

CTSA

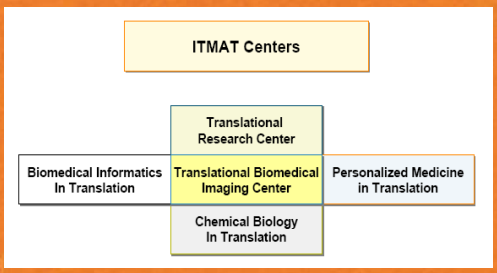
A THREAT AND A PROMISE
THE CLINICAL AND TRANSLATIONAL SCIENCE AWARD

- 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

CTSA

http://www.ncrr.nih.gov/clinicaldiscipline.asp

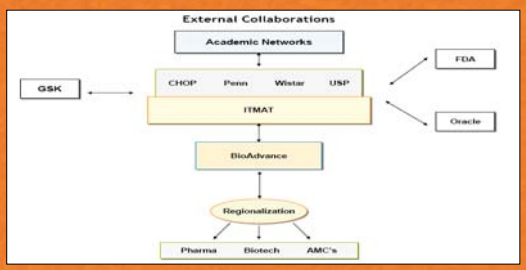
CHOP / UPenn CTSA



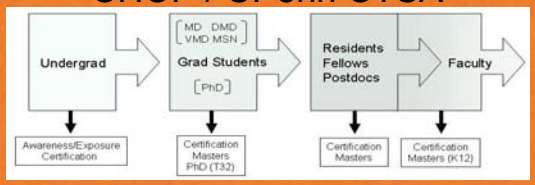
CHOP / UPenn CTSA

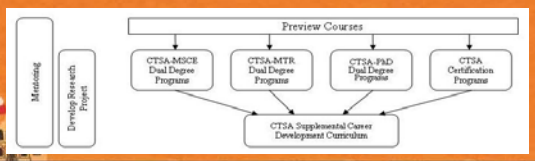
"**. . . Kinetics, Modeling and Simulation** (**KMAS**) Core. This new core will provide crucial infrastructure to the growing translational effort at the partner institutions. Jeffrey S. Barrett, Ph.D. of CHOP and Ian Blair, Ph.D. will co-direct the core. The core will (a) aid in the development of 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."

CHOP / UPenn CTSA



CHOP / UPenn CTSA





CHOP / UPenn CTSA

Pharmacometric Training Unit: 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 on-line 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 site for CTSA students. Furthermore, BioAdvance will facilitate regionalization of access to this program, as to other CTSA supported innovative educational initiatives.

CHOP / UPenn CTSA

- Planning Meeting for CTSA (End of 2006)
- Degree-granting timelines for CTSA
- Approval of external faculty (Metrum staff et. al.)
- GPBA (http://www.gpba-bio.com/) extension to Pharmacometrics – Undergraduate outreach
- Enrollment timelines for Pharmacometrics Track within Translational Medicine Degree
  - Distance Learning Timelines?

CHOP / UPenn CTSA

Pharm Core

- PK / Biopharmaceutics
- PD / Pharmacology
- Disease Therapeutics
- Quantitative Bioanalysis

Stat Core

- Regression Analysis
- ANOVA
- Experimental Design
- Clinical Trial Design

Electives

- DMPK & Drug Transport
- Drug Development
- Regulatory Science
- Decision Analysis
- Special Programming Topics (R, SAS, SPLUS, NONMEM, PERL, etc)

M&S Core

- Pop PK
- Clinical Trial Simulation
- Bayesian Methods & Approaches in Medicine

Programming Core

- Computational Methods / Application
- Intro to Statistical Programming

- Prerequisites: Life Sciences Degree, Stat I, Stat II (or equivalent)
- PhD: Minimum of 45 credits

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

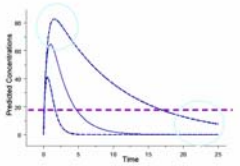
Empirical Dose Calculation

$$Dose_{target} = EC_{target} \times 24(hr/\tau) \times \frac{CL}{F}$$

$$Dose_{load} = EC_{effective} \times V_{ss}$$

Required information:

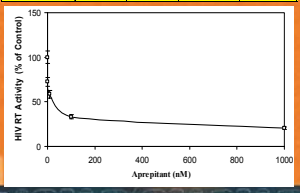
- PK parameters
  - CL
  - V
  - F
- Target concentrations
  - EC_{50}, $C_{effective}$



NK1 Receptor Antagonism
Defining Target Exposure for Aprepitant

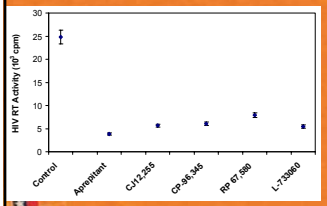
RT Activity (% of Control)				
Virus / Dose	R5		R5X4	X4
	Bal	SF162	89.6	UG024
Aprepitant 10^{-6} M	17.2	14.3	36.9	89.1
Aprepitant 10^{-7} M	13.8	16.6	44.1	93.1
Aprepitant 10^{-8} M	57.6	60.1	52.4	89.9
Control	100.0	100	100.0	100

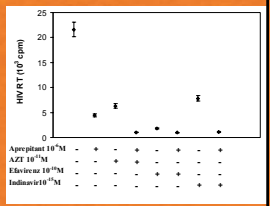
Aprepitant inhibits HIV-1 infection of MDM by down regulating CCR5 expression



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)





Inhibition of HIV (Bal) Infection of MDM by NK-1R Antagonists (10-6 M)

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

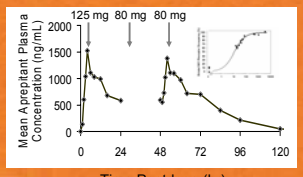
Table 1. Interspecies Pharmacokinetic Data with Aprepitant

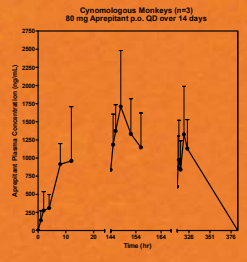
Species	Parameter	Value	Reference
Rat[a]	CL (mL/min/kg) Vdss (L/kg)	13.4 ± 2.6 2.8 ± 0.1	Huskey et. al., Drug Metab Disposit, 1999
Dog[a]	CL (mL/min/kg) Vdss (L/kg)	0.9 ± 0.2 0.9 ± 0.1	Huskey et. al., Drug Metab Disposit, 1999
Ferret	CL (mL/min/kg) Vdss (L/kg)	1.5 ± 0.1 1.3 ± 0.1	Huskey et. al., Drug Metab Disposit, 2003
Human[b]	$AUC_{0\text{-}24h}$ (ng*h/mL)	19455	Aprepitant NDA (# 21-549)

NK1 Receptor Antagonism
M&S Drivers – Preliminary Data

Direct Comparison: Monkey vs Human Exposure

Aprepitant Exposure in Healthy Volunteers (N=12)
Following Standard CINV Dosing

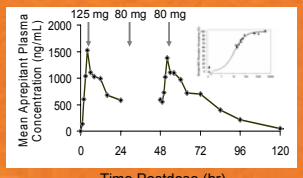




NK1 Receptor Antagonism
M&S Drivers – Preliminary Data

Projecting Doses in HIV Patients – Current Projection

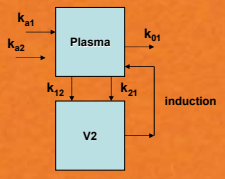
Aprepitant Exposure in Healthy Volunteers (N=12)
Following Standard CINV Dosing



Prior Information:
- Inhibition of HIV Bal strain in MDM by Aprepitant (10-6 M) is 79.5 %
- Assuming that the human exposure target is similar to the *in vitro* activity yields a target trough free drug concentration of ~ 500 ng/mL.
- Aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Seven metabolites of aprepitant (only weakly active) identified in human plasma.
- Enzyme induction reduces the exposure of aprepitant following chronic administration (not published).
- Protein binding ~ 95%
- F ~ 60-65%
- Half-life: 9-13 hours
- Elimination by metabolism; no renal

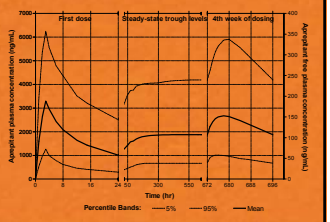
NK1 Receptor Antagonism
M&S Drivers – Preliminary Data

Projecting Doses in HIV Patients – Current Projection



Model Assumptions / Features:
- Induction reduces exposure by 50% at SS (↑ CL by 2 fold)
- Moderate variability in CL and V
- Staged first order input explains absorption

Monte Carlo Simulations from Pop-PK Simulation
Model: Exposure from 375 mg QD Administration of Aprepitant



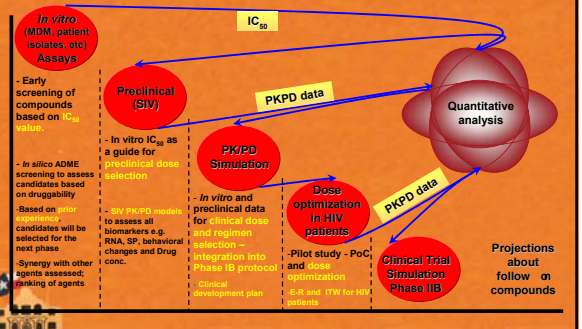
NK1 Receptor Antagonism
Compound Progression

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 IIB 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

NK1 Receptor Antagonism
Compound Progression



VIEWS OF THE FUTURE FROM THE LESSONS OF THE PAST

Shifting coalitions of the willing to address discrete therapeutic opportunities

"I would not say that the future is necessarily less predictable than the past. I think the past was not predictable when it started."

D. Rumsfeld

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