Impact of Modeling and Simulation on Advances in Translational Research

Jeffrey S. Barrett, PhD, FCP

The Children’s Hospital of Philadelphia®
Outline

• Translational Research Defined
  – Concept, design and work flow

• The Landscape with NIH and the CTSA

• Opportunities for Modeling and Simulation
  – Research
  – Education / Training

• Case Study
  – Advancing molecularly targeted pro-apoptotic agents for infant leukemias
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.

Investigations in humans which define the biology of disease and provide the scientific foundation for development of new or improved therapies for human disease.
Drug Development Paradigm
Phase Oriented Approach

Pre-clinical & Proof of Concept
- Target Identification
- Lead Identification
- Candidate Identification
- Preclinical

Proof of Safety, Efficacy & Marketability
- Phase I-IIa
- Phase IIb
- Phase III
- Registration
- Approval
- Life-cycle Mngt

Evolution of Project team
- Site Project team evolves into Global Project team

Evolution of commercial team
- Early Product team evolves into Commercial team

Key Decision Points
- Lead Selected
- EDC Decision
- Phase IIb decision
- Phase III decision
- Decision to File
- Decision to Launch

Key Decision Makers
- SRC
- SRC
- PPRC
- PPRC
- PPRC
- PPRC
Reliant on integration of medical informatics with molecular technologies (genomics and proteomics)
Translational Research
Work Flow and Interrelationships

Necessity for
- Integrated data solutions
- Multidisciplinary teams
- Quantitative methods
- Sophisticated data analysis approaches

- and Modeling & Simulation
Modeling and Simulation
Common Steps in Translational Research

1. Tentative Model
2. Assumptions and Prior Knowledge
3. Analysis of Output and Predictions
4. Model Development and Data Fitting
5. Exploratory Analysis of Data
6. Design and Conduct of Experiment

Defining and characterizing “at risk” populations
Developing discriminatory assays and metrics to subclassify patient subtypes as necessary
Defining and characterizing markers of disease progression in animals and patients

Design efficient and informative experiments and studies to define E-R relationships and correlate E-R with outcomes

Targeted disease therapies
NIH Interest
NIH Roadmap

• NIH Roadmap initiative (http://nihroadmap.nih.gov) - main goal is “to identify major opportunities and gaps in biomedical research that no single institute at NIH could tackle alone.”

• Three main themes:
  – “New Pathways to Discovery”: to stimulate the development of novel approaches to unravel the complexity of biologic systems and their regulation
  – “Research Teams of the Future”: to reduce the cultural and administrative barriers that often impede research and invoke an era in which scientists can cooperate in new and different ways
  – “Re-engineering the Clinical Research Enterprise”: to fund facilities, resources, or both to bolster clinical and translational research.
Create institutional academic “homes” providing integrated intellectual and physical resources for the conduct of original clinical and translational science.

Expectations:

- Enhance the discipline
- Provide much-needed educational programs
- Growth of well-structured and well-recognized career pathways
- Provide a research environment that is more nimble, conducive to, and responsive to the demands of modern translational and clinical research.
CTSA Structure and Function
ITMAT: UPenn / CHOP Example

Institute for Translational Medicine and Therapeutics

Cores
- TRL = Translational Research Laboratories
- SDAB = Study Design and Biostatistics
- TATCO = Translational and Clinical Trial Organization
- CCS = Clinical Core Services
- OHSAP = Office of Human Subject Advocacy & Protection
- RNC = Research Nurse Core
- IDS = Investigational Drug Service
- KMAS = Kinetics, Modeling and Simulation
CTSA Structure and Function

ITMAT: UPenn / CHOP Example

- **Undergrad**
  - Awareness/Exposure Certification

- **Grad Students**
  - MD, DMD, VMD, MSN
  - Certification Masters
  - PhD (T32)

- **Residents Fellows Postdocs**
  - Certification Masters

- **Faculty**
  - Certification Masters (K12)

---

**Preview Courses**

- CTSA-MSCE Dual Degree Programs
- CTSA-MTR Dual Degree Programs
- CTSA-PhD Dual Degree Programs
- CTSA Certification Programs

---

**CTSA Supplemental Career Development Curriculum**
M&S and Translational Research
IMPACT Opportunities

RESEARCH
• Bedside to bench
• Orphan drugs, off-patent drugs (BPCA), small market PoC
• Longitudinal / epidemiologic Disease Progression interface

EDUCATION
• Established investigators – a new trick
• Physician trainees
• Next generation Pharmacometricians / Quantitative Clinical Pharmacologists and DMPK scientists
• Peer groups: Bioinformatics, Pharmacoepidemiology, Therapeutic Area Specialists
RESEARCH

• NK1r antagonists to treat NeuroAIDS

• Animal disease model for infant ALL; molecular targeting strategies targeting MLL translocations observed in infant ALL

• Pediatric – adult mechanisms for understanding long-term cardiotoxicity potential with COX-2 inhibitors

• Human disease model for SMA

• Toxicity mechanisms for actinomycin-D in young children
M&S and Translational Research
IMPACT Examples – Penn/CHOP CTSA

EDUCATION

• 6 Physician Trainees (2 in critical care; 1 neonatology; 1 nephrology; 2 oncology)

• 3 Postdocs (2 Pharmacology/physiology; 1 Chem Eng)

• 2 Faculty appointments; several co-appointments with other departments

• 5 staff members (data management and bioinformatics)

• Numerous investigators
Case Study

Advancing Molecularly Targeted Pro-apoptotic Agents for Infant Leukemias

• Leukemia is the second most common cancer in infants, with ALL being the most prevalent

• 80% of cases have *MLL* translocations, which are poor prognostic factors

• Standard curative therapies for childhood ALL are not curative in infants

• Intensive therapies are toxic in infants

• Molecularly targeted drugs are needed

Case Study
Advancing Molecularly Targeted Pro-apoptotic Agents for Infant Leukemias

Percent

0 10 20 30 40 50 60 70 80 90 100

CCG 107  CCG 1883  POG 8943  BFM 83, 86, 90  EORTC 58881  UKALL VIII, X, pilot  DFCI

[@4 yrs  **@6 yrs]
Case Study

Why target apoptosis with BCL-2 Inhibitors in \textit{MLL}(+) infant ALL?

- \textit{MLL}(+) infant ALL cases over-express \textit{BCL-2} mRNA compared to \textit{MLL}(-) cases
- BCL-2 over-expression is associated with chemotherapy resistance
- Phase I trial indicates GX15-070 has single-agent activity with minimal toxicity in adult leukemias

Robinson, in preparation

Case Study

Hypothesis

Antagonizing BCL-2 family protein interactions will sensitize *MLL*(+) infant ALL cells to cytotoxic drugs.
Case Study
Bedside to Bench Paradigm

Peripheral blood from $\textit{MLL}(+)$ ALL & AML patients

Drug screens; single and combination experiment assay results

Human CD45+ cells; immunophenotype of engraftment in mouse PB

MLL translocation frequency; genotype distribution; clinical outcome time course

NOG mouse - infant ALL model
Case Study
Starts at the Patient – Infant ALL & AML

Patient survival
Response to existing therapies
Disease demographics
Disease genetics

Disease time course
Toxicity, AEs, ADRs and DI potential
Adult E-R relationships with various agents; Priors and models

PK and biomarker data in adults

- Infant ALL: 75%
- Childhood ALL: 6%
- Adult ALL: 7%

- TEL-AML-1
- Hyperdiploidy >50%
- Random
- E2A-PBX1
- BCR-ABL
- MLL rearrangements
- Miscellaneous

(Max ODNA-Baseline) / Baseline

P < 0.015
AUC(0-+1H) / AUC(0-1H)
Case Study
Back to the Bench

Single agent MTT assays

Drug combination experiments – tests for synergy

Patient samples vs cell lines?

Variation in Patient Response
Case Study

Experimental Data – M&S Translation

- **Human CD45+ cells/µL**
  - Week: 3, 4, 5, 6, 7, 8
  - Values: 1, 10, 100, 1000

- **Marrow**
  - Values: 100X, 20X, 40X

- **Spleen**
  - Values: 1000X, 600X, 400X

- **Leptomeninges**
  - Values: 100X, 20X, 40X

- **Pituitary gland**
  - Values: 100X

- **Kidney**
  - Values: 100X

- **Testicle**
  - Values: 100X

- **CD45+ cells in Blood (cells/uL)**
  - Values: 3822.4, 1731.2, 950.6

- **% CD45+ cells in Marrow**
  - Values: 80, 70, 60

- **AUC24hr**
  - Dose (mg/kg) | AUC24hr (ng•hr/mL)
  - 0.6 | 95
  - 1.2 | 173
  - 2.4 | 382

- **Diseased Mice**
  - Mouse injected with 2 million leukemia cells (pt 199)
  - 3 weeks post-injection

- **Healthy Mice**
  - n = 7

- **Tissue sampling**
  - Mouse injected with 2 million leukemia cells (pt 199)
  - 3 weeks post-injection

- **Tissue sampling**
  - Healthy Mice*
  - n = 7
  - 1.2 mg/kg

- **Tissue sampling**
  - Diseased Mice
  - n = 42
  - 1.2 mg/kg
  - n = 21
  - 4.8 mg/kg

- **PK sampling at 0.08, 0.25, 1, 2, 4, 8, 24 h**
  - (3 mice per time point per dose level)

- **Observed**
  - Simulated

- **Time (hr)**
  - Values: 0 to 24

- **Cp (ng/mL)**
  - Values: 0.001, 0.01, 0.1, 1, 10, 100, 1000

- **1.2 mg/kg**

- **1.0 mg/kg methanesulfonate salt**

- **4.5 mg/kg tartrate salt**

- **6.0 mg/kg methanesulfonate salt**
Translational Research
Facilitating Decision Making

**In vitro** (single agent, synergy; combinations)
- Early screening of compounds based on IC\textsubscript{50} value in patient CD45+ cells.
- In silico ADME screening to assess candidates based on druggability
- Candidates selected for the next phase based on decision tree
- Synergy with other agents assessed; ranking of agents

**Preclinical (NOG Mouse Model)**
- Synergy results guide preclinical combinations, doses and regimen selection
- Animal disease model to assess biomarkers e.g. toxicity, Phase II adult human biomarker and drug conc.

**PK/PD Trial Simulation**
- In vitro and preclinical data for clinical dose and regimen selection integration into Phase IB protocol
- Clinical protocol

**Dose optimization ALL patients**
- Phase IB MTD study and dose optimization
- E-R and ITW for ALL patients

**Clinical Trial Simulation – Outcome Trial**

**PKPD – Disease Progression**
- Synergy results guide preclinical combinations, doses and regimen selection
- Animal disease model to assess biomarkers e.g. toxicity, Phase II adult human biomarker and drug conc.

**PKPD - outcome**

**Projections about other BCL-2 inhibitors and other mechanisms to treat infant ALL**

**Quantitative analysis**
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.
## Training Proposal

**Human Pharmacology Core**
- PK / Biopharmaceutics
- PD / Pharmacology
- Disease Therapeutics
- Quantitative Bioanalysis

**Stat Core**
- Regression Analysis
- ANOVA
- Experimental Design
- Clinical Trial Design
- Monte Carlo Methods

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

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

**Programming Core**
- Computational Methods / Application
- Intro to Statistical Programming

---

**Virtual, Global Faculty**

Matriculation at Various Institutions with Diverse, Flexible Curriculum from Global Pool of Courses and Instructors

Pharmacometrics, A Multidisciplinary Field to Facilitate Critical Thinking in Drug Development and Translational Research Settings
Conclusions

• The Translational Research (TR) paradigm provides a rich setting for M&S to influence decision making and facilitate the development of new or improved therapies to treat human disease.

• Examples and case studies of the M&S – TR interface are needed to influence the Academic Medical Research Community to make good on the promise of the CTSA and NIH Roadmap.

• A coordinated, global effort to address training is essential for the various consumers of pharmacometric expertise