Digital Human

Tonglei Li
Bumsoo Han
Kinam Park

Pharmaceutics
Mechanical Engineering
Biomedical Engineering

Purdue University
Symposium on Digital Human for Drug Testing

Purdue + KIST
Needs for Digital Human in Drug Delivery

1. New Drug Development
   Extremely low (10%) success rate in human clinical trials
   Lack of correlation between animal and human PK profiles

2. FDA: testing for new drugs and new delivery systems
   Generic formulations
     Oral vs. Parenteral
     Sustained release depot formulations (1-6 months)
Timeline for the Drug Development

10,000 → 250 → 10 → 6 → 2 → 1

Number of New Chemical Entity

Development Cost of $1 Billion
Timeline for the Drug Development

10,000 $\rightarrow$ 250 $\rightarrow$ 10 $\rightarrow$ 6 $\rightarrow$ 2 $\rightarrow$ 1

Development Cost of $0.3$ Billion
Correlation between Animal and Human Data

Figure 7 | **Prediction by species.** The dog is a better predictor of human toxicities than rodents, and possibly better than primates, although a number of the primate studies reviewed were small. Modified, with permission, from REF. 12 © (2002) Elsevier Science.

Olson H *et al.* (2000) *Regul Toxicol Pharmacol* **32:**56

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**Animal Bioavailability**

<table>
<thead>
<tr>
<th>Species</th>
<th>Graph Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>△</td>
</tr>
<tr>
<td>Rodents</td>
<td>●</td>
</tr>
<tr>
<td>Primate</td>
<td>■</td>
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*Grass and Sinko (2001)*
Clinical Studies

- **Phase 0: PK/PD.** 10-15 people
- **Phase 1: Safety.** 20-80 people
- **Phase 2: Efficacy** 100-300 people
- **Phase 3:** 1,000-3,000 people
Why Now?

- Advances in computing power and visualization hardware
- Maturity and availability of simulation methods at various levels
  
  Multiphase continuum, continuum-discreet simulation methods

- Advances in bioimaging technologies
  
  Cellular, tissue, whole body levels

  Higher resolution & faster response

World experts in drug delivery, PK/PD, nanotechnology, bioimaging, computer simulation, programming, graphics and visualization, fluid dynamics, and systems biology in the same team having the same goal.
Limitations of Current Simulation Approaches

- Current methods treat each organ as “compartment”, a single mathematic point described by differential equations.
- Focus on temporal, not on spatial understanding.
- Little information about sub-organ, tissue-level distribution, which is critical for understanding PD, drug performance, and eventual evaluation of new drug chemicals and delivery systems.
- Poor handling of the complexity of dosage form.
- Lack of disease modeling/simulation.
- Fed from experiments; lack of ab initio input.
  Requirement of many input parameters.
The Proposed Plan

• Build upon current PK, PBPK simulation efforts a new integrated platform.

• Move a level down toward individual cells.

• Develop disease models

  Mathematical description of tumor development to understand drug distribution and performance in a particular organ or tumor.

• Develop a biopredictive model based on the structure of molecule ("holy grail" of drug testing).
Multi-Layer Integrated Predictive Model

Organism → Organ System → Organ → Tissue → Organ-on-a-chip → Cell → Molecule → Gene
Complex Transport Processes around Tumor

Ozcelikkale et al (2013) Mol Pharm
Physiology-on-Chip

New in vitro platforms to estimate transport properties

Tumor-Microenvironment-on-Chip (T-MOC)


Airway-on-Chip

Liver-on-Chip
Advantages of the Proposed Approaches

Multi-scale computational framework of pharmacokinetics, transport and action of drugs and therapeutics

Detailed prediction of biodistribution and permeation at both normal and diseased tissues/organs

Integrated approach to establish database of key physiological transport properties using physiology-on-chip platform
VIRTUAL MOUSE
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Validation of the Digital Human Model

A New Chemical Entity

digital Mouse
From Mouse to Human

The same experimental and computational methodology applies
Bioimaging capabilities
Computational power

Clinical potentials
Disease models
Cancers (breast, lung, pancreatic)
Heart disease
Diabetes
Xenograft tumor model:
Fast growing in a few weeks

Differences in Tumor Microenvironment

Real tumor:
Slow growing over years
VIRTUAL HUMAN

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Digital Human Models

PK, PBPK, Population PK

Disease Development Model
Sub-Organ and Tissue-Level PK Simulation
PD, Toxicity

Prediction of Molecular Properties (PK/PD,
Permeability, Binding Affinity, Diffusivity,
Stability, … from Chemical Structures)

Current State of the Art

Our Model

Holy Grail
FDA
Bioequivalence of products
Brand vs Generic
Oral (IR vs SR)
Injectables (IR vs SR)

PK/PD of
New Chemical Entities
Future of Digital Human

Digital Clinical Trials for New Drug Development

1. Drug development for children
2. Drug-drug interactions
3. Drug administration under special circumstances
Future of Digital Human

Essential Tool in Personalized Medicine
Digital Human Models

Collaboration

Human Cancer Model

Tumor Disease Model

Virtual Human & Mouse