AIMBE/NIH Summit on Validation and Qualification of New In Vitro Tools and Models for the Pre-Clinical Drug Discovery Process

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Validation and Qualification

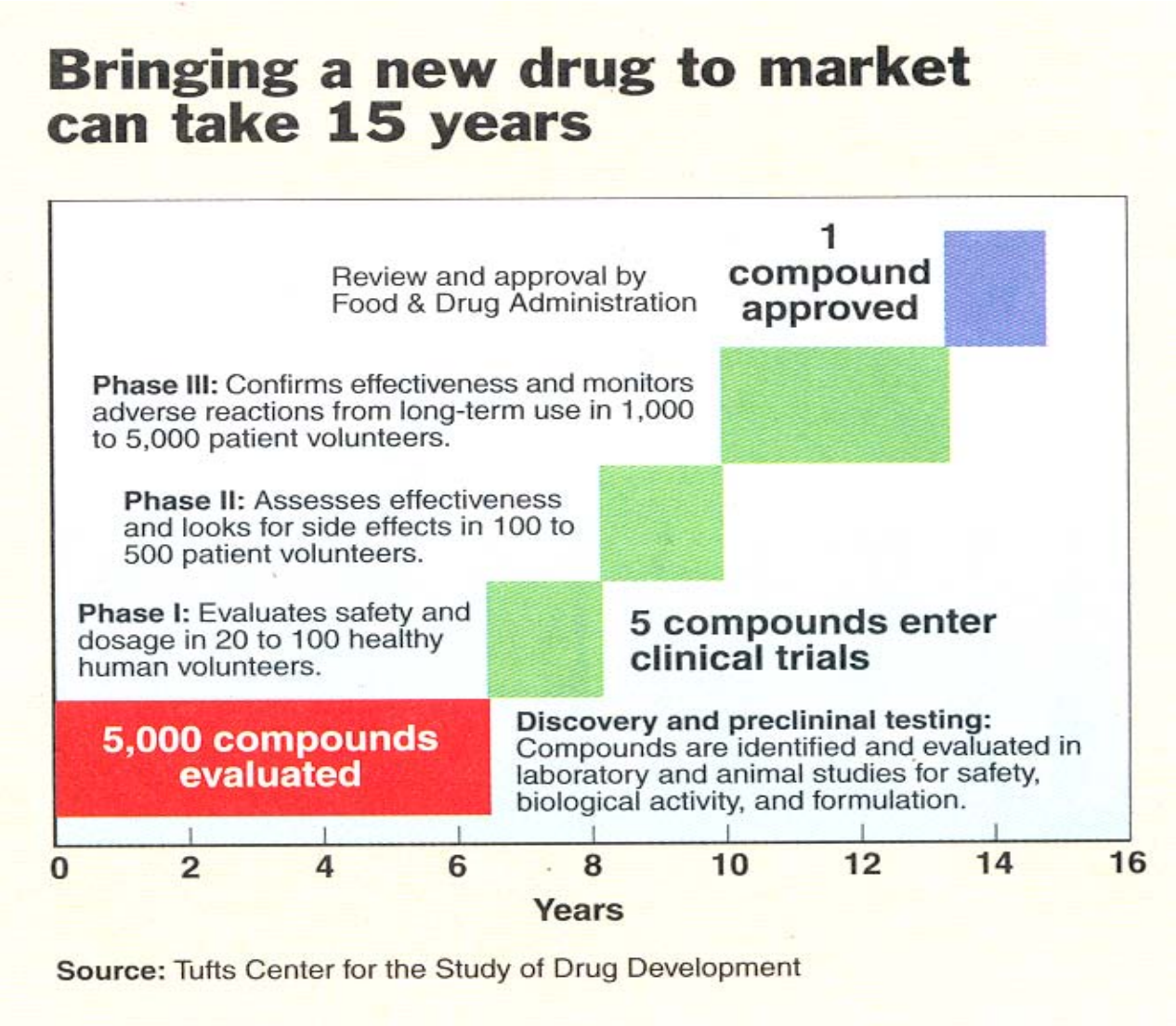
The big question for today: What are the necessary requirements for **validation** and **qualification** of new in vitro pre-clinical tools/technologies/models for use in the drug discovery process?

Validation*: The procedure for establishing documented evidence that a specific system or facility is constructed and operates according to a pre-determined set of specifications and guidelines. (involves accuracy, reproducibility, specificity, etc.).

Qualification*: The action of proving that any equipment or process works correctly and consistently and produces the expected results. Qualification is part of, but not limited to, a validation process.

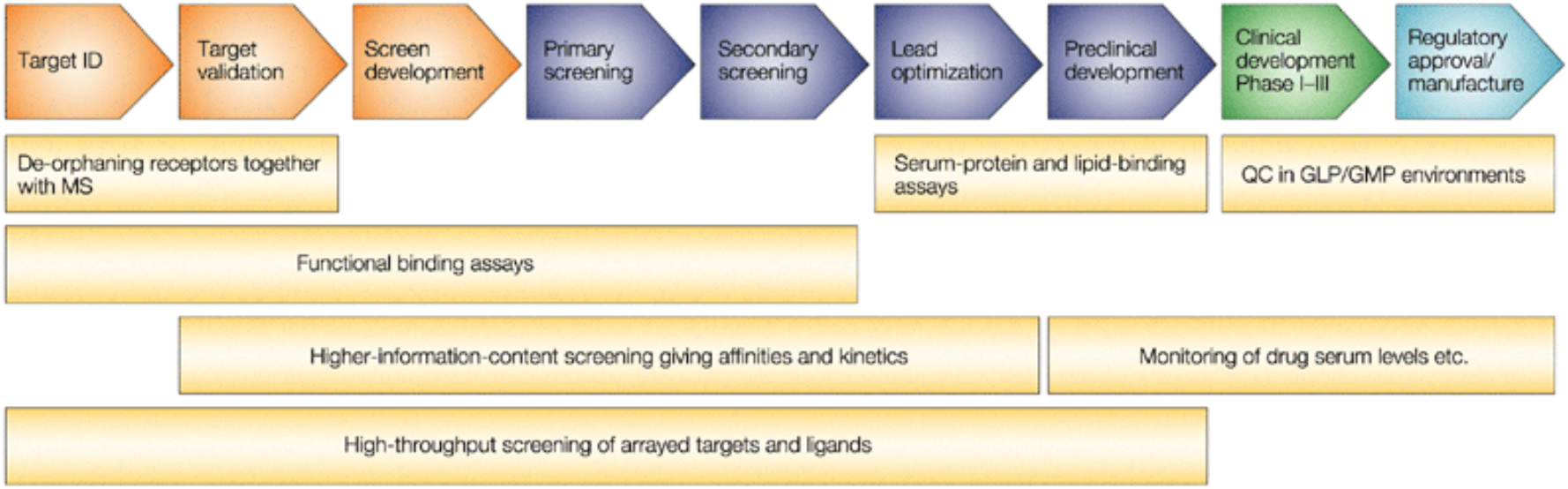
*FDA definitions

Current Landscape for Pharmaceuticals



Expensive and Inefficient!!

Drug Development Process



Nature Reviews | Drug Discovery

Better to fail early to save $$$$ and time.

Major Reasons for Drug Failure in Clinical Trials

- False positives--Drugs which are a hit based on primary and secondary screen but fail in preclinical studies or later in clinical trials.
- Promising Drugs which are found to have unacceptable organ specific toxicity (e.g. liver and heart) in preclinical studies or clinical trials.

Better to fail early to save $$$$ and time.

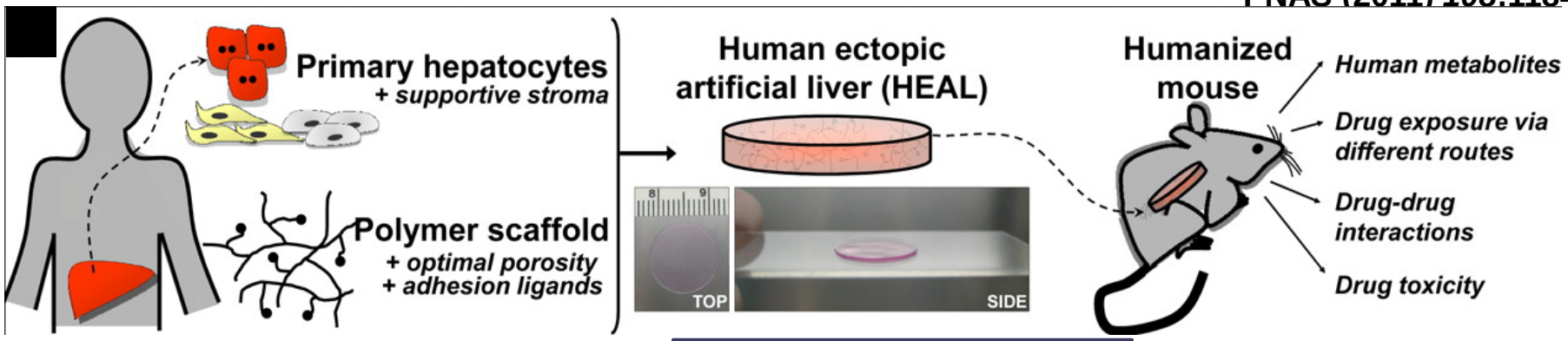
Wish List for Drug Screening:

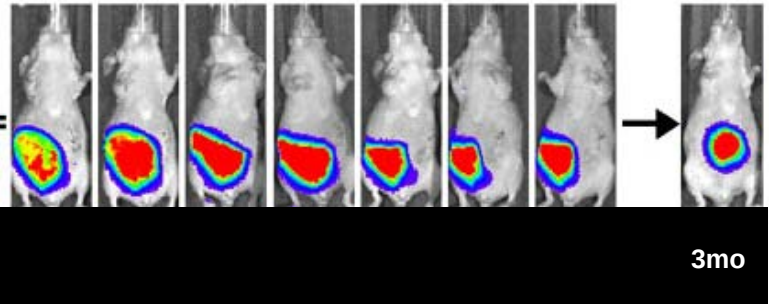
- Provide more relevant assays which can be easily integrated into existing platforms utilizing:
  - Primary Cells
  - Stem and Progenitor Cells
  - Three dimensional Culture System
  - Miniaturization of the Assay

Engineering—Bridging the Concept-Technology Gap with New In Vitro Systems and Models

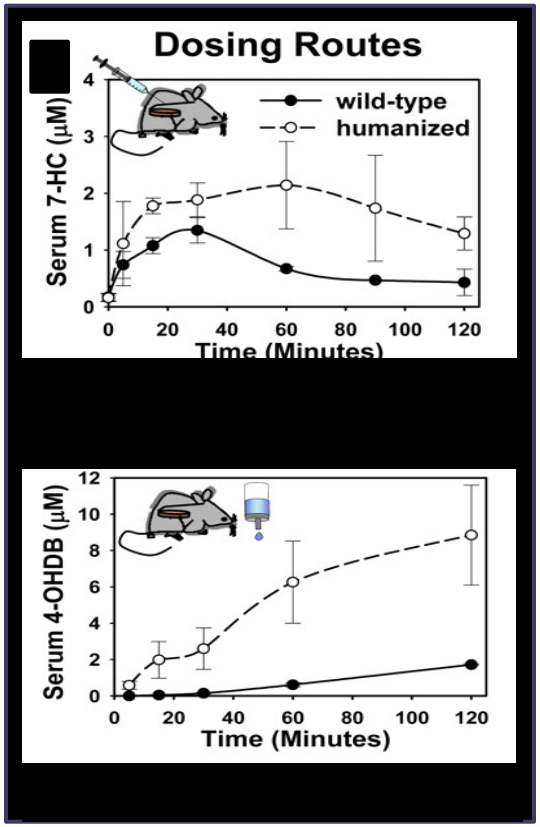
Human Liver Function Duplicated in Mice

PNAS (2011) *108*:11842-





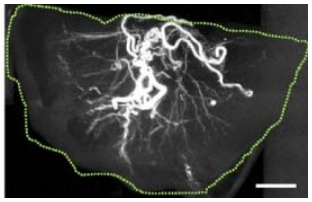
Human reporter gene expression shows persistence of HEALs .



Massachusetts Institute of Technology

R01 EB 8369
(Bhatia and Chen)

Penn
University of Pennsylvania



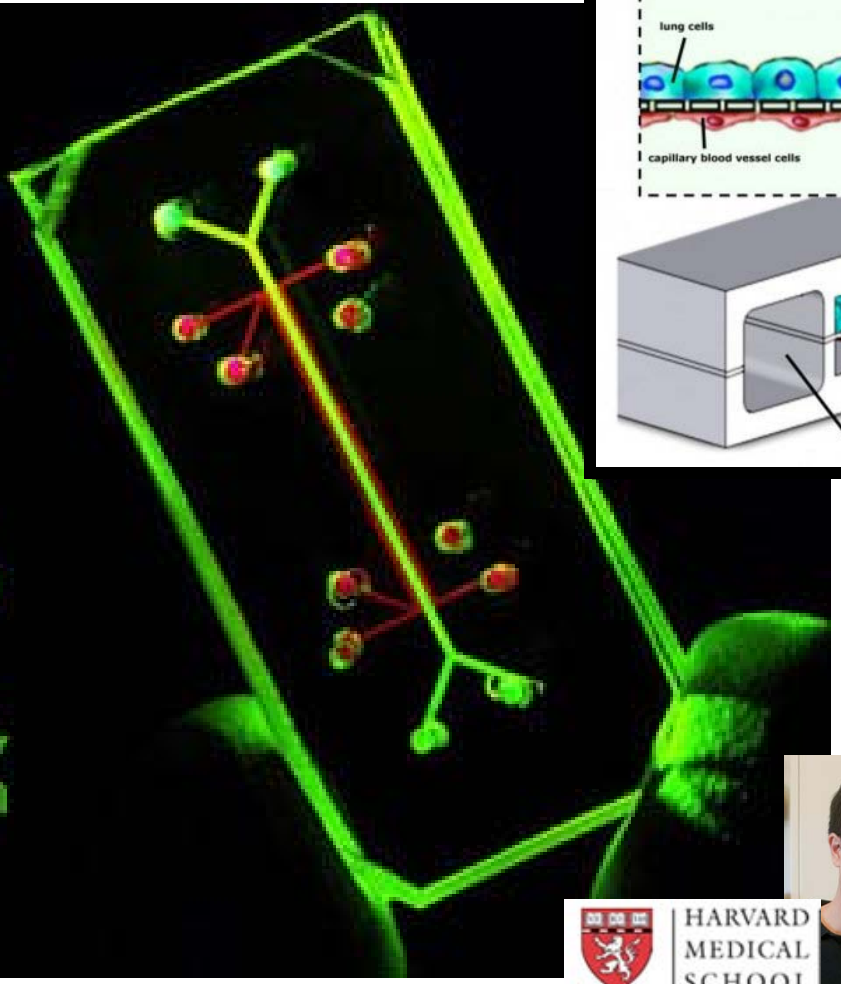
Micro-CT angiography shows vascularized HEALs.

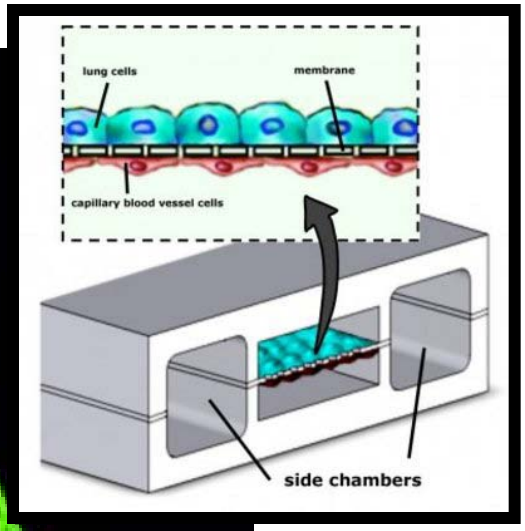
Prototypical human metabolites in serum of mice with stable HEALs post challenge.

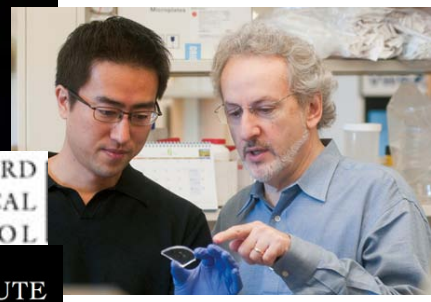
Human Organotypic Function "on a chip"

Science *328*: 1662 (2010)

The lung on a chip, shown here, was crafted by combining microfabrication techniques from the computer industry with modern tissue engineering techniques, human cells and a plain old vacuum pump.







HARVARD MEDICAL SCHOOL

WYSS INSTITUTE

See the video at:
http://wyss.harvard.edu/viewpressrelease/62/

The Dons: Huh and Ingber

NIH Partnering with DARPA and FDA

Microphysiological Systems
DARPA-BAA-11-73

To develop an in vitro platform of human tissue constructs that accurately predicts the safety, efficacy, and pharmacokinetics of drug/vaccine candidates prior to their first use in man.

Holds the promise of authentic human responses to candidate drugs, vaccines, and biologics. Three-dimensional constructs of one or more cell types are able to reproduce relatively authentic human tissue and organ physiology in an in vitro environment.

DARPA seeks in vitro platforms comprised of human tissue constructs that will accurately assess efficacy, toxicity, and pharmacokinetics in a way that is relevant to humans and suitable for regulatory review.

NIH Common Fund Initiative RFA-RM-11-022

Integrated Microphysiological Systems for Drug Efficacy and Toxicity Testing in Human Health and Disease (UH2/UH3)

- For projects that will develop accurate cellular and organ microsystems representative of human physiology for the evaluation of drug efficacy and toxicity.
- These microsystems will have a multicellular architecture representing the characteristics and functions of the tissue of origin and will demonstrate a **reproducible and viable operation under physiological conditions over a long culture period.**
- It is anticipated that these bio-engineered human tissue models could lead to the development and **commercialization of microsystems** that will enable rapid and high fidelity evaluation of safety and efficacy for candidate therapeutics.

NIH Common Fund Initiative RFA-RM-12-001

Stem/Progenitor Cell-Derived Human Micro-organs and -tissues (U18)

For the development of human multi-cellular models that can **replicate aspects of human organ physiology.**

Disease pathogenesis, cell-type diversity, genomic complexity, monitoring of cell to cell and cell to matrix interactions and microenvironment regulation are key aspects to be addressed by these model systems.

The multi-cellular architecture **will demonstrate reproducible cellular signatures and functional outputs** under physiological conditions.

Anticipated that these human cell/tissue models could lead to the development and **commercialization of cellular 3D modules** that would eventually become part of larger organ systems targeted for rapid and high fidelity safety and efficacy evaluation of candidate therapeutics.

Overview of the Day

1. The first session of the Summit will address some current **perspectives on validation** from the NIH, Industry, FDA, and the general drug discovery community.

2. In the second session there will be a series of talks on new, **cutting edge, in vitro pre-clinical drug discovery tools/technologies/models** that have been, are in the process of, or **need to be validated and qualified** for use in pre-clinical drug discovery. These include:

   - computational models
   - imaging tools
   - stem cell technologies
   - 3D engineered tissue constructs
   - organs on chips.

3. The third session will build upon the events of the first two sessions and will include a **group discussion on guidelines and requirements** for validation and qualification of new in vitro pre-clinical tools/technologies /models for use in the drug discovery process.