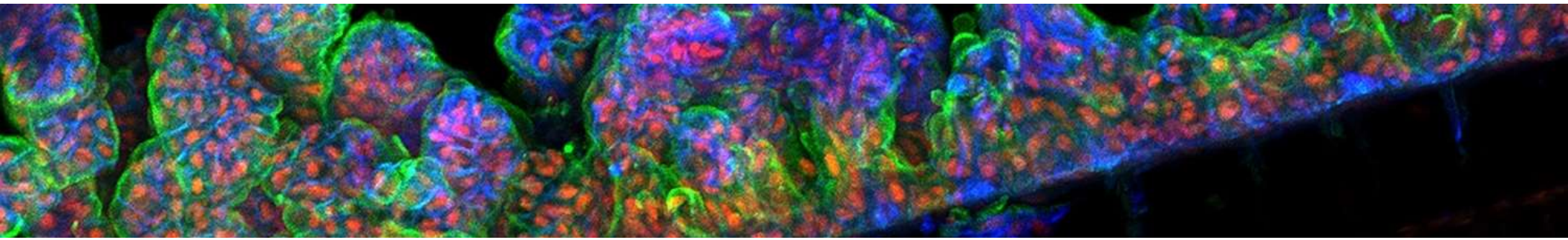
Organ chip and Tissue Chip, from development to regulatory adaptation
Online webinar - Humane Society International/Korea
5th March 2021

Industry's role for OOC development and regulatory applications

Prof. Adrian Roth, PhD
Roche
Basel, Switzerland

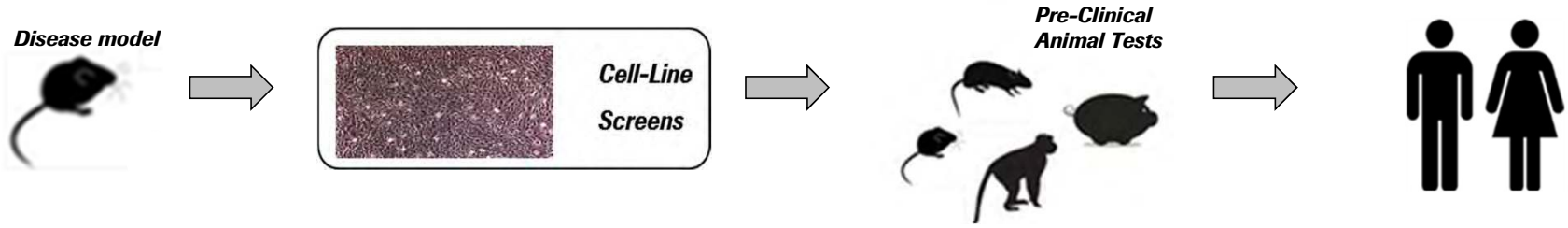


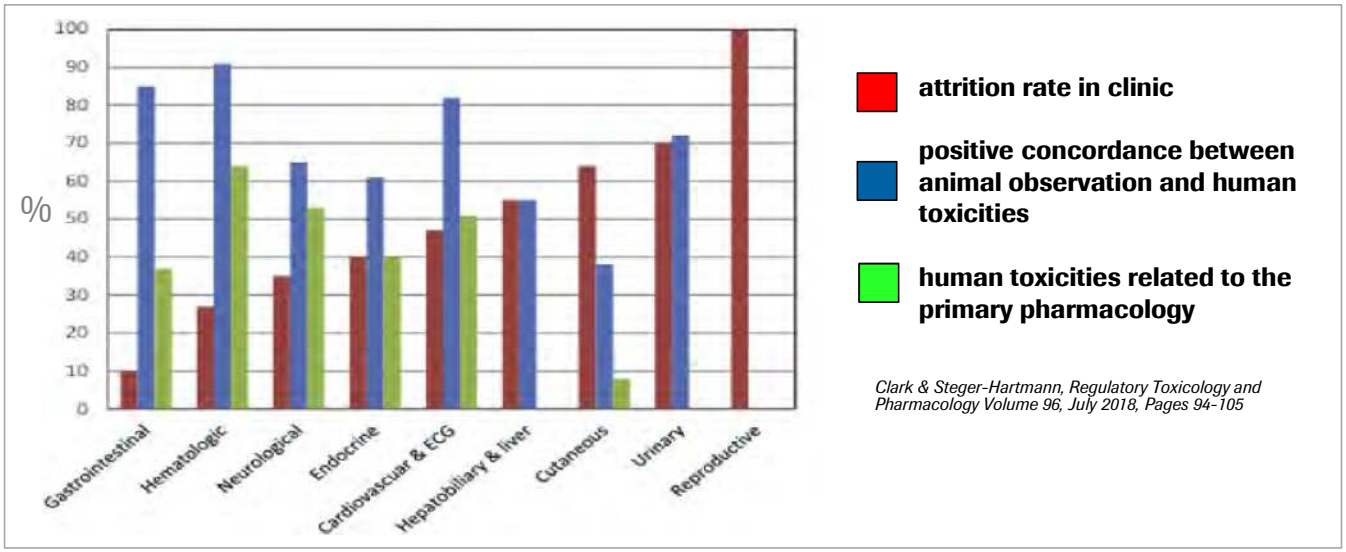
Renewing Drug Development paradigm:

Reduce animal numbers - Increase human predictivity

Roche

Target Selection & Hit identification | Lead identification & optimisation | Pre-Clinical Development | Clinical Development



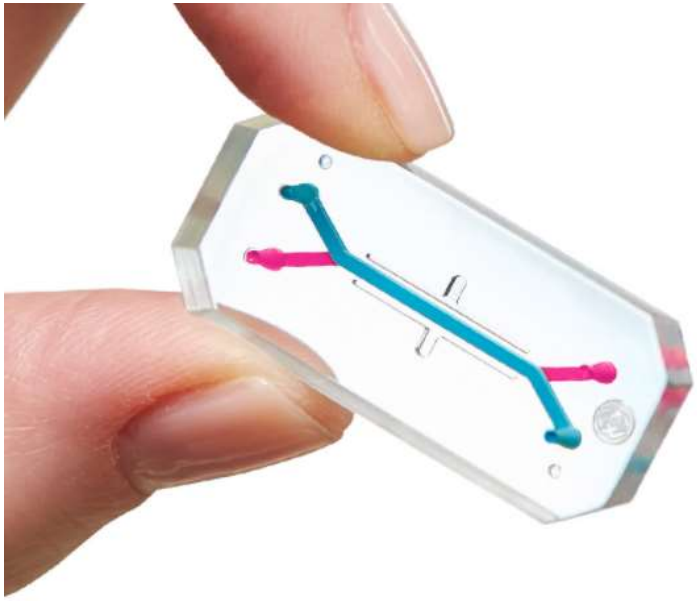


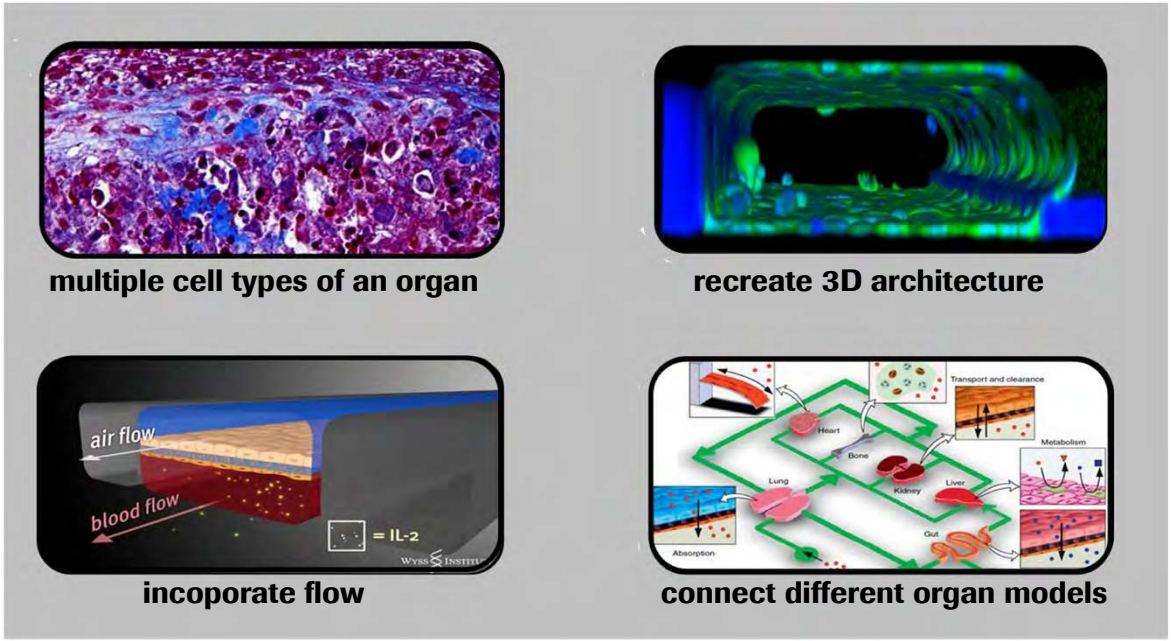
Clark & Steger-Hartmann, Regulatory Toxicology and Pharmacology Volume 96, July 2018, Pages 94-105

→ **Adverse Events that lead to clinical attrition are less / poorly predicted**

Organs on Chips

Address questions that cannot be answered using current models





Extracellular matrix and cell-cell interactions

Organoid-organoid interaction

Resident or circulating immune cells

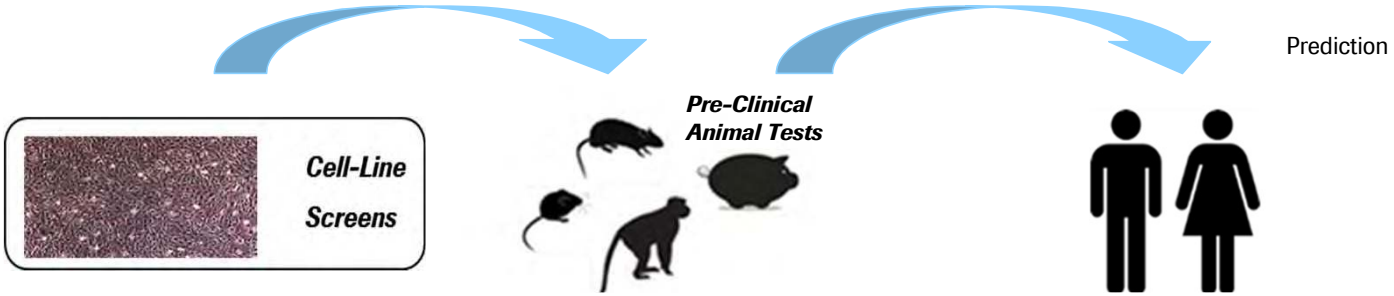
Long term effects

Test drug combinations

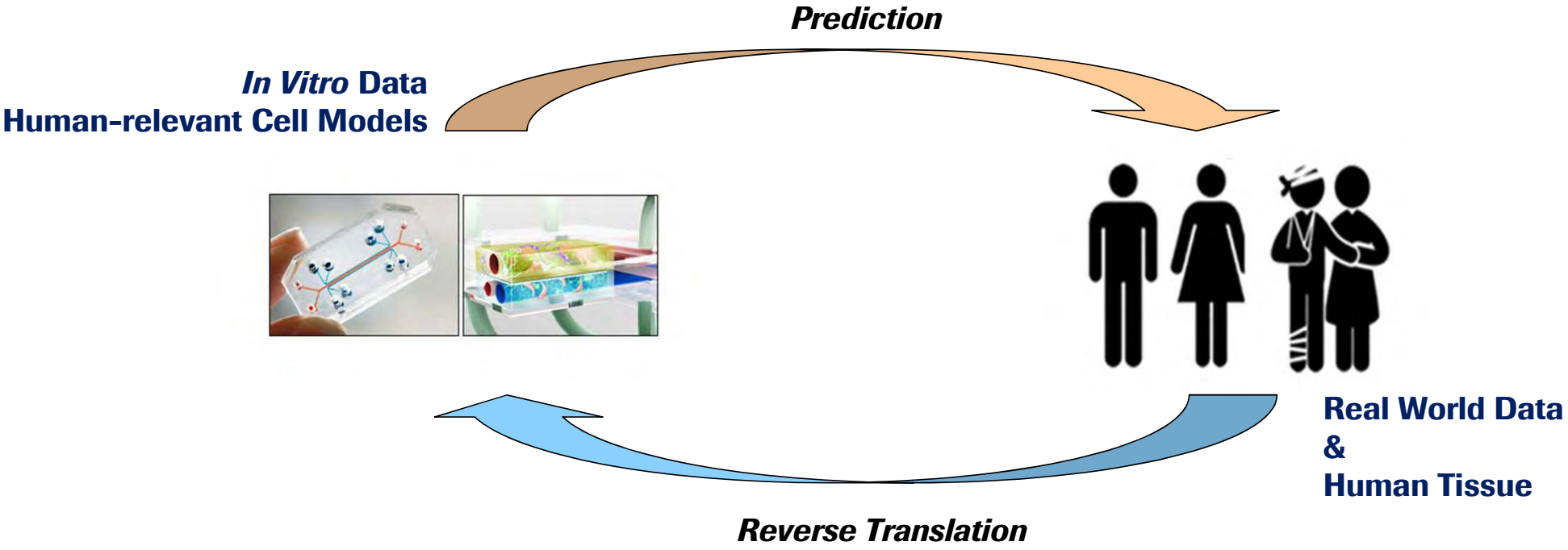
Safety biomarker ID

3D/Organs on Chips/Microphysiological Systems today:

Improve Candidate Selection before *in vivo*
Mechanistic Issue Resolution of Animal Findings



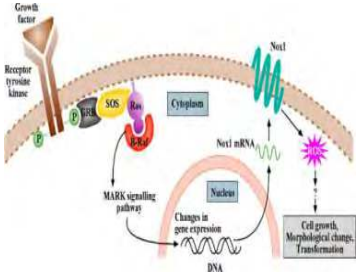
The Vision: Reverse-translate from human to *in vitro* to predict from *in vitro* to human

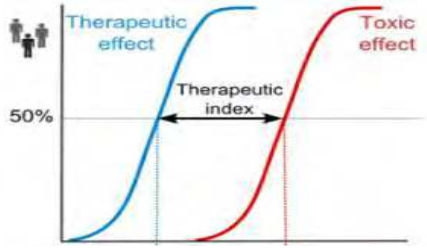


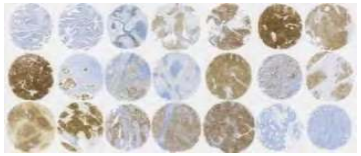
Appliation of advanced cell models & modeling

Roche

Target Selection & Hit identification	Lead identification & optimisation	Pre-Clinical Development	Clinical Development
disease-relevant human *in vitro* model to study pharmacological MoA, Target ID	Generation of "*in vitro* therapeutic index"	Assess key questions for Tox & PK/PD	Enable EIH , support MABEL*, Combination Therapies, «Personalized Safety»





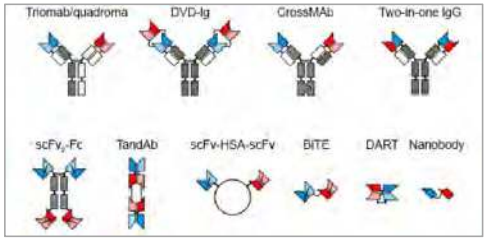


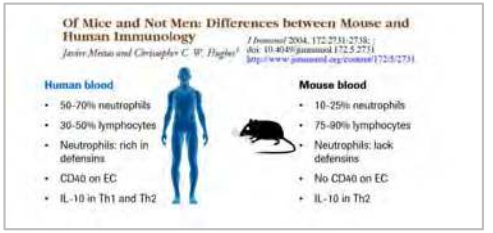
What drives application of Organs on Chips/MPS at Roche?

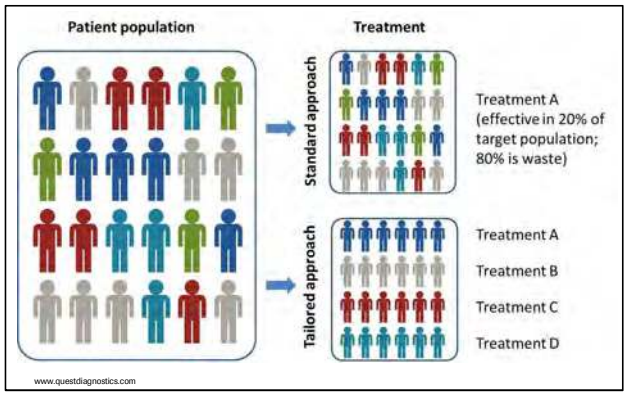
- **Shift in portfolio** from Small to complex, engineered Large Molecules that often have multiple targets (>60%)
- Molecules often **do not cross react with any pre-clinical species** (not even primates)
- **Target(s) & Pathway(s)** are not adequately represented in any animal species (i.e. **Immune-related**)
- **Challenges**:
  - -Need for assessing safety & efficacy in children
  - -Need for assessing safety & efficacy in different ethnicities
  - -Sometimes small patient population
  - -Goal to increase benefit/risk, ie strive for more personalized medicine

➢ **Conventional Pre-clinical in vivo testing may not be relevant or simply not possible**

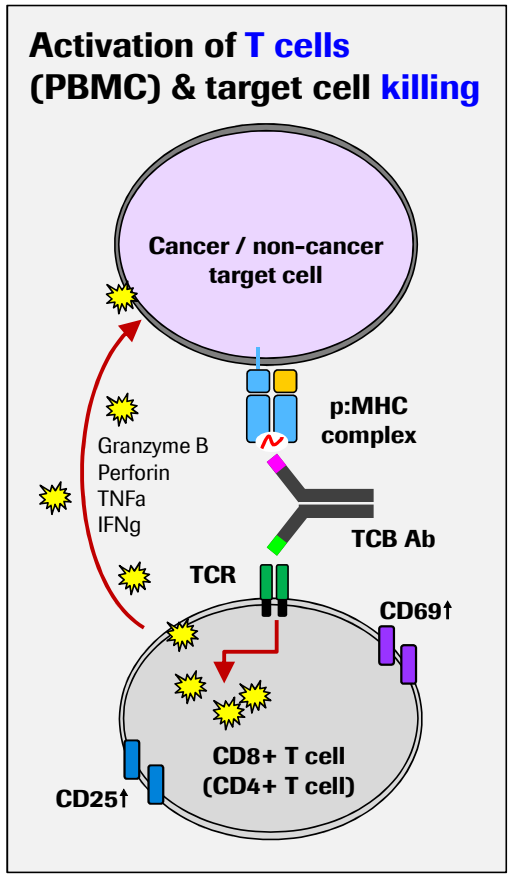
➢ **Urgent need for novel tools to assess the pharmacology & toxicology of these new drug candidates**







Goal: **Establish human cell models that can recapitulate immune-mediated toxicities** (e.g. T cell Bi-Specifics)



T Cell Bispecific Antibodies:

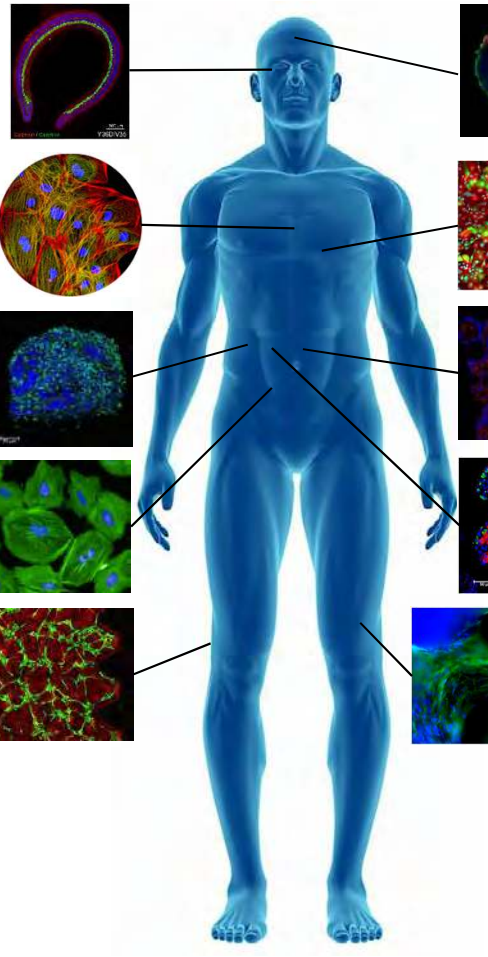
Dual targeting of Cancer cell & T cell and subsequent killing

-> Potential effects:

1. **On target / on tumor cell killing**
2. **On target / off tumor cell killing**
3. **Off target / off tumor cell killing**

-> Build models that can recapitulate this process

Immune-engaging antibodies can provoke a wide range of toxicities



OCULAR TOXICITY
EYE
aPD-1, aCTLA-4
All grades

MYOCARDITIS
HEART
aPD-L1, aPD-1, aCTLA-4
All grades

HEPATITIS
LIVER
aPD-L1, aPD-1, aCTLA-4, aCD40, aCD25, aCD137
All grades

NEPHROTOXICITY
KIDNEY
aCTLA-4, aPD-1 All grades

CRS
VASCULATURE
aCD40, aCD28, aCD19-CD3, aCD20-CD3, CD19 CAR T
All grades

NEUROTOXICITIES
aPD-L1, aPD-1, aCTLA-4, aCD3-CD19, MAGE TCR
All grades
BBB-BRAIN

PNEUMONITIS
aPD-1
G3/4
LUNG

GI TOXICITY
aPD-L1, aPD-1, aCTLA-4, aCEACAM5-CD3
All grades
INTESTINE

PANCREATITIS
aPD-L1, aPD-1, aCTLA-4,
All grades
PANCREAS

CYTOPENIAS
aPD-L1, aCD40, MAGE TCR
All grades
BONE MARROW

IMMUNO-COMPETENT

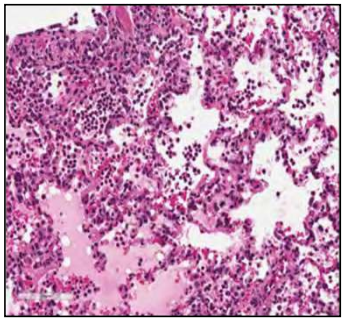
MODELS ESTABLISHED

Example 1:
Recapitulating in vivo lung toxicity findings of TCB

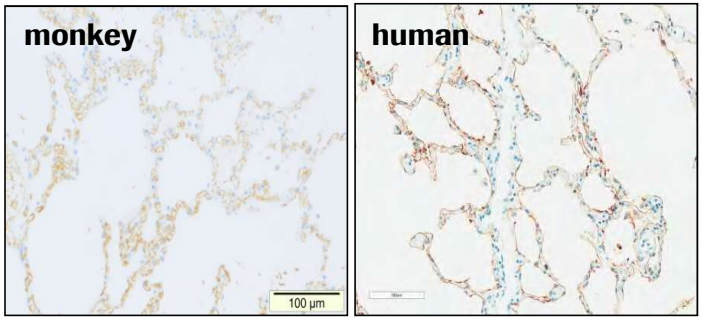
Cyno Findings in Lung

Single Ascending Dose PK Study in NHP

- 2/2 animals at 0.01 mg/kg sacrificed early due to **severe respiratory clinical signs 24 hours after dosing**
- Target expression in monkey & human lung indicates potential binding of TCB to target expressing pneumocytes leading to:
  - CD8+ mediated cytotoxicity
  - massive chemokine release and local acute inflammation

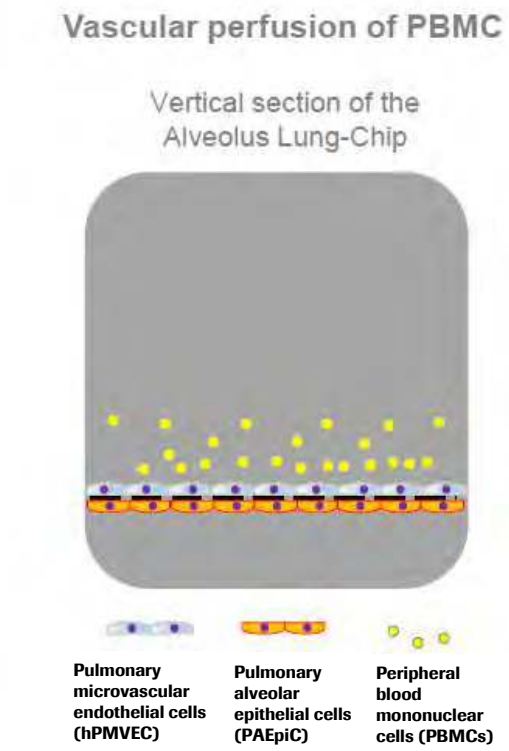


Cyno Lung: leukocytic infiltration



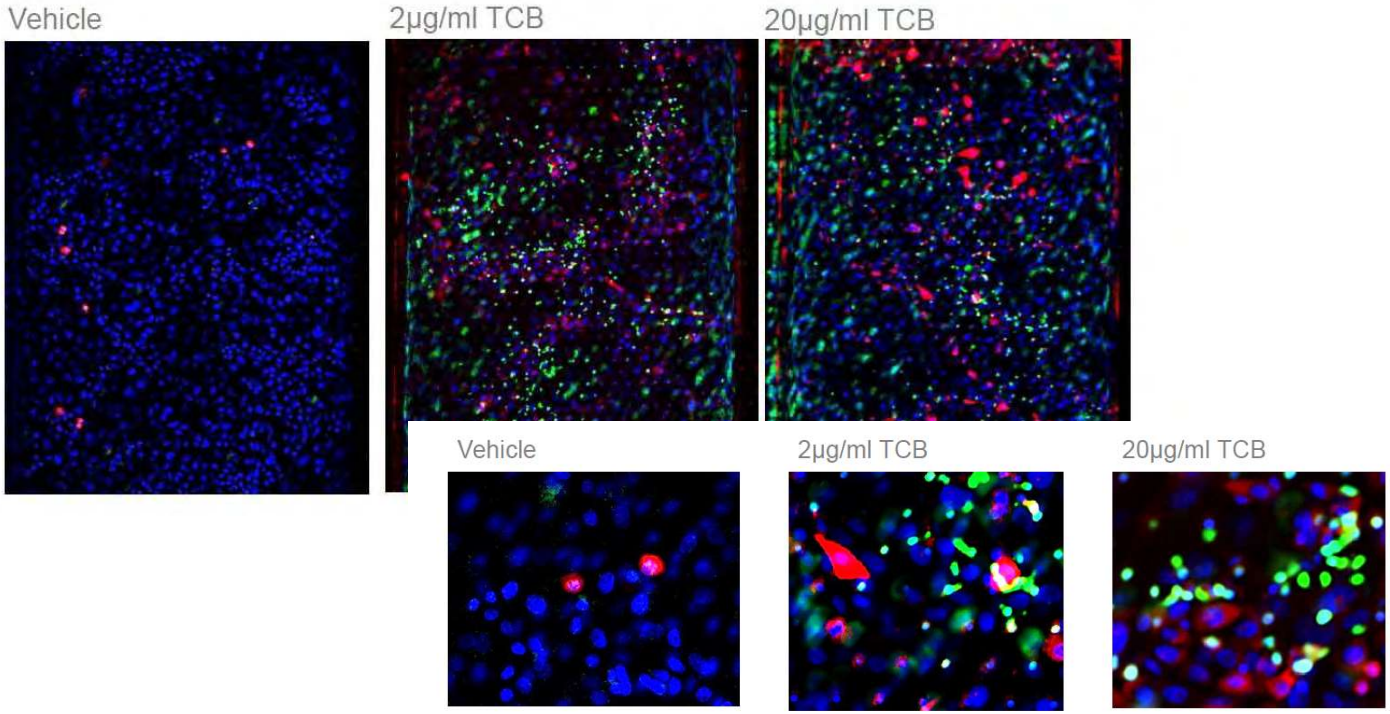
Target protein expression in the lung

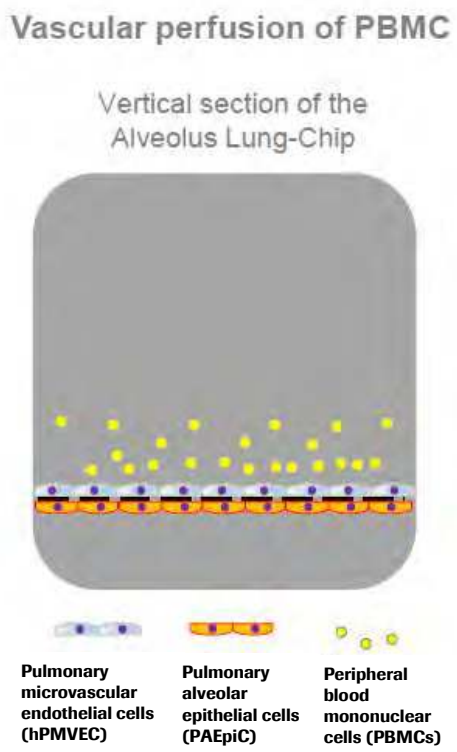
In Vitro Approach



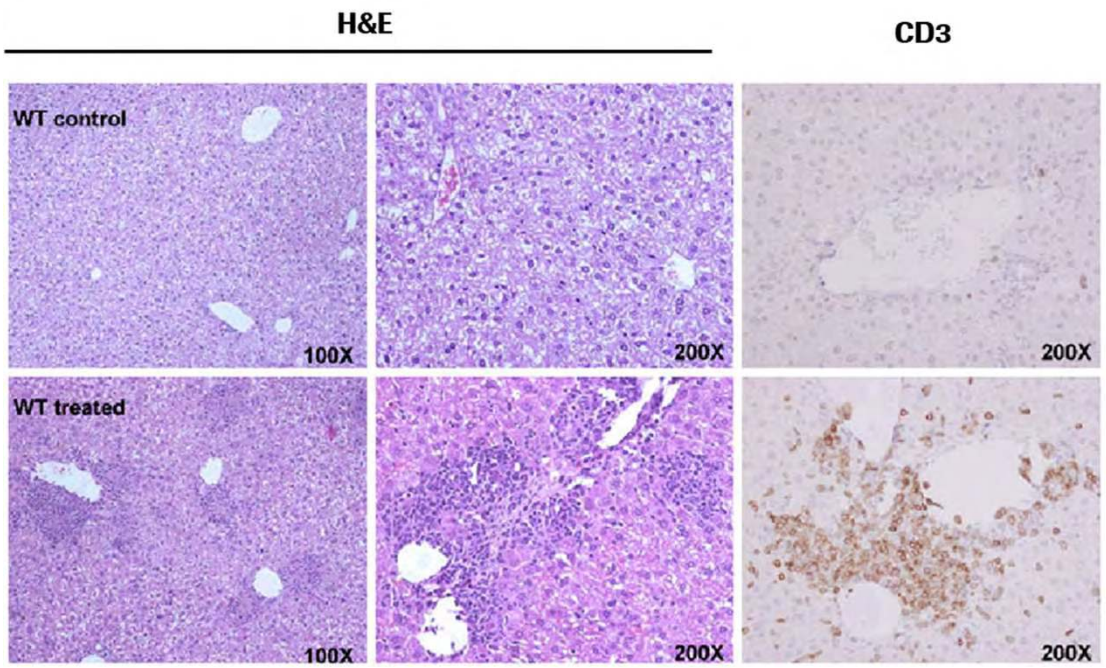
Example 1:
Recapitulating in vivo lung toxicity findings of TCB

CD3+ Dead cells Nuclei





Example 2:
Recapitulating in vivo liver toxicity findings of TCB



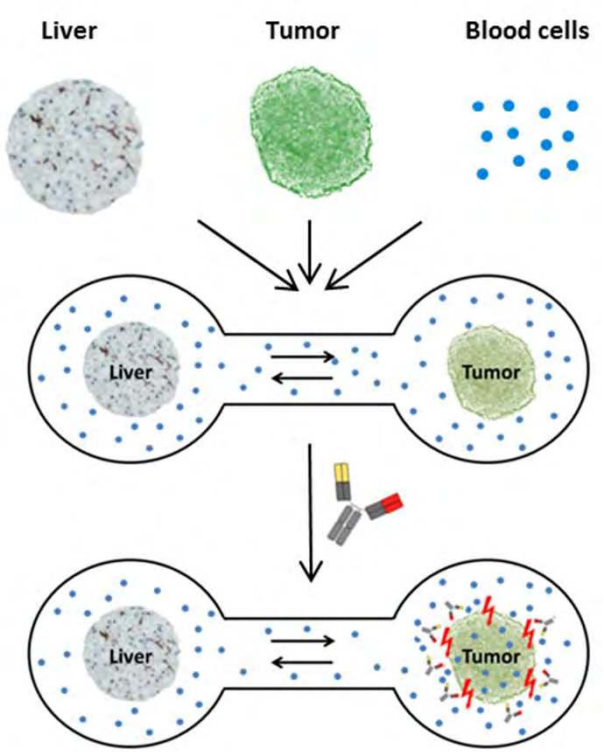
T cell infiltration in mouse liver upon anti-CD137 treatment

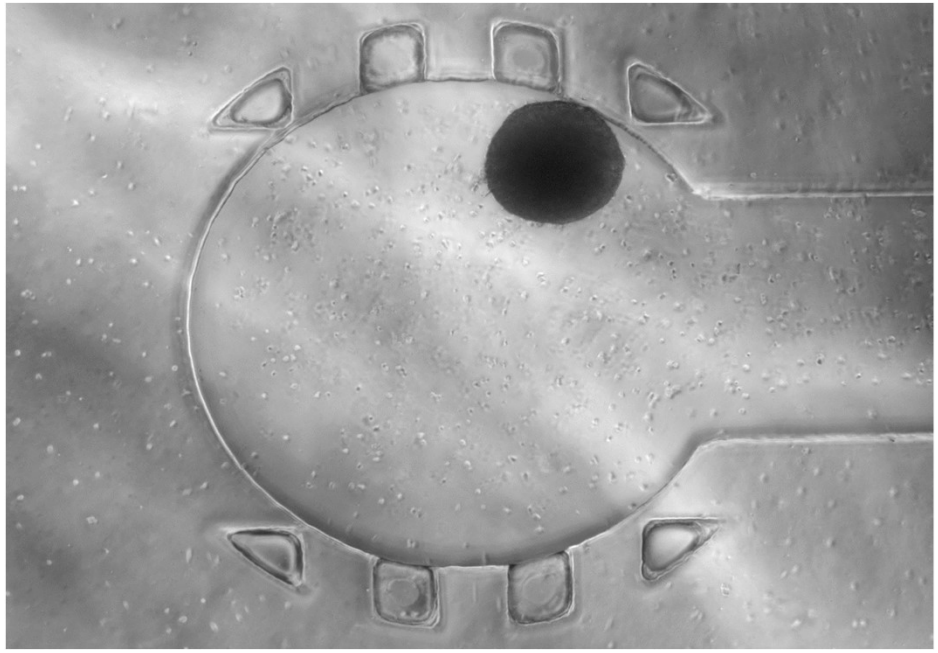
TCB is a mouse surrogate of *Urelumab*

In December 2008, enrolment was stopped for all urelumab studies following the occurrence of two hepatotoxicity-related deaths

CD137 is expressed by activated, but not resting, T cells

Example 2:
Recapitulating in vivo liver toxicity findings of TCB



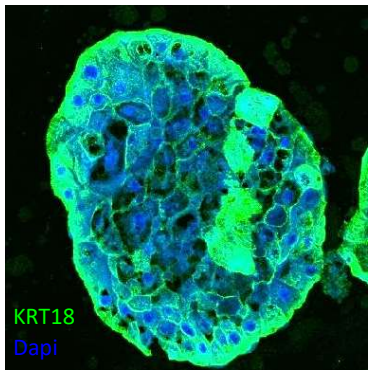


Example 3:
Recapitulating in vivo liver toxicity findings of TCB

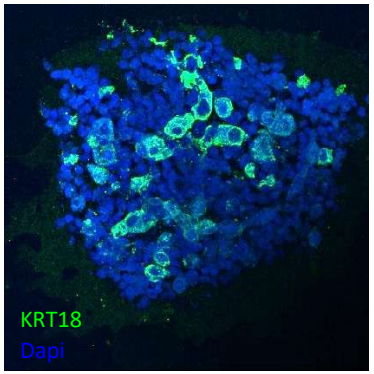
Roche

Hepatotoxicity

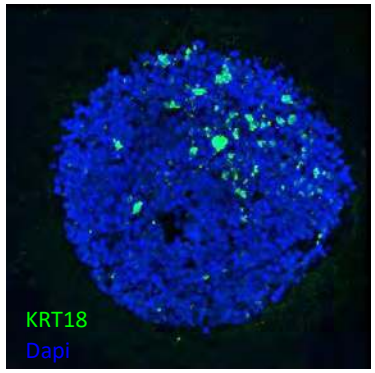
Vehicle



Bi-Specific Ab 5 ug/ml



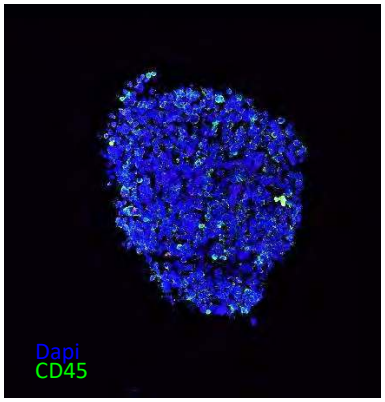
Bi-Specific Ab 50 ug/ml



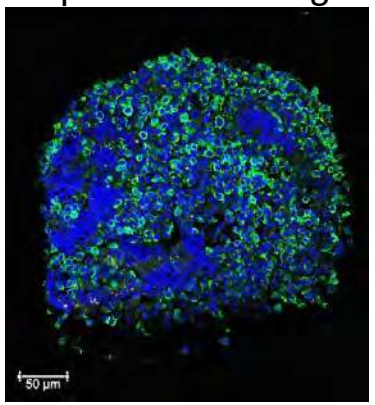
Hepatocytes (KRT18+)
Cell Nuclei

Immune Cell Infiltration

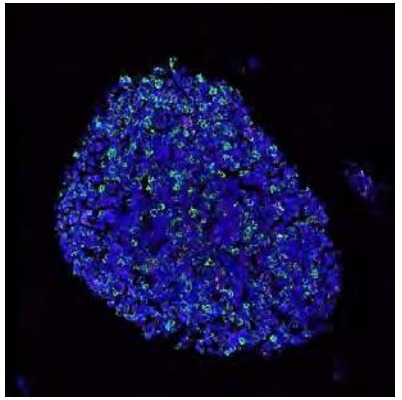
Vehicle



Bi-Specific Ab 50 ug/ml



Non-targeted Ab 50 ug/ml

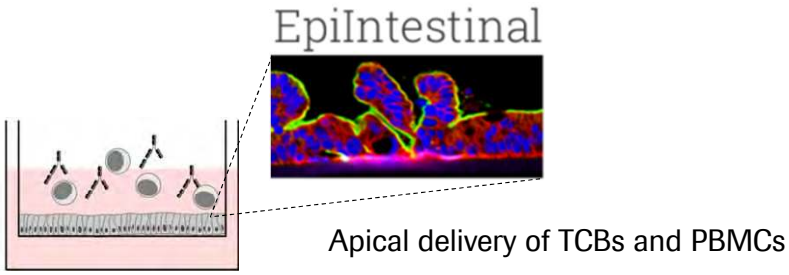


Immune Cells (CD45+)
Cell Nuclei

Example 4: Comparing clinical adverse events in gut of Bi-Specific Antibody in Gut-on-a-Chip to overcome limitations of conventional cell models

Transwell co-culture of intestinal cells and PBMCs

- Primary human intestinal epithelial cells
  - \+ PBMCs
  - \+ XX Bi-spec Ab
- 24 h co-culture

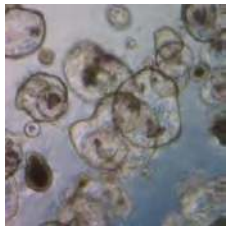


- **While Bi-spec Ab under investigation is known to cause severe dose-limiting gut toxicity in patients, only minimal T-cell activation (CD69 expression, cytokine release) and no epithelial damage observed *in vitro***
- **Can we establish a model that recapitulates the clinical effect on gut epithelia?**

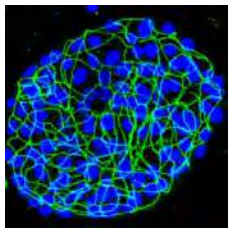
1) Profiling with primary human colon organoids

Patient samples (colon resection)

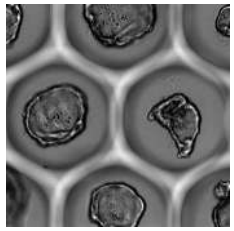
Colon organoids



Target expression

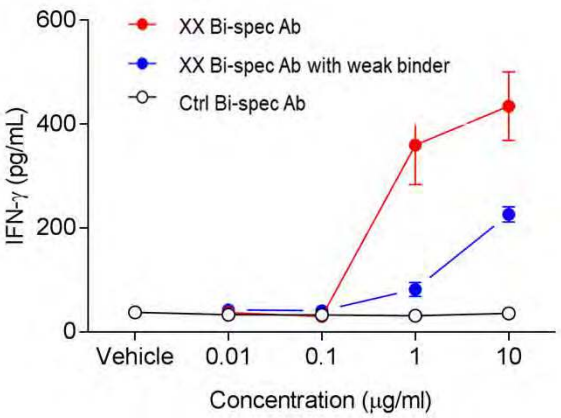


Organoid-PBMC co-culture in hydrogel microwells

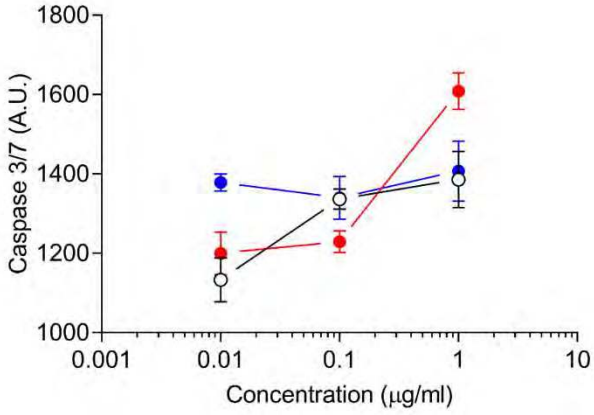


- Human colon organoids
  - \+ PBMCs
  - \+ XX Bi-spec Ab
  - 72 h co-culture
- ➢ ***Basal TCB/PBMC delivery***

Cytokine release



Cell death

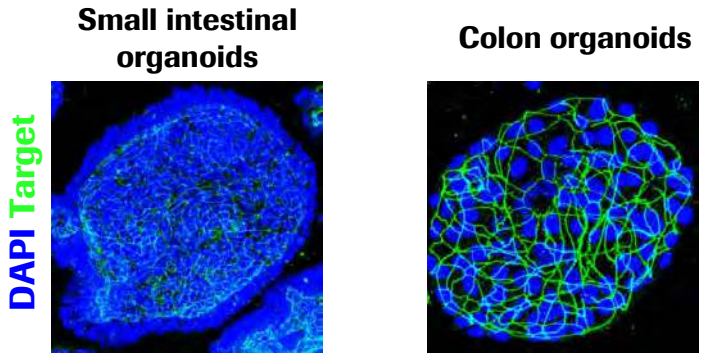


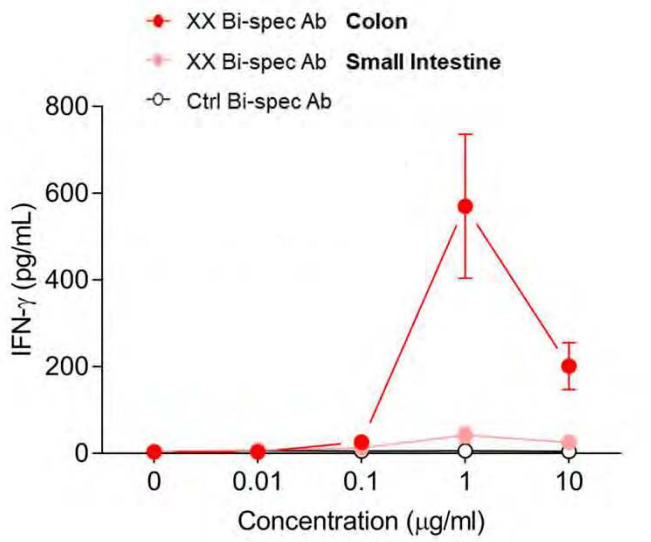
- ➢ **Model recapitulates XX Bi-spec Ab -induced toxicity at clinically relevant concentrations**
- ➢ **Captures different safety profiles of different versions of the Ab observed in the clinic**

Toxicity is intestinal region-specific

- IHC analysis reveals that target is highly expressed in the colon, but only low levels are observed in the small intestine

- Organoids recapitulate in vivo expression levels: target highly expressed in colon organoids, but not in small intestinal organoids



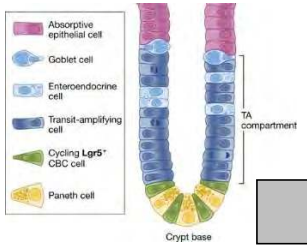


- **XX Bi-spec Ab-mediated T cell activation and toxicity correlates with target expression.**
  - **Significant toxicity-like outcomes only observed upon treatment of *colon* organoids.**
- **Model provides insight into mechanisms and sites of toxicity in patients**

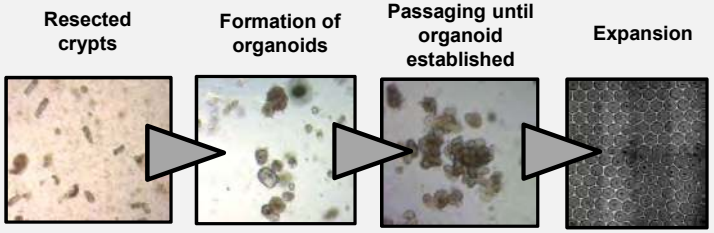
Towards Personalized Safety: Intestinal Model

Roche

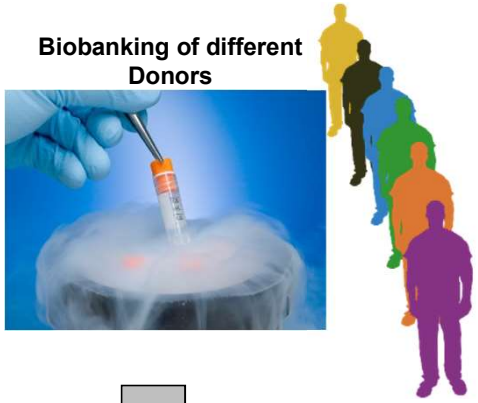
Resection of crypts from patients



Growth & Expansion of primary organoids



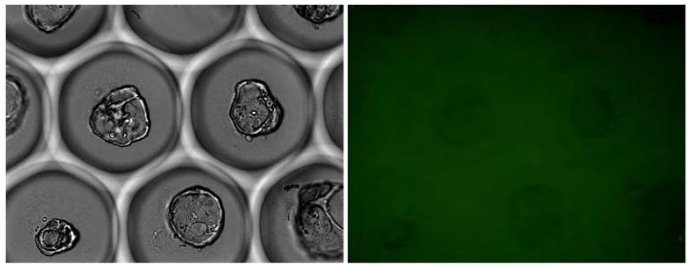
Biobanking of different Donors



Establish Organ on Chip Model

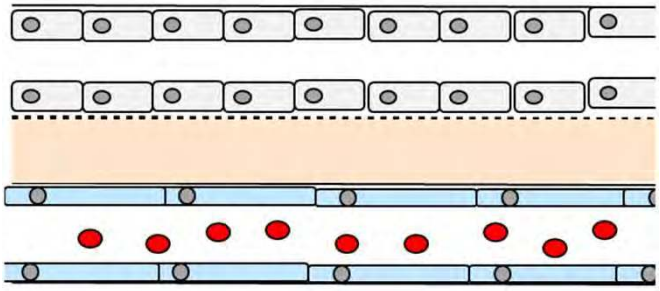
Test Drug Response in different Donors

Organoid-based toxicity screening



Suite of human models established

- **Primary human tissue, polarized where required**
- **PBMCs in flow**
- **Ability for Imaging & Media analysis**



- ✓ **Efficacy / Safety profiling**
- ✓ **Antibody format selection**
- ✓ **Personalized safety**
- ✓ **Clinical trial design and choice of combo therapy**
- ✓ **Discovery → target evaluation**

Work in progress & next steps

- **Generation of a suite of immune-competent autologuous models (tissue + blood from same donor)**
- **Model includes healthy & diseased tissue: combine disease-pharmacology & safety *in vitro***
- **Support personalized approaches (e.g. individuals/patient subpopulations at risk), address ethnic differences, Juvenile vs adult**
- **Automate OoaC Models for increased robustness & throughput**
- **Improve access to human tissue (patient-derived)**

Our approach

The biological question drives the selection of the cellular model and the read outs

As simple as possible but as complex as needed

Ease o
throu
Compound ranking
Candidate selection

Functionality
Unknown MoT
Longterm effect

Tissue cross-talk, PK/PD aspects (?)
Unknown MoT
Known, complex MoT
Metabolites
Organ-Organ interaction

Address specific known mechanism

Generate hypothesis – resolve unexplained issue

Conclusions: Organs on Chips in Pharma Industry

OPPORTUNITIES

- Combine disease-pharmacology & safety *in vitro*
- Support internal decision making – reduce animal tests – (not just add on top)
- Support EiH (e.g. MABEL) and clinical (Combos)
- Strive for more disease-population specific, more personalized testing

CHALLENGES

- Demonstration of physiological relevance will be increasingly difficult with increasing complexity
- Price for increase in relevance versus increase in technical complexity needs to be assessed
- Sourcing of (primary) animal and human cells is central – can be very challenging if different cell types from same human donor needed
- IVIV translation remains key issue – most models 'semi'-validated

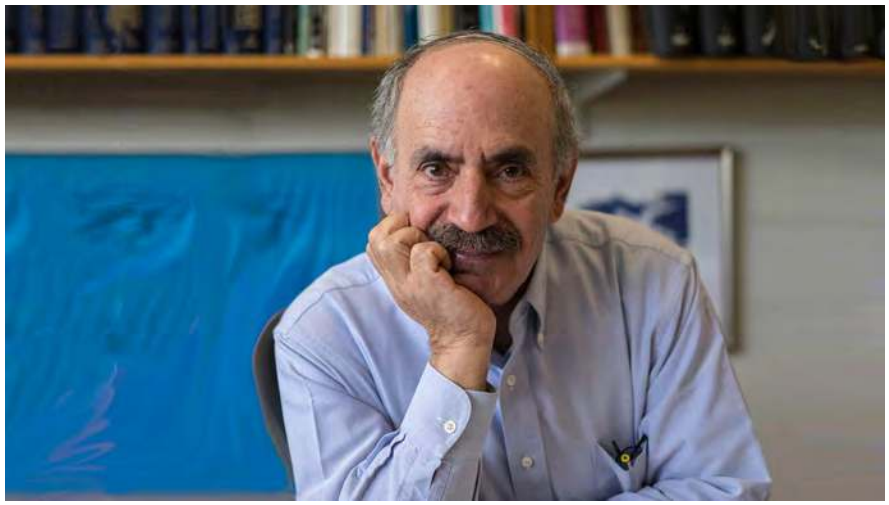
Just because the models are imperfect…

it does not mean they are wrong…

Bob Weinberg

Founding Member of the Whitehead Institute for Biomedical Research

Professor of Biology at the Massachusetts Institute of Technology



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