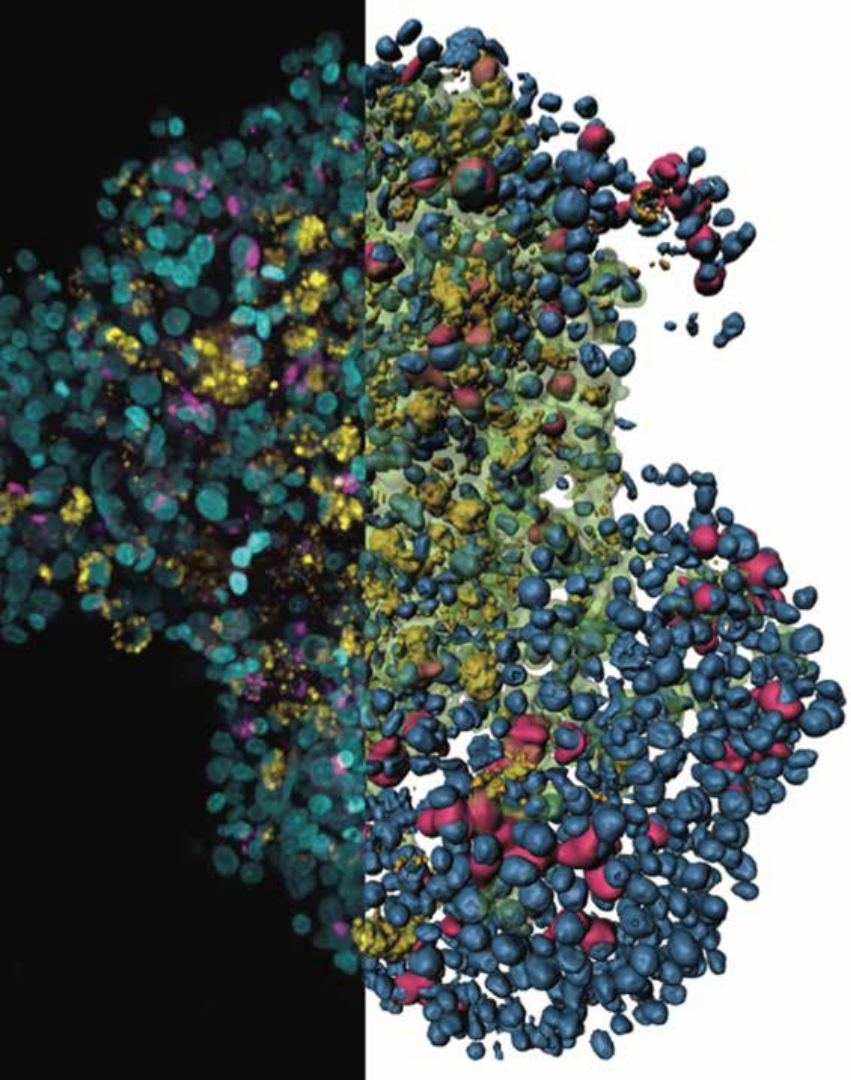


A data-driven decision making framework for the selection, application, and development of advanced in-vitro models for preclinical drug development.

Our Data is our greatest asset and opportunity

Daniela Ortíz Franyuti, Desirée Schubert, Lauriane Cabon, Ekaterina Breous-Nystrom

Roche Pharma Research and Early Development
Investigative and Immuno Safety
Pharmaceutical Sciences
Roche Innovation Center Basel

How do we climb this ladder?

Where are we now and where do we want to go?

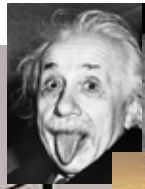
Status Quo

Innovative idea

Data Collection

Data Integration and modelling

Better predictions
New Status Quo



Planetary Motion: The History of an Idea That Launched the Scientific Revolution. https://earthobservatory.nasa.gov/features/OrbitsHistory Images: Wikipedia (CC)

Translation Rate from pre-clinical models to Clinical Trials

We need to **make better predictions**

Alteri, E. & Guizzaro, L. Be open about drug failures to speed up research. *Nature* 563, 317–319 (2018).

What makes it challenging to make good predictions?

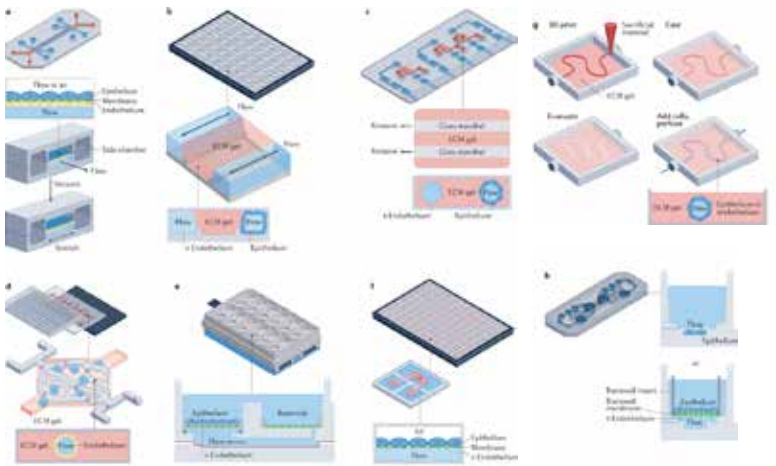
Humans are not animals - Diverse palette of advanced in-vitro models rapidly evolving and expanding

REVIEWS

Ingber, D. E. *Nat Rev Genet* 1–25 (2022)

Human organs-on-chips for disease modelling, drug development and personalized medicine

Donald E. Ingber



3R
Reduce
Refine
Replace

COMMENT

Ewart, L. & Roth, A. *Nat Rev Drug Discov* 20, 327–328 (2021).

Opportunities and challenges with microphysiological systems: a pharma end-user perspective

Lorna Ewart[1] and Adrian Roth[2]

Using human-relevant, translational in vitro models is widely considered to reduce attrition during drug discovery and development. Despite this, the adoption of models based on microphysiological systems — organs-on-chips or organoids — by pharma companies is moderate at best, and realizing the full potential of these models will need greater collaboration between stakeholders.

Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Toxicology

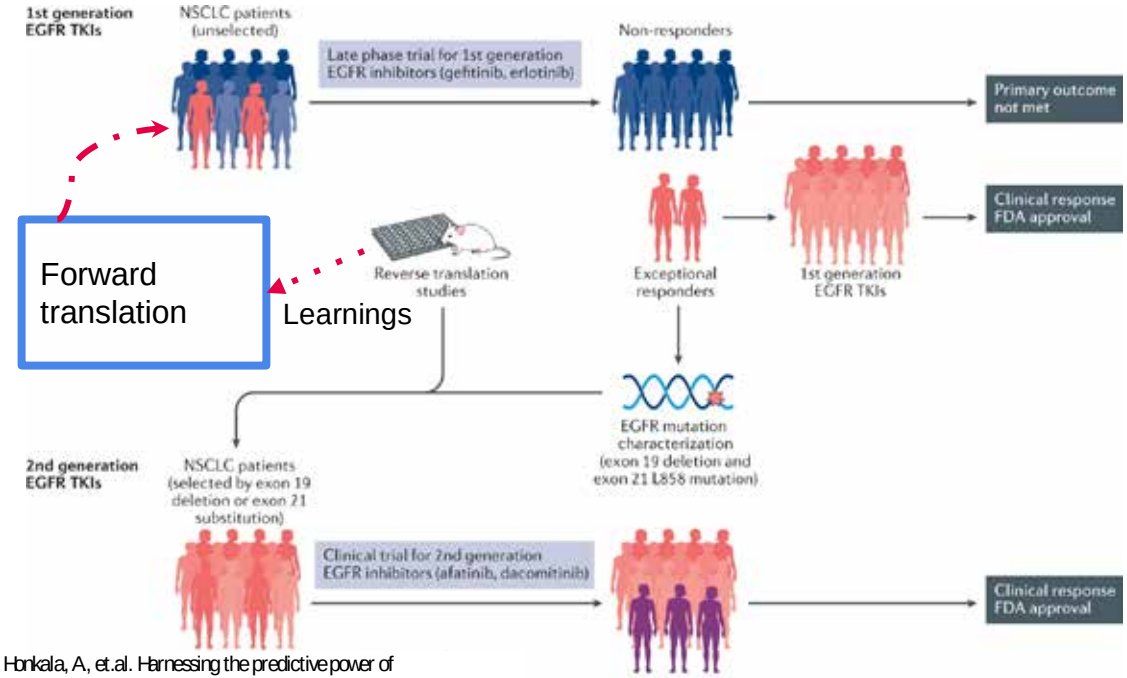
Breous-Nystrom, E et al. Curr Opin Toxicol 23-24, 39-45 (2020).

Transforming preclinical assessment to meet clinical relevance with advanced models

Ekaterina Breous-Nystrom, Sven Kronenberg, Estelle Marrer-Berger, Adrian Roth, Thierry Lave and Thomas Singer

What makes it challenging to make good predictions?

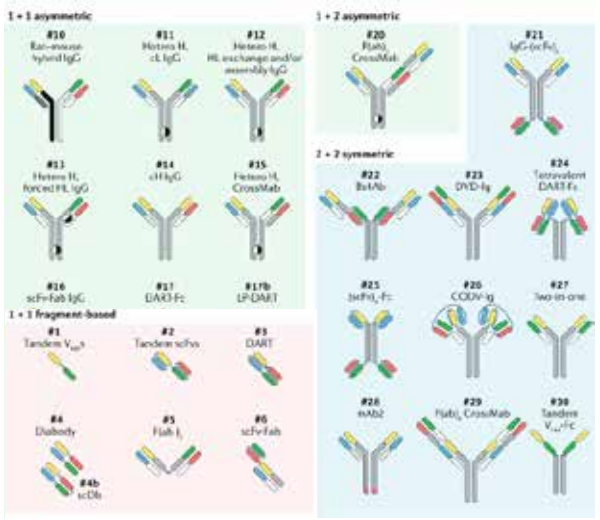
Biological Diversity **-** Why do we respond different to a treatment? - Patient Stratification



Honkala, A, et.al. Harnessing the predictive power of preclinical models for oncology drug development. *Nat Rev Drug Discov* 21, 99–114 (2022).

Growing arsenal of therapeutic modalities - Complex mode of action

Bispecific Antibodies



Labrijn, A F., Janmaat, ML., Reichert, J. M &Parren, P. WH I. Bispecific antibodies: a mechanistic review of the pipeline. *Nature reviews Drug discovery* 18, 585–608 (2019).

What makes it challenging to make good predictions?

Reproducibility is a real challenge - Especially for long term learning cycles

BIOMEDICINE

Key cancer results failed to be reproduced

Project to replicate high-impact preclinical cancer studies delivers sobering verdict

Kaiser J. Science. 2021 Dec 10;374(6573):1311.

SCIENCE FORUM

An open investigation of the reproducibility of cancer biology research

Abstract It is widely believed that research that builds upon previously published findings has reproduced the original work. However, it is rare for researchers to perform or publish direct rep

TIMOTHY M ERRINGTON*, ELIZABETH IORNS, WILLIAM GUNN, FRASER ELISABETH TAN, JOELLE LOMAX AND BRIAN A NOSEK*

Errington, T. M *et al. Elife* 3, e04333 (2014).

REPRODUCIBILITY PROJECT CANCER BIOLOGY

Investigating the replicability of preclinical cancer biology

Timothy M Errington[1]*, Maya Mathur[2], Courtney K Soderberg[1], Alexandria Denis[1†], Nicole Perfito[1†], Elizabeth Iorns[3], Brian A Nosek[1,4]

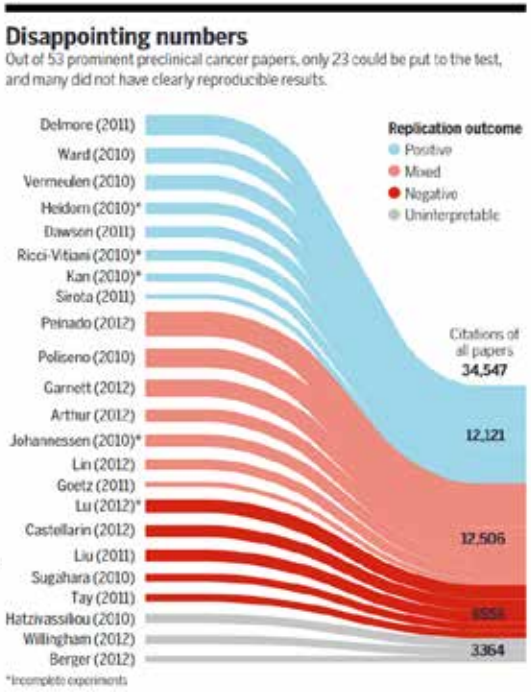
[1]Center for Open Science, Charlottesville, United States; [2]Quantitative Sciences Unit, Stanford University, Stanford, United States; [3]Science Exchange, Palo Alto, United States; [4]University of Virginia, Charlottesville, United States

Errington, T. M *et al. Elife* 10, e71601 (2021).

HALF OF CANCER STUDIES FAIL HIGH-PROFILE REPLICATION TEST

Barriers to reproducing preclinical results included unhelpful author communication.

Mullard, A. Half of top cancer studies fail high-profile reproducibility effort. Nature 600, 368–369 (2021).



Key Learnings

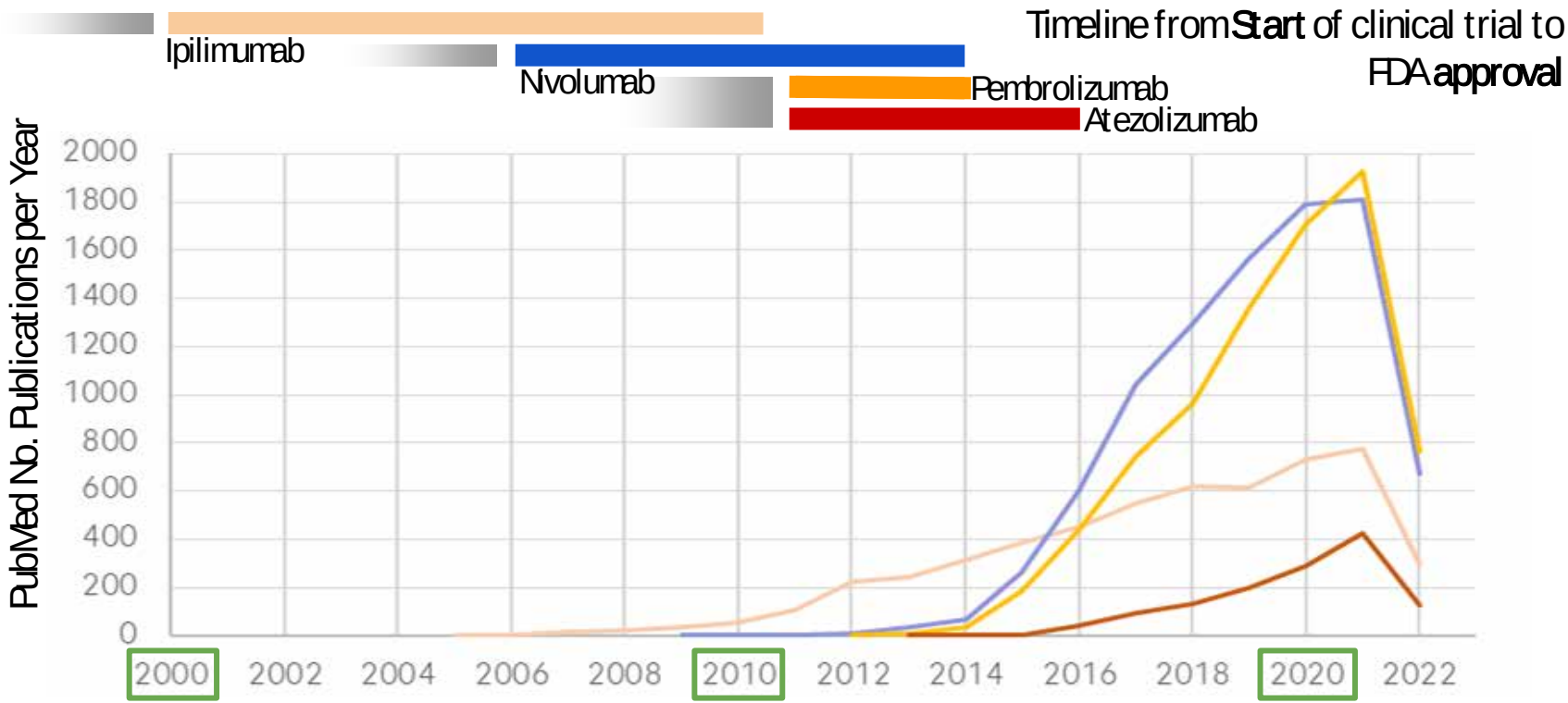
- Reporting Standards
- Documentation:

  Experiment, Materials, Data, Code, Analysis

- Registration
- Transparency
- Incentives for Replication

Learnings on translational power arrive YEARS after clinical trial start

AND we still need to make decisions TODAY before clinical trials get started…

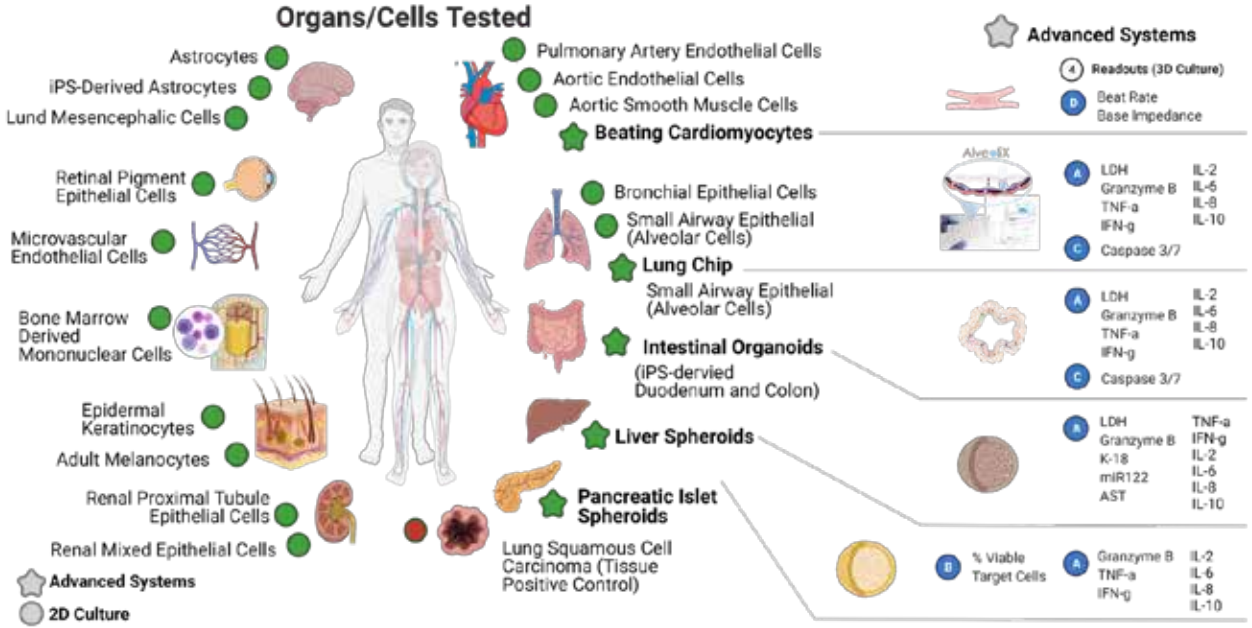


How do we put a molecule in the clinic? Without animal studies

Enabling Entry into Human (EiH) In-vitro ONLY Safety Regulatory Package

TCR-like TCB that binds to a peptide (vs a protein) in the context of the MHC complex- not possible due to the human-animal MHC mismatches and peptidome differences

Animal safety testing



Many Sources

Internal, Collaborators

External (CRO)

Variable Complexity

2D, Organoids, Spheroids

Mcrophysiological Systems

Variable Readouts

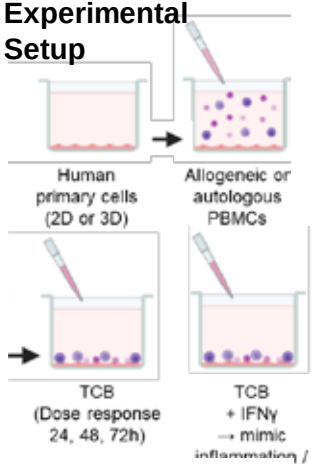
Cytokines, PCR, Functional Low Dimensional, Mcroscopy, Flow Cytometry, OMCS

Pharmaceutical Sciences Cross functional effort including iSafe (Investigative and Immuno-Safety)

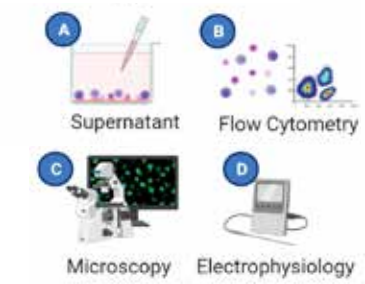
Data integration and interpretation at different levels

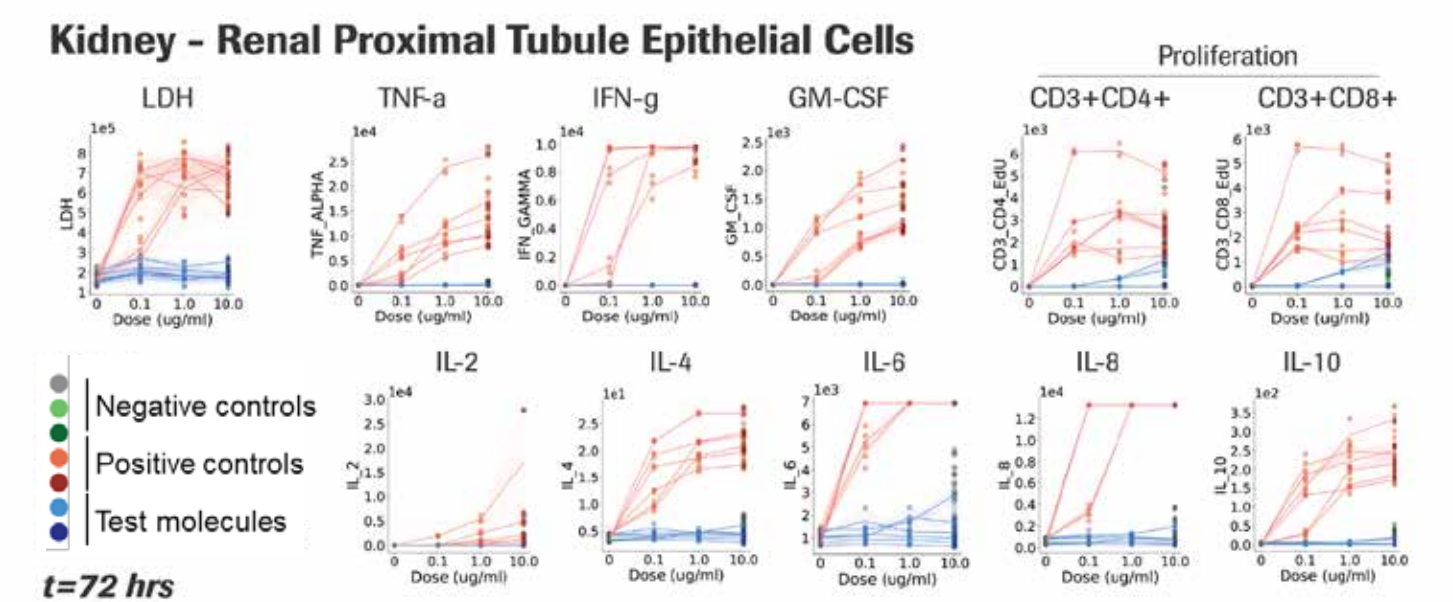
For each model, replicate, timepoint, readout…

Experimental Setup



Readouts





Pharmaceutical Sciences Cross functional effort including iSafe (Investigative and Immuno-Safety)

Today's Challenges - Data driven decision-making

How do we deal with ~3+ Million Conditions?!

Challenges:

- Multi-Model
- Multi-Readout
- Complex integration
- Complex interpretation
- Difficult to proof translatability
- Portfolio with large, complex, evolving molecules
- Physiological Relevance
- Technical complexity
- Evolving models

In Numbers:

- **21** Organ Tissues Tested
- **4** Levels of complexity
- **5**+ different sites/labs (including CROs and collaborators)
- **4**+ Biological Replicates
- **3**+ Technical Replicates on biological samples
- **3**+ Technical Replicates on readouts
- **4**+ Treatments
- **2** (+/-) Inflammation conditions
- **4**+ Doses
- **4**+ Time-points
- **~30**+ Different *Readout Types*

= 2,903,040+ Conditions

(and more…)

Plus Metadata on:

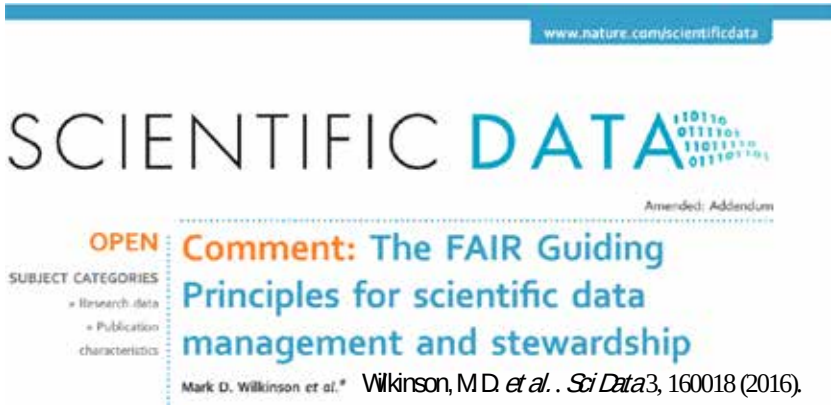
- Individual
- Tissue
- Biospecimen (Cells/ organoids)
- Experiment
- Platform
- Samples
- Readouts
- Analysis

Think about trying to find and understand these data in 10 years time

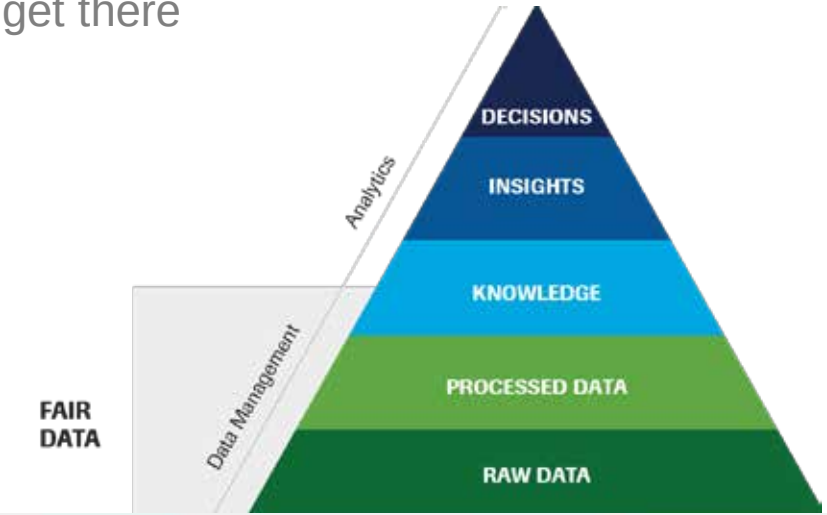
... could you do it?

We can only do it with good scientific data management

Prospective FAIR Data is a framework to get there



Wilkinson, M D. *et al.*. *Sci Data* 3, 160018 (2016).



Findability
Where are our data?

Accessibility
How can I get the data?

Interoperability
How can I connect or integrate the data?

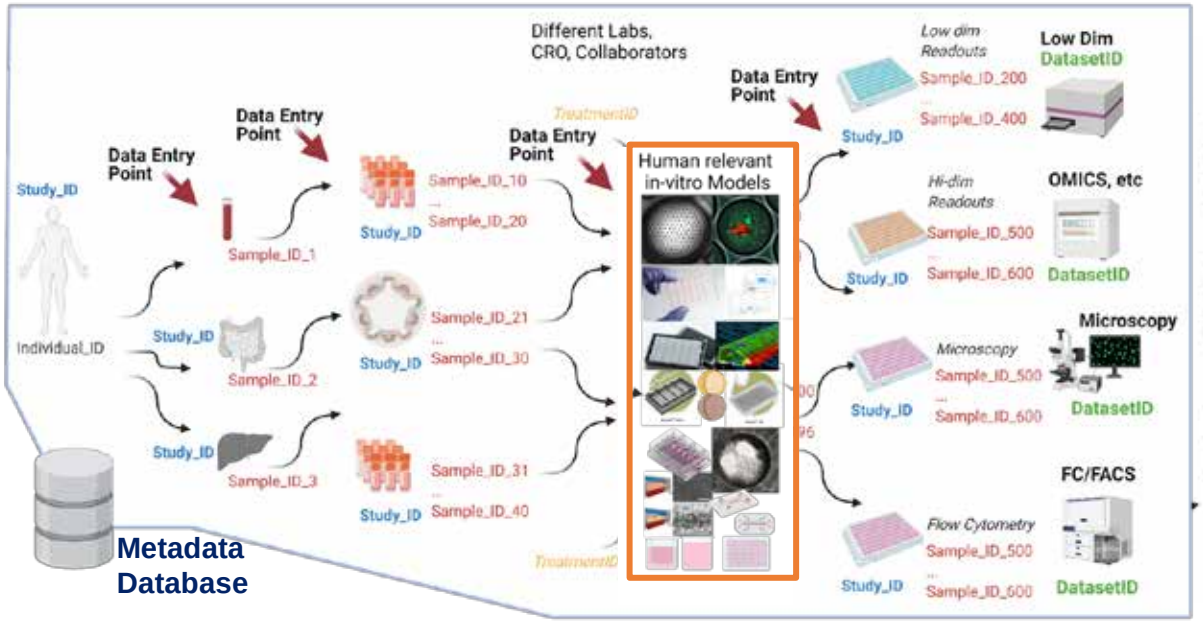
Reusability
Can our data be easily shared and used again?

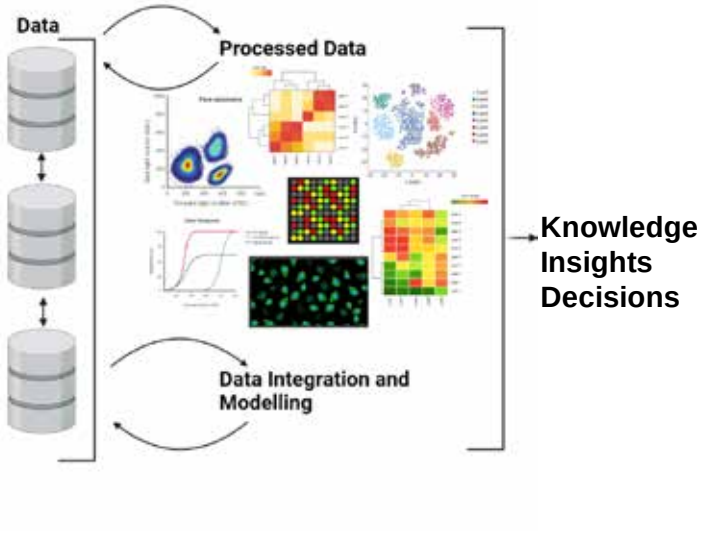
End-to-End FAIR Data Management

Human Biology-centric. Privacy/Confidentiality Compliance
Planning, Sourcing, Implementing, Generating Data…

- **Decision Making-GO/NO-GO?**
- **De-risking Strategy**
- **Regulatory Filing**
- **Connectivity to Clinical Data Repositories**
- **Increase Confidence on Translation Power**

Specimen Lineage, Metadata collection and storage

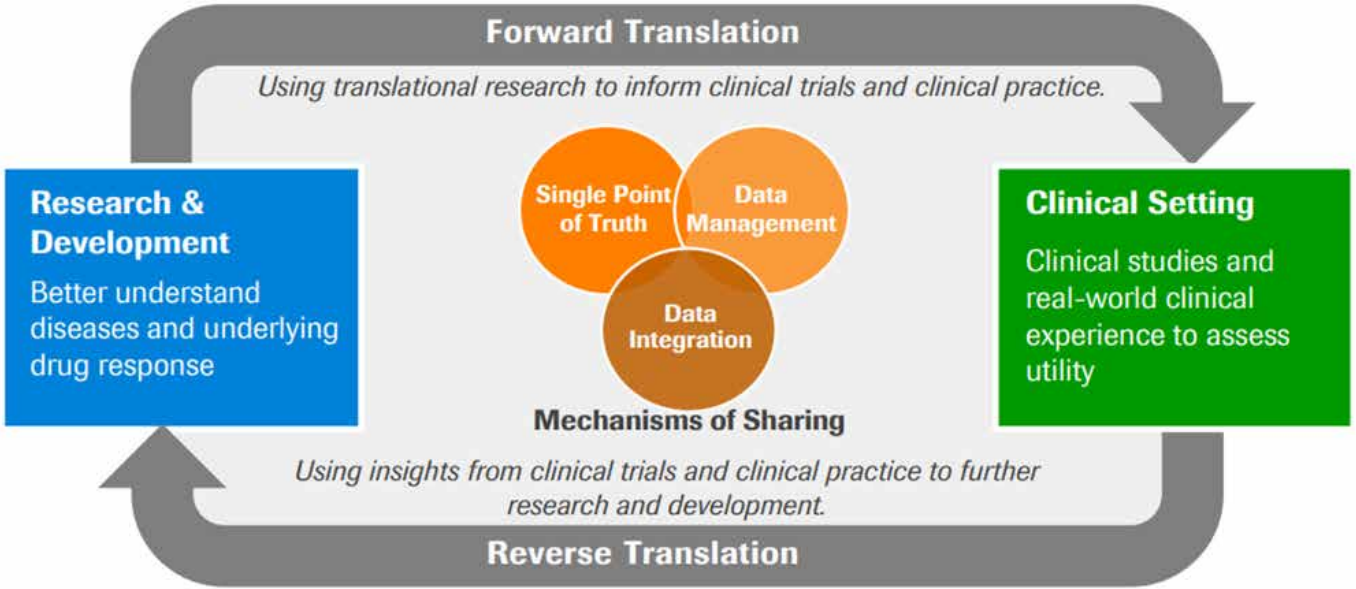




Reverse and Forward Translation rely on long term data

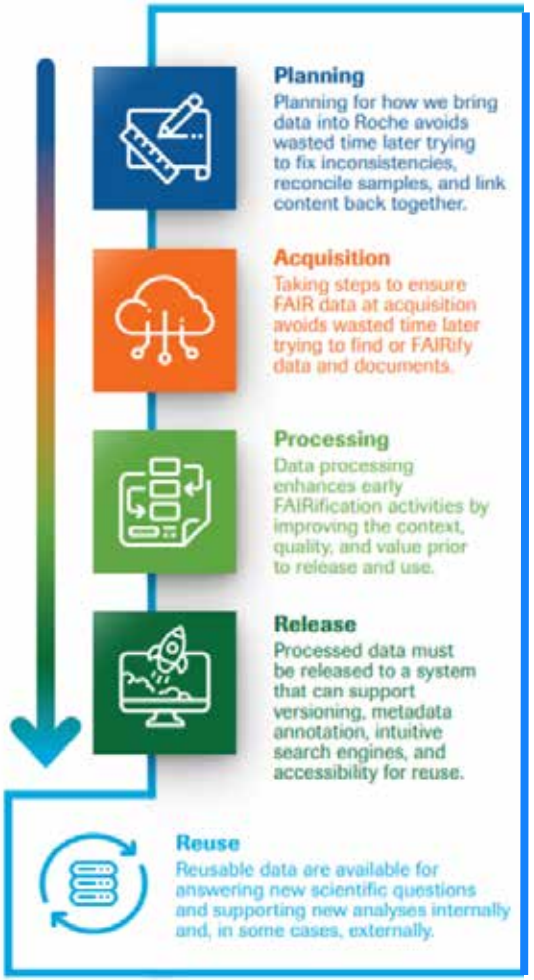
Make our data FAIR and SHARED to accelerate generating meaningful insights

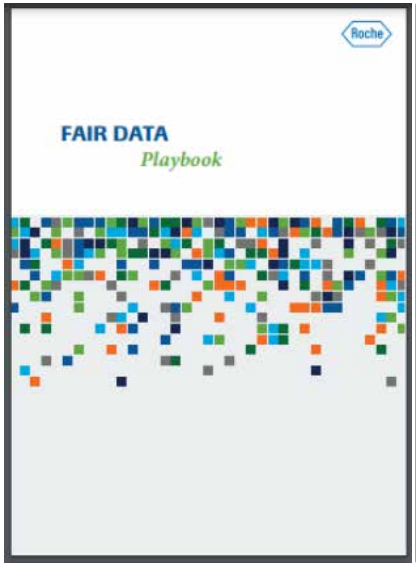
Enhanced Data & Insights Sharing (EDIS) Program

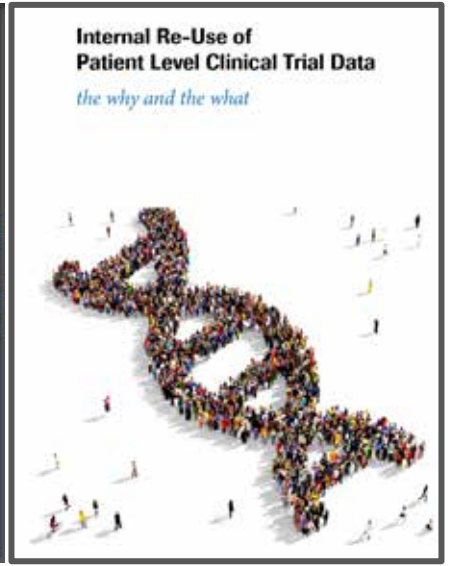


Extend FAIR Clinical Data Practices to in-vitro work

Move toward Prospective FAIRification Internally and with our Partners, Collaborators and Vendors







Linking Clinical with in-vitro pre-clinical data

We need to climb the FAIR data ladder to connect and translate

APIs

Reference Data Services

Layer 5: Analytics & Visualization Tools
Provides the interfaces to the user and opens a playground for experts as well as non-experts.

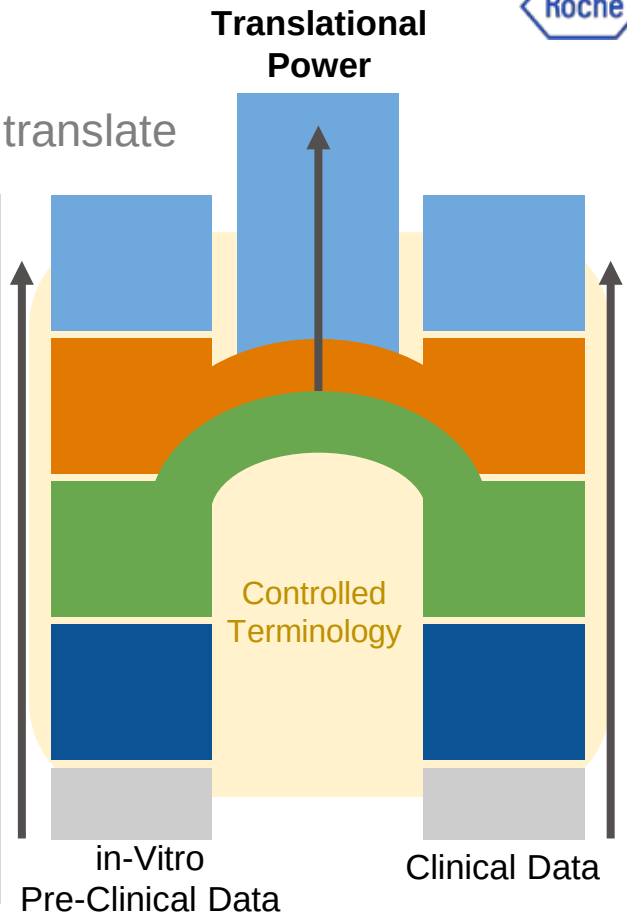
Layer 4: Integrated Data Sets
Allows individuals to integrate data primarily from layer 3 into a meaningful dataset

Layer 3: Harmonized Data Access Points
Provides an abstraction of key data from layer 2 to facilitate searching for data

Layer 2: Scientific Data Assets
Enables data storage and transformation activities so that data can be made available for sharing

Layer 1: Infrastructure
Provides high performance infrastructure and lays the foundation for the various layers in the RDCM

Authentication & Access Control



We get there by standing on the shoulders…
of a GIANT community of incredible colleagues

Lauriane Cabon
Desiree Schubert
Ekaterina Breous-Nystrom
Cyrill Roth
Margery Rousseille
Linda Steinacher
Virginie Micallef
Laurent Juglair
Giacomo Lazzaroni
Nick Corr
Susanne Fischer
Regine Gerard
Blandine Avignon
Nikolche Gjorevski
Salma Sadok
Nathalie Schaub
Evelyne Durr
Ramona Nudischer
Estelle Marrer-Berger
Adrian B. Roth
Tim Hickling
Marianne Manchester

Shanon Seger
Cora Wiesner
Diren Tas
Moritz Gilsdorf
Wojciech Kwiatkowski
Michel Petrovic
Angelo D'Annunzio
Vanessa Schumacher

Laura Badi
Guido Steiner
Cyrill Lopez
David Zhang
Fabian Birzele

Tom Quaiser
Silvia Jimenez
Joachim Rupp

pRED Roche Innovation Center Basel
Pharmaceutical Sciences
OneD In-Vitro FAIR Data Workgroup
Roche Terminology Service
PS FAIR Data Network
pRED Informatics

Collaborators and Contractors:
Alveolix Mimetas In-Sphero CN-Bio Emulate Lonza StemCell Crown Biosciences SUN Biosciences