Nonclinical Tools in Drug Development:

Current Challenges and the Path Forward

March 26, 2025

11:00am-1:00pm ET | 4:00-6:00pm CET

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Agenda

- Welcome
- Keynote Remarks: Dr. Andrew von Eschenbach
- Where are we now? Setting the Stage
- Challenges for industry and next steps moving forward
- Q&A

Moderated by:

Maria Apostolaros

Deputy Vice President

Science and Regulatory Advocacy

P*h*RMA

Keynote Address

Andrew von Eschenbach, M.D

President, Samaritan Health Initiatives;

Urologic Oncologist

Former Director of the National Cancer Institute

Former Commissioner of the Food and Drug Administration

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Where are we now? Setting the stage – nonclinical tools

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Rhiannon David

Director, Microphysiological Systems in Clinical Pharmacology and Safety Sciences

AstraZeneca

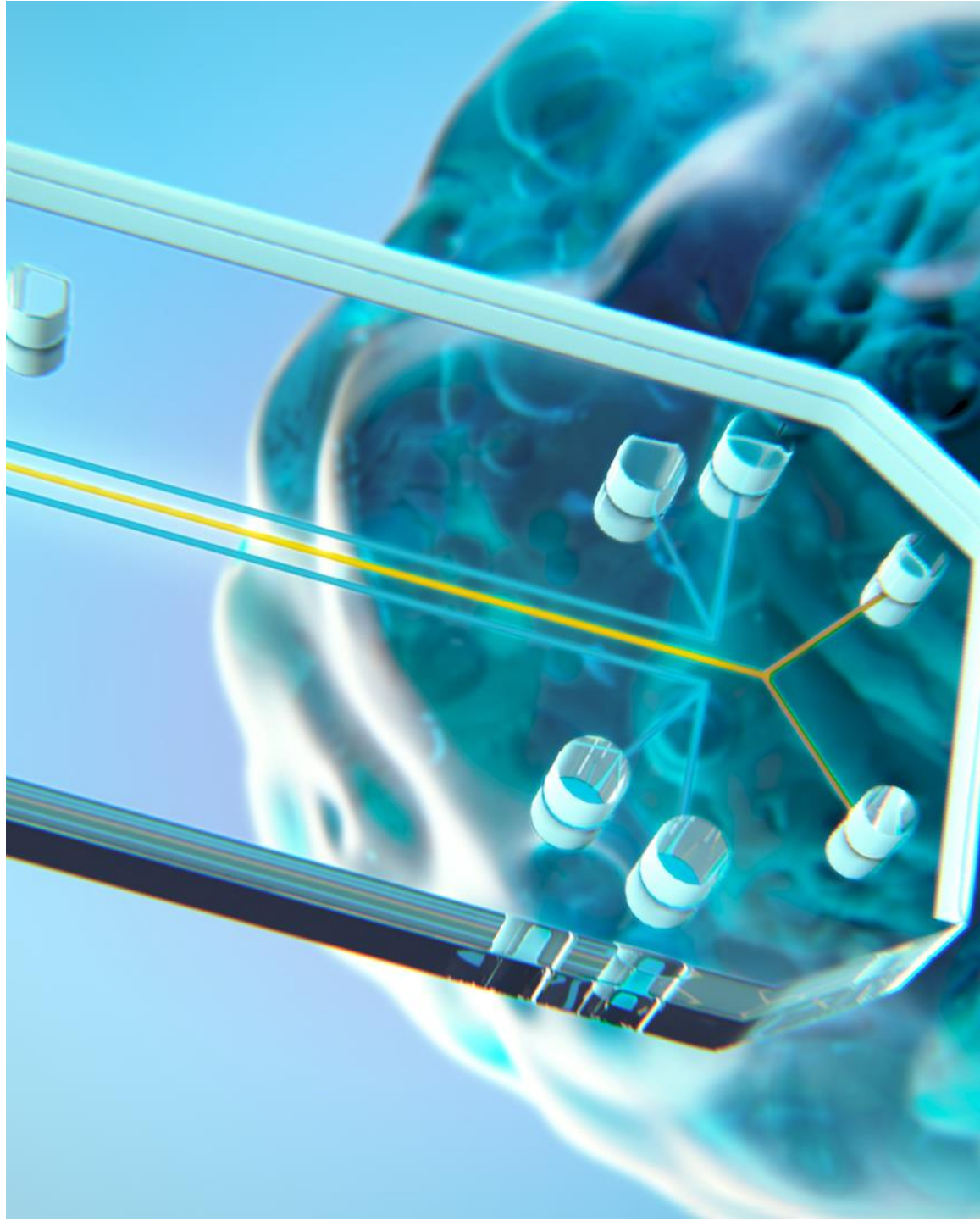
Implementation of Advanced Cell Models for non-clinical safety assessment at AstraZeneca

Rhiannon David

Director, Microphysiological Systems

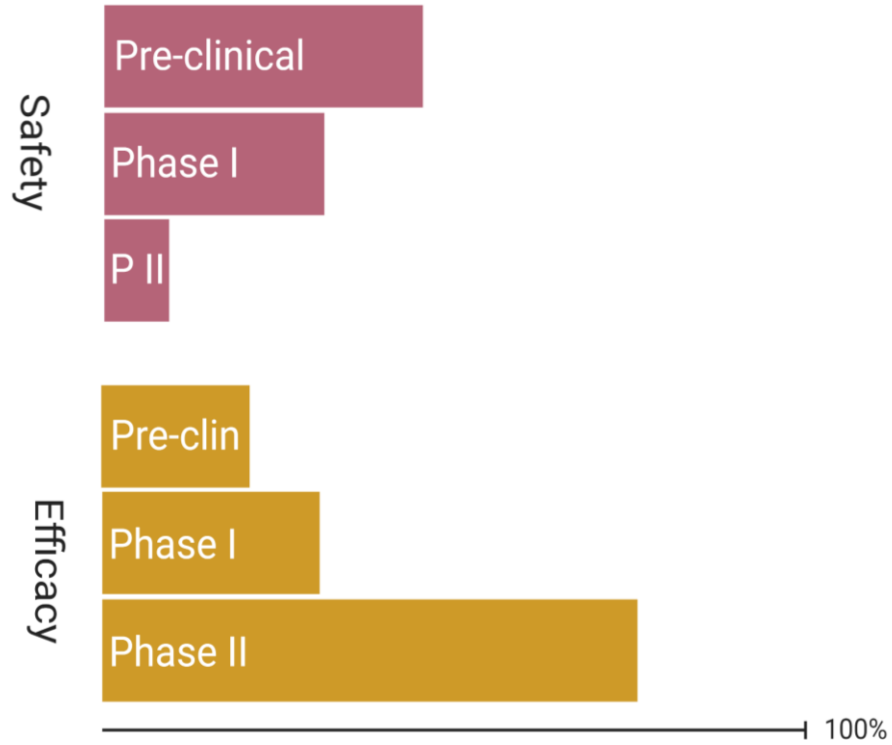
Clinical Pharmacology and Safety Sciences, R&D, AstraZeneca, Cambridge, UK

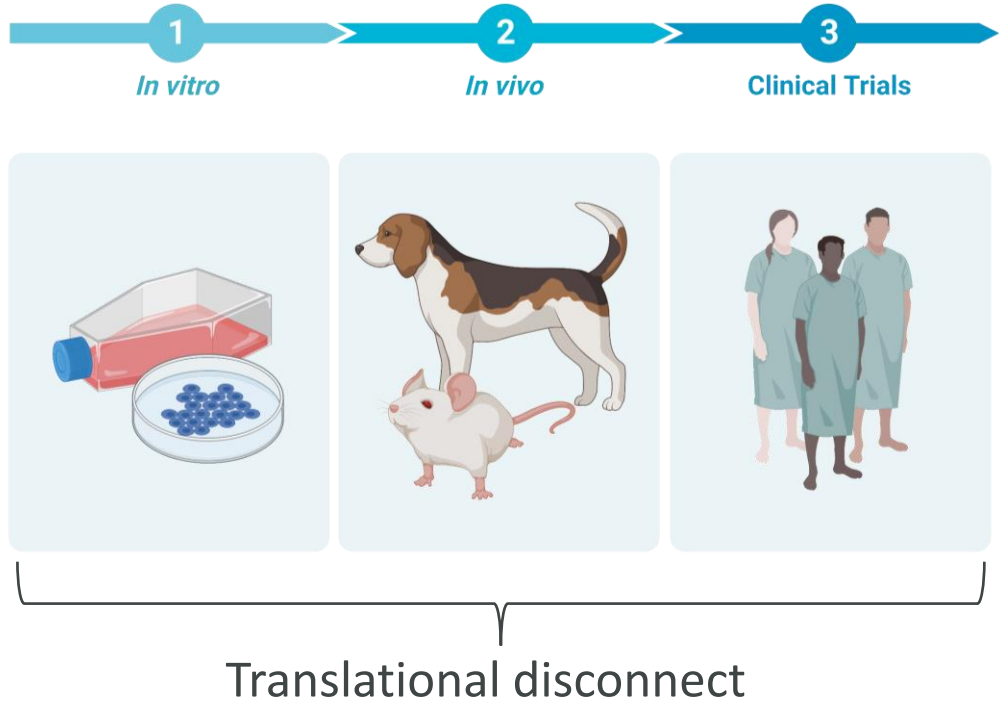
26th March 2025



Enhancing pre-clinical safety assessment in drug development

Drug attrition is a major problem despite improvement in safety-related attrition





Translational disconnect

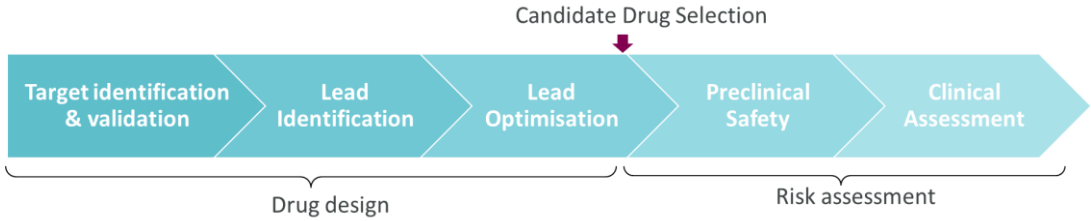
To reduce drug attrition and select more successful drug candidates, we need more human-relevant pre-clinical models

Created with BioRender.com

Morgan, P., Brown, D., Lennard, S. et al. Impact of a five-dimensional framework on R&D productivity at AstraZeneca. Nat Rev Drug Discov 17, 167–181 (2018).

Re-imagining pre-clinical drug development

Safety must be designed in before candidate selection



The Candidate Drug is **THE** molecule

All **molecular properties** are **fixed** (including those driving tox)

Safety must be designed in **before** selecting the candidate

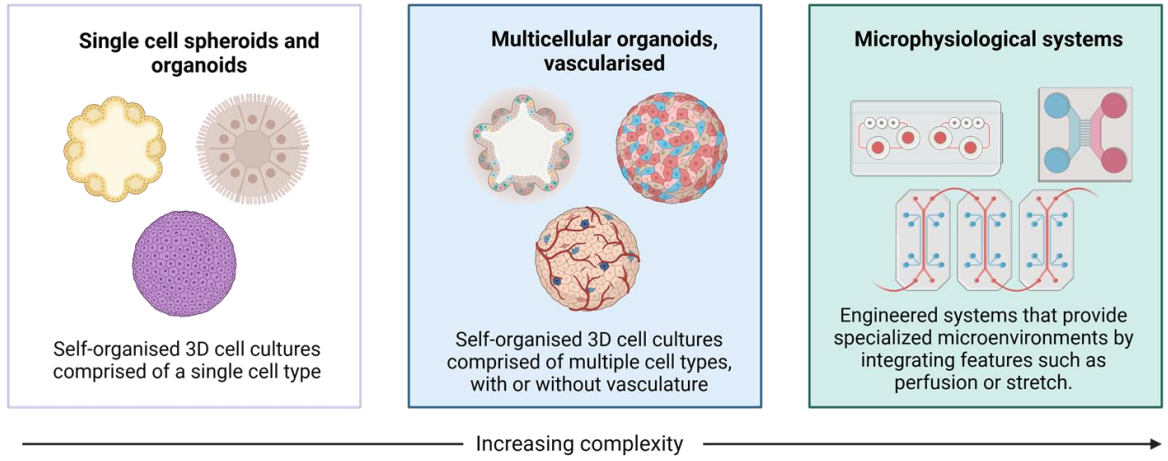
Build **translational understanding** of remaining target/ compound safety risks for clinical prediction

Integrate Human Advanced Cell Models for improved clinical translation

Multiple cell types and organ systems

Less drug used compared to *in vivo*

Human cells/tissues for more relevant models



9 J.J. Hornberg and T. Mow (2014) *Future Med Chem* 6: 481-3.
J.J. Hornberg et al (2014) *Drug Discov Today* 19: 1131-6.

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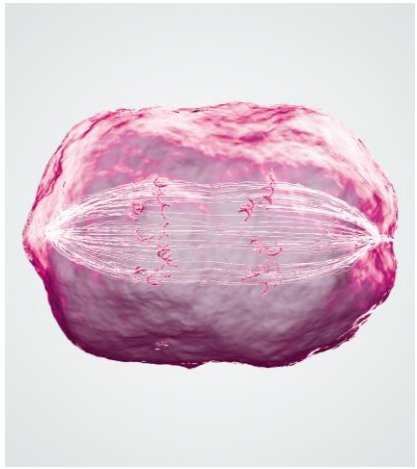
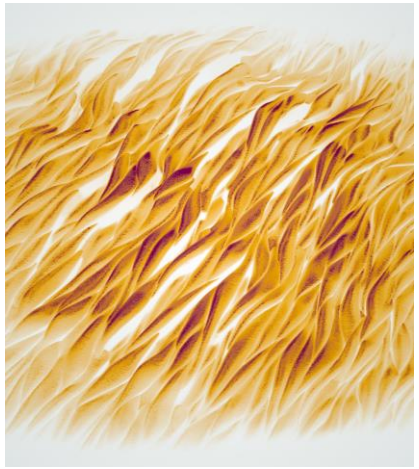
Advanced Cell Models: an opportunity to improve pre-clinical safety assessment



Longevity of cell culture

Enables detection of chronic effects or repeat dosing

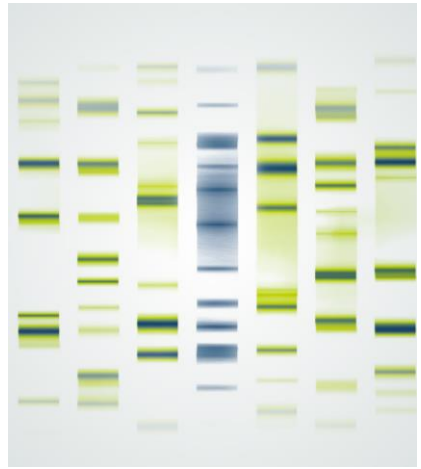


Mixed cell populations

Enable cell-cell interactions/ feedback loops important for organ function/ drug responses

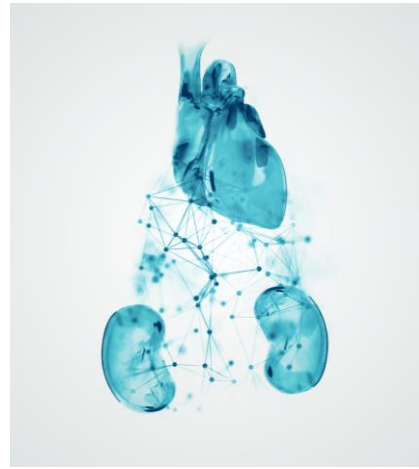
Primary/ iPS cells

More closely resemble cell type of origin



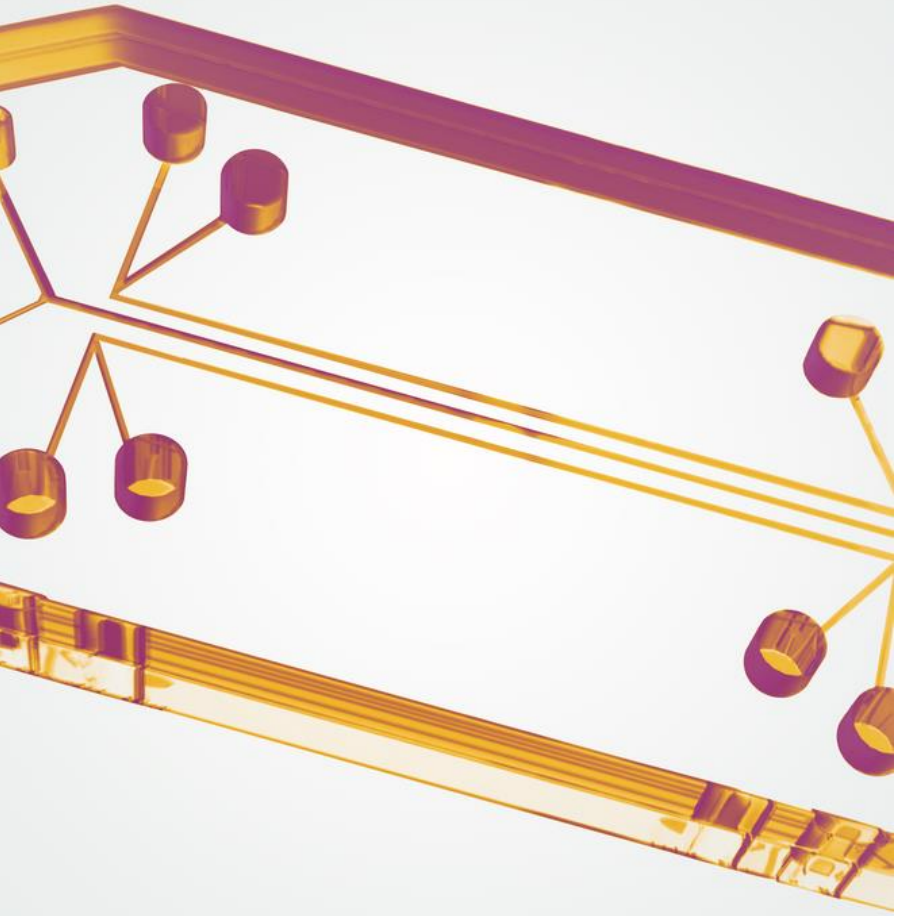
Species differences

Human models could improve clinical translation /animal models could address species differences

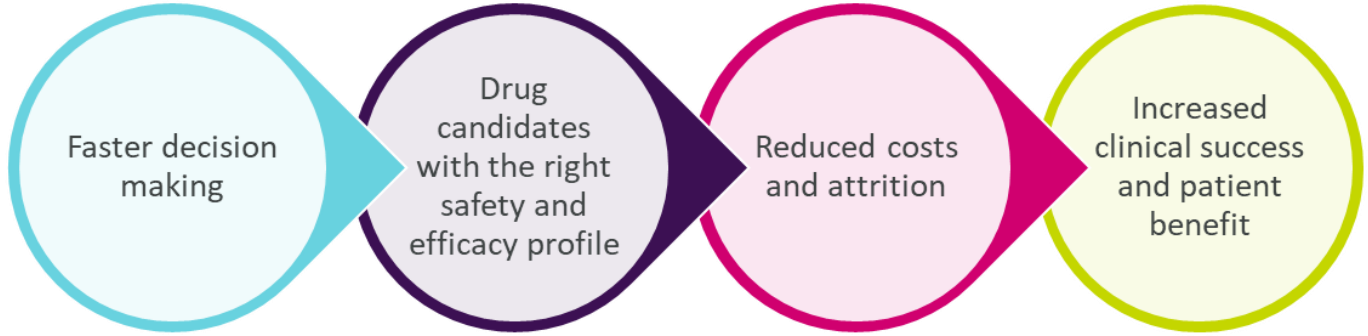


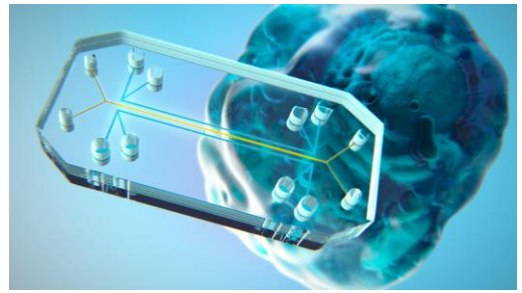
Multiple organs

Drugs can be tested in different organs to determine tissue-specificity of effects



Redefining safety and efficacy prediction with Human Advanced Cell Models





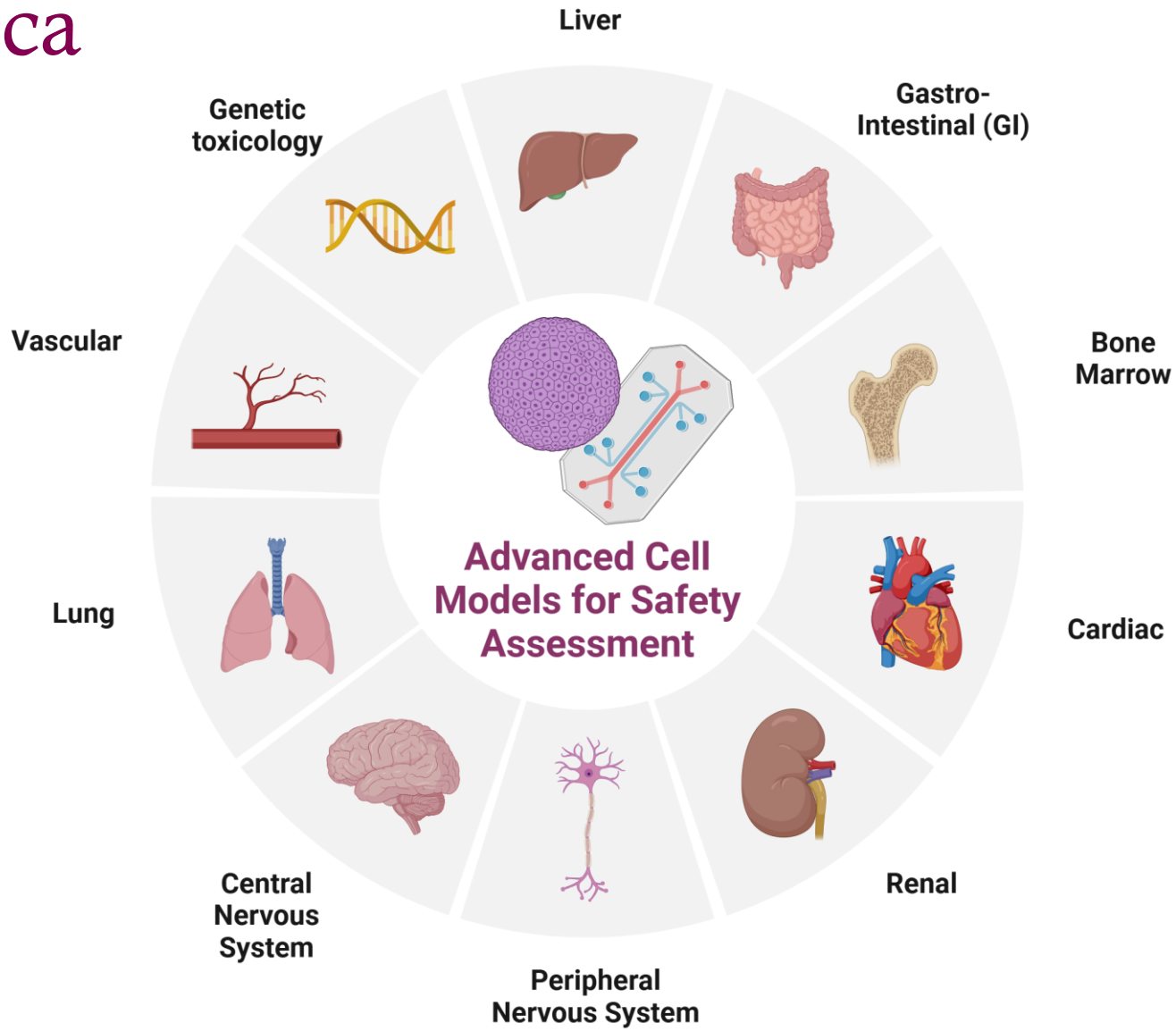
Enhance

- Mechanistic understanding

Enable

- Clinical translation
- 3Rs

Advanced Cell Models for Safety Assessment in AstraZeneca



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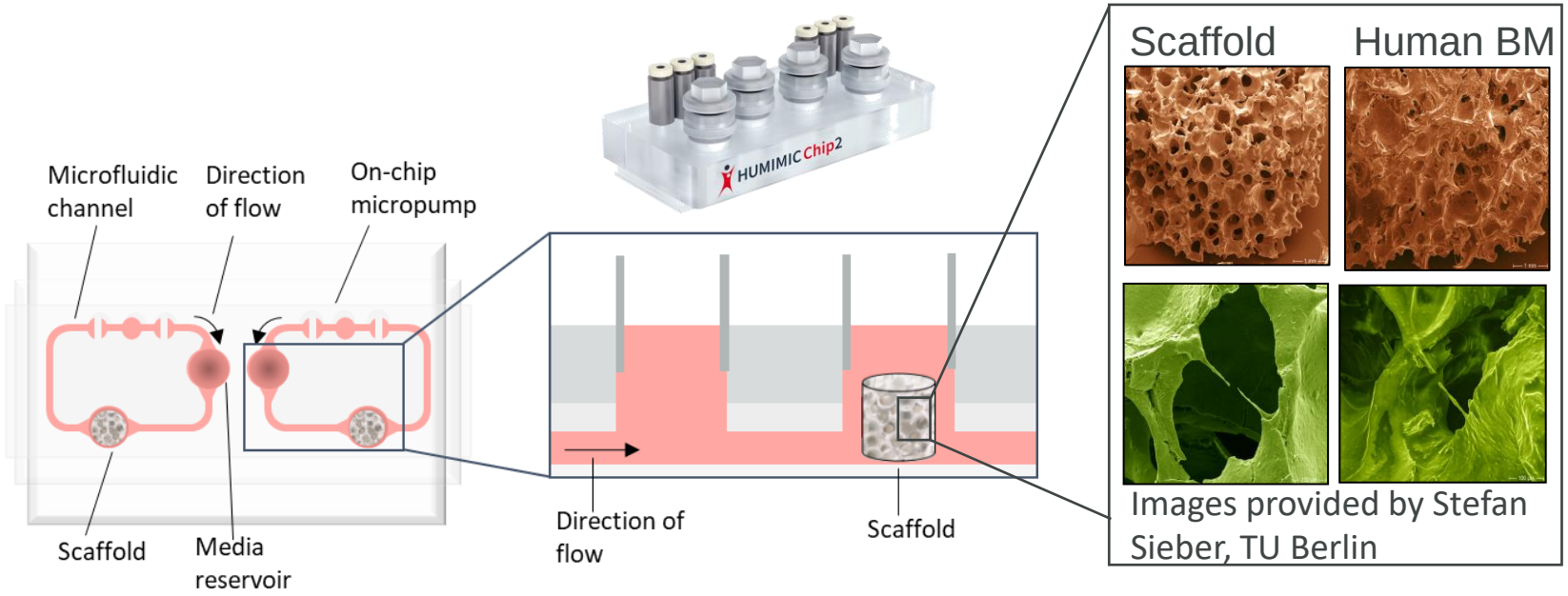
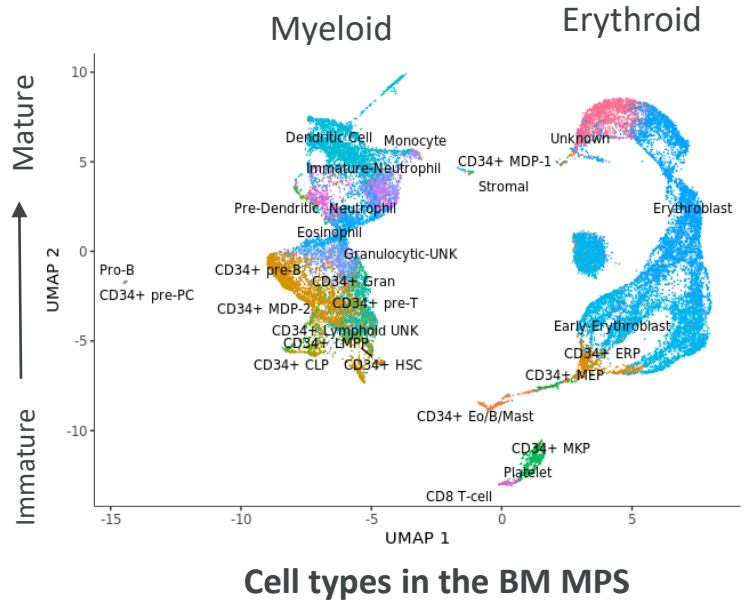
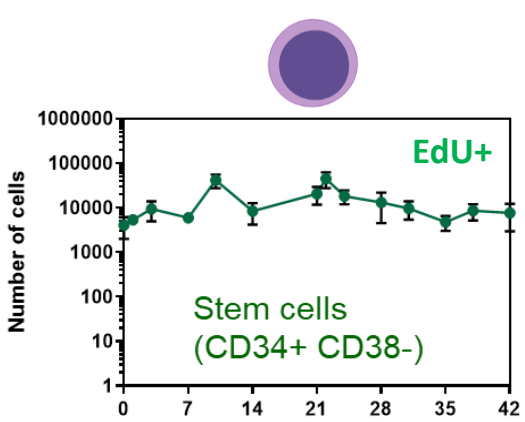
Bone Marrow MPS

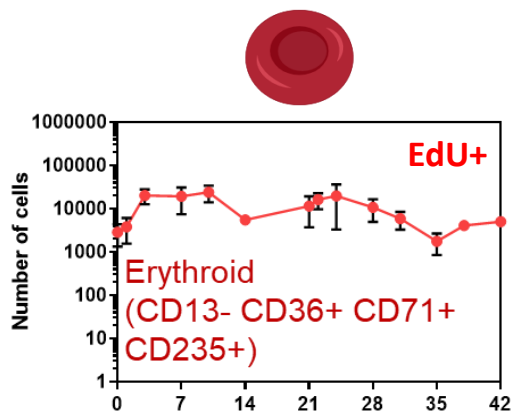
TISSUSE
Emulating Human Biology

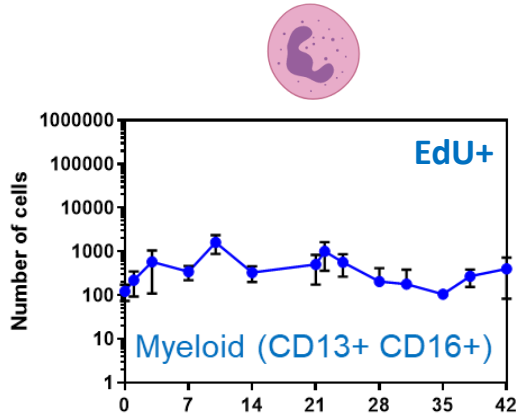


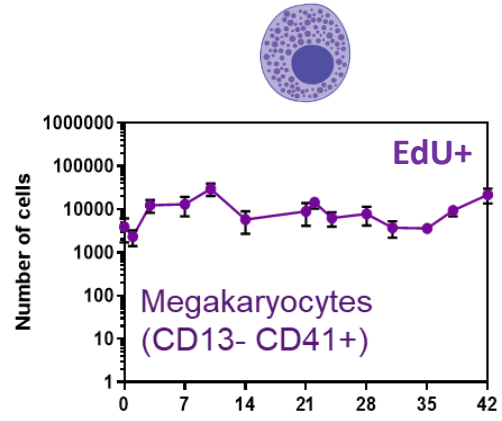


Cell types in the BM MPS



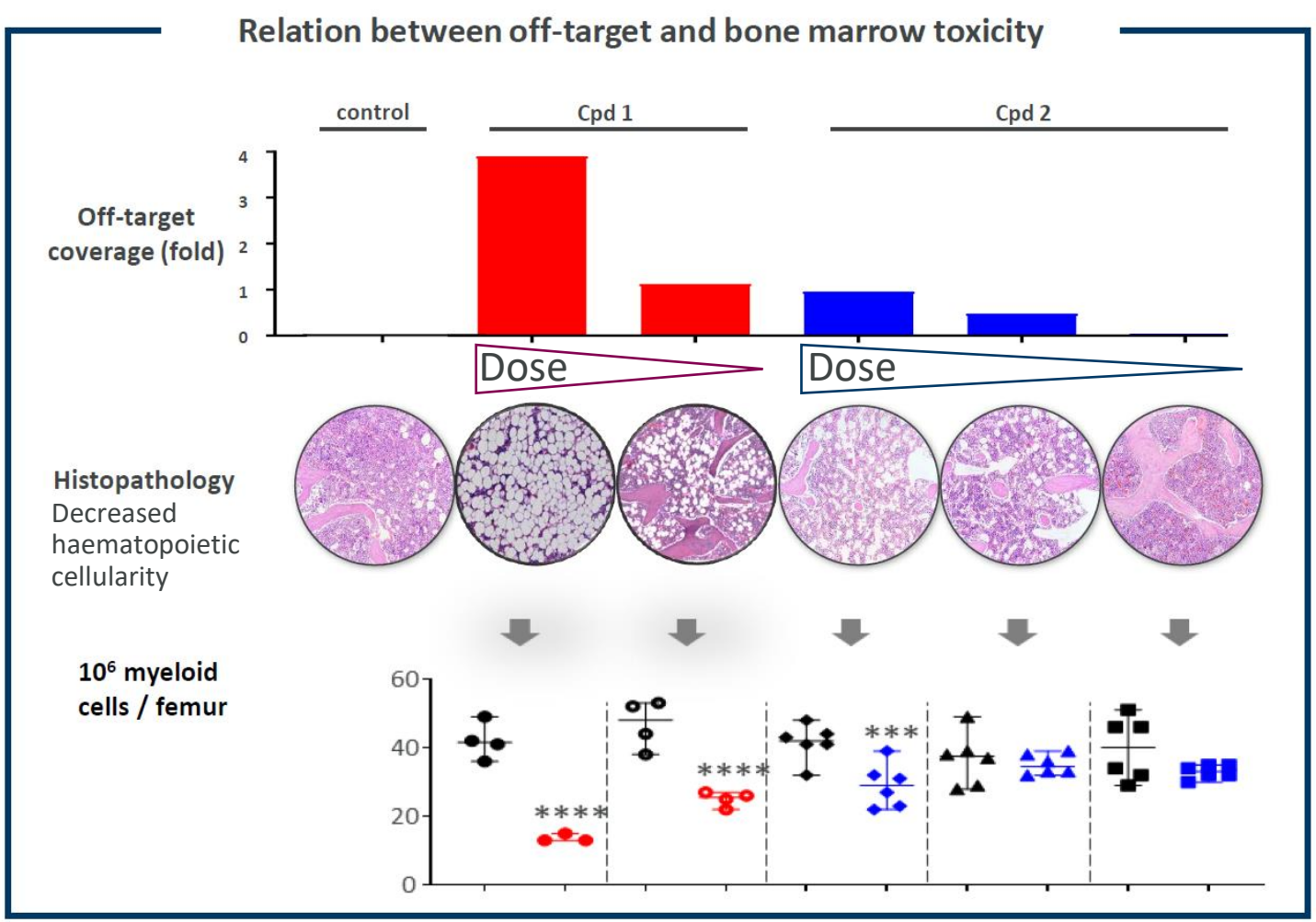


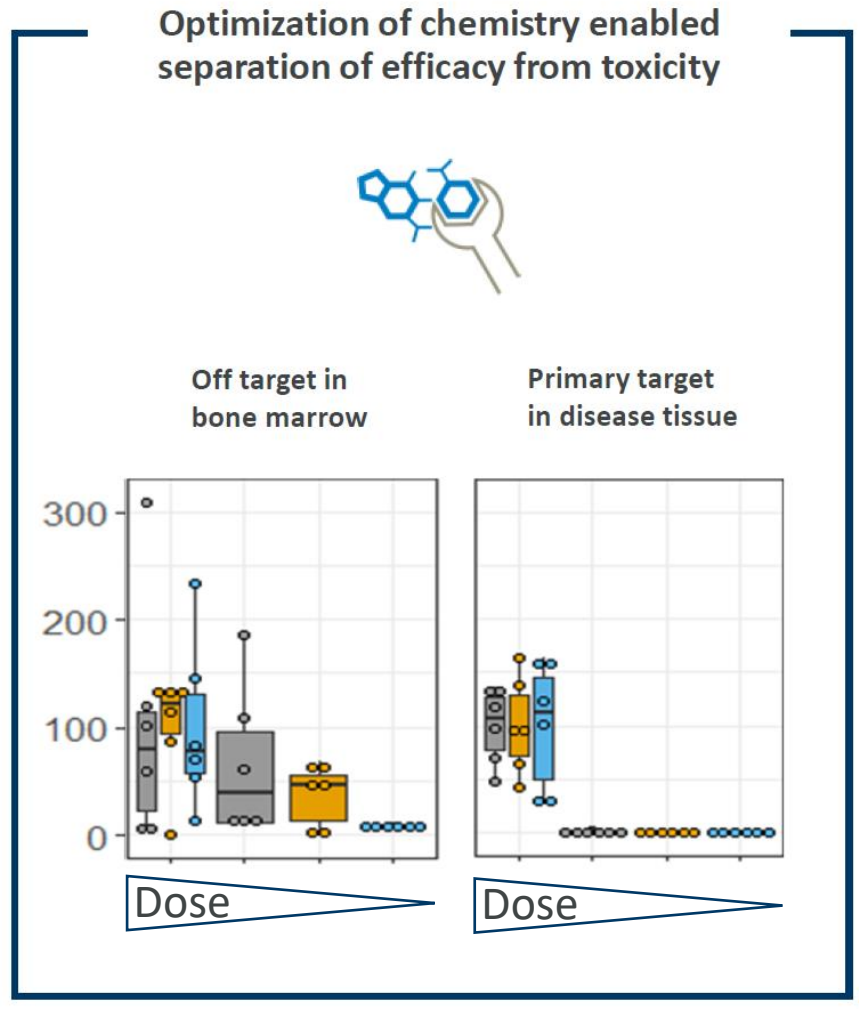




Influencing MONOTHERAPY go/no-go portfolio decisions with quantitative predictions of therapeutic index pre-CDID
Influencing COMBINATION trial optimisation and acceleration to avoid costly clinical investigation of dose and schedule

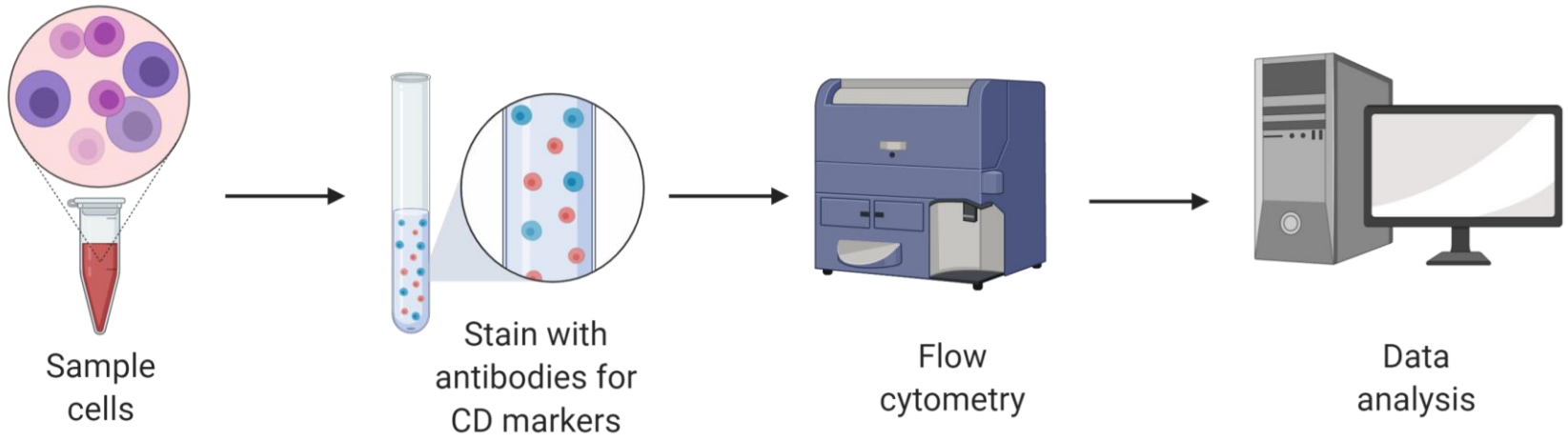
Off-target identification informs chemical optimisation



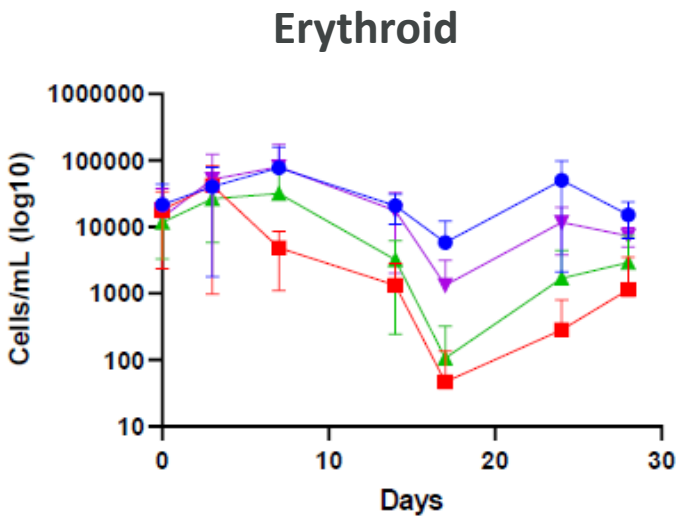


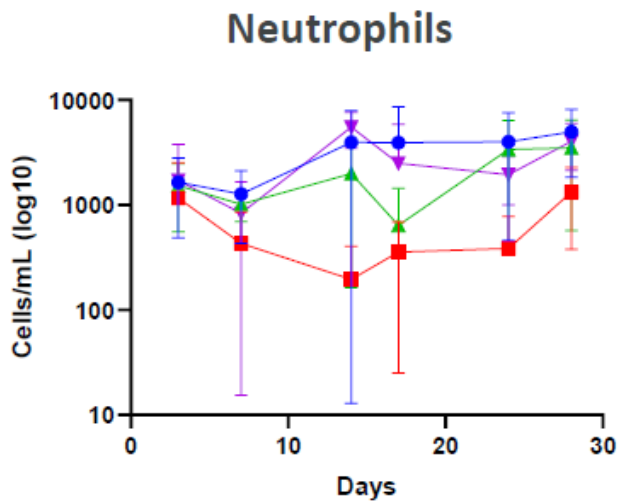
Potential heamatotoxicity risk – will this translate to patients?

Effect recapitulated in bone marrow MPS



28 day study | Continuous treatment





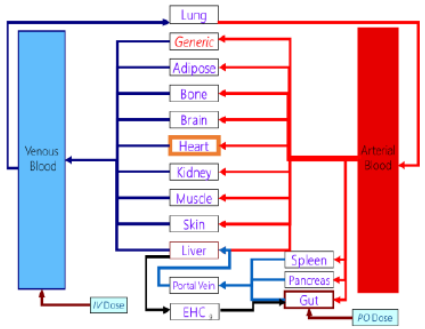
Measure of toxicity over time

What would we see in patients?

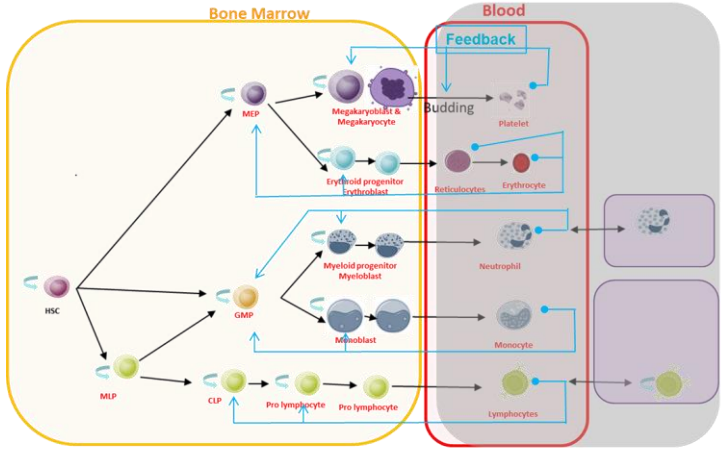
Clinical translation: Quantitative Systems Toxicology Modelling

Systems model of patients' hematology

Exposure: human PK/PBPK model



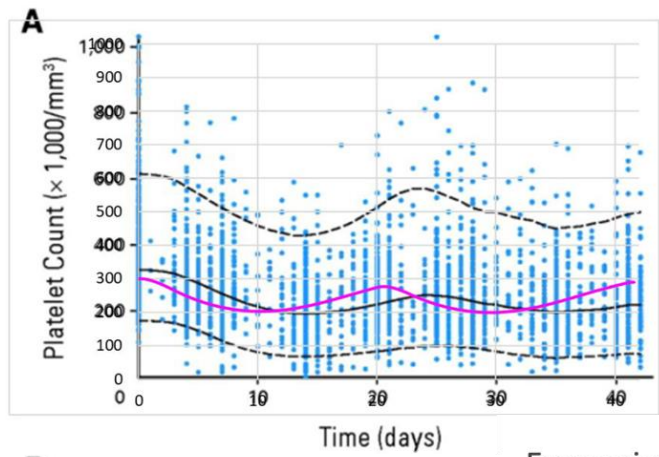
Human haematopoietic model



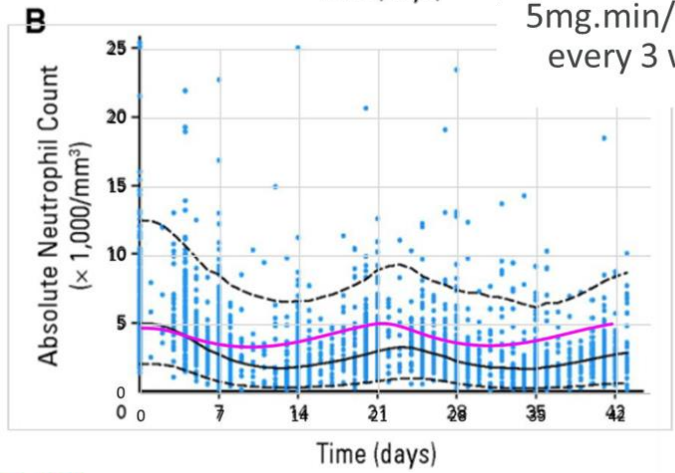
MPS QST model: progenitor cell dynamics

Human QST Haematopoiesis model:
Progenitor and circulating cell dynamics with feedback loops

Does it work?



5mg.min/ml AUC every 3 weeks

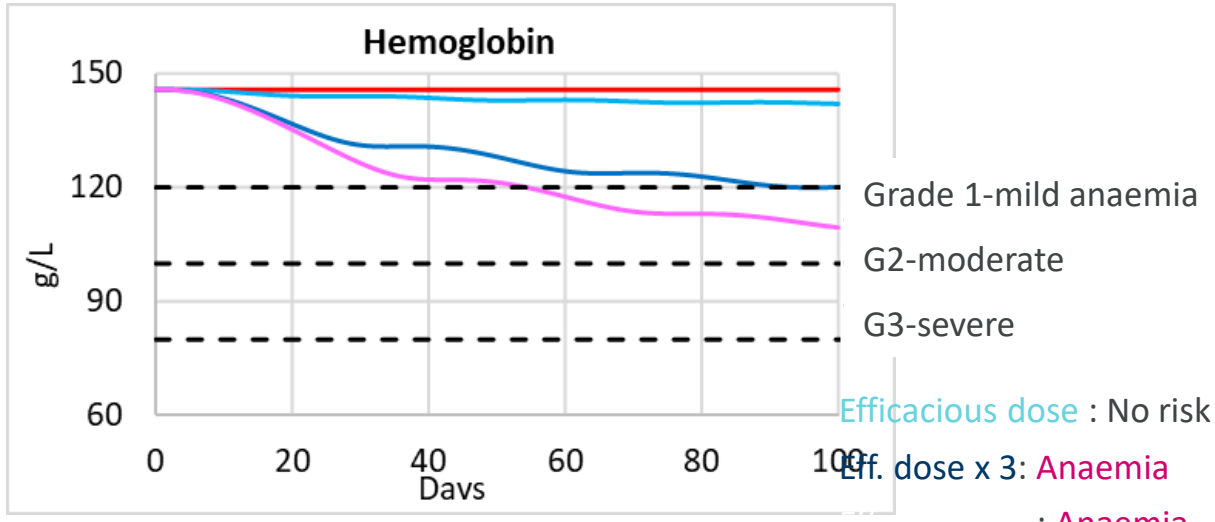


Pink lines are model predictions based on MPS data
Blue dots and **black lines** are data from Schmitt (2010), J Clin Oncol.

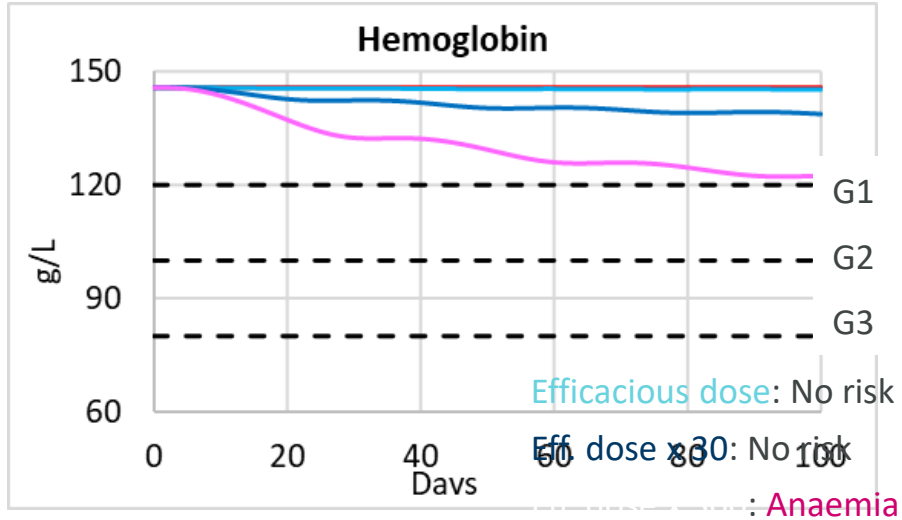
Our modelling approach, based on MPS data, predicts improved safety margin

MPS data-based systems model of patients' hematology expressed as clinical grade of toxicity

Compound 1



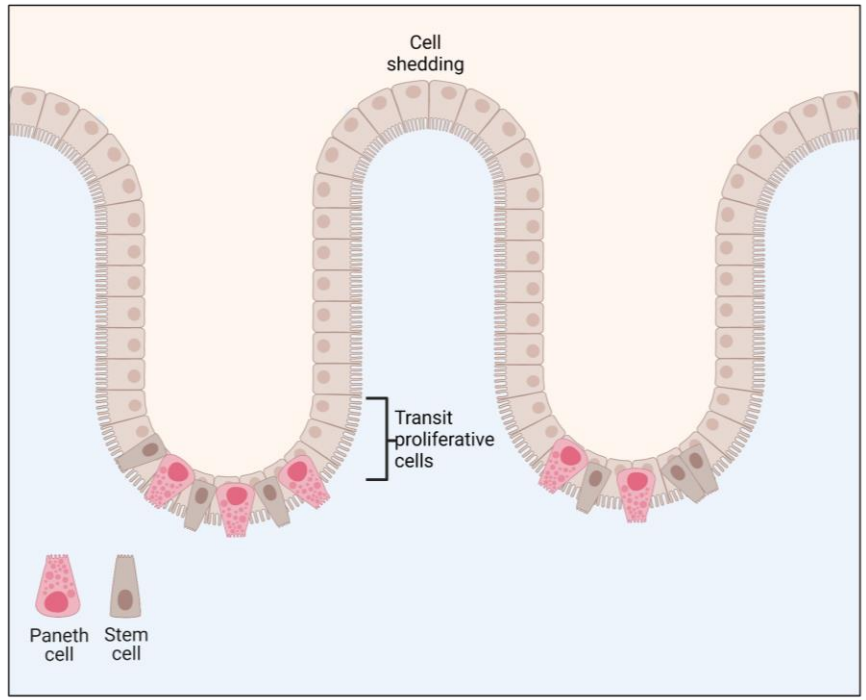
Compound 2



BM MPS coupled with translational mathematical modelling enables early quantitative prediction of clinical haematological risk

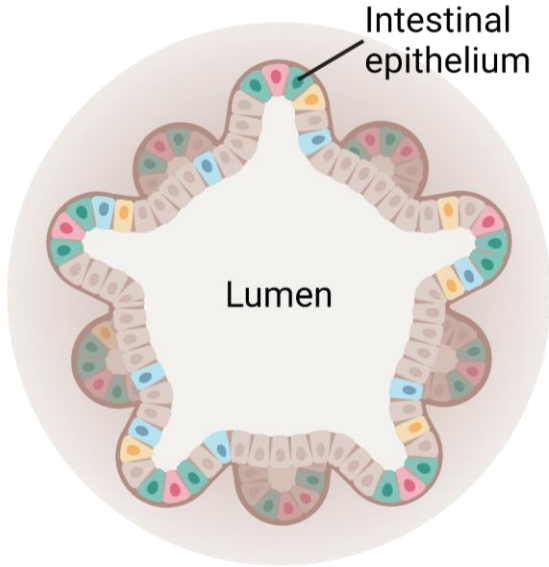
Modelling the intestinal epithelium to detect oncology drug effects

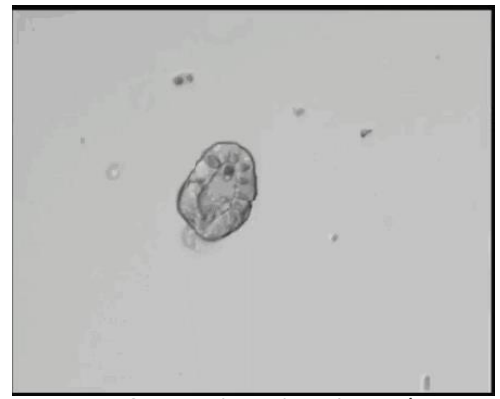
Intestinal crypt



- Compartmentalised, dynamic system
- Makes it very amenable to computational modelling

Model intestine *in vitro*: Organoids



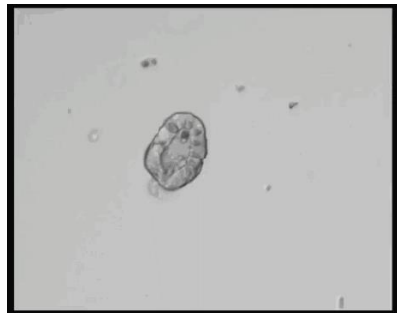


T. Sato, Keio University, Tokyo

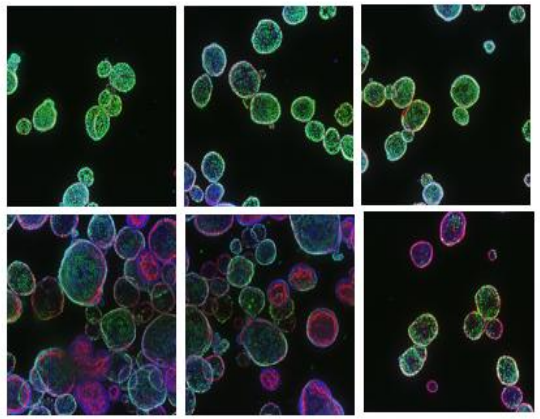
- Mimic crypt and are highly proliferative
- A good model to study oncology drug effects
- We use computational modelling to translate toxicity in GI organoids to clinical endpoints

SMALL MOLECULES: Modelling strategy predicts drug associated clinical diarrhea risk based on intestinal organoids

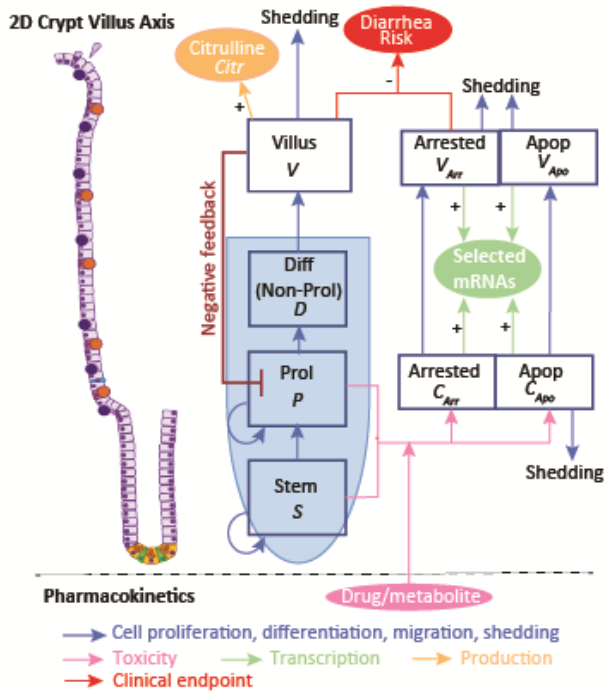
Organoid toxicity modelling



DMSO 0.1 µM 5FU 10 µM 5FU

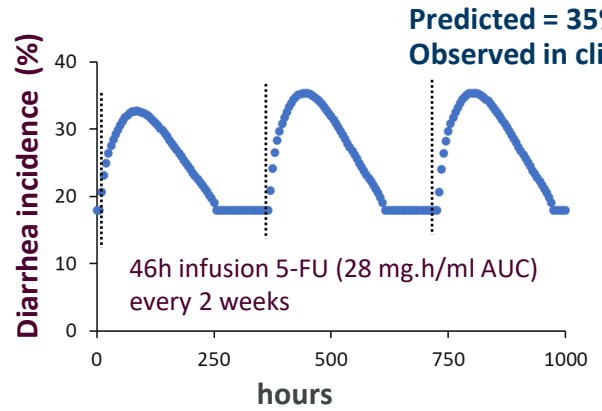


Mathematical model of the human small intestinal epithelium



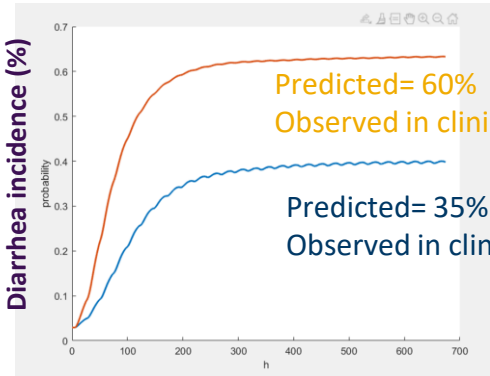
Clinical Diarrhea Risk

Predicted 5FU induced clinical diarrhea



Predicted Gefitinib-induced clinical diarrhea

Gefitinib: 250mg and 500mg QD for 28 days



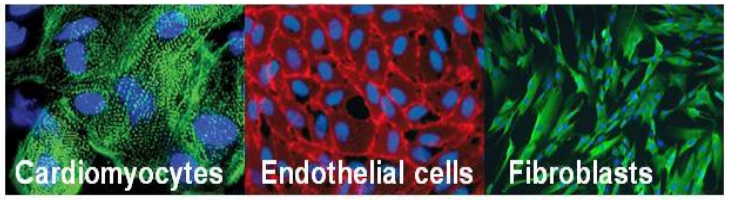
Mouse fails to show GI tox at 50x clinical 500mg equivalent

AstraZeneca: Kenneth Pryde, Louis Gall

TransQST consortium

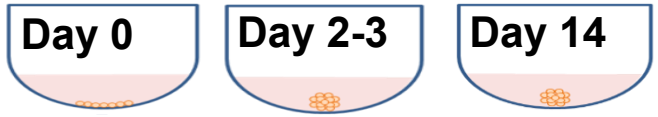
Human Cardiac Microtissues

Humanised Model



Hu-iPS-CM HCMEC HCF

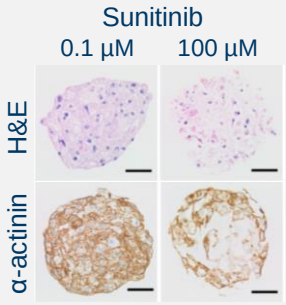
Cells mixed in 4:1:2 ratio



Cell mixture seeded in ULA 384 well plates

Spontaneous beating activity

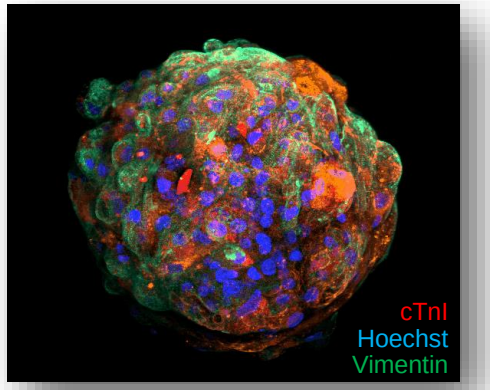
Functional validation



- Lack of hypoxic core
- Morphological integrity maintained for 2 weeks
- Response to cardiotoxins:
  - Loss of cellularity & structural proteins
  - Significant degenerative changes.
  - Release of soluble biomarkers

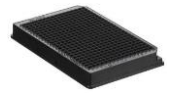
High-Throughput Imaging of Cardiac Microtissues for the Assessment of Cardiac Contraction during Drug Discovery. **Pointon A**, Pilling J, Dorval T, Wang Y, Archer C, Pollard C. Toxicol Sci. 2017 Feb;155(2):444-457.

Characterization and Validation of a Human 3D Cardiac Microtissue for the Assessment of Changes in Cardiac Pathology. Archer CR, Sargeant R, Basak J, Pilling J, Barnes JR, **Pointon A**. Sci Rep. 2018 Jul 5;8(1):10160.



Structural Cardiotoxicity Screen

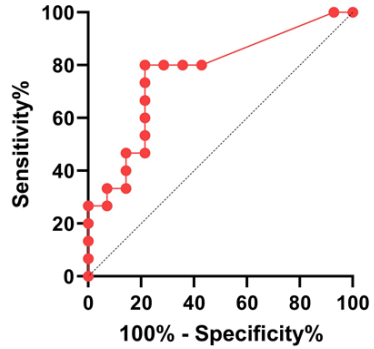
CMT in 384 well plates



- Echo dosing
- 9-point dose curve

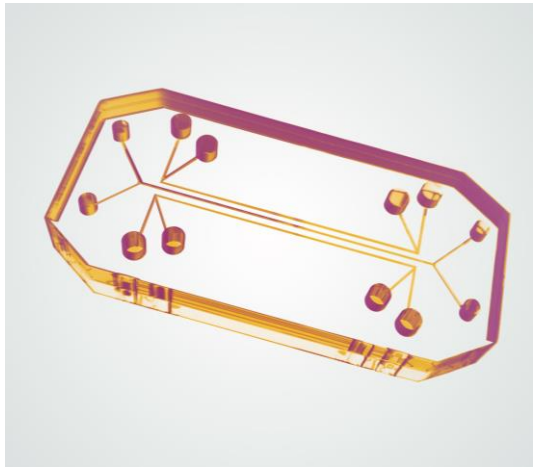
72 h incubation

Mitochondrial membrane potential	Imaging
Endoplasmic reticulum integrity	Imaging
Luminescence-based cell viability	Plate reader



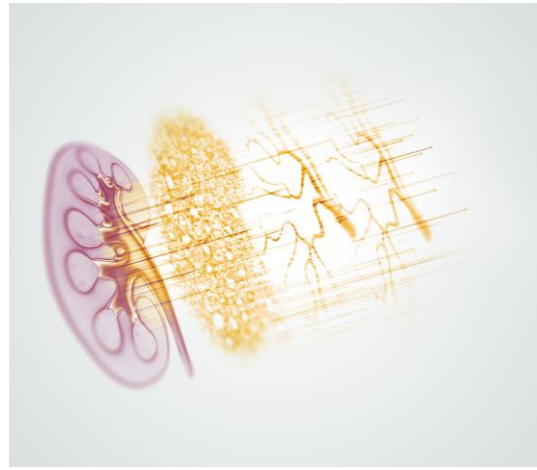
Sensitivity 70%
Specificity 78.6%
Screen shows predictivity of clinical structural cardiotoxicity

Closing remarks



Integration of **Advanced Cell Models** with varying levels of complexity and throughput can **enhance nonclinical safety assessment**

Coupling these models **with QST** modelling can generate **clinical predictions** with reduced data requirements



Combining these models with **advanced technologies can afford novel endpoints** for mechanistic insight to drug toxicity

Challenges to adoption and therefore animal replacement remain

Acknowledgements

AstraZeneca

- Kainat Khan
- Emilyanne Leonard
- Carmen Pin
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- Kenneth Pryde
- Mike Beshiri
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- Marianna Stamou
- Katarina Breitholt
- Kelly Evans
- Catherine Betts
- Ernst Ahlberg
- Lucas Milton
- Anna Jonebring
- Michaela Morlock
- Linda Starnes
- Jose Vicencio
- Carol De Santis
- Amy Pointon
- Jorrit Hornberg

TISSUSE Emulating Human Biology

transQST

NORTIS

IONIS

UNIVERSITY of WASHINGTON

THE UNIVERSITY of EDINBURGH

Radboud Universiteit

AstraZeneca PLC, 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, CB2 0AA, UK
+44(0)203 749 5000
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Frederic Christian Pipp

Global Animal Welfare Officer

Merck KGaA

The 3 Basket Approach for a Roadmap to Phase out Animal Testing

Time to Shift Some Paradigms

Dr. Frederic Pipp, Global Animal Welfare Officer
Merck KGaA, Darmstadt, Germany

Today Animal Testing is Part of Most of Our Value Chains

Changing regulations compelling us to replace animals.

2021 EU Parliament
667 MEPs voted for and 4 against

EU parliament adopted resolution for plan and actions to accelerate transition to **innovation without the use of animals in research.**

2022 ECI Requires the European Commission to:

Modernize Science in the EU. Commit to legislative proposals plotting a **roadmap to phase-out animal testing**

2023 NEW EU Pharma Legislation

… including where possible, the use of new approach methodologies […] in **place of animal testing**…

2024 FDA Modernization Act 3.0

… **reduce and replace the use of animals** in nonclinical research, **improving the predictivity** of nonclinical testing methods…

2024 WHO Draft Guideline for QC of Biologics

Guidelines on the phasing out of animal tests for the quality control of biological products

efpia
European Federation of Pharmaceutical Industries and Associations

There is no such thing as

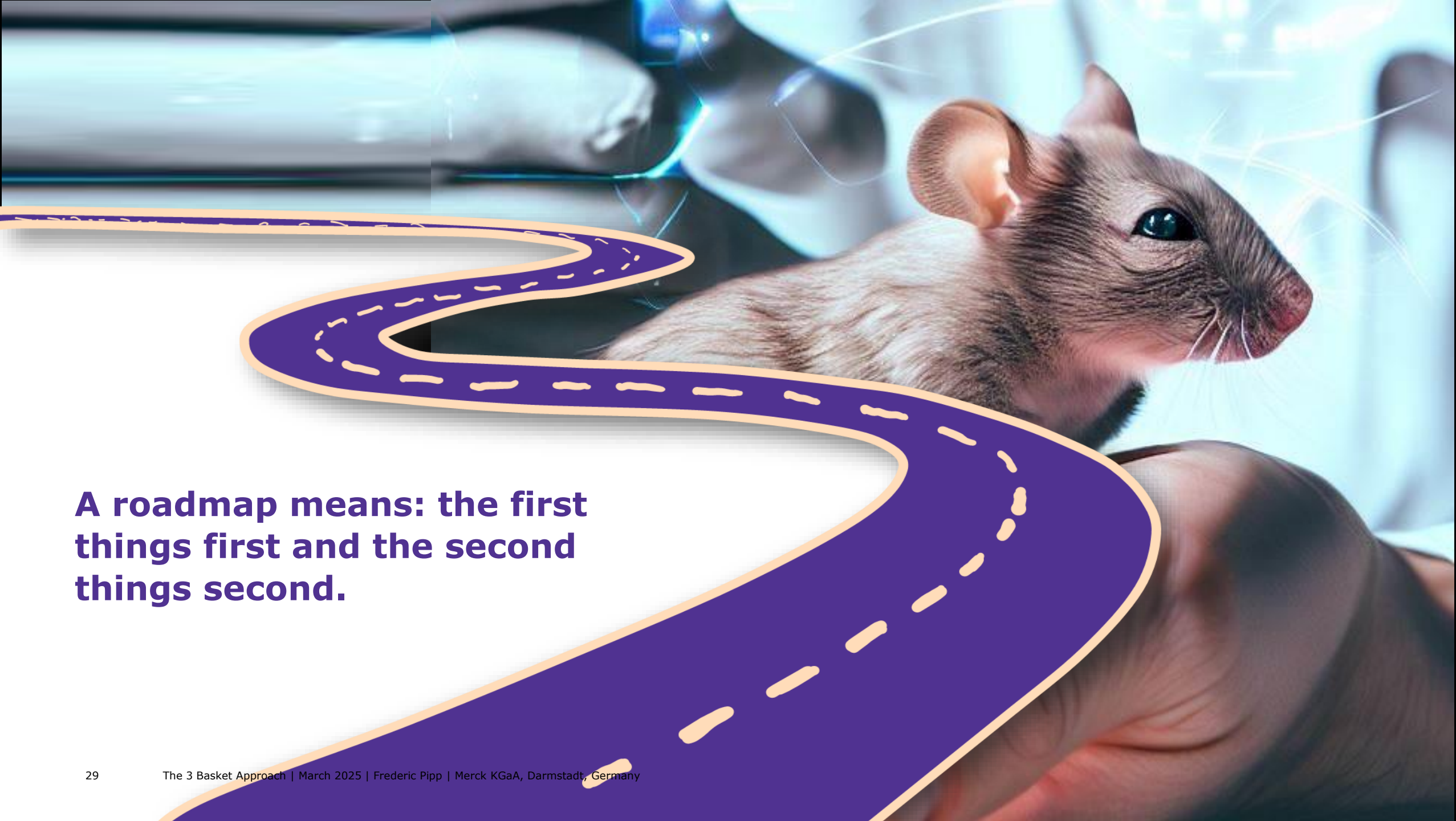
THE Alternative
to animal testing

Just as there is no

THE Animal Test

…and we don´t have
all the solutions yet

Focus on what we can do today, rather than blocking development with discussing what we cannot yet do.



A roadmap means: the first things first and the second things second.

BASKET 1
Alternatives Exist

Animal testing purposes for which, from a scientific standpoint, there are non-animal alternatives. This includes animal experiments mandated by regulatory authorities in one or more countries.

BASKET 2
Hypotheses for Alternatives Exist

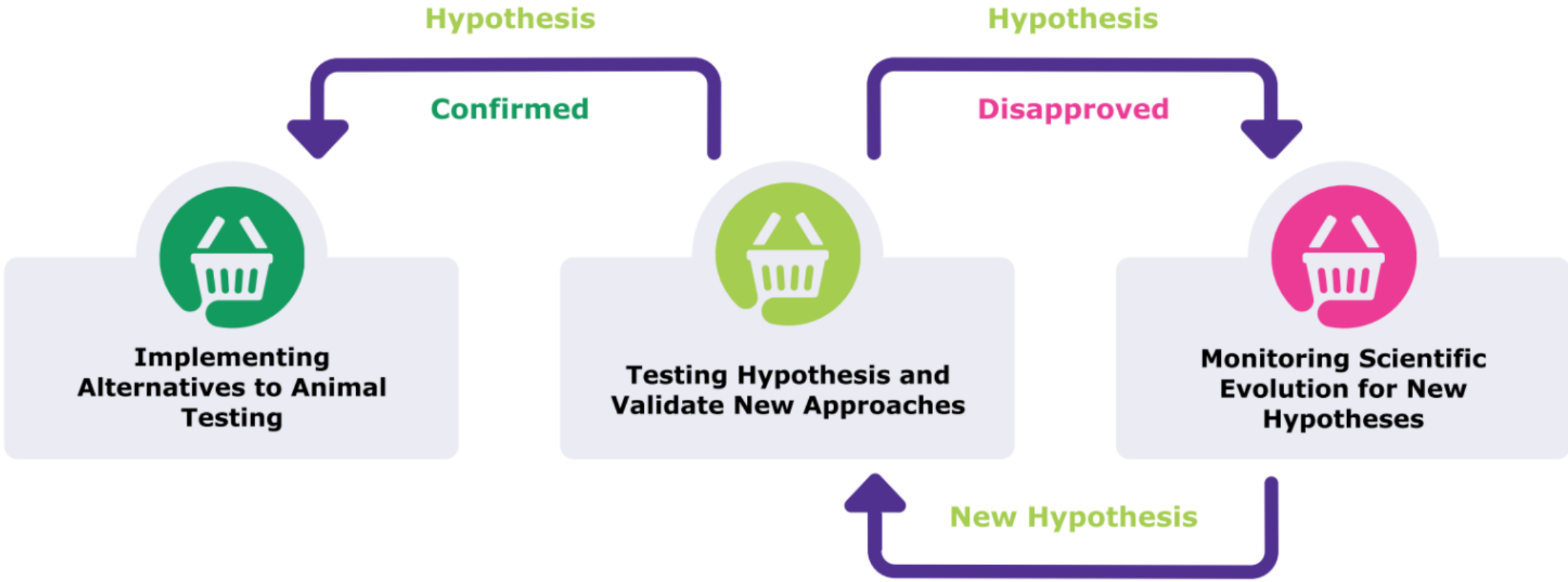
Animal testing purposes for which currently no alternatives exist, but for which hypotheses exist on how animal-free technologies may replace animal testing in the mid to long term.

BASKET 3
No Hypotheses for Alternatives Exist

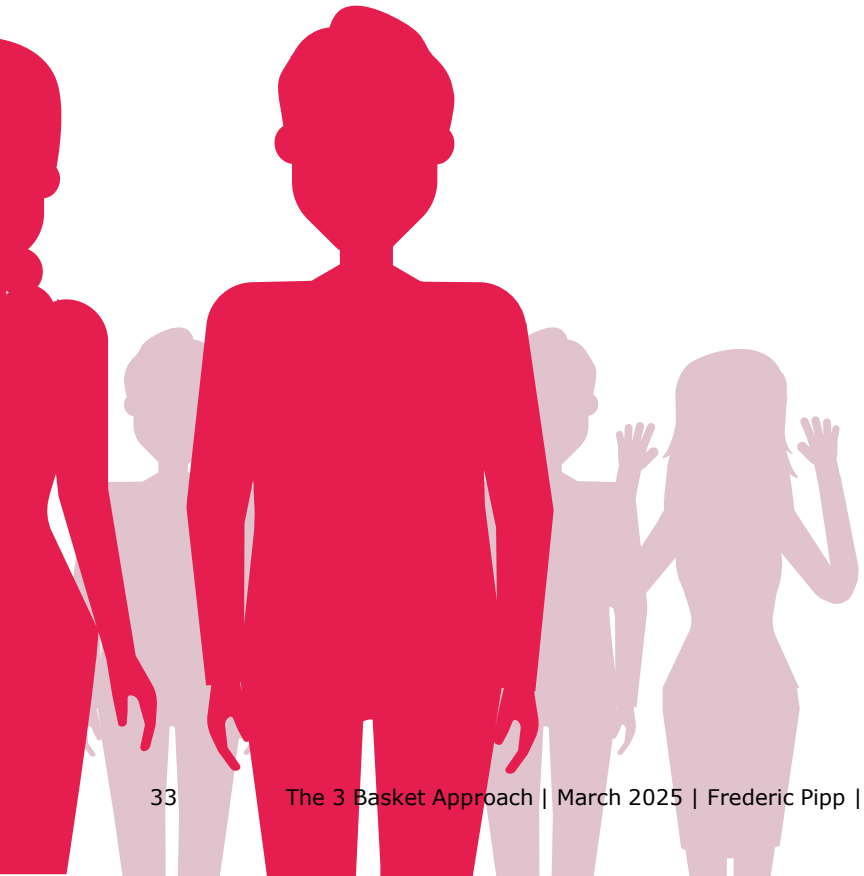
Animal testing purposes for which there are currently no hypotheses on how the scientifically essential knowledge could be achieved without the use of animals.

Subject Matter Experts Sort all Animal Testing Purposes into the 3 Baskets


Alternatives Exist
ADOPTION:
Roadmaps, Milestones,
KPIs
Hypotheses for
Alternatives Exist
ADAPTATION:
Prioritization of
Research Investments
No Hypotheses for
Alternatives Exist
ASSESSMENT:
Greatest Innovation
Potential
Investment Priority: Refine
Investment Priority: Replace


Hypothesis
Confirmed
Hypothesis
Disapproved
Implementing Alternatives to Animal Testing
Testing Hypothesis and Validate New Approaches
Monitoring Scientific Evolution for New Hypotheses
New Hypothesis

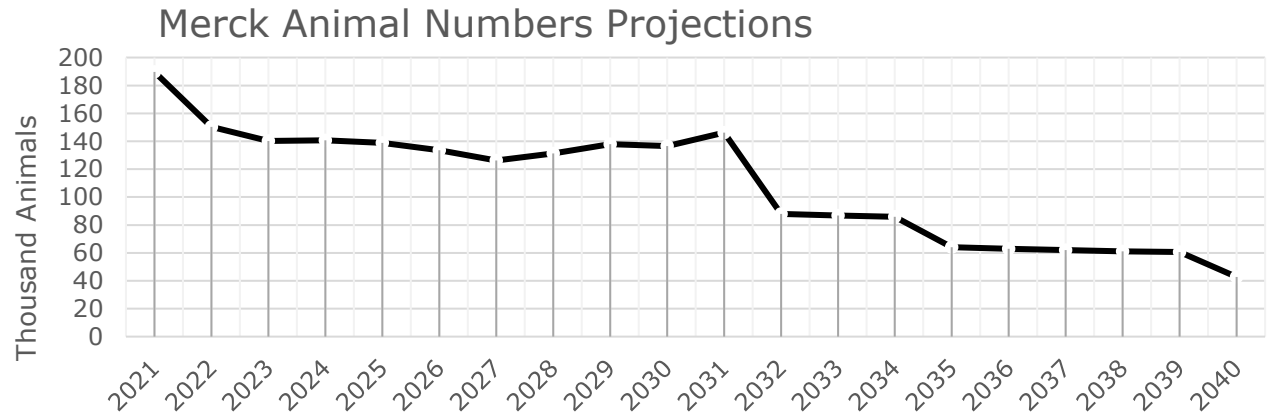
When will we no longer need to conduct animal testing?



That we don´t know.

But we do know that the 3 Basket Approach helps us replacing 75% by 2040, despite the growing business needs.

While creating business advantage.



One-Merck Projected Reduction of Animals Used in Testing Through the 4R Program Launched in 2021.

-50% animals by 2032

-75% animals by 2040

3 Basket Model adoption

Feasible Roadmap
Replacement – not Displacement

Basket 1 → Replacement
Biggest hurdle is global acceptance of alternative methods

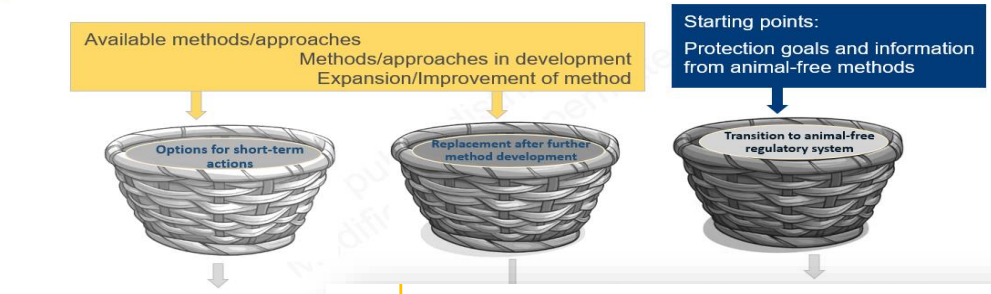
Basket 2 → Innovation
Basket 3 → Acceptance

EFPIA - European Federation of Pharmaceutical Industri...
64,326 followers
1w •

EFPIA is committed to a science-based phase-in of methods to reduce, refine and replace the use of animals. As part of our efforts, EFPIA has taken forward the #3 #Basket approach to support the European Commission in the creation of their #roadmap on the #phase #out of #animals in chemical safety #testing, to reduce reliance on animal testing in the pharmaceutical industry. Today, we are pleased to bring together stakeholders, the European Medicines Agency and the Commission

Exciting: European Commission adopts 3 Baskets

Elements of the roadmap – three baskets



Recommend short-term replacer

Prio
Exp
Rec

11

Elements of the roadmap – three baskets

- Currently, COM WGs on Human Health and Environmental Safety Assessments are identifying potential methods/approaches for 1st and 2nd basket and discuss the way forward to fill the 3rd basket
- Expectation for roadmap:
  - 1st basket: Recommendations for short-term replacements
  - 2nd basket: Recommendations for methods/approaches to be further developed or expanded
  - 3rd basket: Recommendations for performance criteria for future methods/approaches
    Identification of the necessary organisational structures for sustaining the development of animal-free system

→ **Introduction of recommendations into legislation to follow the normal processes (e.g. nt authorities subgroup under pharma legislation + legislative**

European Commission

Commission Workshops

3rd Com Workshop

- 16-17 June 2025, Helsinki
- Topic: Presentation of the draft roadmap
- Feedback from stakeholders on actions and milestones

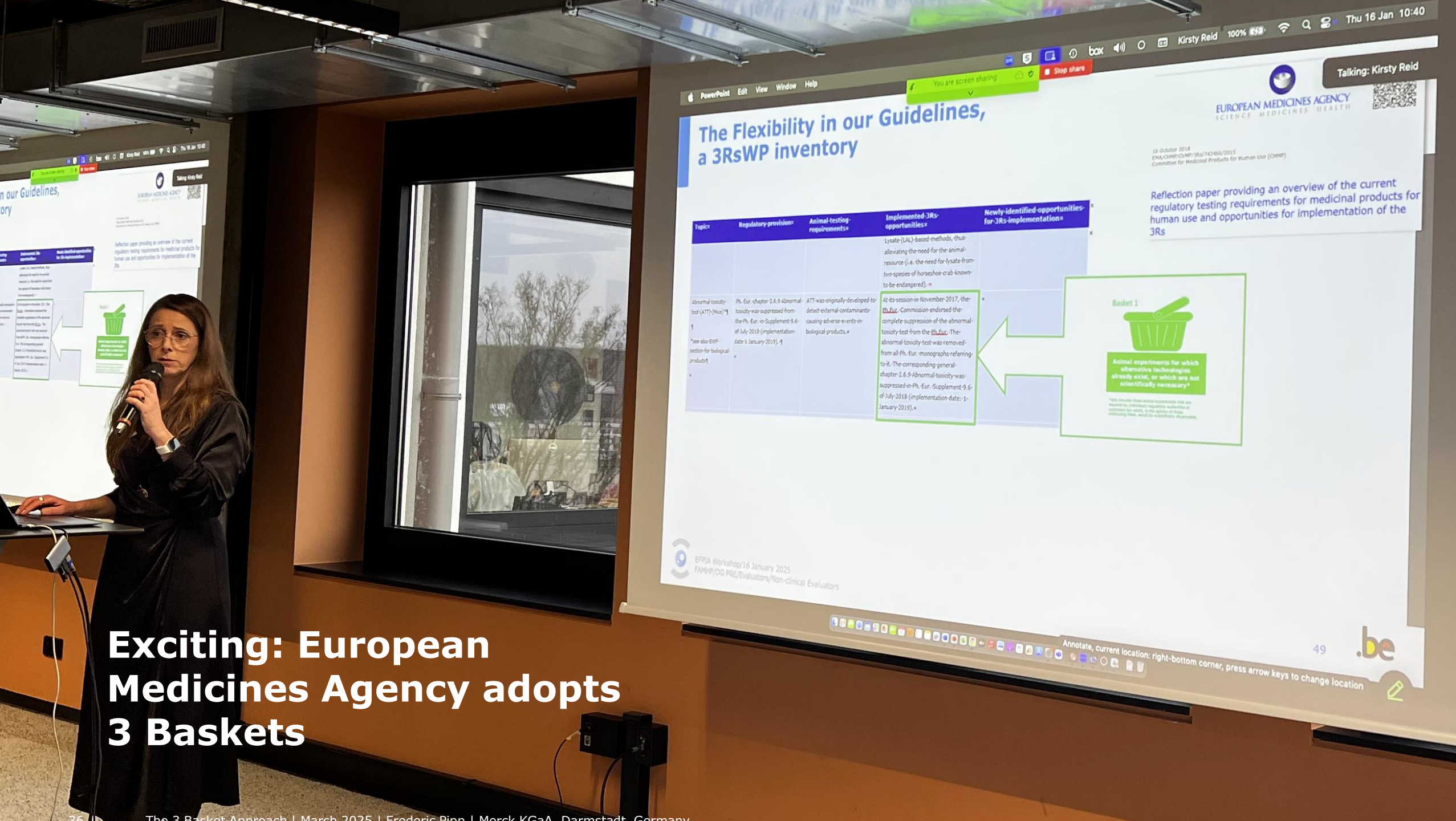
2nd Commission Workshop on 25 Oct. 2024

Report, pre-reads, presentations: https://single-market-economy.ec.europa.eu/events/roadmap-phasing-out-animal-testing-chemical-safety-assessments-second-workshop-2024-10-25_en

1st Commission Workshop on 11/12 Dec. 2023 together with PARC (NGRA route)

Report, presentations and recordings: https://op.europa.eu/en/publication-detail/-/publication/e350d987-3820-11ef-b441-01aa75ed71a1/language-en

European Commission



Exciting: European Medicines Agency adopts 3 Baskets

Exciting

WHO advocates for global acceptance of alternatives in QC

World Health Organization

WHO: DRAFT VERSION
ENGLISH ONLY

Guidelines on the phasing out of animal tests for the quality control of biological products

2024 WHO Draft Guideline for QC of Biologics

Guidelines on the phasing out of animal tests for the quality control of biological products

efpia
European Federation of Pharmaceutical Industries and Associations

Breaking news January 2025

Agencies align to help achieving global acceptance of replacements identified in Basket 1

EMA/27380/2024
Human Medicines Division

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

swissmedic

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Pmda 独立行政法人 医薬品医療機器総合機構 Pharmaceuticals and Medical Devices Agency

Santé Canada Health Canada

FDA U.S. FOOD & DRUG ADMINISTRATION

Terms of Reference (ToR) for the International Medicines Regulators' Working Group on 3Rs[1]

What brought us here did not bring us there.

Cardiac arrest
Multiple sclerosis
Stroke
Hypertension
Cancer
Dementia
Subarachnoid hemorrhage
Glioma/glioblastoma
Bladder cancer
Alzheimer's disease
Psoriasis
Addiction
Osteoarthritis
Traumatic brain injury
Spinal cord injury
Diabetes
Pain
Parkinson's disease
Spinal fusion surgery
Chemical burns
Epilepsy
ACL injury
Obesity
Degenerative disc disease
Bone regeneration
Anxiety
Inflammatory bowel disease
Intracerebral hemorrhage
Dyslipidemia
Meningioma
Musculoskeletal injuries
Atrial fibrillation
Cardiomyopathy
Cartilage defects
Head and neck cancer
Acute myocaridal infarction
Liver failure
Endometriosis
Soft-tissue injury
Gynecological cancer
Inhalation trauma
Pancreatitis
Cardiotoxicity
Fatty liver disease
Meniscal tears
ARDS
Laparoscopic liver surgery
Lung cancer
Leukemia
ALS
Wound infection
OCD
Effects of brain radiation
Cell transplantation

Prioritizing laboratory animal health means improving

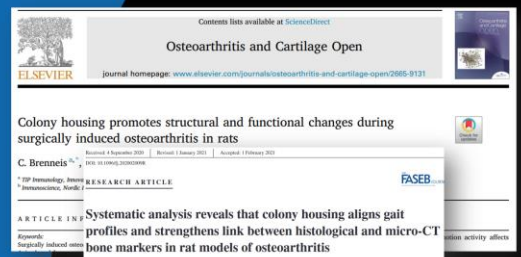
Today, more tha
developments i

70% fail becau
transferability
animal experim

- Lack of efficacy 40-50%
- Toxicity 30%

Sun et al. Acta Pharm Sin B. 2022 Jul; 12(7): 3049–3062.

>150 publications confirm the negative effects of laboratory animal housing systems and stress-inducing handling of animals,


Contents lists available at ScienceDirect

Osteoarthritis and Cartilage Open

journal homepage: www.elsevier.com/journals/osteoarthritis-and-cartilage-open/2665-9131

Colony housing promotes structural and functional changes during surgically induced osteoarthritis in rats

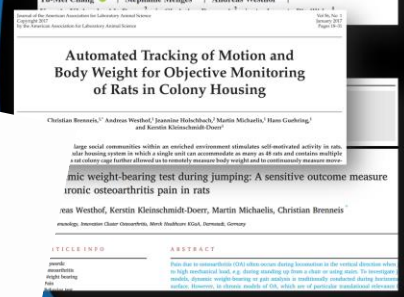
C. Brenneis

RESEARCH ARTICLE

FASEB

Systematic analysis reveals that colony housing aligns gait profiles and strengthens link between histological and micro-CT bone markers in rat models of osteoarthritis

Yu-Mei Chang | Stephanie Menges | Andreas Westhof


Automated Tracking of Motion and Body Weight for Objective Monitoring of Rats in Colony Housing

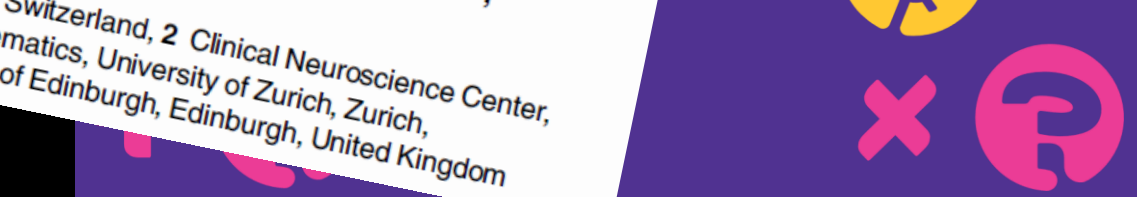
Christian Brenneis, Andreas Westhof, Jeannine Holschbach, Martin Michaelis, Hans Gaebeling and Kerstin Kleinschmidt-Doerr

mic weight-bearing test during jumping: A sensitive outcome measure
ronic osteoarthritis pain in rats

eas Westhof, Kerstin Kleinschmidt-Doerr, Martin Michaelis, Christian Brenneis

ARTICLE INFO

ABSTRACT



META-RESEARCH ARTICLE

Analysis of animal-to-human translation shows that only 5% of animal-tested therapeutic interventions obtain regulatory approval for human applications

Benjamin V. Ineichen[1,2*], **Eva Furrer**[1], **Servan L. Grüninger**[1,3], **Wolfgang E. Zürrer**[1], **Malcolm R. Macleod**[4]

1 Centre for Reproducible Science, University of Zurich, Zurich, Switzerland, **2** Clinical Neuroscience Center, University of Zurich, Zurich, Switzerland, **3** Department of Mathematics, University of Zurich, Zurich, Switzerland, **4** Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh, United Kingdom

Health is not only not sick

Every species has specific basic needs.

The Marseille Declaration improves conditions for lab animals globally

Join Us in Prioritizing Animal Welfare

Together we

PRIORITIZE
Animal Welfare

and signed the Declaration of Marseille on Animal Welfare Standards

Merck KGaA, novo nordisk, sanofi, NOVARTIS, LEO, Lundbeck, ascendis pharma

Signatory Contract Research Organizations:

BioReliance, EyeCRO, preclinics, NUVISAN

- 6/13/22 FELASA Meeting guiding coalition
- 9/08/22 EFPIA RAW Presentation
- 9/09/22 Signature of Version 1 by Merck, Sanofi, Novo Nordisk and Novartis
- 3/27/23 Signature Leo Pharma, Lundbeck
- 8/11/23 Signature EyeCRO
- 10/5/23 Signature Preclinics GmbH
- 26/3/24 Signature Nuvisan
- 17/6/24 Signature Ascendis

Steve Hoffmann

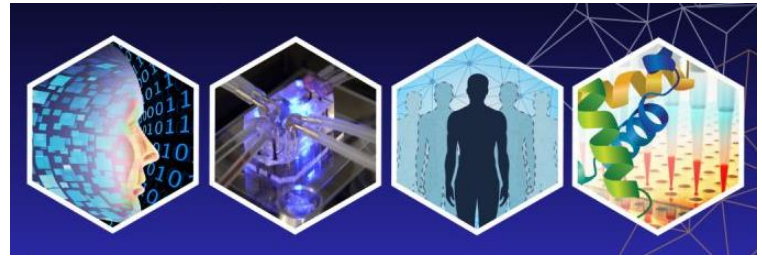
Vice President, Science Partnerships, Translational Science

Foundation for the National Institutes of Health

NIH/FNIH Public-Private Partnership

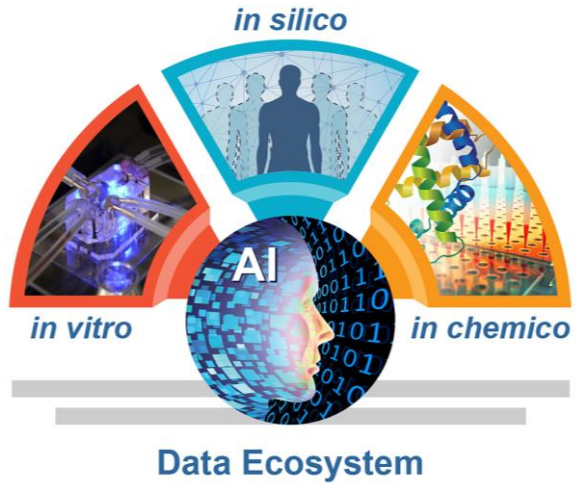
Validation and Qualification Network (VQN) for the Adoption and Implementation of New Approach Methodologies (NAMs)

- Developing an NIH/FNIH Public-Private Partnership to bring industry, NGOs, non-profits, etc. into the network leveraging existing FNIH PPP infrastructure
- Pre-competitive data sharing and potentially supporting validation activities across labs and locations for specific use cases for implementation
- Support community outreach and training
- Provide a fluid funnel for potential solutions which may be developed through the comprehensive centers
- Include additional Federal partners
- Synergize and coordinate with other global activities on NAMs



Goals of the Complement Animal Research In Experimentation Program **(Complement-ARIE)**

Purpose: To catalyze the development, standardization, validation and use of **human-based new approach methodologies (NAMs)** that will transform the way we do basic, translational, and clinical sciences

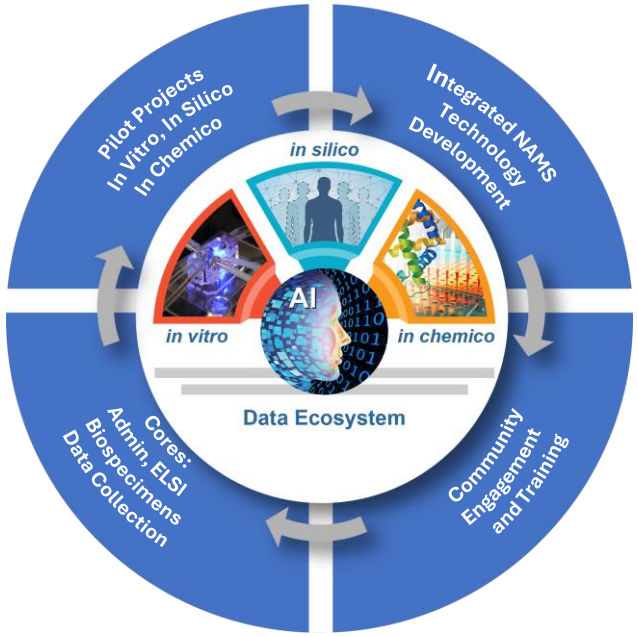


Goals:

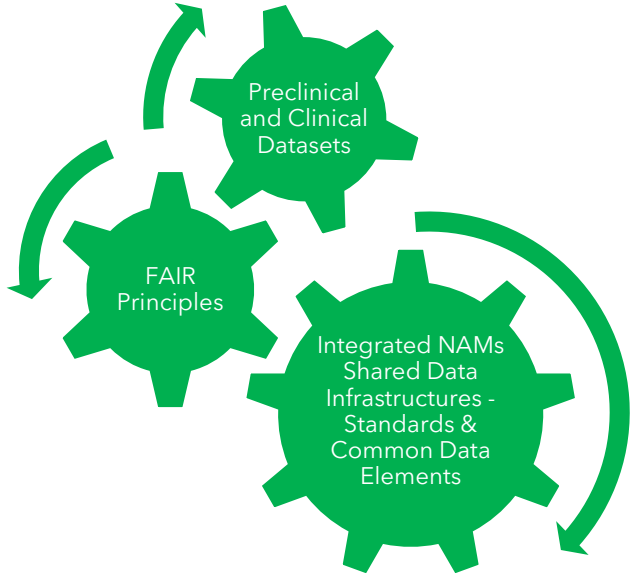
1. Better model and **understand human health and disease** outcomes **across diverse populations**.
2. Develop NAMs that **provide insight into specific biological processes** or disease states.
3. Validate mature NAMs to **support regulatory use** and standardization.
4. Complement traditional models and **make biomedical research more efficient and effective**.

Summary: Complement-ARIE Consortium

NAMs Tech Dev Centers

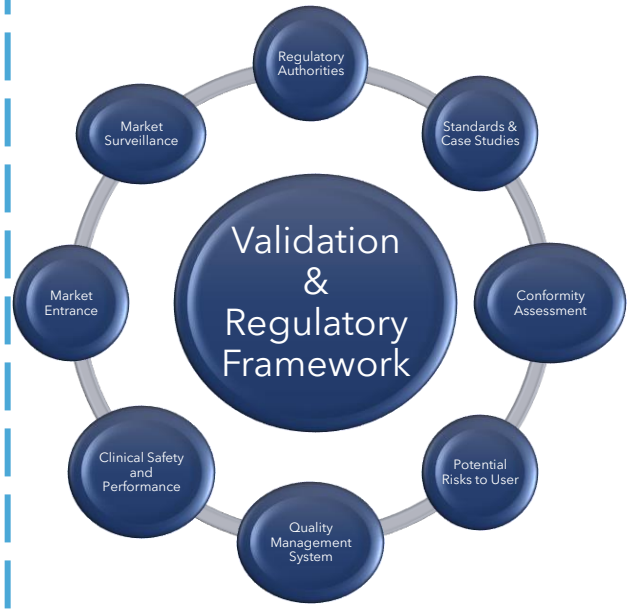


NAMs Data Hub and Coordinating Center



Validation and Qualification Network

FNIH

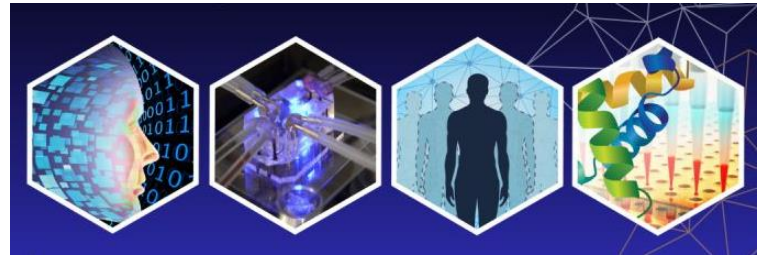


- Regulatory Partners
- Industry Partners
- ICCVAM/Other Agencies
- International Partners
- Non-Profits
- Other end users

FNIH

Validation and Qualification Network (VQN) will:

- Accelerate the implementation and adoption of NAMs in research and regulatory contexts by **ensuring NAMs are robust, reliable, and reproducible**
- Demonstrate **biological relevance of NAMs** to ensure each NAM is “fit for purpose”
- Multi-pronged approach:
  - Replication of key experiments
  - Establish common data elements and standardized reporting
  - Ensure NAMs have well-described protocols
  - Conduct quality assessment



VQN Timeline: A Phased Approach

1

DESIGN
(FY25)

- Plan, develop network with Industry, NGOs, CROs and fed partners
- Determine scope of validation efforts
- Develop governance/criteria selection of use cases
- Workshops with stakeholders

2

IMPLEMENTATION
Phase I
(FY26-30)

- Implement validation efforts with partners
- Select and fund 4-8 Use Case Validation studies
- Bi-annual reporting
- Coordinate with other Complement-ARIE components

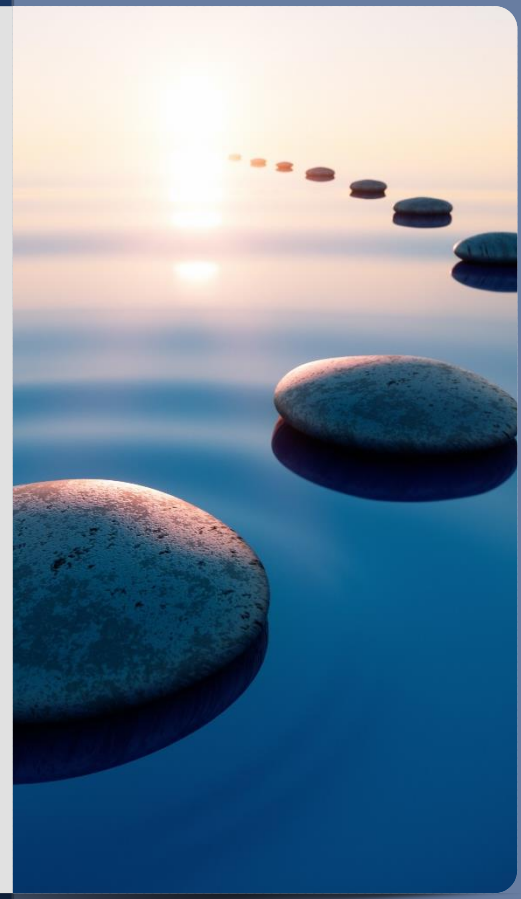
3

IMPLEMENTATION
PHASE II
(FY31-35)

- Nominate mature NAMs from Complement-ARIE for Validation Network
- Apply reporting standards to new NAMs from Complement-ARIE
- Foster interactions between researchers and regulators/industry
- Training opportunities with partner orgs

FNIH

Challenges for industry and next steps forward



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Amanda Roache

Deputy Vice President

Science and Regulatory Advocacy

P*h*RMA

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Discussion

Rhiannon David, Director, Microphysiological Systems in Clinical Pharmacology and Safety Sciences, AstraZeneca

Steven Hoffmann, Vice President, Science Partnerships, Translational Science, Foundation for the National Institutes of Health

Frederic Christian Pipp, DVM, Global Animal Welfare Officer, Merck KGaA

Amanda Roache, Deputy Vice President, Science and Regulatory Advocacy, PhRMA

Moderated by **Maria Apostolaros**, Deputy Vice President, Science and Regulatory Advocacy, PhRMA

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