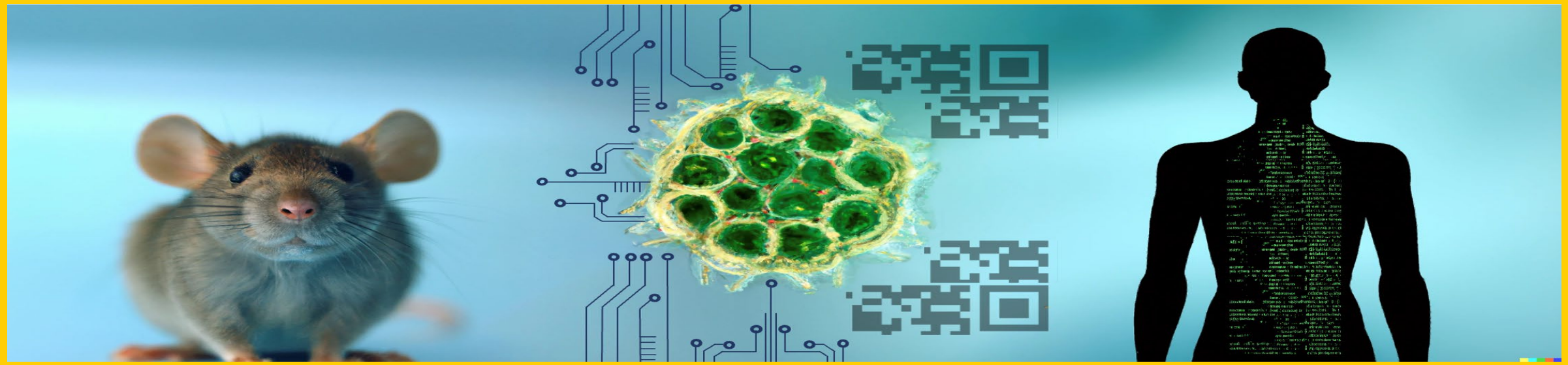
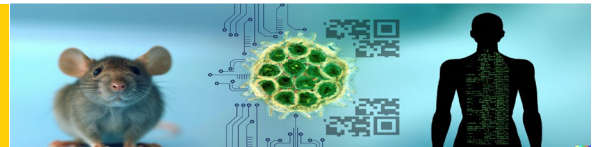
Beyond the hype: what are NAMs?
- and what is their place in biomedical research?

Jeffrey Bajramovic



Overview presentation

- What are NAMs?
  - Acronym use – confusion and history
  - Recent definitions
- NAMs and the 3Rs
  - NAMs and Replacement
  - NAMs vs animal research?
- The place for NAMs in biomedical research
  - Learning from toxicology
  - COPs



What are NAMs?

- and why should we care

Technological capability

Organoids, organ-on-chip, microfluidics, 3D bioprinting, AI, and bioinformatics now enable richer target-species models

Policy support

Recent policy signals, including FDA Modernization Act 2.0 and ECHA/EU initiatives, support animal-free or animal-reduced approaches

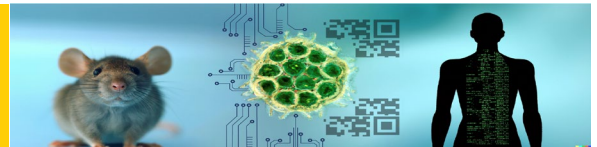
Momentum to move away from animal reliance

Human relevance

Target-species data can reduce the need for interspecies extrapolation that often limits translational value

Ethical imperative

Reducing dependence on experimental animals aligns with humane science while preserving rigor



Based on: Ahluwalia et al. (2026), Lab Animal
doi.org/10.1038/s41684-026-01731-8

What are NAMs?

- and why should we care

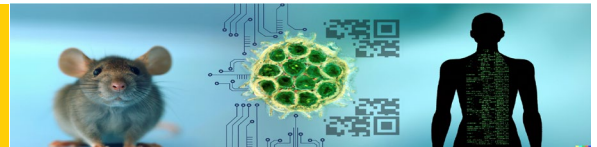
Never-ending acronym madness

New Approach Methodologies
New Approach Methods
Non-Animal Methods
Non-Animal Models
Novel Alternative Methods
New Alternative Methods

Definitions differ across organizations

ECHA/EFSA/FDA	Often centered on chemical safety, toxicity, and regulatory use
NC3Rs/3RsCs	Often connected to replacement or non-animal methods more broadly
NIH working group	Initial focus on in silico, in chemico, and in vitro approaches
EPA	Any approach for hazard/risk assessment that avoids intact animals

Risk: overgeneralization can enable misuse, greenwashing, or marketing claims and undermine credibility



LaFollette, M. et al. (2026). NAM Journal
doi: 10.1016/j.namjnl.2026.100085

What are NAMs?

- a bit of history

NAMs: From toxicology and regulatory science to broader biomedical research

2007
NRC report "Toxicity Testing in the 21st Century"

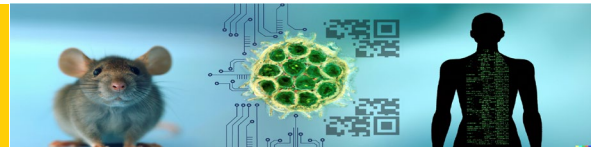
2016
ECHA workshop coins/uses "NAMs" in regulatory science

2022+
Policy milestones expand acceptance of non-animal approaches

2025-26
Broader debate about definitions, scope, and 3Rs

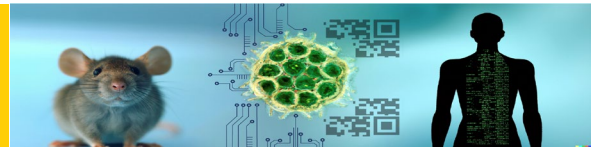
Why it spread

Successes such as QSAR and read-across helped build interest beyond toxicology



Recent definitions

- *"**New Approach Methodologies (NAMs)** are technologies that do not directly involve live animals and that generate mechanistic or predictive information to advance biological understanding or support decisions related to human, animal, or environmental health. They usually rely on target-species data, cells, tissues, or computational approaches, and may — but do not necessarily — contribute to the 3Rs"*



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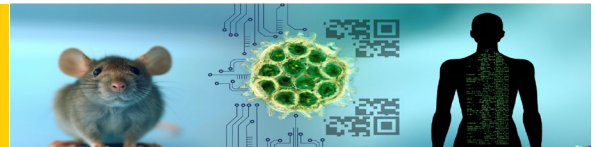
- *"**NAMs** are species-specific methodologies, excluding the use of living animals"*



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“NAMs are species-specific methodologies - not including the use of living animals”

Species-specificity is the core criterion. *Important boundary: using a living whole organism - even the target species - does not qualify as a NAM under this definition.*

Direct relevance

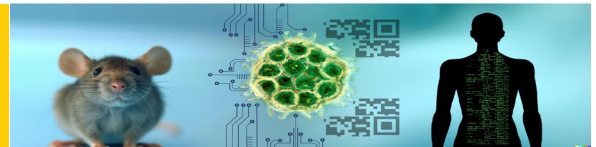
NAMs should produce data directly relevant to the target species - for example, human data for human disease or human toxicology questions

No interspecies extrapolation

NAMs avoid relying on animal-to-human or cross-species translation; intermethod extrapolation may still be needed

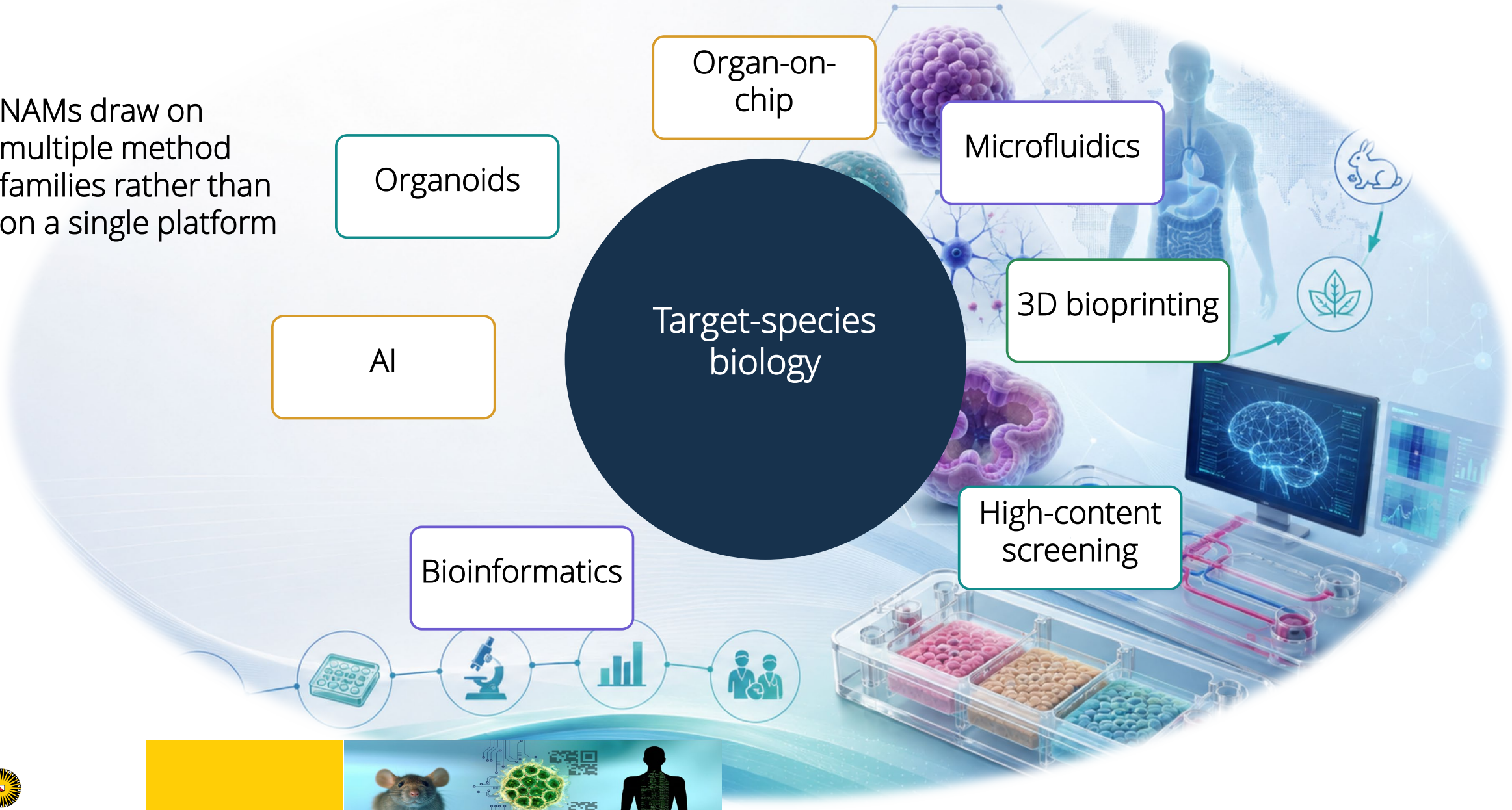
Beyond toxicology

The definition applies to basic, applied, translational, preclinical, and regulatory research



New technologies drive the development of NAMs

NAMs draw on multiple method families rather than on a single platform



What NAMs add scientifically

Deep mechanistic understanding

NAMs can interrogate human-specific or target-species-specific mechanisms that animal models may not capture

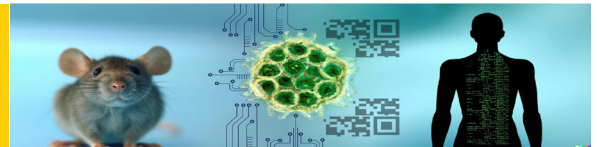
Dynamic systems views

High-content screening and systems biology can track dynamic cell-state changes, signaling, and interactions over time

Regulatory precision

Human-centered or target-species-centered data can improve relevance for risk assessment, therapeutics, and translational decisions

Example: Toll-like Receptor (TLR)7/8-mediated signaling differs across species, so primary human PBMC systems can reveal immune activation patterns that animal models fail to reproduce



Some practical examples

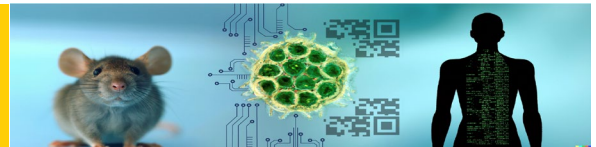
Core test: target species + no living animal + no interspecies extrapolation

NAM

- Human-derived *in vitro* systems for human disease or toxicity questions
- *In silico* models built from target-species data
- Organoids/organ-on-chip models that use target-species material
- Approaches that avoid living animals and minimize interspecies extrapolation

NoNAM

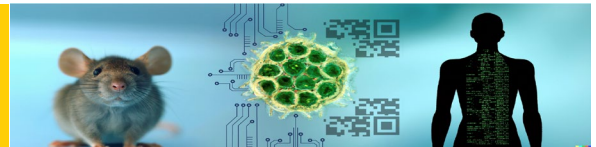
- Non-human animal models for human questions, including zebrafish or insects
- Microdosing in dogs for canine compounds: species-specific, but living animals
- Human volunteer microdosing: may replace animals, but uses living humans
- Animal-derived *in vivo* datasets used as the core basis for human prediction



NAMs and the 3Rs

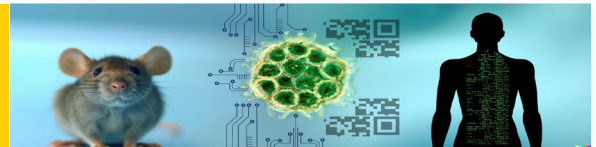
Russell and Burch's original definition of the 3Rs:

- Replacement: *any scientific method employing non-sentient material which may in the history of animal experimentation replace methods which use conscious living vertebrates*
- Reduction: *means of minimising, other than by Replacement, the number of animals used to obtain information of a given amount and precision*
- Refinement: *measures leading to a decrease in the incidence or severity of inhumane procedures applied to those animals which have to be used*



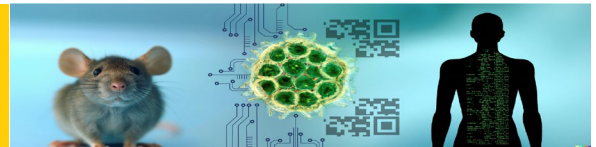
NAMs represent another vantage point

- The **vantage point is not the animal** (Replacement), but the **target species**
- If your **target species is human**, this excludes the use of experimental animals
- How are NAMs and Replacement related?



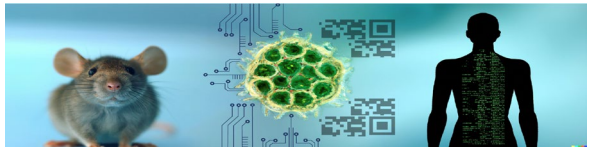
NAMs and the 3Rs are related - but not identical

NAM \ Replacement	No	Yes
No	Canine *in vivo* imaging to reduce animal use in a canine cancer model	Human volunteer microdosing studies, if they replace animal experiments
Yes	Human *in vitro* systems for a disease where no animal model exists	Human stem-cell based *in vitro* systems used instead of rodent *in vivo* disease studies



Unused potential

- The 3Rs are rooted in **laboratory animal science**, whereas NAMs researchers and developers are often more **focused on technological advances**
- **NAMs** are rarely developed to **Replace** animals, but rather to provide insight in (species-specific) biological processes
- **One NAM ≠ one animal**
- There is a risk that NAMs that have been developed, will **not be tested for their potential to Replace** animal experiments



Tracking NAMs and building the ecosystem

BioMedModelHub (BimmoH)

EURL-ECVAM resource using ML to identify biomedical models with translational potential

SMAFIRA

International PubMed library curated by German Federal Institute for Risk Assessment

NAT Database

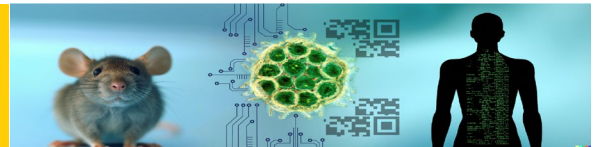
International non-animal technologies database by Doctors Against Animal Experiments

TSAR

EURL-ECVAM tracking system for regulatory acceptance of alternative methods

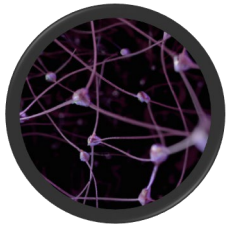
RE-Place

Alternative methods database; mostly Belgium



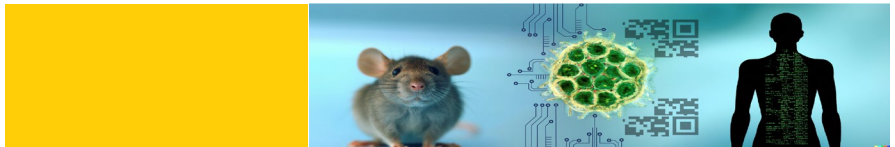
Rephrasing research questions!

Animal Welfare Body Utrecht



One NAM ≠ one animal

- What physiological process(es) are you interested in in particular?
  Define them as exact as possible, also your read-out methods or proxies thereof
- What would you need in order to replace (part of) your *in vivo* experiments by NAMs?
  Think not only of -nearly- existing methods, but define your needs as exact as possible
- If you would have the resources, what could and would you do to develop/implement NAMs in the near future?
- Would you be interested to be involved in, or to perform, parallel studies to assess the utility/applicability of NAMs?



Suppo^{3}Rt

- With the rapid advances in technological innovations, **knowledge about NAMs** is becoming **more complicated to keep up-to-date** in e.g. databases

- **Rather than** a database for **NAMs technology**, this initiative therefore focuses on **NAMs experts**

- A **staffed helpdesk to facilitate access to NAMs expertise** (supported by the **TPI** program of the **Dutch ministry of LVVN**)

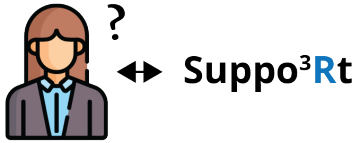
- Suppo^{3}Rt draws from a **pool of international NAMs experts** (recently developed under the **EU COST action IMP$_3$ROVE**)

IMP$_3$ROVE

NAMs Expert Pool	Personal data			Expertise								
				In vitro								
Name and title	Email addre	Full affiliatic	Country of residence	Tissue/Orga	Cell type(s	Species	Method(s)	*In vivo (Y/N*	*Ex vivo (Y/N*	*In silico (Y/N*	Keywords (e.g. process, diseas	Basic or Applied Research (B/A or both)

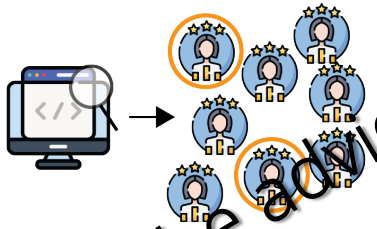
Suppo³Rt

Step 1: Question definition



You have a question about NAMs and contact Suppo³Rt; we plan an intake with you

Step 2: Seek experts



We search our NAMs Expert Database from EU COST Action IMP³ROVE and select one or more experts

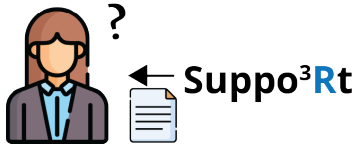
Step 3: NDA

You, the expert(s) and Suppo³Rt sign NDAs to ensure complete confidentiality

Step 4: Discuss

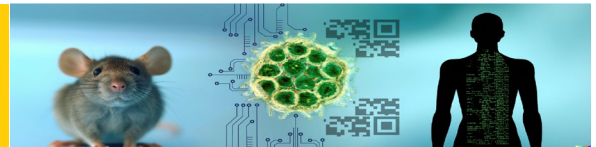
We bring you together with the expert(s) where Suppo³Rt acts as a moderator

Step 5: Advice



The conversation results in a confidential and non-binding advice

The entire process, including the advice, is confidential



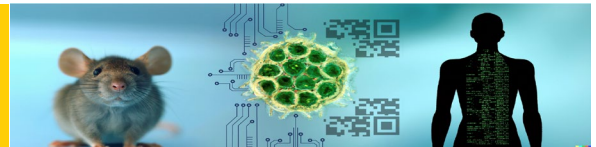
Suppo^{3}Rt

- Recently, we discussed a research proposal with researchers from the University Medical Center Utrecht in which they studied the **restoration of auditory function (deafness).** To do so, mouse experiments were proposed

- While discussing their proposal we took **a different approach** and helped them to dissect their research questions. We did so by focusing on the **processes involved** in their research **rather than by focusing on the clinical outcome**

- This approach helped to **uncover the two major processe**s they were interested in, i.e. the potential of stem cells to differentiate into functional hair cells and the restoration of neuronal connectivity in the inner ear. For **these processes NAMs could be identified**, and **contacts were made with researchers with hands-on expertise**

- We are conducting **case studies** with **end-users (funders, ethical committees, animal welfare bodies, researchers)** to test the added value and functioning of Suppo^{3}Rt



NAMs vs animal research?

- It is important to acknowledge that the aspiration to **reduce/replace** animal use in research carries **independent ethical weight** that extends beyond translational performance, but we should move beyond the **false dichotomy** of NAMs versus animal studies toward an integrated, context-of-use framework

- A biologically relevant model is **not defined by its type**, but by **its fitness for a specific purpose** and biological scope – scientifically, it is not a binary choice between one or the other

- Context-of-use as the governing framework (different questions ask for different approaches)

1. Separate problems

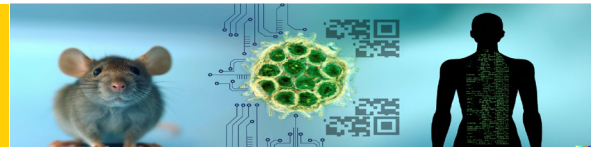
Chemical hazard assessment has a throughput problem; drug development has a translation, mechanism, and decision problem

2. Improve all tools

Both animal and non-animal models need better endpoints, exposure relevance, design rigor, and validation

3. Build evidence

Use model combinations to resolve stage-gate uncertainty for patients, rather than forcing platform substitution

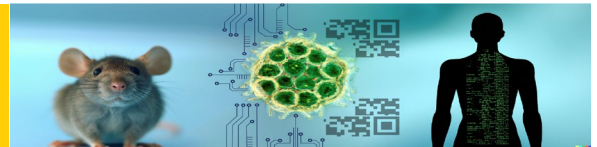


Gaburro, S. et al. *Submitted for publication*

Context-of-use: the governing framework

- Start with the decision, then choose the biology, model, endpoint, and validation standard
- This logic applies equally to animal, *in vitro, in silico*, and hybrid approaches
- The imperative is ethical, the tools scientific

Decision	Biology	Model(s)	Endpoints	Validation
What stage-gate or regulatory choice must the study support?	Which mechanisms and biological scope are relevant?	Which platform or combination captures those mechanisms?	What objective readouts anchor the biology?	How much confidence is needed for this decision?



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The place for NAMs in biomedical research

- Different fields and questions require different approaches, but can we also learn from the successful implementations?

- Toxicology has advanced NAM adoption, but applied and translational biomedical research (roughly 70% of the EU animal use) has not kept pace

TOXICOLOGY

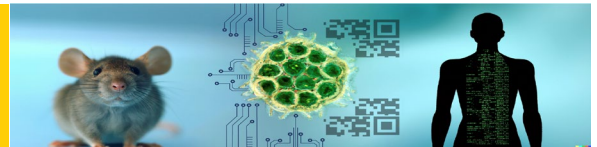
Systematic progress

- Regulatory mandates and dedicated funding accelerated NAM development
- Standardized frameworks helped structure method use
- AOPs shifted emphasis from apical animal endpoints to mechanisms
- NAMs are often linked to chemical safety assessment

BIOMEDICAL RESEARCH

High potential, slower uptake

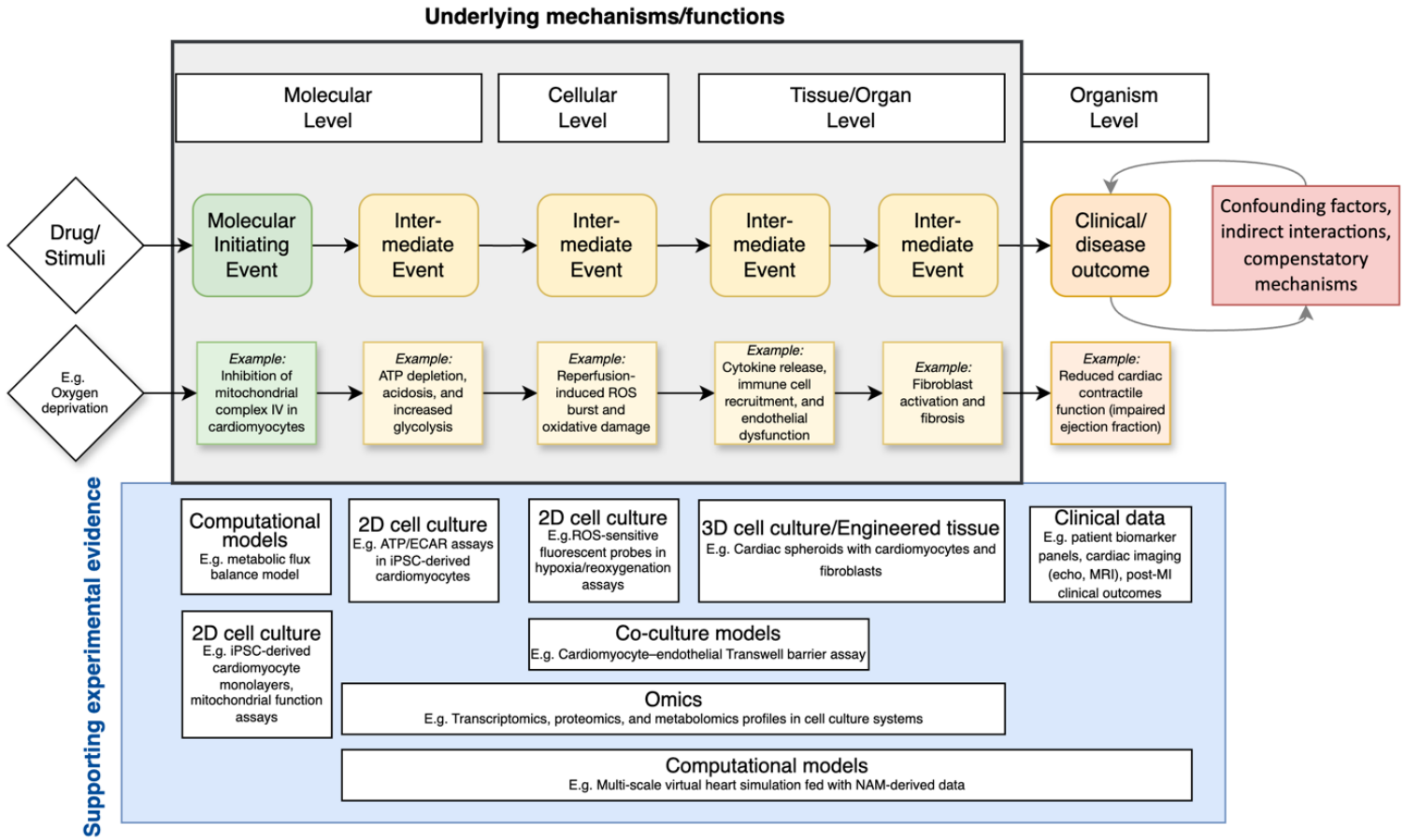
- Basic, applied, and translational studies still rely heavily on animals
- Biomedical goals include disease mechanisms, therapies, efficacy, and biomarkers
- Models must address complex, interacting human biology
- The research culture and incentives are harder to change



Schaffert, A. et al. *In press*.

Clinical outcome pathways (COP)

COPs can help match NAMs to mechanisms, evidence gaps, and clinically meaningful outcomes.

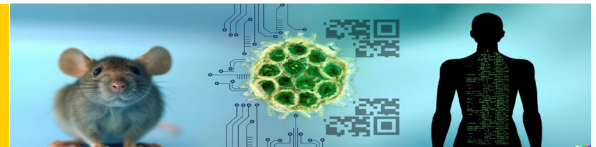


What COPs do

Link molecular initiating events to intermediate events and clinical or disease outcomes across biological levels

Why this will advance NAM uptake

Clarifies which mechanism a NAM should capture, how readouts fit into disease biology, and where model gaps remain



Schaffert, A. et al. *In press*.

A stepwise transition from complimentarity to core-use

- Create a deliberate pause between the biological question and the selection of experimental models
- The path is not **forced substitution**; it is **evidence-guided integration** and gradual confidence building

Step 1

Expand collaboration

Bring together animal-model users, NAM users, engineers, clinicians, and method developers

Step 2

Run parallel studies

Compare NAMs alongside animal models to identify strengths, discrepancies, and species-specific differences

Step 3

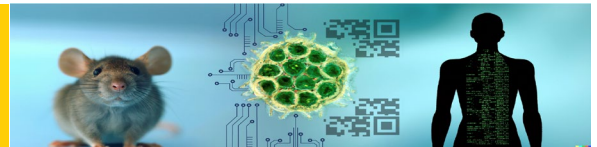
Evaluate relevance

Use comparative evidence, systematic reviews, and meta-analyses to identify where NAMs match animal models or human relevant data

Step 4

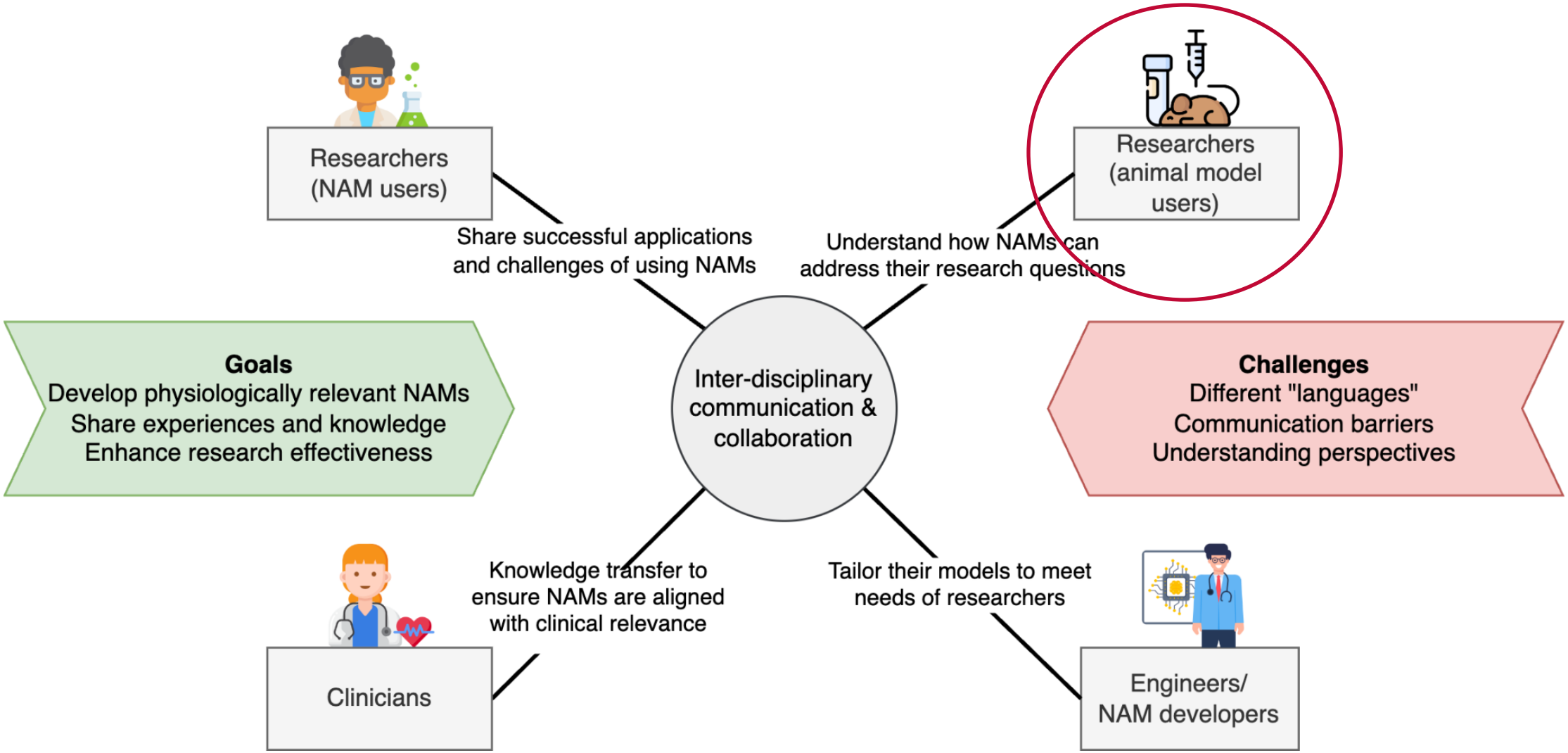
Invest in infrastructure

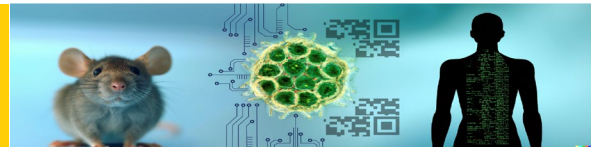
Fund NAM-focused work, shared resource centers, education, training, and accessible technologies



Schaffert, A. et al. *In press.*

Collaboration is the implementation engine





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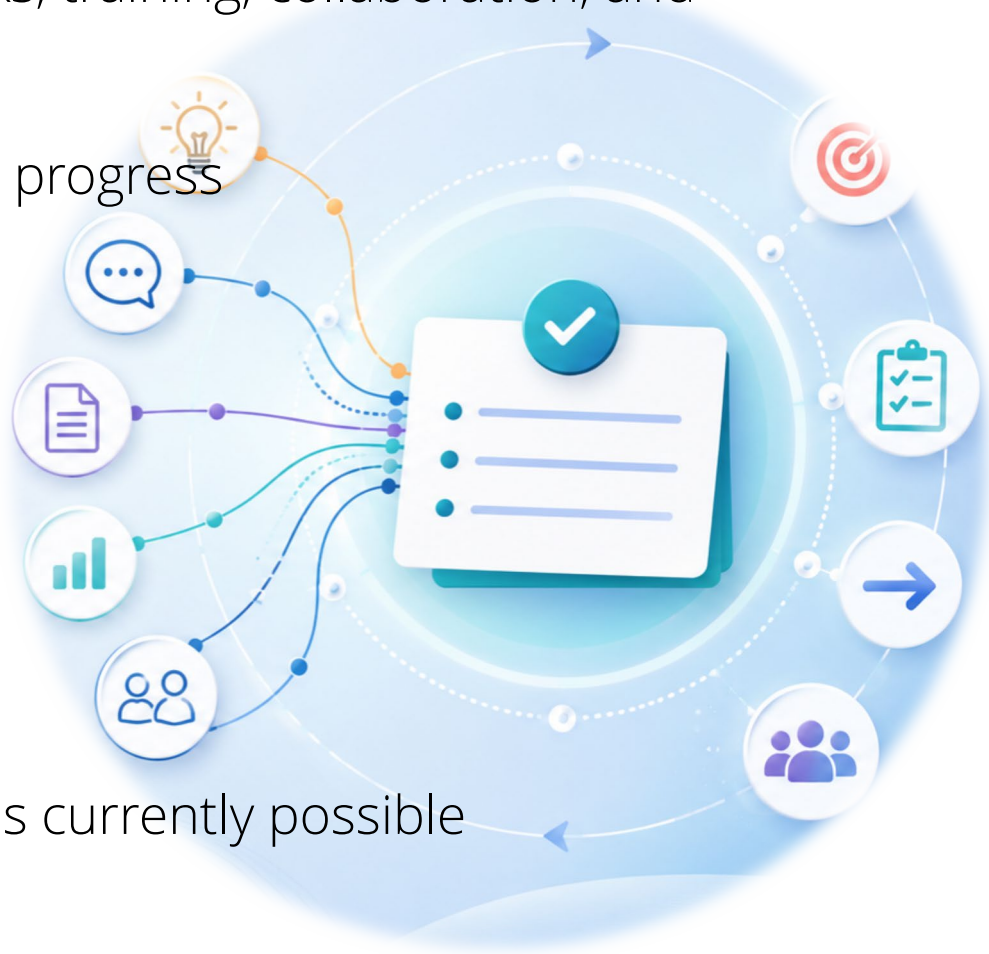
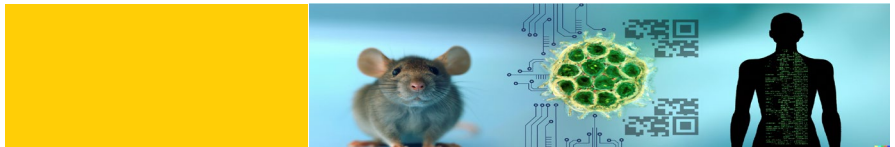
Take home messages

- NAMs can advance basic and translational biomedical research by generating human-relevant mechanistic data, but adoption requires frameworks, training, collaboration, and sustained investment
- NAMs vs animals is a **non-productive dichotomy** that blocks progress
- NAMs can complement the 3Rs toolbox
- Define **context-of-use**, and be fair about limitations
- **Rephrase** research questions
- Apply scientific rigor to all models, be realistic
- **COPs** may help to extend the use of NAMs beyond purposes currently possible
- **Work together with LAS – bridge LAS and NAMs/MPS fields**





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Sharing science, *shaping tomorrow*

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DANONE
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