In finite opportunities
in long-term-safety

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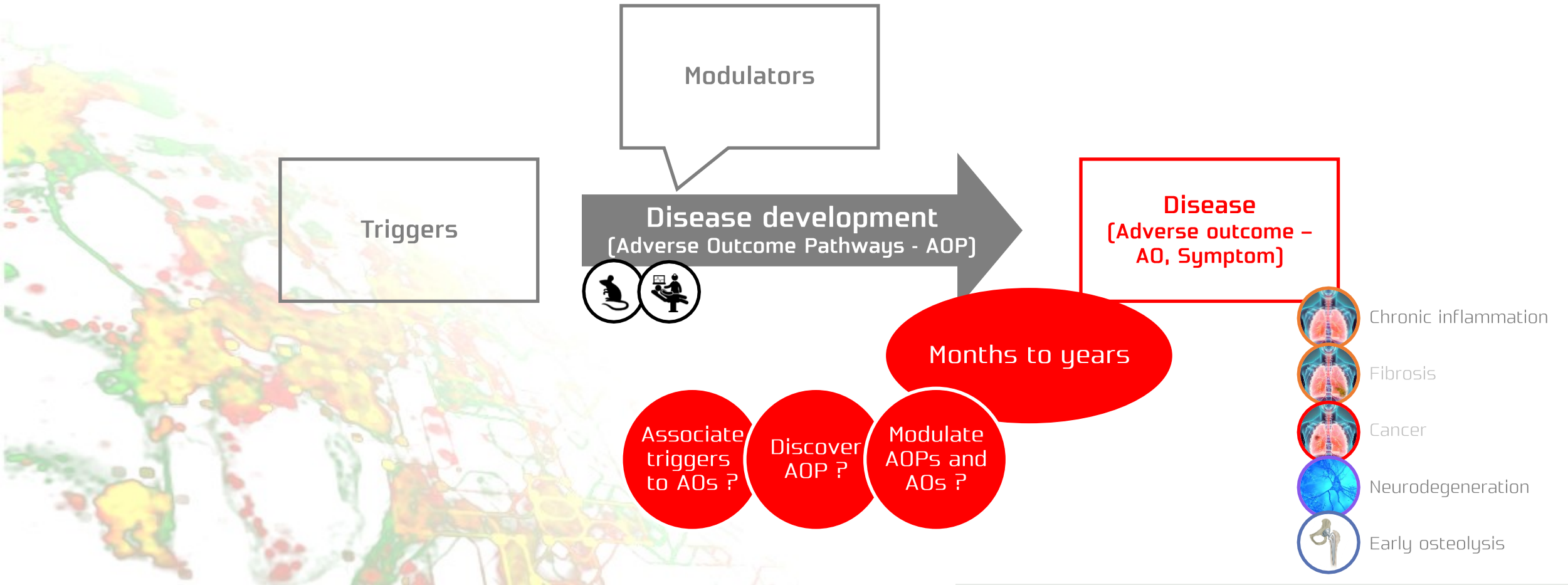
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Slowly-evolving disease prediction challenge – **evolution time**!

Modulators

Triggers

Disease development
(Adverse Outcome Pathways - AOP)

Disease
(Adverse outcome – AO, Symptom)

Months to years

Associate triggers to AOs ?

Discover AOP ?

Modulate AOPs and AOs ?

Chronic inflammation

Fibrosis

Cancer

Neurodegeneration

Early osteolysis

In finite prediction of slowly-evolving diseases – ahead of time!

Modulators

Triggers

AOP

In vitro → In silico

$\frac{d\vec{q}}{dt} = \underline{M}\vec{q}$

Disease

1 week

Chronic inflammation

Fibrosis

Cancer

Neurodegeneration

Early osteolysis

μIND™ engine
by Infinite

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Challenge

About us

Possible types of triggers and modulators

Modulators

Triggers

AOP

In vitro | In silico

Concept of solution

In vitro models

Early event monitoring

In silico model

$$\frac{d\vec{q}}{dt} = M\vec{q}$$

Validation

Possible types of applications

Workplace safety

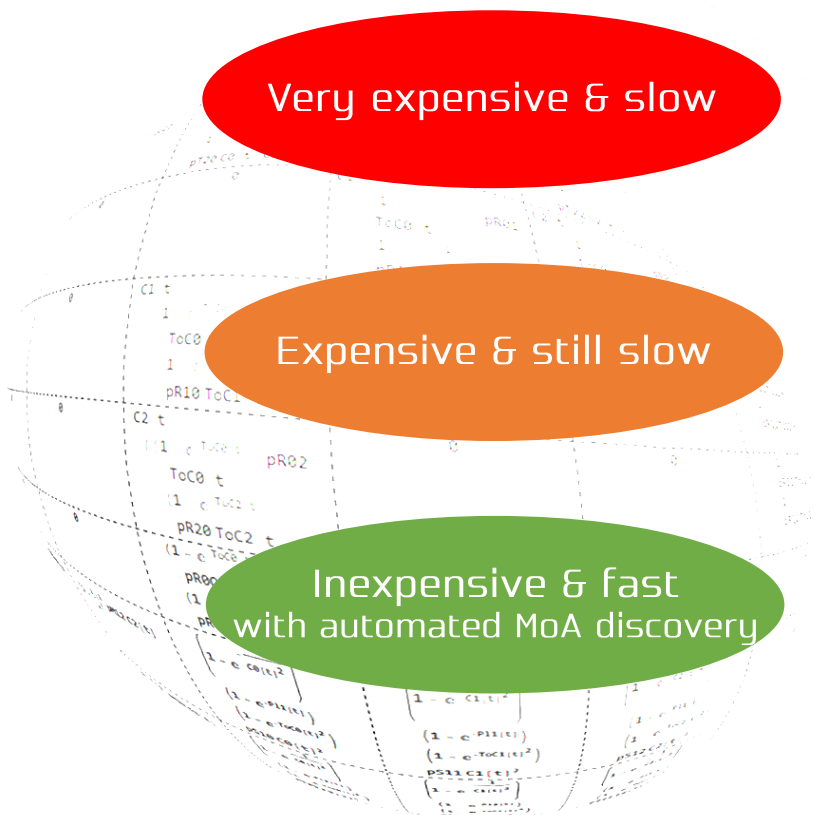Long-term health safety

Safe-by-design in R&D

Disease
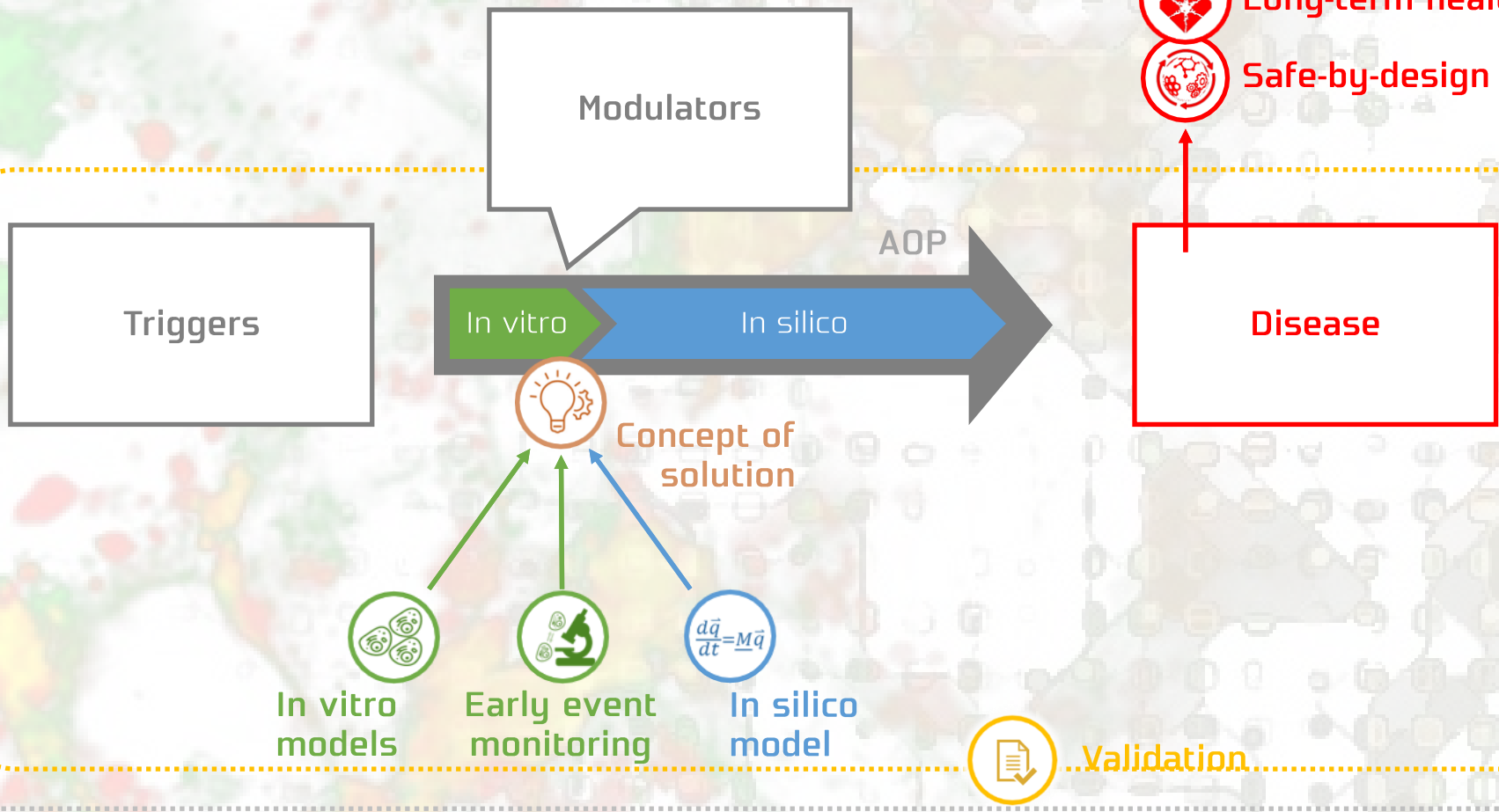
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Proof-of-Concept

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What is prediction ahead of time based on?

Modulators

Triggers

unknown | known parts of AOP

Adverse outcomes

Our solution
proof-of-concept

All possible
solutions
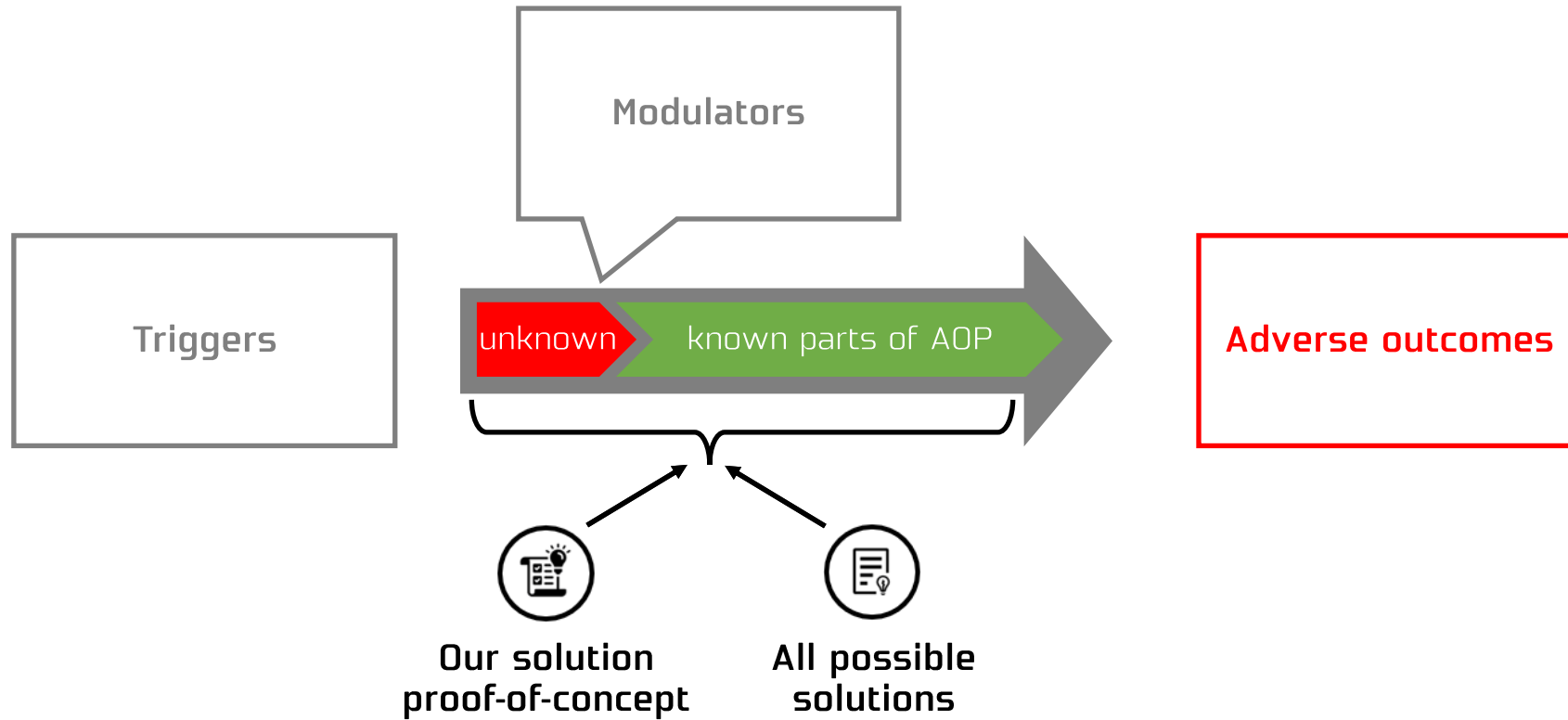
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What are possible ways to predict slowly-evolving diseases?

Very expensive & slow

AOP

Adverse outcomes

Expensive & still slow

AOP

Organ-on-chip / organoids

Adverse outcomes

Inexpensive & fast
with automated MoA discovery

AOP

In vitro | In silico

$$\frac{d\vec{q}}{dt} = M\vec{q}$$

Adverse outcomes
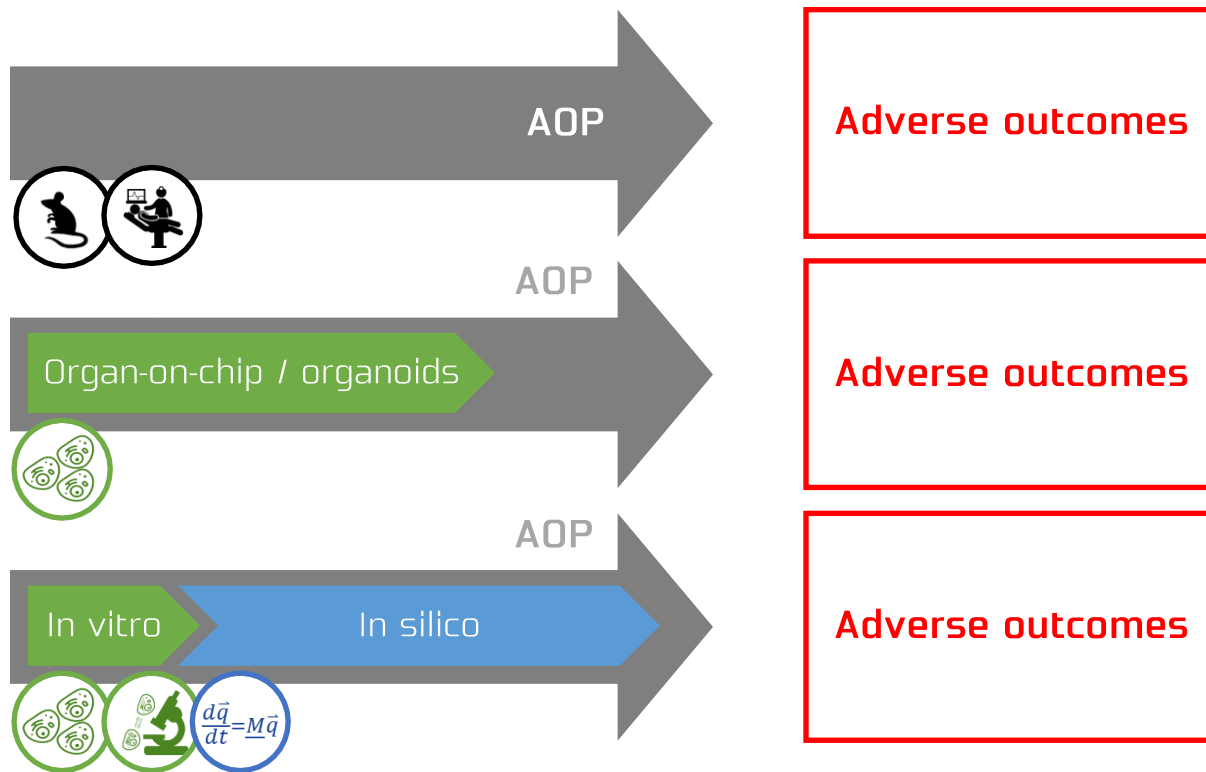
μIND™ engine
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Where the proof of concept originate?

Nanomaterial inhalation

Inflammation prediction

Unraveling the mode-of-action

In vitro Probing & *in silico* Modeling

SmartNanoTox
Smart Tools for Gauging Nano Hazards
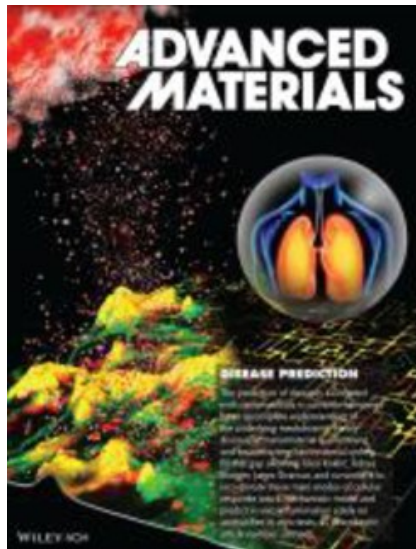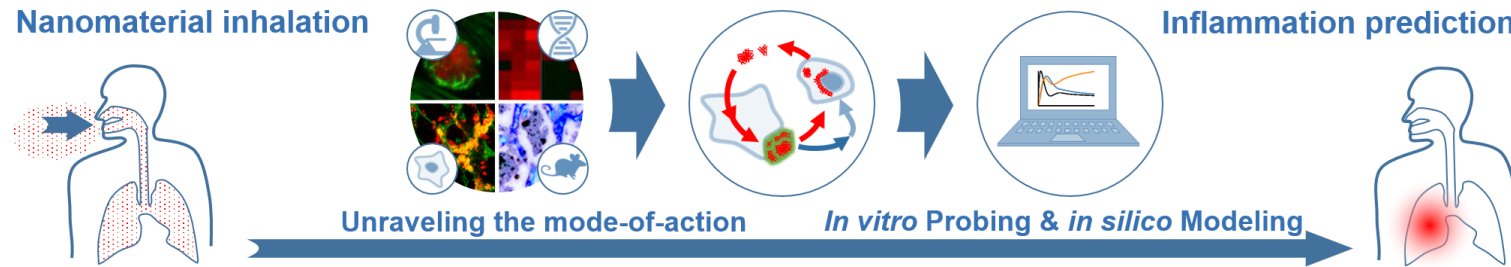
1. Discovered quarantining and cycling of a material after single exposure that drives chronic response
2. While knowing the MoA, used the mathematical system to predict the response relying only on in vitro measurements

Problem - resources spent:
- **2 years**, 36 researchers, 34 exp.methods on in vitro and in vivo, 290 pages of supp.info, 200GB time lapse movies, huge amount of omics,
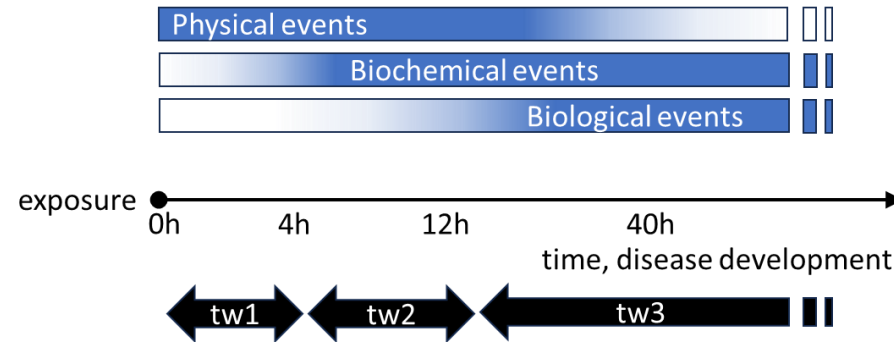 **2 MIO EUR**

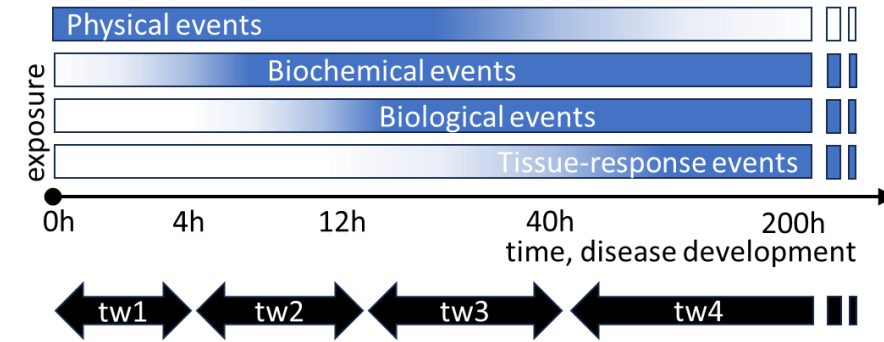Kokot et al. Adv.Mat. 2020, 32, 47, 2070353

In vitro models

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How we select in vitro cellular models?

Cells able to express events

- *In finite* perception of the relevant model:
  - Ability to express and mimic AOP to reach days time scale
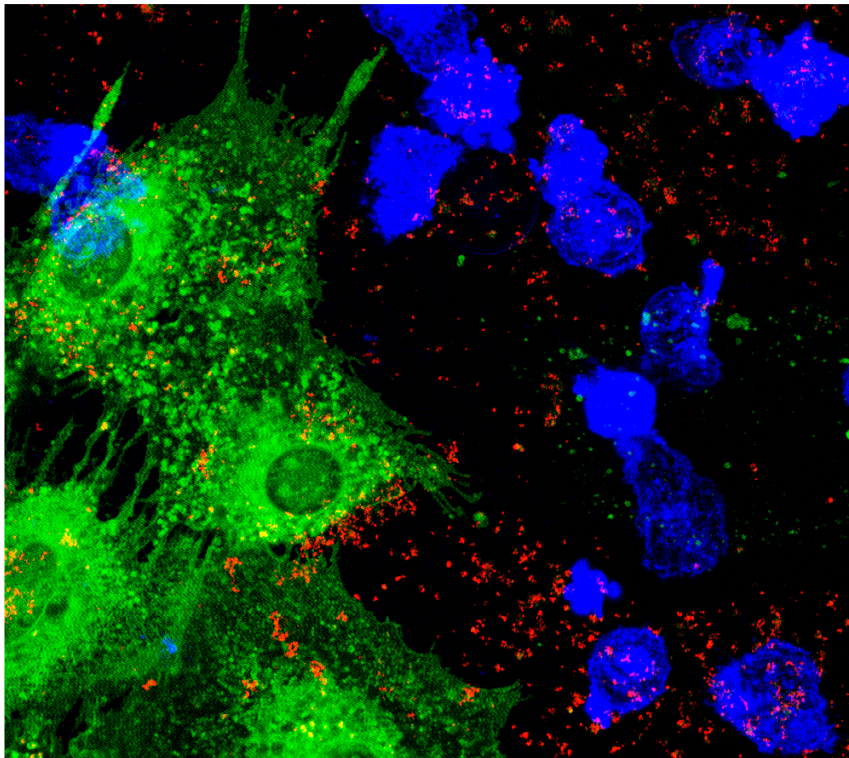
- Classical perception of the relevant model:
  - Ability to express and mimic structure and function of the relevant tissue to reach weeks time scale
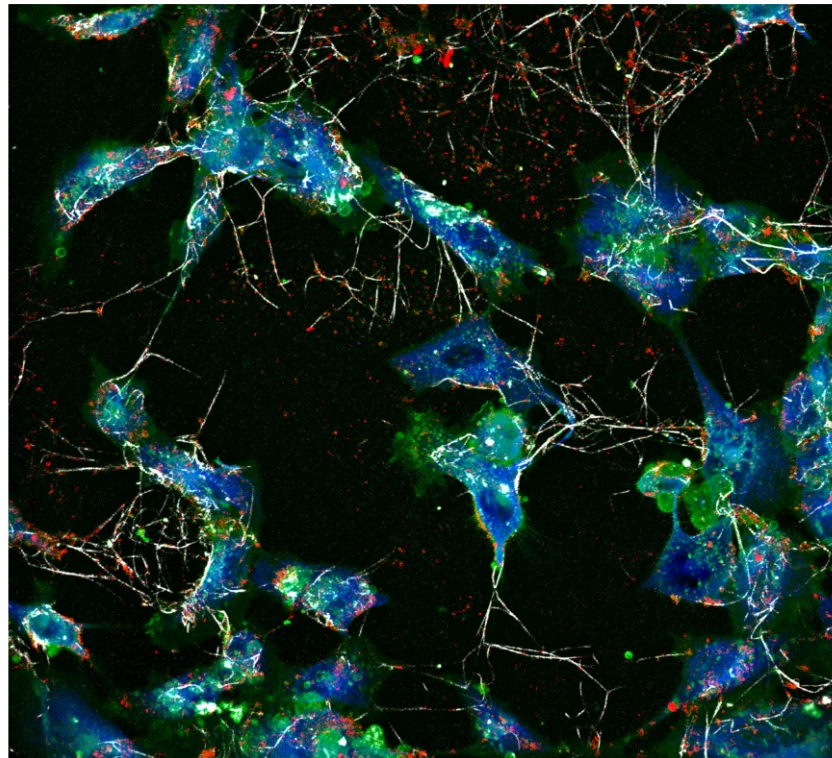
Physical events
Biochemical events
Biological events

exposure

0h   4h   12h   40h

time, disease development

tw1   tw2   tw3

Physical events
Biochemical events
Biological events
Tissue-response events

exposure

0h   4h   12h   40h   200h

time, disease development

tw1   tw2   tw3   tw4

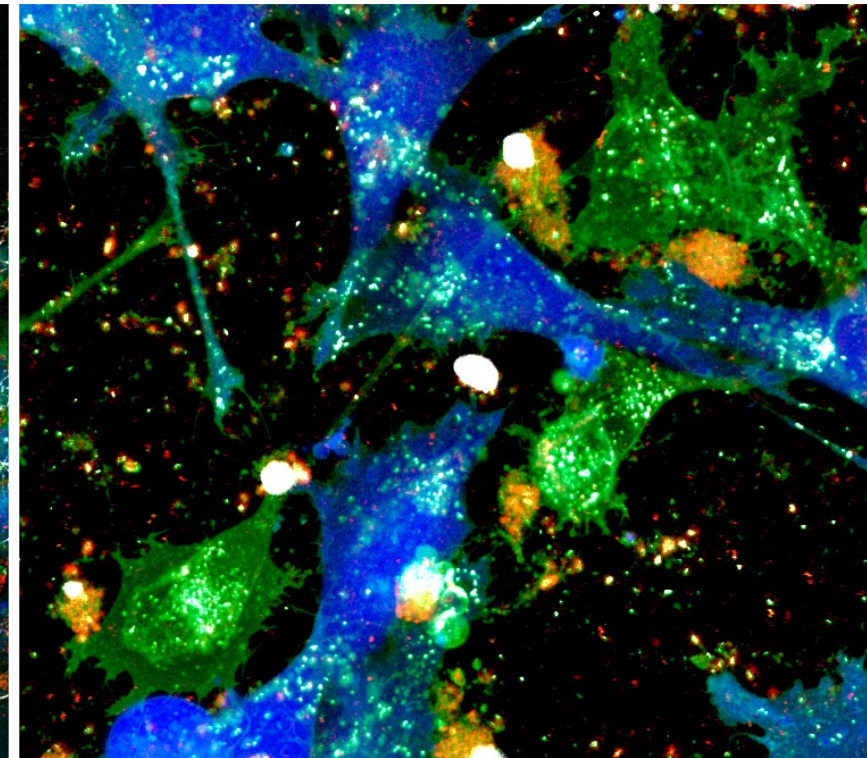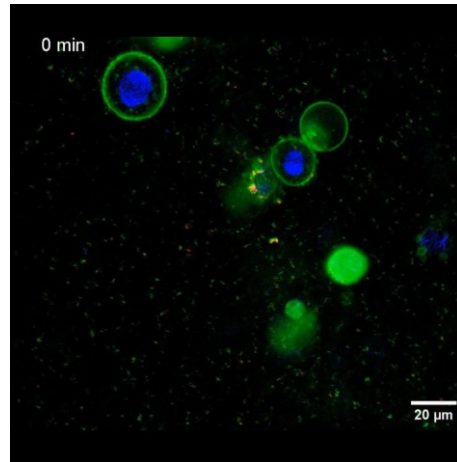# What kind of cellular models (In vitro) we use?
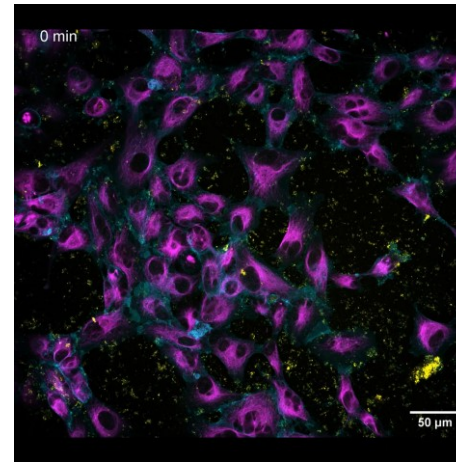
Lung

Osteo

Neuro

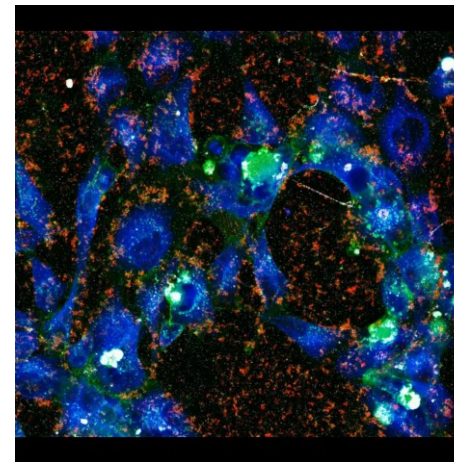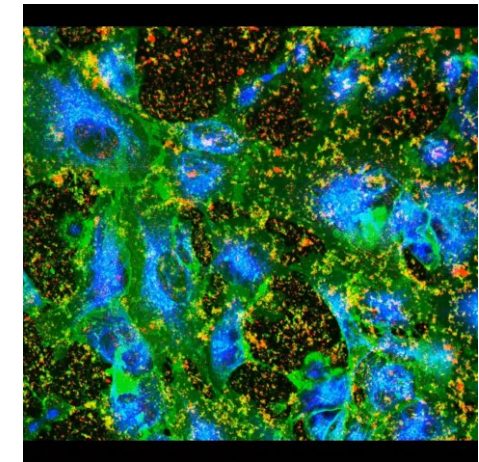**Early event monitoring**

What kind of data we acquire?

division
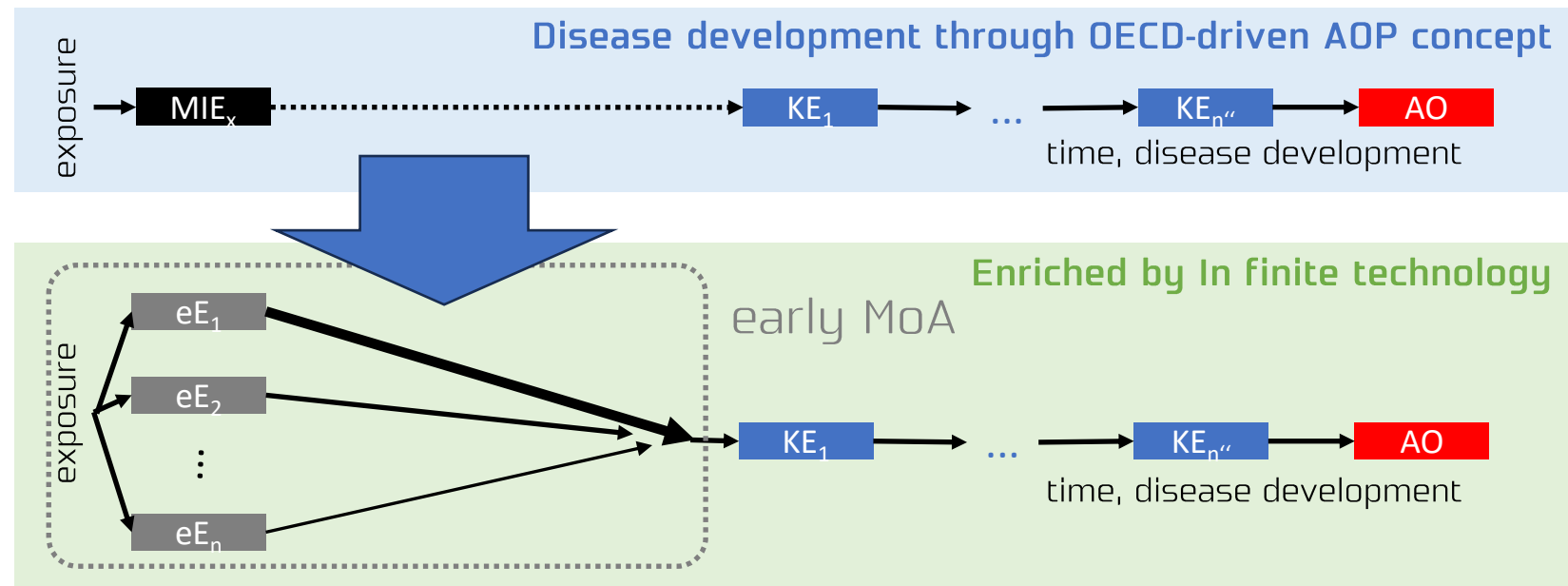
morphology

disfunctional ECM

intracellular damage

$$\frac{d\vec{q}}{dt} = \underline{M}\vec{q}$$

In silico model

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How we translate from in vitro to in silico?

In vitro data is translated into early mode-of-action by using predefined large group of early events

Automated MoA detection

Disease development through OECD-driven AOP concept

exposure

MIE$_x$ ┈┈┈┈┈► KE$_1$ → ... → KE$_{n''}$ → AO

time, disease development

Enriched by In finite technology

early MoA

exposure

eE$_1$
eE$_2$
⋮
eE$_n$

KE$_1$ → ... → KE$_{n''}$ → AO

time, disease development

- Molecular initiating events (MIEs)
- Early events (eEs)

- in vivo observed Key events (KEs)
- associated Adverse outcome pathway (AOP)
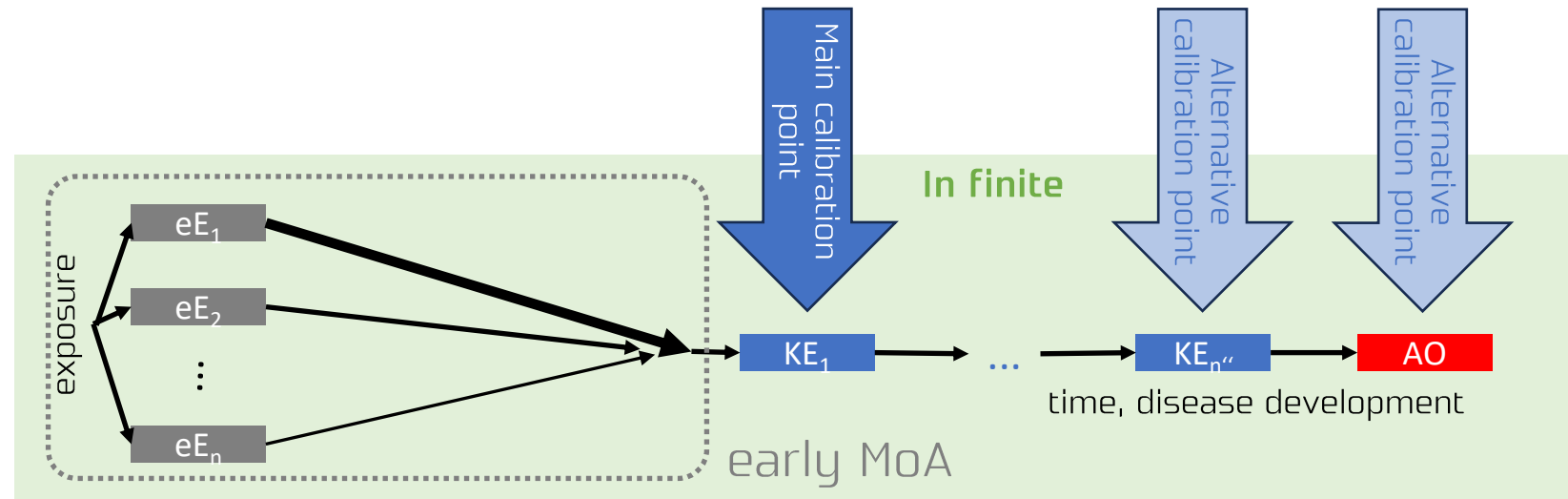
- targetted Adverse outcome (AO)

How we calibrate the translation concept?

Known
late events for
calibration

In finite approach is calibrated against the earliest KEs observed:

- *in vivo* (animal data)
- *in human* (clinical or epidemiological data)

Main calibration point

Alternative calibration point

Alternative calibration point

In finite

exposure

eE_1

eE_2

...

eE_n

KE_1 → ... → $KE_{n''}$ → AO

time, disease development

early MoA

Validation

Validation framework

- Large „Lung inflammation" validation study in progress (Jan 2023 – Dec 2023) wit
  Horizon Europe project NanoPASS
  - Using one of the largest in vivo database in the world @ NRCWE (Denmark)
  - >50 nano-, micromaterials in form of powders to derive sensitivity/specificity
  - >8 materials to derive repeatability
  - Several families of materials (metal oxides, carbonaceous, carbon nano materials, ceramics, intermetalics, alloys, clays, functionalized materials, polymers)
  - Many doses spaning 3 orders of magnitude
  - Time points from 1 day to 180 days
  - Interlaboratory testing done + intralaboratory testing planned
  - OECD TG document No.34 compatible

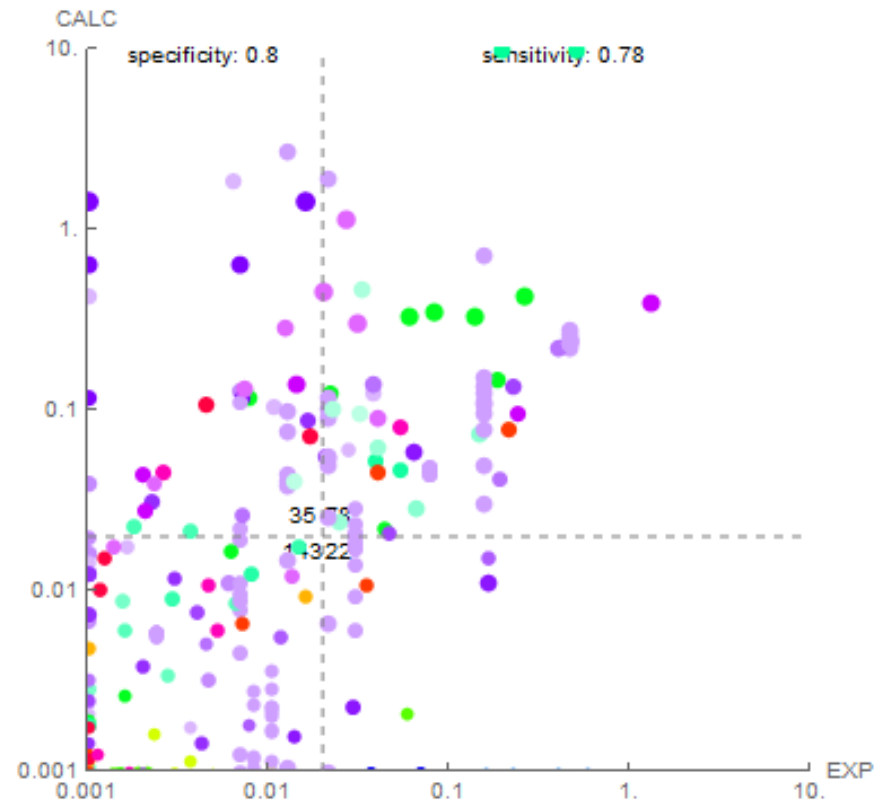# Prediction validation - preliminary
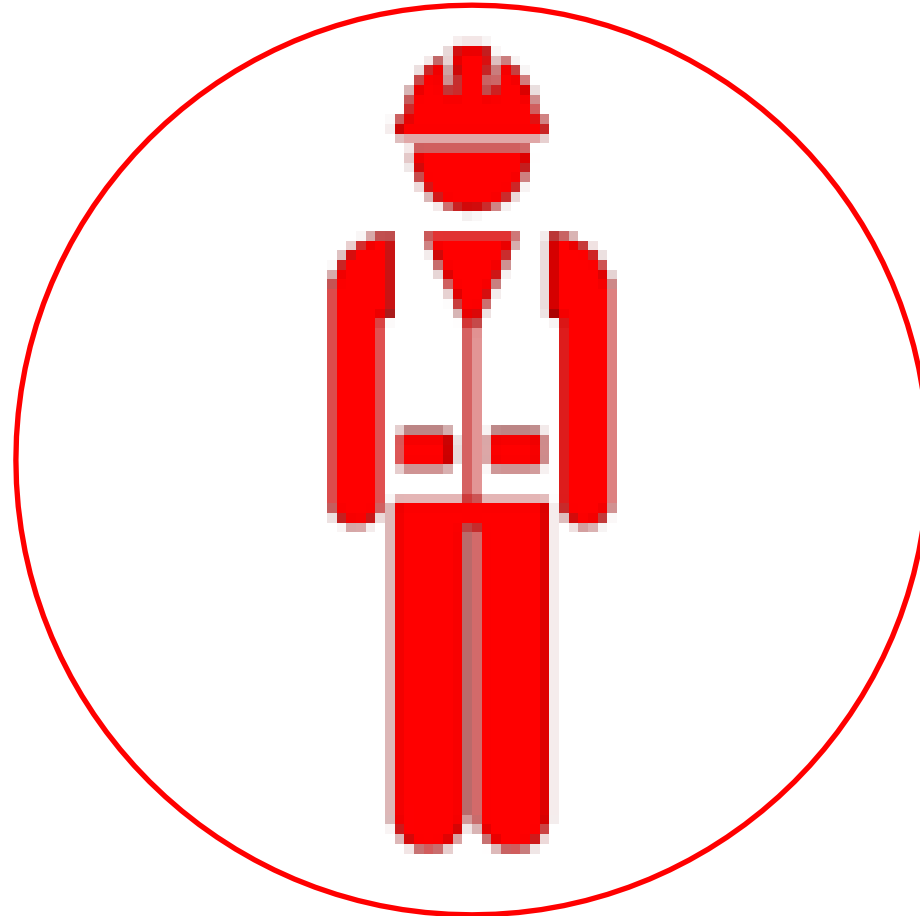

materials

dose

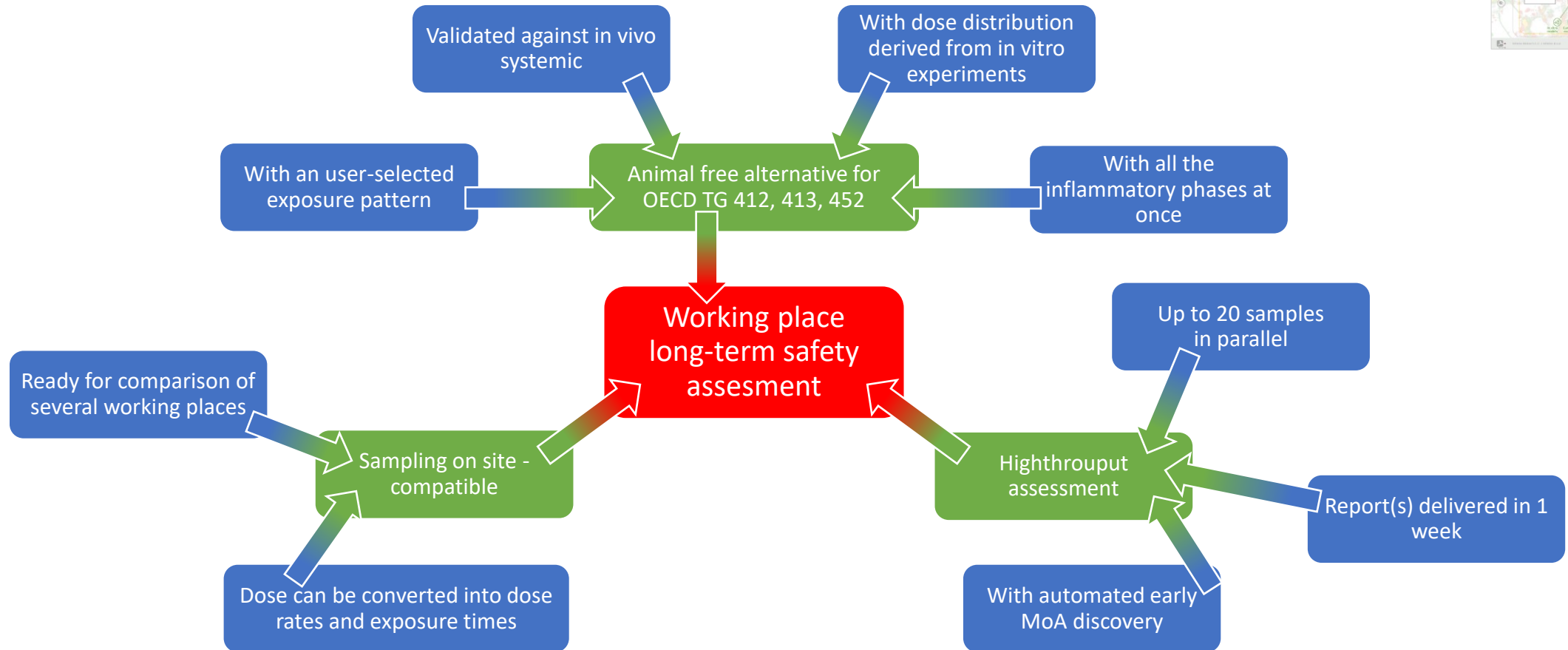SPECIFICITY

80-90%

SENSITIVITY

80-90%

34 materials
300 materials & doses & time points
2000 mice

Workplace safety

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How can the working place long-term safety assesment benefit?

Validated against in vivo systemic

With dose distribution derived from in vitro experiments

With an user-selected exposure pattern

Animal free alternative for OECD TG 412, 413, 452

With all the inflammatory phases at once

Working place long-term safety assesment

Up to 20 samples in parallel

Ready for comparison of several working places

Sampling on site - compatible

Highthrouput assessment

Report(s) delivered in 1 week

Dose can be converted into dose rates and exposure times

With automated early MoA discovery

Long-term health safety

Enabling **understanding disease development** and dose responses