SmartNanoTox

Smart Tools for Gauging Nano Hazards

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Horizon 2020
European Union funding
for Research & Innovation

Project overview

Horizon 2020 RIA NMBP call “Increasing the capacity to perform nano-safety assessment”

SmartNanoTox: Smart Tools for Gauging Nano Hazards

Overall funding: €8M

Duration: 52 months

Project consortium: 12 partners

Coordinator: University College Dublin

SmartNanoTox

Smart Tools for Gauging Nano Hazards

Imperial College London

UCD DUBLIN

STAMI

STATENS ARBEIDSMILJØINSTITUTT

UNIVERSITÉ DE LORRAINE

VITROCELL SYSTEMS

Finnish Institute of Occupational Health

FORSKNINGSCENTER FOR ARBEJDSMILJØ

NATIONAL RESEARCH CENTRE FOR THE WORKING ENVIRONMENT

UNIVERSITET STOCKHOLMS

Stockholm University

DASSAULT SYSTEMES

inrs

Institut National de Recherche et de Sécurité

HelmholtzZentrum münchen

German Research Center for Environmental Health

Jožef Stefan Institute

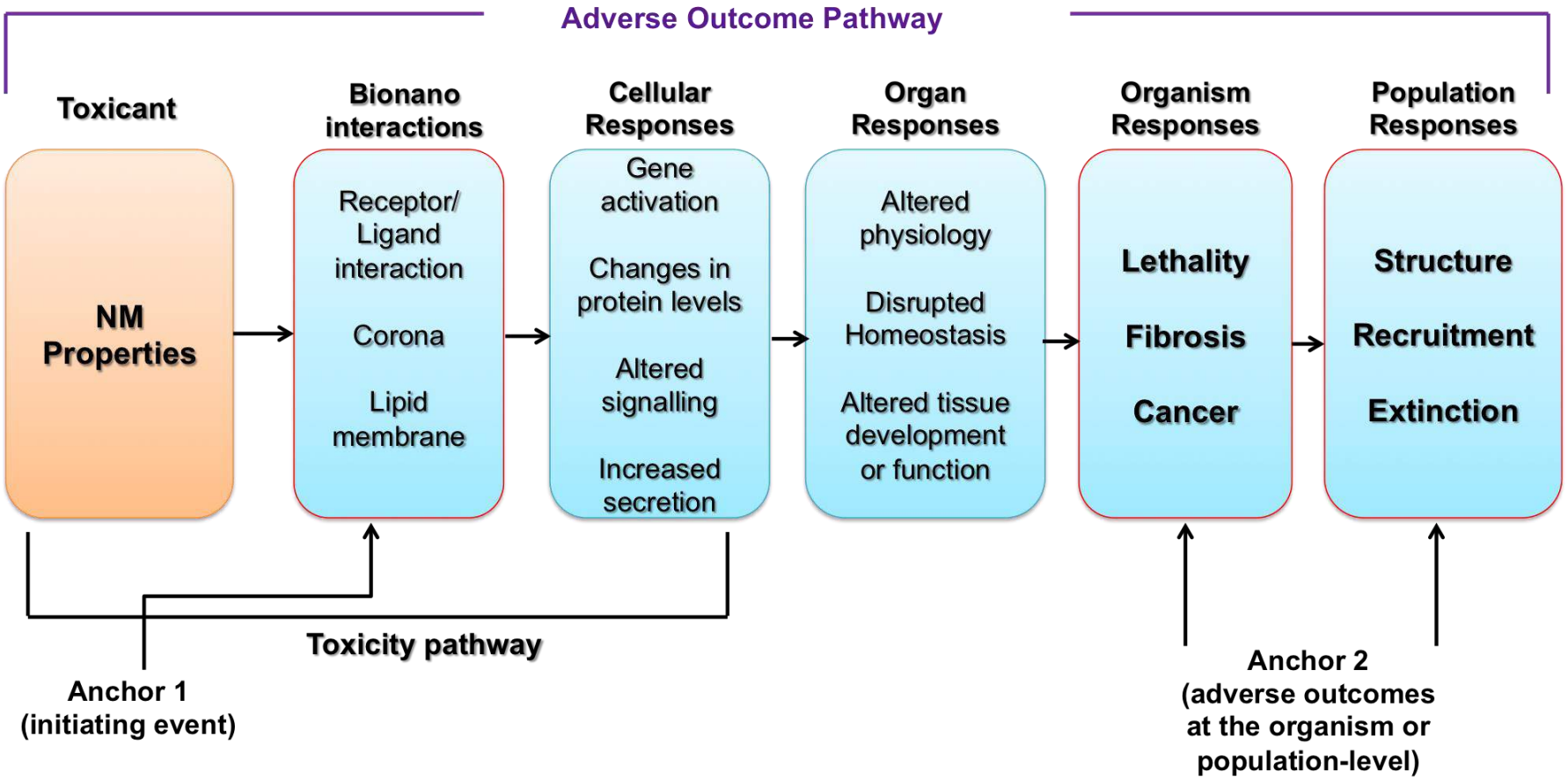
Motivation

- Limited capacity to predict hazard for new materials as the properties of concern are not known
- Limited capacity to model the NP-caused hazards at the molecular level except for local damage
- Systemic responses not known
- Bionano interface poorly understood: no relevant descriptors from experiment/simulation
- Real dosage/NP state after uptake not known
- Many in vitro toxicity endpoints are irrelevant or not predictive of in vivo outcomes

The central idea of the project

The game-changing screening approach should be based on the detailed understanding of the response of the organism to exposure to nanomaterials from the initial contact to the adverse outcome.

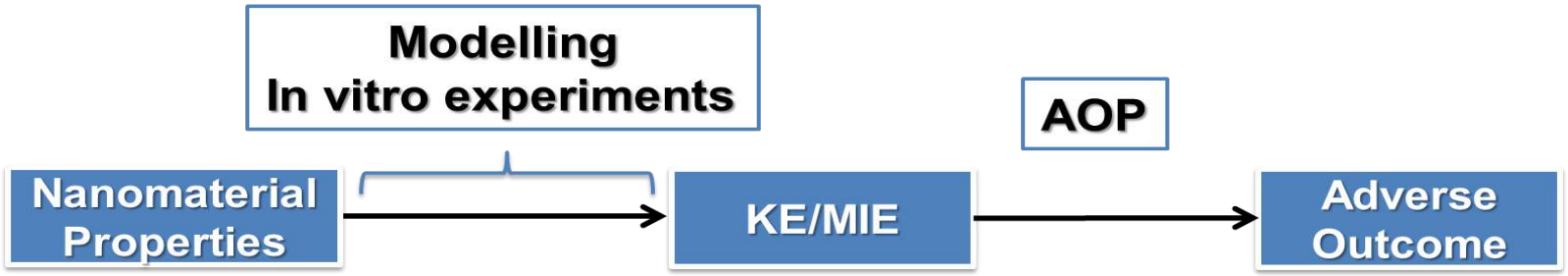
Mechanistic Understanding of Toxicity



T. E. H. Allen et al., Defining Molecular Initiating Events in the Adverse Outcome Pathway Framework for Risk Assessment. *Chem. Res. Toxicol.* 2014, **27**, 2100−2112

New toxicity assessment paradigm

Pathway-based assessment:



Understanding of bionano interactions is needed to address Molecular Initiating Events, Key Events and predict the pathways

The objectives

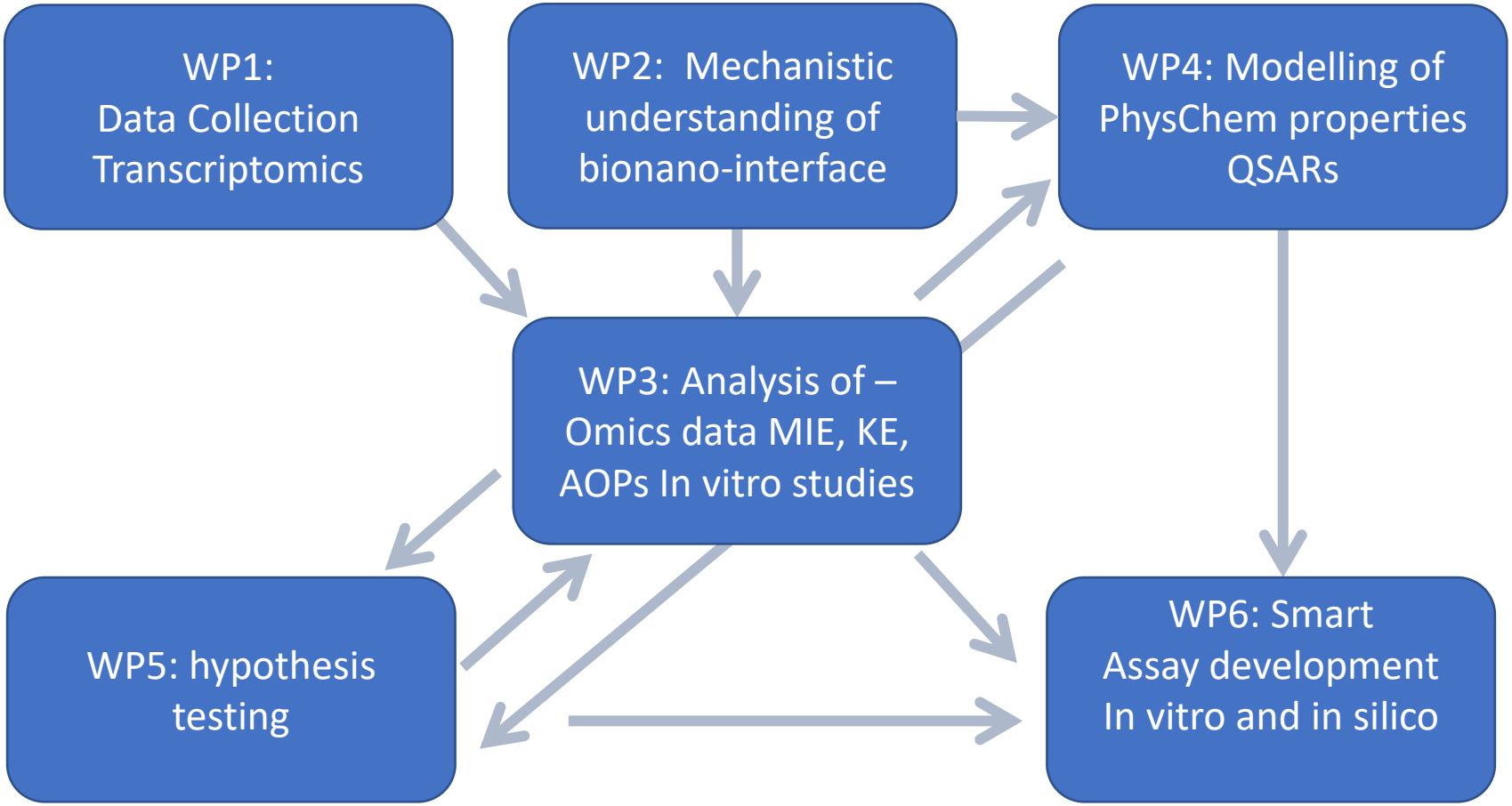
- Identify main **pulmonary adverse outcomes** induced by common NMs, identify associated MIE, KEs and toxicity pathways leading to AO.
- Establish **relationships between physchem properties of NMs and KEs** steering the TP leading to AO, and suggest descriptors for grouping of NMs according to toxicological mode-of-action
- Create a **database of bionano interactions** that will enable development of read-across and QSAR tools for the toxicity assessment of new NMs
- Develop a **smart screening approach**, where predictions of toxicity of a NM can be made on the basis of purely computational or limited *in vitro* **screening tests focused on crucial bionano interactions**

The approach step-by-step

- Study in vivo toxicity pathways for NMs of regulatory importance using in vivo experiments and systems biology
- Identify MIEs and KEs steering the toxicity pathways finally leading to an AO
- Identify molecular mechanisms of NM involvement in these KEs
- Describe structure and content of NM-biomolecule complexes after NM uptake

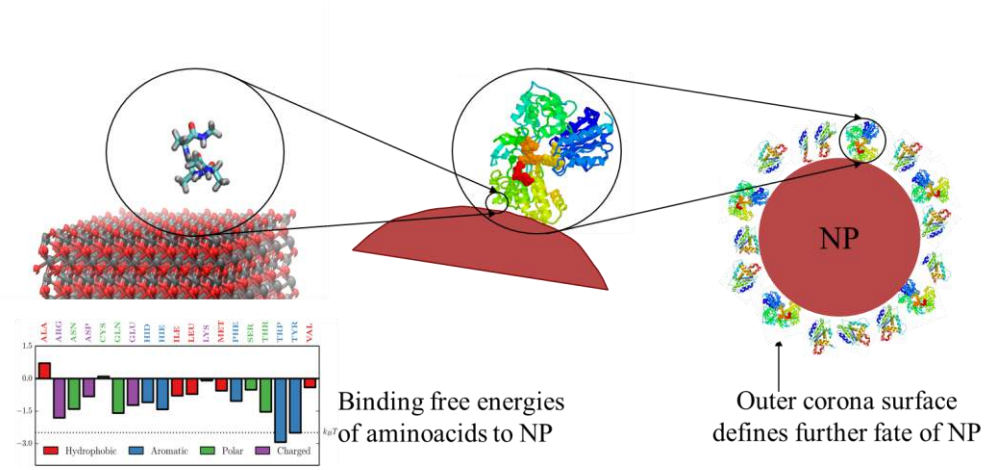
The key step in the development of the smart screening approach is to combine the systems biology analysis of the responses of organisms to the NM exposure, resulting in a clear identification of the resulting pathways and KEs, with the analysis of the whole chain of bionano interactions involving the NM inside the organisms.

Work Packages

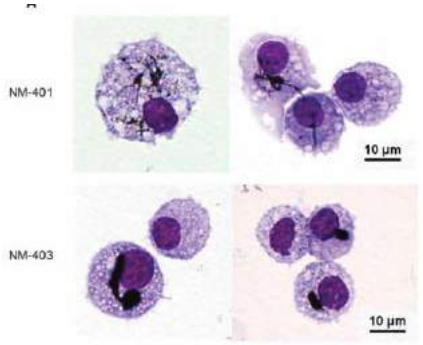


SmartNanoTox methods

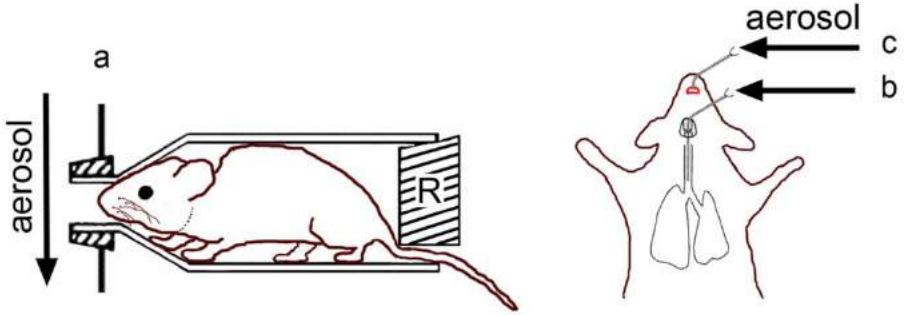
Molecular simulation

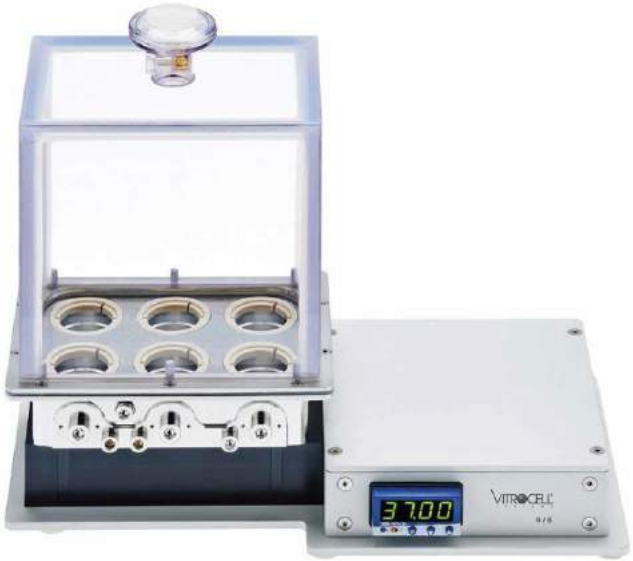


In vitro exposure



In vivo exposure





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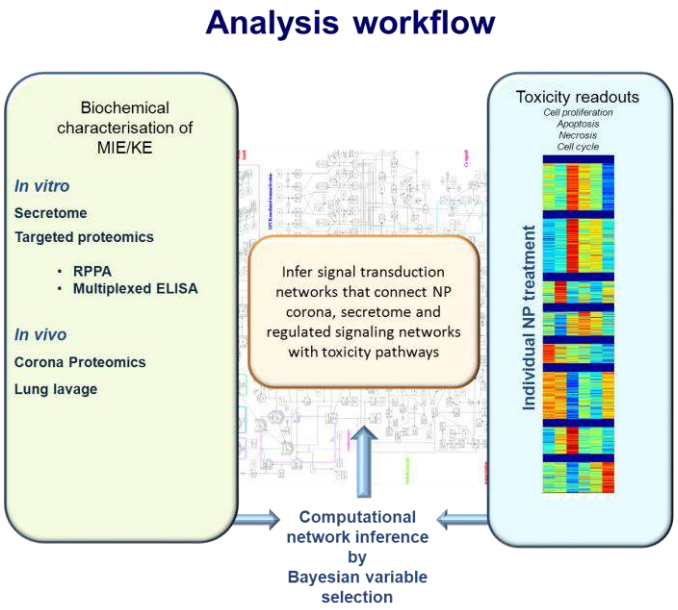
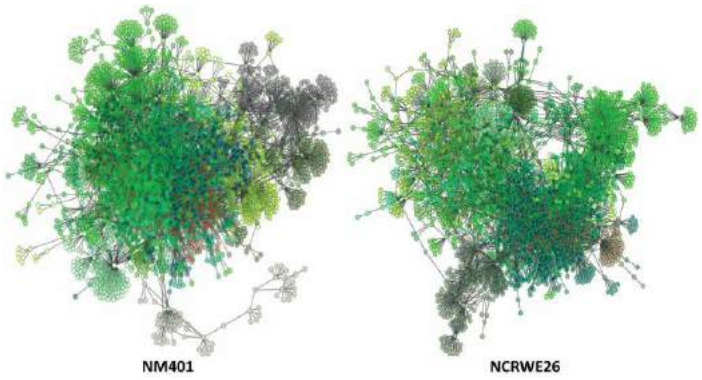
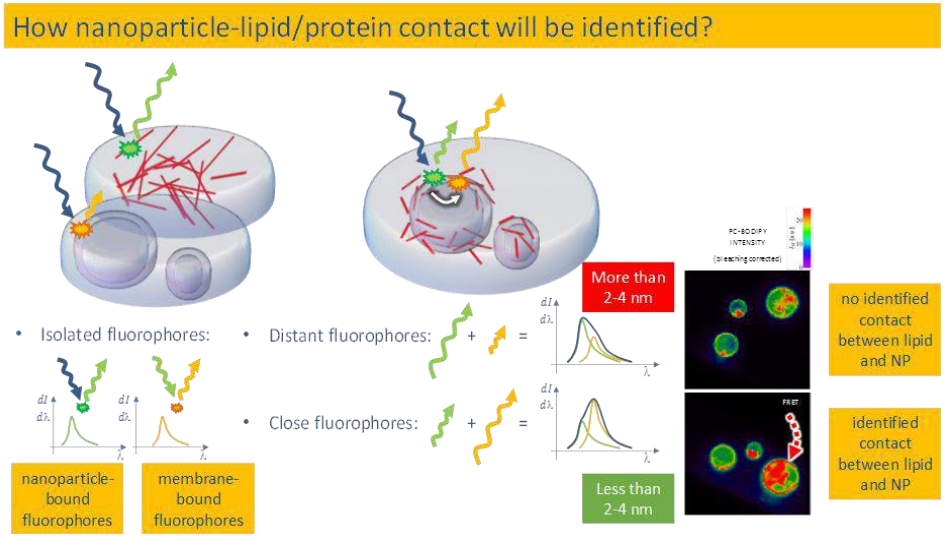
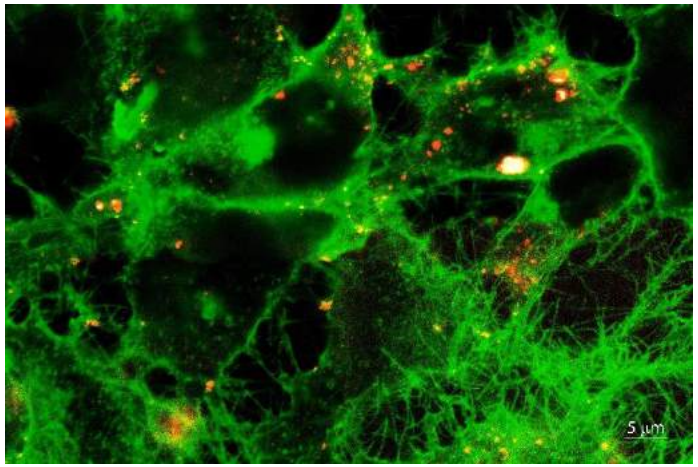
Omics, systems biology





NP tracking, post-uptake characterisation





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materials

- Titania (TiO_2): 16 NMs – rutile, anatase, spheres, tubes
- Quartz and Silica: 3 NMs
- Metal oxides: 7 NMs Fe_2O_3, ZnO, $Ni_xFe_yZn_zO_u$
- Carbon black: 2 NMs
- Carbon nanotubes: 28 SWCNTs and MWCNTs
- Graphene: 3 NMs
- Asbestos: Crocidolite

SmartNanoTox projected impacts

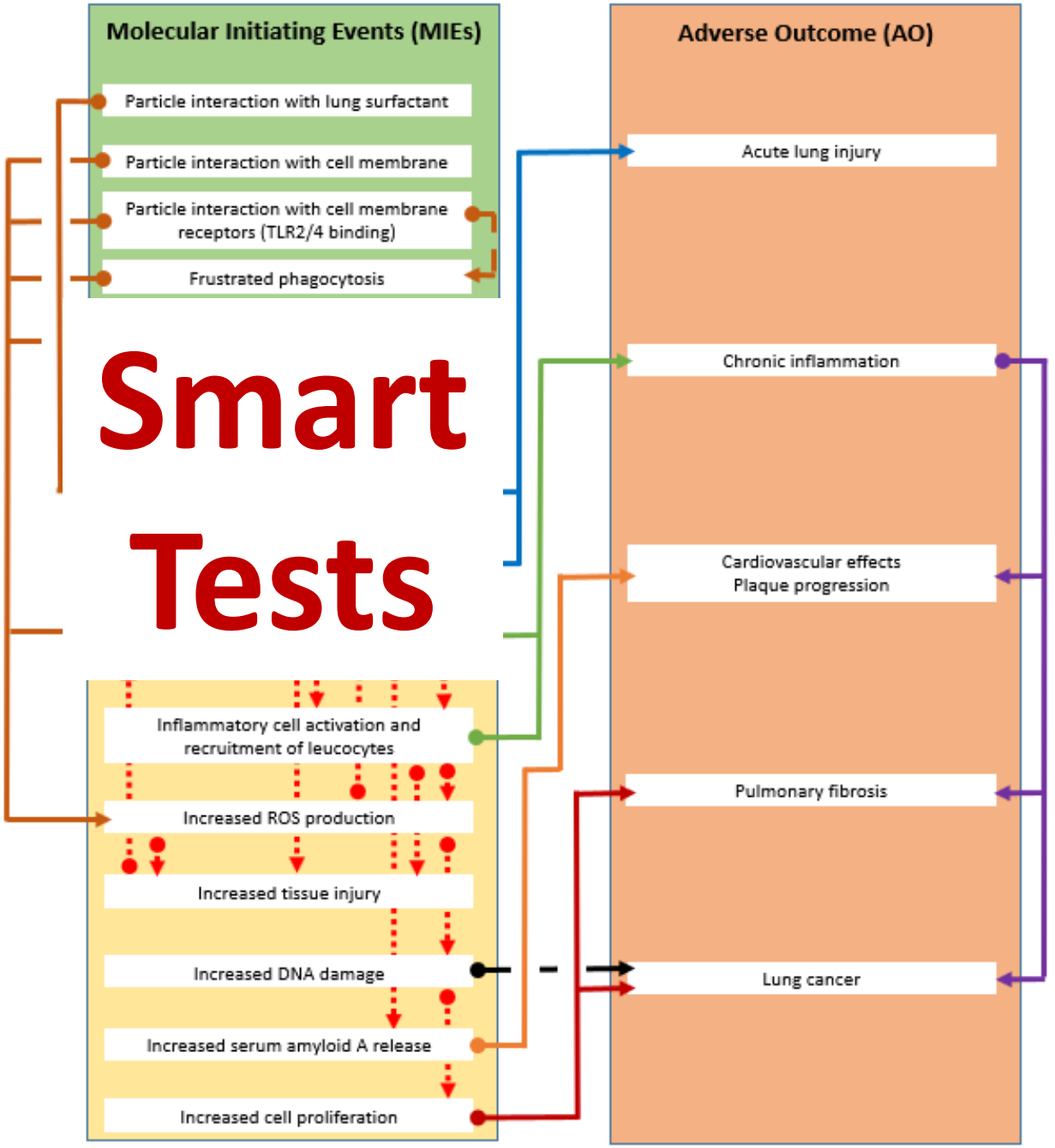
Smart Tools for Gauging Nano Hazards

- 5 described / validated respiratory AOPs
- Database of bionano interactions for 60+ NMs with proteins and lipids
- Identified NM properties of concern
- Mechanism-aware toxicity assessment tools
- Methods for NM tracking inside the tissues and post-uptake characterisation
- 40+ publications (currently 55 papers published)

AOP

MIE

KE


Molecular Initiating Events (MIEs)
Particle interaction with lung surfactant
Particle interaction with cell membrane
Particle interaction with cell membrane receptors (TLR2/4 binding)
Frustrated phagocytosis
Adverse Outcome (AO)
Acute lung injury
Chronic inflammation
Cardiovascular effects
Plaque progression
Pulmonary fibrosis
Lung cancer
Smart Tests
Inflammatory cell activation and recruitment of leucocytes
Increased ROS production
Increased tissue injury
Increased DNA damage
Increased serum amyloid A release
Increased cell proliferation

SmartNanoTox Conference 24.06

SmartNanoTox Overview: 9.00 CEST

Session 1: 9.10 – 10.30 CEST
“Grouping of Nanomaterials”

Session 2: 11.00 – 12.30 CEST
“Development of AOPs and identification of KEs“

Session 3: 13.30 – 15.00 CEST
“In vivo – in vitro mapping”

Session 4: 15.30 – 17.00 CEST
“Databases/Data management”