SmartNanoTox

Smart Tools for Gauging Nano Hazards

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2017 nanotexnology 1-8 JULY 2017, THESSALONIKI, GREECE
INTERNATIONAL CONFERENCES & EXHIBITION ON NANOTECHNOLOGIES - ORGANIC ELECTRONICS & NANOMEDICINE

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: 48 months

Project consortium: 11 partners

Coordinator: University College Dublin

SmartNanoTox

Smart Tools for Gauging Nano Hazards

Imperial College London

Finnish Institute of Occupational Health

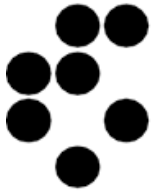
UNIVERSITÉ DE LORRAINE

NATIONAL RESEARCH CENTRE FOR THE WORKING ENVIRONMENT

Stockholm University

HelmholtzZentrum münchen

German Research Center for Environmental Health



Jožef Stefan Institute

Where we are

- Limited capacity to predict hazard for new materials as the properties of concern are not known

Standard NM characterisation is not sufficiently informative

Toxicity mechanisms are not known

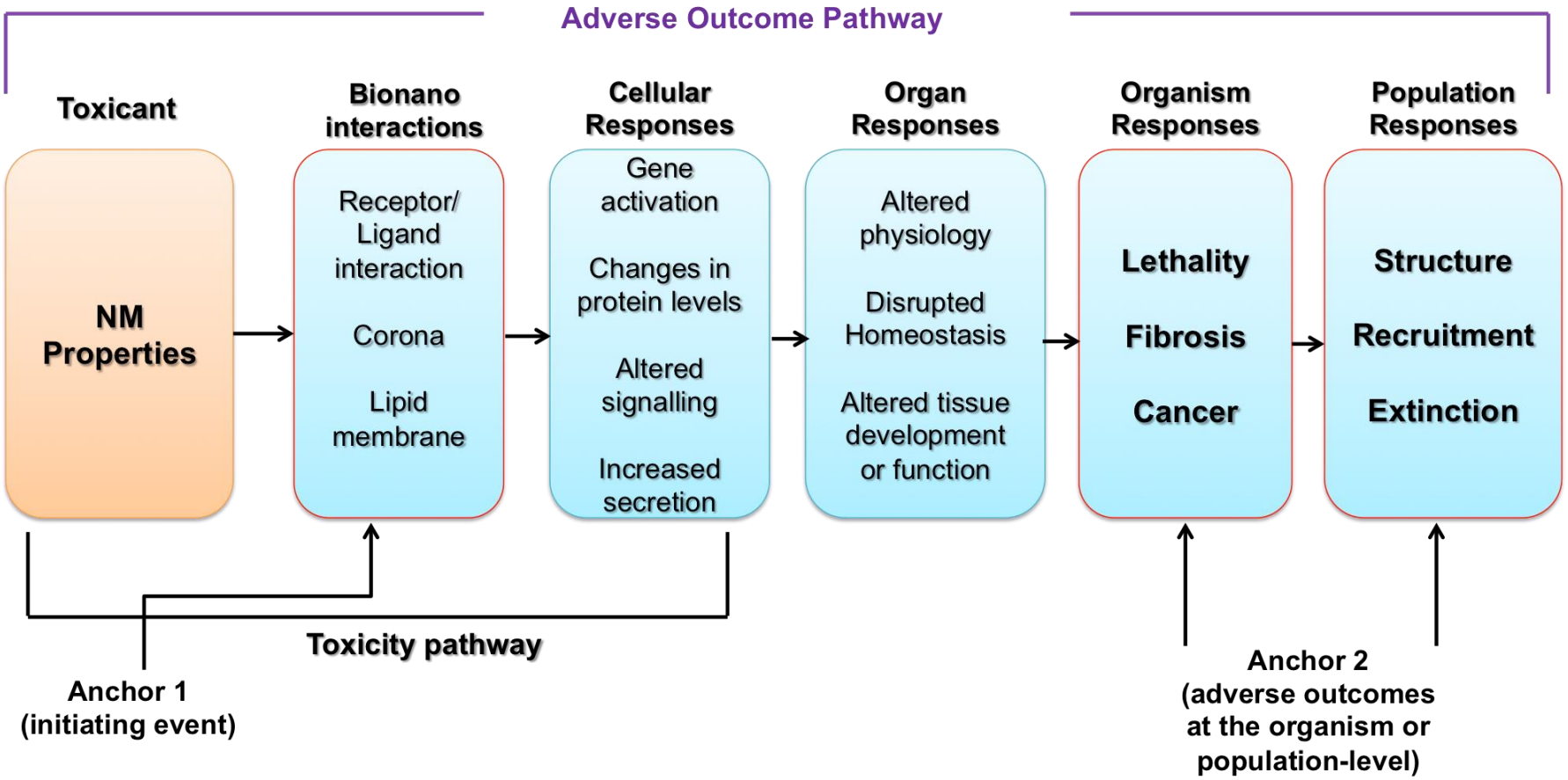
- Real dosage/NP state after uptake not known
- Many in vitro toxicity endpoints (e.g. EC50) are irrelevant

Mechanistic understanding of nanotoxicity

New level of complexity:

- Knowing the nanomaterial chemistry and structure is not enough: coating, adsorbed materials, surface energy, dielectric properties may be important
- Nanoparticles use specific ways of systemic distribution, which are unavailable for individual molecules or micron-sized particles. Exposure route can be equally important
- Toxicity and adverse outcomes may be related to molecular perturbation of cell structures/pathways and not direct damage

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

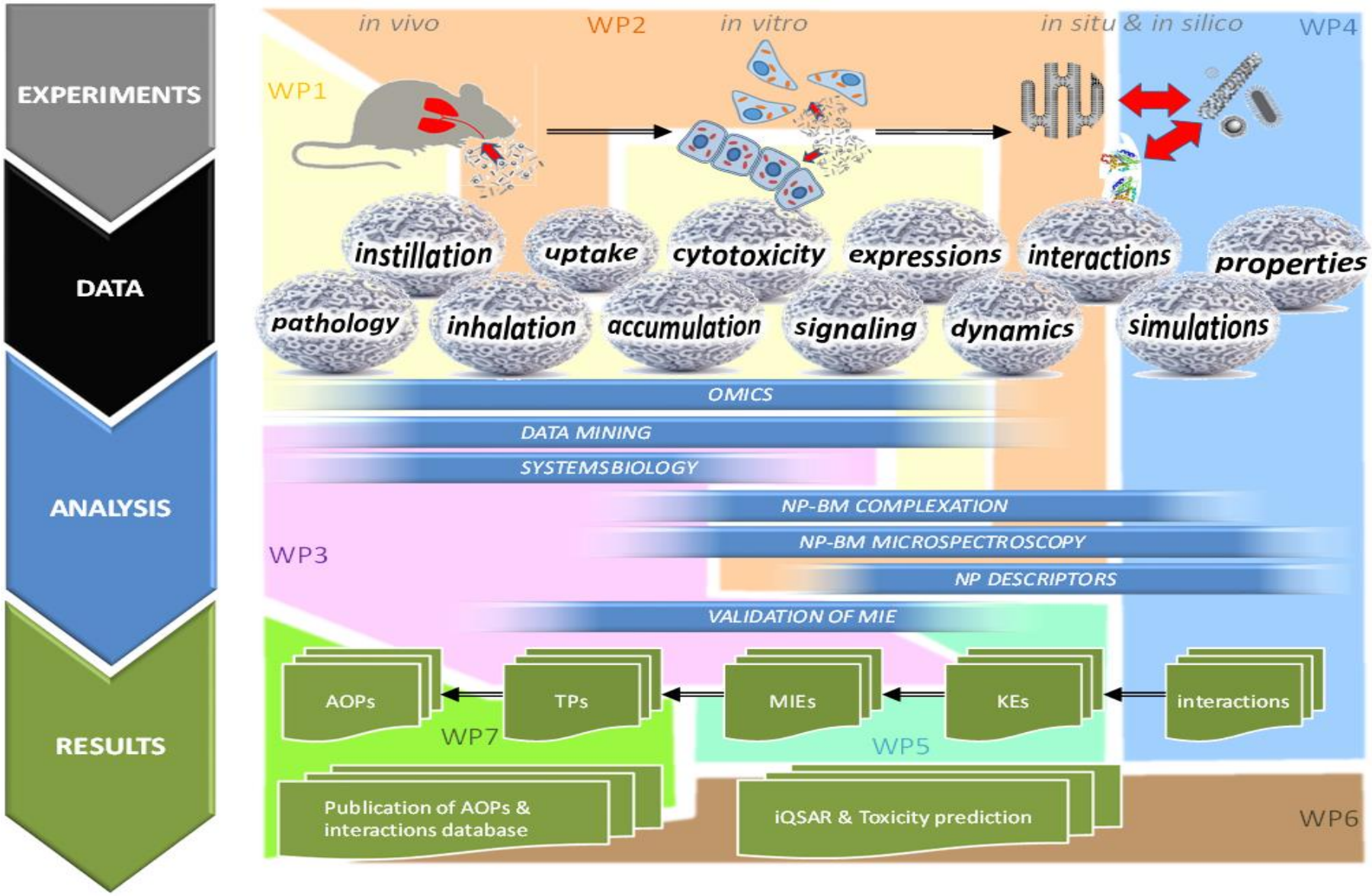
Pathway-based assessment:

Understanding of bionano interactions is needed to address Molecular Initiating Events, systemic transport

Project objectives

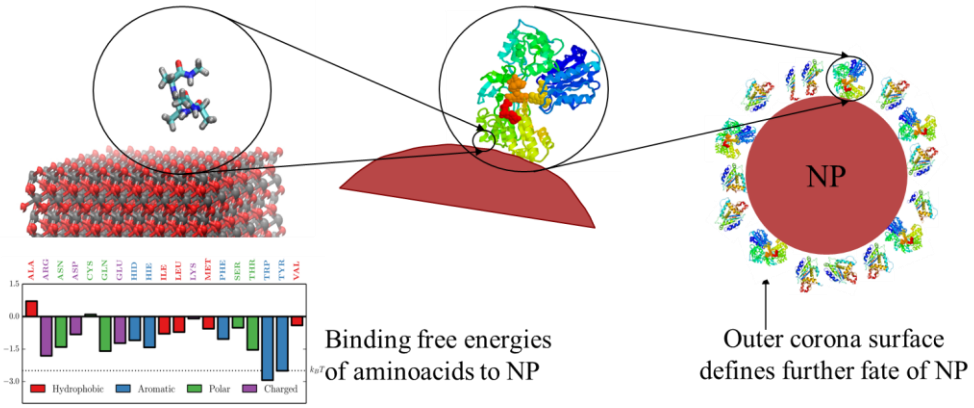
- Identify main **pulmonary adverse outcomes** induced by common NMs, and identify associated MIE, KEs and toxicity pathways leading to AO.
- Establish **relationships between physchem properties of NMs and KEs** steering the TP leading to AO, and suggest descriptors for grouping of NMs according to 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**

SmartNanoTox approach

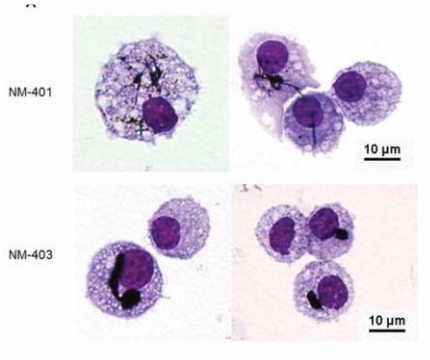


SmartNanoTox methods

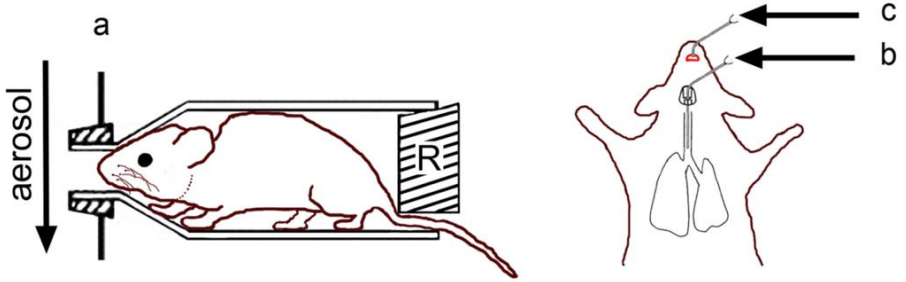
Molecular simulation

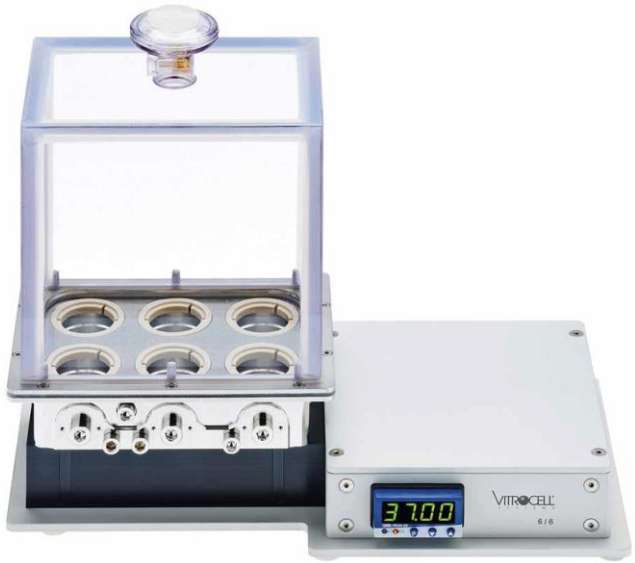


In vitro exposure



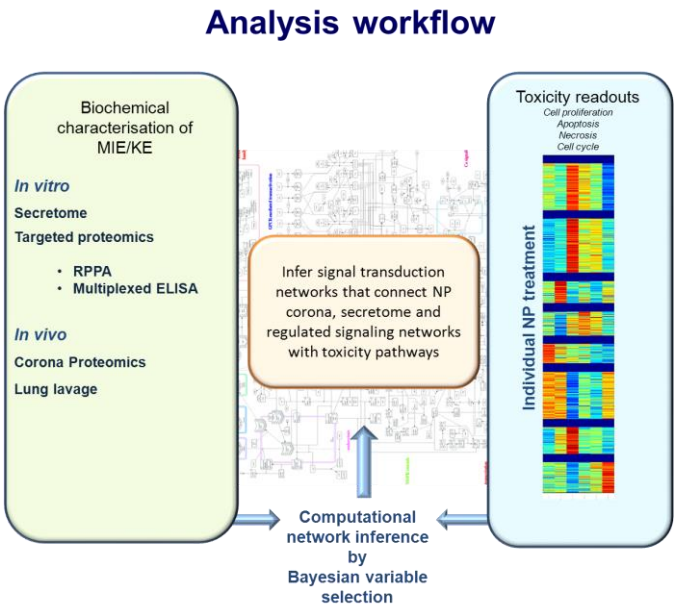
In vivo exposure

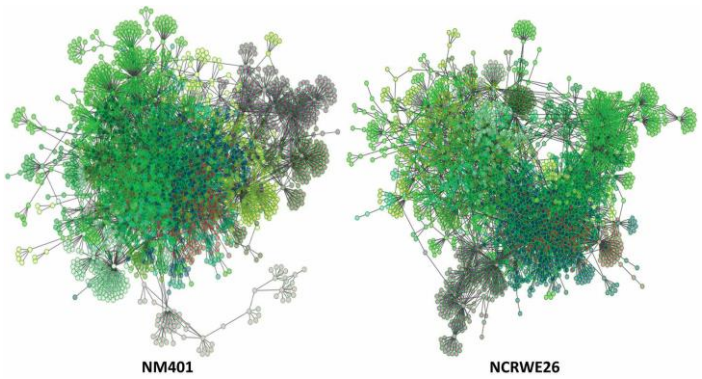




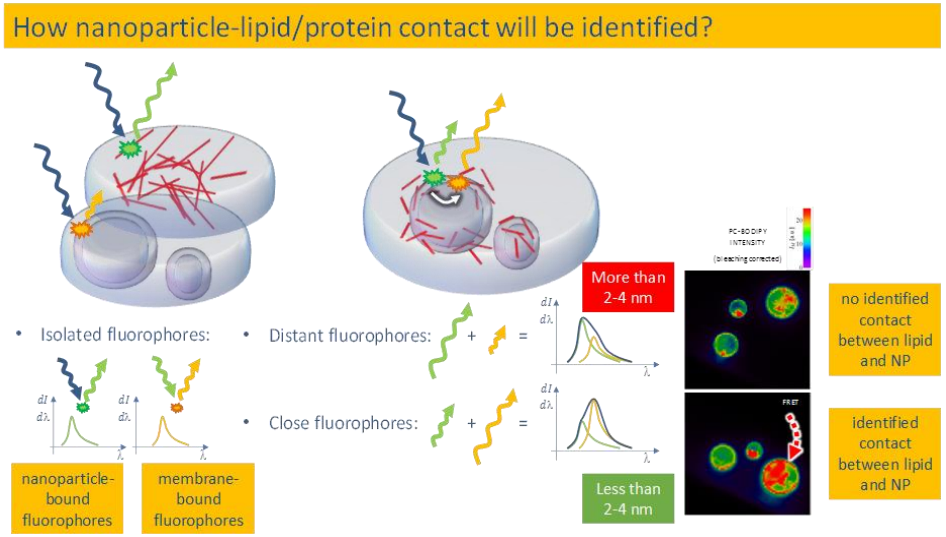
SmartNanoTox methods

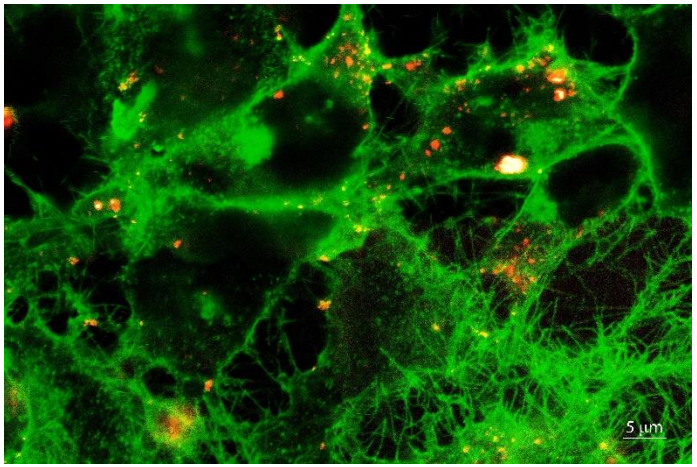
Omics, systems biology





NP tracking, post-uptake characterisation





Beyond the state-of-the-art

S&T Objective	SmartNanoTox offers:
Relating the NM descriptors to the toxicity end point	AO pathway-based mechanism-aware intelligent QSARs
Determining the hazardous effect of engineered NMs	In vivo study of the acute and chronic toxic effects, with relation to the adverse outcome, in depth analysis of the pathologies
Understanding of the mechanisms underlying the observed adverse effects from engineered nanomaterials	The biomolecular corona of the NPs will be analysed, NMs will be tracked inside the biological fluids and molecules involved in bionano interactions identified
Create basis for grouping of engineered nanomaterials by	Identify generic properties responsible for pulmonary toxicity for carbonaceous

SmartNanoTox projected impacts

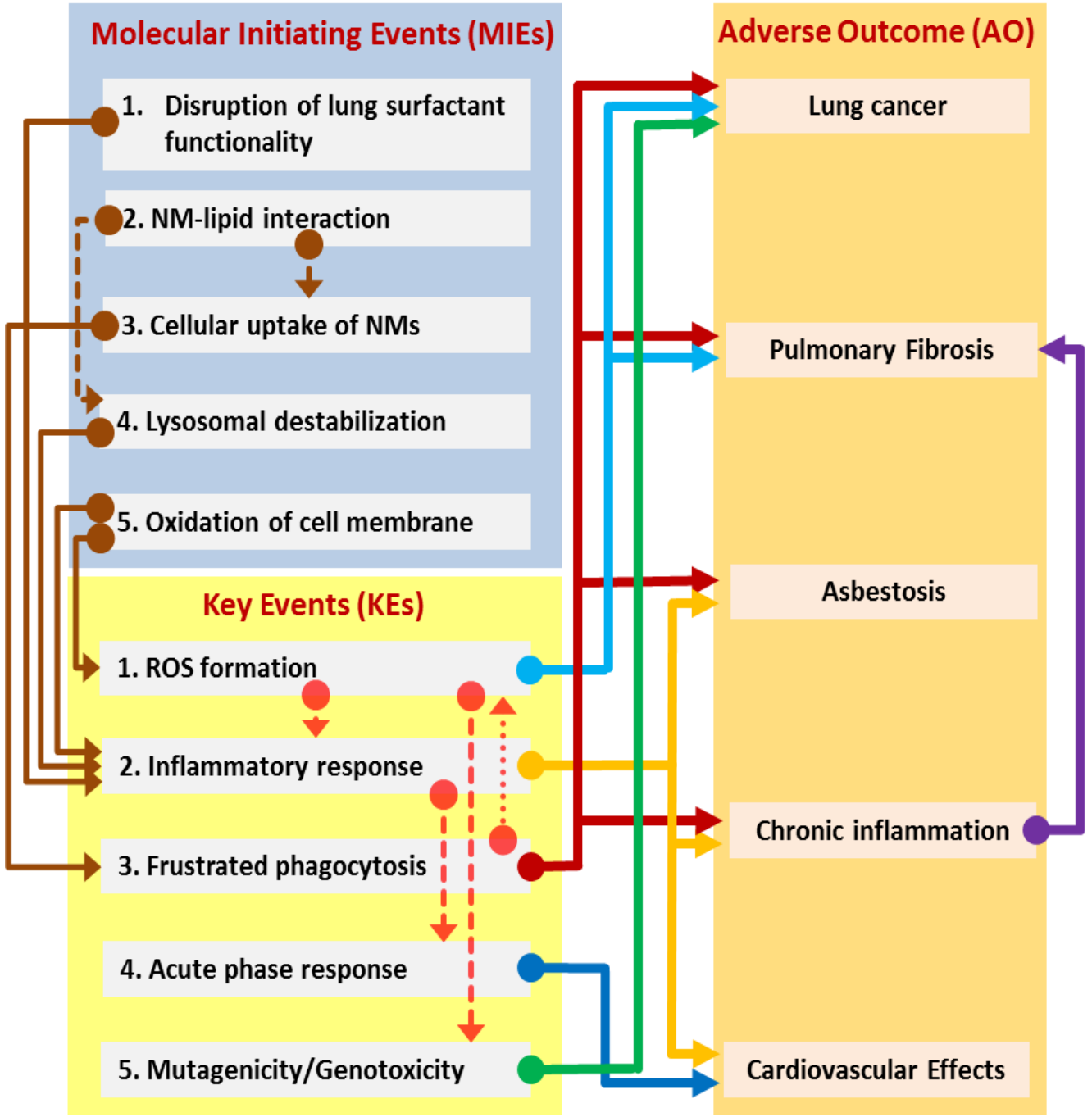
Smart Tools for Gauging Nano Hazards

- Described and 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 characterization
- Replacement of animal experiments by in vitro/in silico tests

AOP

MIE

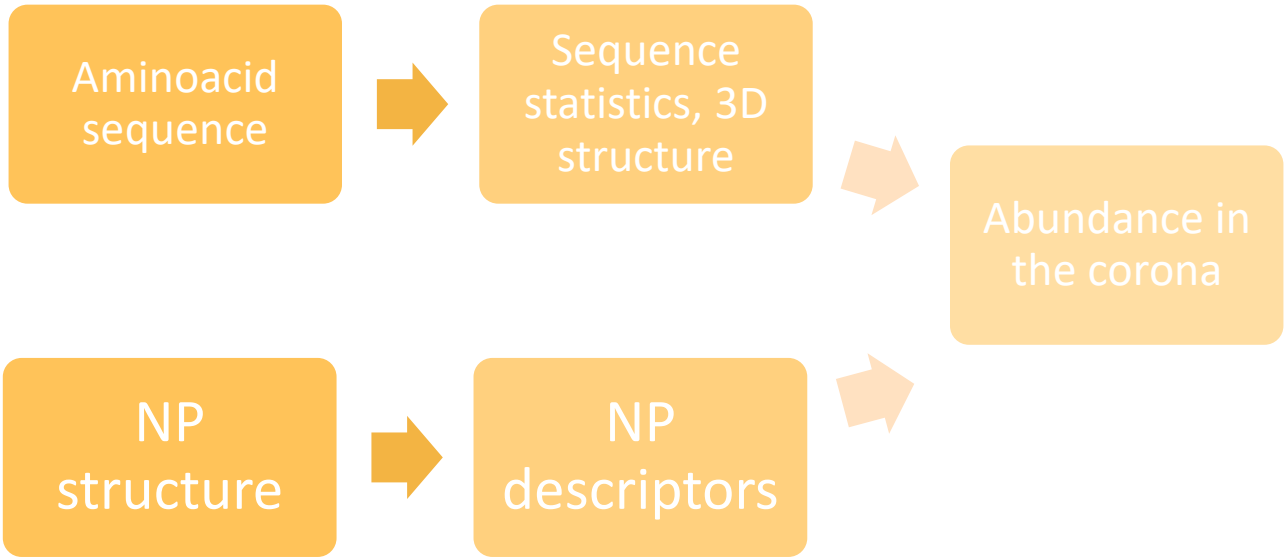
KE


Molecular Initiating Events (MIEs)
1. Disruption of lung surfactant functionality
2. NM-lipid interaction
3. Cellular uptake of NMs
4. Lysosomal destabilization
5. Oxidation of cell membrane
Key Events (KEs)
1. ROS formation
2. Inflammatory response
3. Frustrated phagocytosis
4. Acute phase response
5. Mutagenicity/Genotoxicity
Adverse Outcome (AO)
Lung cancer
Pulmonary Fibrosis
Asbestosis
Chronic inflammation
Cardiovascular Effects

MIEs / KEs	Detection Assays	In Vitro Lung Models	
		Cell free (Surfactant)	Alveol. cells
Disruption of lung surfactant (LS) functionality	Constrained drop surfactometer, MD simulation	✓	
NM-lipid interaction	Microscopy (FRET, FRET-FMS, pFMS, DLS, EPR), MD simulation	✓	✓
Cellular uptake of NMs	Microscopic localization (pFMS)	✓	✓
Lysosomal destabilization	Membrane leakage, cell viability, MD simulation	✓	✓
Oxidation of cell membrane	Antioxidant depletion, 'Band Gap' calculation	✓	
ROS formation	Redox sensitive dyes & marker genes, Electron paramagnetic resonance (EPR)	✓	✓
Inflammatory response	Inflammatory gene & protein expression		✓
Frustrated phagocytosis	Lysosomal damage, inflammasome activation		✓
Acute phase response	Release of acute phase reactants		✓
Mutagenicity/Genotoxicity	Marker gene & protein expression		✓

NP-protein interactions
Bio/Nanoinformatics approach

Prediction of corona content using NP and protein descriptors:

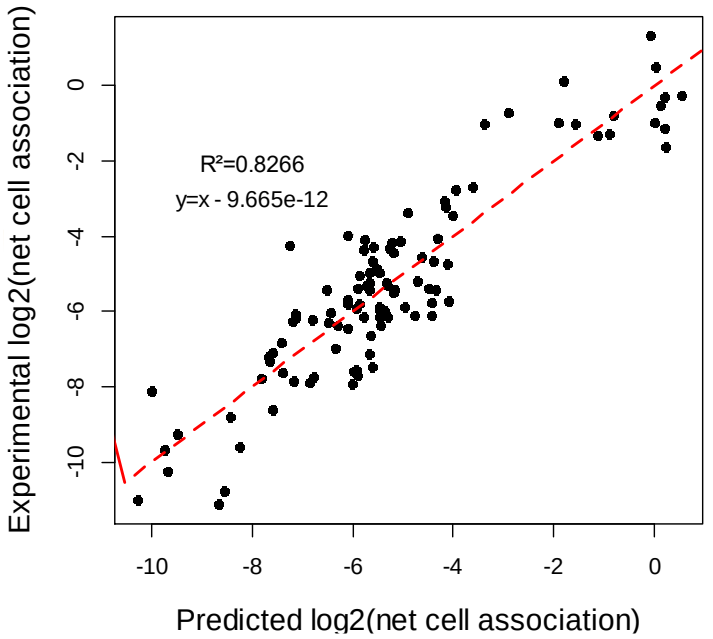


Sequence descriptors (PepStat), 3D structure (I-TASSER)

NP-protein interactions Bio/Nanoinformatics approach

Prediction of Key Events of the AOP using protein descriptors:

Protein descriptors → Relative abundance



Experimental data from Walkey et al. ACS Nano 2014.
Kamath et al. Current Topics in Medicinal Chemistry, 2015

NP-protein interactions
Bio/Nanoinformatics approach