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: 48 months

Project consortium: 11 partners

Coordinator: University College Dublin

SmartNanoTox
Smart Tools for Gauging Nano Hazards

Imperial College London

UCD DUBLIN

inrs
Institut National de Recherche et de Sécurité

Finnish Institute of Occupational Health

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UNIVERSITET STOCKHOLMS
Stockholm University

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HelmholtzZentrum münchen
German Research Center for Environmental Health

Jožef Stefan Institute

Where we are

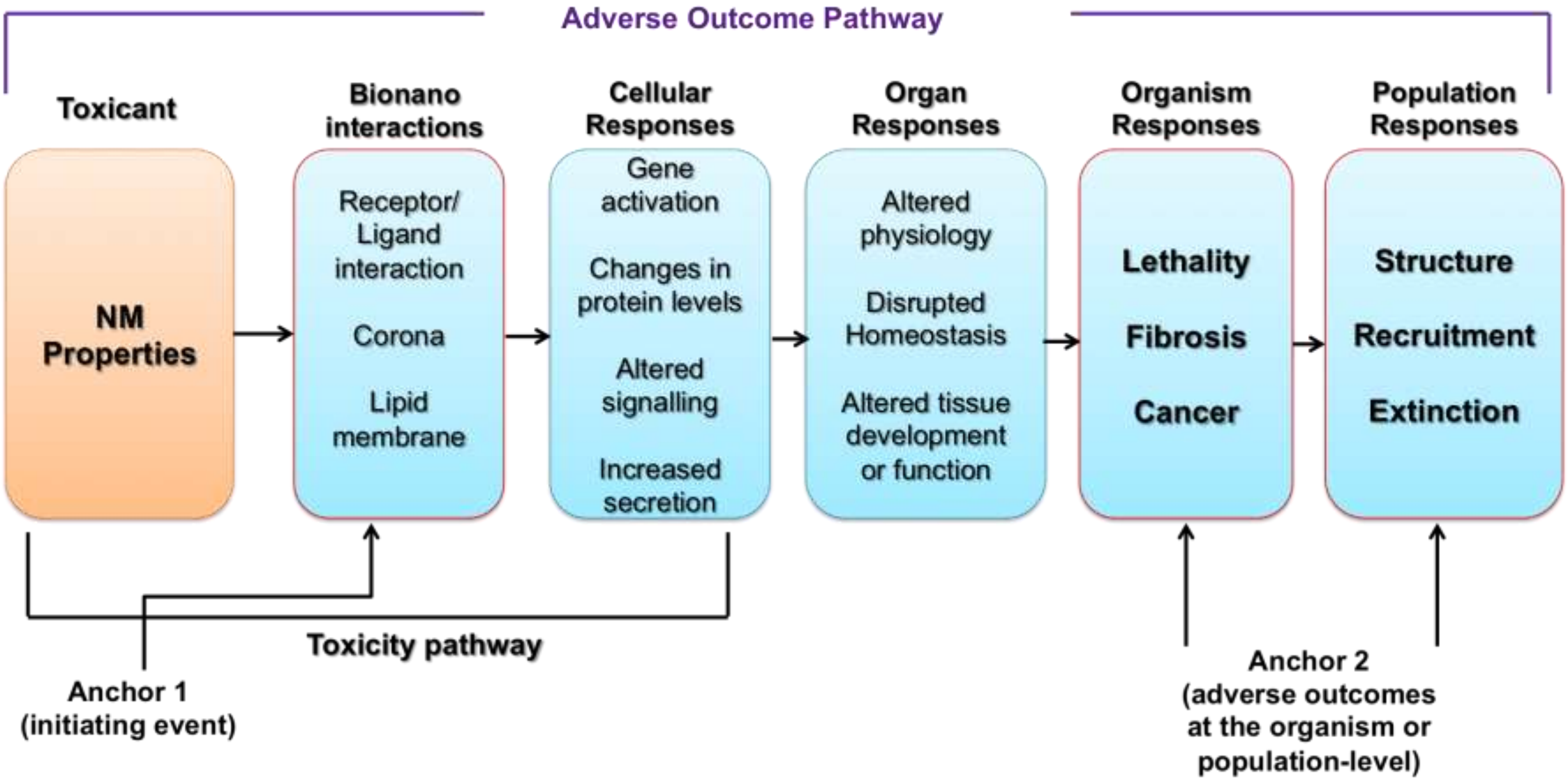
- Limited capacity to predict hazard for new materials as the properties of concern are not known

Standard NM characterisation is not sufficient for predictions

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 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**

projected impacts

- 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

Project outcomes

Deliverables/ Exploitation Pathways	**QSAR (Tox) Models**	**Simulation Potentials**	**Simulation Models**	**Simulation Codes**
Industrial / Commercial	✦	✦	✦	✦
Regulatory Agencies	✦			
Interaction with other EU-funded projects	✦	✦	✦	
Training courses	✦	✦	✦	✦

SmartNanoTox outcomes 2018-20: Research

- Description of 7 respiratory AOPs, KE/MIE
- Gene expression profiles for *in vivo* respiratory exposure
- Novel ALI systems to imitate realistic exposure conditions
- Novel analysis protocols for inference of GRNs from transcriptomics data, identification of Core Regulatory Genes
- Demonstration of equivalence between rat/mouse/human models

Project outcomes: Research

- Novel NM labelling techniques
- Novel protocols for corona analysis
- Novel algorithms for image analysis / colocalization
- Protein corona-based NM fingerprints
- NM tracking techniques, post-uptake characterisation data
- Atomistic, coarse-grained force fields for common materials (30 materials)
- Multiscale simulation tools for bionano-interface
- Novel advanced NM and protein descriptors (over 30 new descriptors, 60 materials)
- Publicly available database of bionano interactions

Project outcomes 2018-20: Industry/Regulation

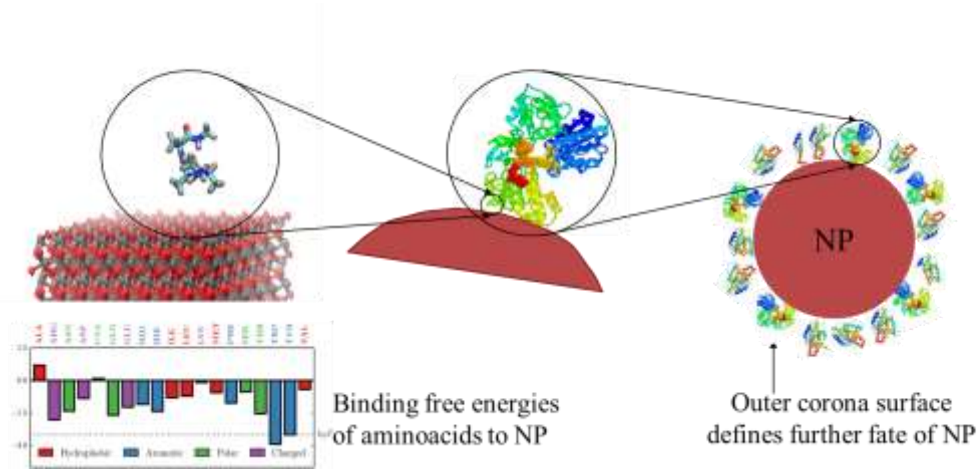
- Development and validation a novel mechanism-aware testing strategy that can be used for risk assessment of new NMs
- Novel ALI systems imitating realistic exposure conditions
- Demonstration of mapping inhalation-instillation
- Demonstration of equivalence between rat/mouse/human models
- Novel toxicity endpoints bound to *in vivo* AOPs
- Novel in vitro assays targeting MIE/KE based on reporter gene

Project outcomes 2018-20: Industry/Regulation

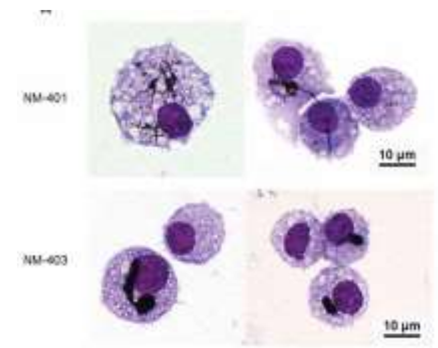
- Elucidation of toxicity mechanisms for oxides, carbonaceous materials
- Creation of basis for grouping NMs by their ability to induce specific AOPs
- Creation of basis for read-across and safety by design through identification of NM properties of concern
- Mechanism-aware QSARs relating NM properties to biological activity
- Database of NM properties, bionano interactions

SmartNanoTox methods

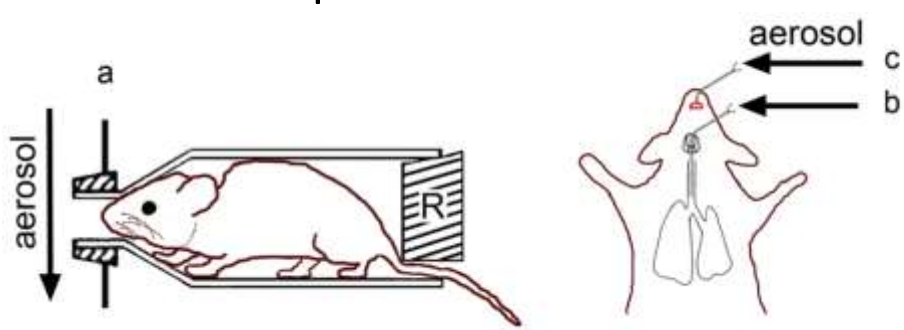
Molecular simulation



In vitro exposure

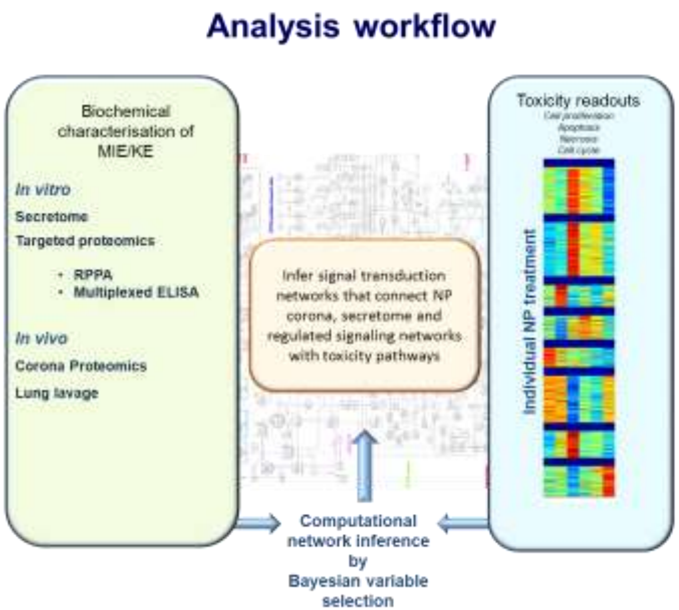


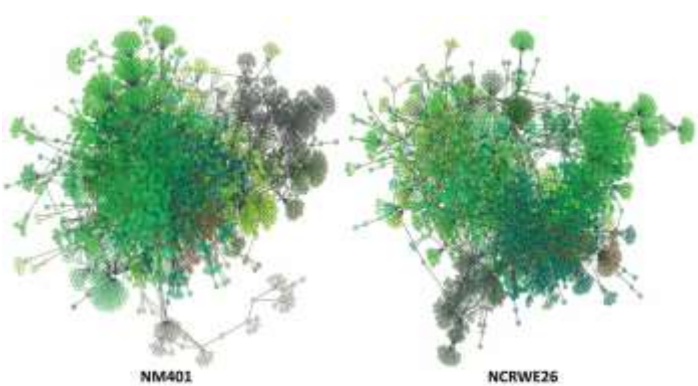
In vivo exposure



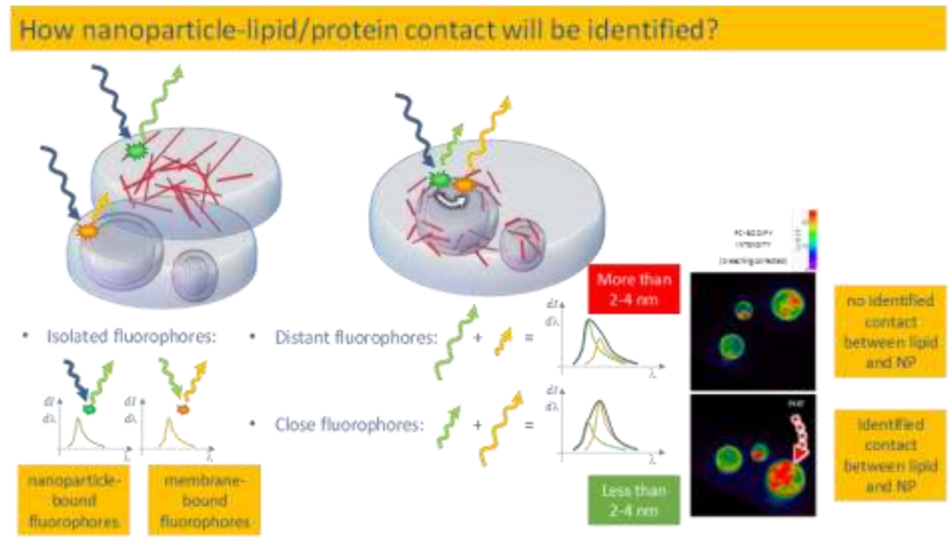
SmartNanoTox methods

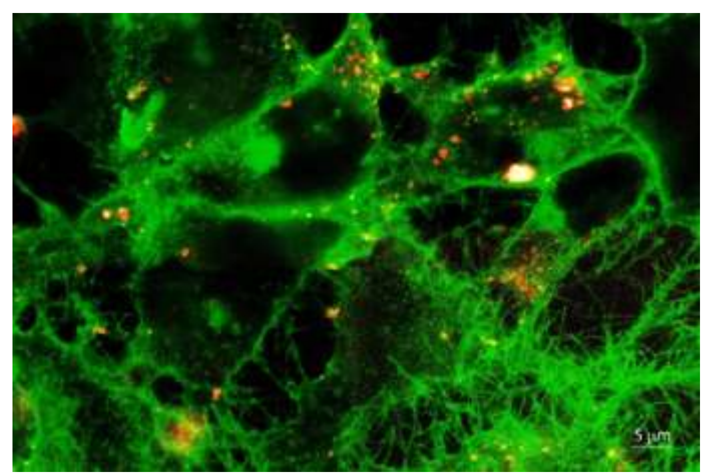
Omics, systems biology



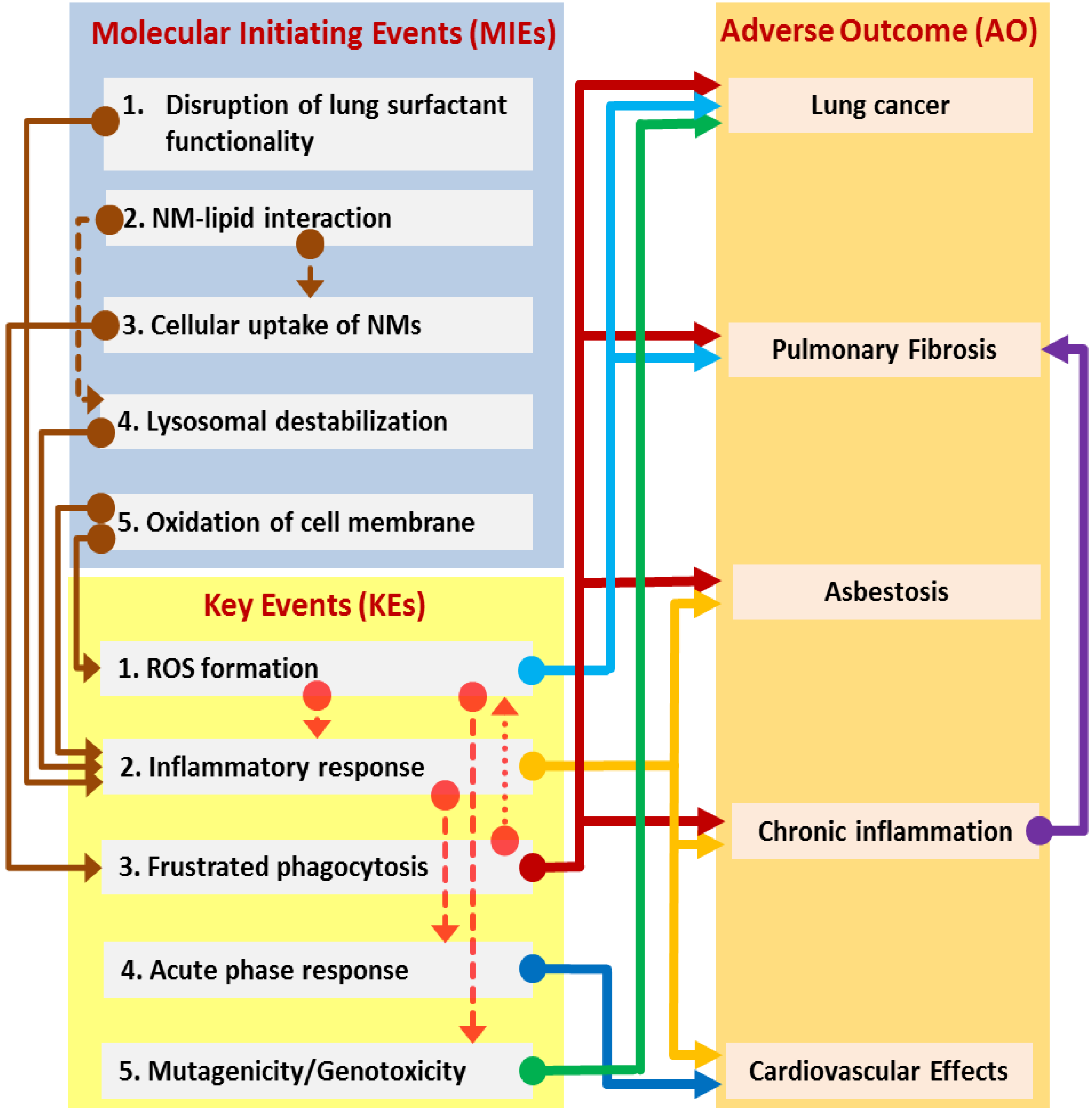


NP tracking, post-uptake characterisation





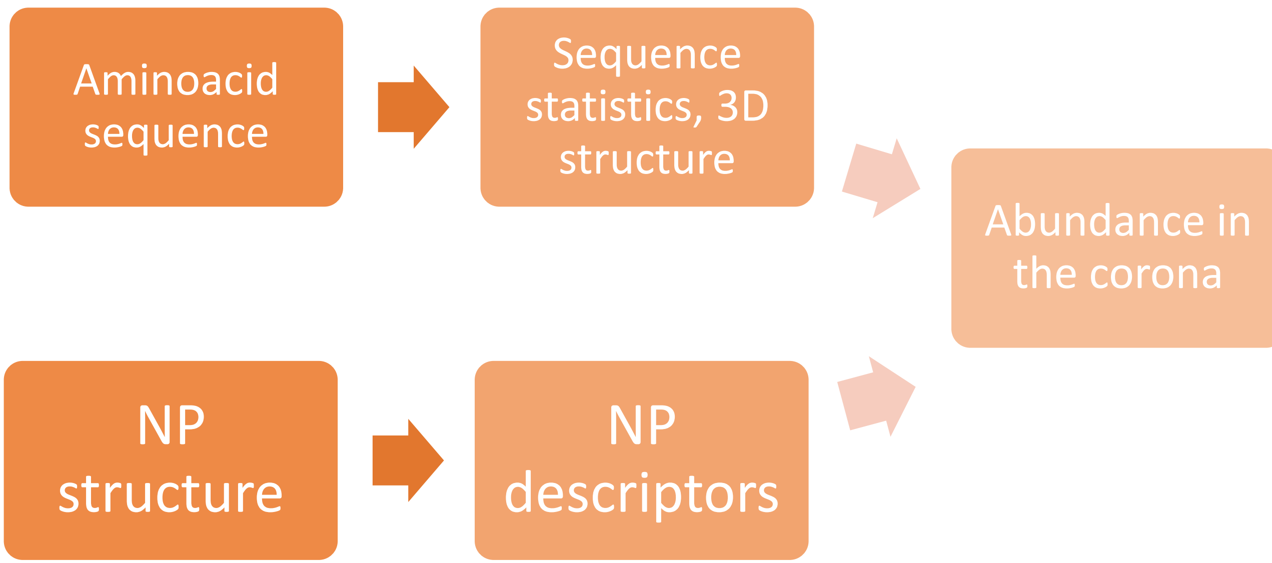
AOP
MIE
KE



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

NP-protein interactions
Bio/Nanoinformatics approach

Prediction of corona content using NP and protein descriptors:

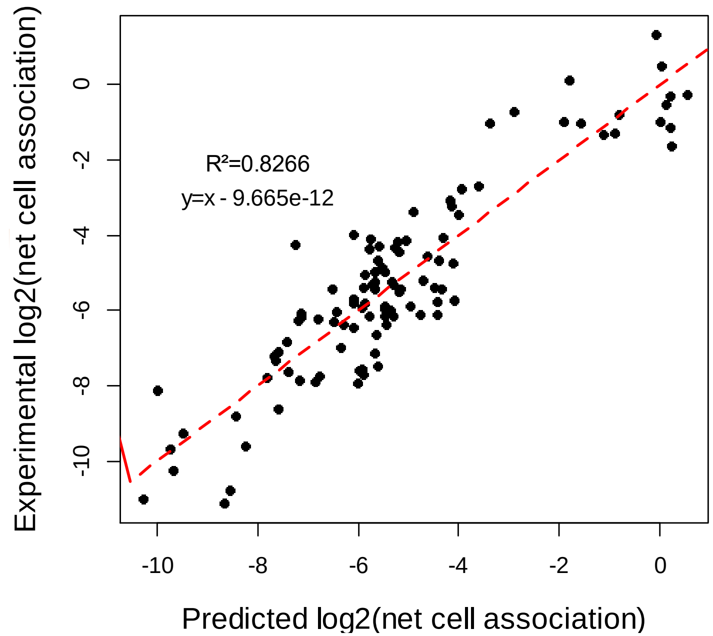


Sequence descriptors (PepStat), 3D structure (I-TASSER)

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