The Adverse Outcome Pathway Approach in Nanotoxicology

Kirsten Gerloff

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Stimulating innovation
Supporting legislation

Background – Adverse Outcome Pathway (AOP)

- a **conceptual framework** that portrays existing knowledge on the links between a **Molecular Initiating Event (MIE)** and an **Adverse Outcome (AO)**

→ adverse health or ecotoxicological effect of regulatory concern

Launched by OECD in 2012: Guidance document available on OECD webpage

→ http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm

→ http://ihcp.jrc.ec.europa.eu/our_activities/alt-animal-testing-safety-assessment-chemicals/improved_safety_assessment_chemicals/adverse-outcome-pathways-aop

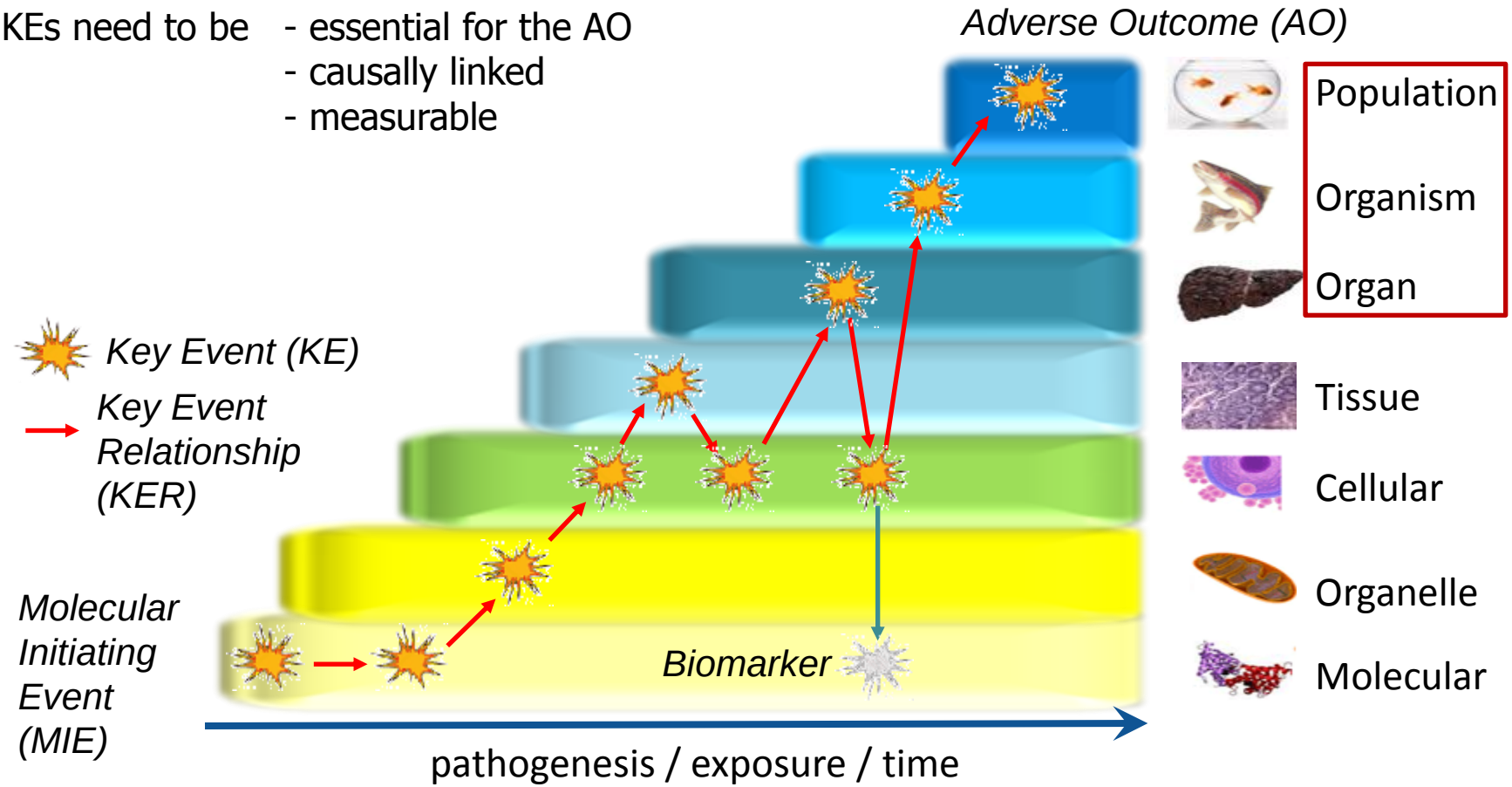
Systematic AOP development in the "AOP-wiki" → formation of an AOP network

Adverse Outcome Pathway Wiki https://aopkb.org/

Joint Research Centre

Background – Adverse Outcome Pathway (AOP)

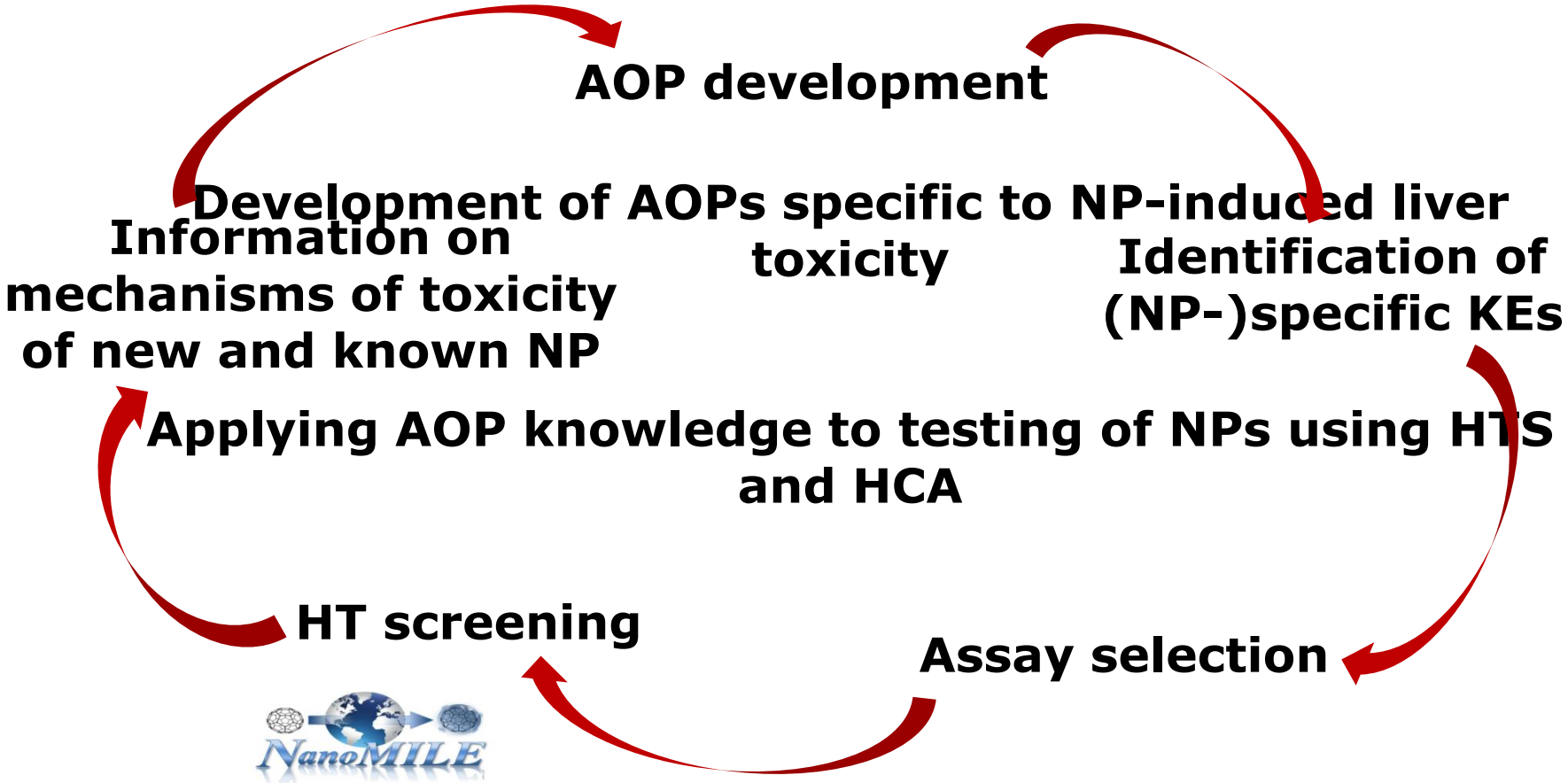
→ KEs need to be
- essential for the AO
- causally linked
- measurable



Why develop AOPs?

- Make better use of mechanistic understanding in risk assessment and decision making
- Reduce reliance on animal testing
- Facilitate integration and use of newer 'non-standard' data such as HTS and 'omics
- Faster assessment of data-poor materials
- Aid identification of knowledge gaps to inform intelligent testing strategies
- Inform the OECD Test Guidelines Programme in the selection of methods to be developed into international Test Guidelines
- Guide the development of computational profilers for forming chemical categories and doing read-across in the QSAR Toolbox

Objectives


AOP development
Development of AOPs specific to NP-induced liver toxicity
Identification of (NP-)specific KEs
Applying AOP knowledge to testing of NPs using HTS and HCA
Assay selection
HT screening
Information on mechanisms of toxicity of new and known NP

Nano-AOP development
translating theory into practice

Organ of interest: liver

Adverse Outcome of interest: inflammation / hepatitis

NP category: metal oxides (starting with TiO_2 and including ZnO, SiO_2, CeO_2… to facilitate read-across)

→ Literature data mining
→ Development of structured MS access database

- *in vitro* and *in vivo* data (primary literature)

- capturing major mechanisms of toxicity in a structured way
- facilitating tailored searches and further individual structuring

→ Data generation using HTS and HCA (NanoMILE WP4)

Challenges specific to nano-AOP development

- No availability of human data (for liver effects)

- Properties of nanomaterials vary hugely even for the same material

  example: TiO_2 → rutile versus anatase, particle size,…

  → Small NP (5nm) might lead to a different AO than larger NP (100nm)

- Studies are difficult to compare in terms of:

  treatment protocols, tested endpoints, tested species, cell types,…

- Initial fate of nanomaterials often unknown

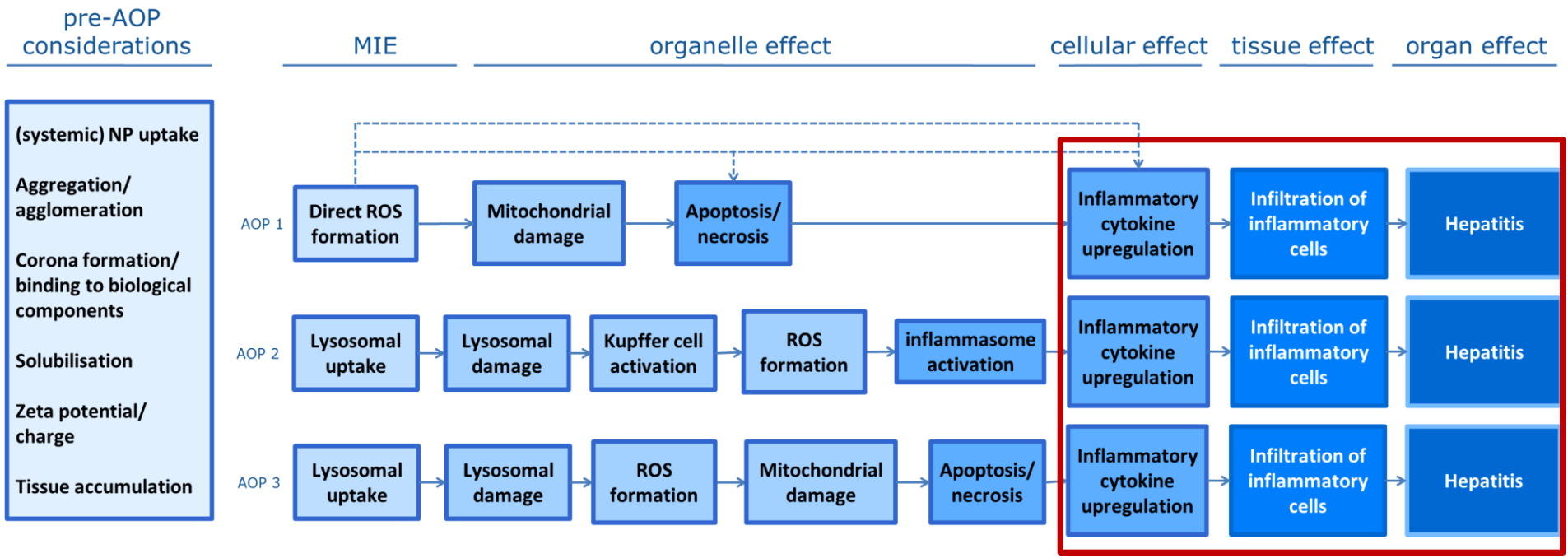
  → do they act as "nanomaterials"?

  → Relevance of biological barriers and NP life cycle

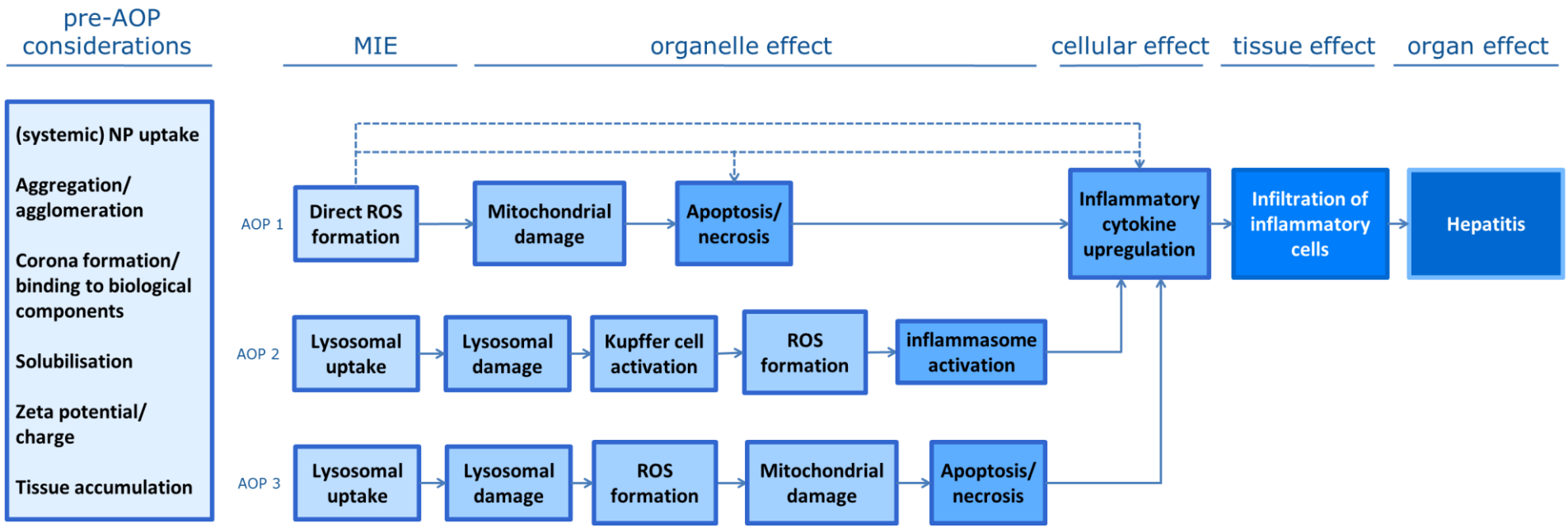
  → **challenge for defining the relevant MIE**

  → **still "nano"-specific?**

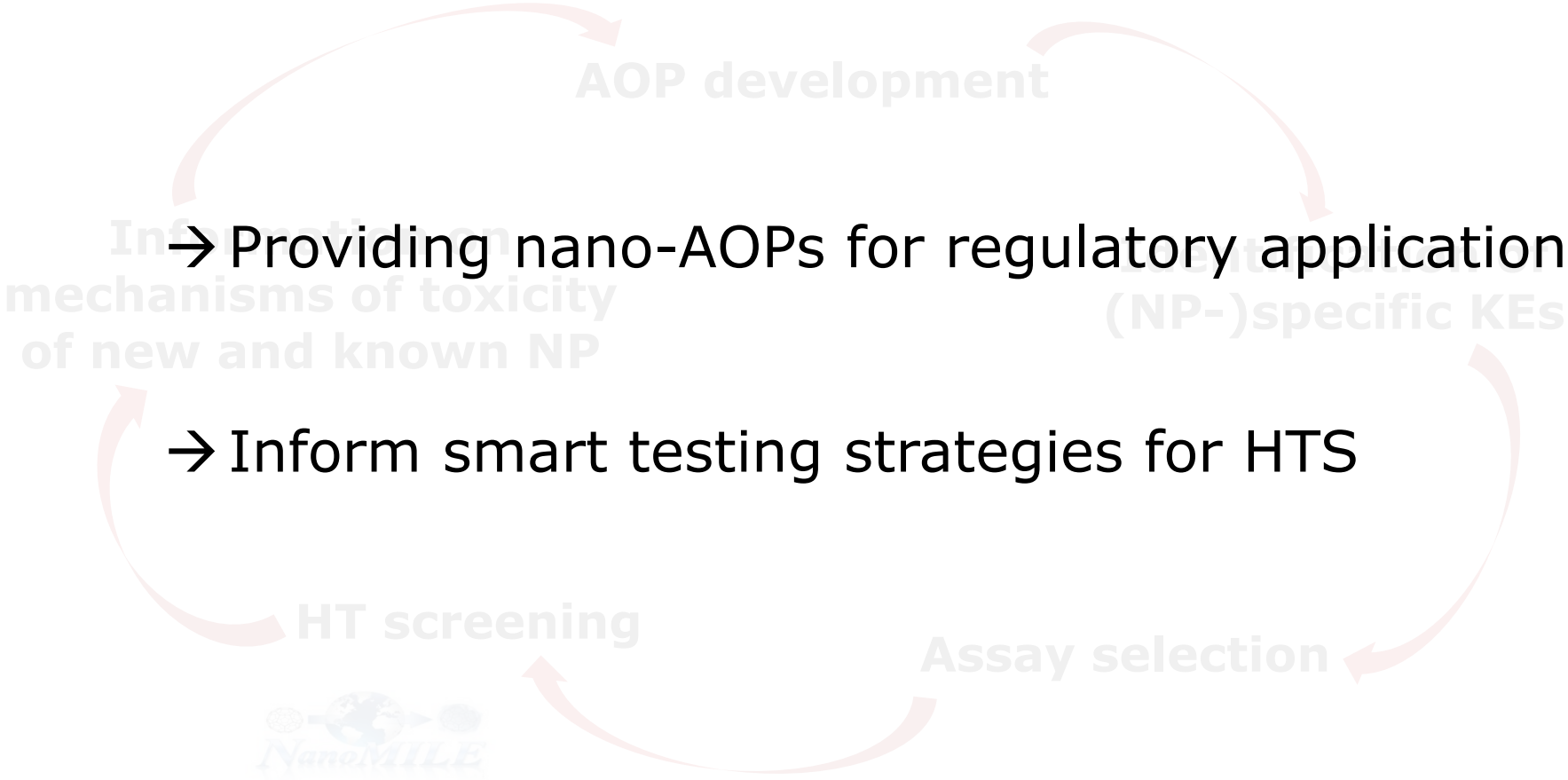
Putative AOPs for metal oxide-induced hepatitis



Putative AOPs for metal oxide-induced hepatitis



Nano-AOP development – a dynamic process



→ Providing nano-AOPs for regulatory application

→ Inform smart testing strategies for HTS

Joint Research Centre (JRC)

The European Commission's in-house science service

Maurice Whelan
Brigitte Landesmann
Sharon Munn
Andrew Worth

Taina Palosaari
Elisabeth Joossens
Peter Macko

www.jrc.ec.europa.eu

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