The use of Predictive Nano EHS and Risk Assessment to build a Sustainable Nanotechnology Enterprise

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Nanotechnology as a Sustainability Science
vs
The Sustainability of Nanotechnology

Nano as a Sustainability Science

- Environmental cleanup
- Decreasing carbon footprint
- Societal acceptance
- Energy, food, water impact
- Green manufacturing
- Nanomedicine/POC delivery
- Education and Outreach

Sustainability of Nanotechnology

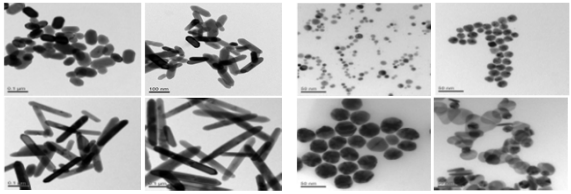
- Prospective knowledge and predictive decisions
- Nano EHS and the development of a 21st-century high throughput, predictive and computational platform for Nano EHS
- Adaptable risk assessment
- Life Cycle analysis
- Legal & Policy considerations

UNIVERSITY OF CALIFORNIA

UC CEIN Center for Environmental Implications of Nanotechnology

UC CEIN

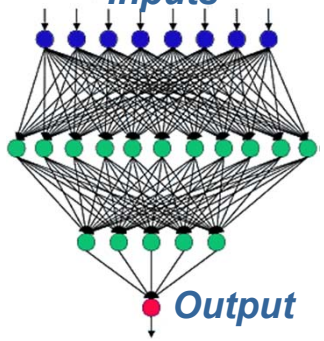
Nanomaterial libraries



Compositions and Properties

Structure Activity Relationships (Nano-SARs)

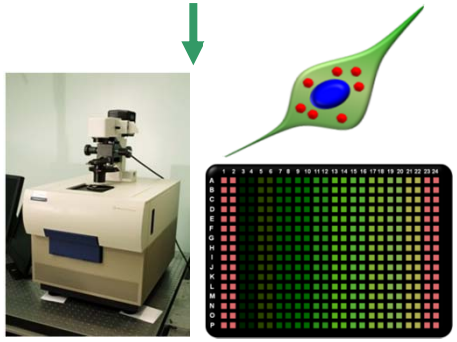
Inputs



Output

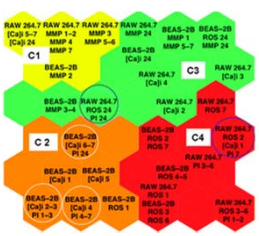
- Data repository, transformation
- Feature analysis
- In silico decision making tools
- Machine learning

Fate
Transport



Cell & biomolecular screening

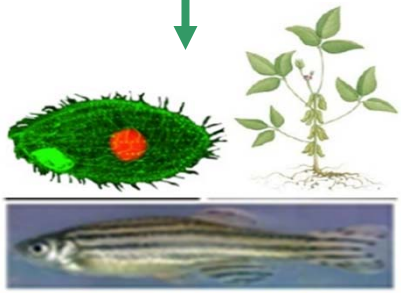
In vitro/In vivo predictions



SOM

SSMD

Exposure



In vivo screening-Organisms, populations, mesocosms

- Hazard ranking
- QSARs
- Exposure modeling
- Environmental Decision Analysis
- Safer-by-design strategies

Life Cycle Analysis

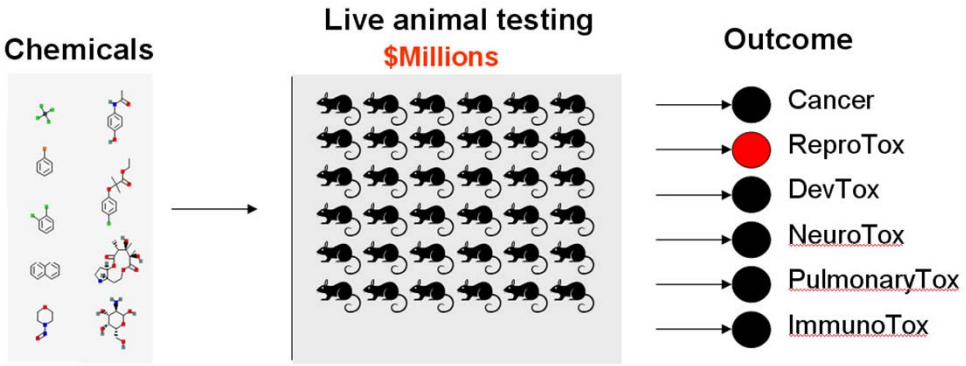
Multimedia Analysis

"Toxicity Testing in the 21st Century: A Vision and a Strategy"

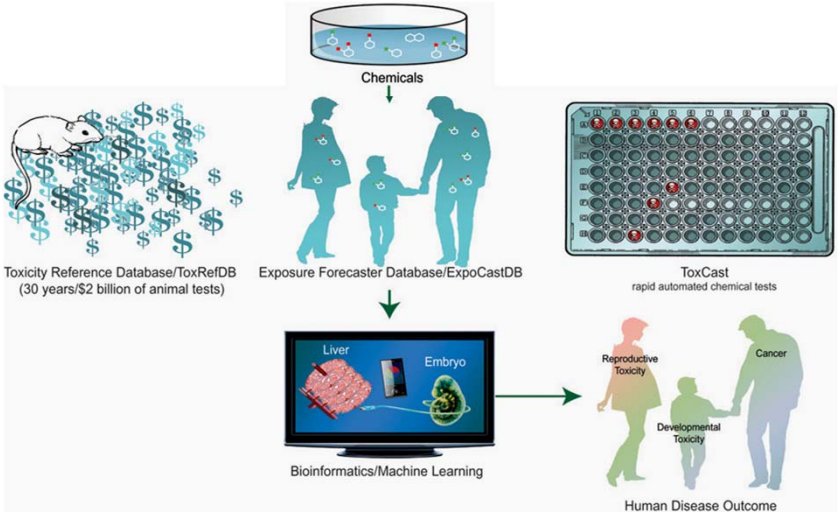
Current: One material at a time descriptive animal testing

US National Academy of Science (2007)

- Wide coverage of toxicants
- Robust scientific platform for screening
- Predictive tests utilizing toxicity mechanisms
- High throughput discovery
- Connectivity to *in vivo*

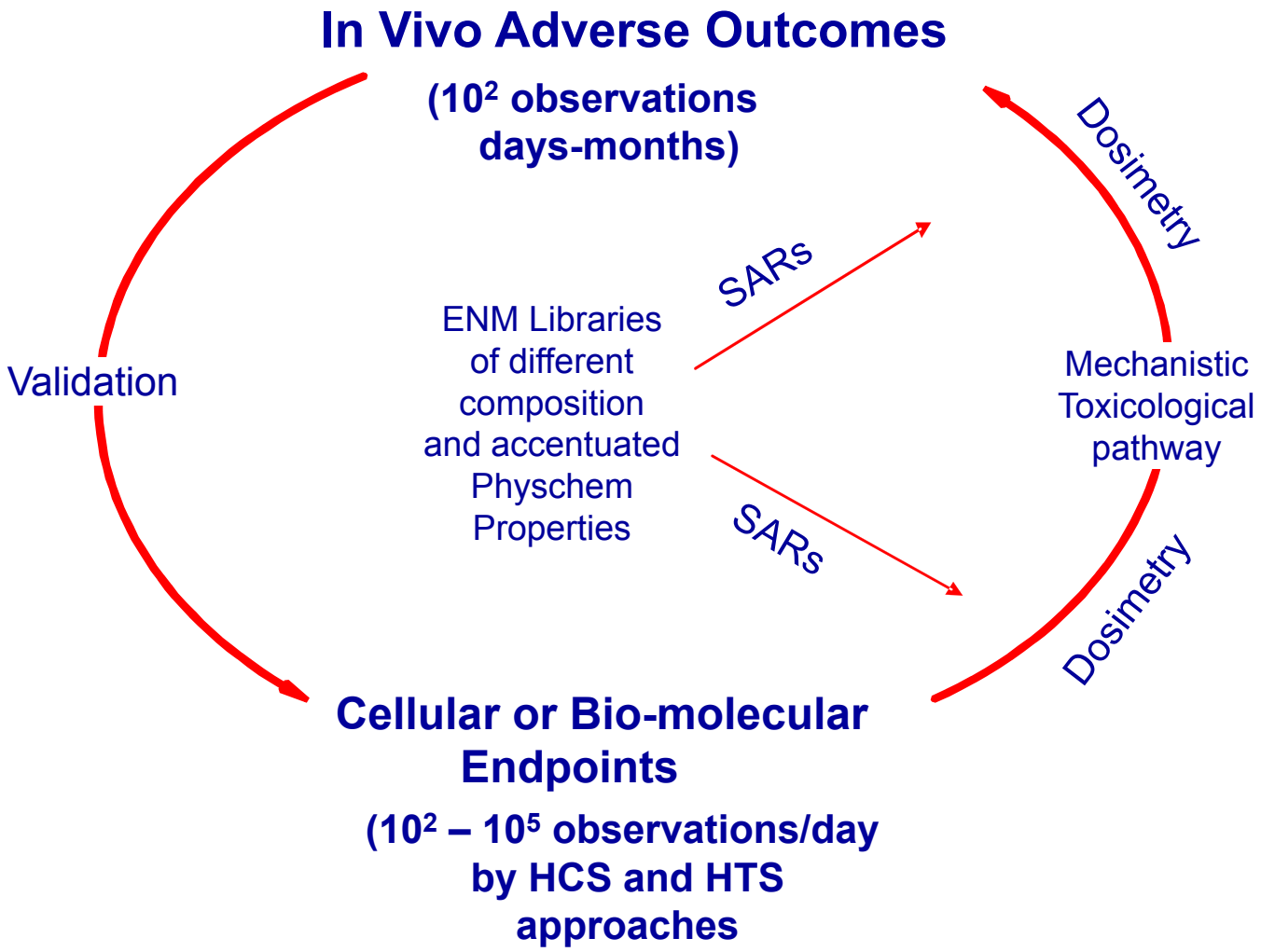


Proposed: Rapid mechanism-based predictive testing



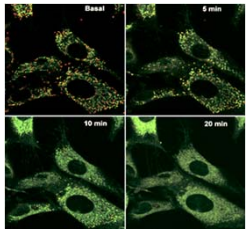
Meng et al. ACS Nano. 2009
Nel et al. Accounts Chem Res, 2012
http://www.nap.edu/catalog.php?record_id=11970
http://www.epa.gov/ncct/toxcast

Nanomaterial Predictive Toxicology
(proportional weighted discovery)



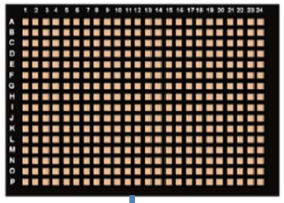
Meng et al. ACS Nano. 2009
Nel et al. Accounts Chem Res, 2012

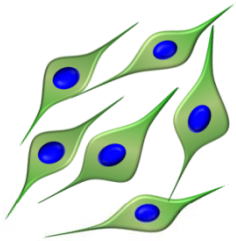
Tools: Cellular High Throughput Screening



Mitochondrial damage
ROS generation
Stress response
Cellular apoptosis

Epifluorescence microscopy

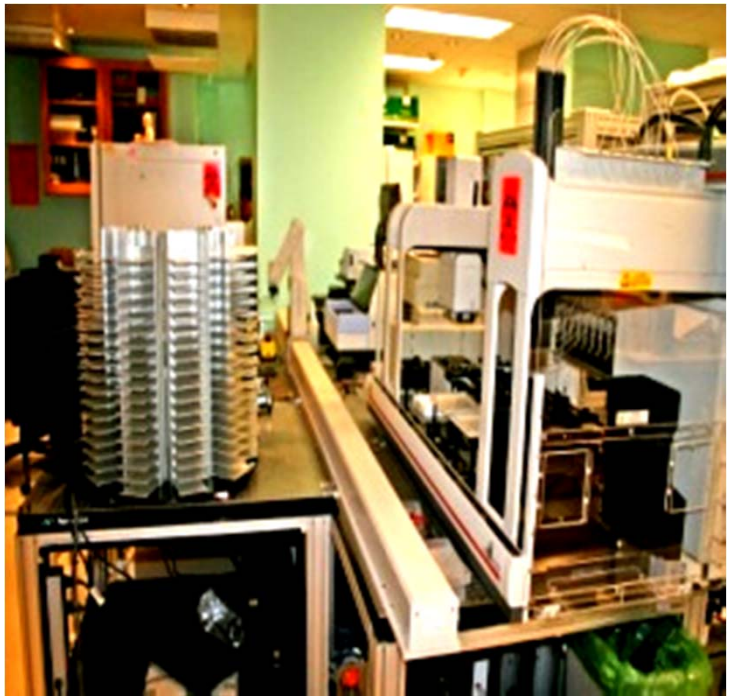




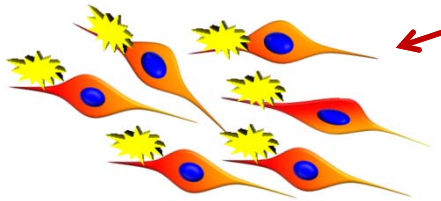
Cell growth

RBC lysis

UV-Vis spectroscopy

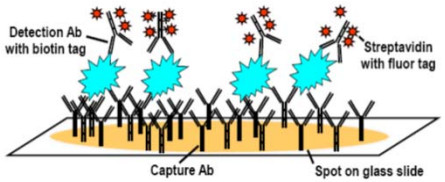


Luminescence



Reporter genes for sublethal effects

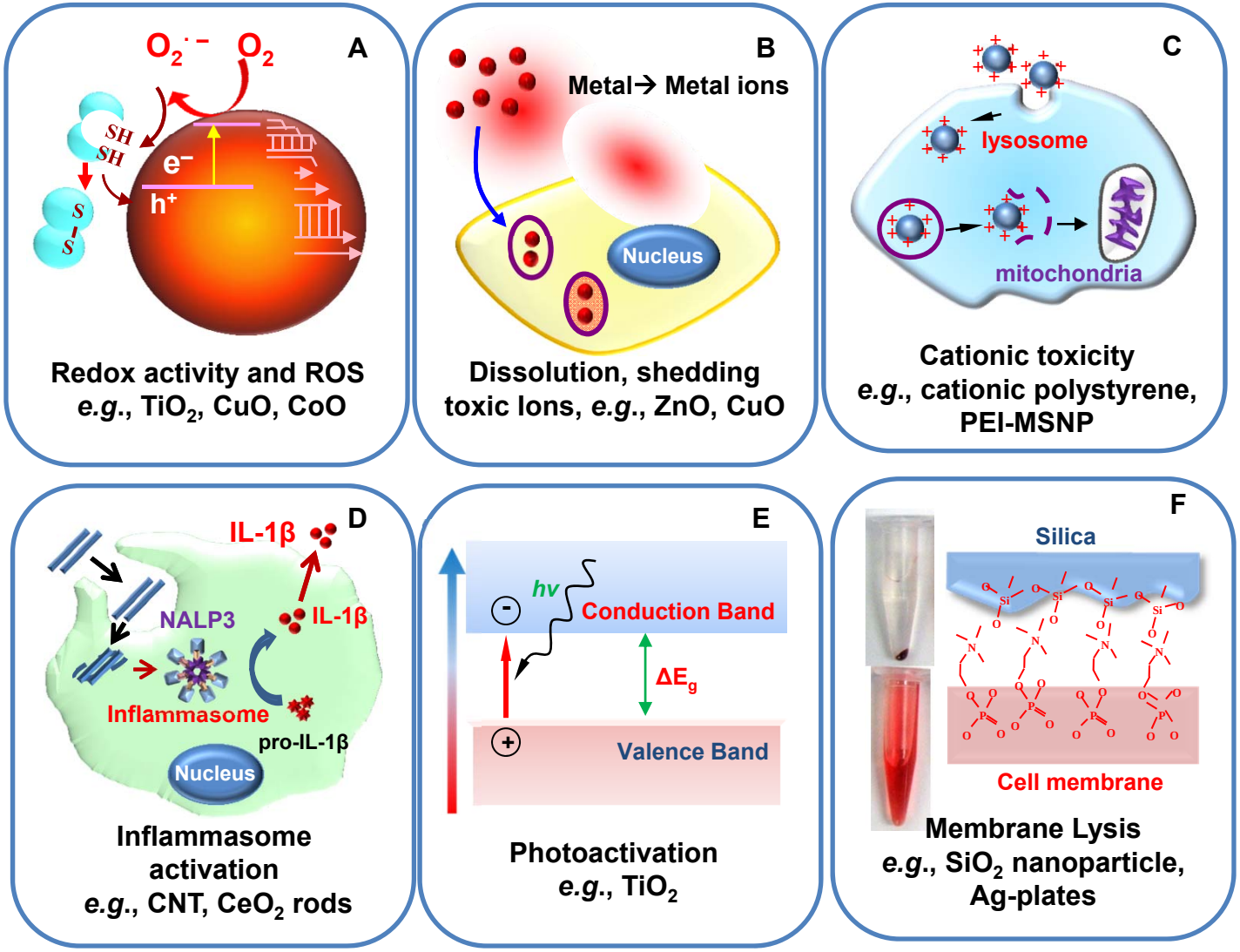
Multiplex cytokine &Chemokine assay



Assessment of Inflammation

George et al. ACS Nano. 2010
George et al. ACS Nano. 2011
Nel et al. ACR. 2012

Tools: Mechanistic Toxicological Pathways in Cells for Predictive Toxicological Modeling



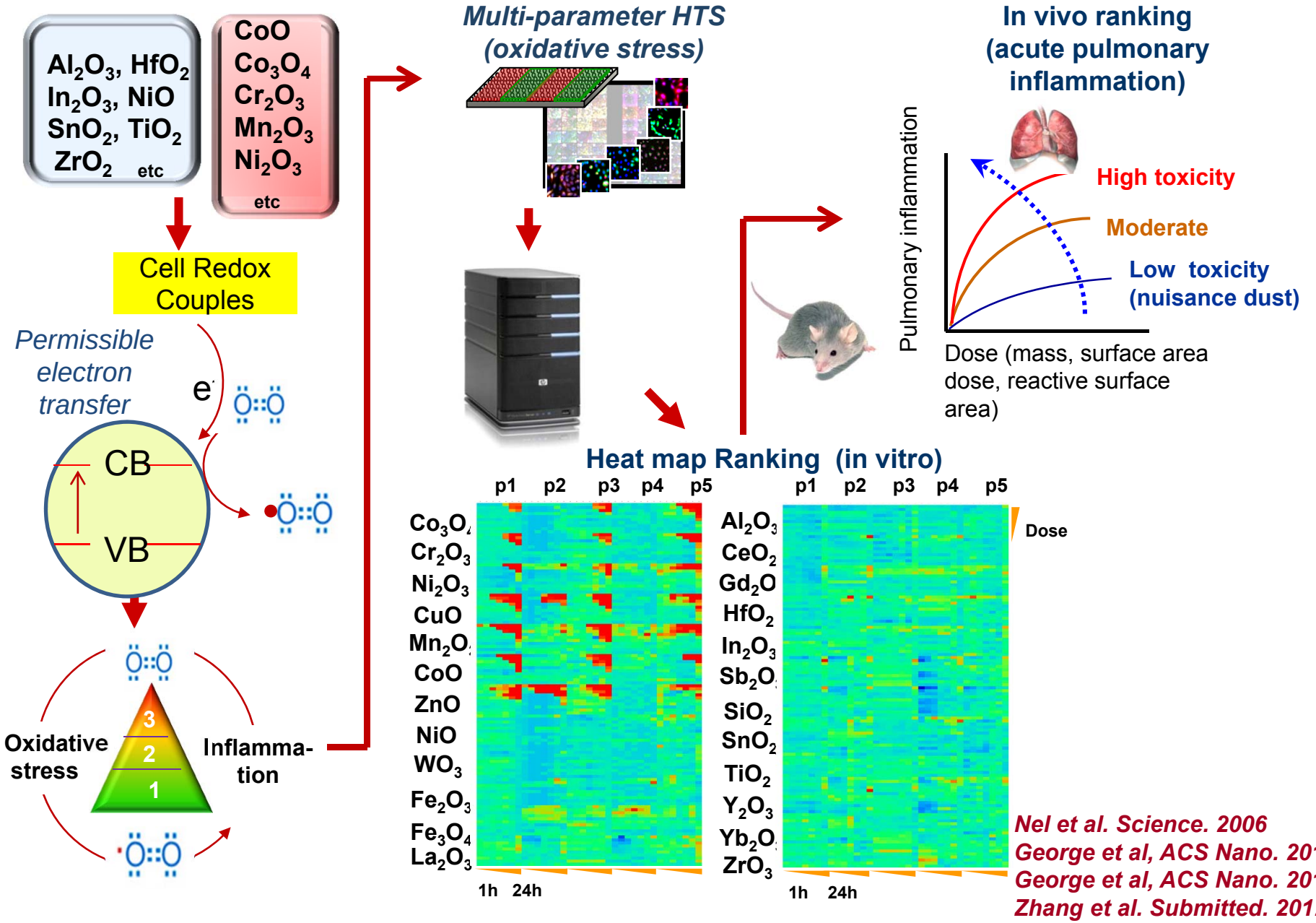
Nel et al. Nature Material, 2009
Xia et al, ACS Nano, 2008
Xia et al. ACS Nano. 2011

George et al. ACS Nano. 2010
George et al. ACS Nano. 2011
George et al JACS 2011

Lin et al. ACS Nano. 2011
Xia et al ACS Nano. 2009
Zhang et al ACS Nano 2011

Wang et al. ACS Nano. 2010
Wang et al ACS Nano. 2011

Predictive HTS-based Paradigm for Oxidative Stress

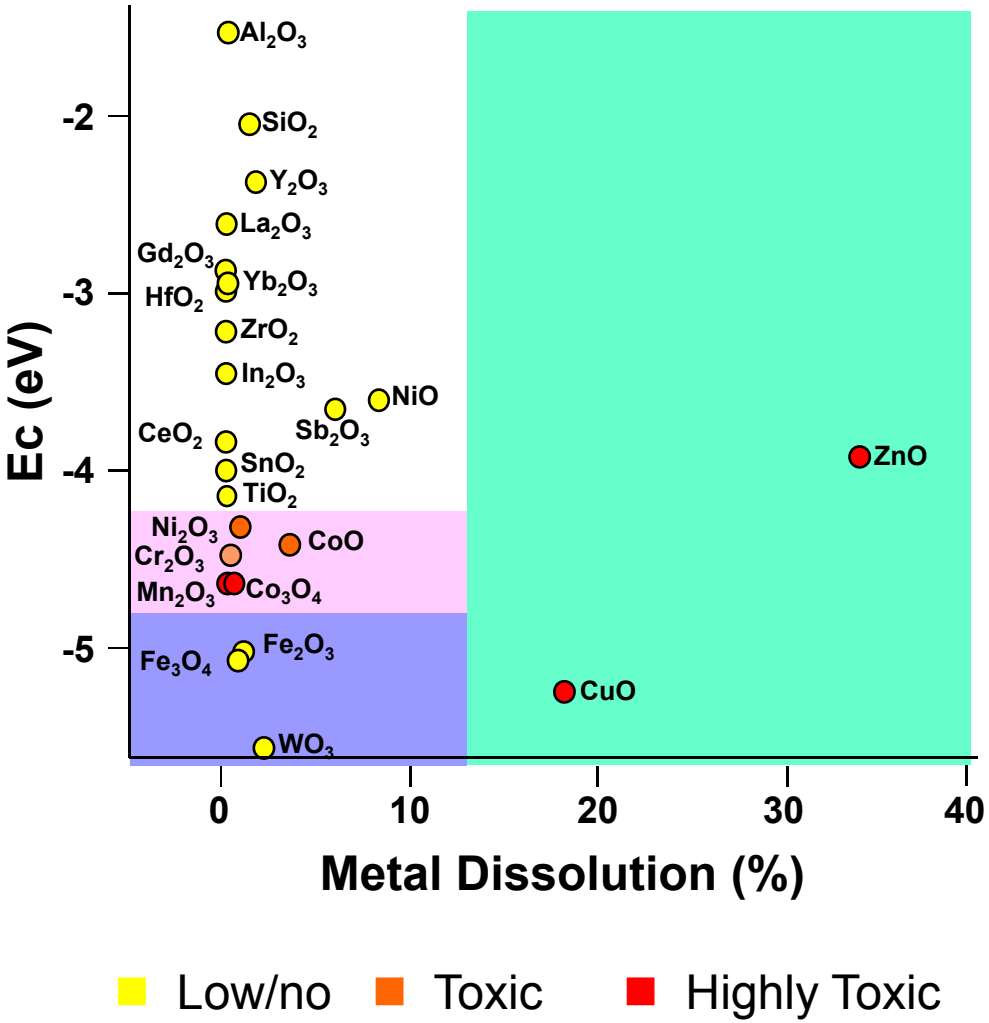


Nel et al. Science. 2006
George et al, ACS Nano. 2010
George et al, ACS Nano. 2011
Zhang et al. Submitted. 2012

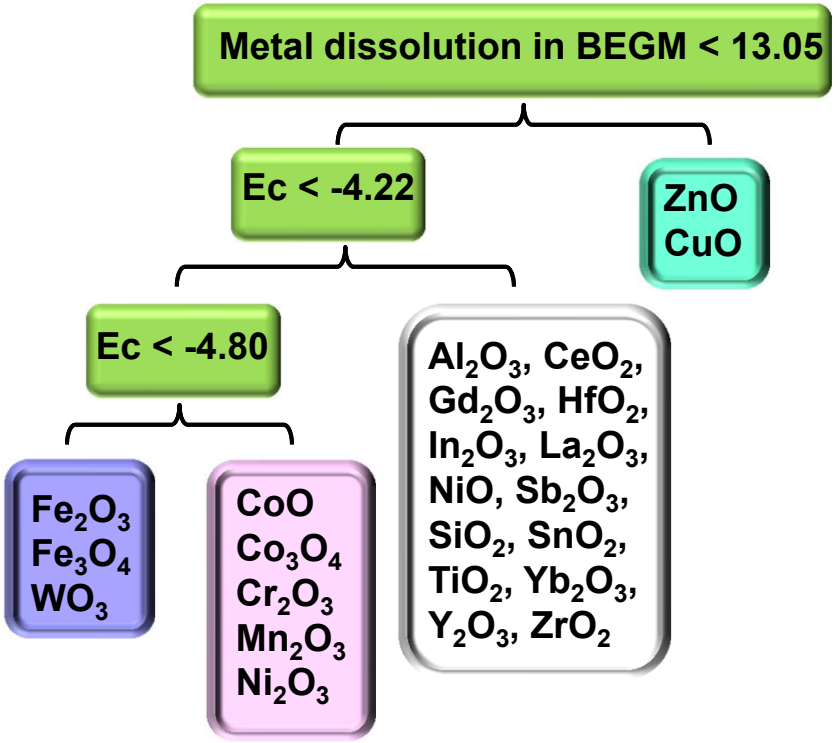
Toxicity explained by Dissolution and Conduction Energy

(statistical testing of scientific hypothesis)

- Highly non-linear effects of dissolution and conduction energy explain MoX toxicity in agreement with biochemical theories.

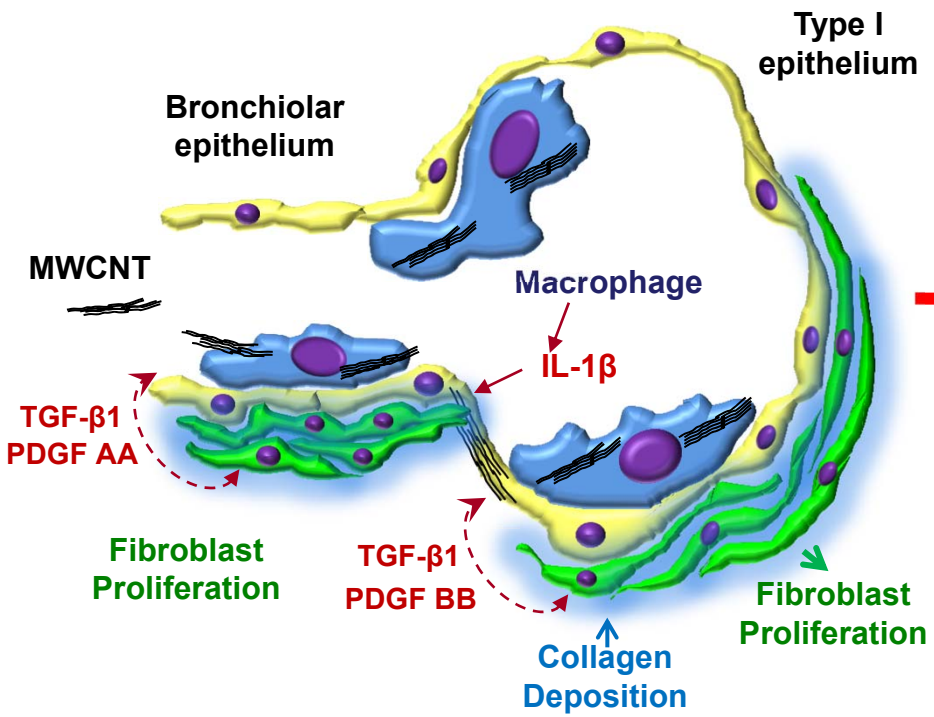


Regression Tree



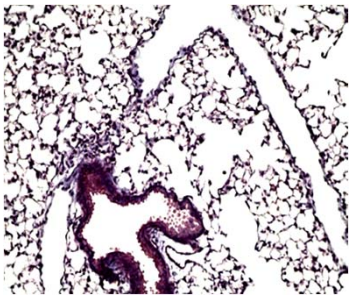
George e al. ACS Nano. 2010
Xia et al. ACS Nano. 2011
Zhang et al. ACS Nano. 2012

Quantifiable Cooperative Cellular Interactions as Biomarkers for CNT Disease Pathogenesis in the Lung



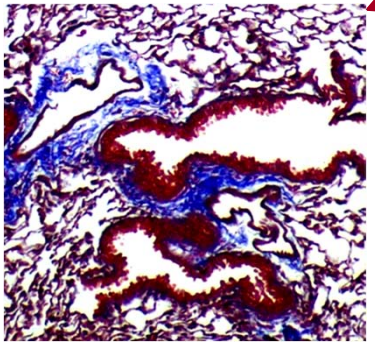
Lung

Normal



Tubes with Harmful Characteristics

Collagen Deposition



In vitro

Macrophage ↑ IL-1β

Epithelial cells ↑ TGF-β1

Co-culture

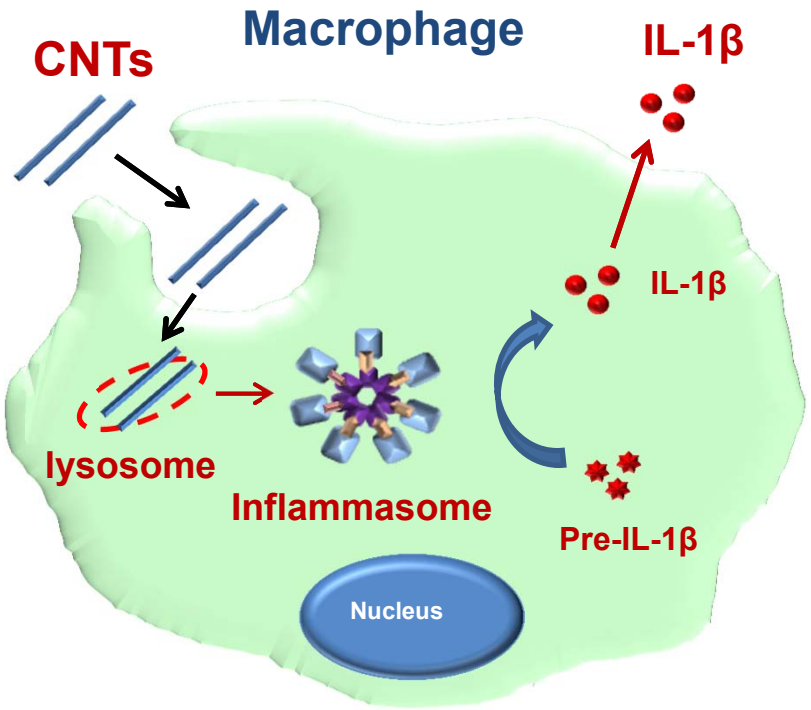
↑ PDGF

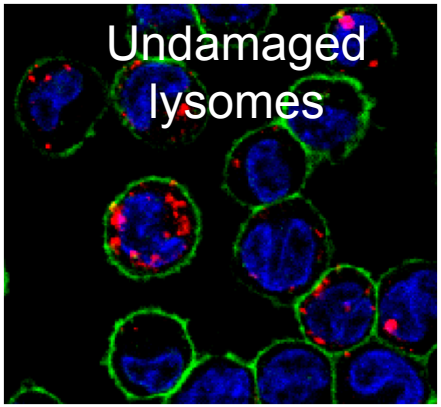
BAL Fluid Biomarkers

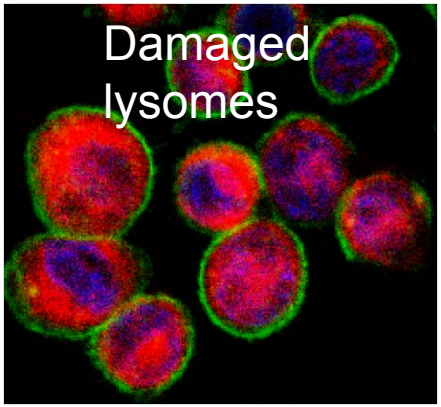
Day 1: ↑ IL-1β

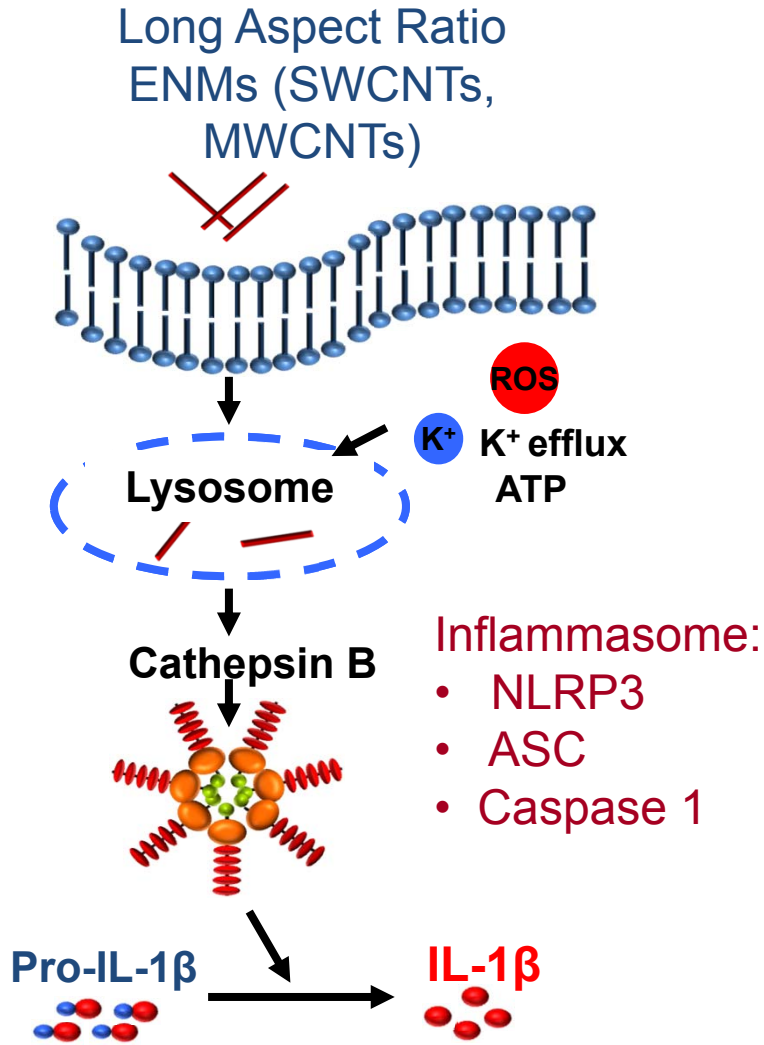
Day 7-21: ↑ TGF-β1
↑ PDGF-AA

Use of the Macrophage to develop a Predictive Toxicological Paradigm for Lung Damage





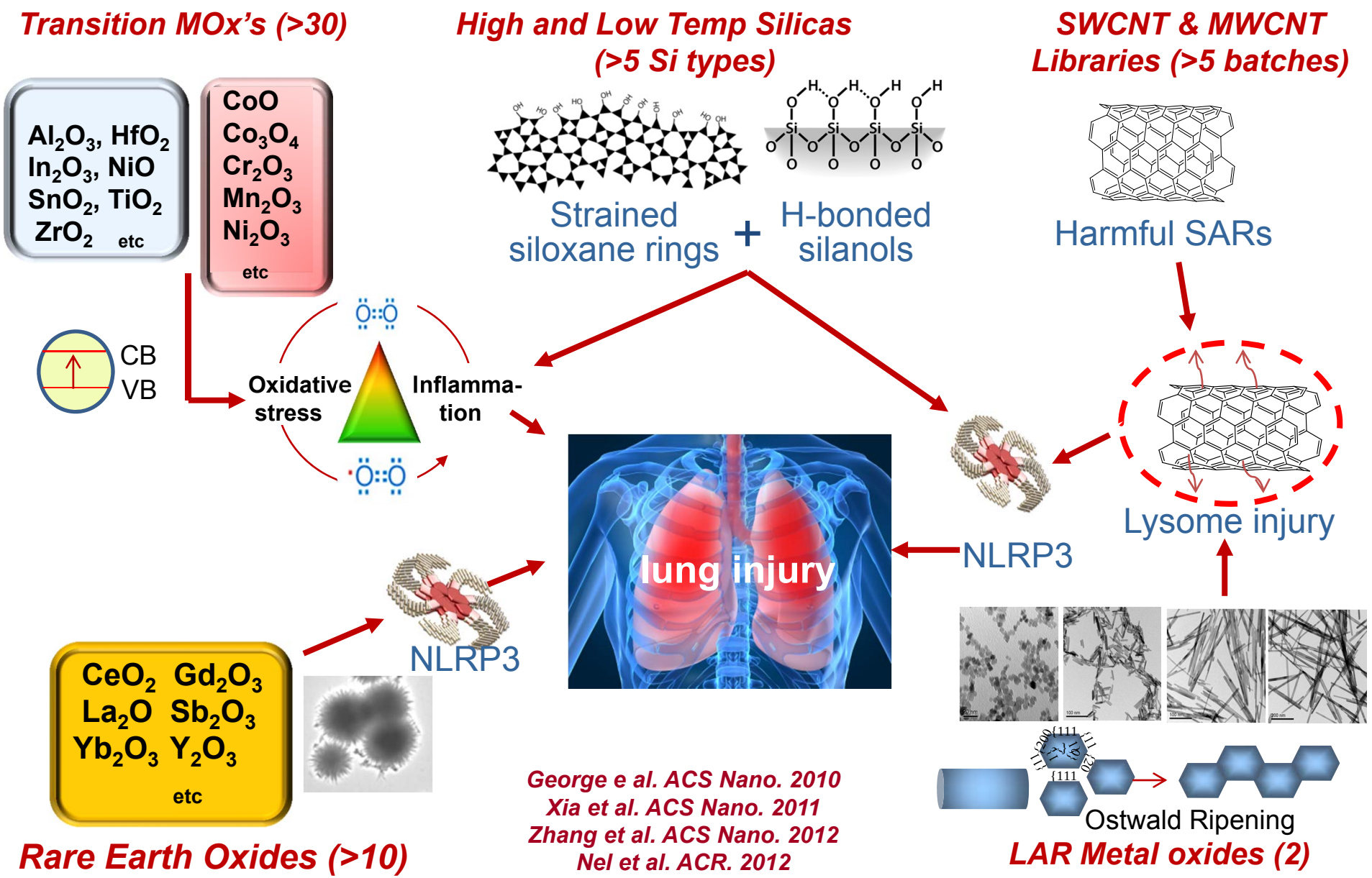




Inflammasome:
- NLRP3
- ASC
- Caspase 1

Wang et al. ACS Nano. 2010
Wang et al ACS Nano. 2011

Predictive Toxicology Approaches allows Large Numbers of Materials to be grouped in Hazard Band Categories



Tiered Approach Using Predictive Toxicological Modeling for Hazard Ranking and Risk Translation

- 1st tier – *In vitro*
  - Predictive assays to study specific mechanisms of injury
  - Rank potency of test materials *vs* well-defined positive and negative controls from libraries
  - Develop quantitative SAR analysis for *in silico* predictions

- 2nd tier – short term *in vivo*
  - Test selected materials within a category/mechanism/SAR
  - Focused/limited animal studies
  - Validate mechanism and potency within a group
  - *In vivo* hazard ranking (pathophysiology of disease outcome)

- 3rd tier – short-term or 90 day inhalation studies
  - Test the most potent materials within a tier 2 category/group
  - Dose-response extrapolation using benchmark materials to allow risk assessment
  - Establish OEL's
  - Use for read-across regulatory decision making

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PERSPECTIVE

A Multi-Stakeholder Perspective on the Use of Alternative Test Strategies for Nanomaterial Safety Assessment

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Provisional Consensus about ATS use for nano EHS

- ATS widely accepted to prioritize ENM hazard assessment but not yet ready for quantitative risk assessment or regulation
- Hazard ranking and grouping of ENMs could assist regulatory and occupational decision making
- ATS and predictive toxicological paradigms can be used to establish hazard categories and material grouping as a 1st tier of testing, which is used to prioritize more costly and elaborate animal studies
- Any framework that considers ATS for regulatory purposes needs to be transparent, participatory and engage a broad stakeholder community
- A predictive toxicological approach for CNT is potentially helpful for hazard ranking, prioritizing animal experiments, and grouping of materials
- The development of hazard ranking, material grouping and SARs can become an integral part of new product development
- It is important to consider dose-response extrapolation and exposure scenarios that link mechanistic and predictive toxicological assessment to risk assessment

IN THE SENATE OF THE UNITED STATES: a bipartisan bill to modernize title I of the Toxic Substances Control 14 Act (15 U.S.C. 2601 et seq.) –May 24 2013

"IMPLEMENTATION OF ALTERNATIVE TESTING METHODS.—To promote the development and timely incorporation of new testing methods that are not laboratory animal-based…..":

‘‘(A) ….develop a strategic plan to promote the development and implementation of alternative test methods and testing strategies to generate information used for any safety-standard determination made that reduce, refine, or replace the use of laboratory animals, including toxicity pathway-based risk assessment, in vitro studies, systems biology, computational toxicology, bioinformatics, and high-throughput screening"

‘‘(B) beginning on the date …and every 5 years thereafter, submit to Congress a report that describes the progress ……"

‘‘(C) fund and carry out research, development, performance assessment, and translational studies to accelerate the development of test methods and testing strategies that reduce, refine, or replace the use of laboratory animals in any safety-standard"