SmartNanoTox

Five AOPs developed in SmartNanoTox

Ulla Vogel, NRCWE on behalf of SmartNanoTox partners

SmartNanoTox
Smart Tools for Gauging Nano Hazards

European Commission

Horizon 2020
European Union funding
for Research & Innovation

Inhalation of particles cause several severe diseases

ORIGINAL ARTICLE

Respiratory disease mortality among US coal miners; results after 37 years of follow-up

Judith M Graber,[1,2] Leslie T Stayner,[1] Robert A Cohen,[3] Lorraine M Conroy,[3] Michael D Attfield[4]

- 8827 miners
- 37 years of follow-up (1969/71-2007)
- 67% dead (cause of death known)

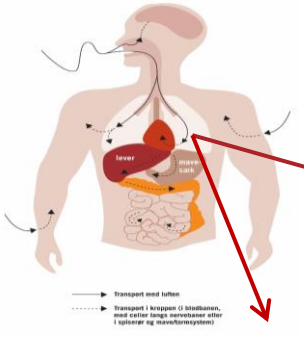
Table 2 Overall and stratified SMRs for selected underlying causes of death and percentage of ever smokers, mean cumulative coal mine dust and respirable silica exposure category by coal-rank region, radiographic status at enrolment, race and calendar year of death

	Pneumoconiosis*		COPD		Lung cancer		Ever smoked at enrolment	Mean cumulative exposure*	
Category	Obs.	SMR	Obs.	SMR	Obs.	SMR	Per cent	Coal mine dust mg/m^3-years	Respirable silica
Total	403	79.70	309	1.11	568	1.08	79.6	81.0	3.2
Region									
Eastern Pennsylvania	181	365.29	11	0.61	26	0.79	77.0	97.7	2.6
Eastern Appalachia	65	86.91	48	1.26	77	1.01	82.4	77.4	2.8
Western Appalachia	101	38.21	157	1.05	334	1.17†	82.3	82.3	3.8
Midwest	14	17.38	53	1.44†	101	1.47†	86.7	72.8	2.7
West	42	53.74	40	1.10	30	0.49†	81.7	77.5	2.5
Race									
White	389	67.44	293	1.09	542	1.09†	82.5	80.4	3.3
Black	14	129.84	16	1.60	26	0.88	78.1	90.4	3.8
Baseline radiograph									
Category 0	237	48.50	250	1.06	510	1.13†	83.0	76.4	3.2
Category 1	56	92.67	29	1.15	39	0.89	78.9	99.3	3.6
Category 2	65	192.82	24	1.85†	14	0.62	75.7	113.0	3.6
Category 3	45	409.78	6	1.39	5	0.61	82.5	122.0	3.6
Calendar year of death									
1970–1989	170	63.25	85	0.86	233	0.95	83.60	n/a	
1990–1999	143	106.20	118	1.19	208	1.31†	81.90		
2000–2007	90	127.59	106	1.26†	127	1.23†	80.90		

*SMRs from pneumoconiosis are artificially high as there is no valid comparison group in the general population. We included them to show comparisons within levels of covariates and for consistency with previously published studies of this cohort. We do not include statistical testing given the lack of a valid comparison group.
†Statistically significant at p<0.05.

Graber JM, *et al. Occup Environ Med* 2014;**71**:30–39. doi:10.1136/oemed-2013-101597

Low clearence of inhaled nanoparticles from the lung



Fine particles

Nanoparticles
Ultrafine particles

Airways

Particle deposition and removal by mucociliar clearance

Particle phagocytosis by macrophage

INFLAMMATION

release of mediators

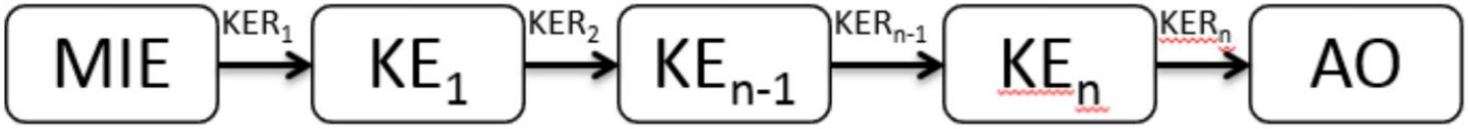
ROS

Inflammatory cells and inflammatory mediators

Marianne Dybdahl

Inhalation of nanomaterials has been linked to cancer, cardiovascular disease, and fibrosis

Adverse Outcome Pathways as a tool to understand nanomaterial-induced toxicity



- An **adverse outcome pathway** (**AOP**) is structured representation of biological events leading to adverse effects and is considered relevant to risk assessment
- The AOP links in a linear way existing knowledge along one or more series of causally connected **key events** (**KE**) between two points — a **molecular initiating event** (**MIE**) and an **adverse outcome** (**AO**) that occur at a level of biological organization relevant to risk assessment. The linkage between the events is described by **key event relationships** (**KER**) that describe the causal relationships between the key events.

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https://aopwiki.org/

AOPs are useful in nanotoxicology

- Can be used to identify new, relevant AOs based on MIE or KE
- Identify and provide evidence for causal relationships between agent and disease for classification and labelling (regulation)
- Understanding of the underlying mechanism of action guides preventive measures in the working environment
- Understanding which physico-chemical properties that drive the toxic response guide safe-by-design approaches in innovation of new nanomaterials

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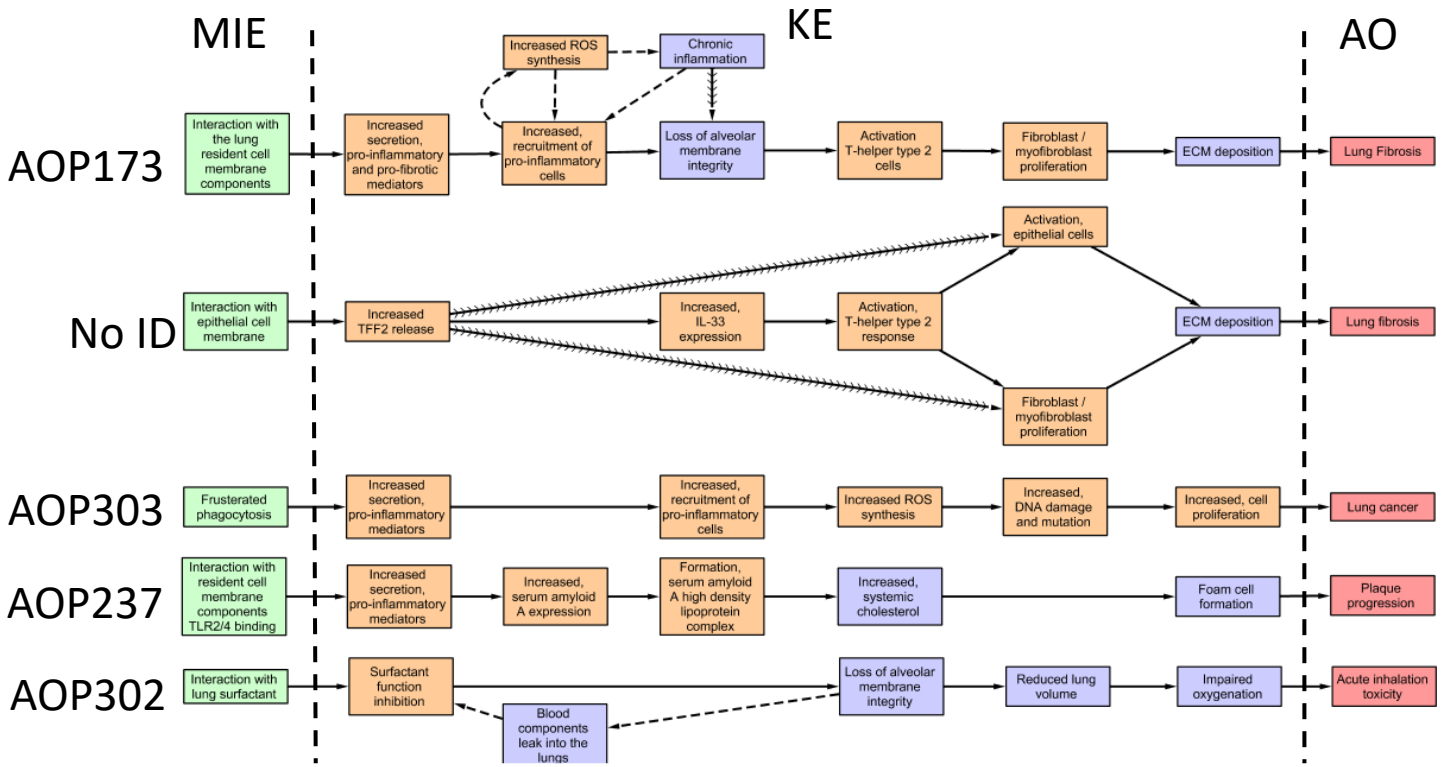
Five Nano-relevant AOPs developed in the EU H2020 project SmartNanoTox



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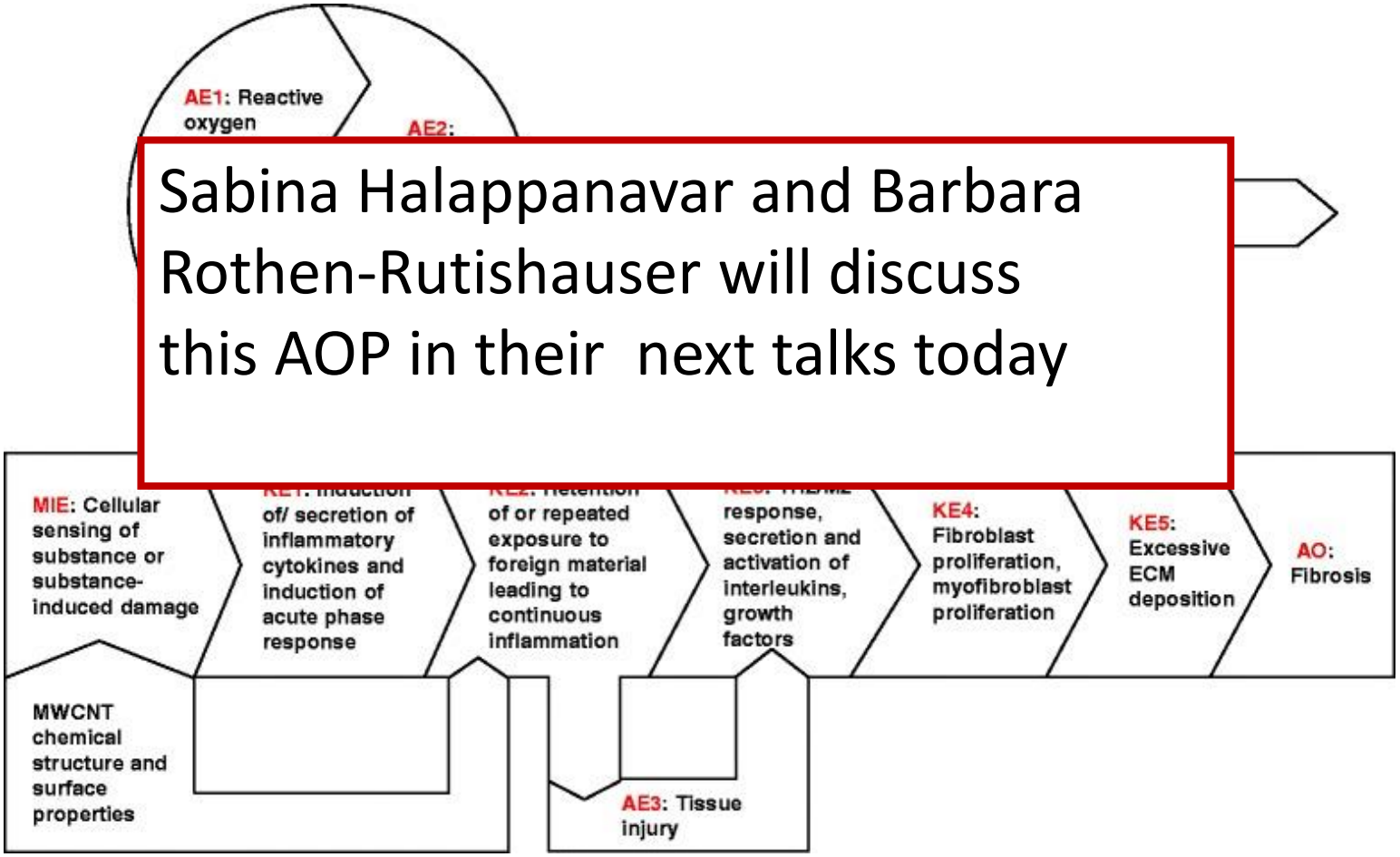
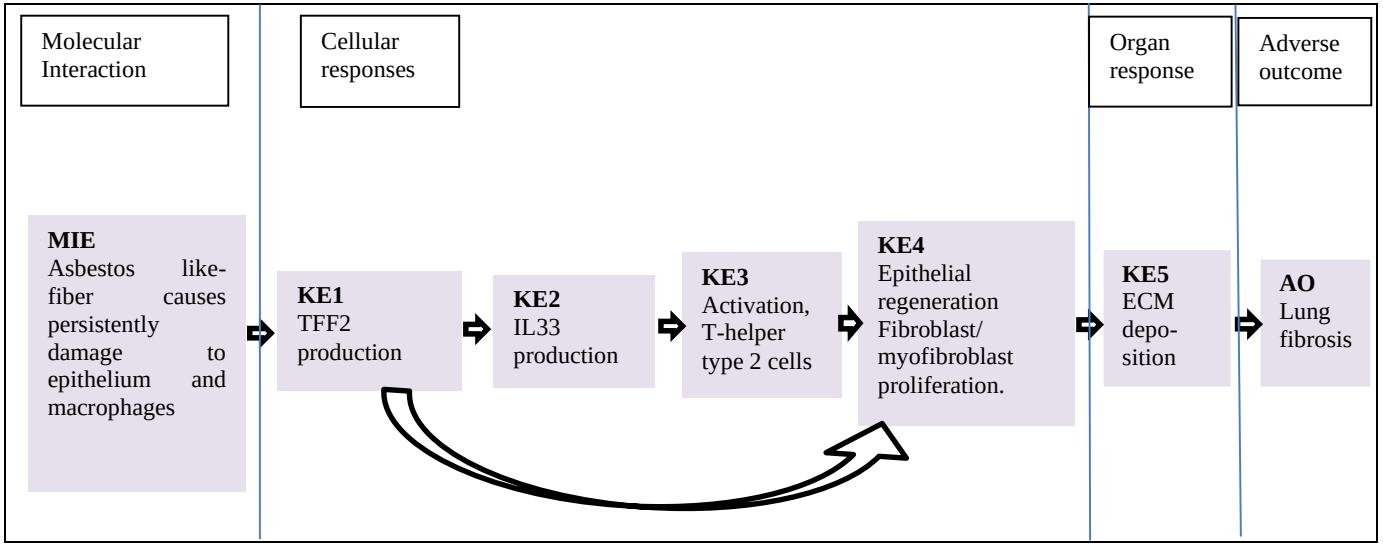
Halappanavar et al, 2020, PF&T

Fibrosis AOP 273 *(devloped by Sabina Halappanavar)*



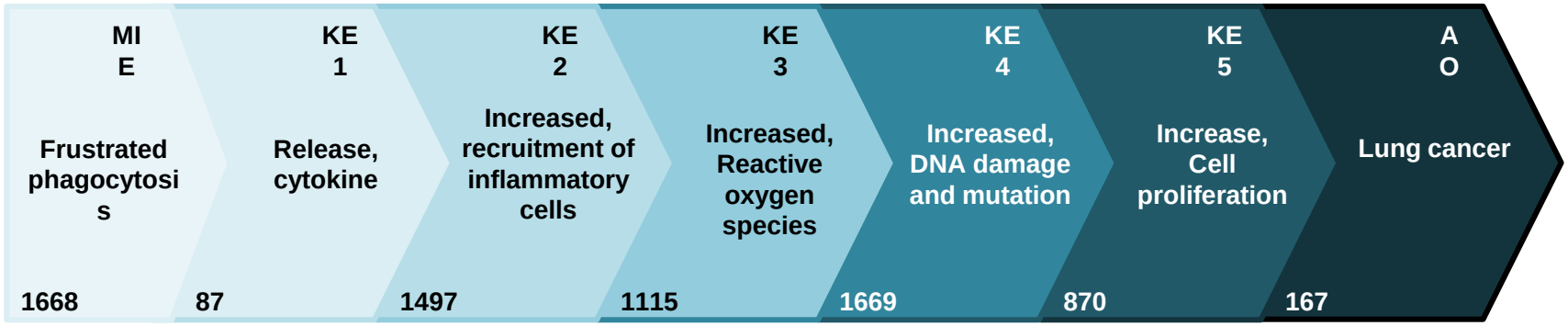
Copied from:
Nikota J, Banville A, Goodwin LR, Wu D, Williams A, Yauk CL, Wallin H, Vogel U, Halappanavar S. Stat-6 signaling pathway and not Interleukin-1 mediates multi-walled carbon nanotube-induced lung **fibrosis** in mice: insights from an adverse outcome pathway framework. ***Part Fibre Toxicol.*** 2017 Sep 13;14(1):37.

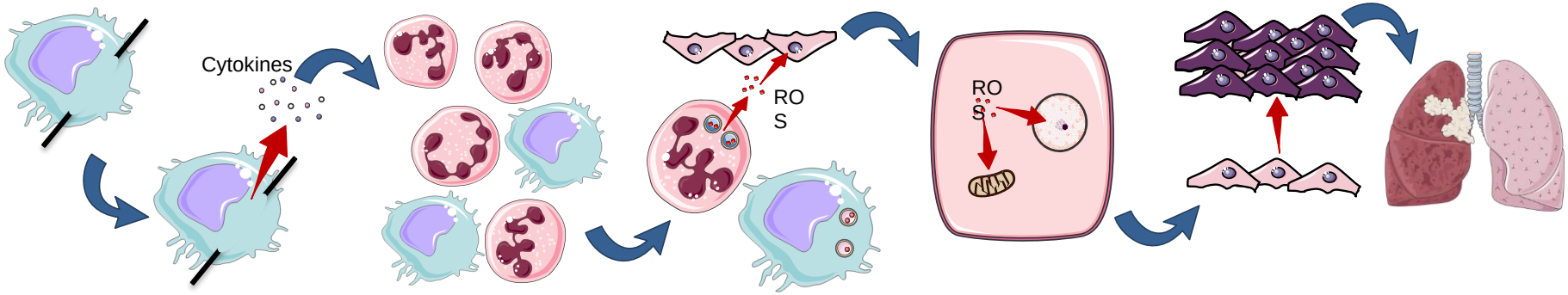
Interactions with lung tissues leading to lung fibrosis via a pathway involving Trefoil Factor 2



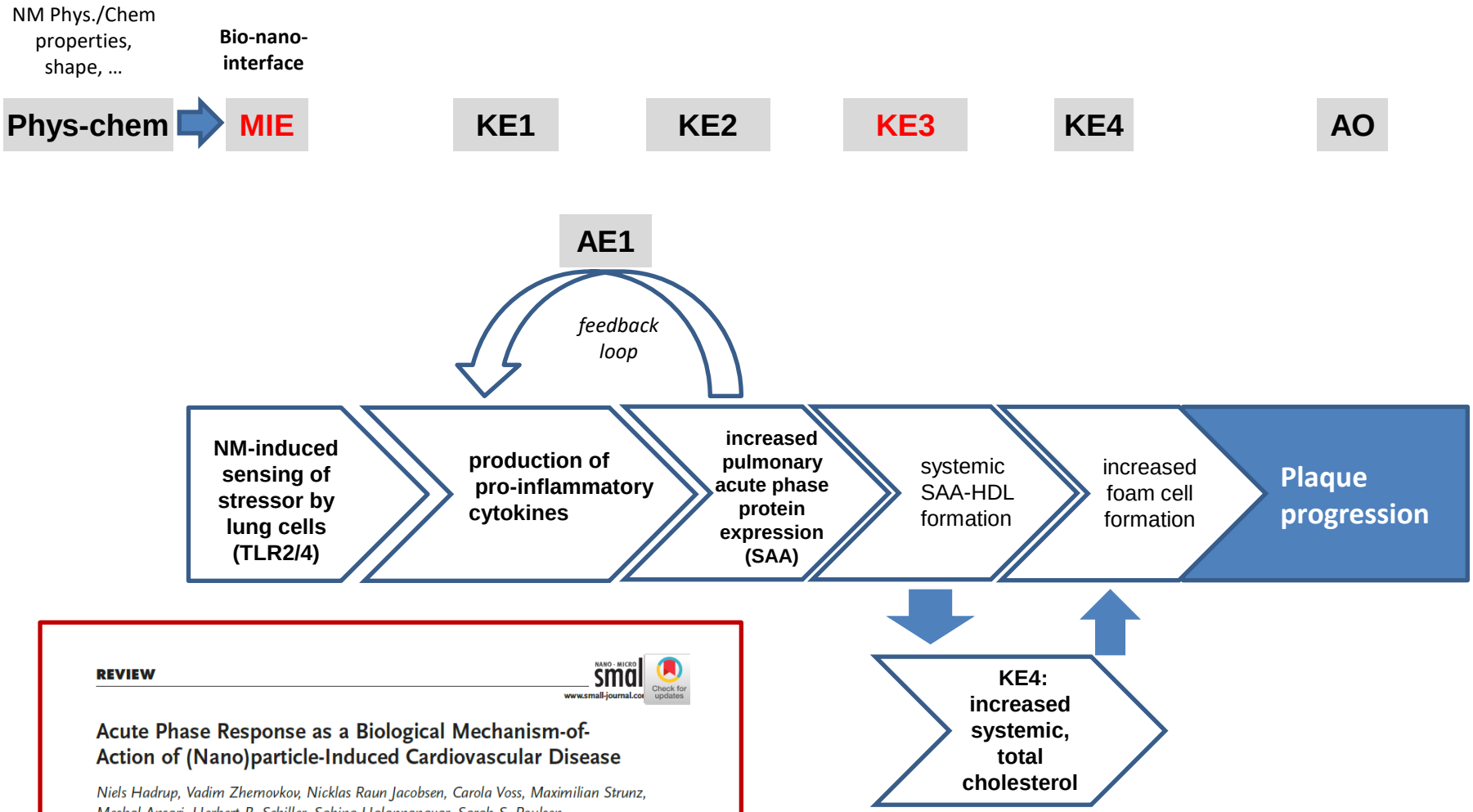
We propose that the presence of asbestos -like fibers causes damage to epithelial cells and macrophages in the lung (MIE) and, if the fibers persist, will cause a persistent TFF2 release (KE1) that in turn will cause the release of IL-33 (KE2) that will generate a Th2 type of milieu (KE3). Both the Th2 milieu and TFF2 will directly induce proliferation of fibroblast and myofibroblast and regeneration of epithelial cells (KE 4). Extracellular matrix is subsequently produced (KE5) leading to the AO of fibrosis. In addition to fibrosis, as this pathway includes regenerative events, we believe it is likely it is involved in carcinogenesis.

AOP 303: Frustrated phagocytosis-induced lung cancer





AOP237: Pulmonary acute phase response leading to CHD



REVIEW

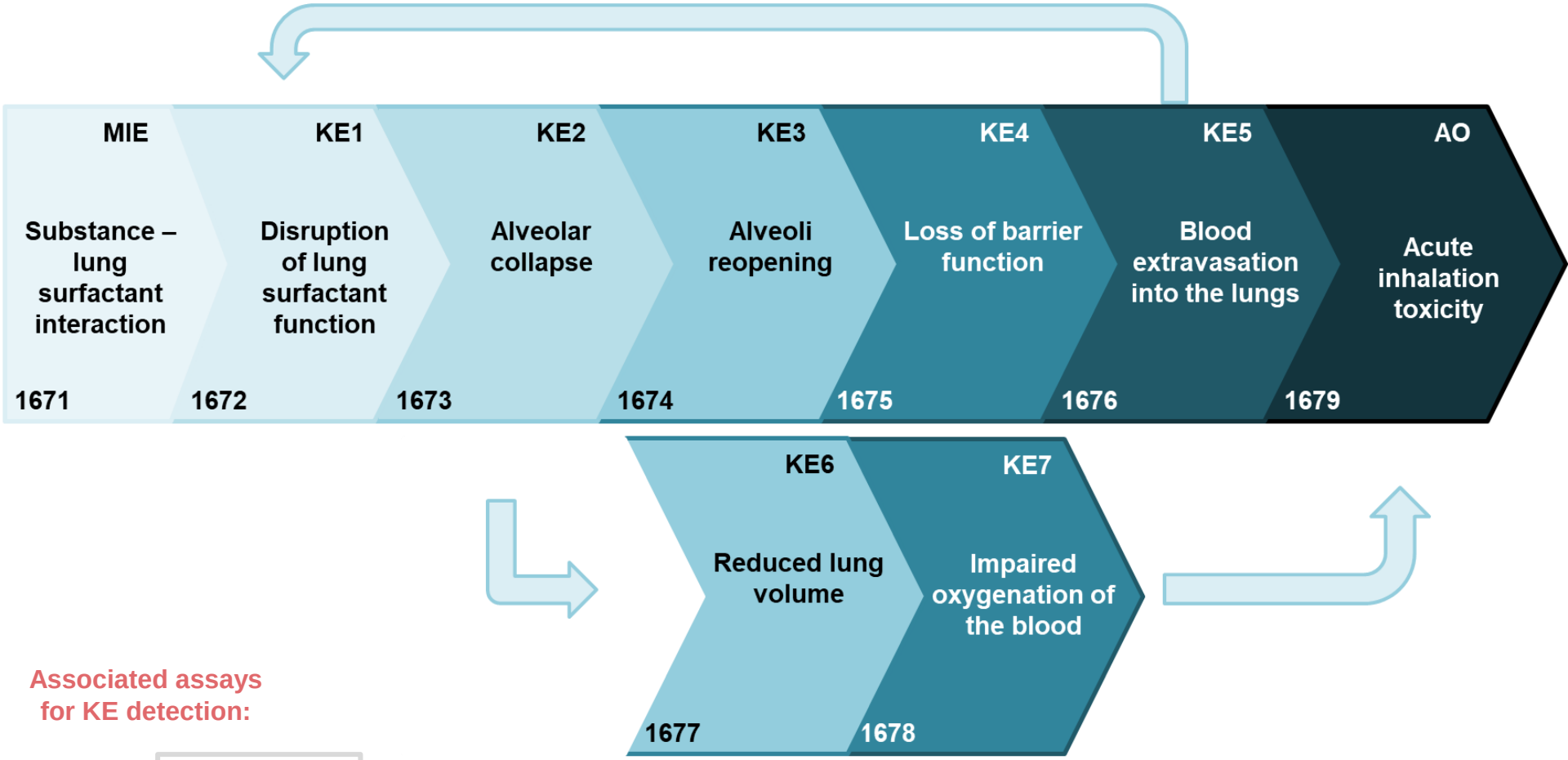
Acute Phase Response as a Biological Mechanism-of-Action of (Nano)particle-Induced Cardiovascular Disease

*Niels Hadrup, Vadim Zhernovkov, Nicklas Raun Jacobsen, Carola Voss, Maximilian Strunz, Meshal Ansari, Herbert B. Schiller, Sabina Halappanavar, Sarah S. Poulsen, Boris Kholodenko, Tobias Stoeger, Anne Thoustrup Saber, and Ulla Vogel**

Open access: PMID: 32227434

AOP302: Disruption of lung surfactant function – acute inhalation toxicity

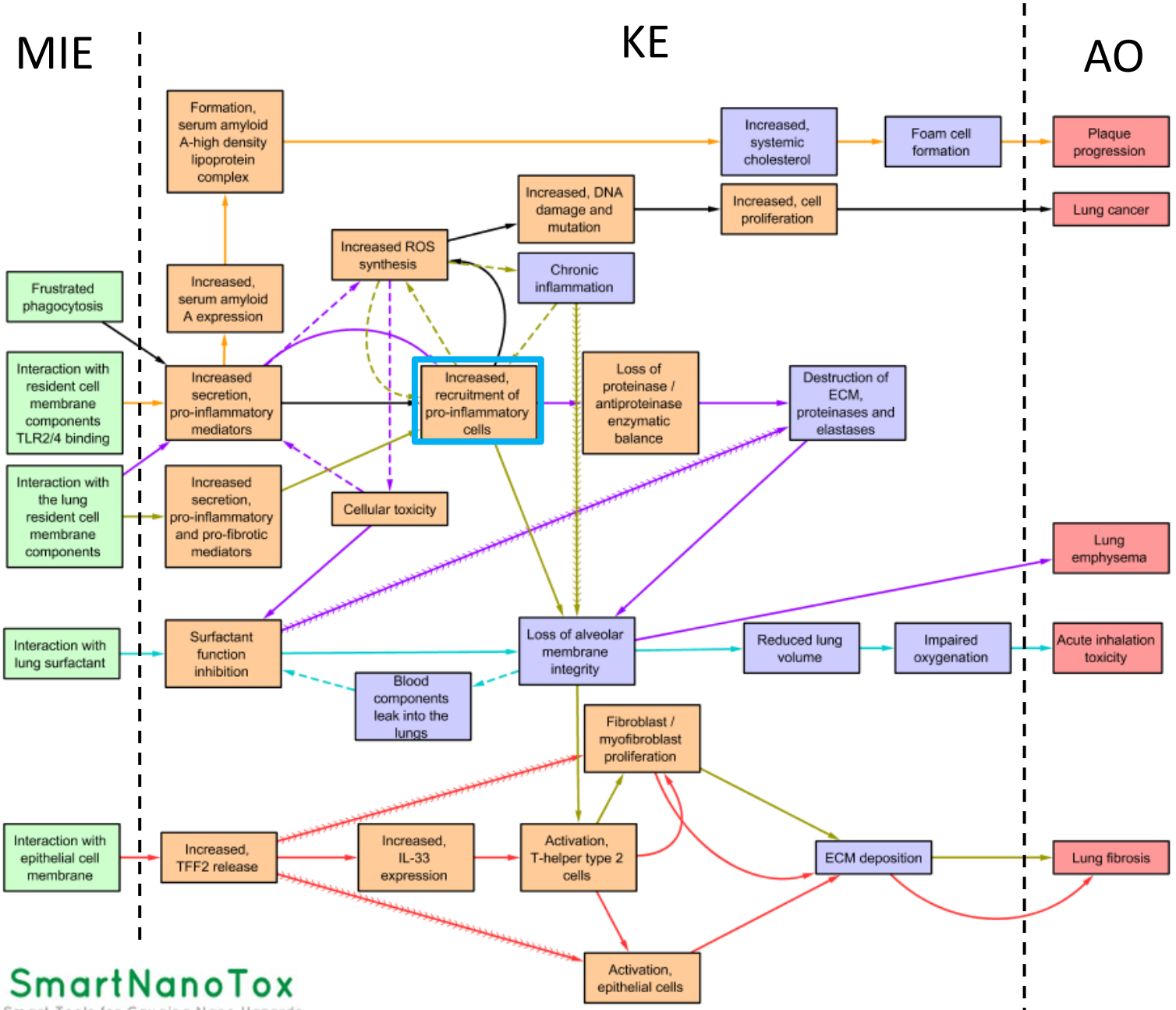
Jorid Sørli, Janez Štrancar , Jesus Perez-Gil, Otmar Schmid, Ulla Vogel



Associated assays for KE detection:

Constrained drop surfactometer

The AOPs are heavily interconnected and share KEs



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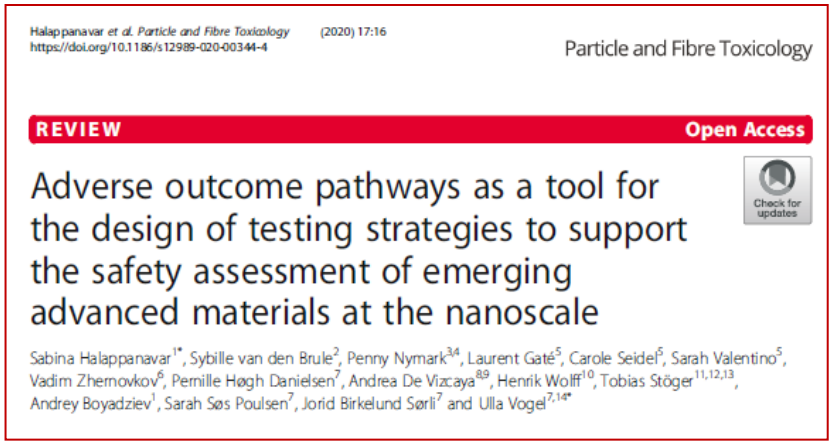
Halappanavar et al 2020 PF&T

Summary

- SmartNanoTox has contributed to the development of five AOPs for nanomaterial-induced fibrosis, lung cancer, cardiovascular disase and acute lung toxicity
- 4 of the AOPs can be found at https://aopwiki.org/
- Further descriptions and discussions of the AOPs can be found in the open access review: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7249325/pdf/12989_2020_Article_344.pdf



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Thank you for your attention!

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