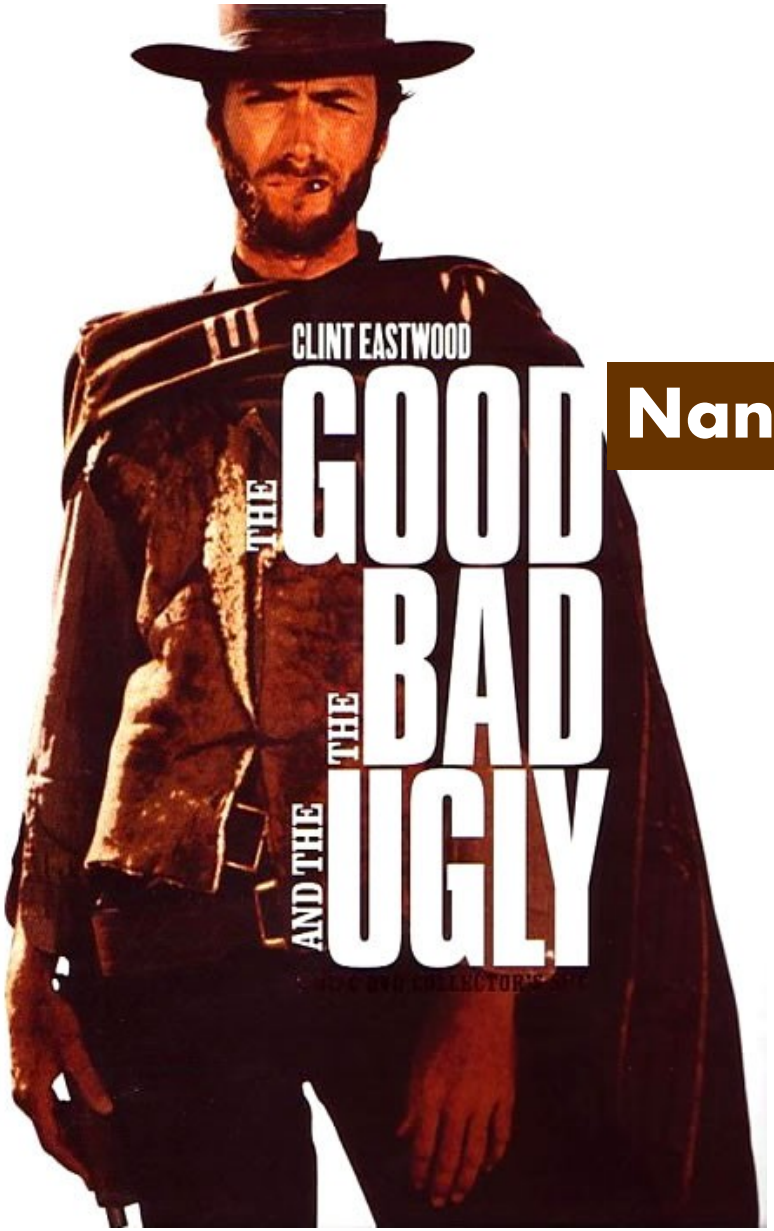
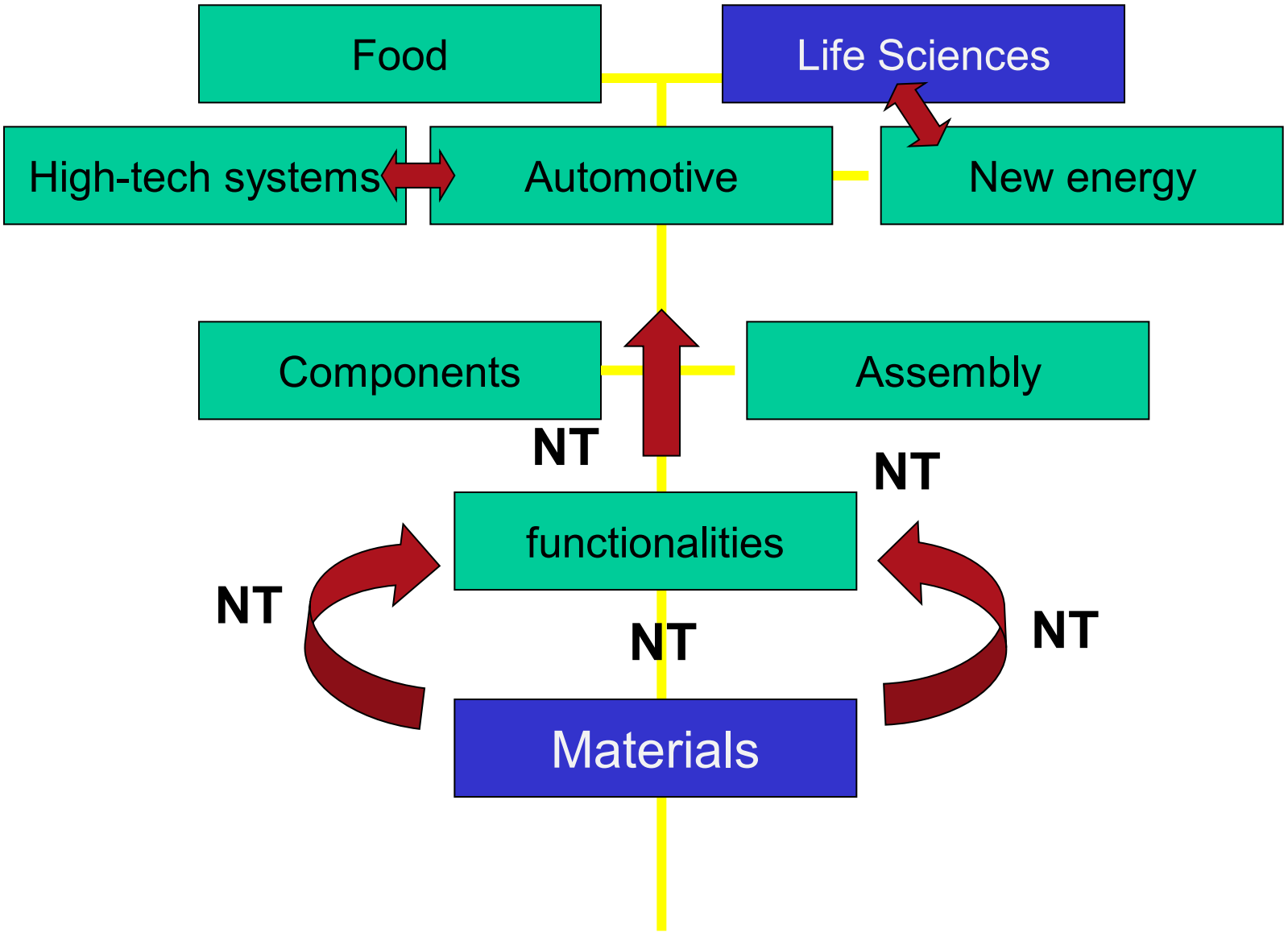
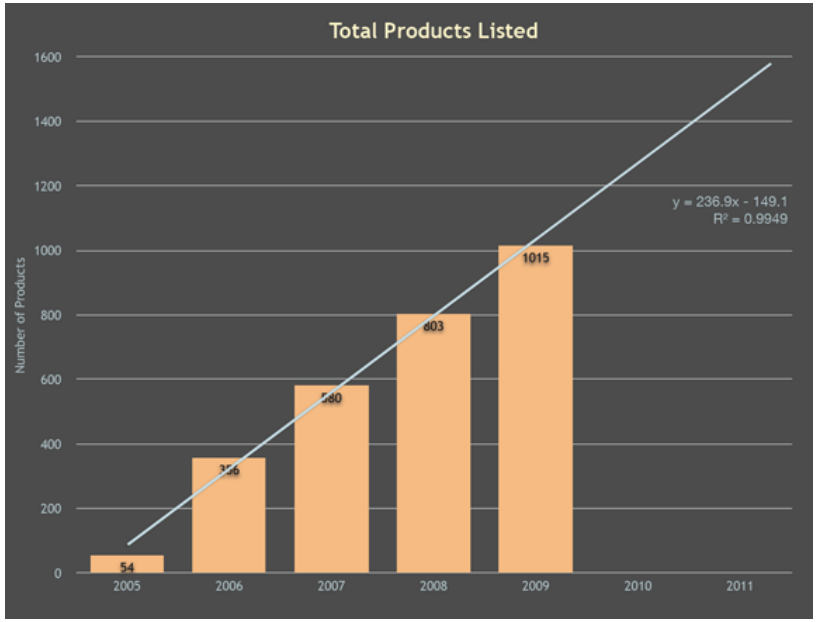


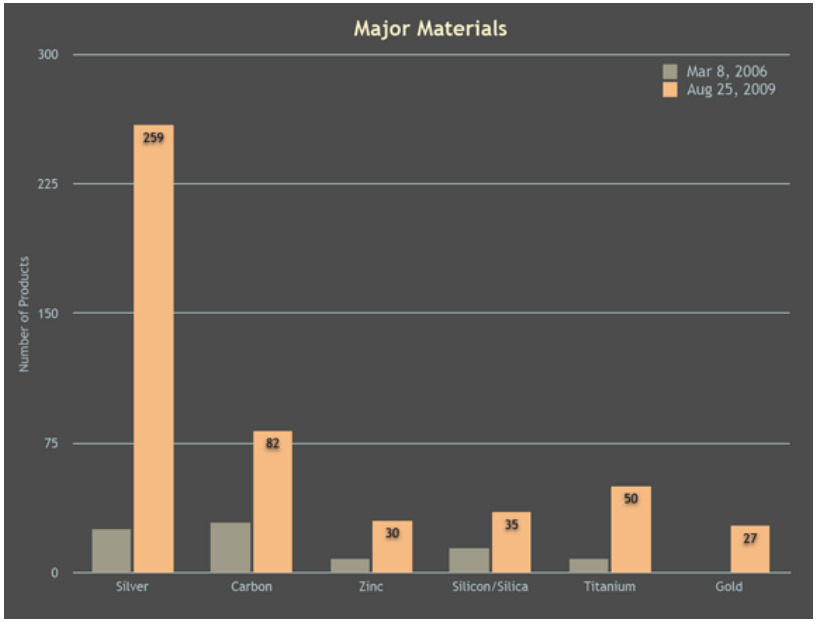
NanoMaterials

Paul J.A. Borm

New materials are at 80 % of innovation in industry-
Nanotechnology is a catalyst for its development and application







Total products (left panel) with nanocomponents on the US-market, And –right- the major **nanocomponents** determinings its functionality

Data from Woodrow-wilson database (jan 2010).

Nano4Imaging
YOUR HEALTH - OUR VISION

Nanoparticles and imaging: A bright couple

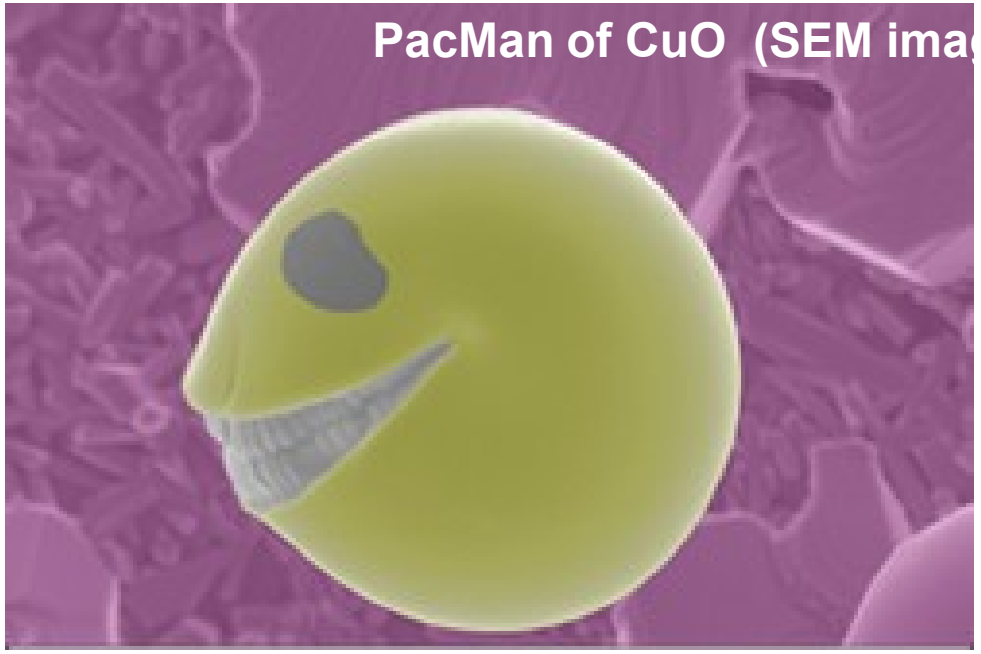
Fluorescent labeled nanoparticles (latex, silica) for in vitro use, cell trafficking. Short stability . Well defined 20- 2000 nm.

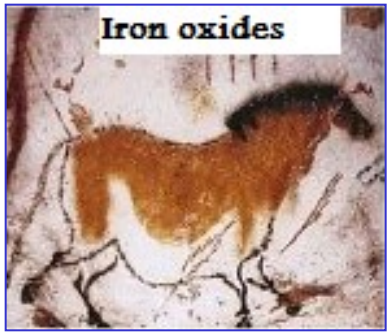
Gold nanoparticles (colloidal gold, immunogold) is used to stain specific structures for TEM imaging.

Quantum dots: fluorescence in vitro and in vivo (double phtoton excitation) (CdSe, CdTe-sulfide complexes). Well defined 5- 30 nm. Long stable

Carbon nanotubes: IR excitation, can be filled with existing contrast agents (SWCNT, MWCNT). Different lenghts ,diameter and surface treatment to tune Distribution and kinetics

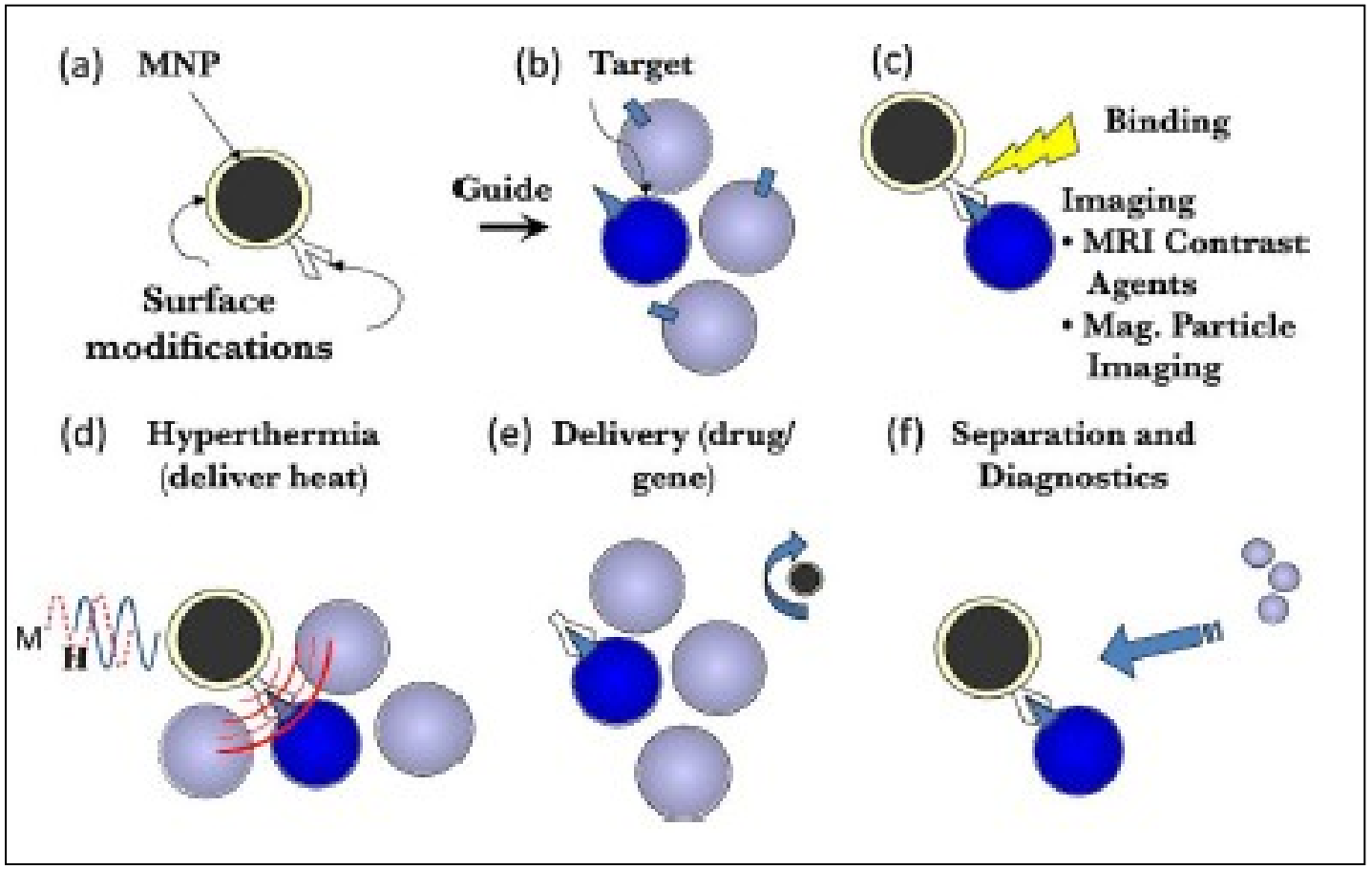

Au spaghetti (100 nm) with Si- meatballs


PacMan of CuO (SEM ima



Nano4Imaging
YOUR HEALTH - OUR VISION

Iron oxide nanoparticles: A new iron age thanks to nanotechnology



Nano4Imaging
YOUR HEALTH - OUR VISION

Our target

Make current medical devices visible for MRI, in combination with CT/X-ray and echo.
Developing new methods to enable imaging of artificial implants during and after operation.

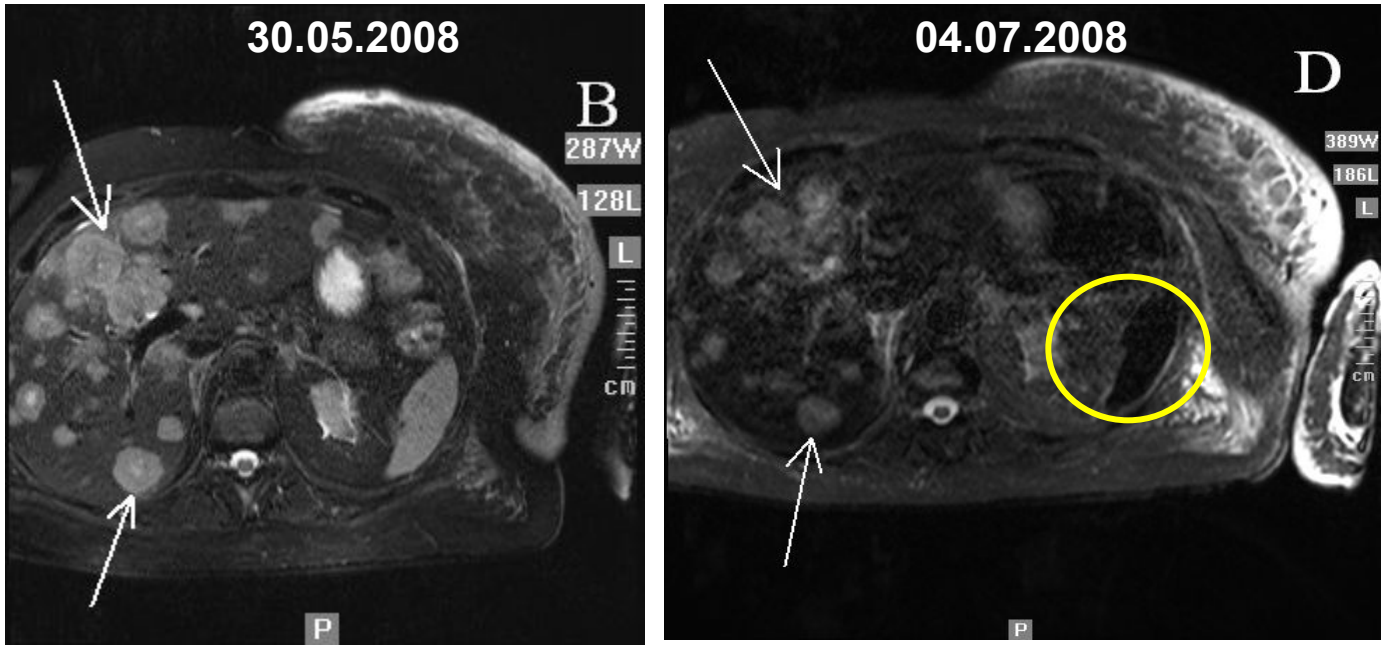
Medical benefits

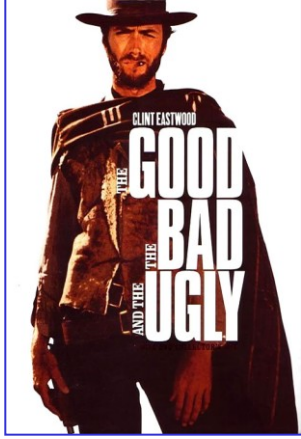
- Interventions in soft tissues superior
- Less radiation and contrast agent exposure
- One stop-shop combination of anatomy and physiology

Nano4Imaging
YOUR HEALTH - OUR VISION

Patient KL, treated with mitoxantrone-FF (100 mg/m^2) liver metastasis reduced from 14.9 to 8.0 cm^3

Liver function back to normal (GOT, AP, y-GT)
No gastro-intestinal complications and no hairloss
Normal kidney function
Temporal loss of leucocytes and thrombocytes.
iron accumulation in the spleen





Are all nanoparticles equal (ly bad)?

Please consider application (benefit-risk)
Consider exposure
Consider exposure group and alternative

Considerations in clinical Imaging

Contrast agent for medical intervention
MRI reduces radiation exposure
No release from Nanoparticles from device
Different choice available for imaging routine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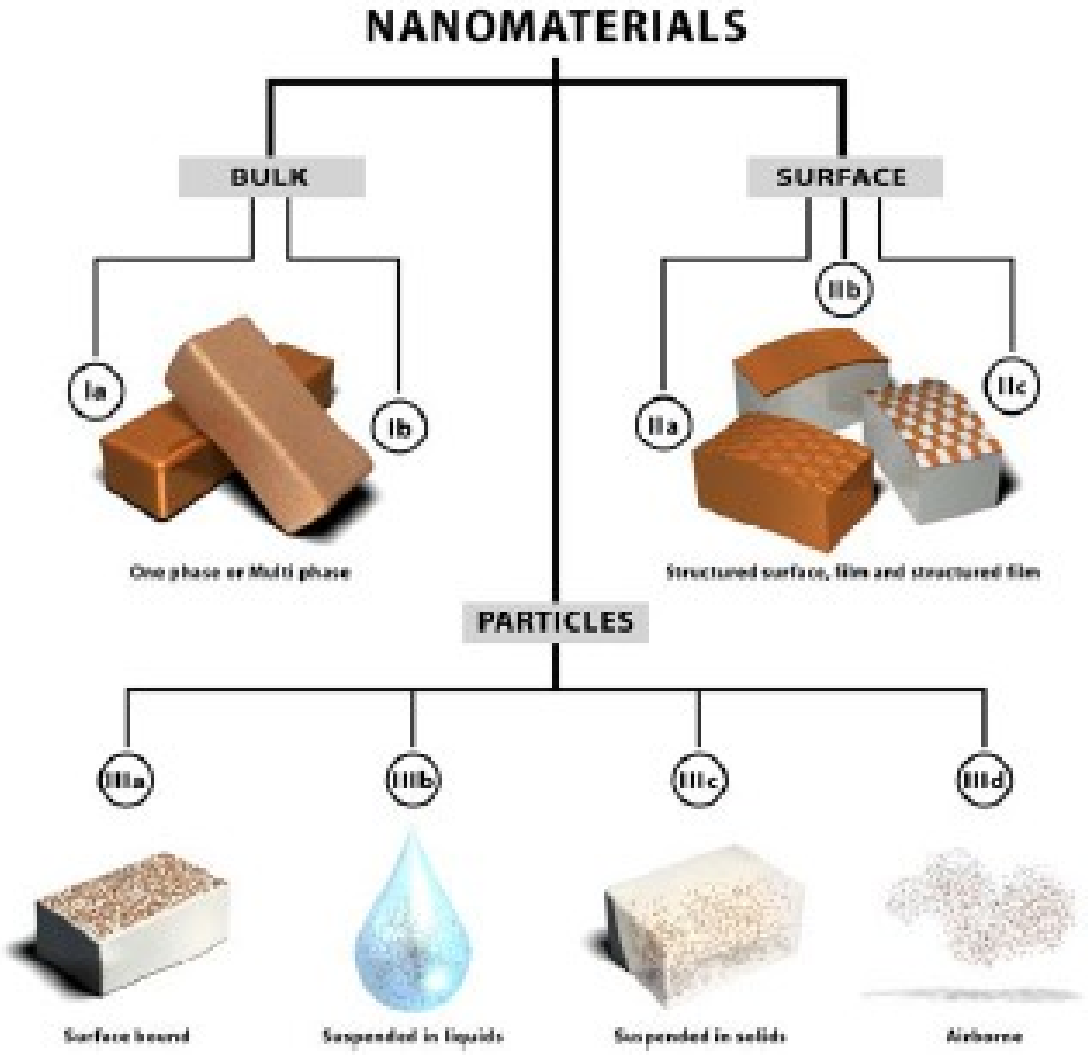
Risk = hazard x exposure

Hazard: the “ability” of a chemical to cause harm

Risk: the “probability” it will do so


NANOMATERIALS
BULK
SURFACE
Ia
Ib
IIa
IIb
IIc
PARTICLES
IIIa
IIIb
IIIc
IIId

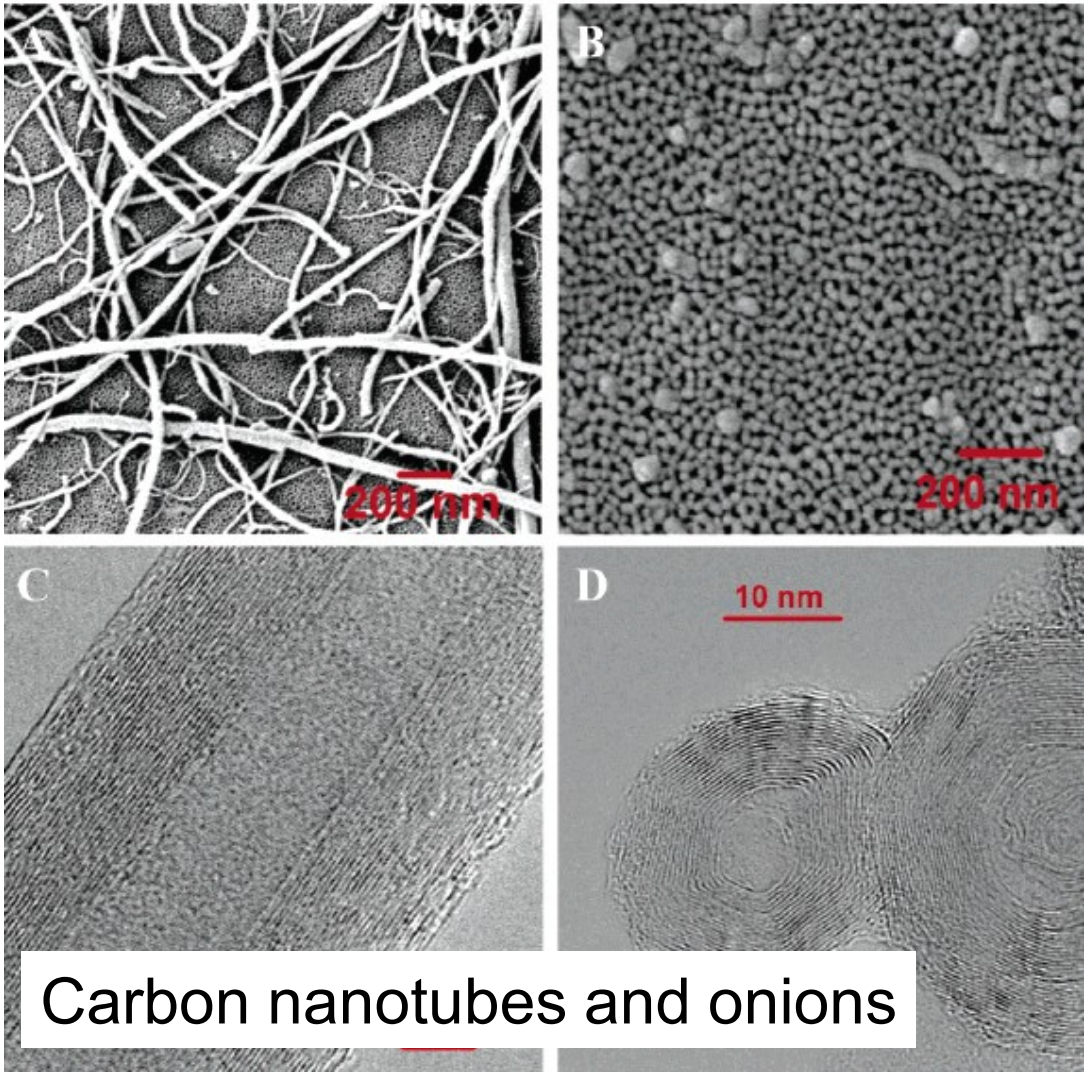
General paradigms in nanoparticles: true or not true?

- Size matters for many dynamic and kinetic issues.
- Inflammation is the key hallmark in effects.
- Surface area is the best metric for inflammation. For other effects no such consensus is present.
- At fine size, aggregates of nanoparticles have a larger effect than one fine particle of the same material.
- Aggregates of nanoparticles cannot be dissociated in epithelial lining fluid. Does that impede single NP uptake?
- Size is the main driver for current studies.

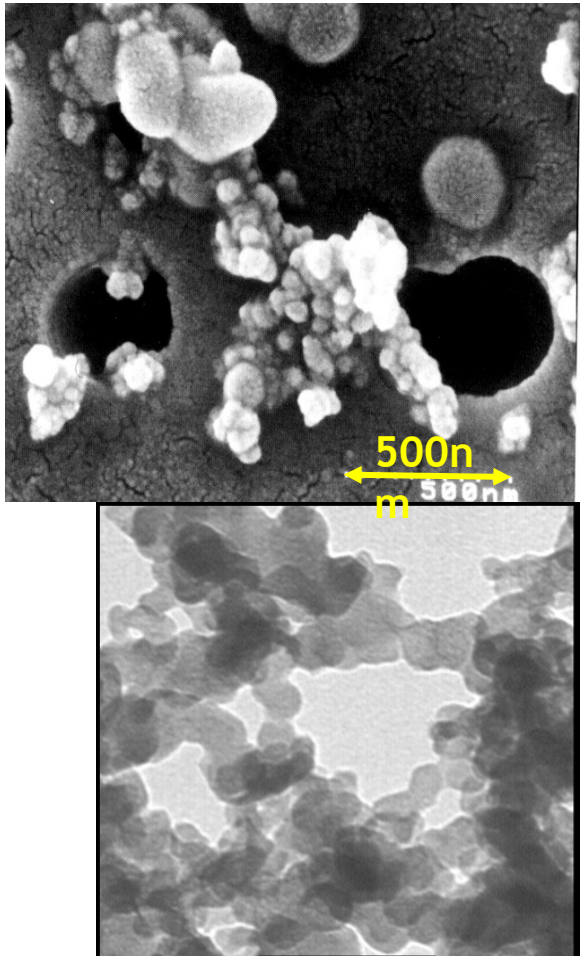
Priority questions and tasks

- What effects are caused by NP beyond those of fine particles? If so what are the mechanisms of these effects?
- What is the distribution of kinetics of NP in the body and its compartments? Is this relevant for the biological effects (ADME).
- Communicate that Nanomaterials are much more than just nanoparticles.
- Are we interested in stronger but similar effects (eg MWCNT, blood coagulation), or in effects not seen before (brain and cognition)?

Case: carbonaceous nanoparticles



Carbon nanotubes and onions



Diesel exhaust particles

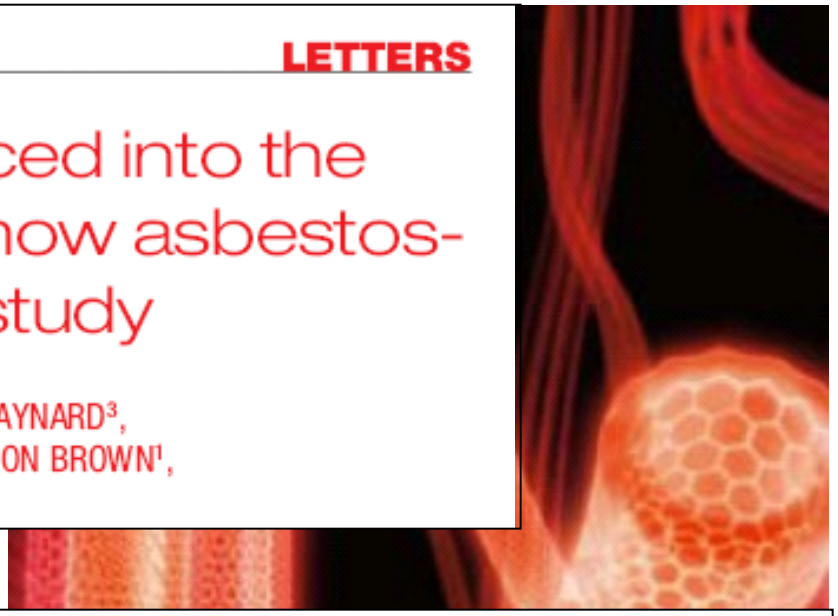
Animal studies with CNT- initial focus on inflammation.

Exposure + model	material	outcome	reference
Intracheal instillation, guinea pigs (12.5 mg)	NanoLab CNT	Granuloma, Fibrosis (lung)	Huzcko 2005
Intracheal instillation, (0.25 and 1.25 mg/rat)	SWCNT	Inflammation Mutiple granuloma	Warheitet al 2004
Intracheal instillation, mice (0.1, 0.5 mg/mouse)	SWCNT	Granuloma Inflammation> CB	Lam et al, 2004
Intracheal instillation, rats (0.5- 5 mg/rat)	MWCNT	Inflammation Fibrosis	Muller et al, 2005
Pharyngeal aspiration (10- 40 ug/mouse)	SWCNT	Progressive fibrosis Granulomas	Shevdova et al, 2005
Inhalation, mice (0.3- 5 mg/m^3, 12 wks)	MWCNT	Systemic immune effects	Mitchell et al, 2007
Intraperitoneal injection P53 +/- mice	MWCNT C60	Granuloma formation	Takagi et al, 2008
Intraperitoneal injection Mice (C57BI/6)	SWCNT, MWCNT (specially fabricated)	Granuloma formation with MWCNT	Poland et al, 2008

LETTERS

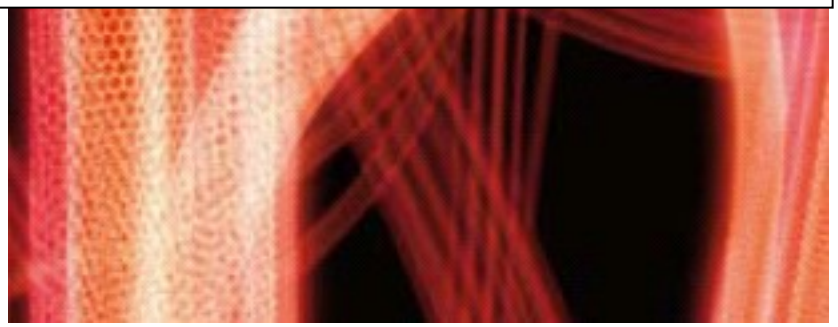
Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study

CRAIG A. POLAND[1], RODGER DUFFIN[1], IAN KINLOCH[2], ANDREW MAYNARD[3], WILLIAM A. H. WALLACE[1], ANTHONY SEATON[4], VICKI STONE[5], SIMON BROWN[1], WILLIAM MACNEE[1] AND KEN DONALDSON[1]*



Induction of mesothelioma in p53+/– mouse by intraperitoneal application of multi-wall carbon nanotube

Atsuya Takagi[1], Akihiko Hirose[2], Tetsuji Nishimura[3], Nobutaka Fukumori[4], Akio Ogata[4], Norio Ohashi[4], Satoshi Kitajima[1] and Jun Kanno[1]



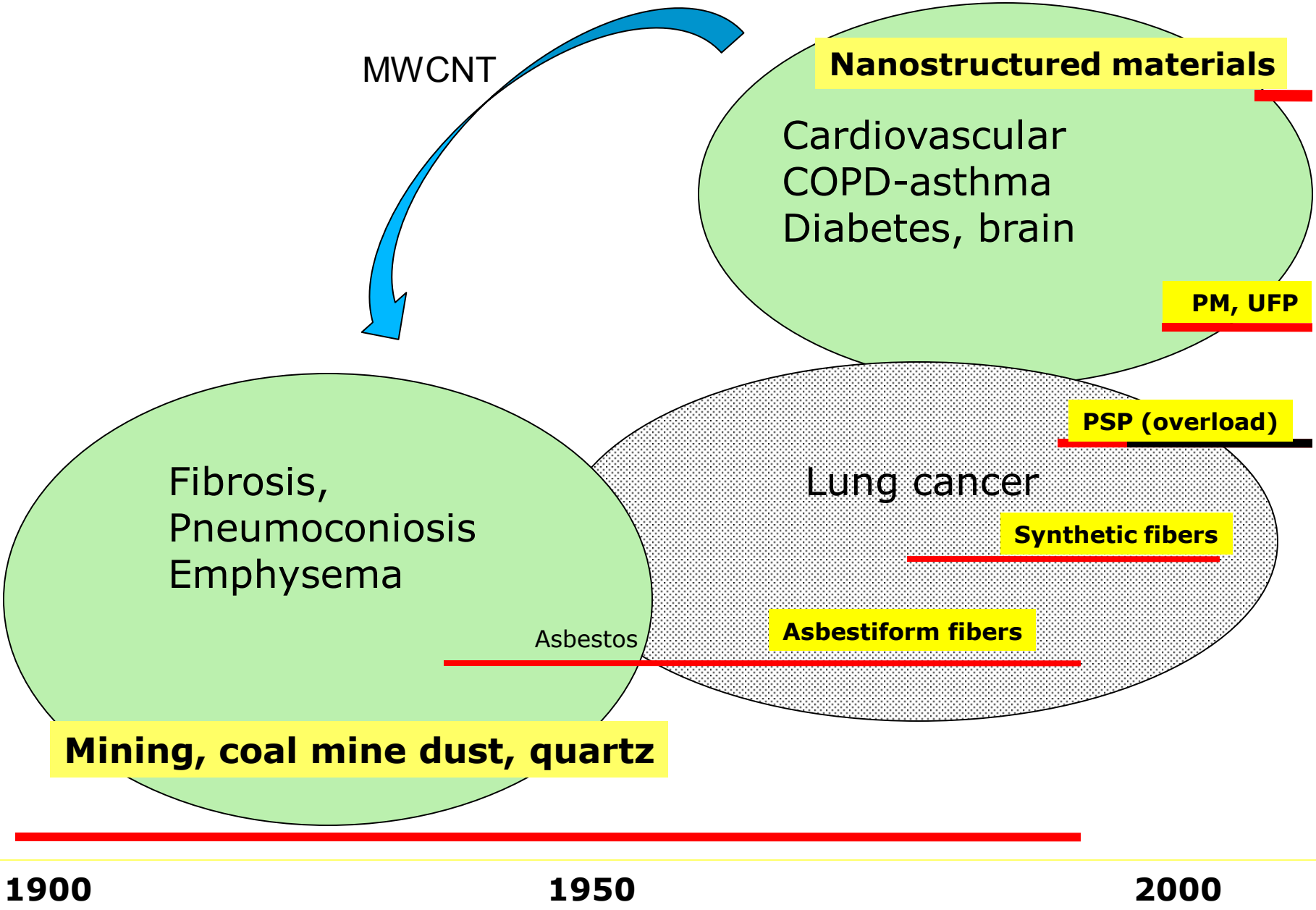
General conclusions:

- Ip model intended for hazard finding, but sensitive to artifacts and false positives.
- Poland et al is a short-time, mechanistic study not aiming to predict long term outcome.
- Takagachi study uses highly dosed in sensitive mouse model. Little data available for benchmarking.
- Both studies have used dose in a high-dose range that have been positive for most long fibres in rats. Unfortunately, little benchmark data are available in mice.
- The administration route and the test are only accepted in Europe, but recognized as overly sensitive.
- Pleural injection and inhalation of same materials at relevant dose are the logical next steps.

Animal studies with CNT- continued

Exposure + model	material	outcome	reference
Inhalation, mice (30 mg/m^3 for 6 hours)	MWCNT (Helix Materials)	Reach subpleural tissue, causing fibrosis	Ryman-Rasmussen 2009
Inhalation, Wistar rats (11 and 241 mg/m^3 for 6 hours), 3 months follow-up	MWCNT BayTubes, Micronized Quartz as reference	Dose-response inflammation. Septic fibrosis. Role of Co	Ellinger-Ziegelbauer & Pauluhn (2009)
Inhalation, Wistar rats (13 weeks, 0.1-6 mg/m^3)	MWCNT BayTubes, micronized	Granuloma and hyperplasia at overload conditions (> 0.4 mg/m^3)	Pauluhn, 2010

Based on the sub-chronic study, Bayer has suggested a OEL of 0.05 mg BayTubes/m^3 (Pauluhn et al, Reg Toxicol Pharmacol).


MWCNT
Nanostructured materials
Cardiovascular
COPD-asthma
Diabetes, brain
PM, UFP
PSP (overload)
Fibrosis,
Pneumoconiosis
Emphysema
Lung cancer
Synthetic fibers
Asbestos
Asbestiform fibers
Mining, coal mine dust, quartz
1900
1950
2000

Future tasks and challenges

- Inventory of relevant nanoparticles and applications.
- Priority should be at preventing exposure
- Connect particle properties and effects
- Discriminate between role of particle size and chemistry.
- Are we interested in stronger but similar effects (eg MWCNT, blood coagulation), or in effects not seen before (brain, protein corona)?
- Communication and inclusion of new professional groups in debate (e.g.material scientists)