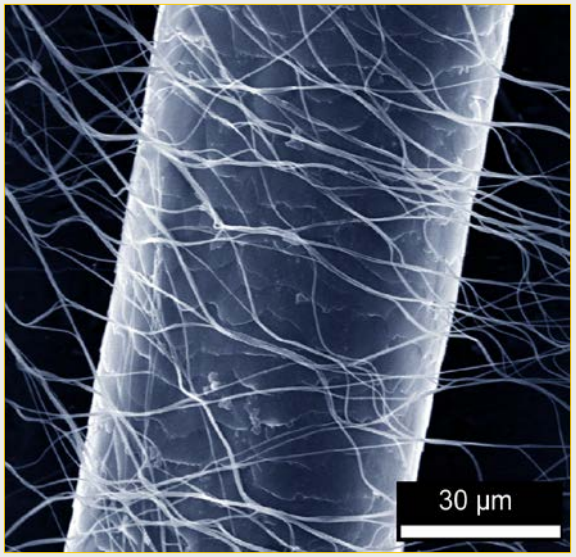
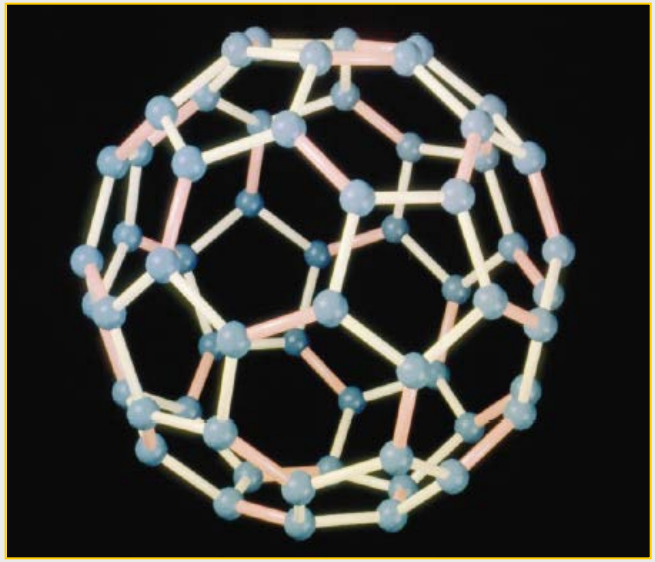
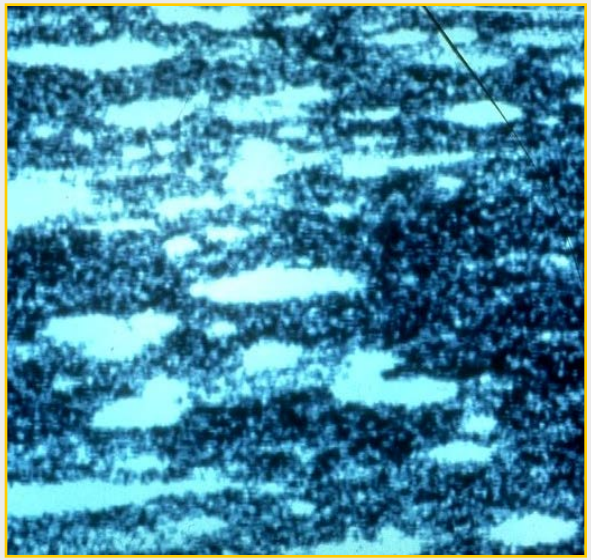
Nanotechnology for Medical Devices
Challenges, Changes and Risks

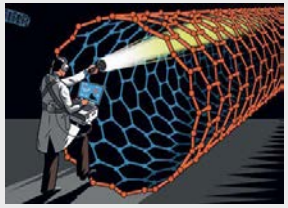




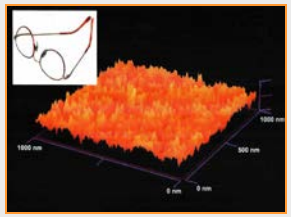


Jörg Vienken
BioSciences, Fresenius Medical Care
Bad Homburg, Germany

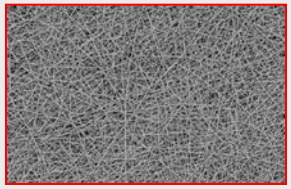
Nanotechnology for Medical Devices
Challenges, Changes and Risks



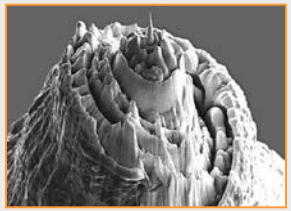
Nanomed-Tech
Figures of today, facts of tommorrow



Nanomed-Tech application
Risks and chances

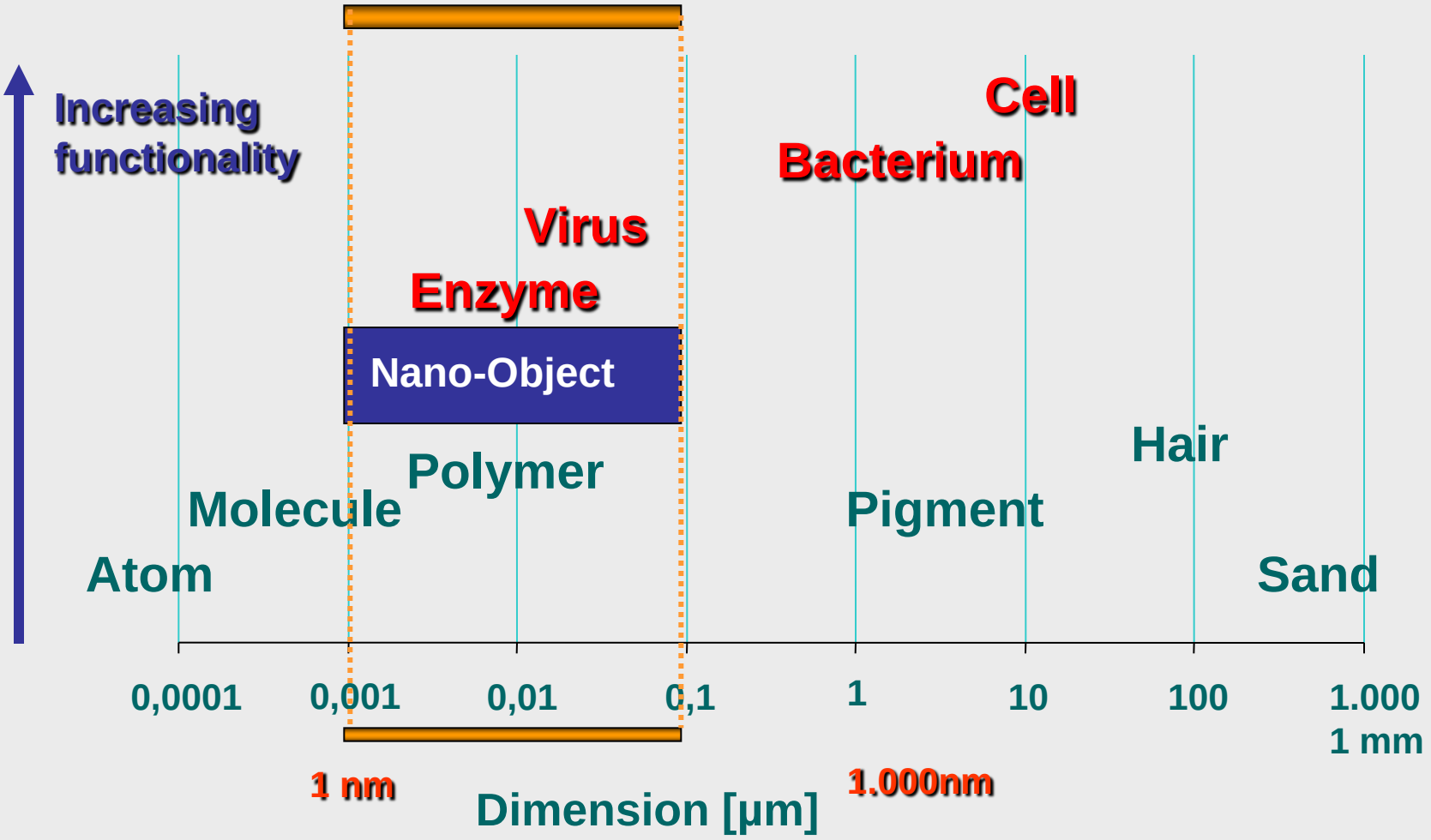


Nanomed-Tech
Company profiles



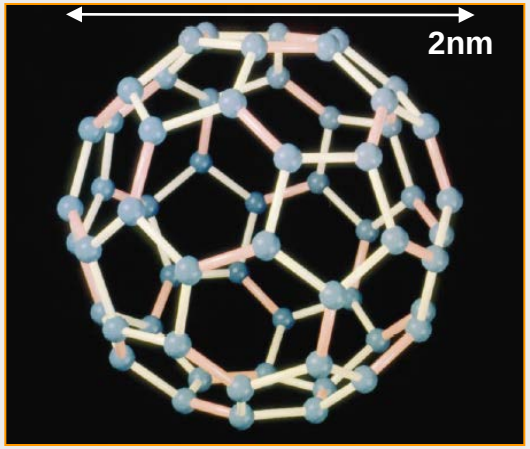
Quo vadis?
Expectations and requirements

The Nanoscale – A Biological Medical Scale



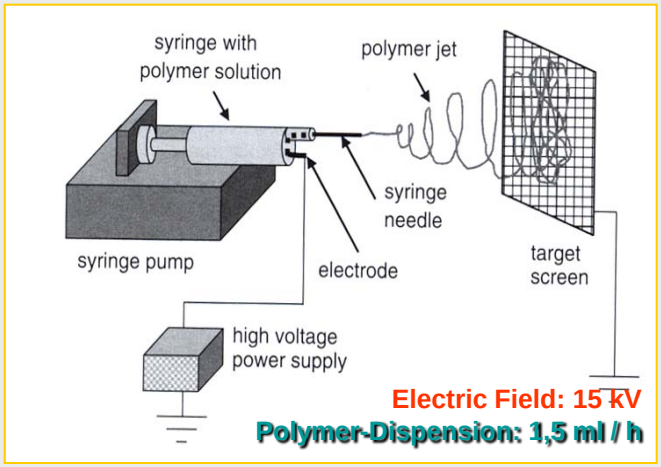
Toys or Tools?

Nanocages Nanopores



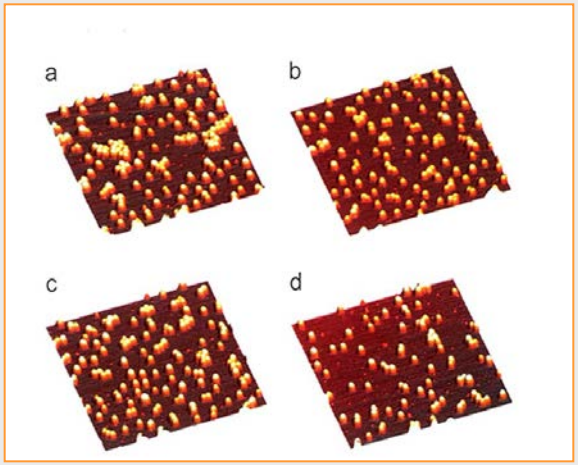
Fulleren cages
B. Fuller (1895-1983)

Nanofibres, - tubes Cantilever

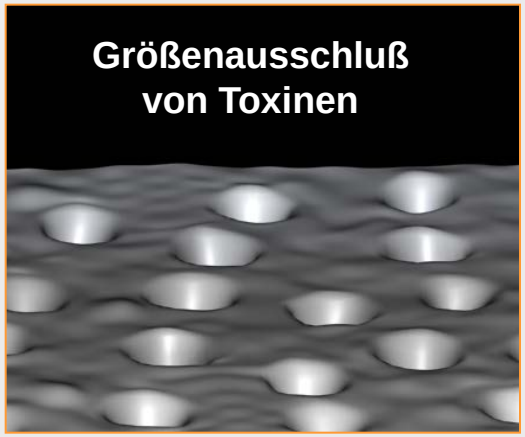


A Badami et al.,
Biomaterials, 27:596-606 (2006)

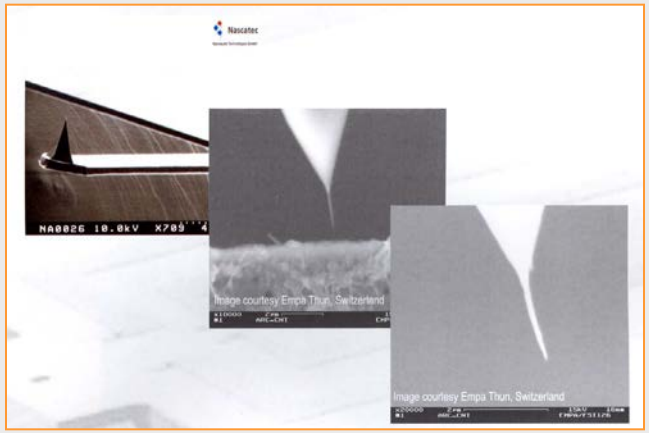
Surfaces, particles Nanomachines



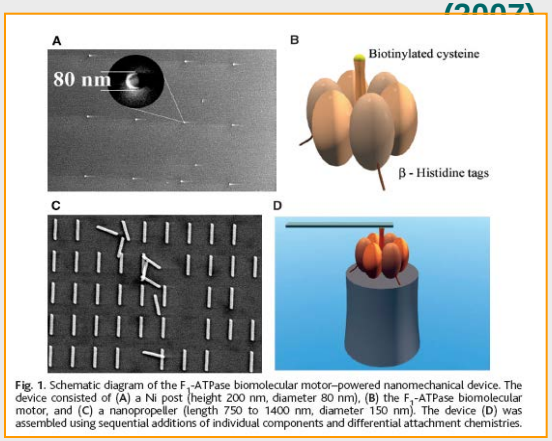
T Kunzler et al.,
Biomaterials, 28:5000-5006 (2007)



Membranpores
Fresenius Medical Care,
Bad Homburg

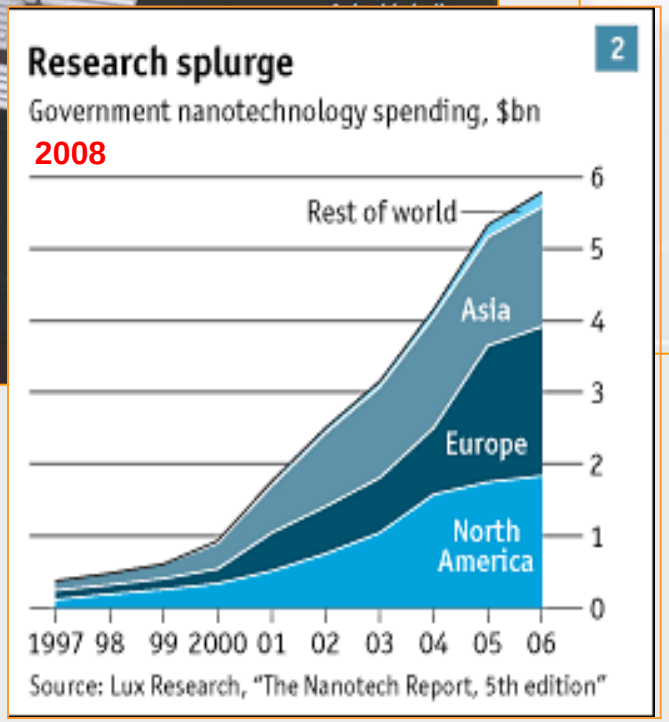


Cantilever
Nascatec,
Stuttgart



Nanomachines
Science, 290:1555-58 (2000)

Spending for Nano & More

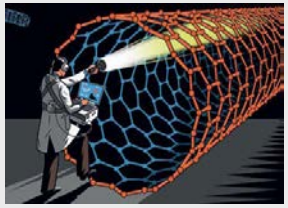


Scientists have already learned to use this relabelling trick to win funding from politicians, says Hilborn. A project he heads, to develop miniature scaffolds for tissue engineering, recently won €1.7 million from the European Union's Framework programme, following a call for nanobiotechnology projects. "I could have very well written the proposal without nano in there," he says. "I didn't lie to get the money; I just used the word they like to hear."

!

From: Nature, 440:262 (2006)

Nanotechnology for Medical Devices
Challenges, Changes and Risks



Nanomed-Tech
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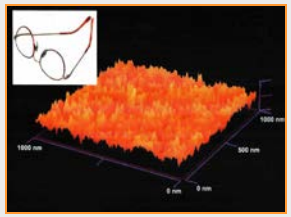
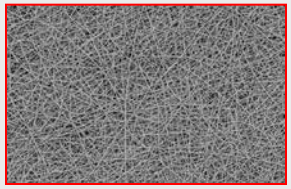
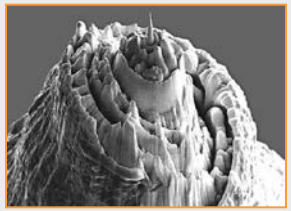


Nanomed-Tech application
Risks and chances



Nanomed-Tech
Company profiles



Quo vadis?
Expectations and requirements

Expectations and Risk Assessement of Nanotechnology not in Line!

COMMENTARY

Scientists worry about some risks more than the public

DIETRAM A. SCHEUFELE[1]*, ELIZABETH A. CORLEY[2], SHARON DUNWOODY[3], TSUNG-JEN SHIH[3], ELLIOTT HILLBACK[3] AND DAVID H. GUSTON[4]

are in [1]the Department of Life Sciences Communication, University of Wisconsin–Madison, 440 Henry Mall, Madison, Wisconsin 53706, USA; [2]the School of Public Affairs, Arizona State University, 411 North Central Avenue, Phoenix, Arizona 85004, USA; [3]the School of Journalism & Mass Communication, University of Wisconsin–Madison, 821 University Avenue, Madison, Wisconsin 53706, USA; [4]the Department of Political Science, Arizona State University, PO Box 874401, Tempe, Arizona 85287, USA.
*e-mail: scheufele@wisc.edu

A comparison between two recent national surveys among nanoscientists and the general public in the US shows that, in general, nanoscientists are more optimistic than the public about the potential benefits of nanotechnology. However, for some issues related to the environmental and long-term health impacts of nanotechnology, nanoscientists were significantly more concerned than the public.

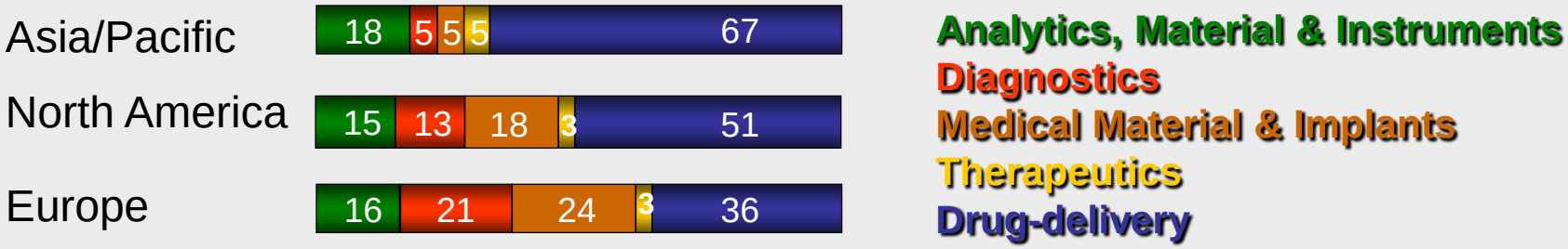
Re: Nature Nanotechnology, 2:732-734 (2007)

NanoStructures and Biomedical Effects
Scientists concerned, Public not yet interested

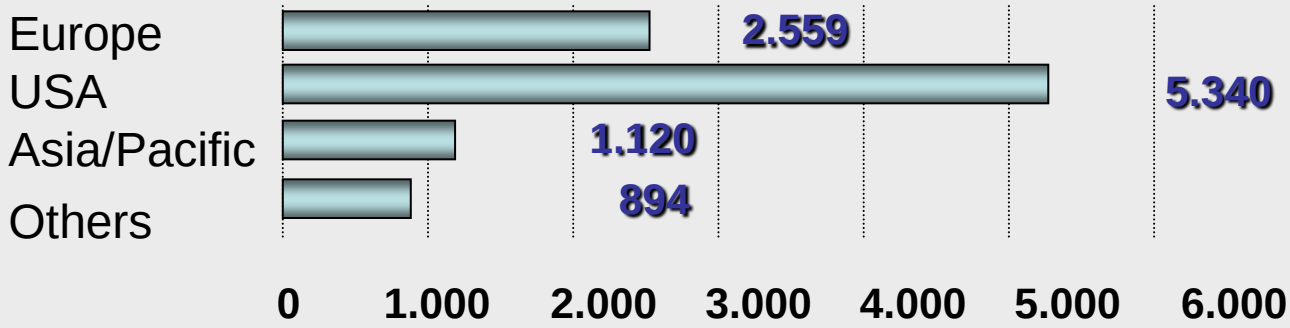
Nanotechnology in medical applications: possible **risks for human health**	WH DeJong, B Roszek, RE Geertsma RIVM Report 265001002/2005
Ultrafine particles exert **prothrombotic** but **not inflammatory** effects on the hepatic microcirculation	A Khadonga et al., Circulation, 109:1320-1325 (2004)
Toxic potential of materials at the nanolevel	A Nel Science, 311:622-627 (2006)
Nanoparticles as **catalysts** for protein fibrillation	V Colvin & K Kulinowski PNAS, 104:8679 – 8680 (2007)
Nucleation of protein fibrillation by nanoparticles	S Linse et al., PNAS, 104:8691-8696 (2007)
Interaction of **erythrocytes** with magnetic nanoparticles	M Soler et al., J Nanosci Nanotechnol, 7:1069-1071 (2007)
Protein adsorption and **cellular uptake** of cerium oxide nanoparticles as a function of zeta potential	S Patil et al., Biomaterials, 28:4600-4607 (2007)
Chemotaxis of non-biological collodial rods	Y Hong et al., PhysRev Letters, 99:178103-1 (2007)

Nanotechnology & Medical Applications 2007

Nanomedical Applications



Patents (cumulative till 2004)



Re: N Dunzweiler, Ernest & Young
CHEManager, 18/2007, p.3

TECHNICAL SPECIFICATION

ISO/TS 27687

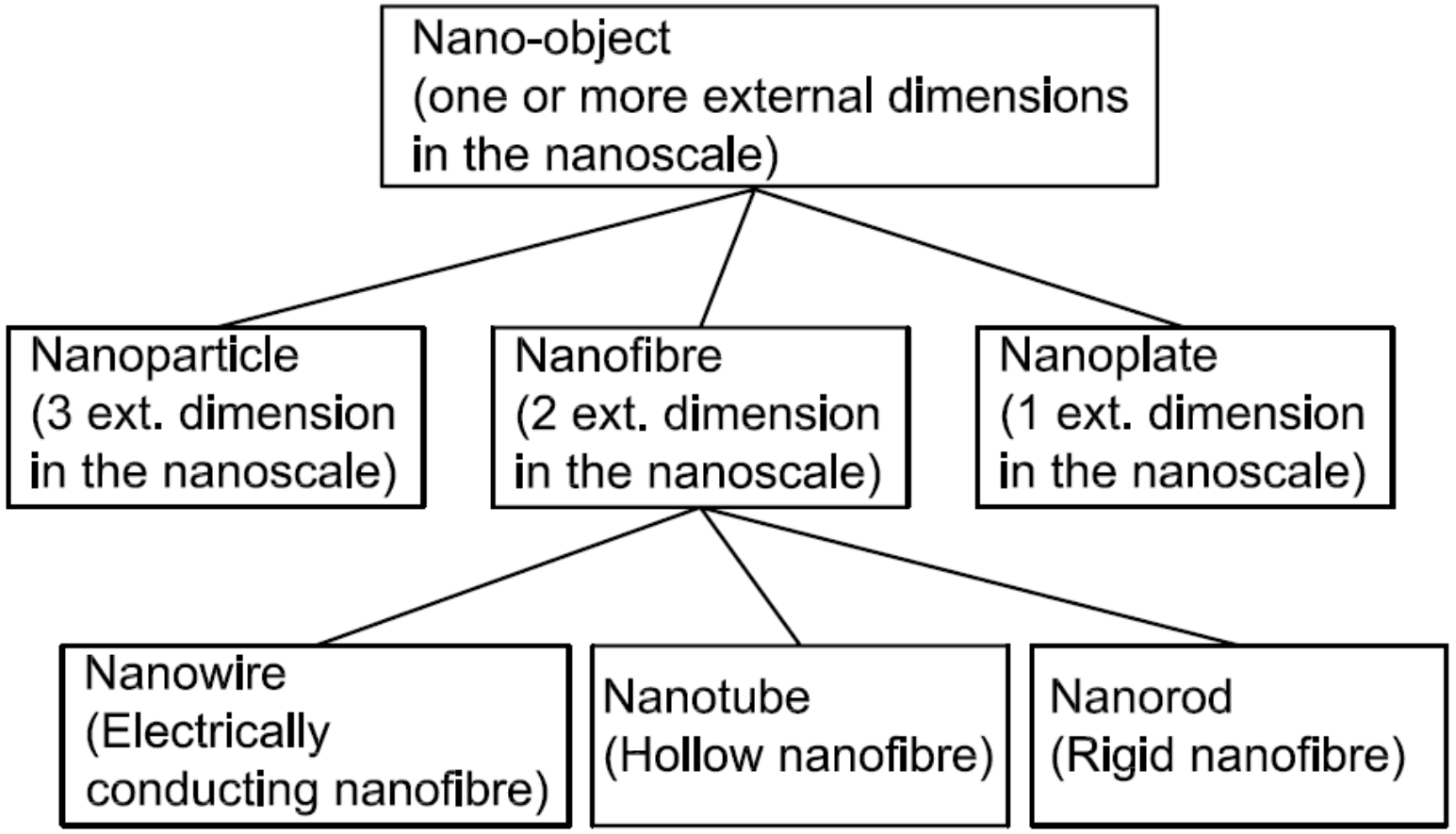
Reference number
ISO/TS 27687:2008(E)

First edition
2008-08-15

Nanotechnologies — Terminology and definitions for nano-objects — Nanoparticle, nanofibre and nanoplate

Nanotechnologies — Terminologie et définitions relatives aux nano-objets — Nanoparticule, nanofibre et nanoplat

Reference number
ISO/TS 27687:2008(E)



Nanotechnology for Medical Devices
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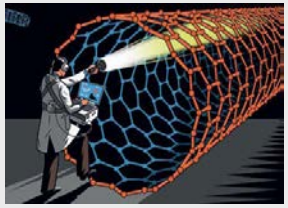

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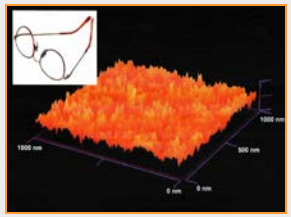
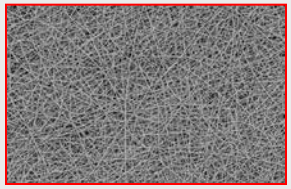
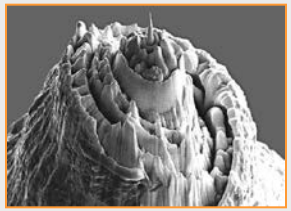


Nanomed-Tech application
Risks and chances

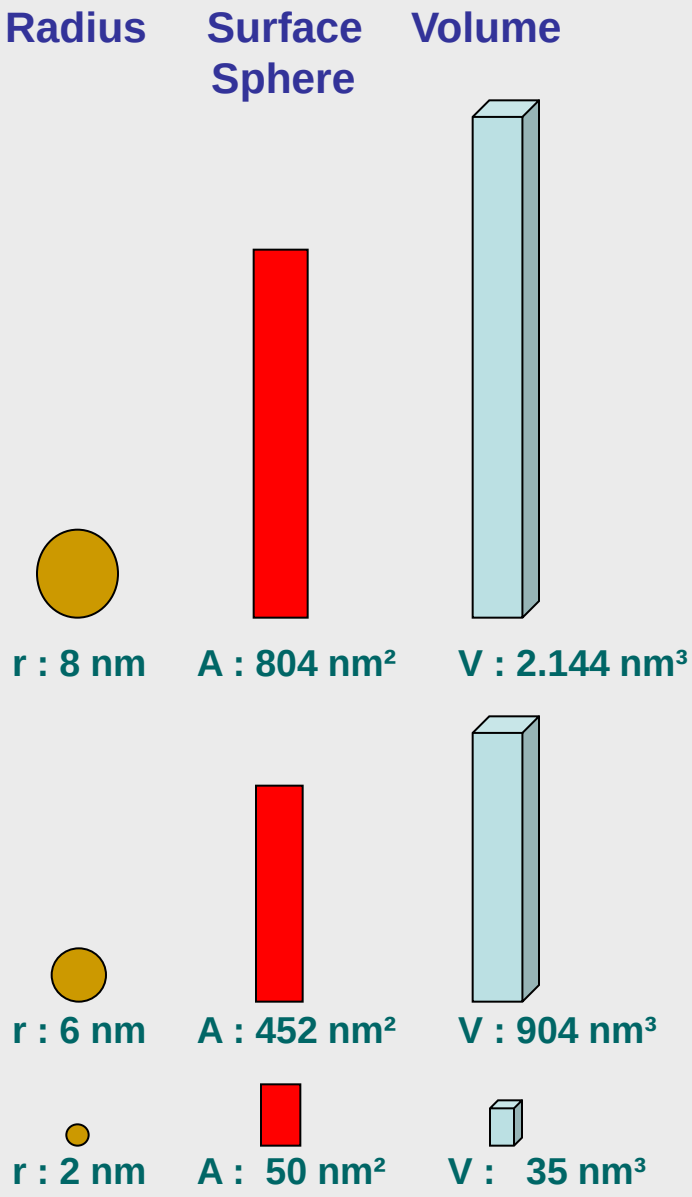


Nanomed-Tech
Company profiles



Quo vadis?
Expectations and requirements

Nano-scaled Biomaterials

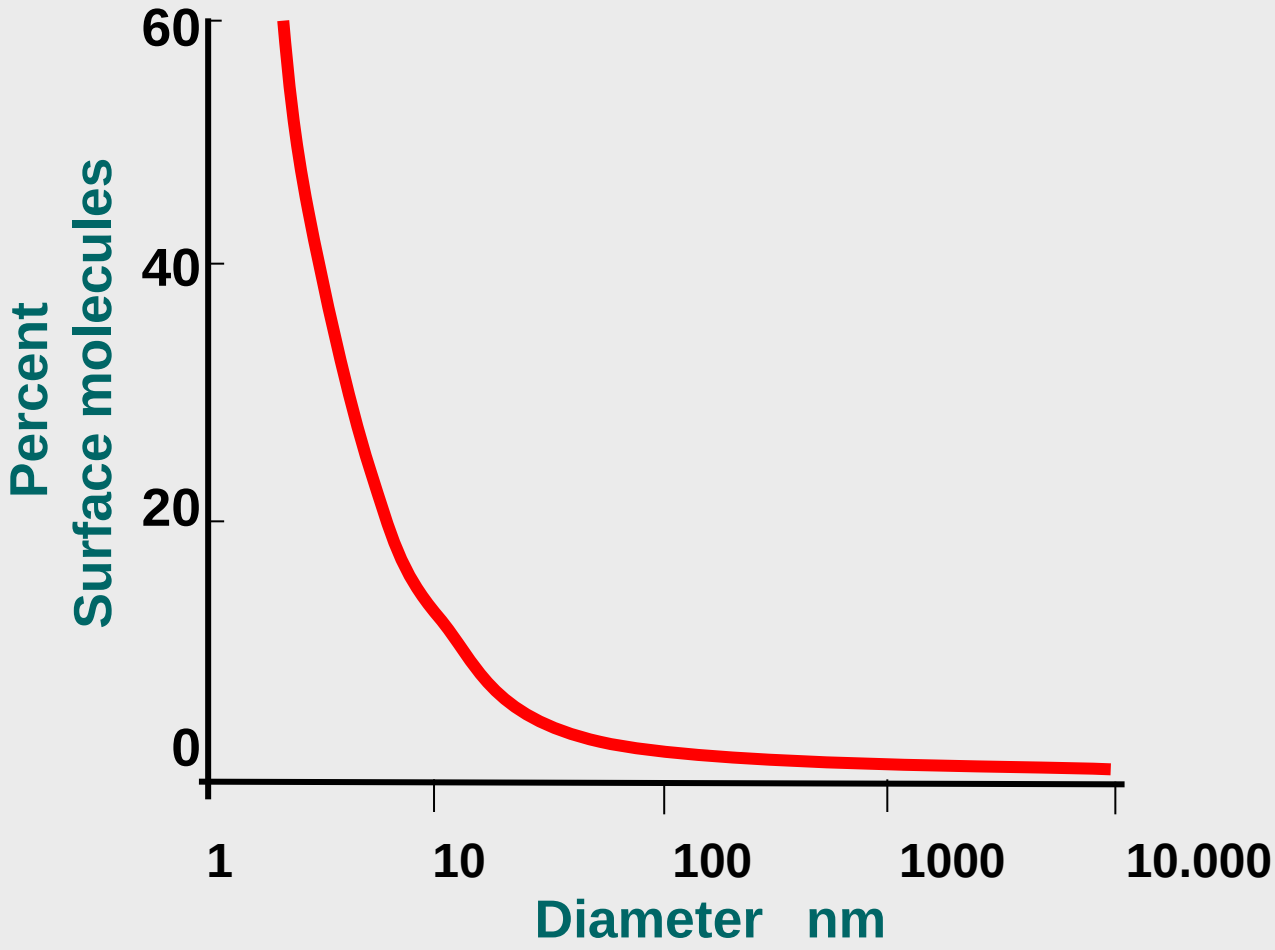


With decreasing radius magnitudes for Volume drop faster than for areas!
Radius dependence:
r^3 *vs* r^2

Thus: Nanoeffects always
Surface effects

Particle Size and Number of Molecules Expressed on Surface

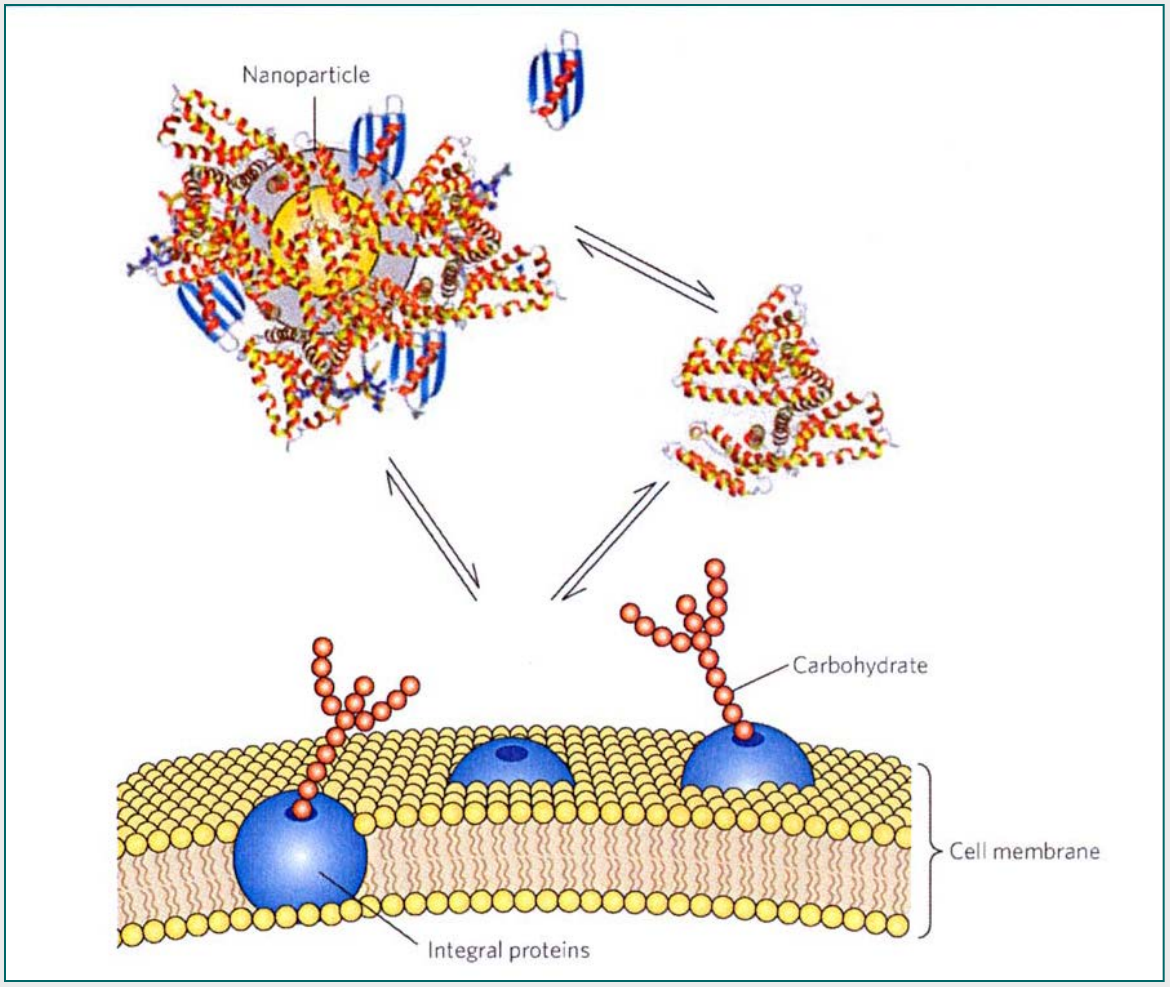
Consequences for leachables



Re: A Nel et al., Science, 311:622 (2006)

What does a cell see?

Interaction of nanoparticles with biological cells determined by protein-coating



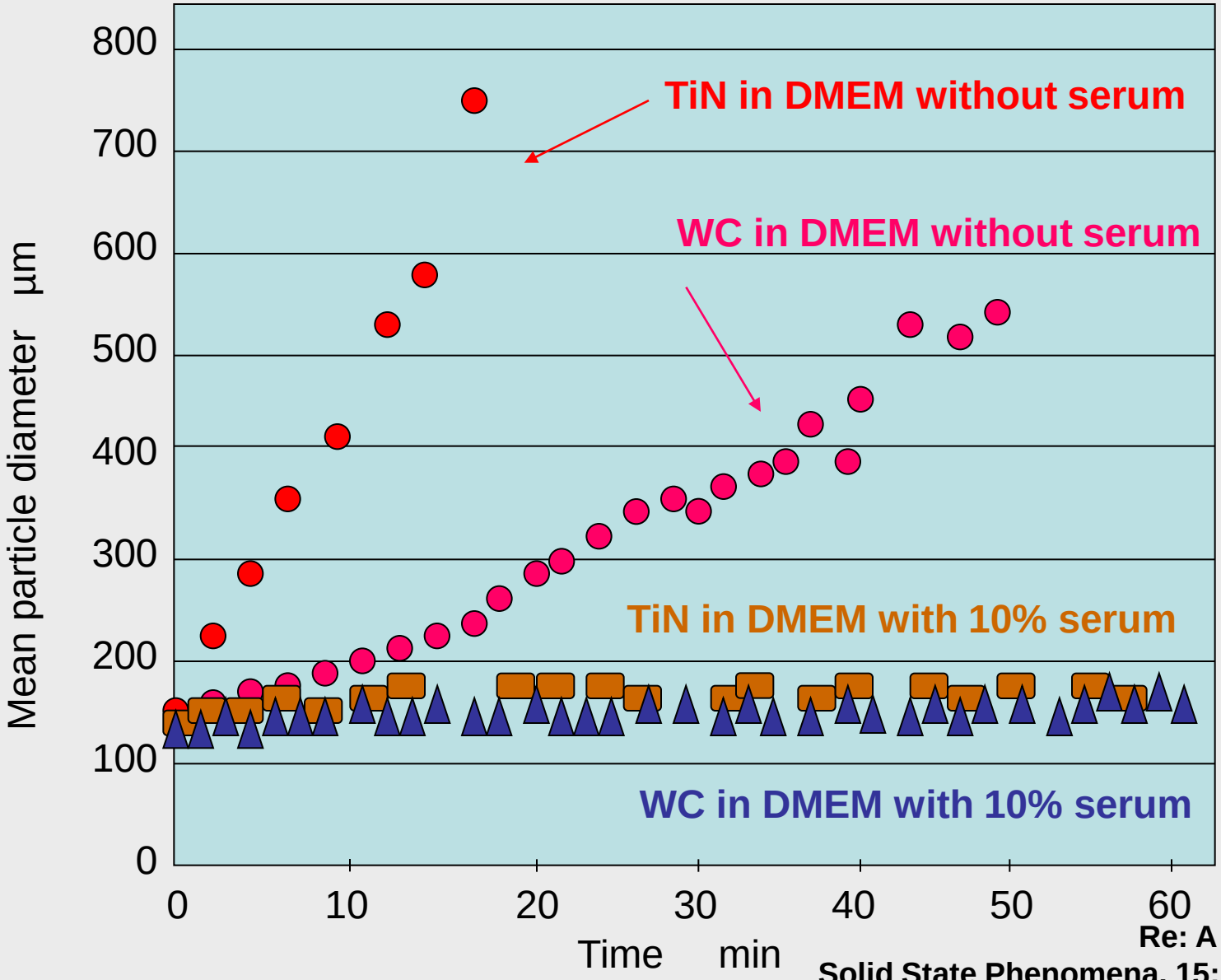
Re: I Lynch
Nature Nanotechn, 4:546-547 (2009)

Protein Deposition on Biomaterials
Sequence under Flow-Conditions

	Depositiontime [s] a=50%	Timefactor for boundary layer formation [s]
Albumin	0,050	9
Fibrinogen	7,4	13
Factor XII	140,0	8
HMWK	68,0	8
Platelets	260,0	18

D Basmadjian et al.,
Biomaterials, 18: 1511-1522 (1997)

Agglomeration Behaviour of WC and TiN Particles
- at a concentration of 10 µg/ml -

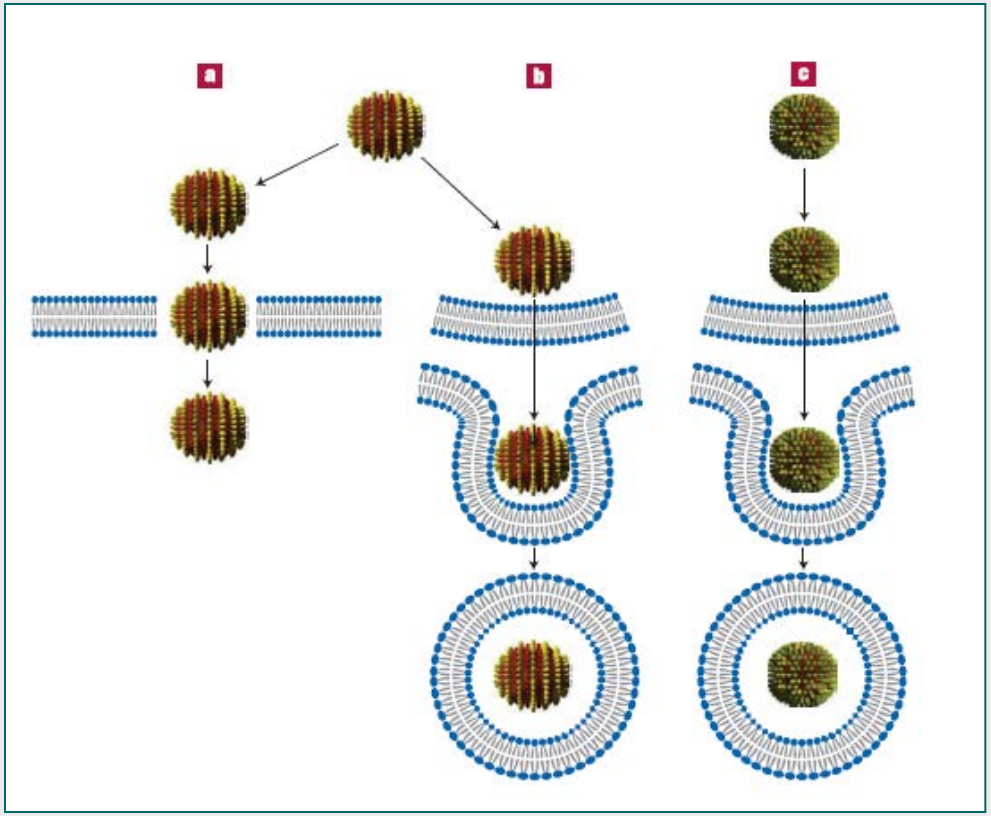


Re: A Potthoff et al.,
Solid State Phenomena, 15:183-189 (2009)

NANOBIOLOGY

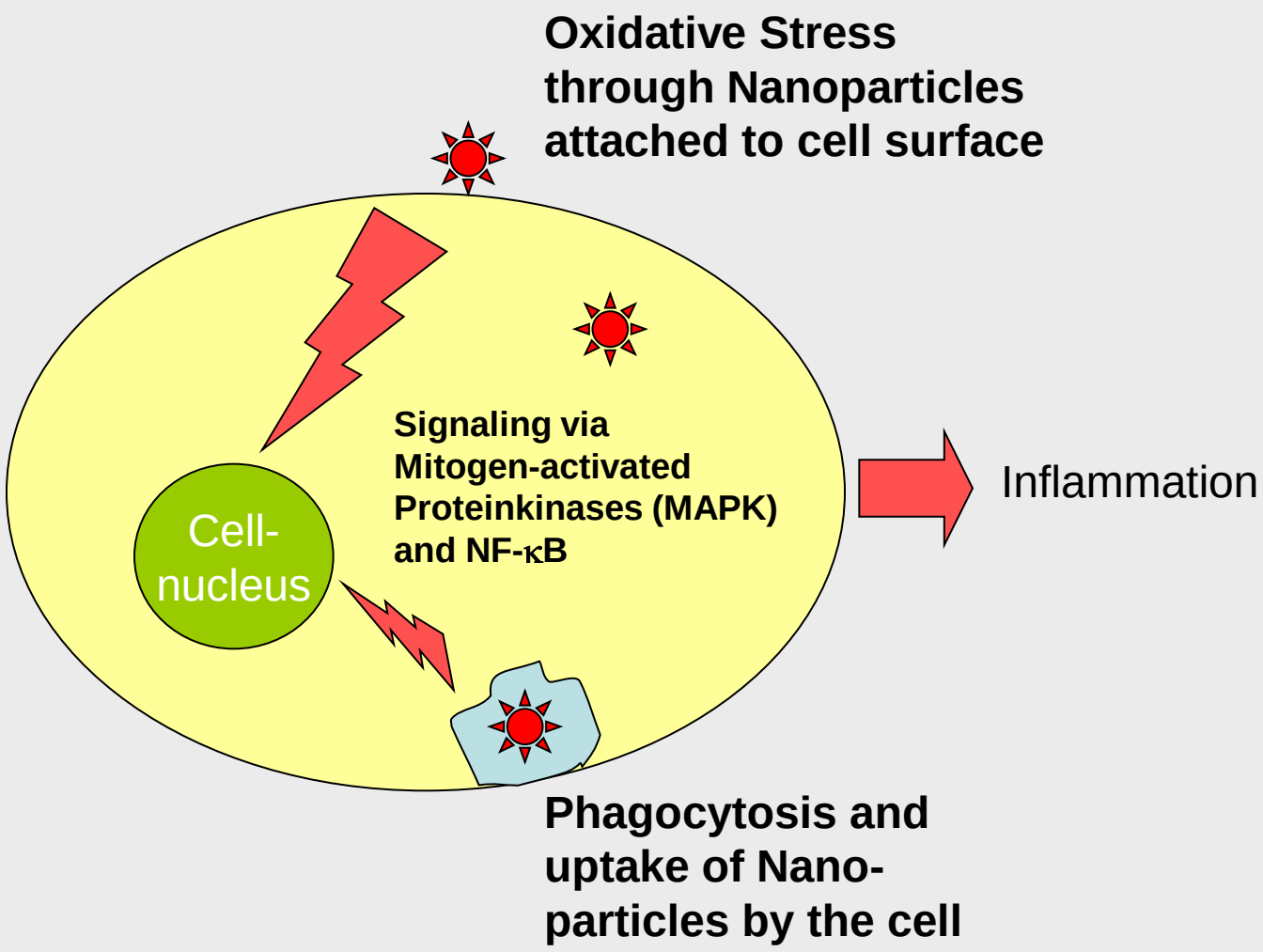
Particles slip cell security

Nanoparticles with alternating striations of hydrophobic and hydrophilic ligands cross the cell membrane by a direct mechanism — a route that delivers them to the main compartment of the cell while leaving the membrane undisrupted.



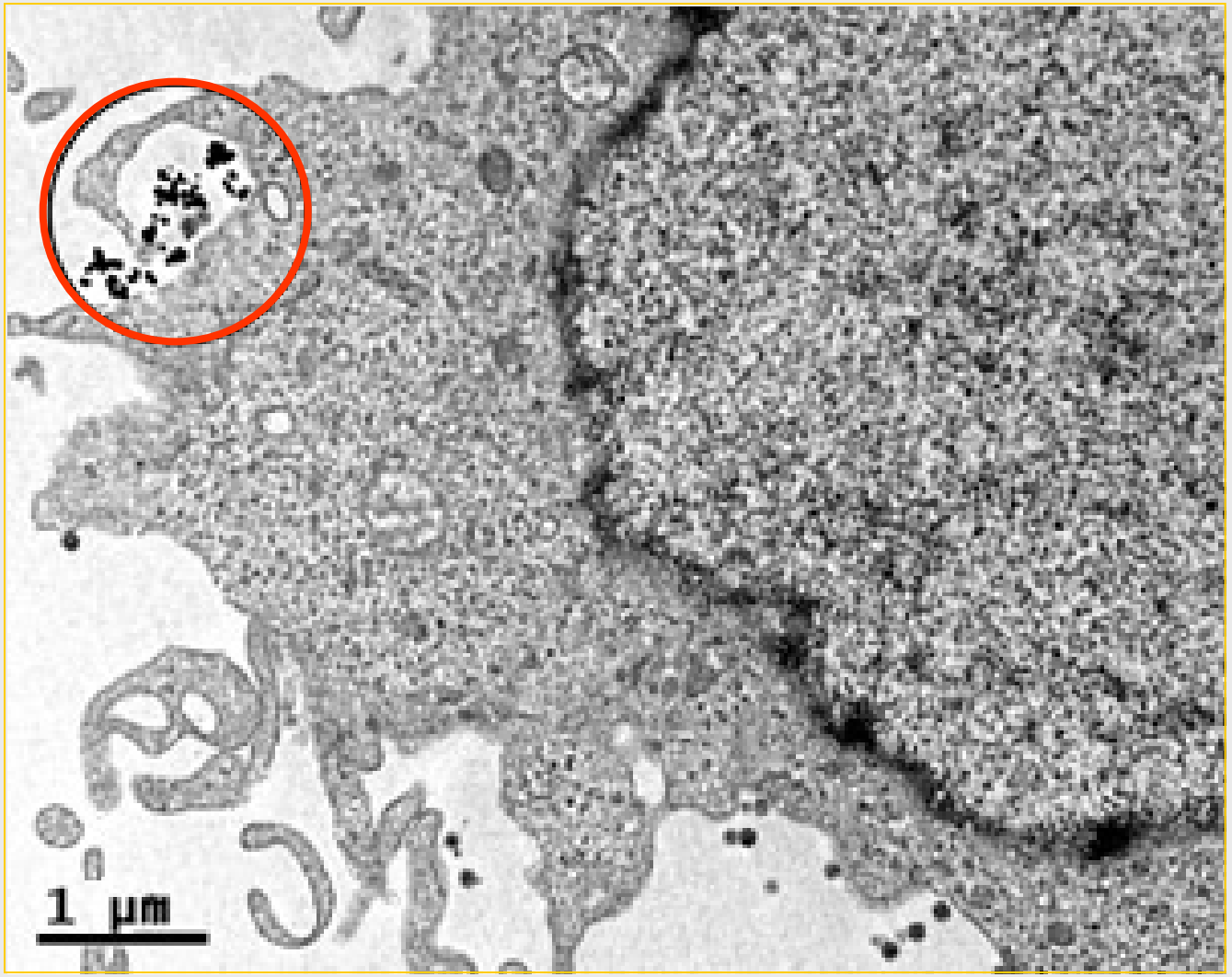
Re: T Xia et al.,
Nature Materials, 7:519-520 (2008)

Mechanisms of Cell-Activation by Nanoparticles



Phagocytosis of TiO_2 - Nanoparticles

TiO_2-Particles
∅: 30 nm

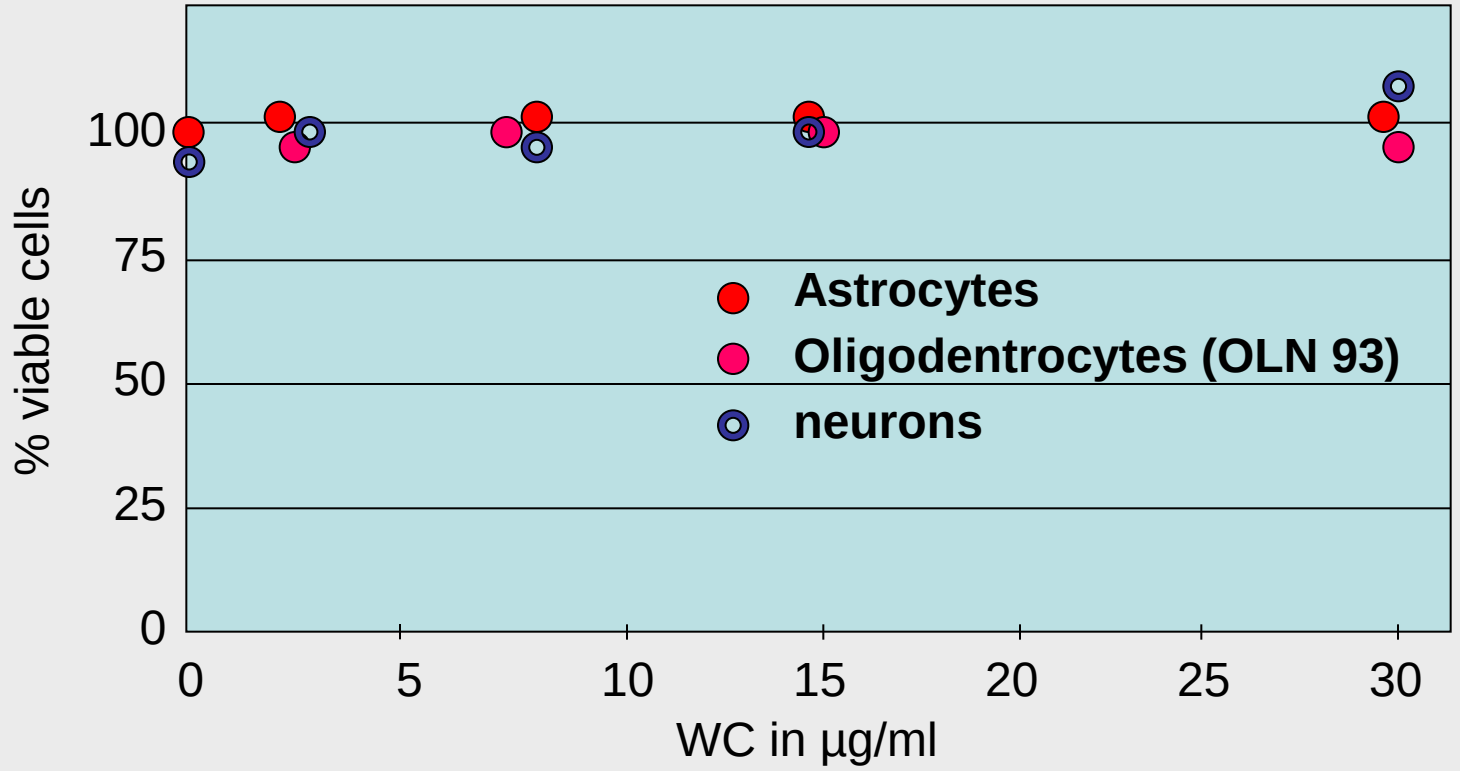


Gliacell

Re: FAZ-Sonntagszeitung
25.06.2006

Viability of WC particles exposed to rat brain cells

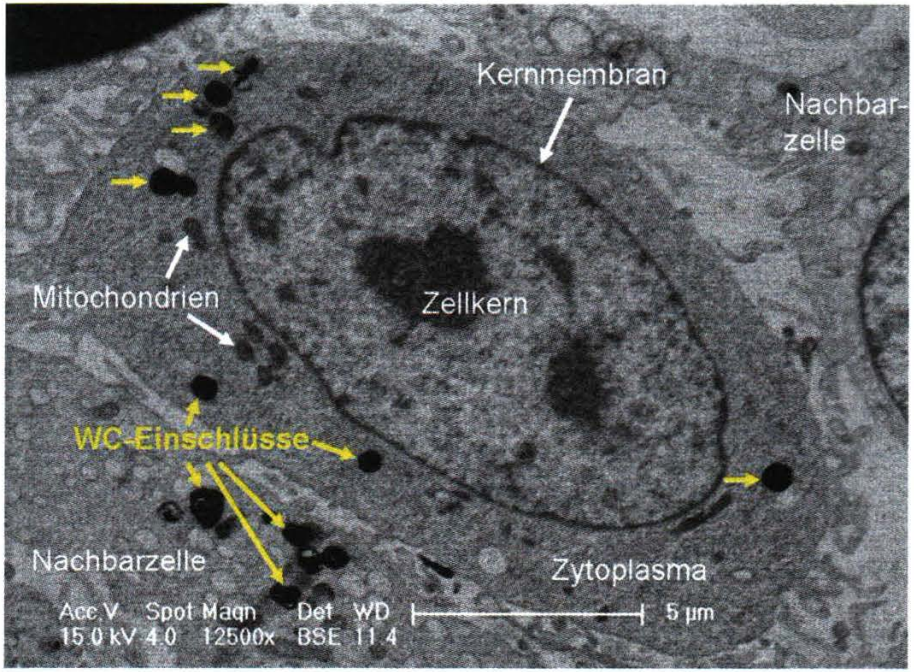
- short term viability, 2 days exposure -

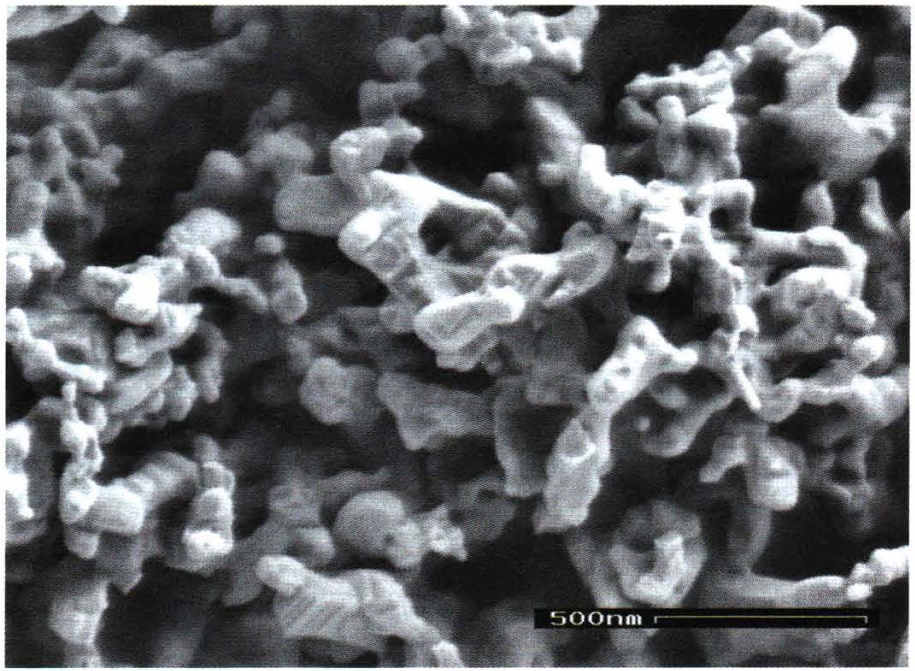


Re: A Potthoff et al.,
Solid State Phen, 15:183-189 (2009)

Gliacell and Uptake of Tungsten carbide Nanoparticles,

Synergistic effects between W and Co





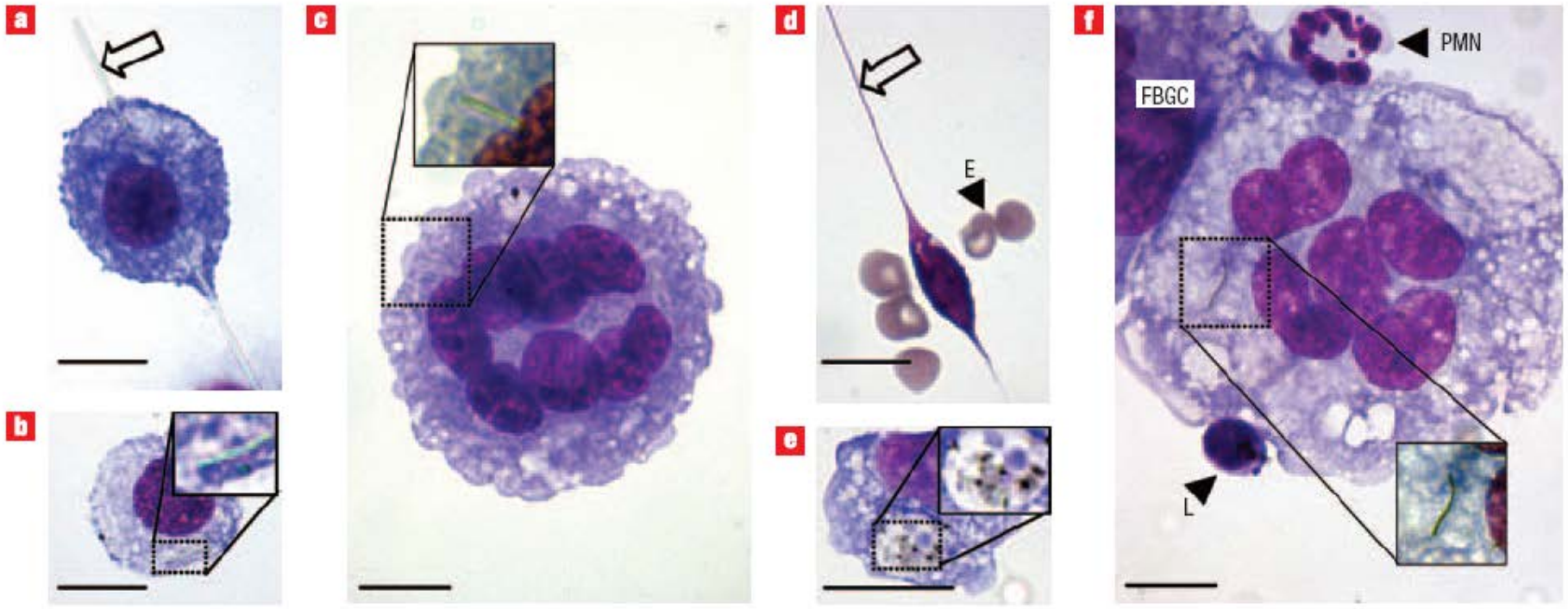
Magnification: x 12.500

Tungsten carbide particles without acute toxicity when present alone.

Toxicity observed, however, if Cobalt nanoparticles present.

Lessons learnt from Asbestos?

Frustrated Phagocytosis of Carbon Nanotubes



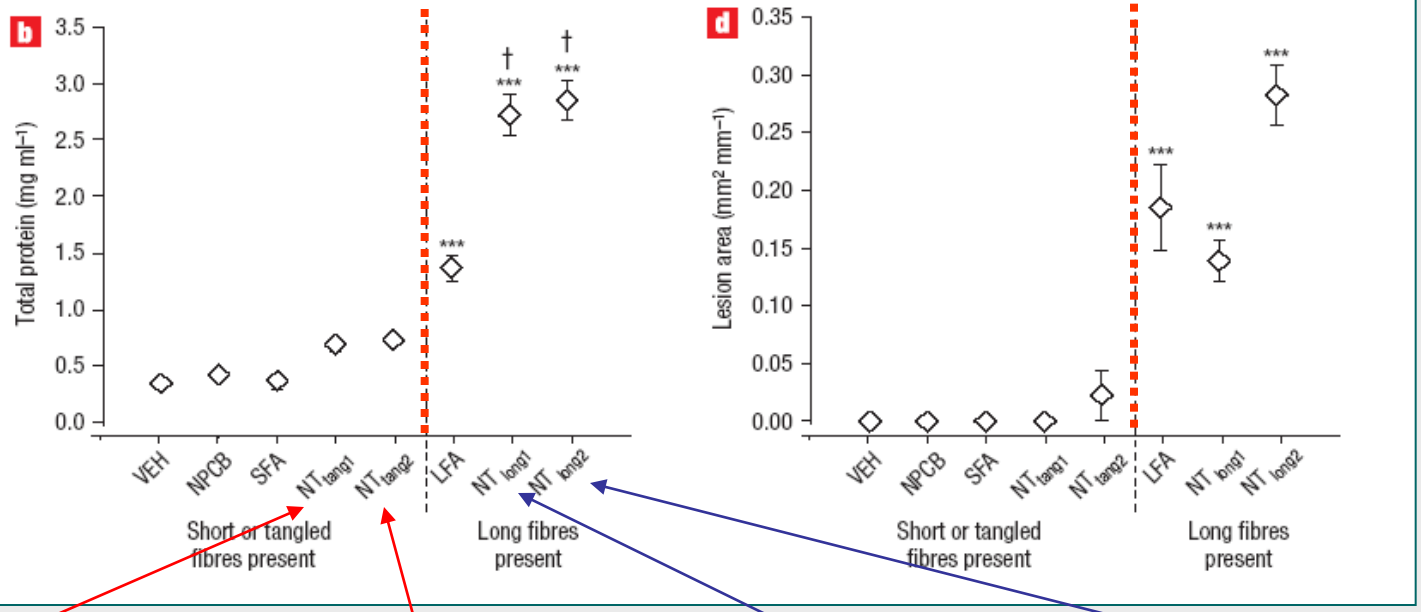
Re: CA Poland et al
Nature Nanotech, 3: 423-428 (2008)

Fibre length / -diameter of Nanotubes: - determinants for inflammatory processes -

Inflammatory response (24 h post-instillation)

Only through long NT´s (> 10 µm)

Granuloma response (7 days post-instillation)



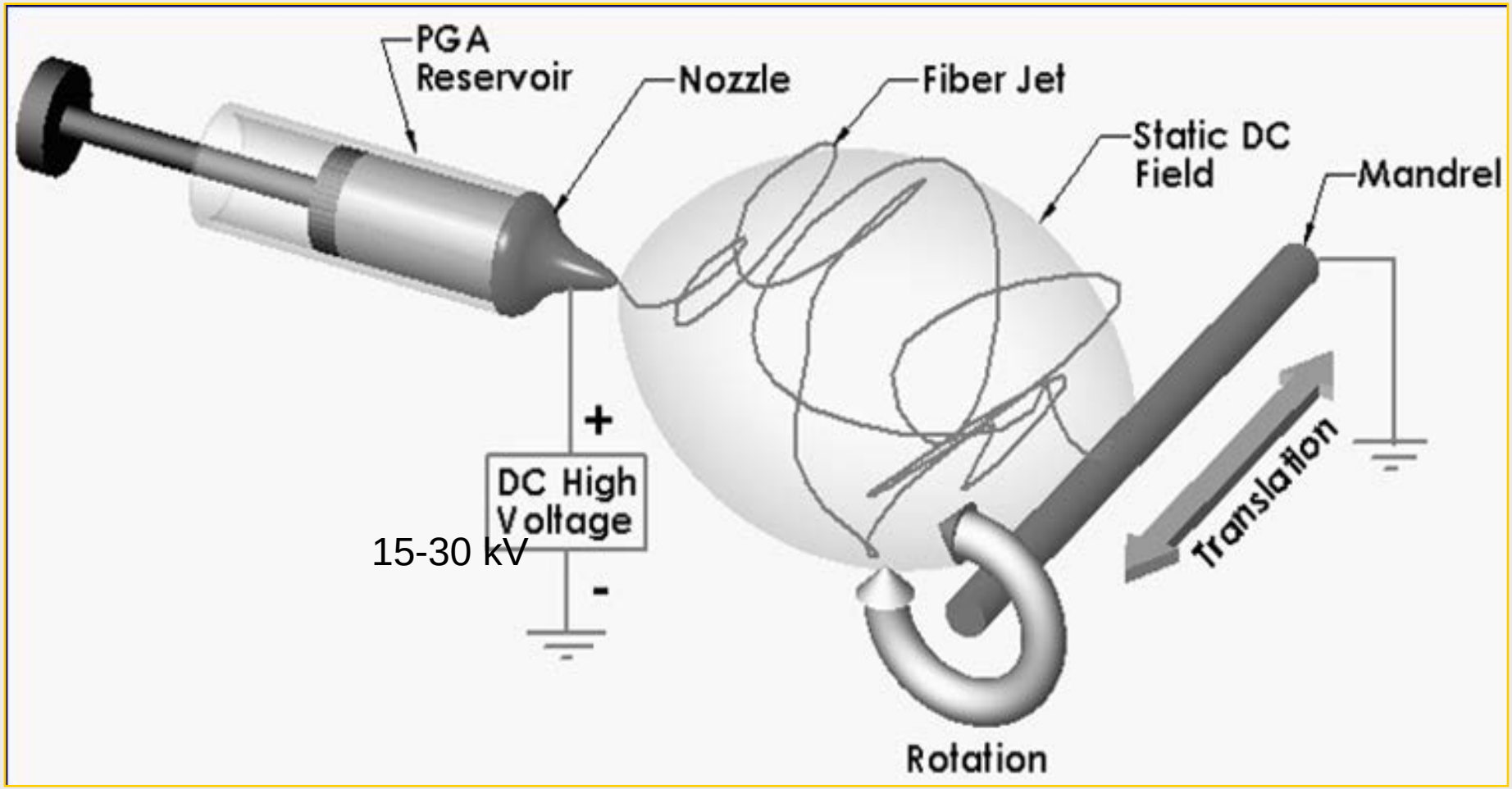
	NT-short1	NT-short2	NT-long1	NT-long2
Diameter as supplied by the manufacturer (nm, mean ± s.e.m.)	15 ± 5	15 ± 5	40–50	20–100
Diameter as determined by authors (nm, mean ± s.e.m.)	14.84 ± 0.50	10.40 ± 0.32	84.89 ± 1.9	165.02 ± 4.68
Length as supplied by the manufacturer (µm)	1–5	5–20	Mean 13	Max 56

* Carbon nanotubes in abdomen of rats

** NT nanotubes

Re: CA Poland et al Nature Nanotech, 3: 423-428 (2008)

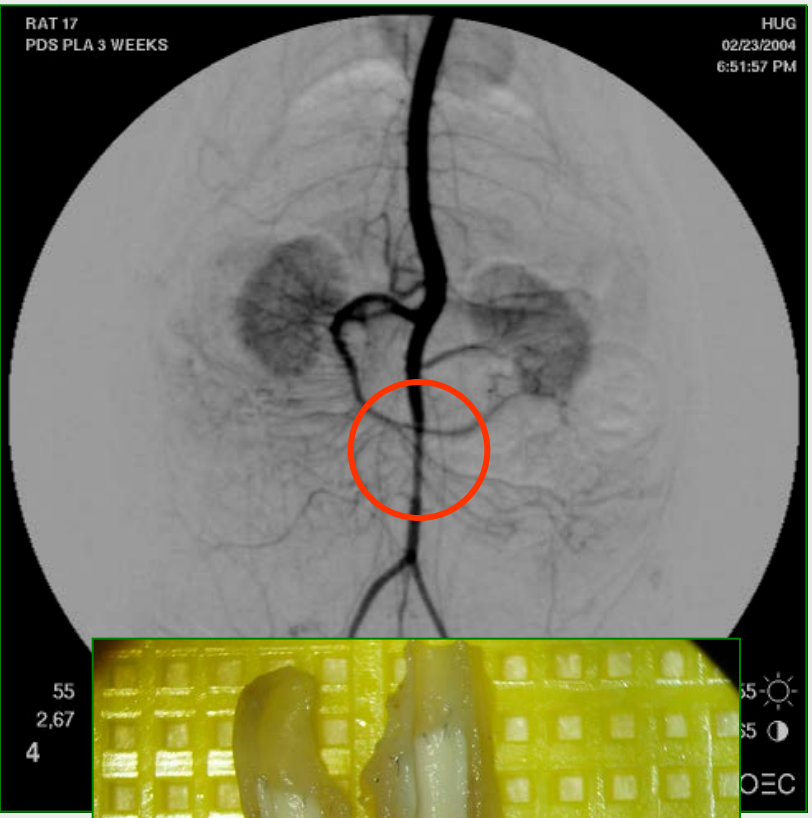
New Vascular Prostheses
with the help of the "BARBAPAPA" Technique

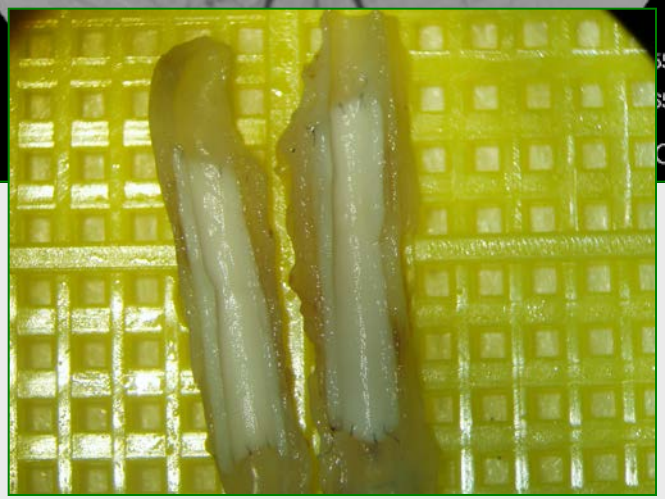


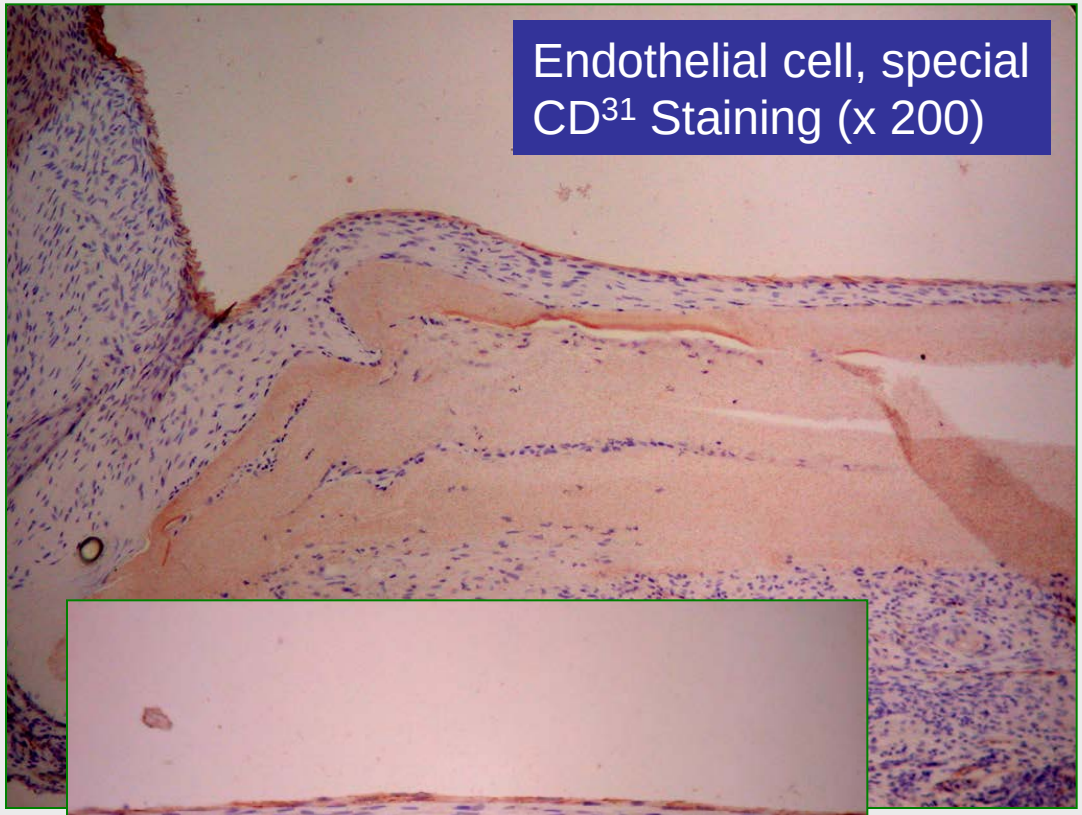
JA Mathews et al.,
Biomacromolecules, 3:232-238 (2002)

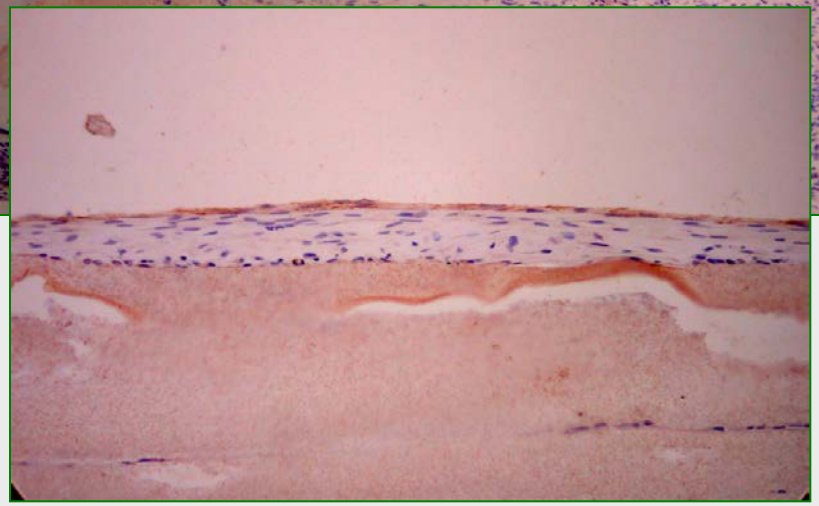
PDS GRAFTS mixed with slowly degradable PLA

n=3, 3 Weeks after Implantation (Rat model)



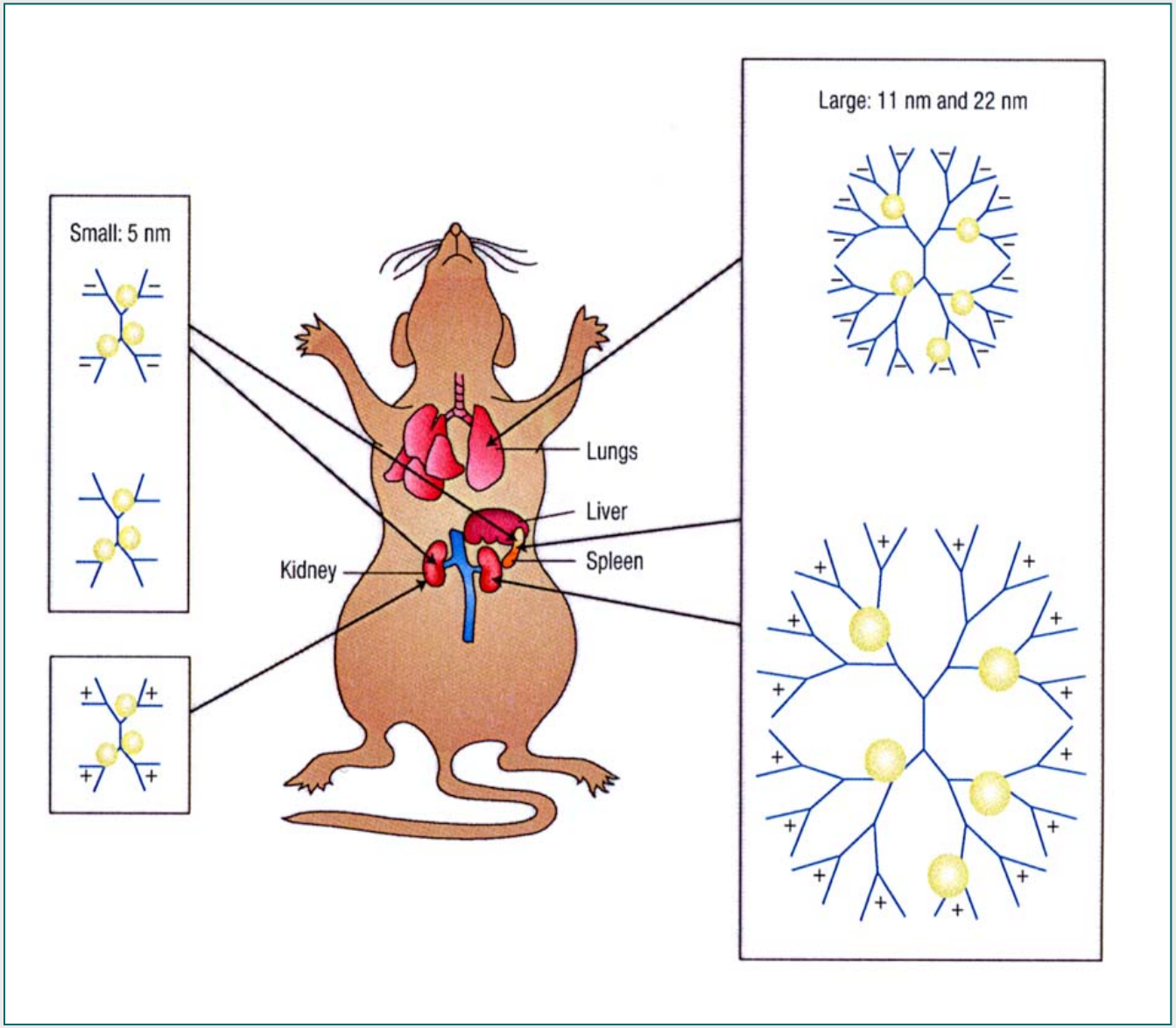






Re.: B Walpoth,
HUG Genf 2007

Gold-Dendrimer Particles and Their Biodistribution



- Charge

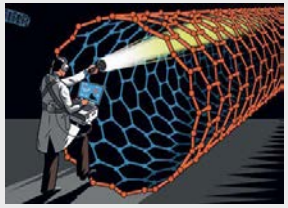
+ Charge

Re: R Minchin
Nature Nanotech, 3:12-13 (2008)

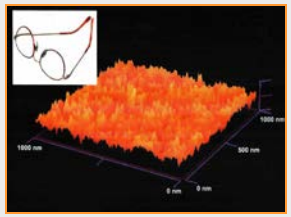
Unsolved Problems and Open Questions

- Standardisation of test-procedures for risk analysis?
- Standardisation of manufacturing
- Dose – response principles?
  - Individual nano-object / agglomerate?
  - Mass or particlenumber?
  - Analysis of nano-objects in tissue?
  - Threshold values / limits for cell-activation?
  - *In vitro* / *in vivo* differences
  - Biokinetics? Bioburden?
- Approval criteria for medical devices: Case-by-case consideration/general approach?

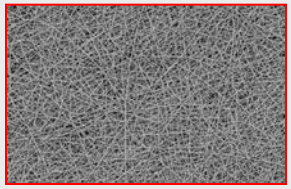
Nanotechnology for Medical Devices
Challenges, Changes and Risks



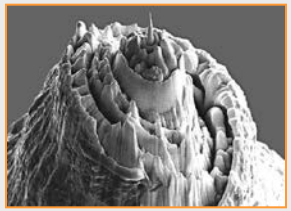
Nanomed-Tech
Figures of today, facts of tommorrow



Nanomed-Tech application
Risks and chances



Nanomed-Tech
Company profiles



Quo vadis?
Expectations and requirements

Companies involved in NanoMedTech
- Example Germany -

Germany 2010: 950 companis involved in development and marketing of NANO products, majority SMEs

→ 60.000 FTE-positions involved

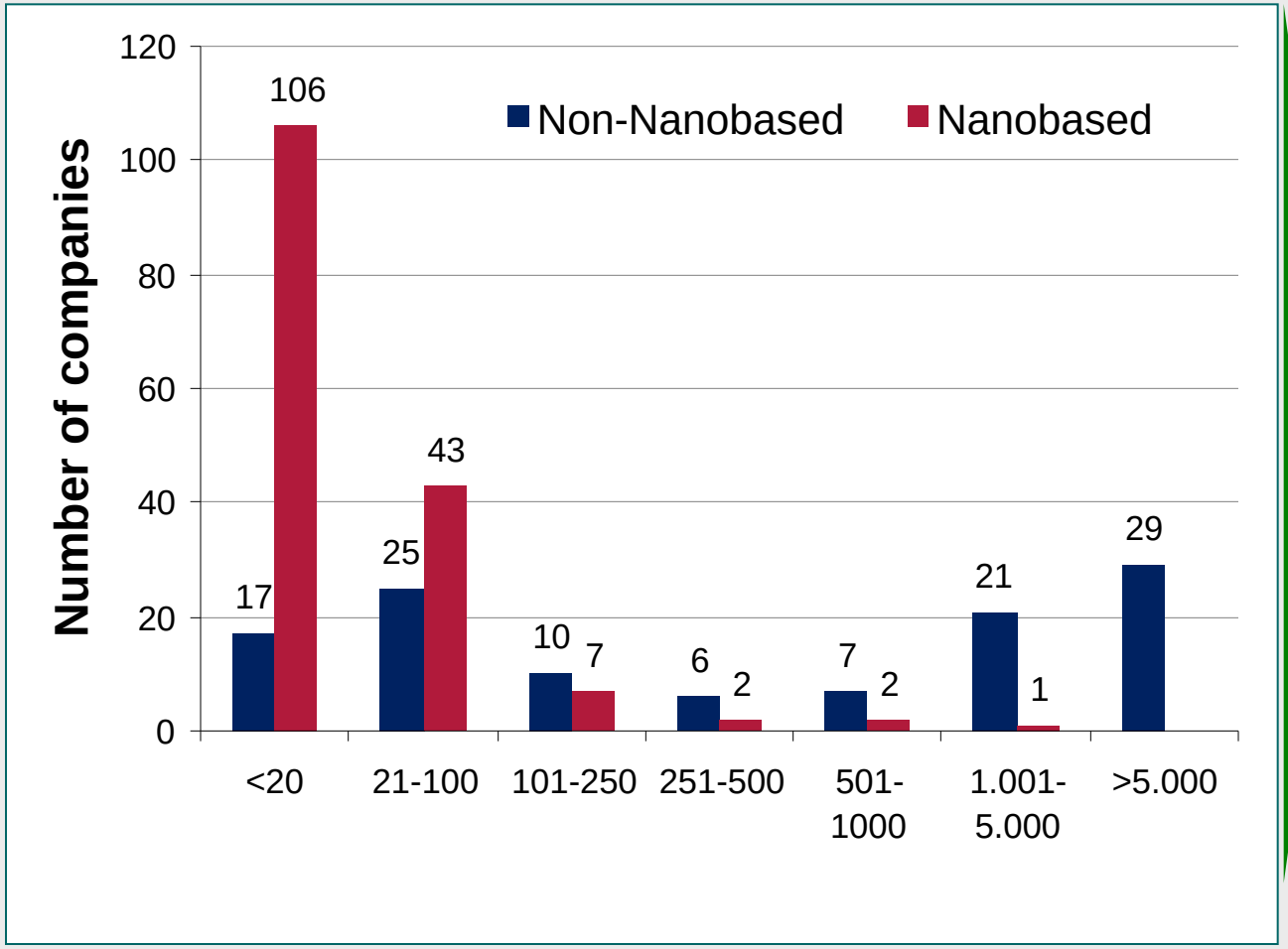
Company-types:

1. Science-driven companies targeting innovations

2. Traditional science-driven companies with capacity for large production volumina

3. Large, multinational companies addressing global markets

Number of FTE´s in Nanotech Companies

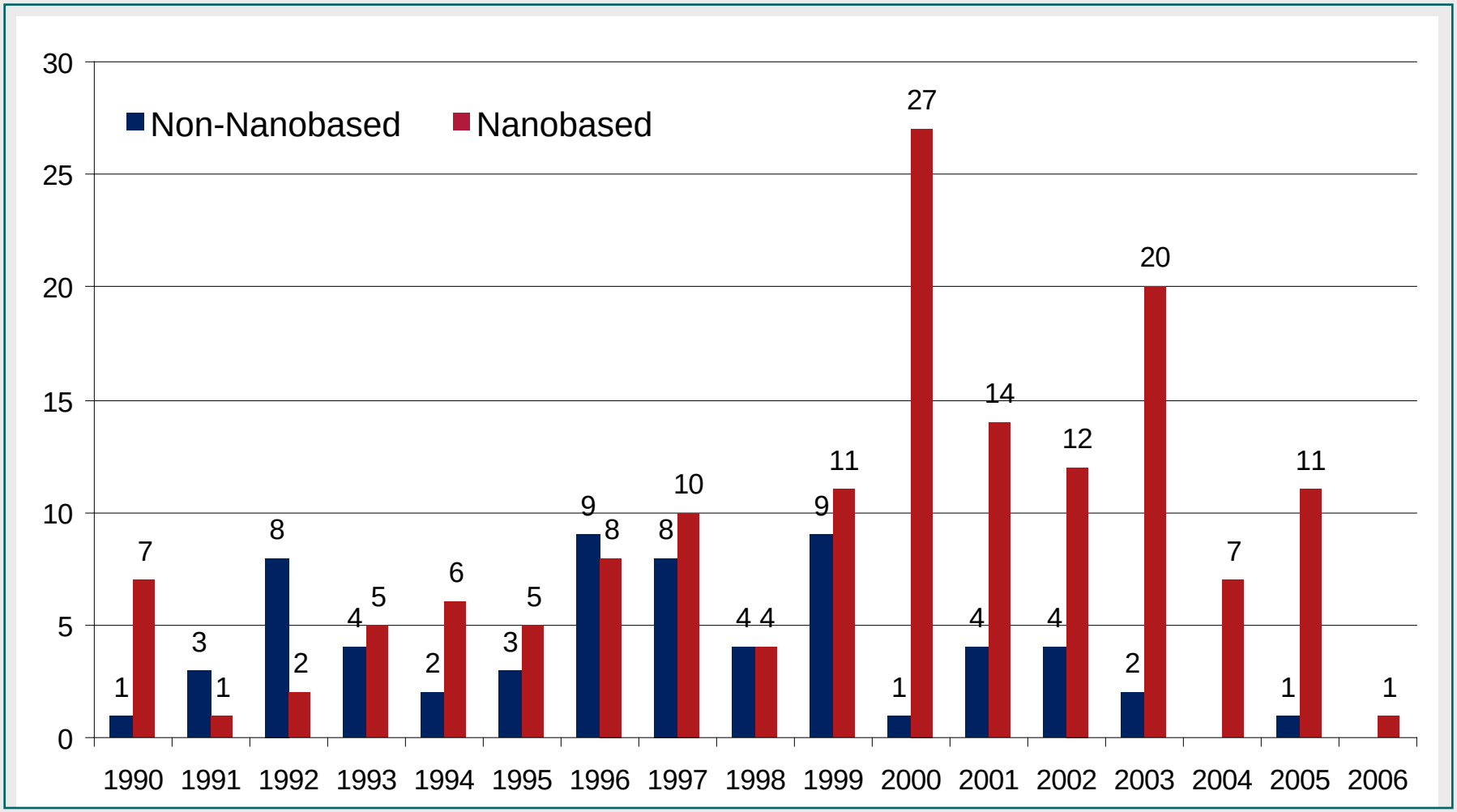


97 % of Nanobased-companies with less than 250 FTEs →SMEs.

54 % of Non-nanobased-companies with more than 250 FTEs.

Re: Nanotechnology in Medicine Report Ernst & Young 2007

Company Foundations1990-2006

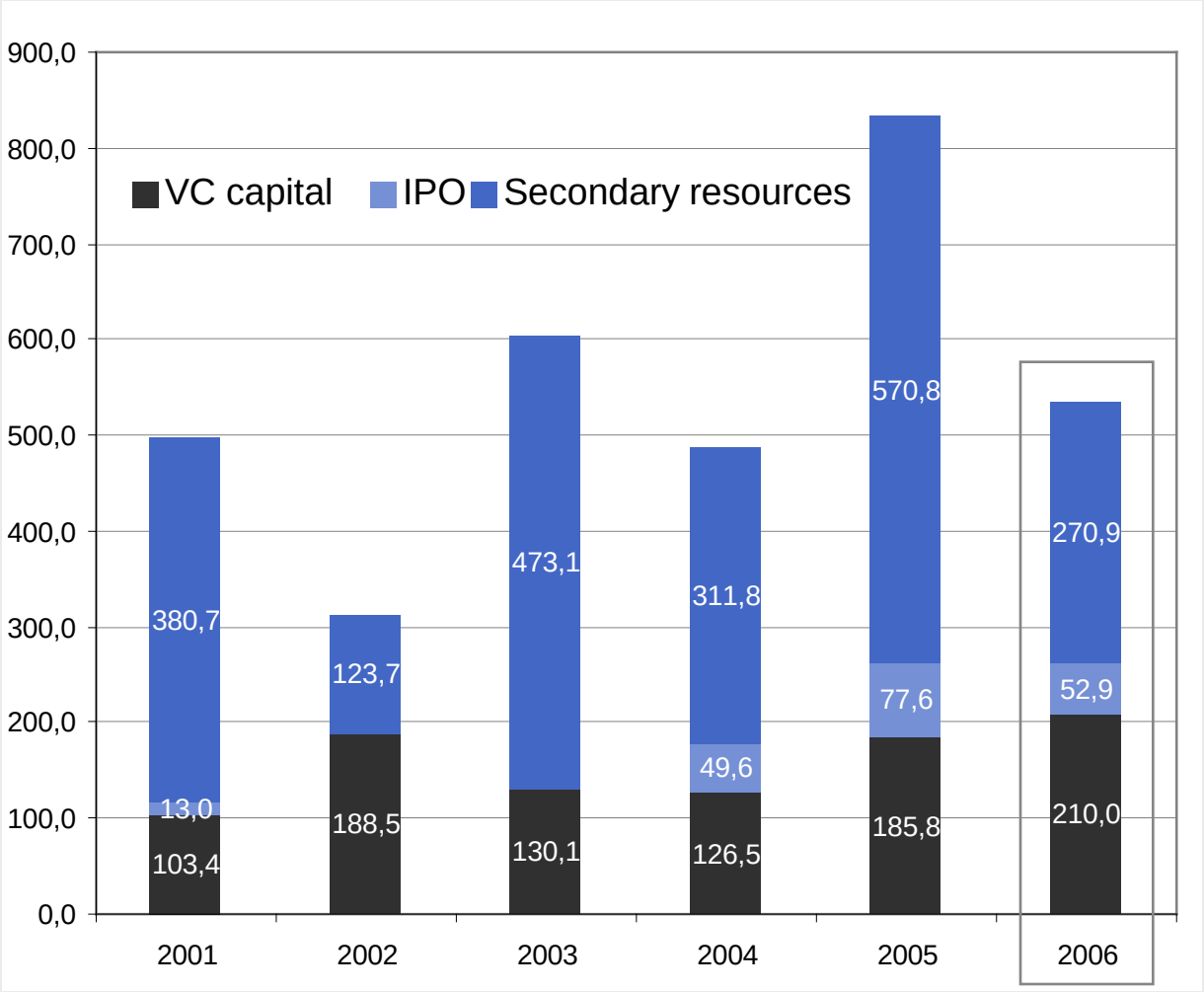


→ 83 % of Nanobased-companies are younger than 15 years

→ Average age of non-Nanobased-companies : 37 years.

Re: Nanotechnology in Medicine
Report Ernst & Young 2007

Capital Resources of Nanobased-Companies per Year (in Mio. €)

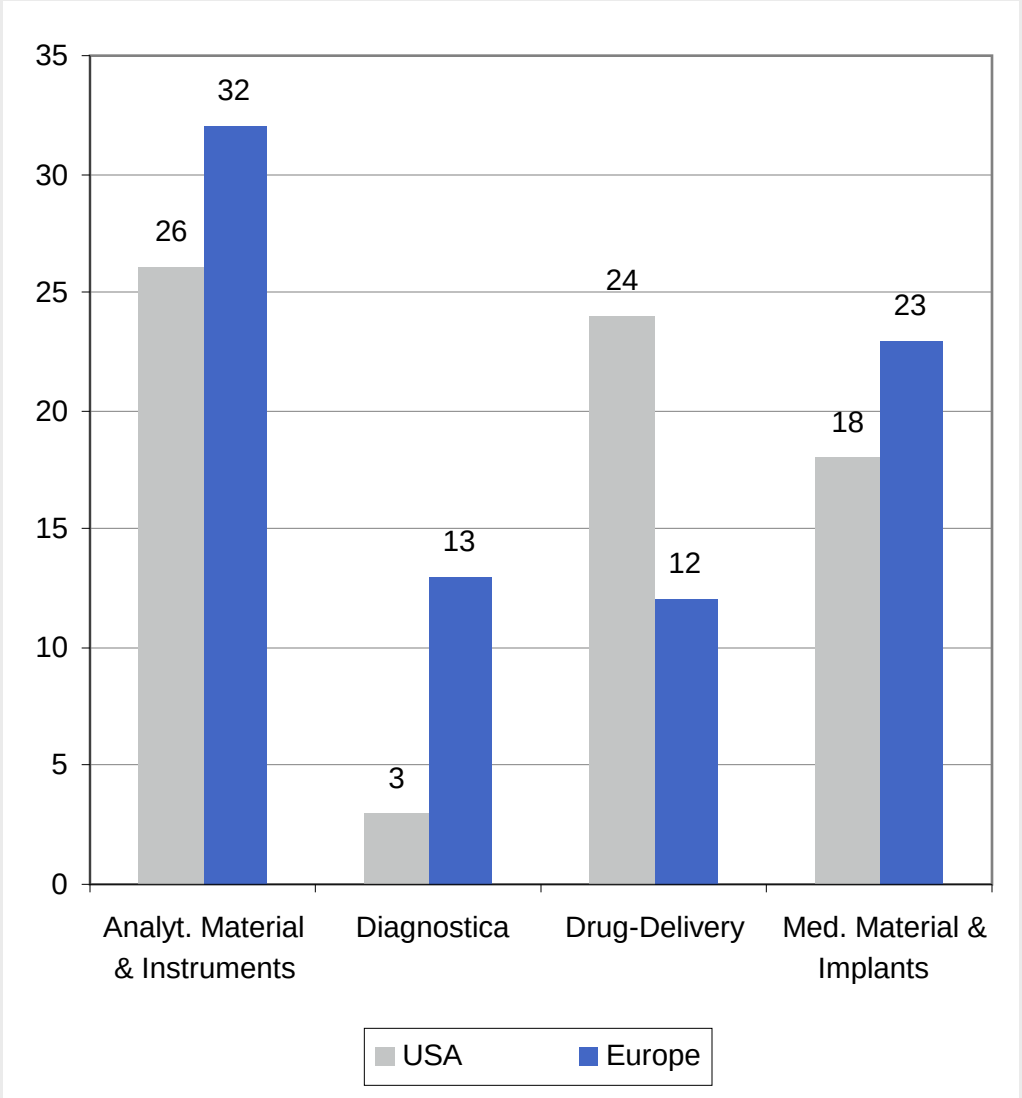


In 2006, nanobased-companies collected **534 Million €** worldwide.

VC (Risk) capital for the majority of the private companies added only to 210 Mio. €.

IPO: initial public offering, stock market launch

Number and Types of Nano-Products in the Medical Marketplace 2007



Majority of products (38 %) in the realm of „Analytic Materials & Instruments“.
→ Europe leading in this segment.

Second place: „Biomaterials & Implantats“ (27%).
→ Europe in front of North Amerika

The most promising segment „Drug Delivery“ with 25% at third place.
→ USA in front of Europe

Re: Ernst & Young, 2007

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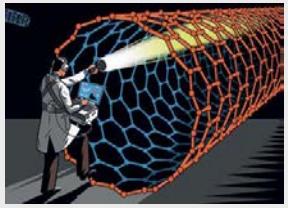

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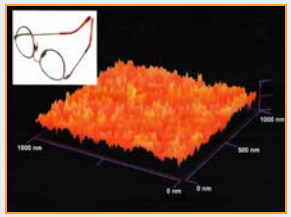
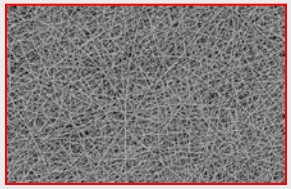


Nanomed-Tech application
Risks and chances



Nanomed-Tech
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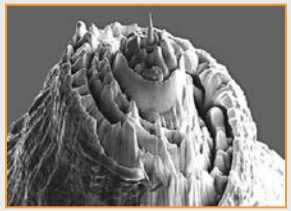
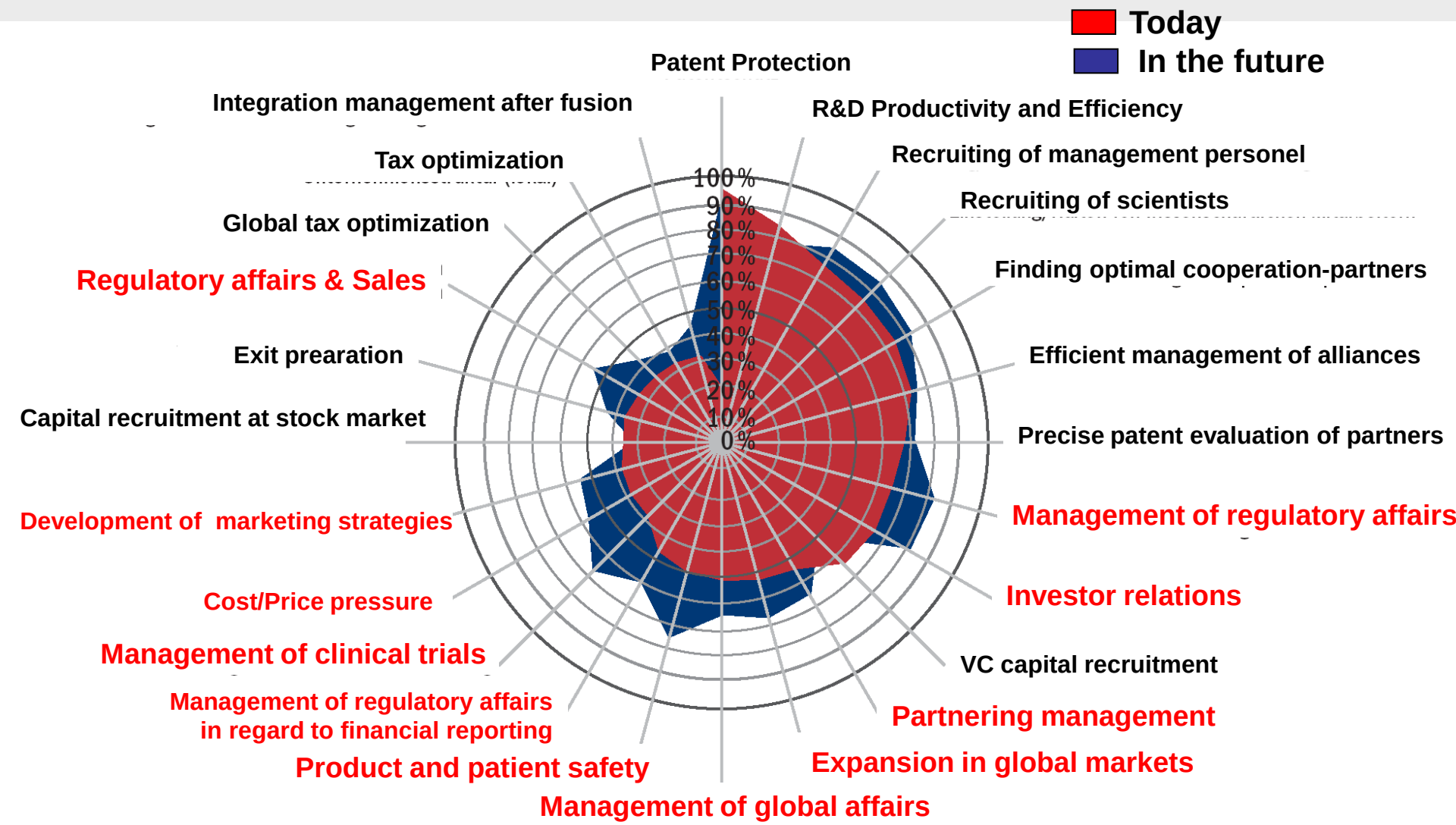


Quo vadis?
Expectations and requirements

Challenges for NanoMed-Tech Companies Strategy and Operations, an enquiry.



Re: Nanotechnology in Medicine
Report Ernst & Young 2007

Impact factors for market success of nanoscaled medical devices

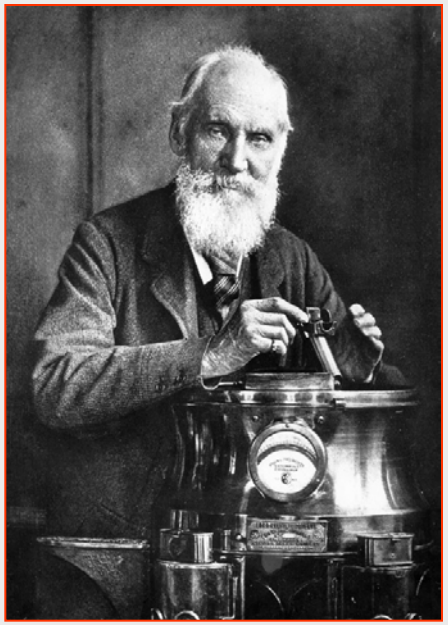
Approval:
Harmonsation of approval procedures and shortening of approval time

Safety: Acute vs chronic effects

Definitions:
A nanoparticle must have been engineered
vs
A nanoparticle can be a leachable

Funding Spin-off companies / SMEs
Exclusivity reasonable?
or: model to be envisaged that involves large multinational companies

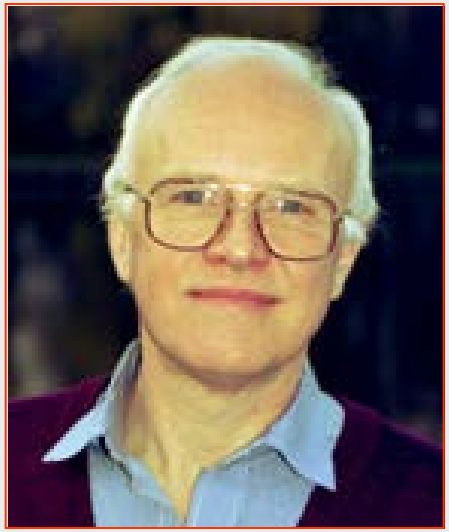
The Experts´ Opinion
“Who measures is right!”



“When you can measure what you are speaking about, and express it into numbers, you know something about it!

When you cannot express it in numbers your knowledge is of meager and unsatisfactory kind.“

Lord Kelvin, physicist (1824 – 1907)



"You cannot **control** what you cannot **measure**."

Tom deMarco, modern software-guru, (*1940)