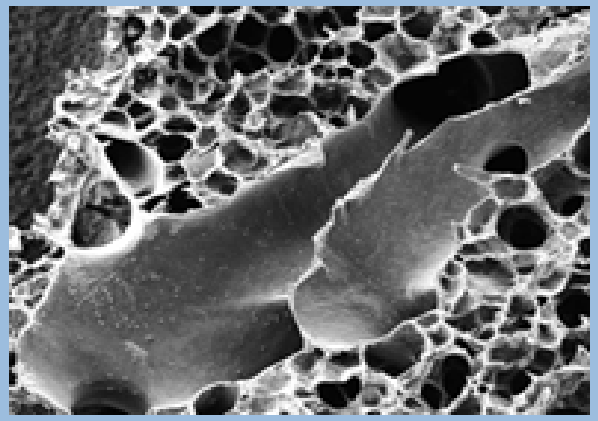
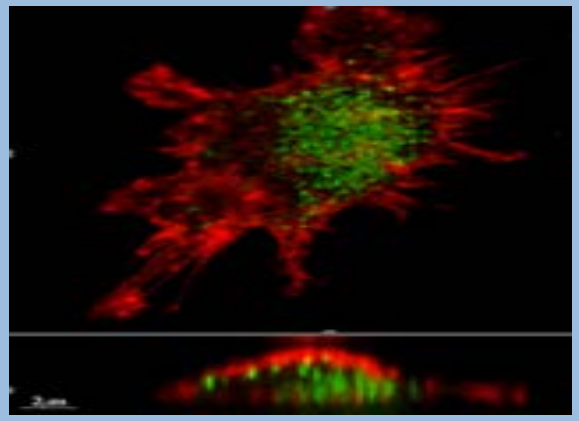
Conference on Air Pollution
AQM
Teheran
January 12, 2016

UNIVERSITÄT BERN

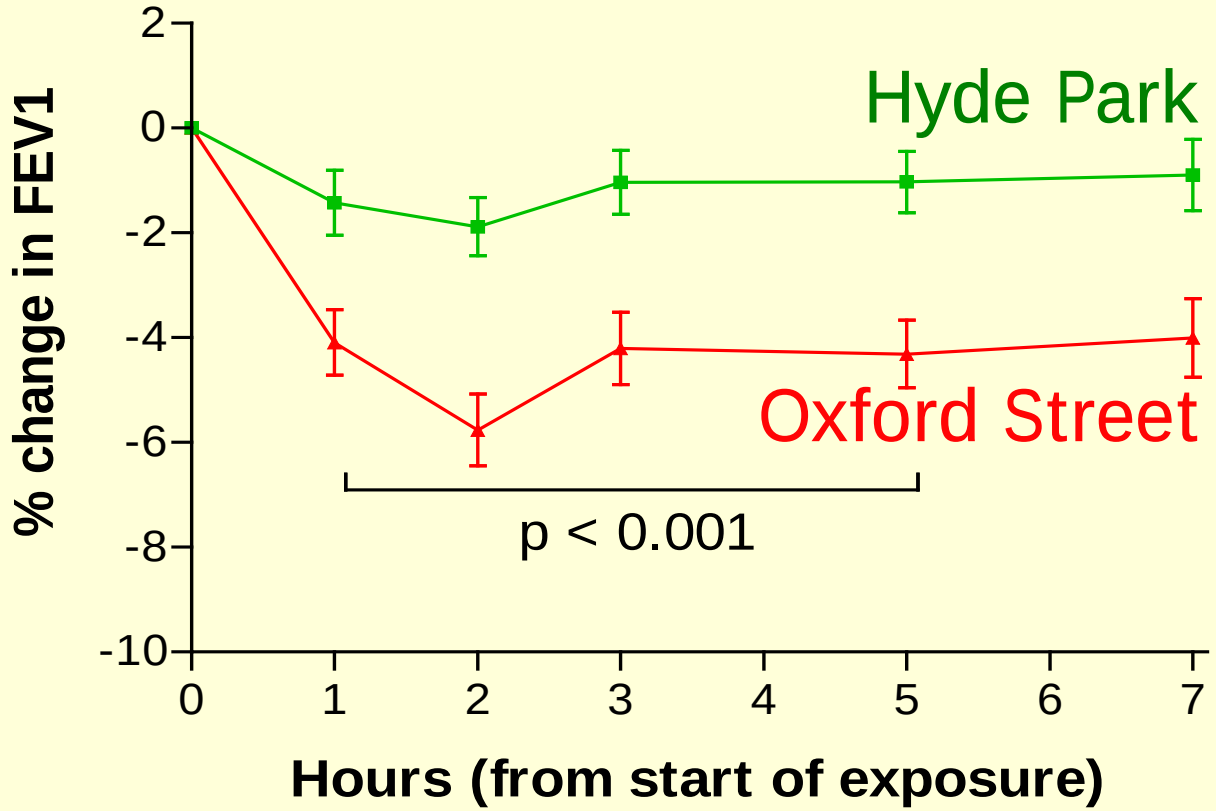
HEALTH EFFECTS OF COMBUSTION GENERATED PARTICLES

HOW COMBUSTION GENERATED NANOPARTICLES (UFP) CAN ENTER THE HUMAN ORGANISM – SIZE MATTERS

Peter Gehr
Prof. em.
University of Bern
Bern
Switzerland

LUNG FUNCTION OF ASTHMATICS WHILE WALKING ALONG THE DIESEL BUS ROUTE OXFORD STREET, THROUGH HYDE PARK



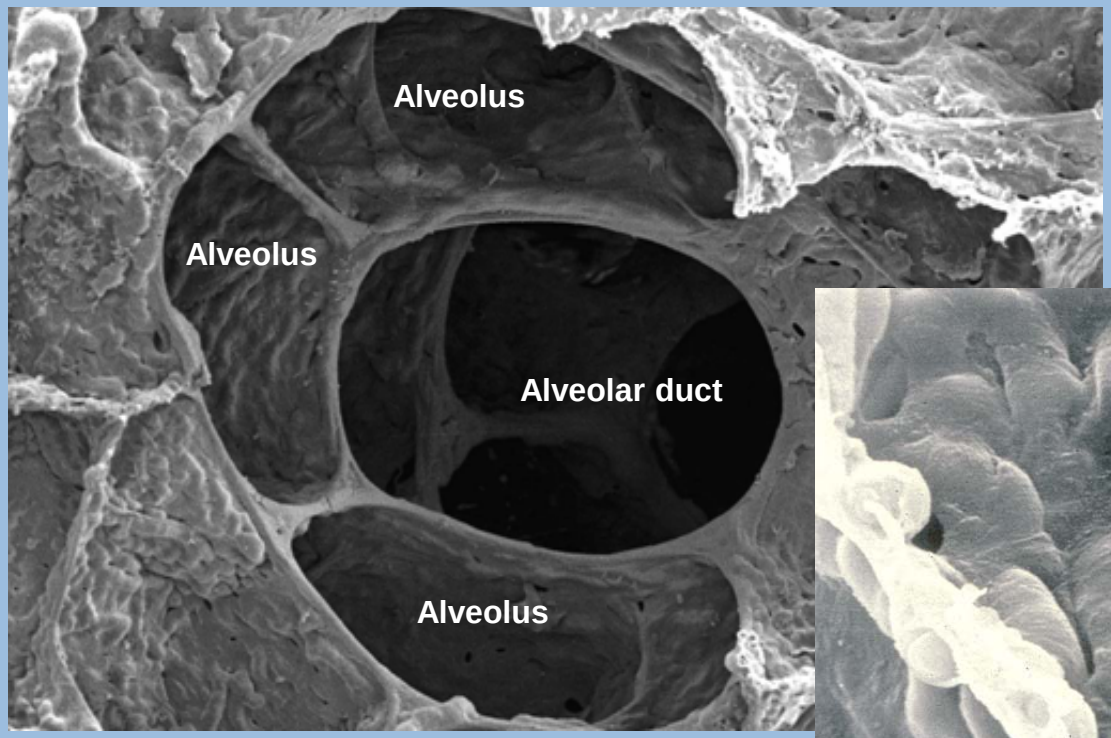
WHO (IARC):

- Diesel exhaust is carcinogenic, June 12, 2012
- Air pollution is carcinogenic, October 17, 2013

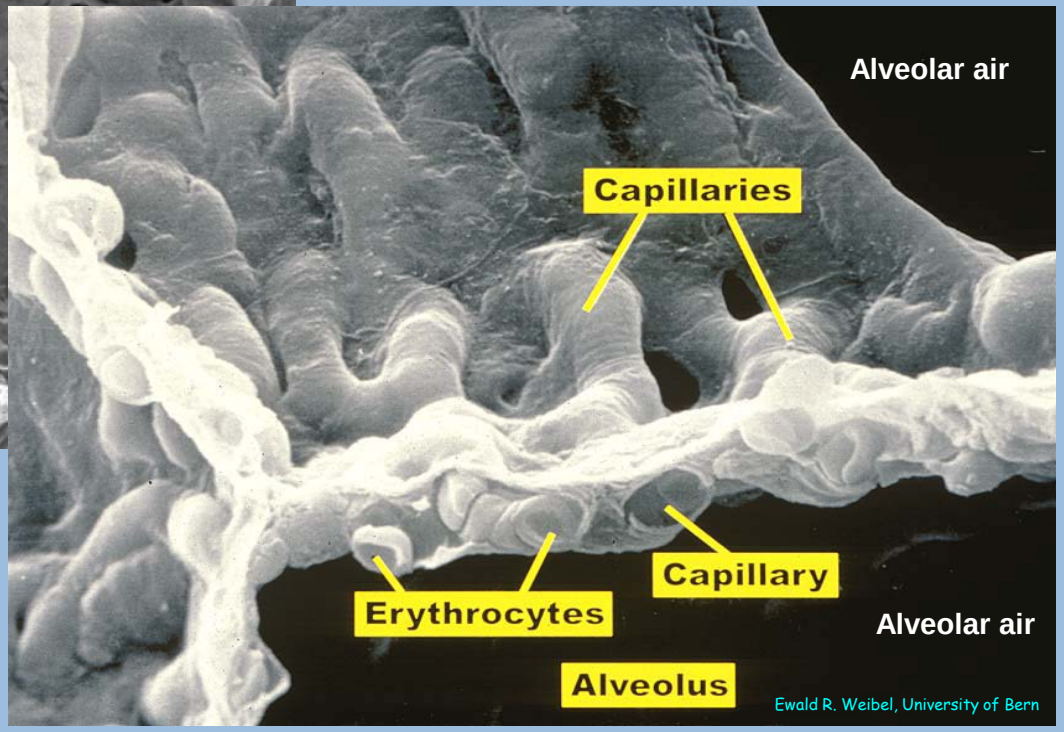
McCreanor et al, NEJM 2007

Courtesy:
Nino Künzli
Swiss Tropical and Public Health Institute
Basel, Switzerland

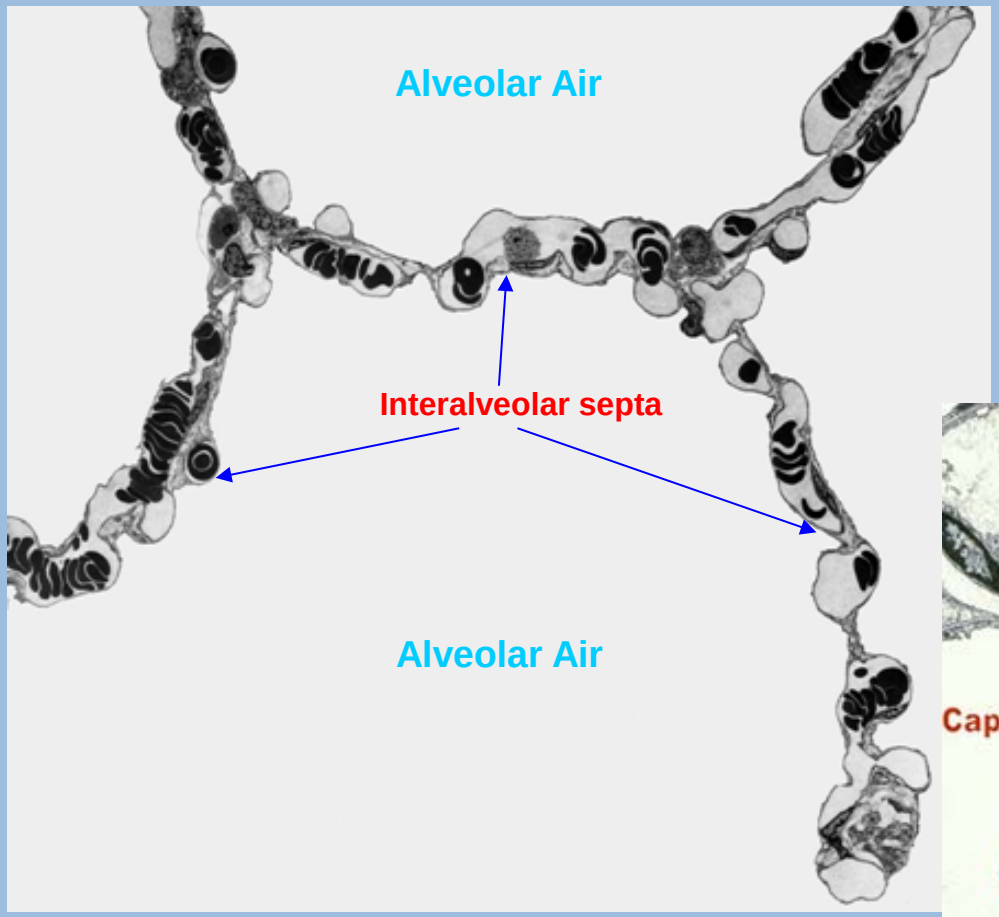
MAIN PORTAL OF ENRTRY: LUNG



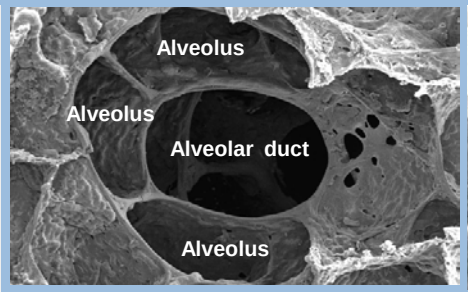
Gehr et al., Respir. Physiol. 1978

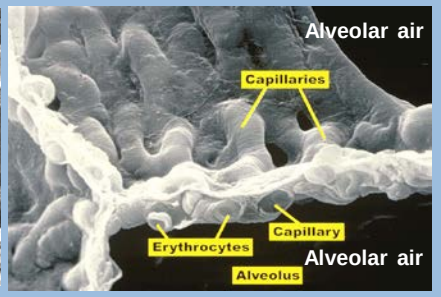


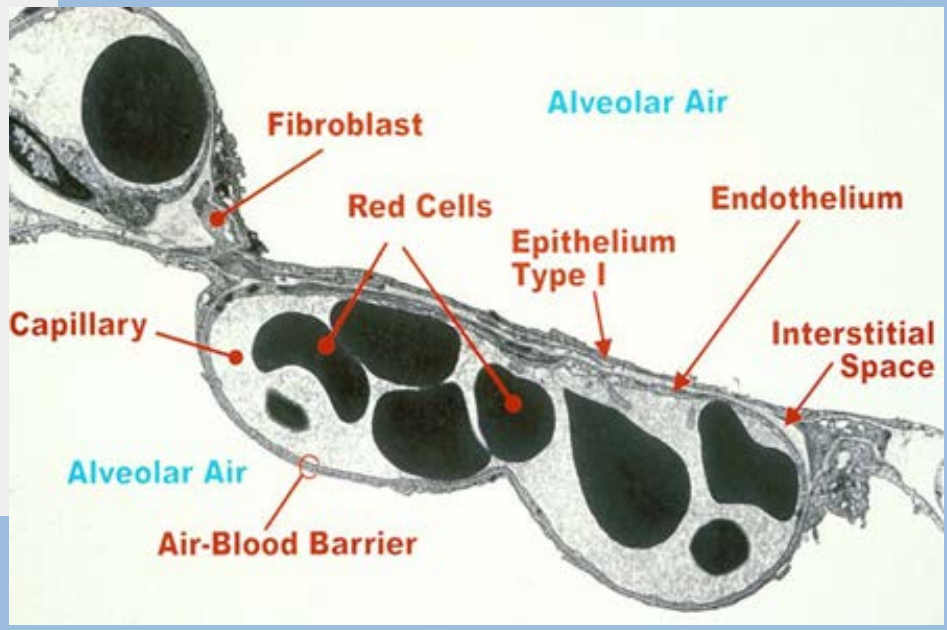
ALVEOLI, INTERALVEOLAR SEPTA



Gehr et al., Respir. Physiol. 1978







DID YOU KNOW THIS ABOUT THE HUMAN LUNG?

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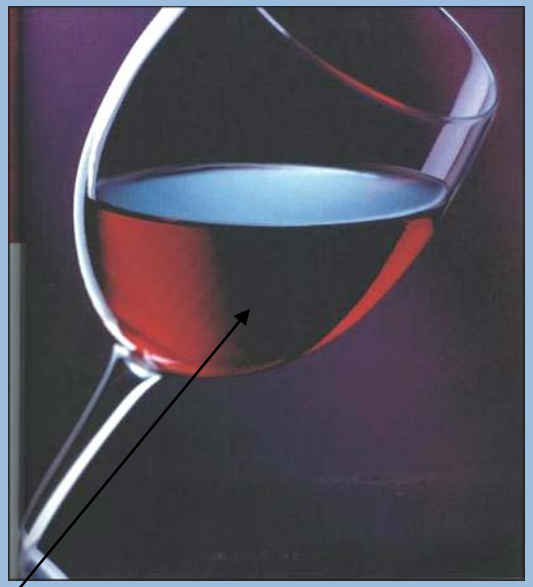
Tennis field

450 Mill. alveoli (M. Ochs, Univ. of Bern) with a surface area of **140 m²**

(diameter ¼ mm, gas-exchange region 80-90%)

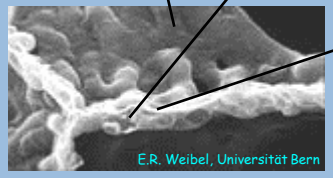


Red wine glass

Volume of capillary blood involved in gas exchange: **210cm³**

1/50 of the thickness of a women's hair

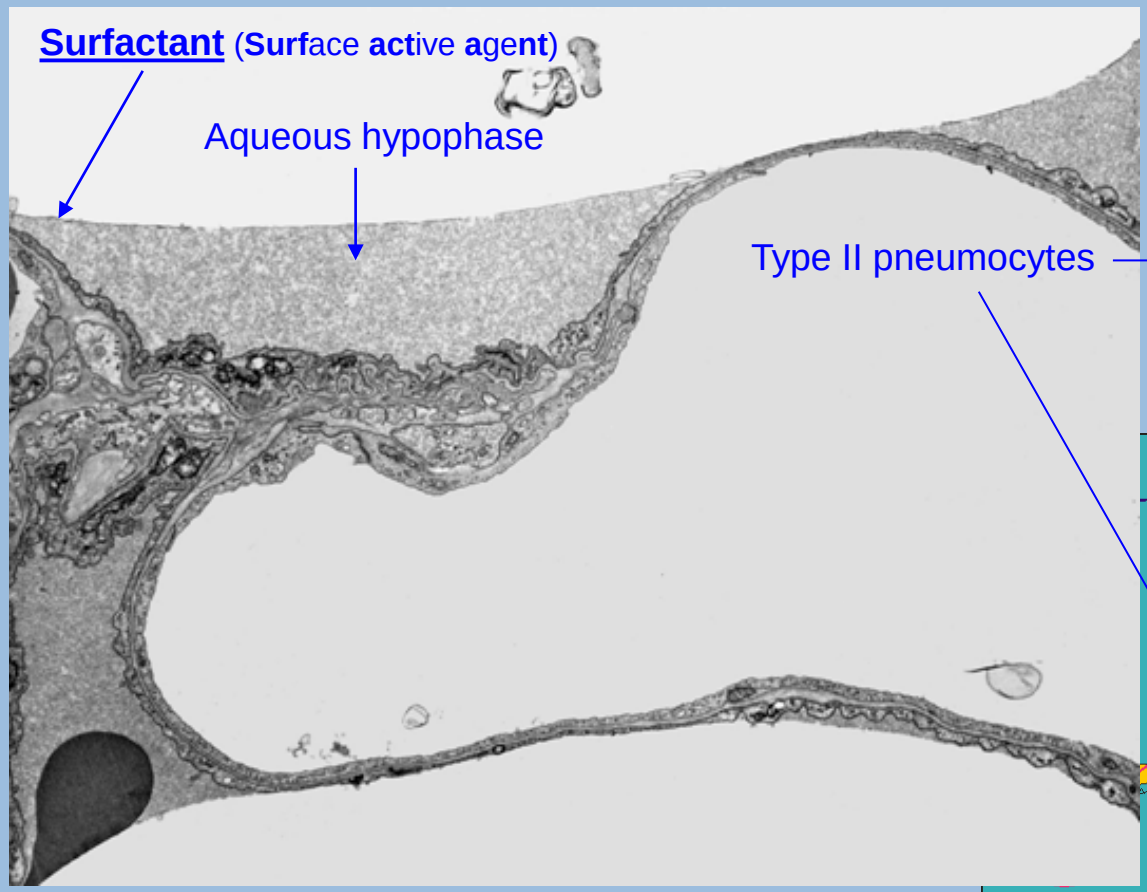
Thickness of tissue barrier: **<1µm**

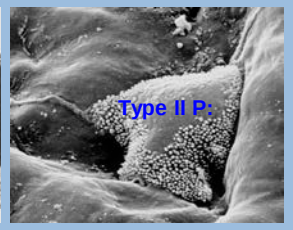


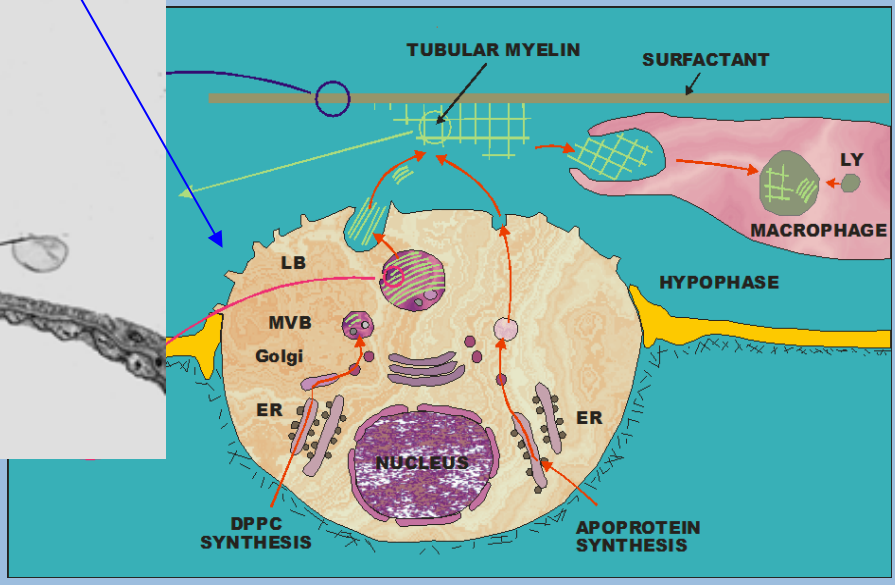
(B. Rothen-Rutishauser, Universität Bern)

Gehr et al., Respir. Physiol., 1978

SURFACTANT, AQUEOUS HYPOPHASE







PARTICLES DEPOSITED IN THE LUNGS →DISPLACEMENT

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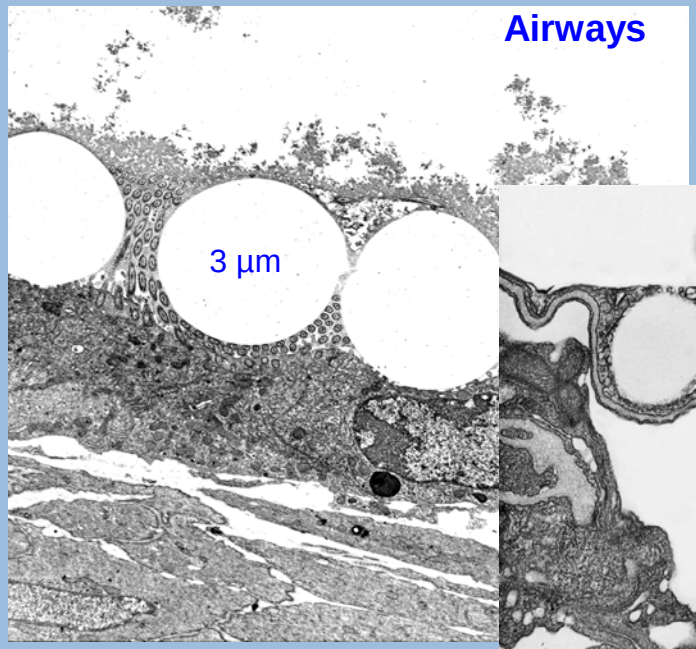
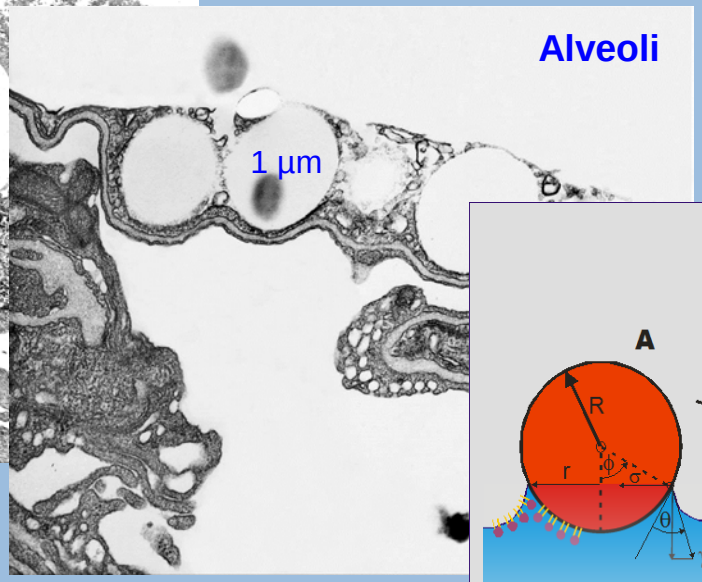
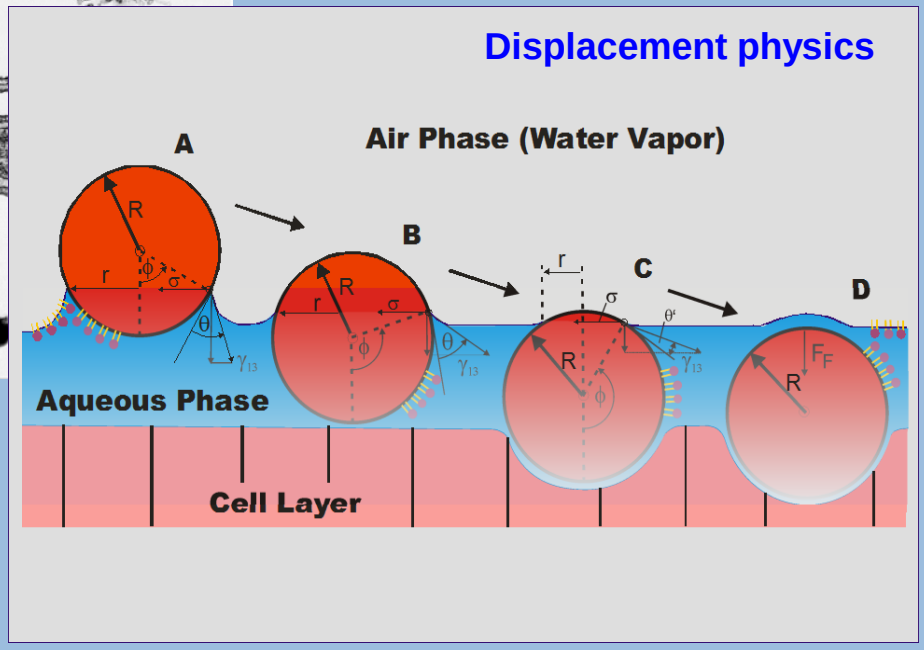


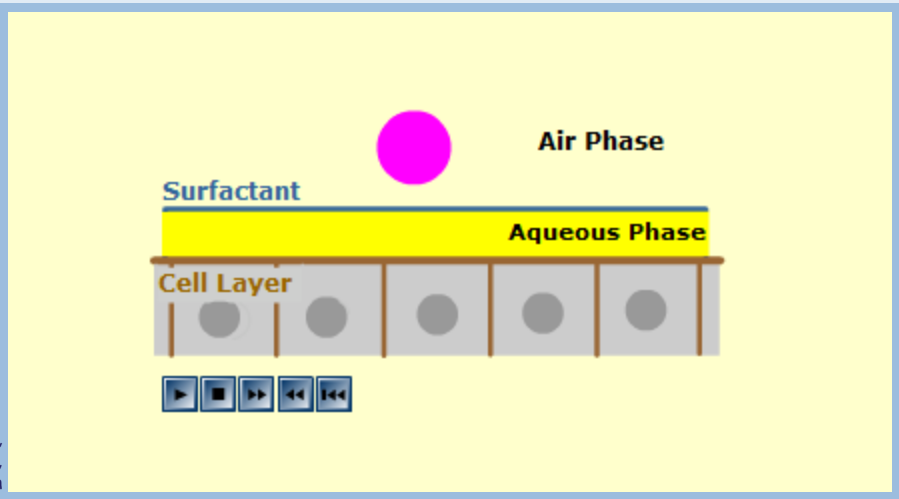


Gehr et al., J. Aerosol Med., 1990
Schürch et al., Respir. Physiol., 1990

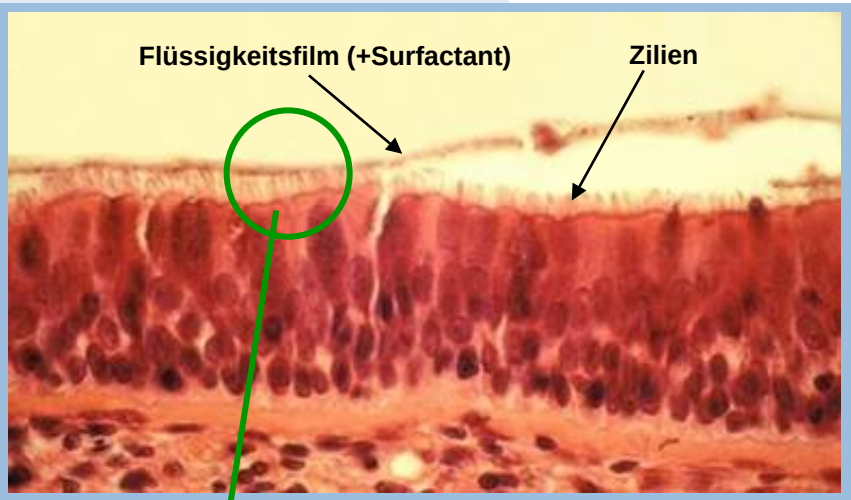


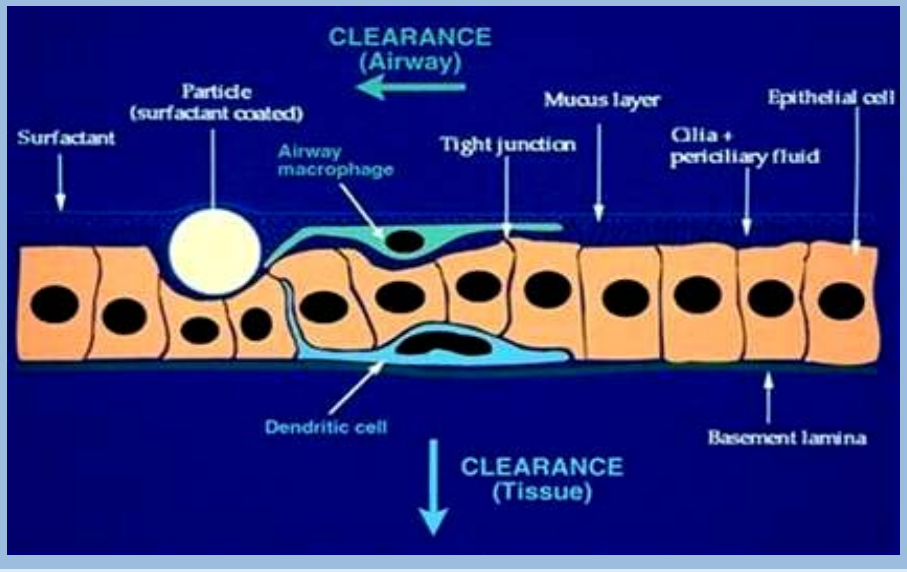
STRUCTURE AND DISPLACEMENT

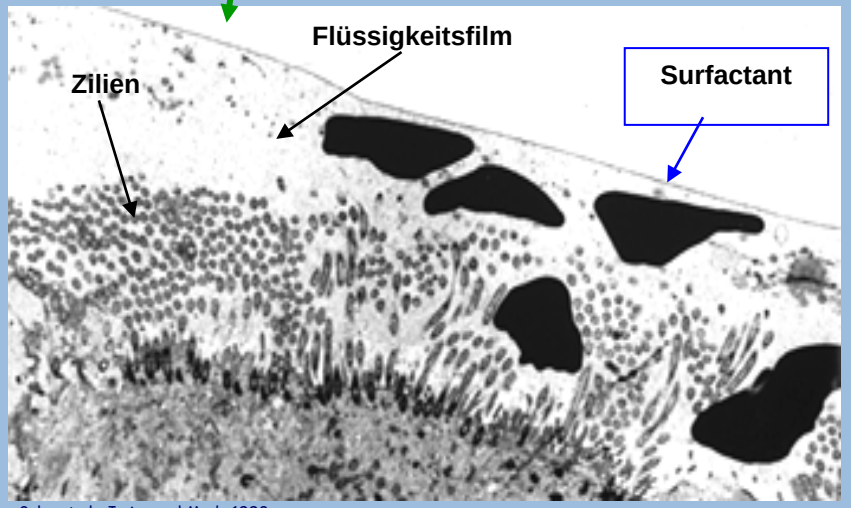
(FILTER FUNCTION: SURFACTANT)



S. Schürch, S. Tschanz, Univ. Bern







Gehr et al., J. Aerosol Med., 1990
Schürch et al., Respir. Physiol., 1990
Gehr et al., J. Aerosol Med., 1996

TRANSLOCATION OF NANOARTICLES (UFP) FROM AIR INTO BLOOD

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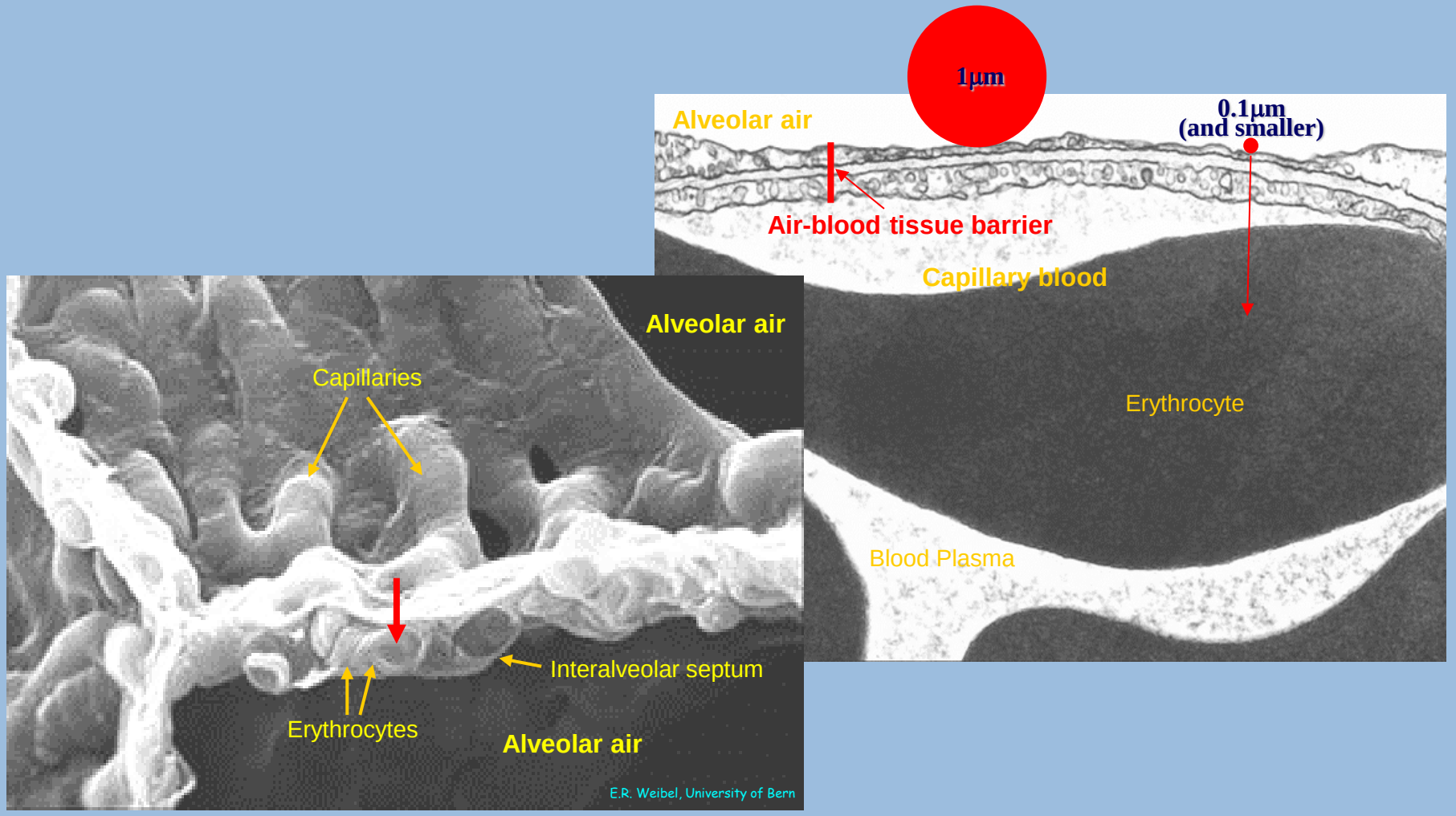

IN VITRO MODEL: BREATHING MOVEMENTS MAY STIMULATE NANOPARTICLE UPTAKE BY CELLS

Courtesy **David Schürch**, **Adolphe Merkle Insitute**, University of Fribourg

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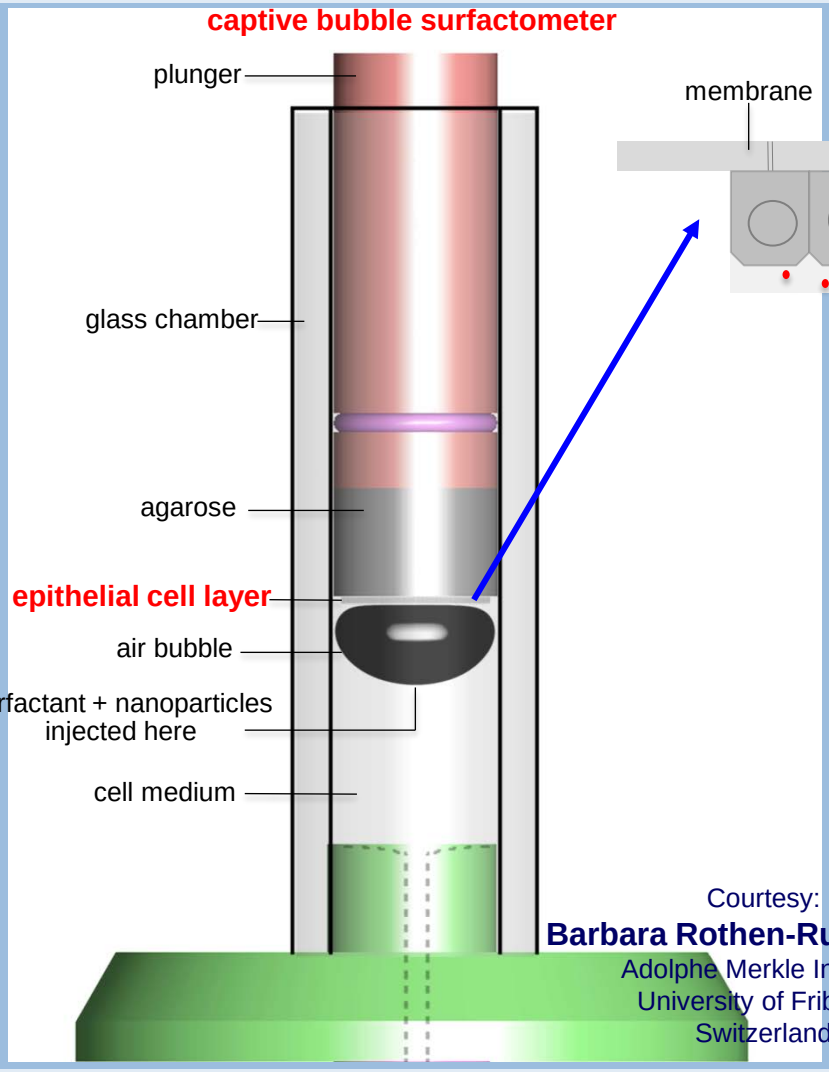
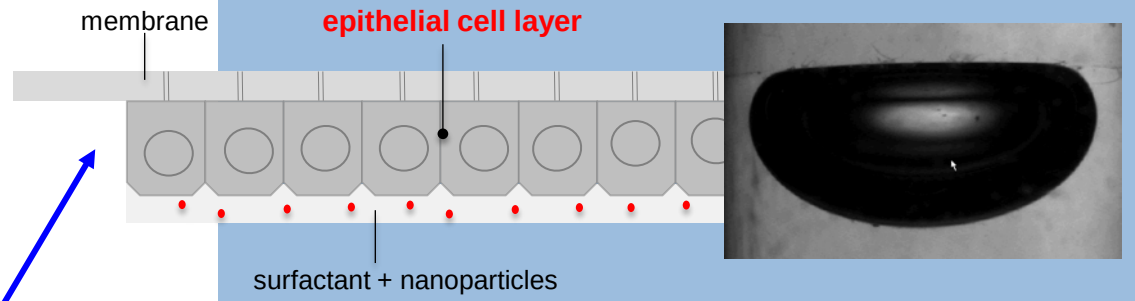
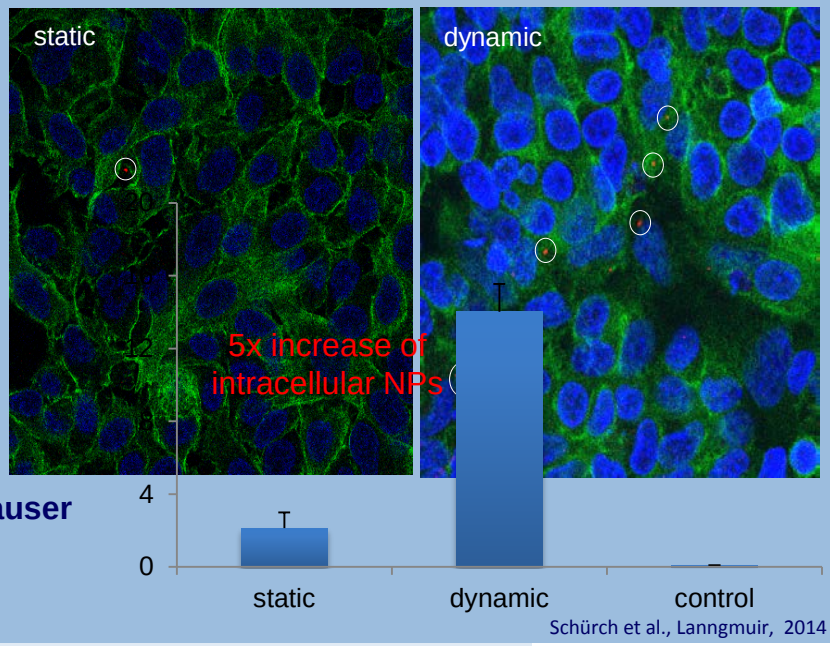




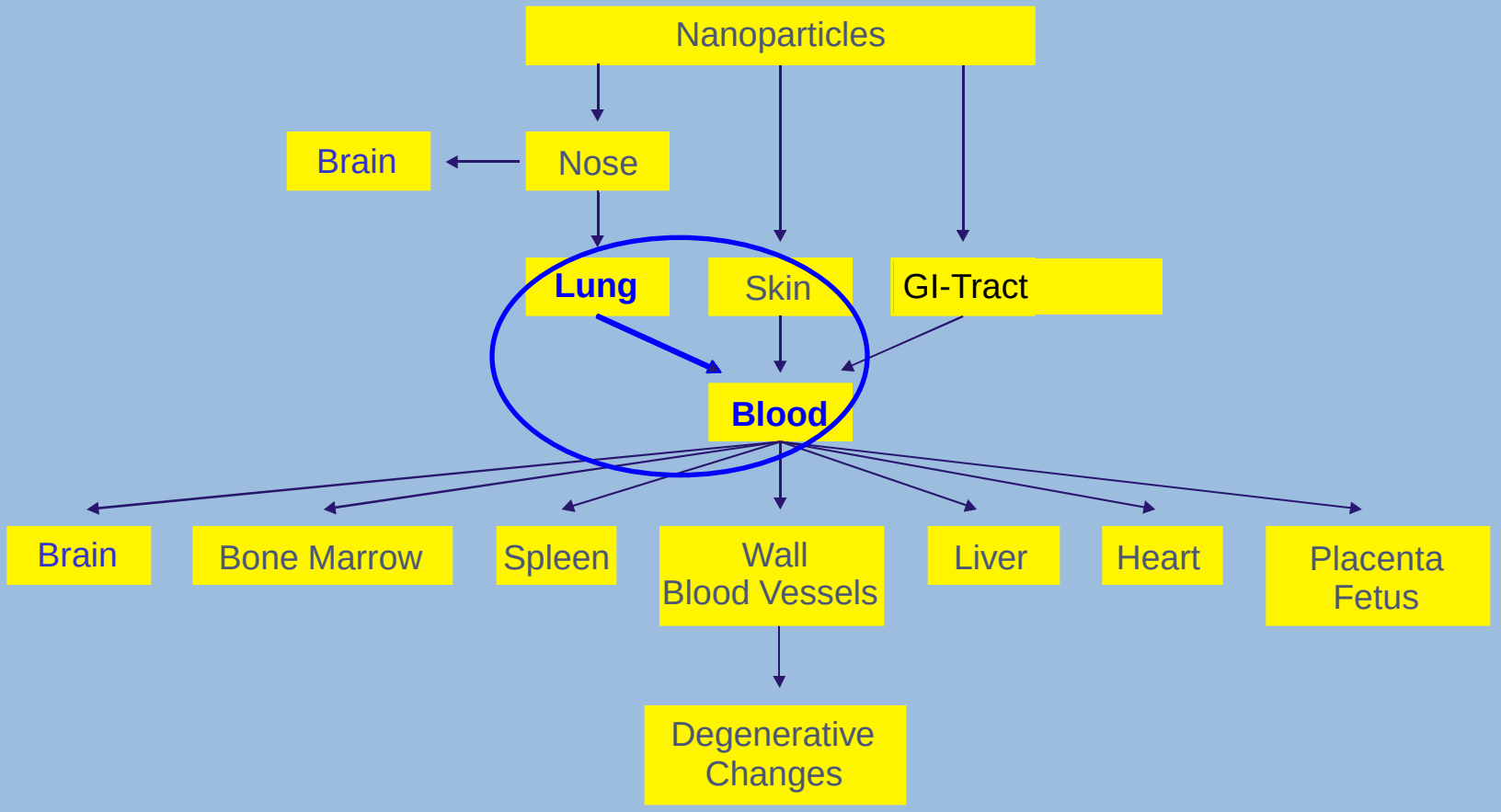


Courtesy:
Barbara Rothen-Rutishauser
Adolphe Merkle Institute
University of Fribourg
Switzerland

Schürch et al., Lanngmuir, 2014

TRANSLOCATION

WITH BLOOD TO OTHER ORGANS



TRANSLOCATION OF GOLD-NANOPARTICLES: EFFECT OF PARTICLE SIZE

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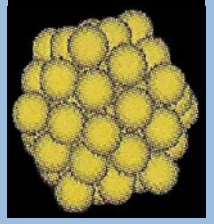
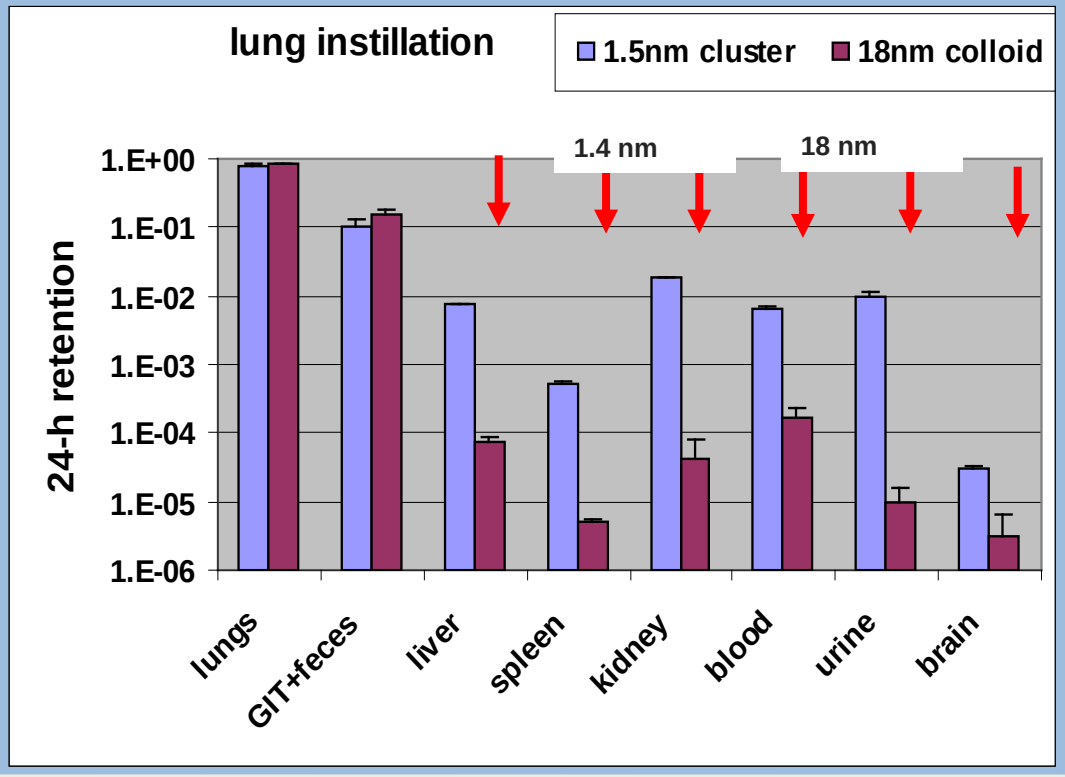
^{198}Au55 cluster 1.4 nm

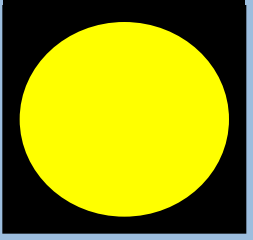


Intratracheal instillation in WKY rats
1-10 µg ^{198}Au particles in 50 µL saline, negative ionic surface charge
# of particles: 1 10^{14} (1.4 nm cluster) 2 10^{11} (18 nm colloid)
G. Schmid, Univ. of Essen, Germany

➢ **Mass fractions of gold nanoparticles in different organs after 24 h**



^{198}Au colloid 18 nm



Courtesy:
W.G. Kreyling
Helmholtz Zentrum Munich

Semmler-Behnke et al., Small, 2008

HelmholtzZentrum münchen
German Research Center for EnvironmentalHealth

CPC iLBD Institute of Lung Biology and Disease

Focus Network Nanoparticles and Health

WHAT HAS TO BE CONSIDERED OF NANOPARTICLES FROM COMBUSTION AEROSOLS

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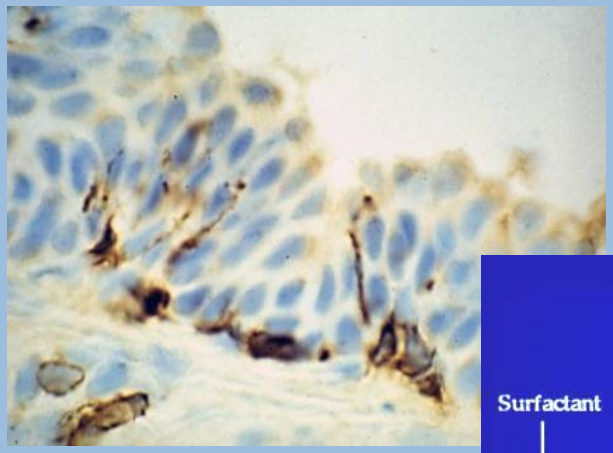
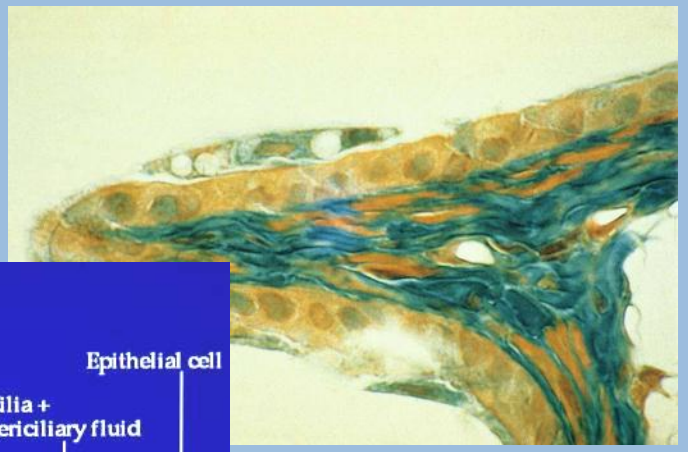
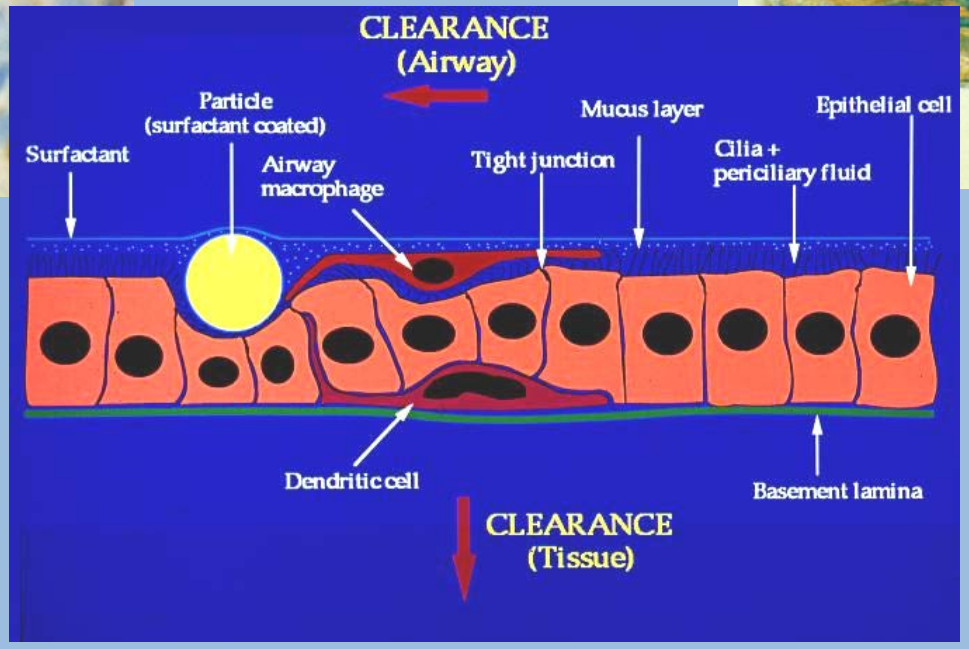
- **Size of particles** (nanoparticles)
- **Displacement of nanoparticles** towards epithelial layer (surfactant, surface forces)
- **Distance to capillaries** (translocation)
- **Distance to sensitive cells** (interaction), effect: immune modulation?
- **Interaction with cells** (uptake/penetration, effect: immune modulation, oxidative stress, inflammatory reaction a.o.?)

MAIN ACTORS ARE CELLS

EPITHELIAL CELLS, MACROPHAGES, DENDRITIC CELLS …

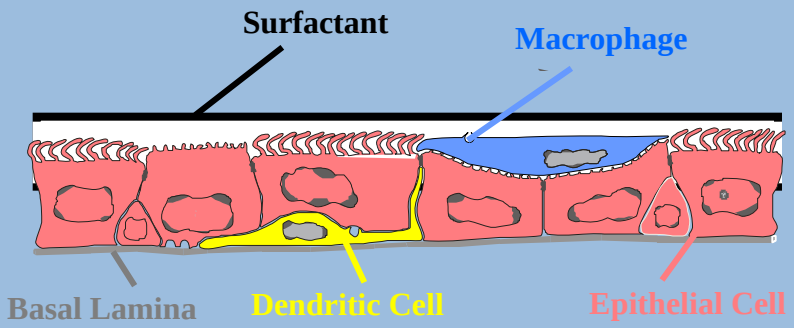


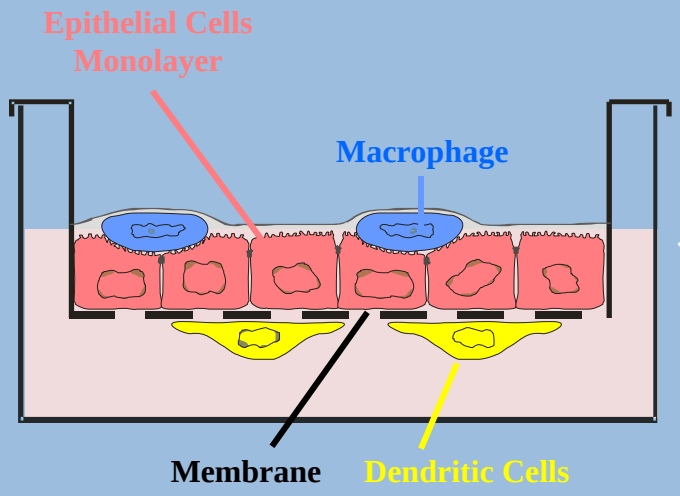


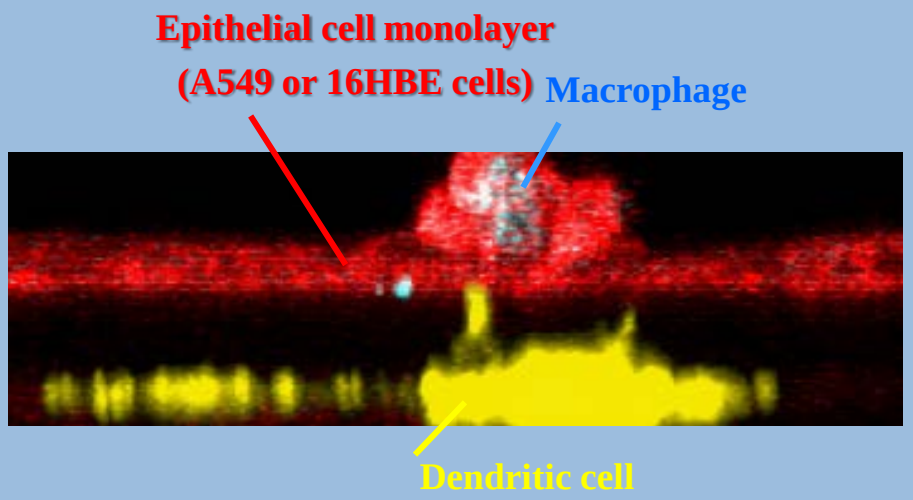


… DO THEY COLLABORATE?
THE CELL MODEL TO TEST THIS

THE TRIPLE CELL CO-CULTURE MODEL







Rothen-Rutishauser et al., *Am. J. Respir Cell Mol. Biol.* 32: 281-899, 2005
Rothen-Rutishauser et al., *Expert. Opin. Drug Metab. Toxicol.* 4: 1075-1089, 2008

STRUCTURAL VICINITY OF DENDRITIC CELLS AND MAKROPHAGES

(THROUGH THE EPITHELIAL CELL LAYER)

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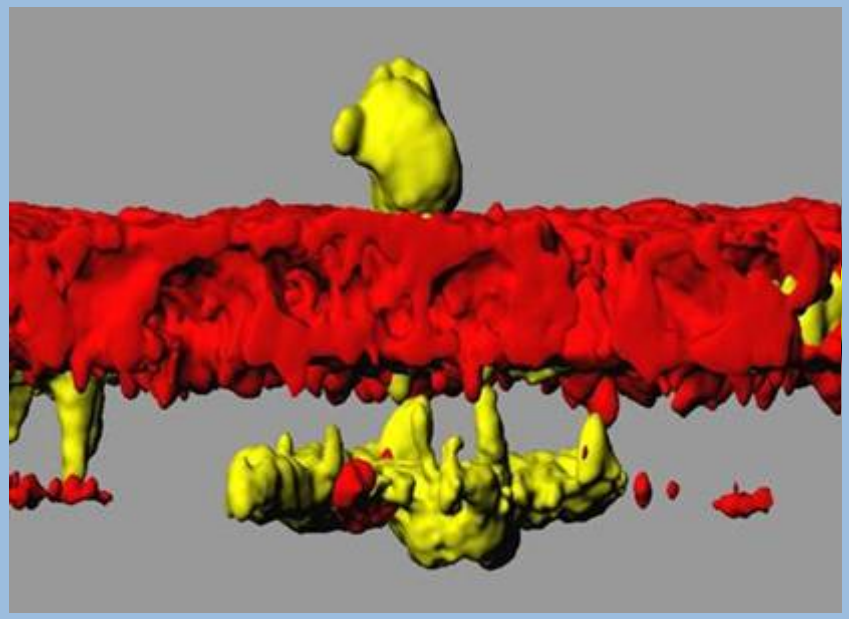
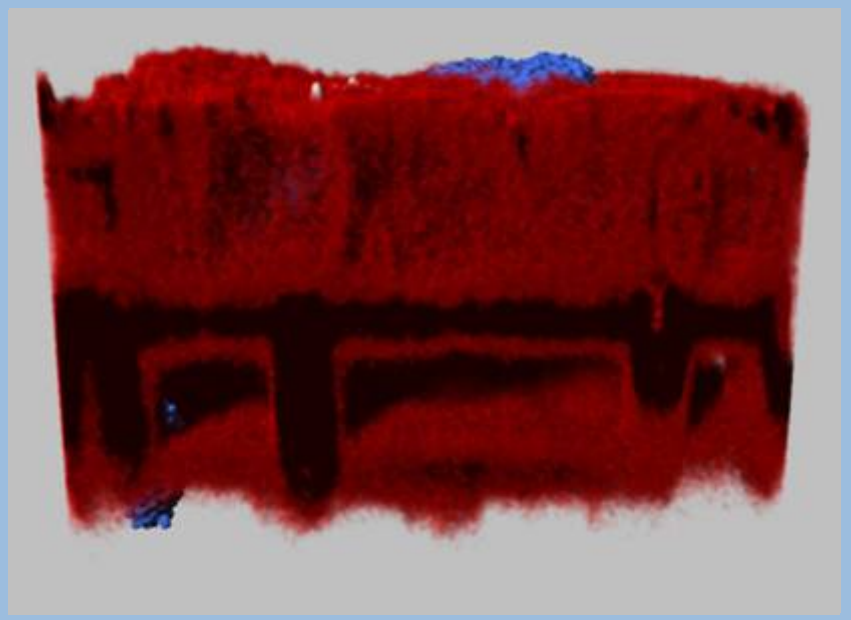


Blank et al., AJRCMB 36: 669-677, 2007



Deconvolution technique
IMARIS 3D&4D Image Analysis Software
Bitplane AG, Scientific Software

CELL-CELL INTERACTIONS

CELLULAR INTERPLAY ->THE CELLS DO COLLABORATE!

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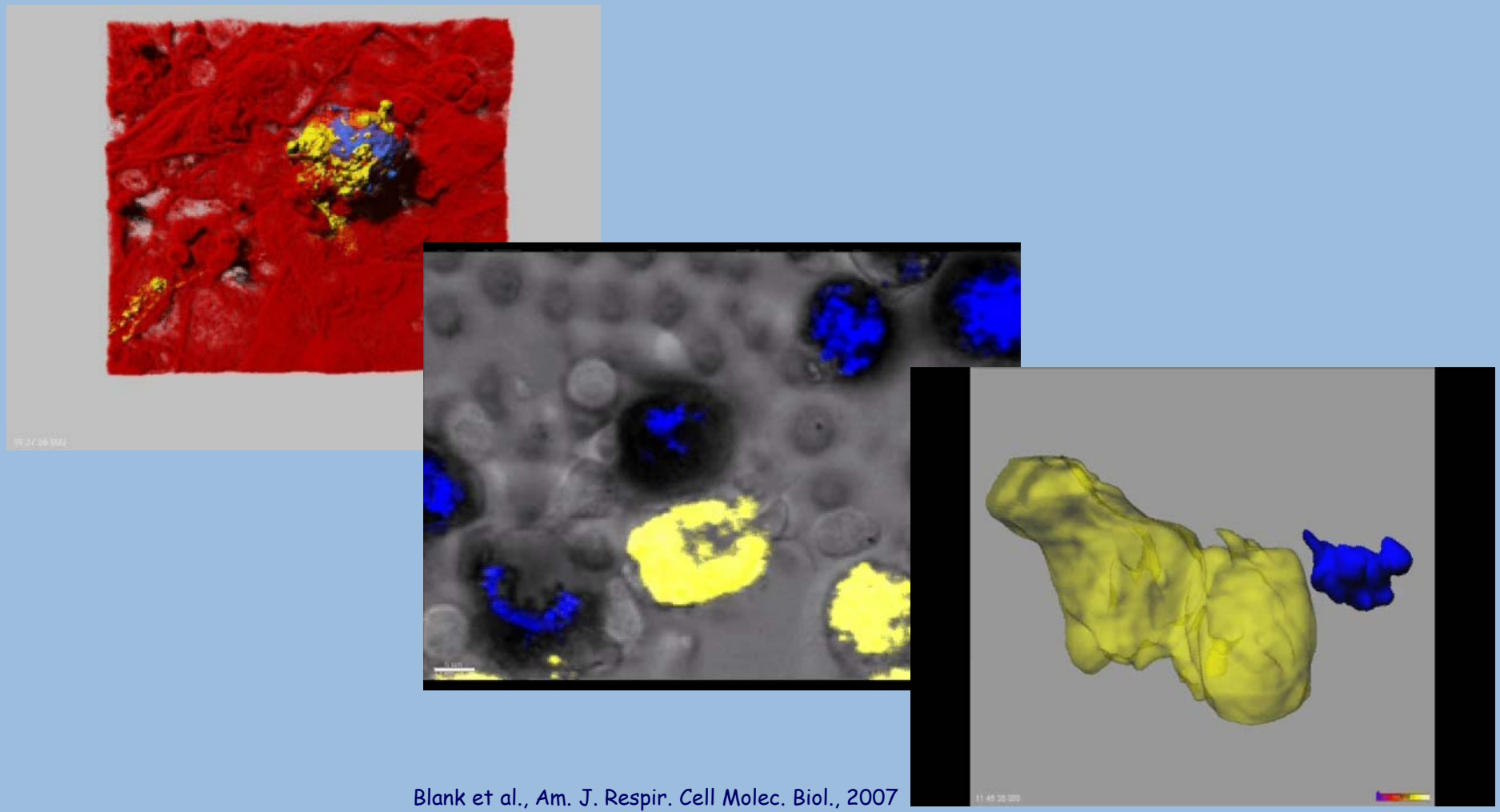
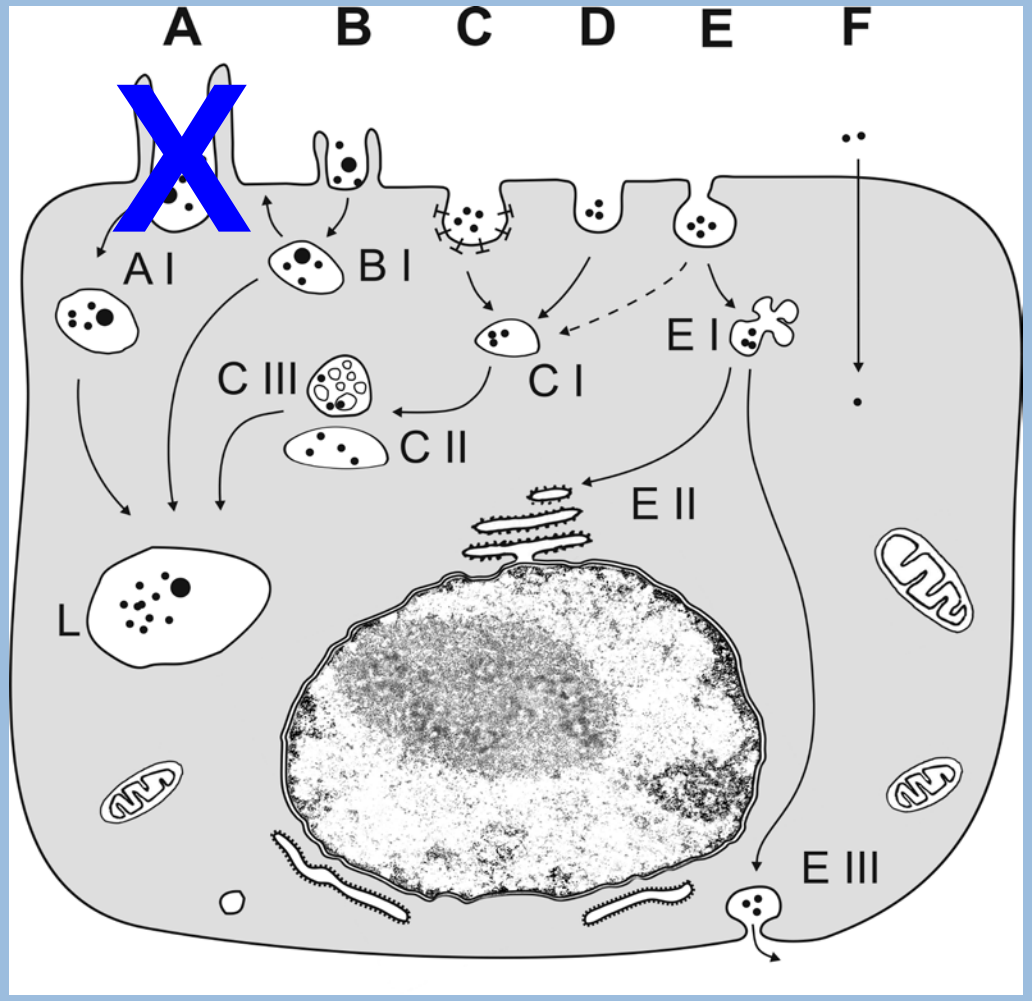


Blank et al., Am. J. Respir. Cell Molec. Biol., 2007

A BURNING QUESTION:
HOW DO NANOPARTICLES ENTER CELLS?



Brandenberger et al., Small, 2010

(A: Phagocytosis)

B: Macropinocytosis

C: Clathrin-mediated endocytosis

D: Clathrin and caveolae independent endocytic pathways

E: Caveolae-mediated endocytosis

F: Adhesive interaction (entering): *interaction of nanoparticles with cell membrane, effect on fluidity, nanoparticles may slip into cell between phospholipid molecules*
*(→ **U. Nienhaus**, KIT)*

… AND AN ANSWER:

ELECTROCHEMISTRY AND SURFACE-ENHANCED INFRARED ABSORPTION SPECTROSCOPY ON MODEL MEMBRANES (DAP-QDs)

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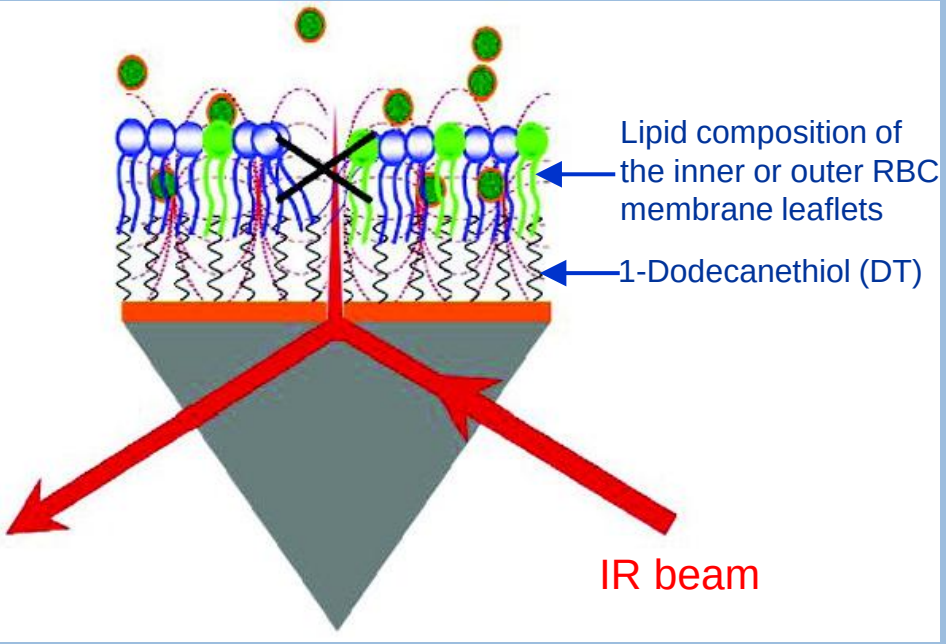
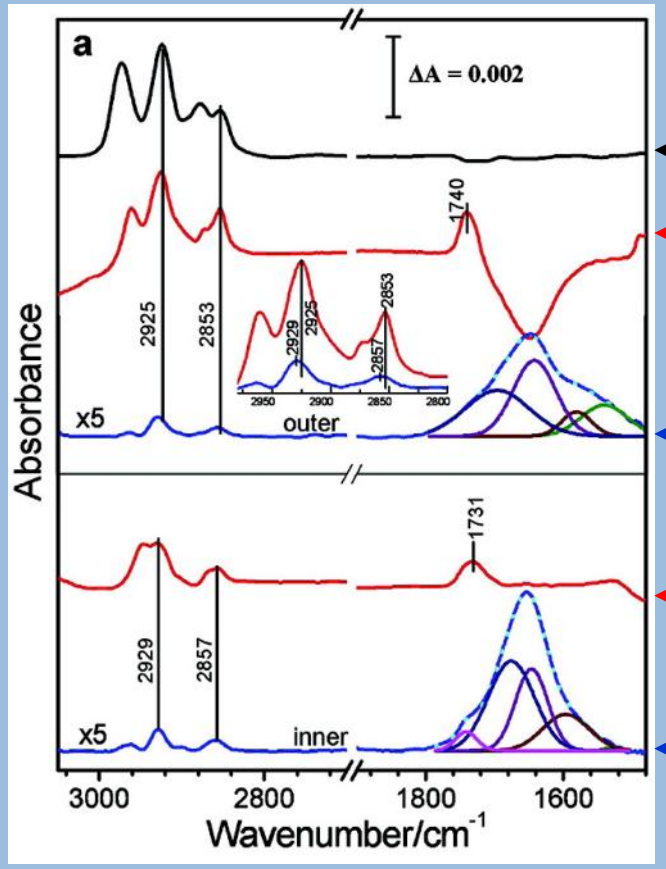


Electrochemistry: voltammograms indicate that lipid layers do not conduct current upon DPA-QD exposure → no holes formed!

Courtesy:
G.U. Nienhaus,
Institute of Applied Physics, KIT

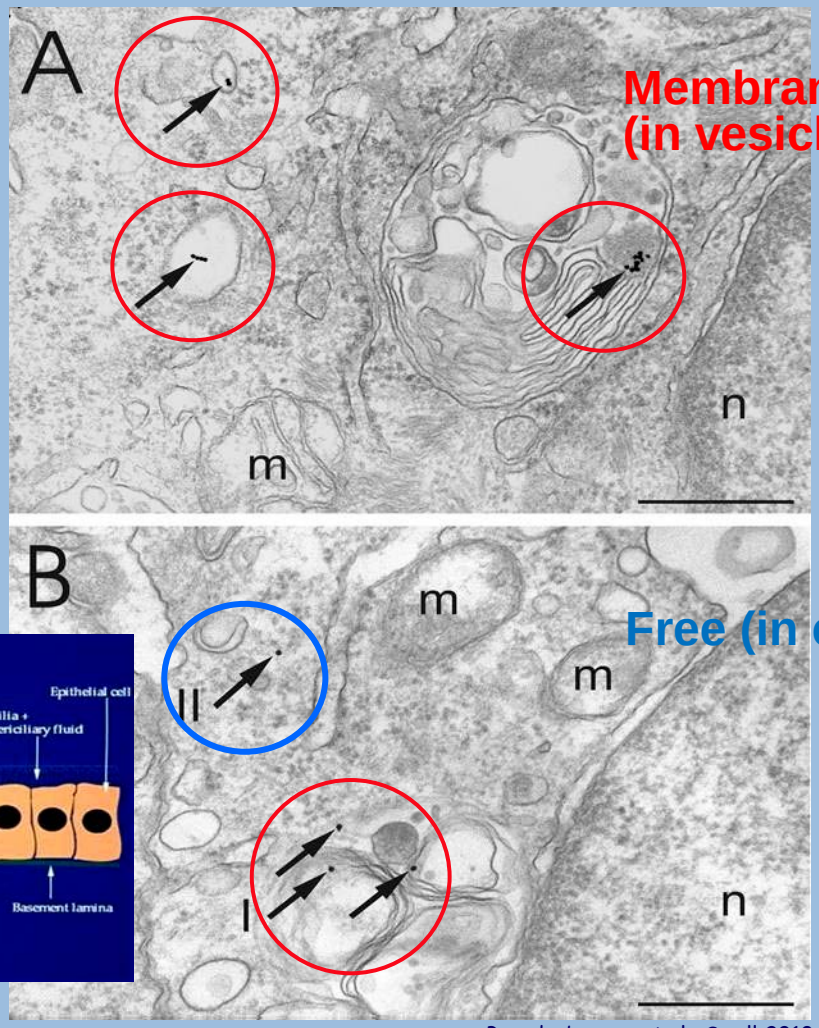
Wang et al., *ACS Nano* 6 (2012) 1251-1259



SEIRAS: Membrane flexibility is enhanced in the presence of DPA-QDs

(Rothen-Rutishauser et al., Environ. Sci. Technol., 2006)
(Rothen-Rutishauser et al., In Donaldson and Borm, Taylor&Francis, 2007)

NANOPARTICLES IN CELLS



Membrane bound (in vesicles/lysosomes)

Plain Au nanoparticles

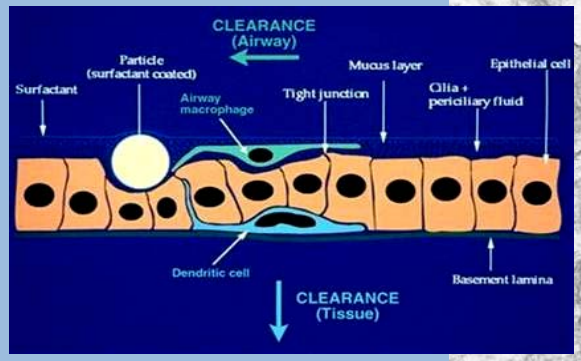
Free (in cytosol)

PEG coated Au nanoparticles

→ more nanoparticles in cytosol

Brandenberger et al., Small 2010

Particle-cell interaction



EFFECTS OF DIESEL EXHAUST ON BIOLOGICAL SYSTEMS

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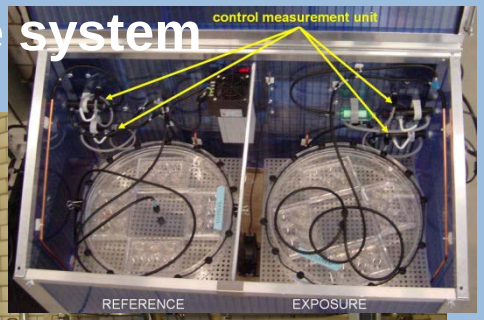
Exposure system



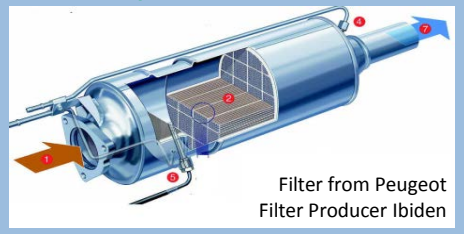
Exhaust system

Müller et al. Environ Sci Technol 2009;
Steiner et al. Tox Letters 2012

- Opel Astra X20DTL, 35 km/h
- Fuel: low sulfur diesel (>10mg/kg, Greenergy SA)
- Lube oil (V10.237, Motorex)
- Exhaust dilution 1:10

⇒ Without particle filter

⇒ With a silicon carbide diesel particle filter

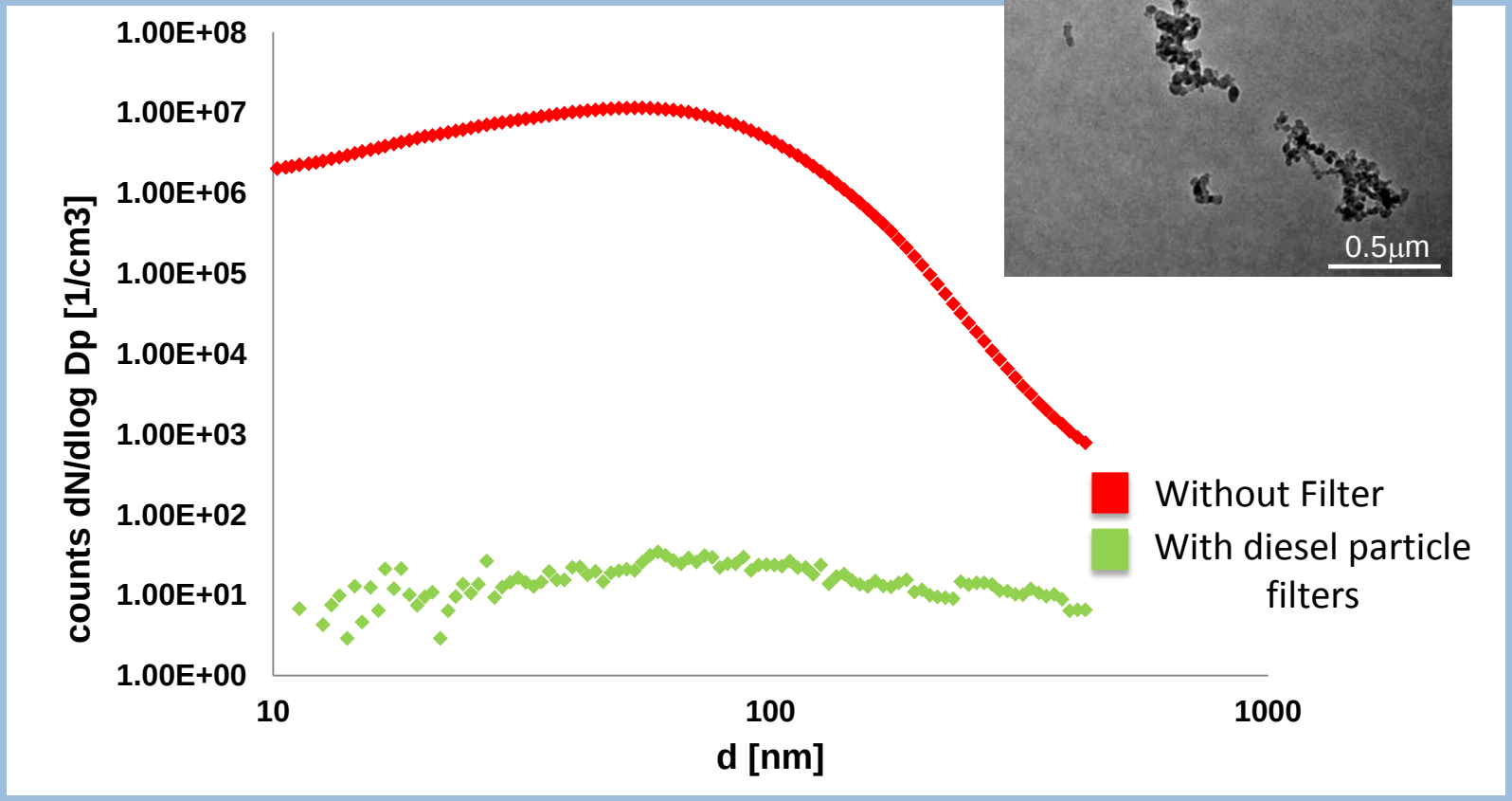


Filter from Peugeot
Filter Producer Ibiden

Courtesy:
Barbara Rothen-Rutishauser
Adolphe Merkle Institute
University of Fribourg
Switzerland

DIESEL EXHAUST

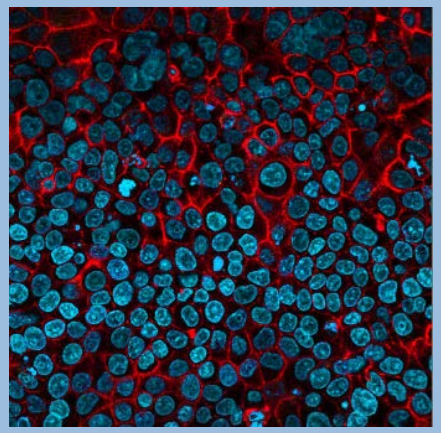
PARTICLE SIZE DISTRIBUTION, FILTER EFFECT



Steiner et al., Atmos. Environ., 2013

Courtesy:
Barbara Rothen-Rutishauser
Adolphe Merkle Institute
University of Fribourg
Switzerland

DIESEL EXHAUST
INFLAMMATORY REACTION, FILTER EFFECT



Confocal light micrograph
(blue: nuclei, red: actin)

Courtesy:
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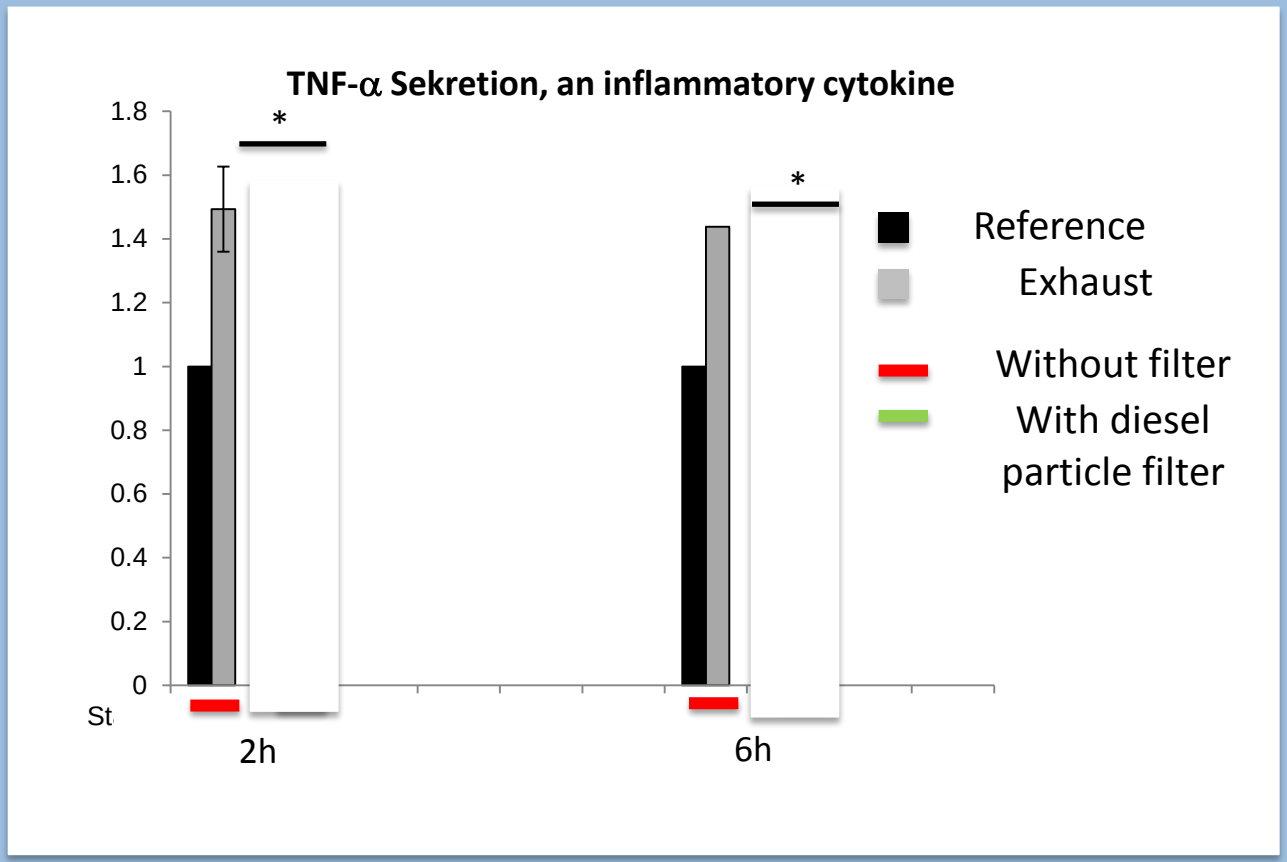

Steiner et al., Atmos. Environ., 2013

WHAT SHOULD BE CONSIDERED

SIZE MATTERS! UFP CAN TRANSLOCATE INTO BLOOD IN LUNGS!

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- **Diesel exhaust, air pollution were declared carcinogenic** (many UFP)
- **Distance to source of air pollution** (e.g. traffic) **is crucial**
- **Filters contribute substantially to reducing adverse health effects from diesel exhaust particles** (>99% removed form exhaust)
- **UFP enter cells and tissue very easily**
- **UFP can translocate into blood in the lungs, translocation to secondary ofrgans -> lung is main portal of entry for UFP**
- **Effects on lungs:**
  - Reduced pulmonary function in adults (asthmatics) (1st slide)
  - Reduced development and function of lungs in neonates (not shown)
- ***Speculations*** *(Translocation through internal tissue barriers)* ***e.g.:***
  - Blood-brain-barrier *(Altzheimer's disease?)*
  - Blood testis barrier *(Development/maturation of sperms?)*
  - Blood thymus barrier *(Development of T-lymhocytes?)*

Traffic related PM from Highway 405 cause atherosclerosis in mice

Araujo et al, Circul Res 2008

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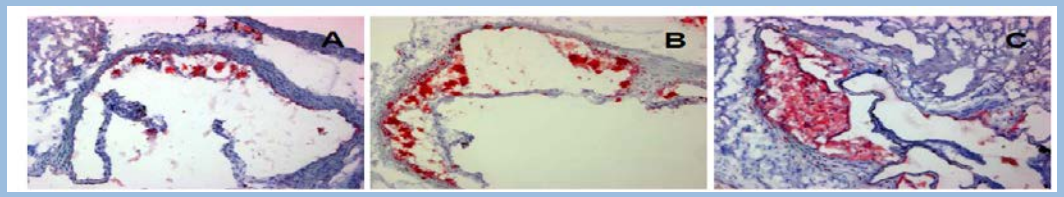
Exposure:

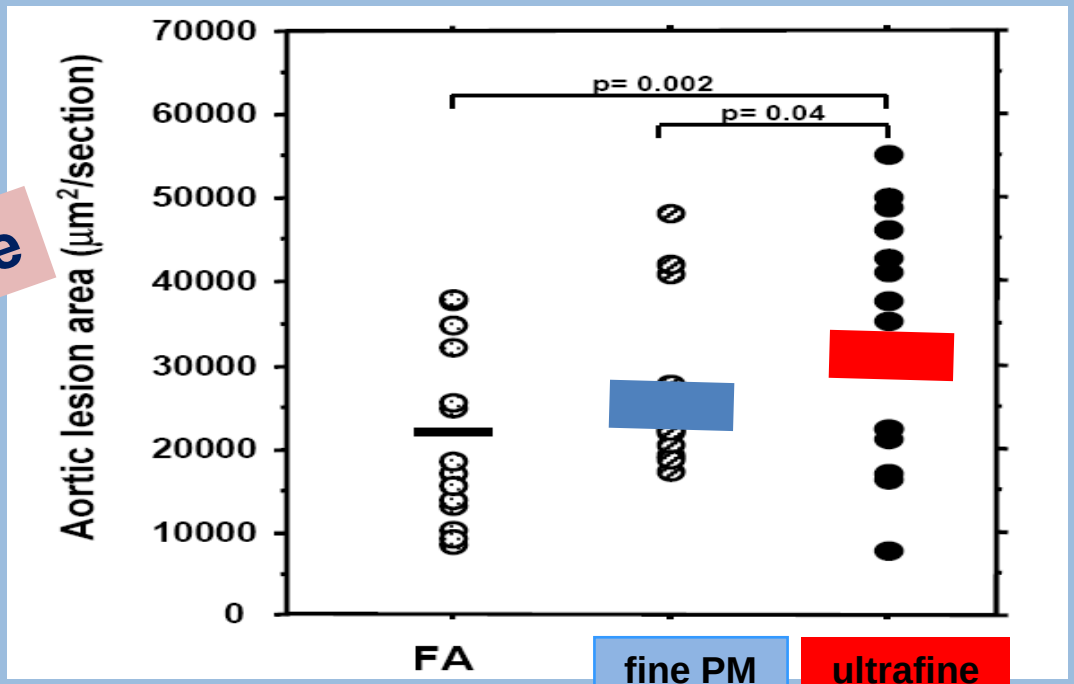
40 days

5h / day

3 days / week

Toxicology example





Picture from

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HEALTH EFFECTS UFP?

- **Ischemic Heart Disease mortality i… Californian Teacher's Study**
  Ostro et al; Env H Perspect 2015
- **Risk of mortality in association to long-term exp… to traffic-related air pollution. European Studies**
- **Elemental carbon or Black Smoke are ass… with all-cause mortality (8 cohort studie…**
  Review by Hoek et al , Env Health 2013
- **Life expectancy of reduction in PM2.5 mass…**
- **Lung growth was affected by home outd…**
  (Southern Californian Children's Health Study, Gauderman et…

A NEW long-term effect study with UFP available !
But no 2-pollutant model with UFP, controlling for PM2.5

Are «effects of NO2» due to ultrafine particles…?

… are «effects of EC» explained by (unmeasured) UFP?

… are «effects of EC» explained by (unmeasured) UFP?

… but same associations with elemental carbon…
and … no UFP data available…. – but might look similar… ?!

Courtesy
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CONCLUSIONS
HEALTH EFFECTS CAUSED BY UFP

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- **Experimental evidence for long-term effects of UFP**
- **Epidemiological studies: very few with UFP data, thus, no final interpretation possible**
- **New evidence for possibly high correlation of exposure to UFP with exposure to other «classic pollutants»**
- **Need to understand to what extent abundant evidence of long-term effects of PM is (in part?) explained by UFP**
- **Need state-of-the-art exposure assessment for UFP as well – incl. consideration of exposure from outdoor origin while indoors**

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KEEP IN MIND

WHEN WORKING WITH NANOPARTICLES (UFP)

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- **risk = f(hazard, exposure**time**)** for a given size
- **effect = f(dose, time**after exposure**)** for a given size

- **Interaction of nanoparticles with biological systems is primarily a function of size: *size matters!*):**
  peneatration, translocation, effect/reaction
- **Important are furthermore:**
  material, corona, agglomeration, time after exposure etc.

CONCENTRATION OF PARTICLES AND HEALTH – DISTANCE FROM BUSY ROAD

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Concentration of particles

Relative Concentration

100 %

80

Fine PM, homogenously distributed

Ultrafine PM – and other

Health

1µm

Alveolar air

0.1µm (and smaller)

Air-blood tissue barrier

Capillary blood

Ery hrocyte

Blood Plasma

00

Residential distance from highway [m]

Alveolar air

Capillaries

Interalveolar septum

Erythrocytes

Alveolar air

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