Nanoparticles in Fundamental and Applied Research

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Scientific Seminar on Nuclear Physics at the Institute of Nuclear Physics,
Moscow State University
Online Seminar

06.04.2021

Outline

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Introduction

Part I: Nanoparticles in Fundamental Research

- Experiments on the structure and dynamics of isolated nanoparticles in the gas phase

- Nanoparticles in levitated Microdroplets

Part II: Nanoparticles in Life Sciences

- Spatially resolved studies for probing nanoparticle-based drug delivery using label-free spectromicroscopy

Summary and Conclusions

Acknowledgments

Freie Universität Berlin

Part 1 (Fundamental studies):

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Part 2 (Nanoparticles in life sciences):

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Fiorenza Rancan (Charité)
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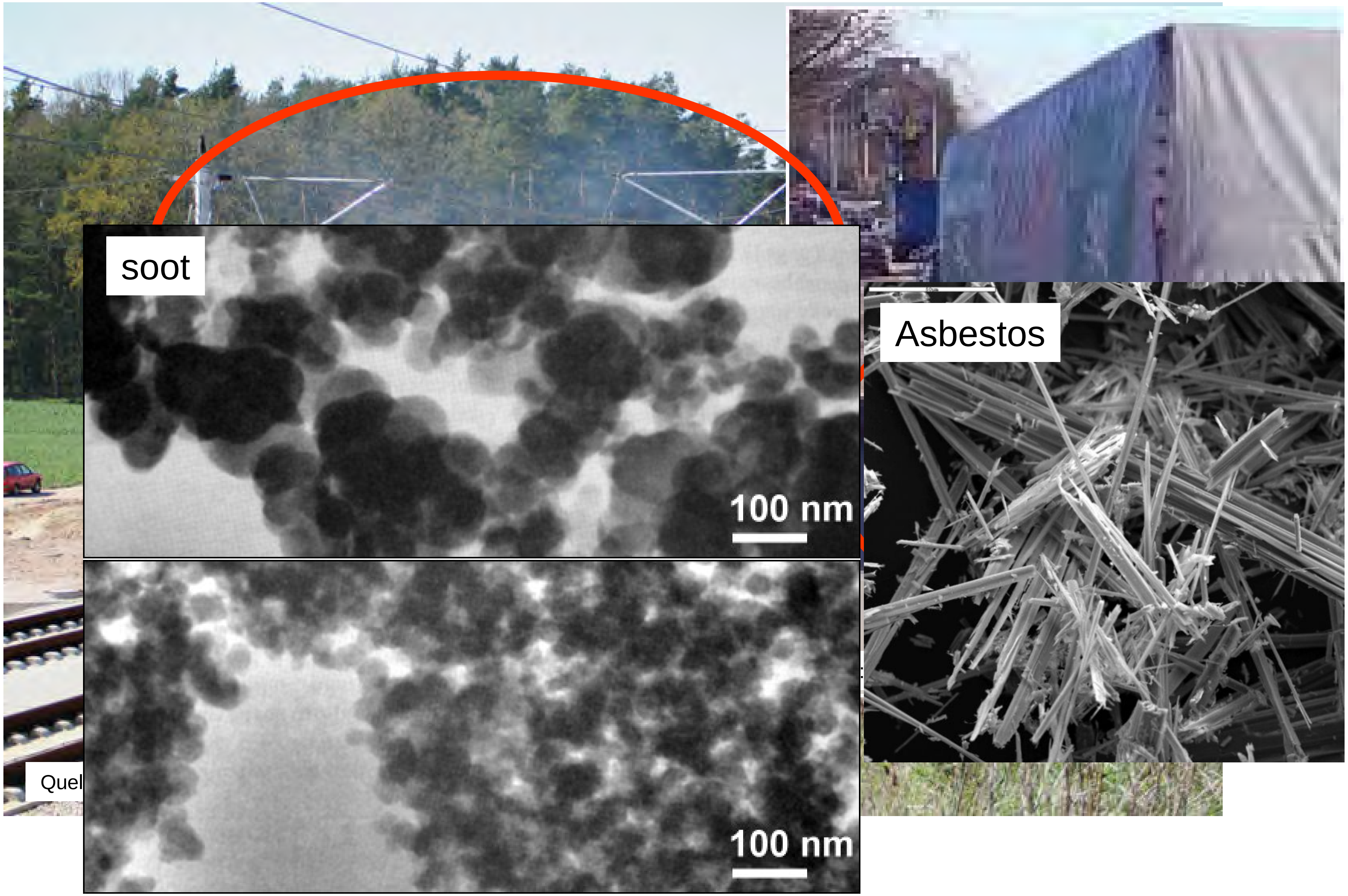
RISKS

Nanoparticles in the Environment – Health Issues



RISKS

The *Lancet* Commission on pollution and health

Philip J Landrigan, Richard Fuller, Nereus J R Acosta, Olusoji Adeyi, Robert Arnold, Niladri (Nil) Basu, Abdoulaye Bibi Baldé, Roberto Bertollini, Stephan Bose-O'Reilly, Jo Ivey Boufford, Patrick N Breysse, Thomas Chiles, Chulabhorn Mahidol, Awa M Coll-Seck, Maureen L Cropper, Julius Fobil, Valentin Fuster, Michael Greenstone, Andy Haines, David Hanrahan, David Hunter, Mukesh Khare, Alan Krupnick, Bruce Lanphear, Bindu Lohani, Keith Martin, Karen V Mathiasen, Maureen A McTeer, Christopher J L Murray, Johanita D Ndahimananjara, Frederica Perera, Janez Potočnik, Alexander S Preker, Jairam Ramesh, Johan Rockström, Carlos Salinas, Leona D Samson, Karti Sandilya, Peter D Sly, Kirk R Smith, Achim Steiner, Richard B Stewart, William A Suk, Onno C P van Schayck, Gautam N Yadama, Kandeh Yumkella, Ma Zhong

Executive summary

Pollution is the largest environmental cause of disease and premature death in the world today. Diseases caused by pollution were responsible for an estimated 9 million premature deaths in 2015—16% of all deaths worldwide—three times more deaths than from AIDS, tuberculosis, and malaria combined and 15 times more than from all wars and other forms of violence. In the most severely affected countries, pollution-related disease is responsible for more than one death in four.

Pollution endangers planetary health, destroys ecosystems, and is intimately linked to global climate change. Fuel combustion—fossil fuel combustion in high-income and middle-income countries and burning of biomass in low-income countries—accounts for 85% of airborne particulate pollution and for almost all pollution by oxides of sulphur and nitrogen. Fuel combustion is also a major source of the greenhouse gases and short-lived climate pollutants that drive climate change. Key emitters of carbon dioxide, such as electricity-generating plants,

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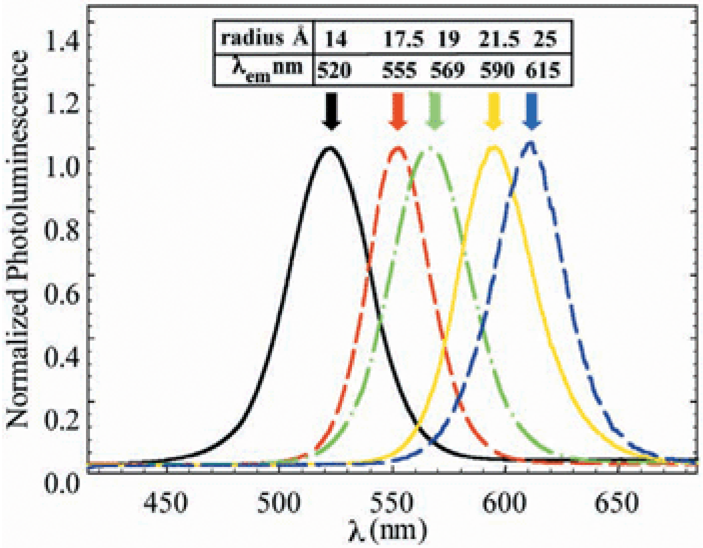
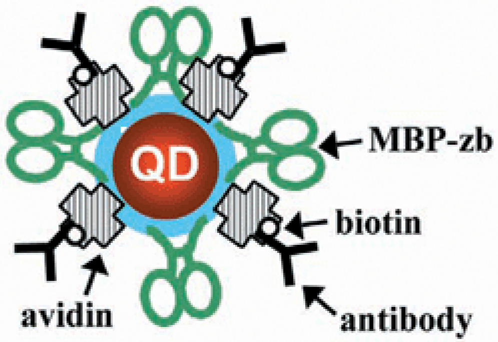
http://dx.doi.org/10.1016/S0140-6736(17)32545-X

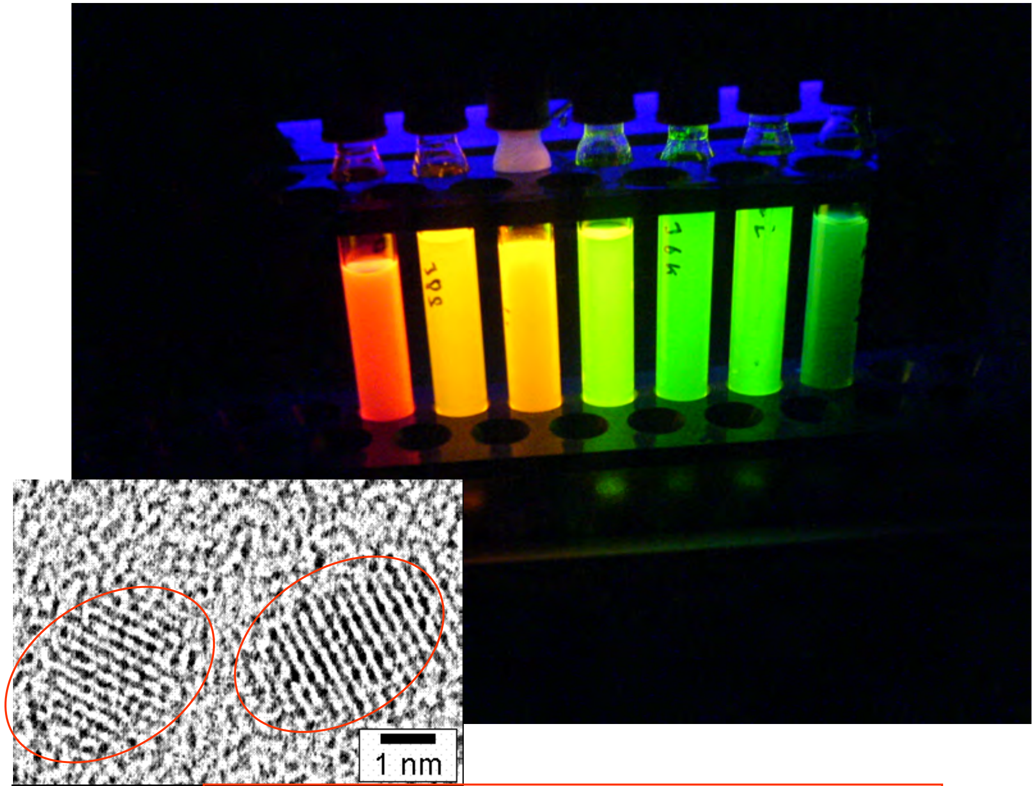
Arnhold Institute for Global Health (Prof P J Landrigan MD), **Mount Sinai Heart**

PERSPECTVIES

Quantum Dots







Use of Quantum Dots

- Solid-state quantum computing
- Non-bleaching dyes in biology
- Photovoltaic devices
- Light emitting devices

PERSPECTVIES

Nanoparticle Imaging in Medical Diagnostics

30 *Current Radiopharmaceuticals,* 2008, *1,* 30-36

Nanoparticles in Cancer

Kalevi Kairemo[1,2], Paola Erba[3], Kim Bergström[2,4] and Ernest K.J. Pauwels*[3,5]

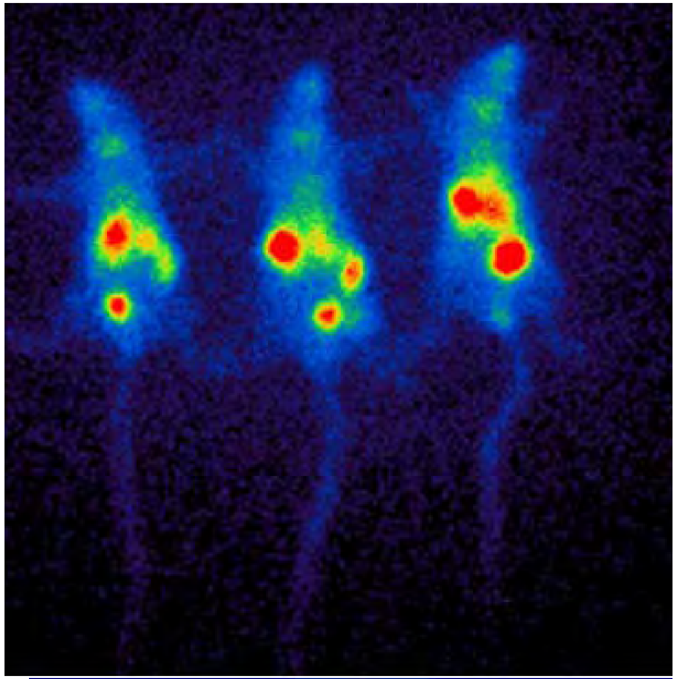
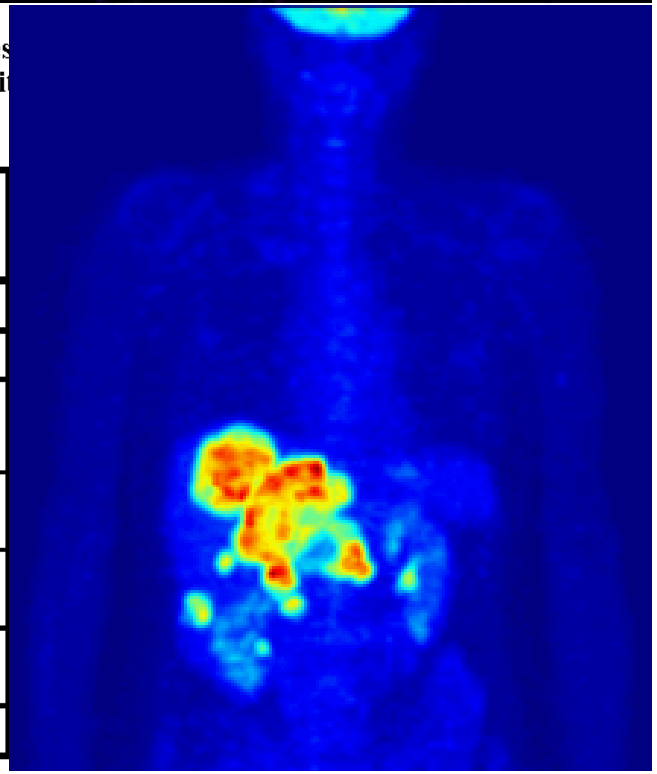


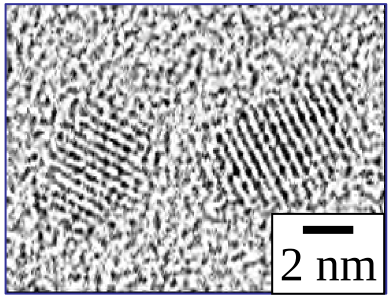
Table 1. **Summary of the Differences Between Imaging Modalities and their Possibilities Characteristics (Spatial Resolution, Depth Resolution, Temporal Resolution, Sensitivi Modified from the Data in the Literature [77]**

Modality	Spatial resolution	Depth	Temporal resolution	Sensitivity (mol/L)	Molecular probe
PET	1-2 mm	No limit	10 s-min	10^{-11} - 10^{-12}	ng
SPECT	0.5-1 mm	No limit	min	10^{-10} - 10^{-11}	ng
Bio-luminescence	3-5 mm	1-2 mm	sec-min	10^{-15} - 10^{-17}	g-mg
Fluorescence	2-3 mm	<1 mm	sec-min	10^{-9}-10^{-12}	g-mg
MRI	25-100 µm	No limit	min-hrs	10^{-3}-10^{-5}	g-mg
CT	50-200 µm	No limit	min	10^{-1}-10^{-4}	N/A
Ultrasound	50-500 µm	mm-cm	sec-min	10^{-1}-10^{-4}	g-mg

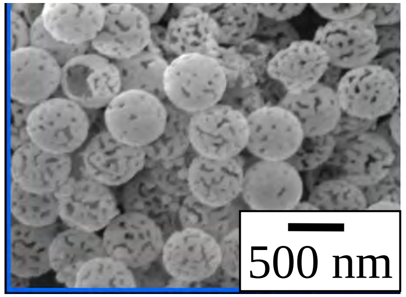


Chemical Synthesis of Nanoparticles by Colloidal Chemistry

Biology



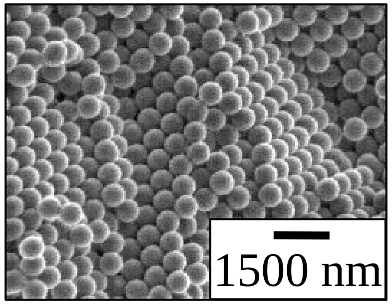
CdSe quantum dots



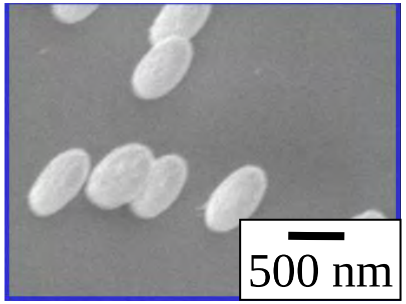
Hollow nanospheres

Basic Research

Nano-photonics



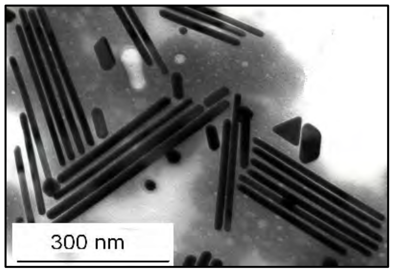
Silica nanoparticles



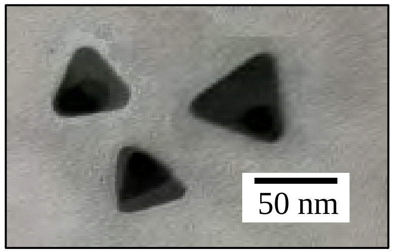
anisotropic nano-particles

Materials Science

Medical Research



gold nanorods



gold prisms

Often Used Approach: Deposited Nanoparticles

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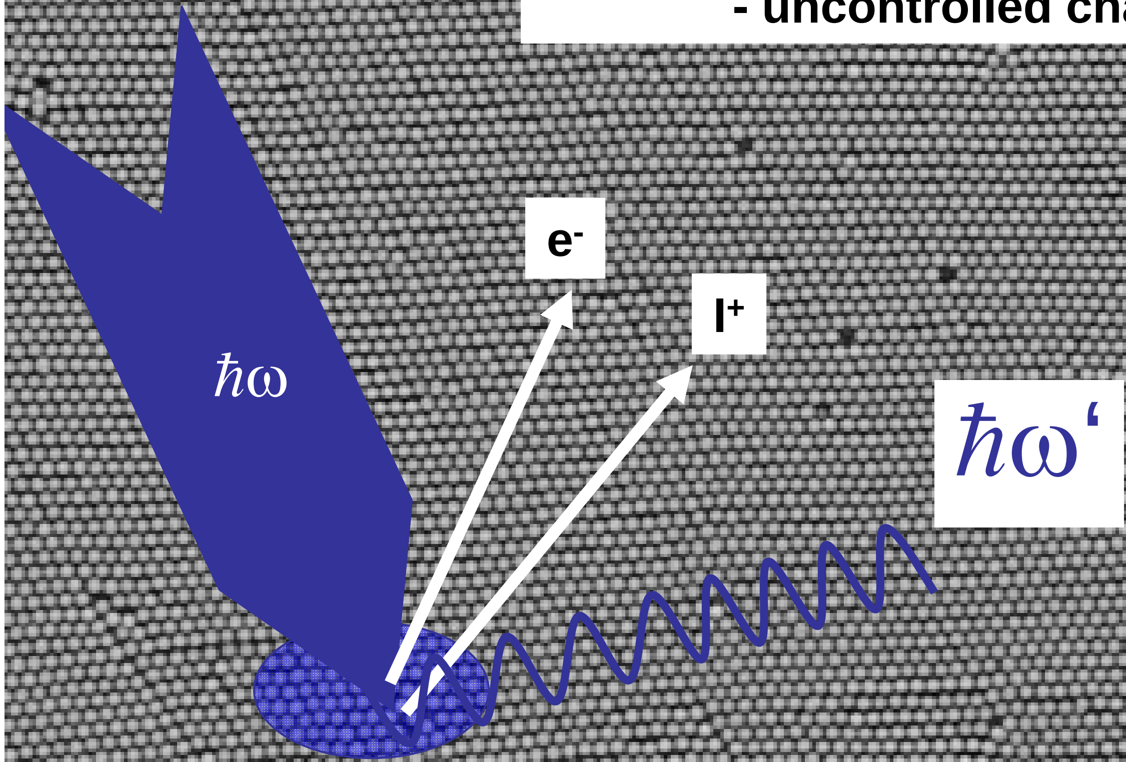
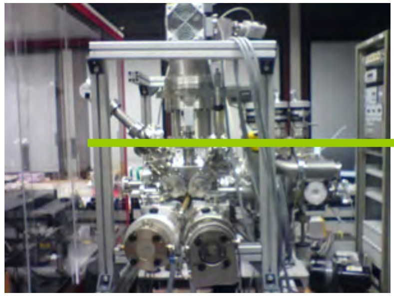
Intense Photon Fields lead to:
- **radiation damage**
- **uncontrolled charging of insulating nanoparticles**





Schematic Setup of the Nanoparticle Beam

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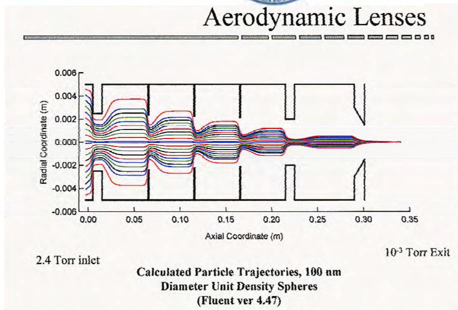
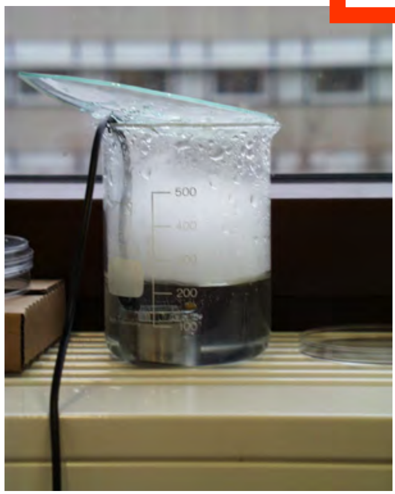
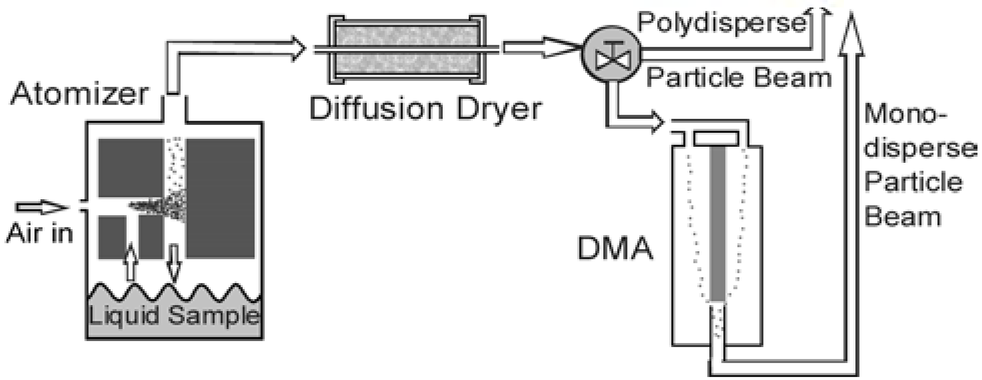


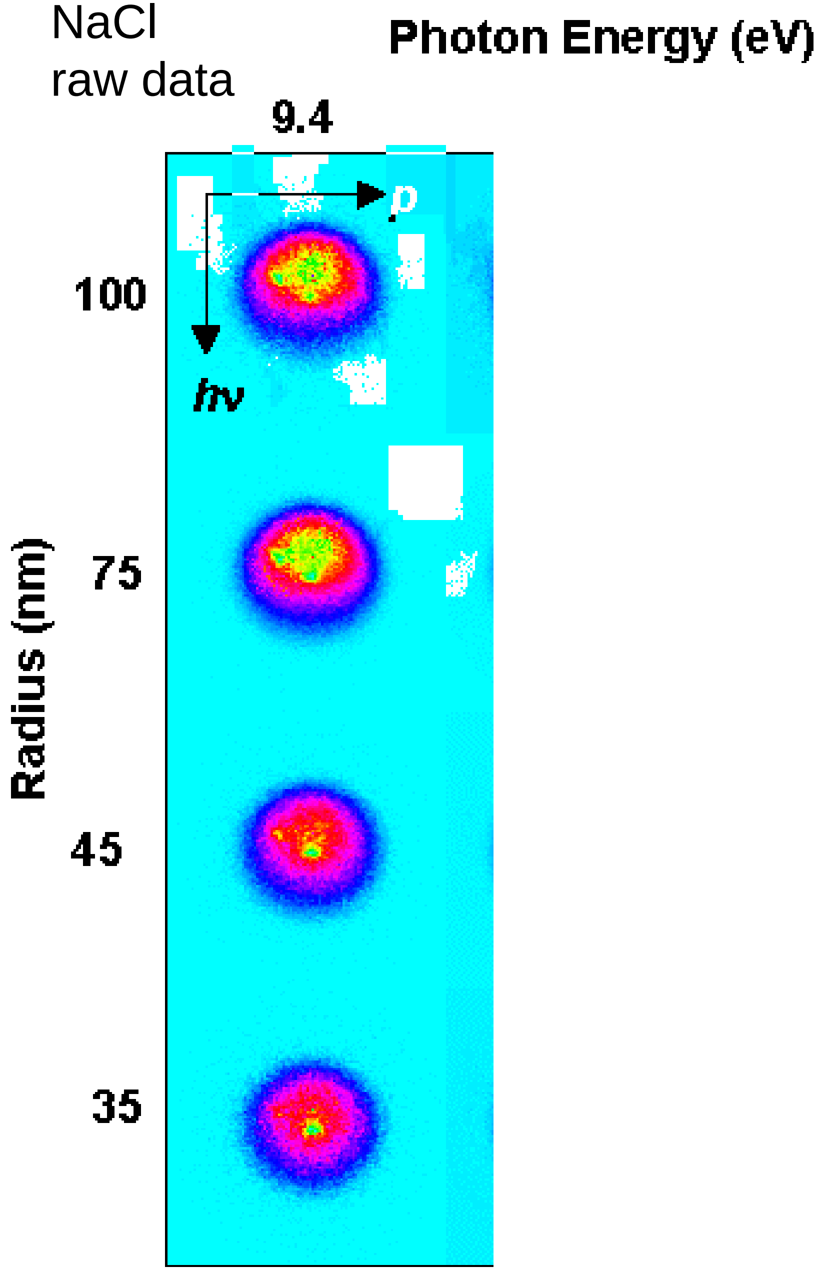
Aim:
- Intrinsic properties of isolated nanoparticles
- Avoiding radiation damage
- Size effects beyond the atomic scale
- Interactions with intense photon fields
- Ultrafast dynamics



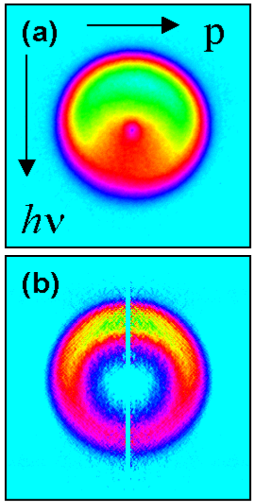


Size Effects in Nanoparticles using Synchrotron Radiation

NaCl
raw data



Asymmetry of Electron Emission from NaCl Nano-particles



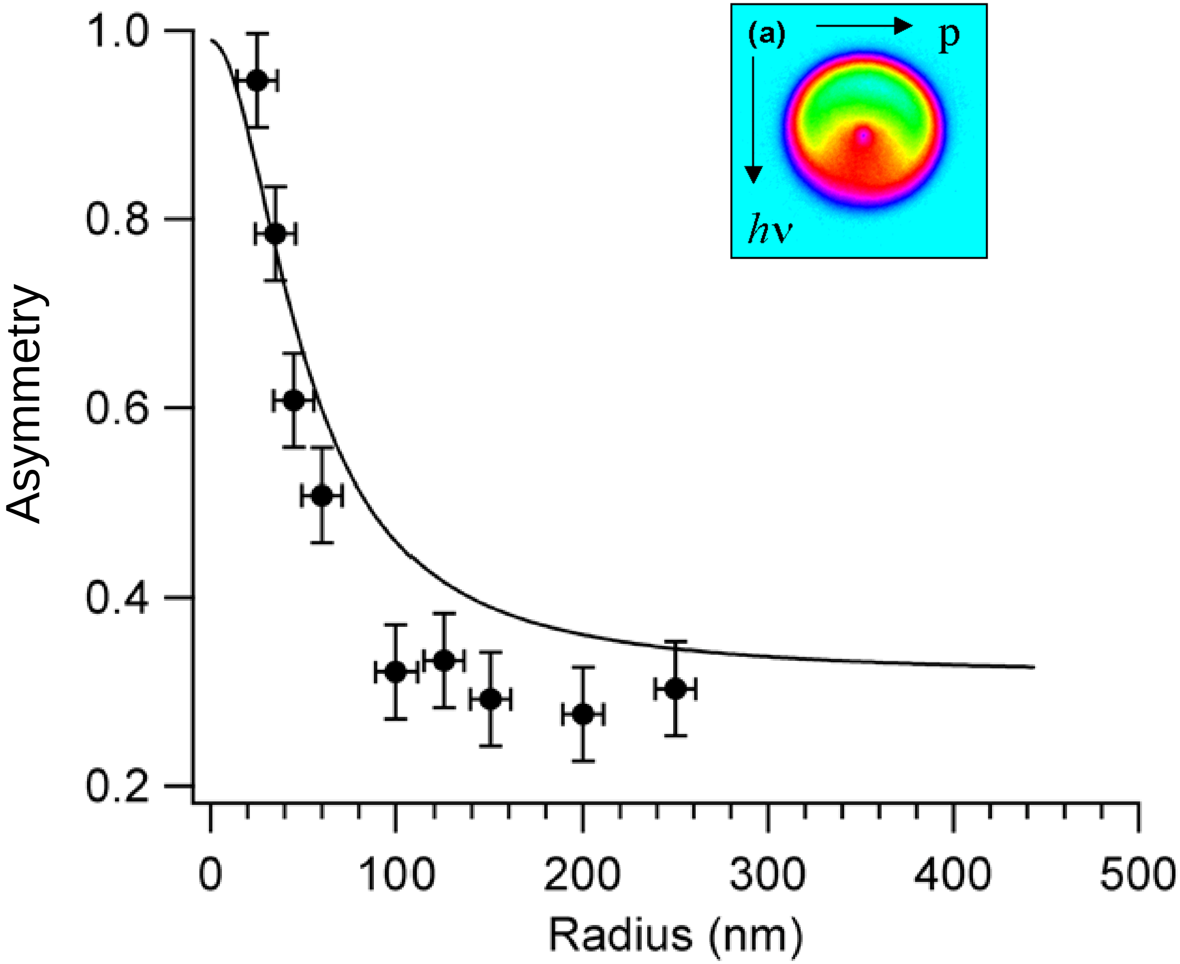
raw data (E=12 eV)

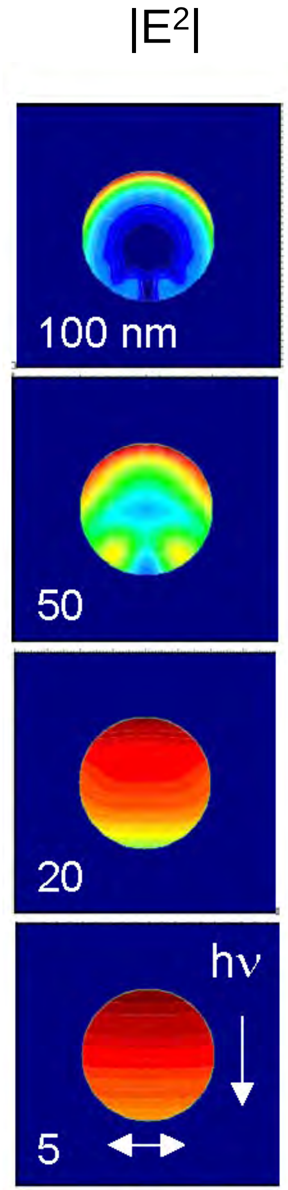
reconstructed data

Entire size distribution

K.R. Wilson et al.,
Nano Lett. **7**, 2014 (2007)

Asymmetry in Electron Emission from NaCl Nanoparticles





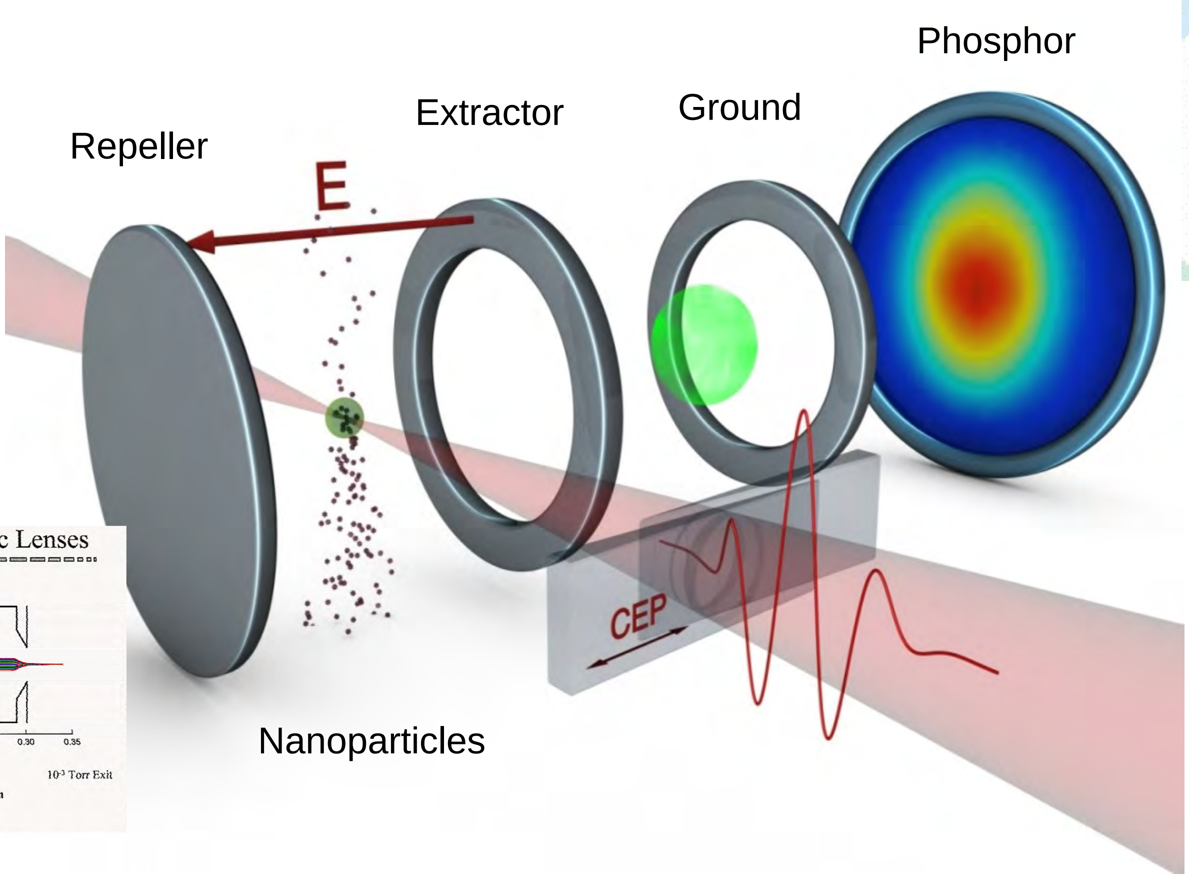
$$f_{foward} = \sum_{pol=x,y,z} \sum_{x,y,z} \sum_{\theta=0}^{90^o} \sum_{\phi=0}^{nphi=360^o} |E(x,y,z)|^2 \exp(-r/r_{abs}) \sin^2\delta \sin\theta$$

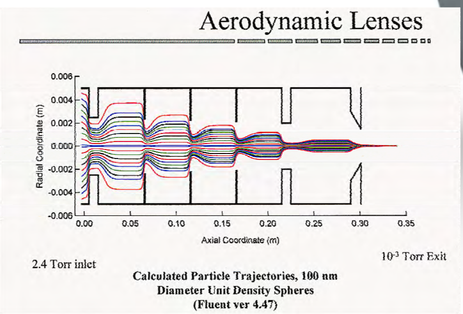
Asymmetry: $\alpha = f_{forward}/f_{backward}$.

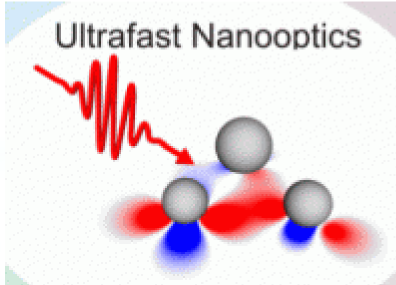
Stephen Leone, Musa Ahmed
Kevin Wilson, Jinian Shu, G.C. Schatz, Nano Lett. 2007

Photoionization of Nanoparticles by 4-6 fs Phase Stabilized IR-Pulses

λ=720 nm







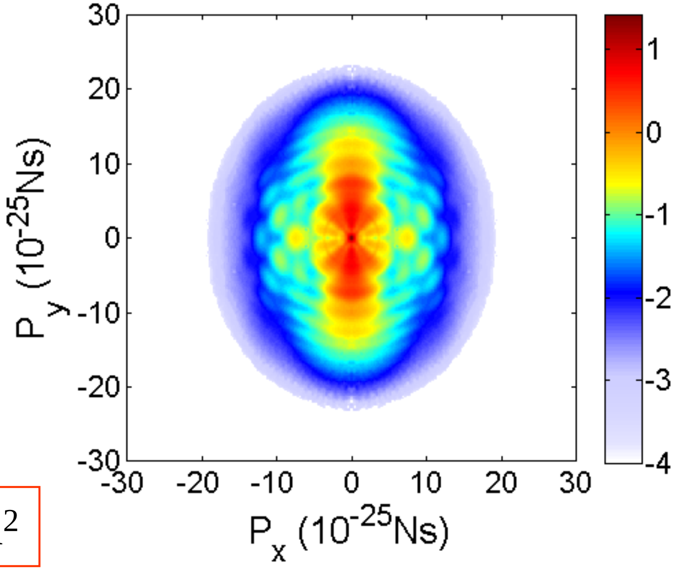
Collaboration with:
M. Kling (Garching/Munich)
Th. Fennel (Rostock)

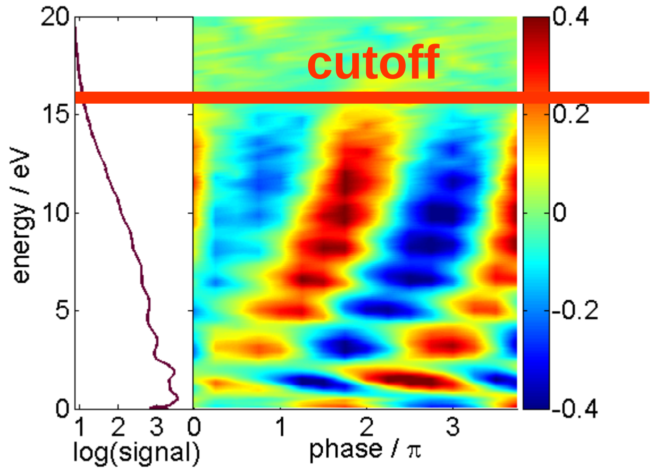
Photoionization of Nanoparticles by 4-6 fs Phase Stabilized IR-Pulses

Xenon

$$U_p = \frac{e^2 E_0^2}{4 m_e \omega_0^2}$$

$1.9 \cdot 10^{13}$ W/cm^2



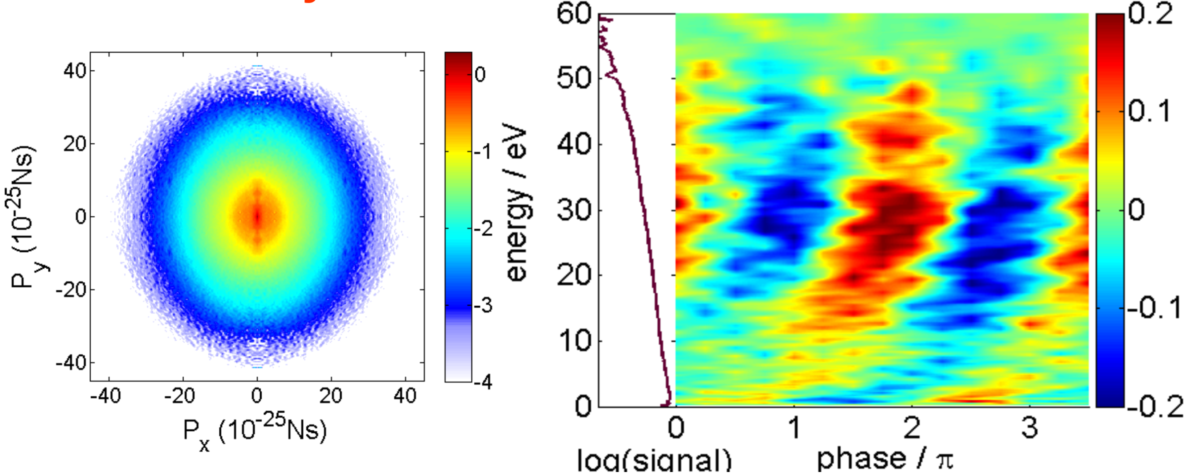


Strong phase dependence of electrons up to 10 U_p (ca. 16 eV)

Controlled near-field enhanced electron acceleration from dielectric nanospheres with intense few-cycle laser fields

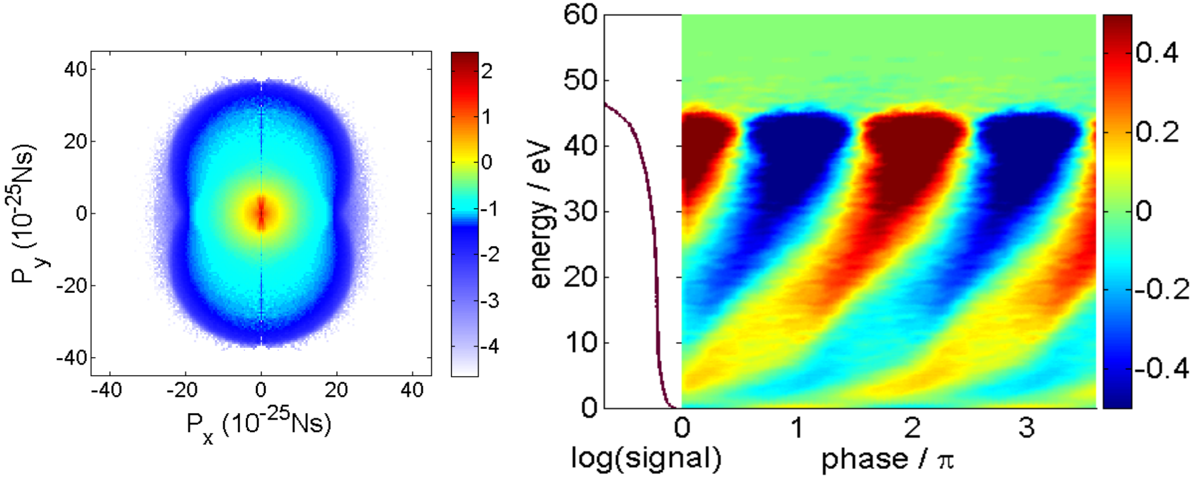
Silica Nanoparticles
109±6 nm

Cutoff: 54 U_p



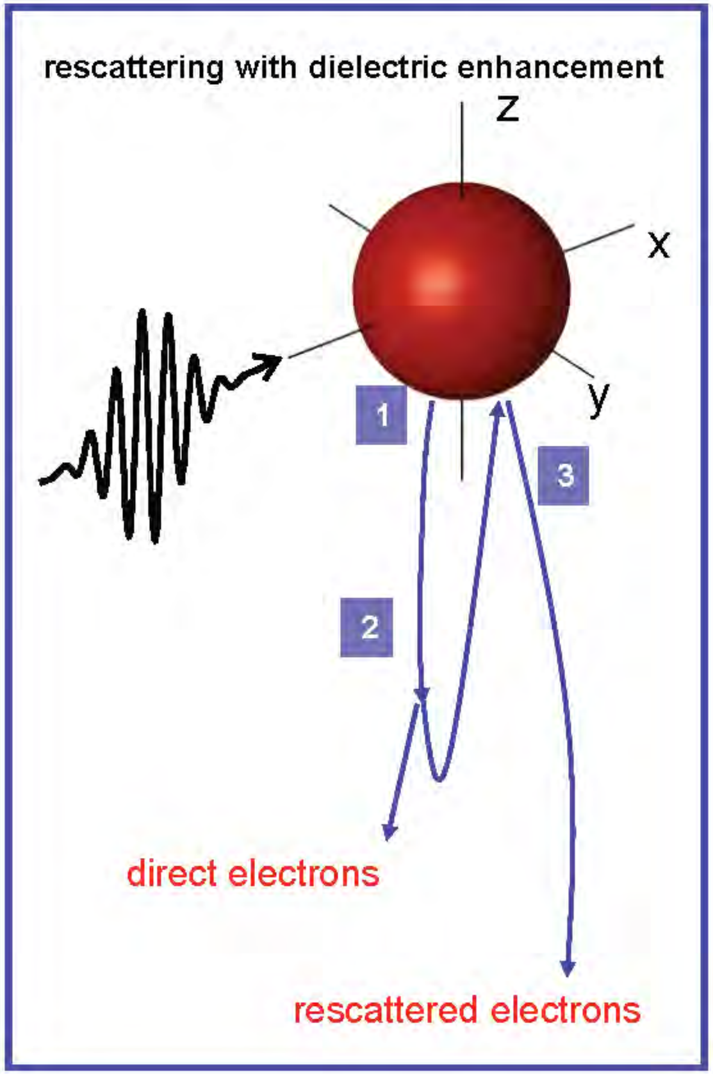
Simulation

Th. Fennel, Rostock:
Quasi classical trajectory-based Monte-Carlo approach



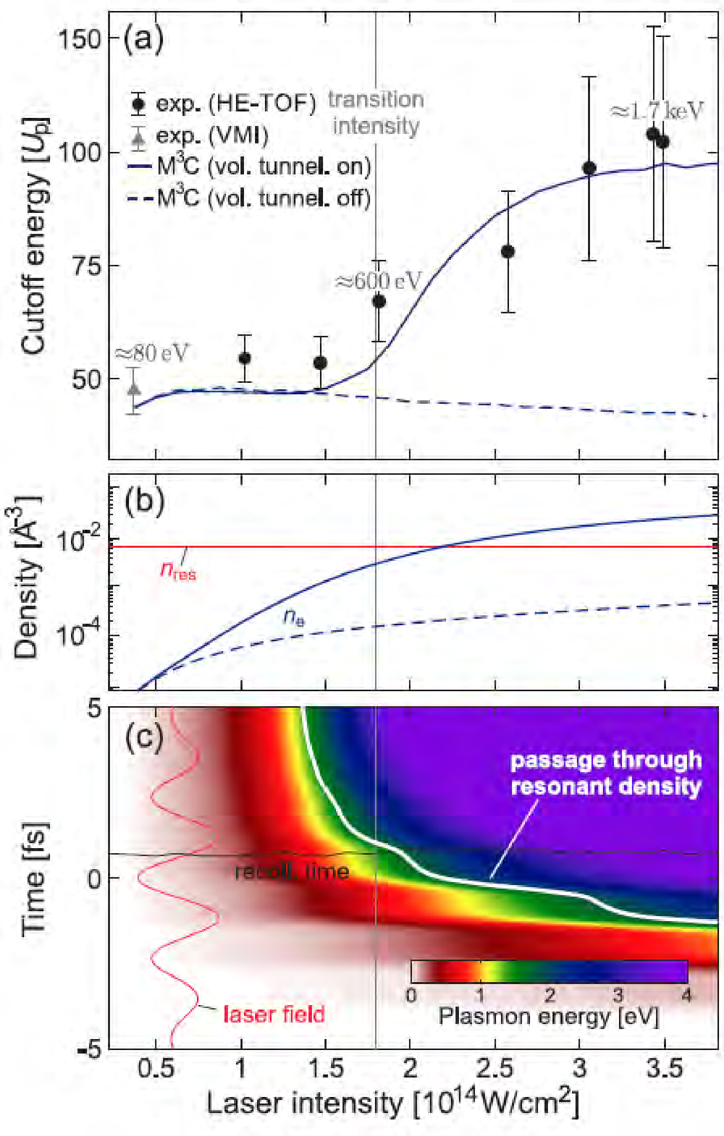
S. Zherebtsov et al., Nature Physics **7**, 656 (2011)

Emission of Fast Rescattered Electrons from Nanoparticles



S. Zherebtsov et al., Nature Physics **7**, 656-662 (2011).

$$U_p = \frac{e^2 E_0^2}{4 m_e \omega_0^2}$$

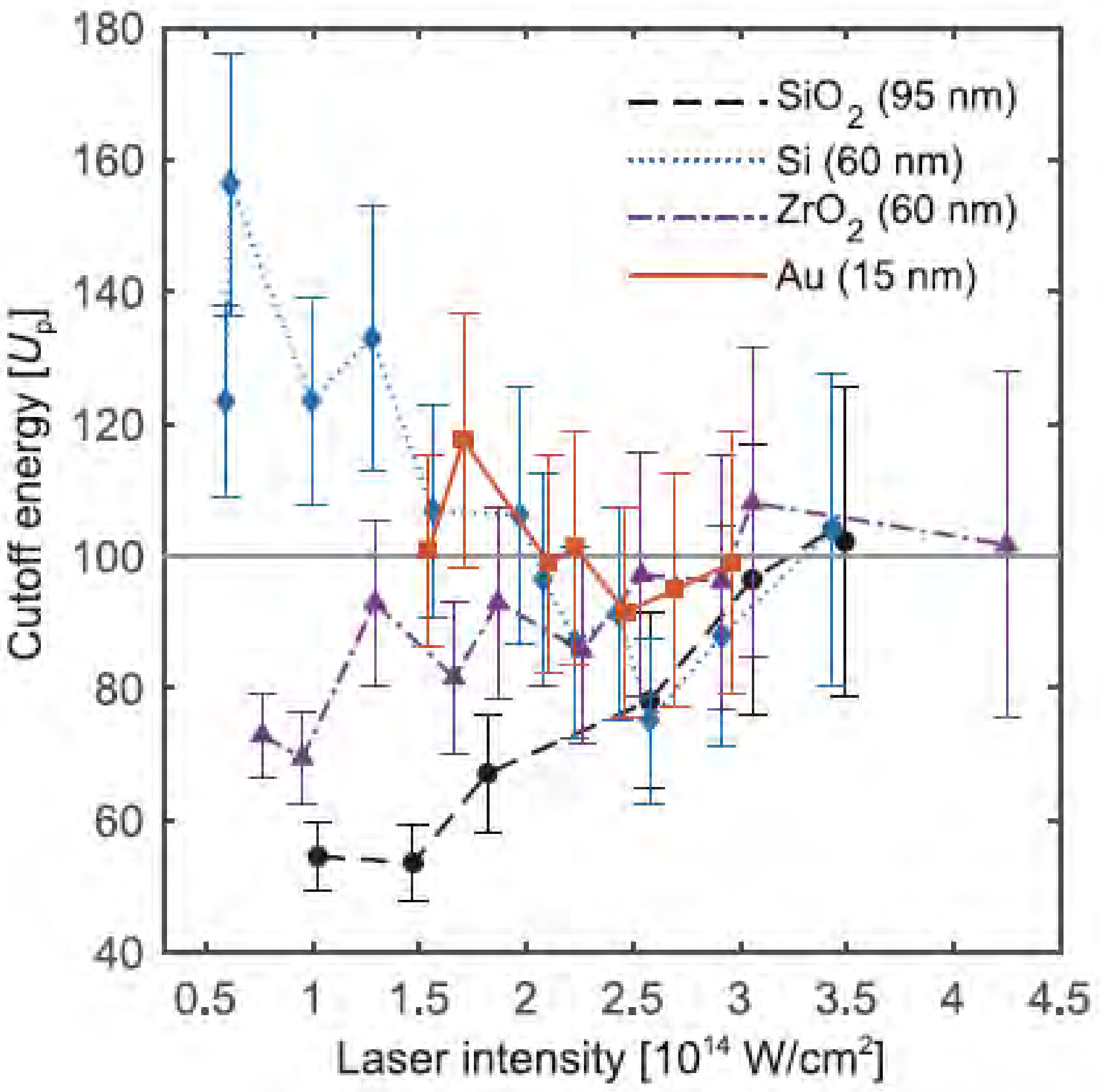


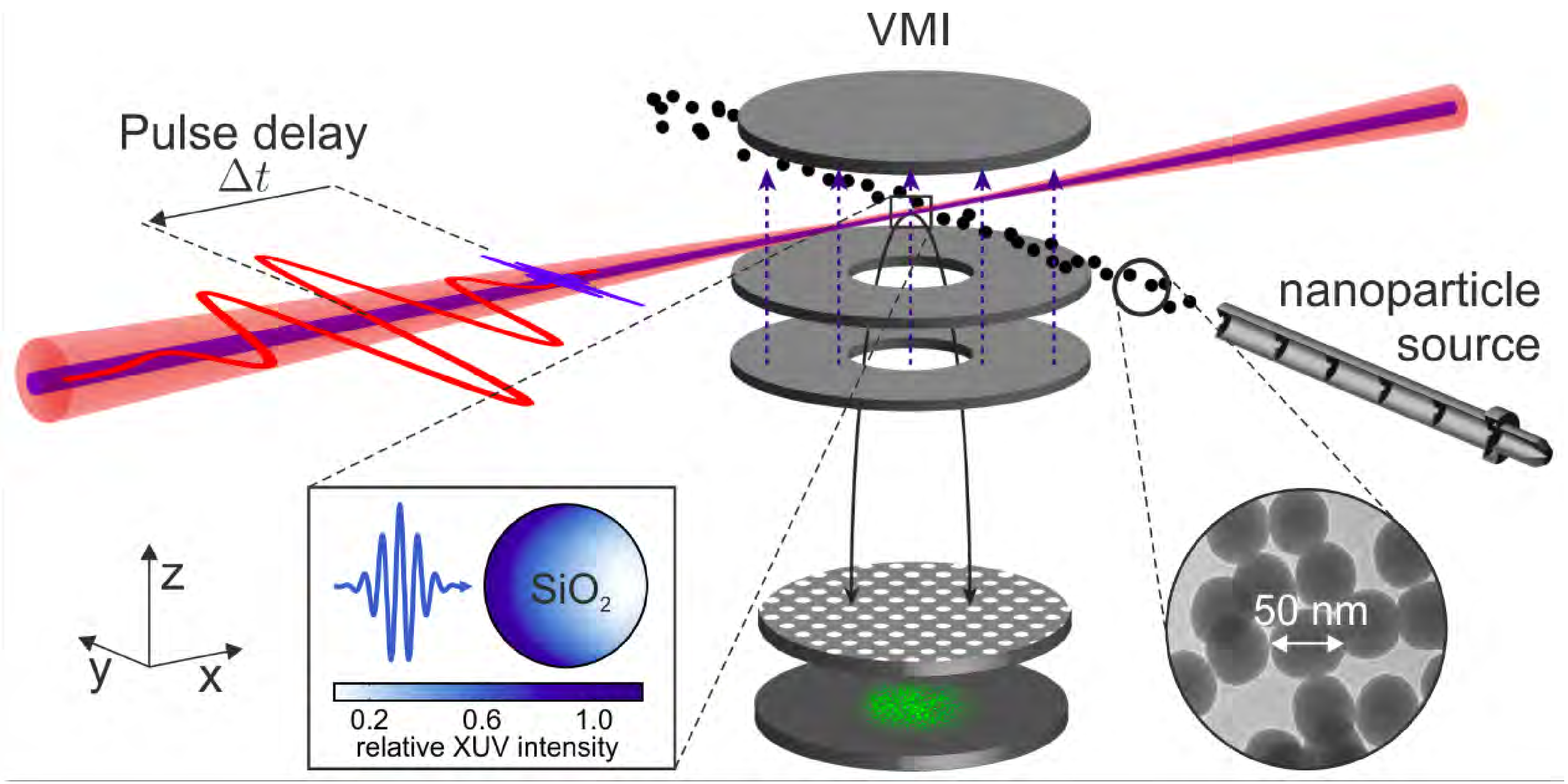
Semiclassical mean-field Mie Monte-Carlo (M3C) trajectory simulations

λ=720 nm

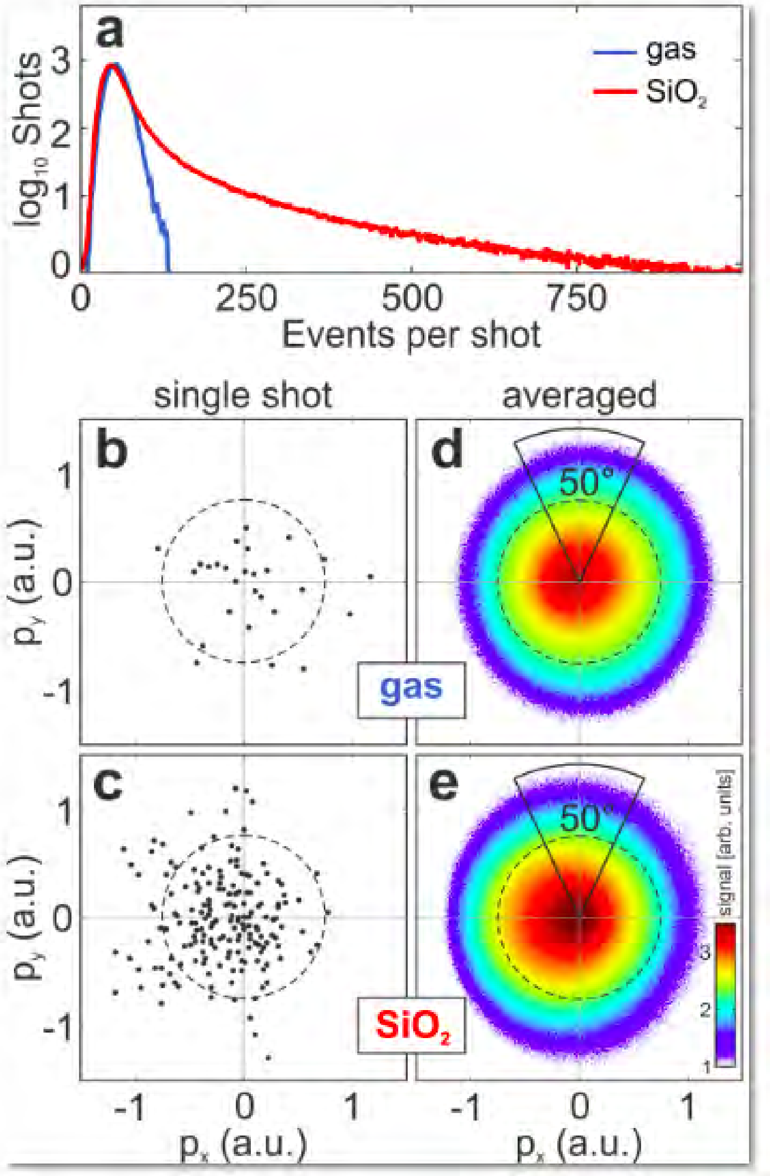
$$\omega_p = \sqrt{\frac{n_{ion} e^2}{3 m_e \varepsilon_0}}$$

ACS Photonics **7**, 3207 (2020)


SiO2 (95 nm)
Si (60 nm)
ZrO2 (60 nm)
Au (15 nm)
Cutoff energy [Up]
Laser intensity [10^14 W/cm^2]
180
160
140
120
100
80
60
40
0.5
1
1.5
2
2.5
3
3.5
4
4.5

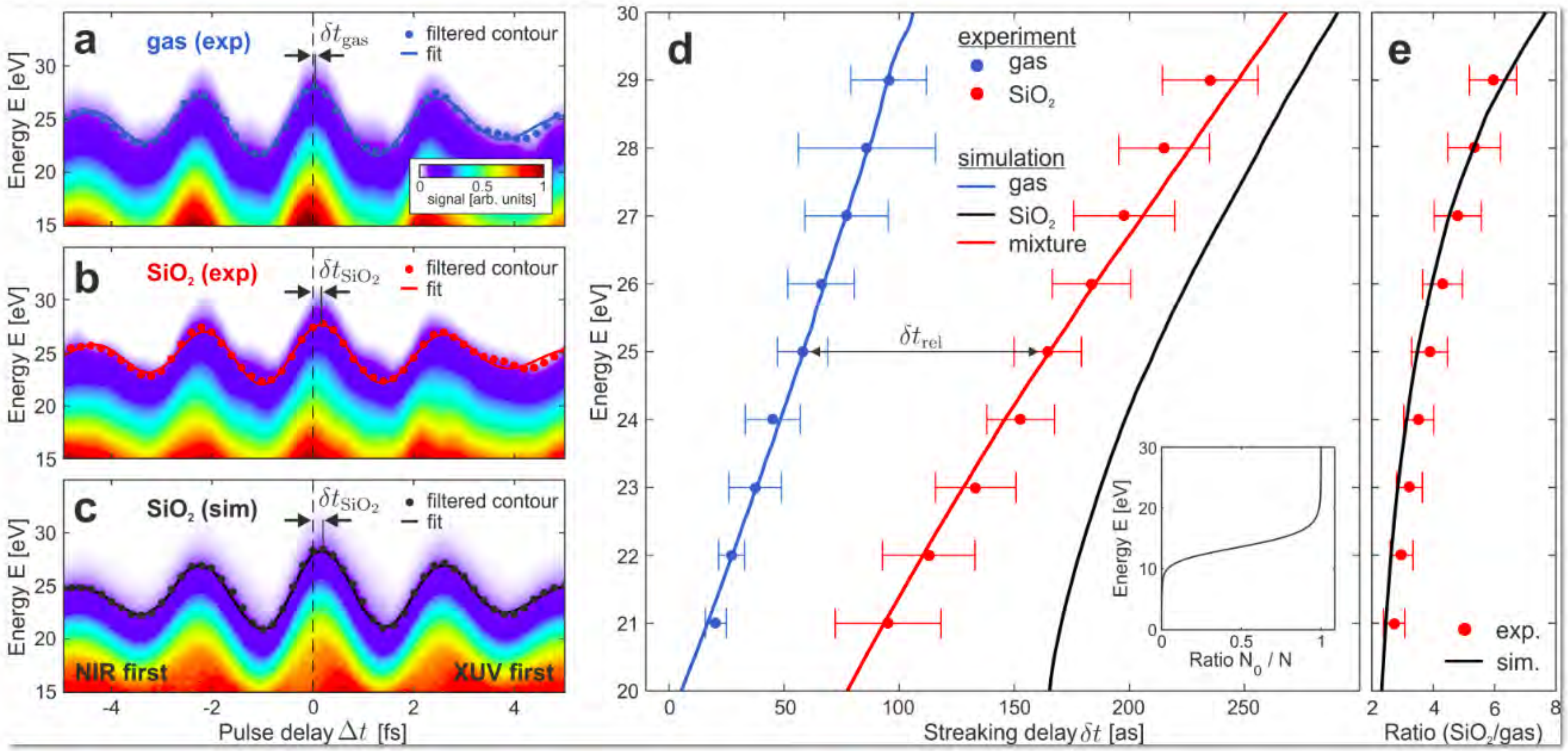


L. Seifert et al., Nat. Phys. **13**, 766-770 (2017).



L. Seifert et al., Nat. Phys. **13**, 766-770 (2017).

Streaking patterns: Characterization of electron scattering time

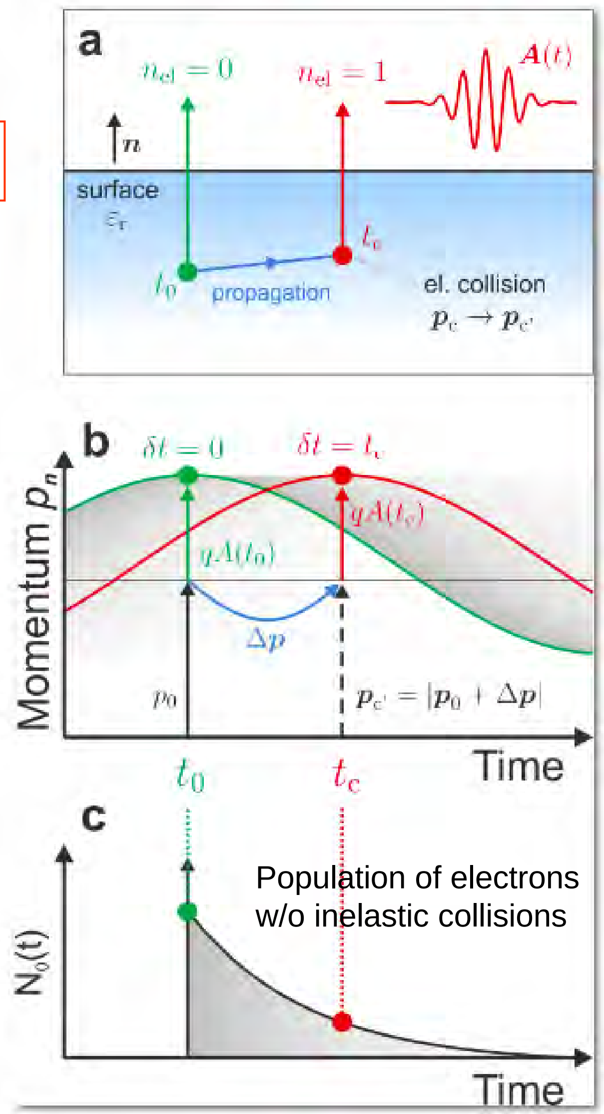


Simulations by trajectory-based mean-field Mie Monte Carlo transport (T. Fennel)

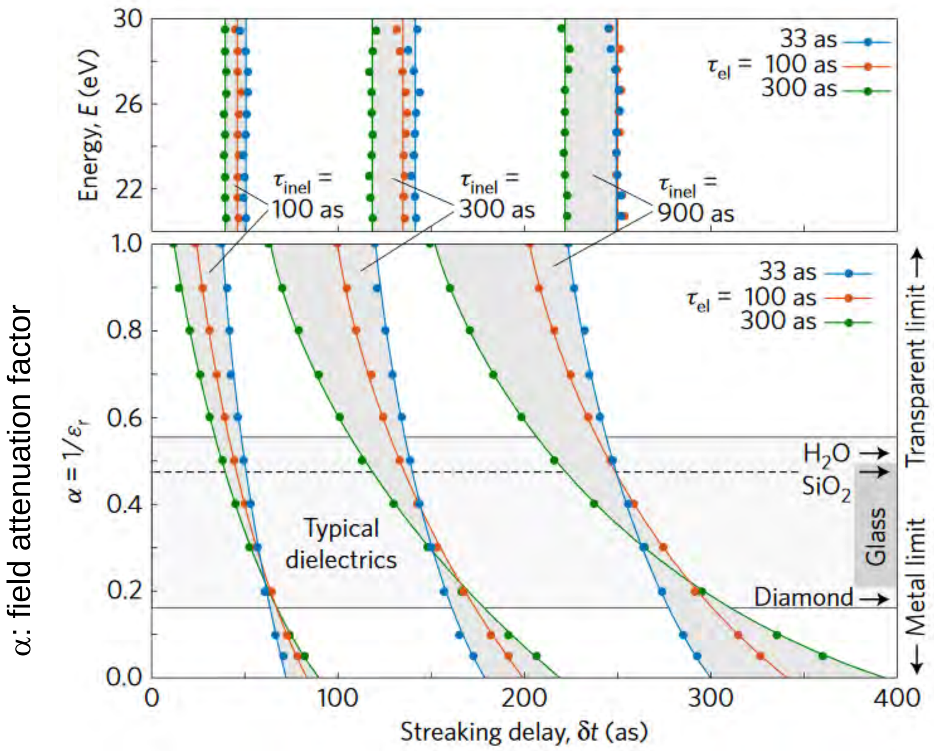
L. Seifert et al., Nat. Phys. **13**, 766-770 (2017).

Attosecond Dynamics: Elastic and Inelastic Scattering

$\varepsilon=1$



Variation of inelastic scattering time in 50 nm SiO_2



$\varepsilon\neq1$

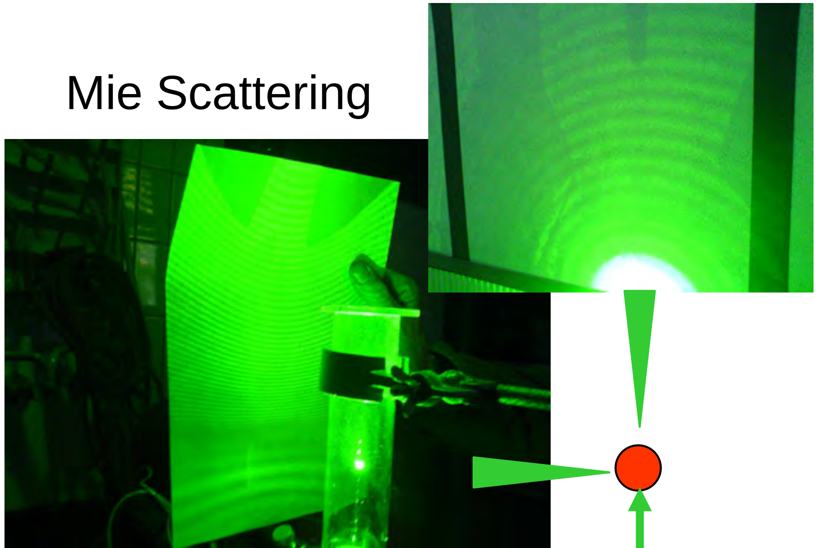
$\tau_{inealstic}$=370 as for 25 eV electrons

L. Seifert et al., Nat. Phys. **13**, 766-770 (2017).

Alternative to electrodynamic levitation

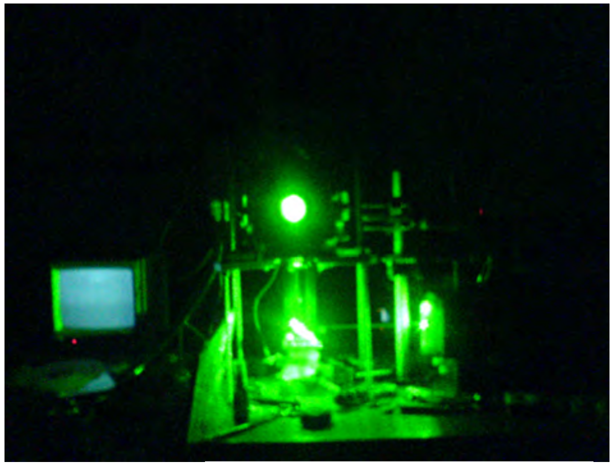
Optical Levitation of a Single Micro-Particle

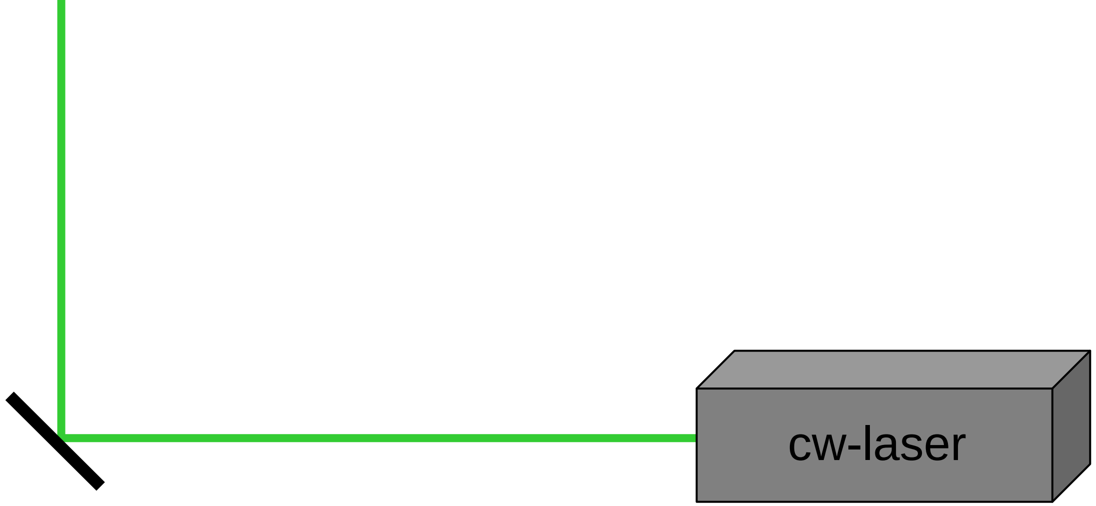
Mie Scattering



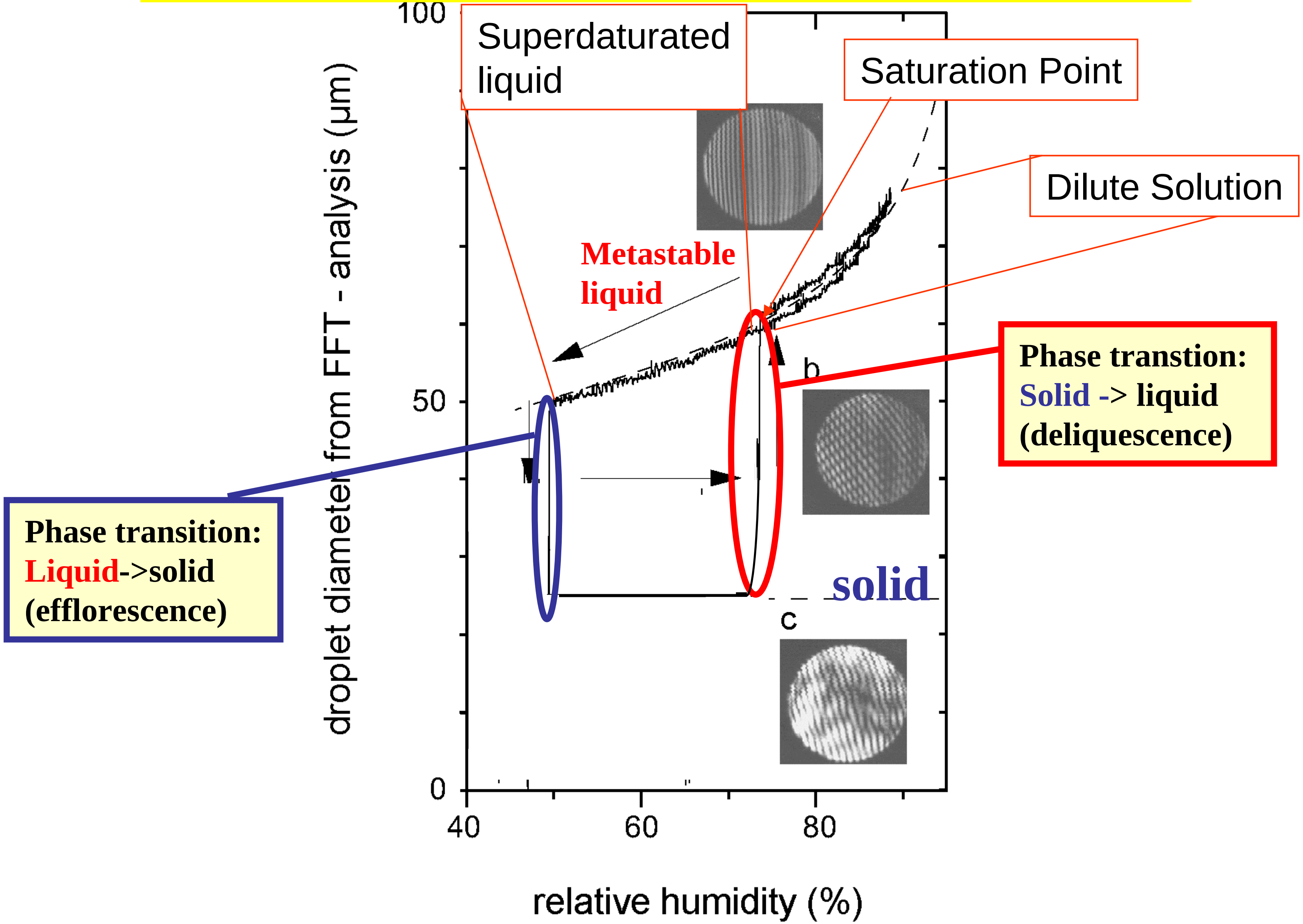
No electrical charges are needed for levitation

Droplet size: 20-50 μm
Stored in ambient conditions with controlled humidity

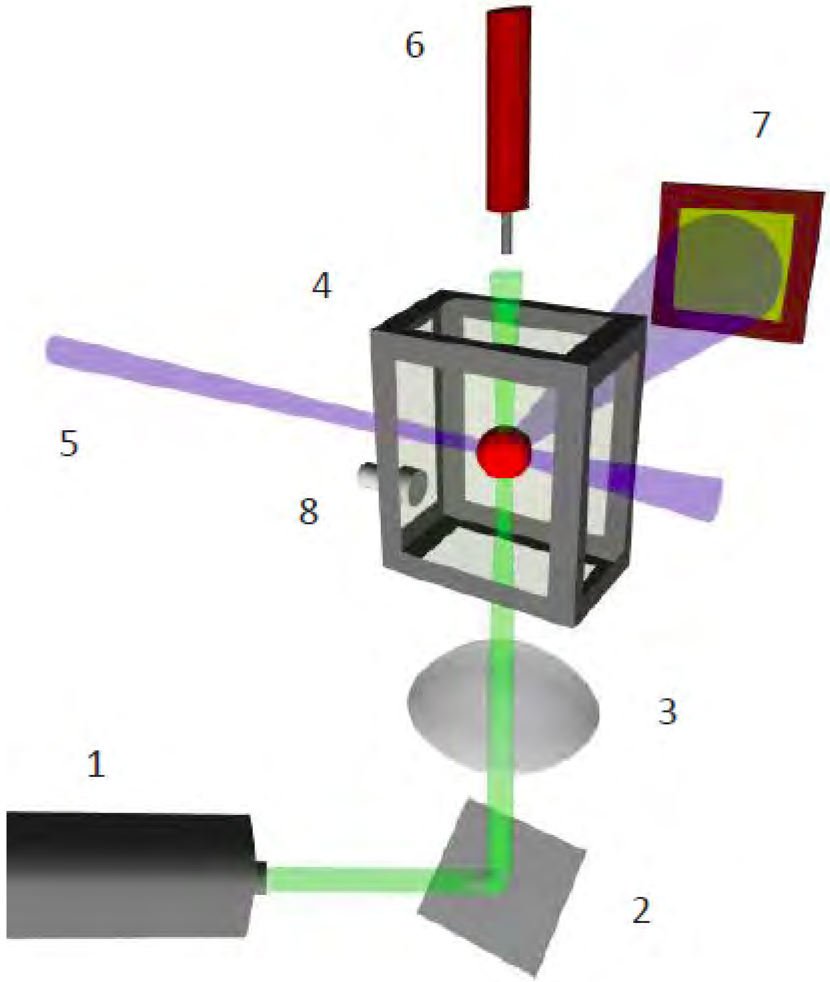


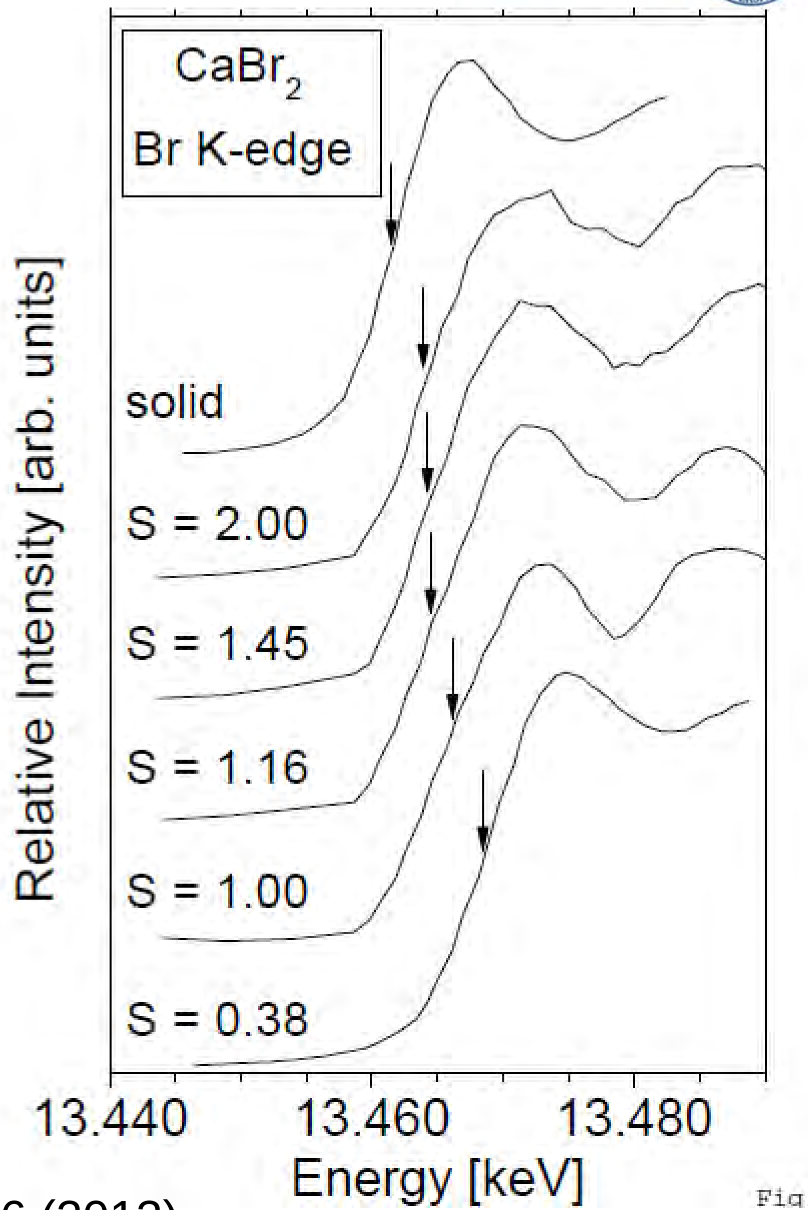


Humidogramm of a Single NaCl-Micro Particle Probed by Mie Scattering

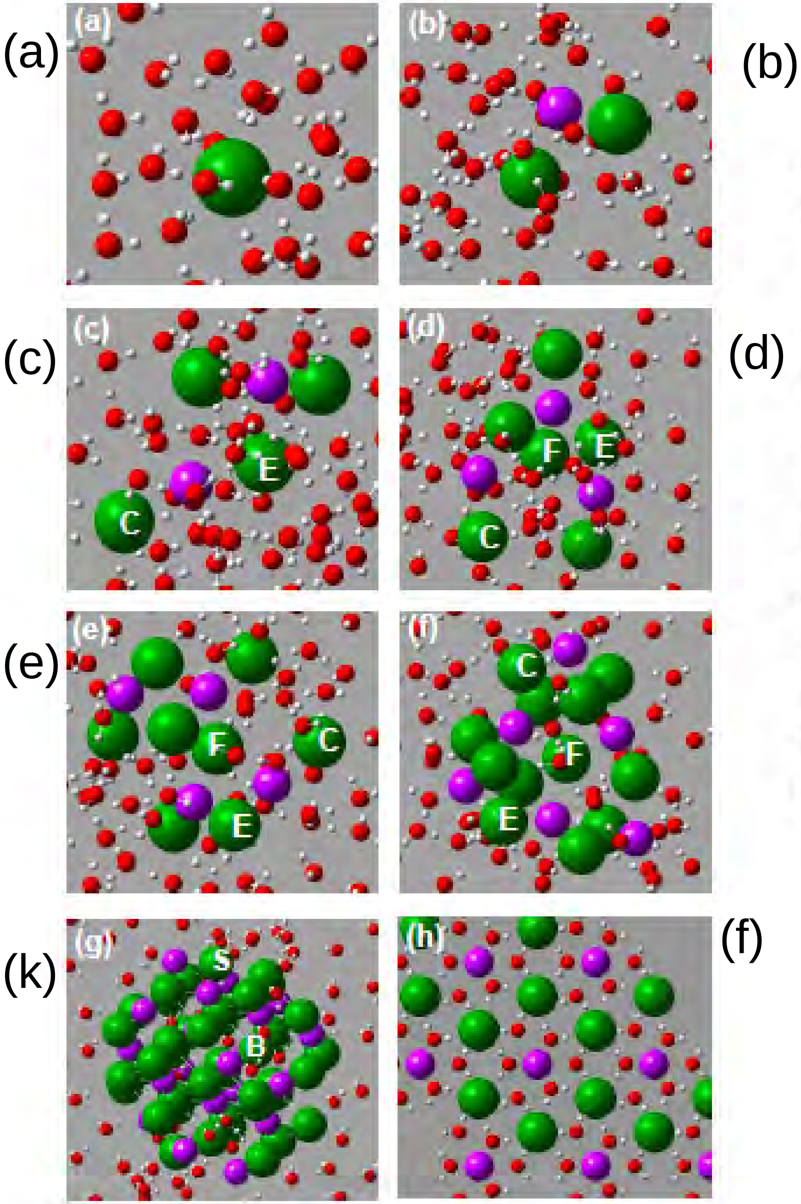


Formation of Pre-Nucleation Clusters in Solution





Y. Zhang et al., J. Chem. Phys. **139**, 134506 (2013)



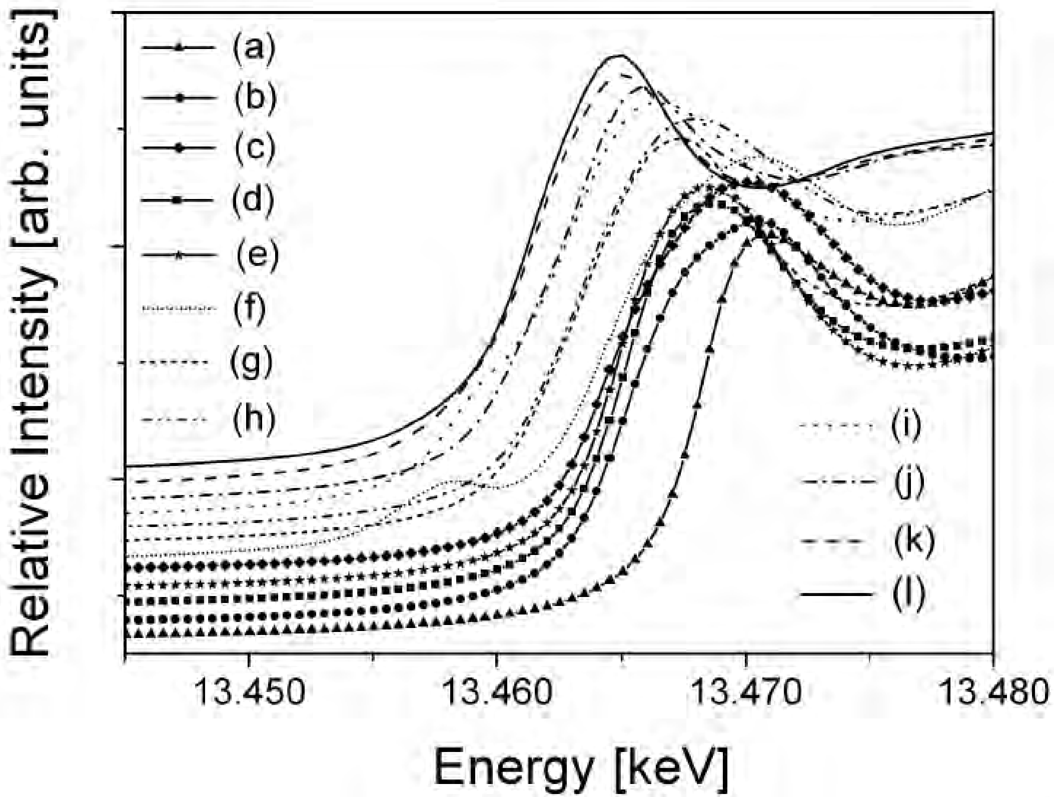
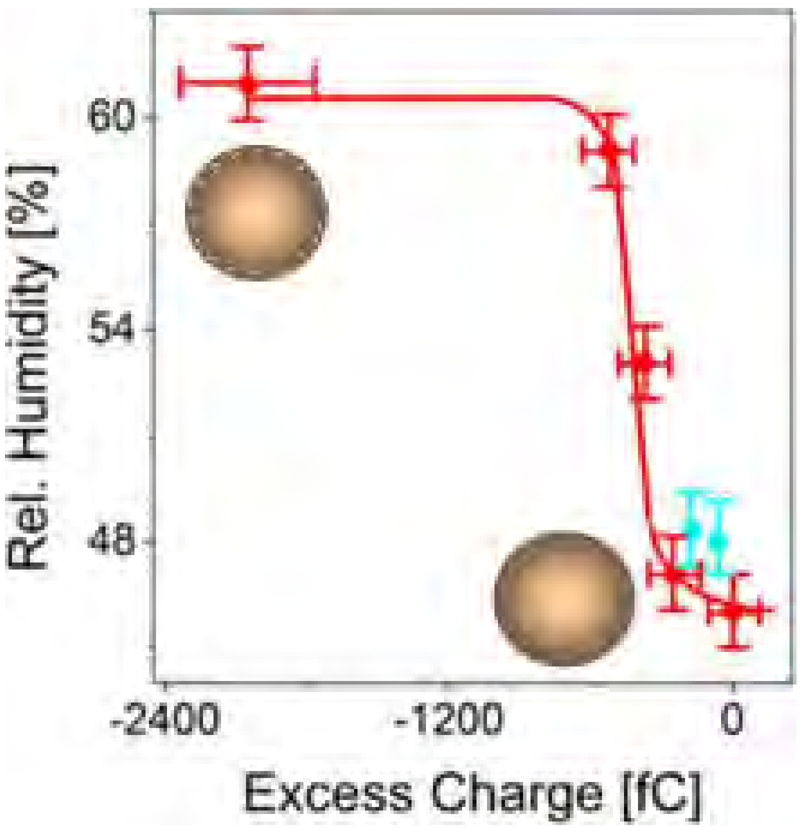
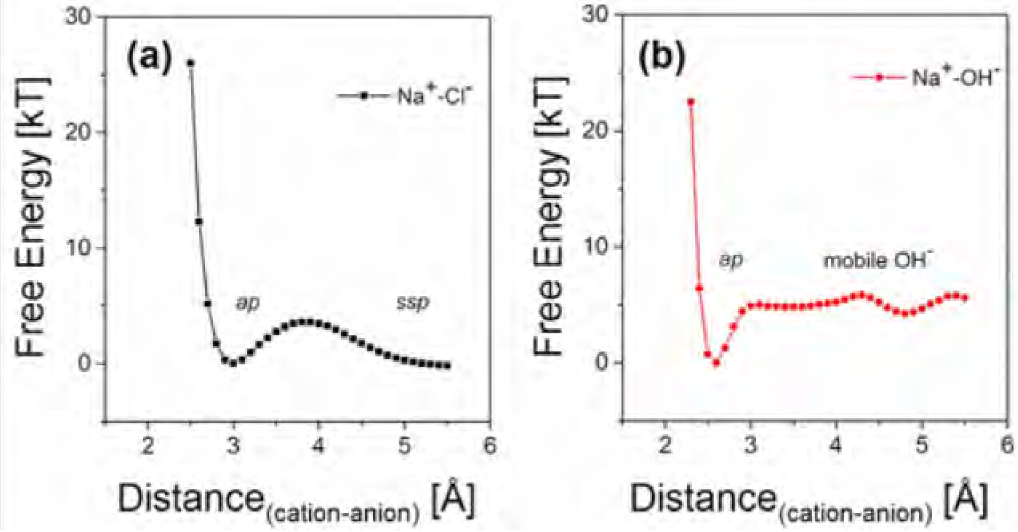


FIG. 4. Calculated near-edge structures of the structural motifs shown in Figure 3: (a) solvated Br^-; (b) solvated monomer $CaBr_2$; (c) solvated dimer: corner site; (d) solvated trimer: corner site; (e) solvated tetramer: corner site; (f) $CaBr_2 \cdot 6\,H_2O$ crystal; (g) solvated dimer: edge site; (h) solvated trimer: edge site; (i) solvated tetramer: edge site; (j) solvated tetramer: face site; (k) $CaBr_2)_{22}$: surface site; (l) anhydrous crystal of $CaBr_2$: bulk site. Distinct shoulders in the pre-edge regime are due to hydrogen bonding with the surrounding water (the spectra are vertically slightly displaced, see text for further details).

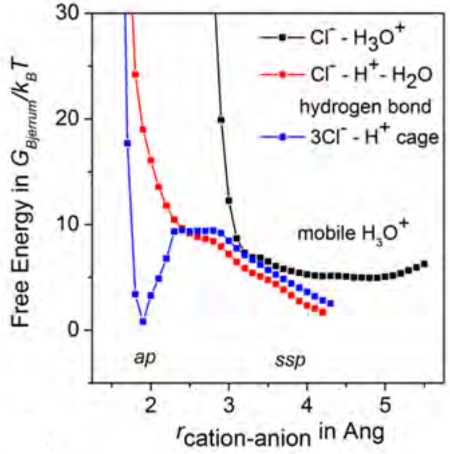
Excess Charges on Microparticles

Efflorescence humidity





Smaller effect for positive excess charge

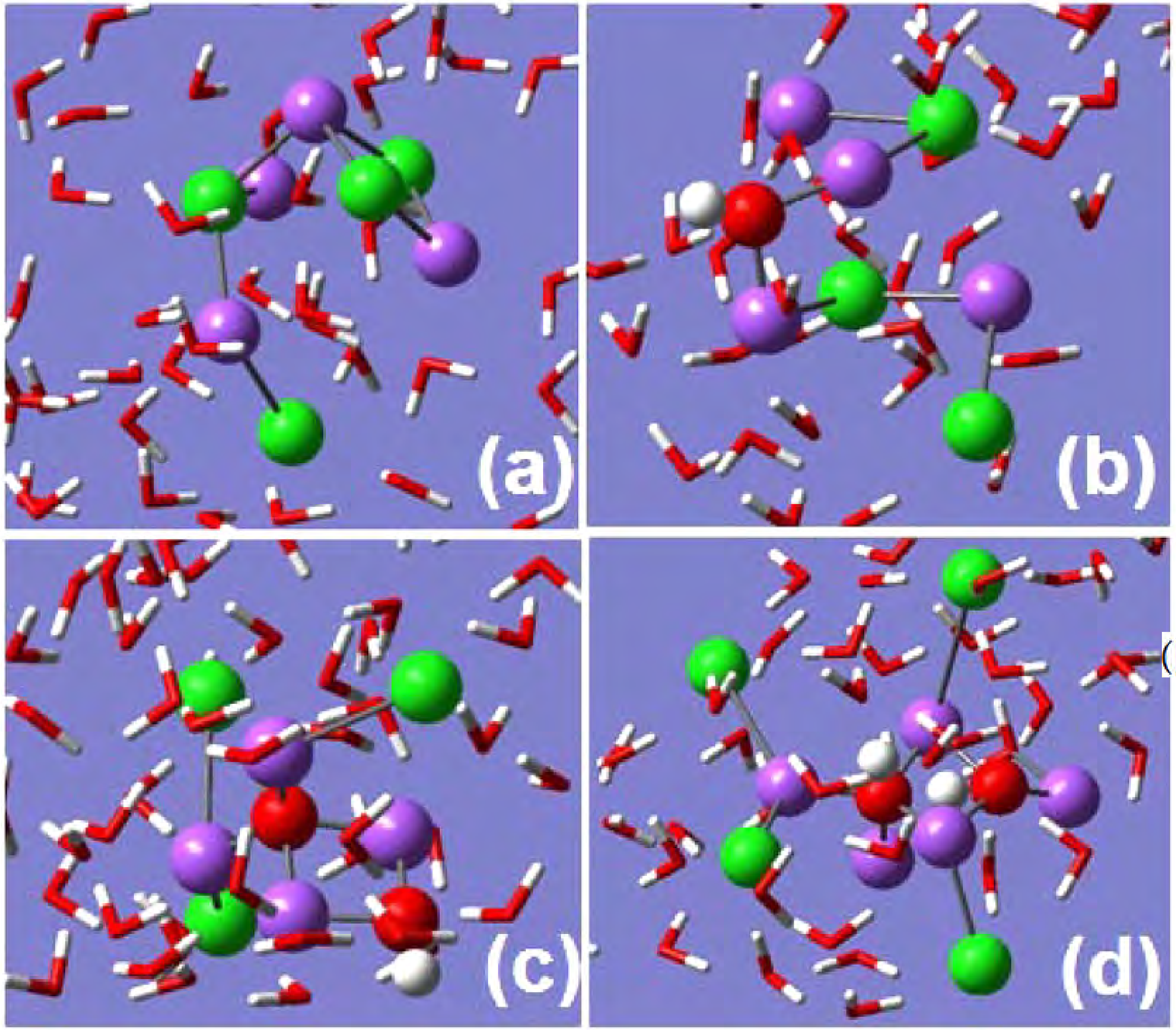


G. Herrmann et al., J. Phys. Chem. A **121**, 6790-6799 (2017)

Charge-Induced Nucleation: MD Simulations

Na_4Cl_4

$Na_4(OH)Cl_3$



$[Na_4(OH)_2Cl_3]^-$

$([Na_5(OH)_2Cl_4]^-$

J. Phys. Chem. A 2017, 121, 6790−6799

Isolated Nanoparticles Prepared in Beams

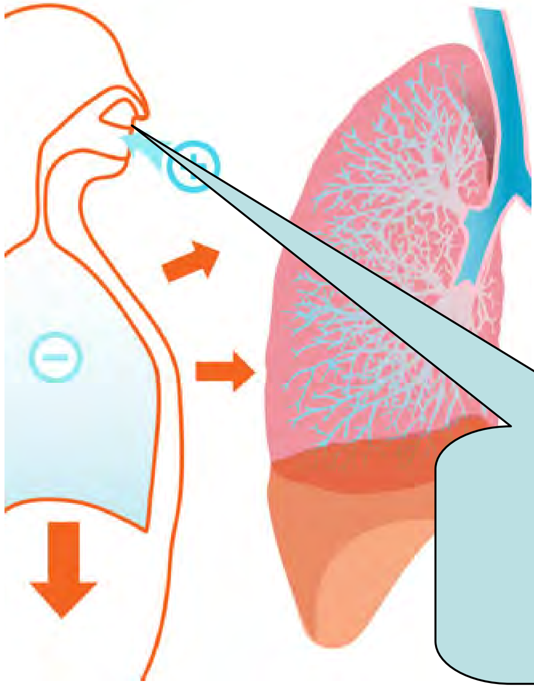
- Universal preparation scheme for nanoscopic matter
- Novel photoionization processes leading to the emission of fast electrons and metallization processes in intense laser fields
- Femtosecond dynamics of metallization, surface melting, and Coulomb explosion
- Attosecond dynamics of elastic and inelastic scattering processes

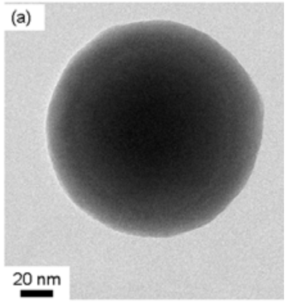
Levitated Nanoparticles

- Universial preparation scheme for production of meastable liquids
- Distinct structures are formed as pre-nucleation clusters
- Excess charges facilitate nucleation

Possible Uptake Routes of Nanoparticles into Humans

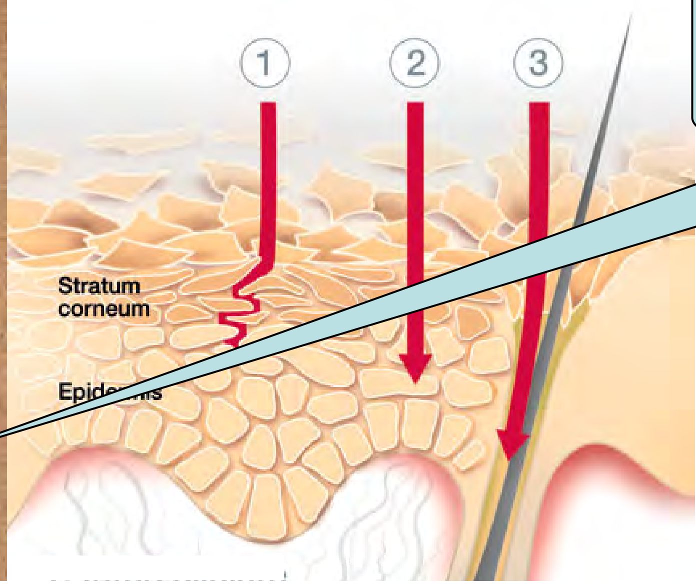
Freie Universität Berlin



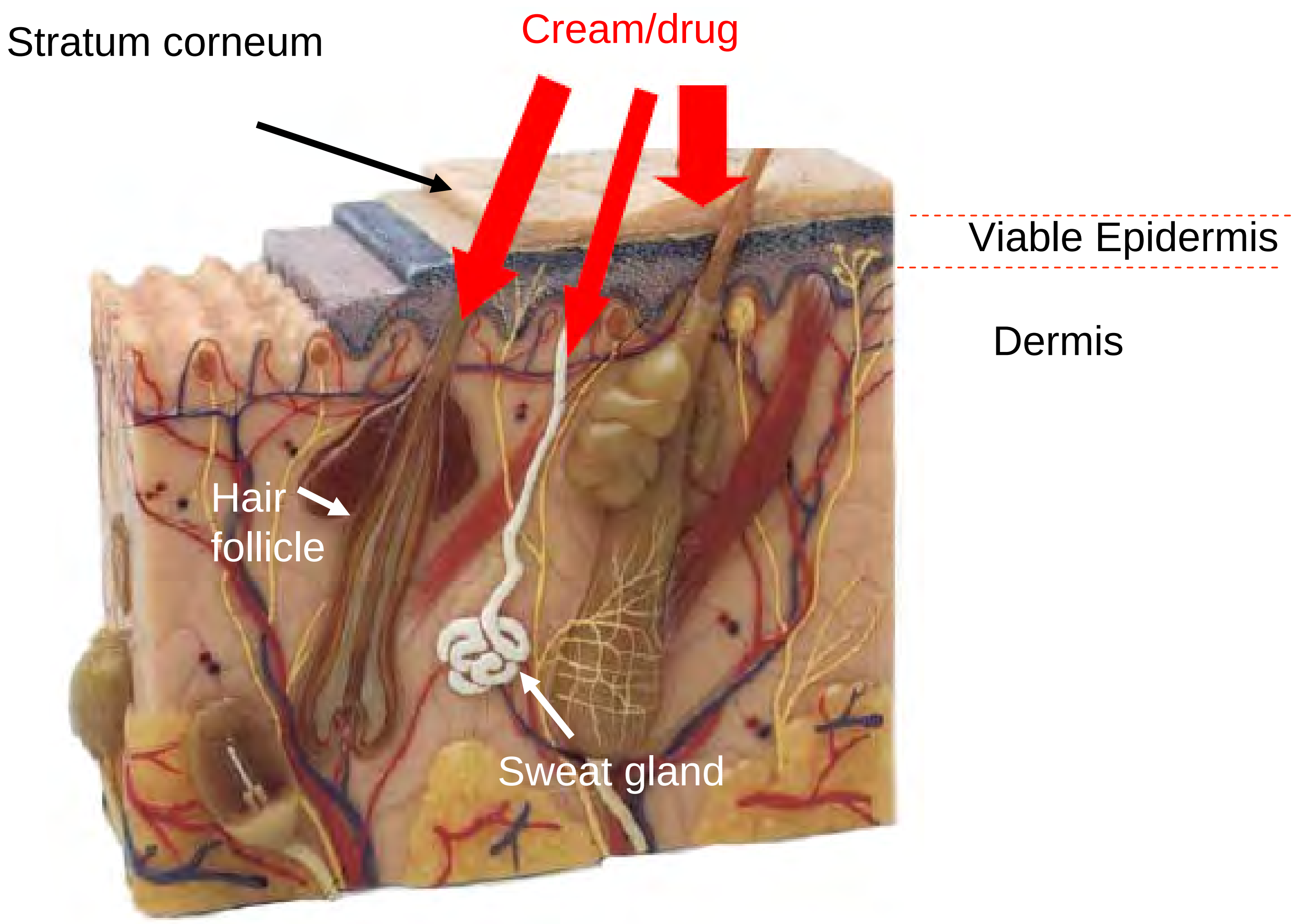


Inhalation

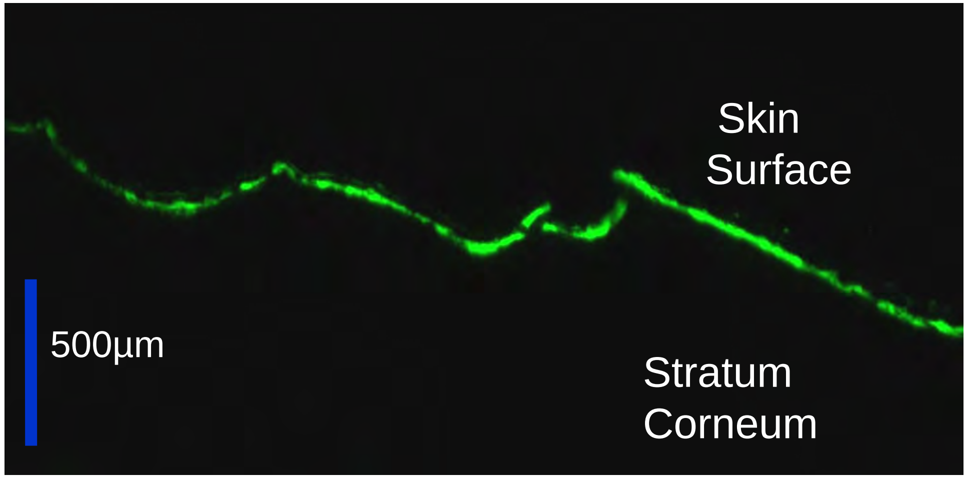
Ingestion



Skin Exposure


Stratum corneum
Cream/drug
Viable Epidermis
Dermis
Hair follicle
Sweat gland

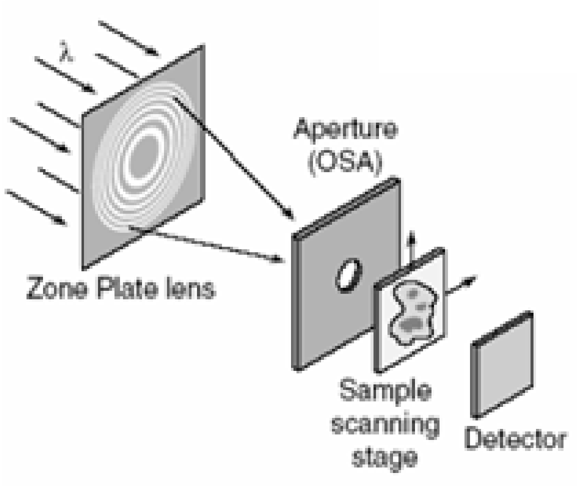
Fluorescent Nanoparticles on Human Skin



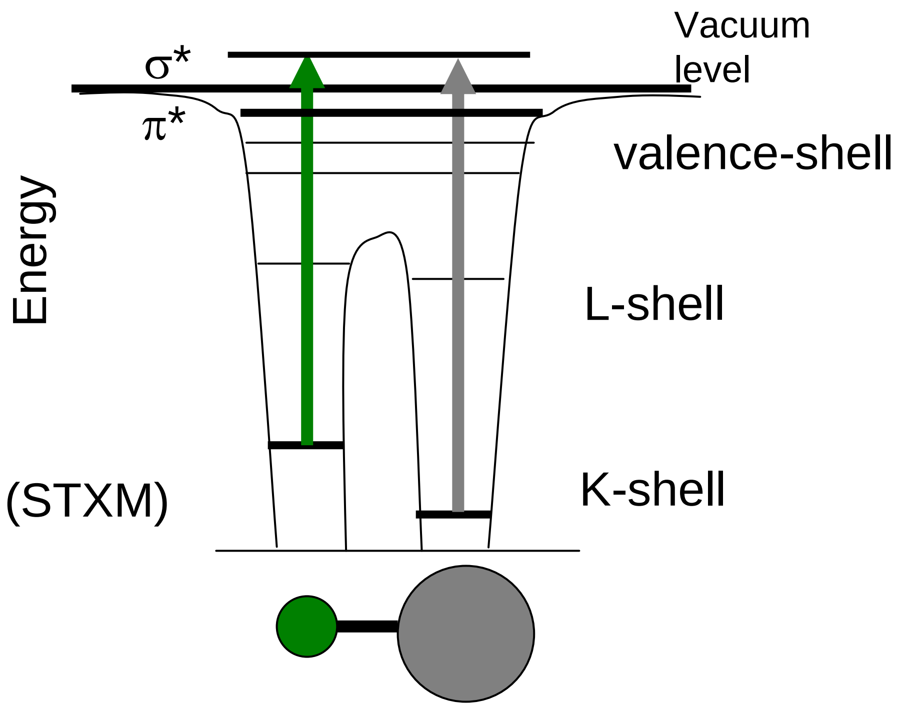
Aims:

- Label-free detection of nanoparticles and drug delivery in cells and skin (X-ray microscopy, Raman-based spectromicroscopy, AFM-based spectromicroscopy: optical near-field microscopy, photothermal expansion)
- Identification of harmful interactions of nanoparticles with organisms
- Mechanistic foundation for nanoparticles-based dermatotherapies

Scanning Transmission X-ray Microscopy (STXM)



Scanning Transmission X-ray Microscope (STXM)
Use of tunable soft X-rays

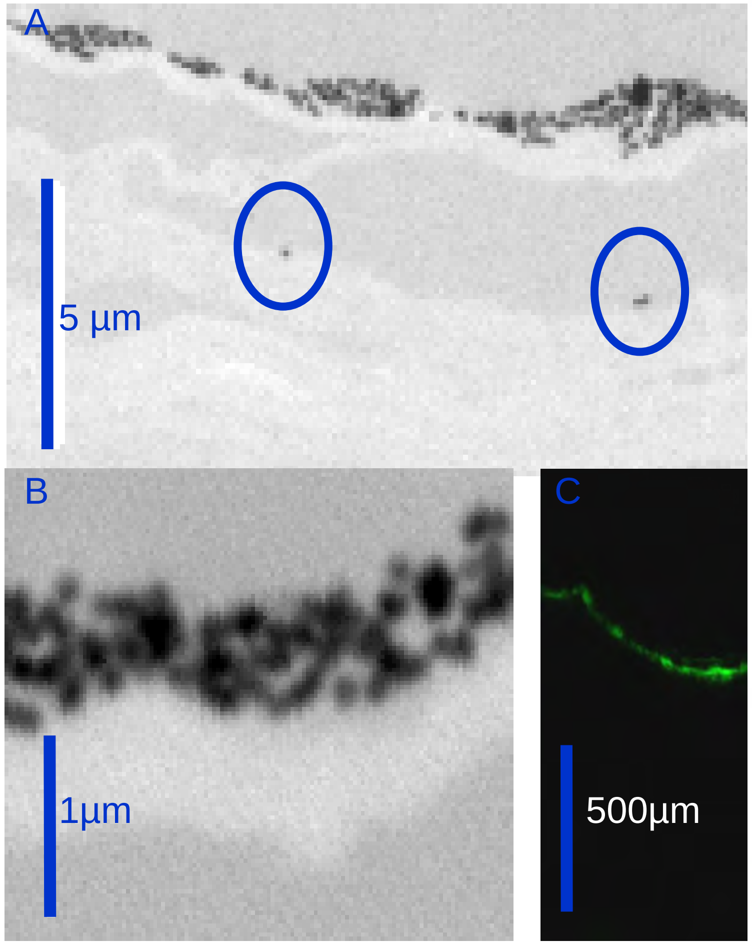


Core Level Excitation

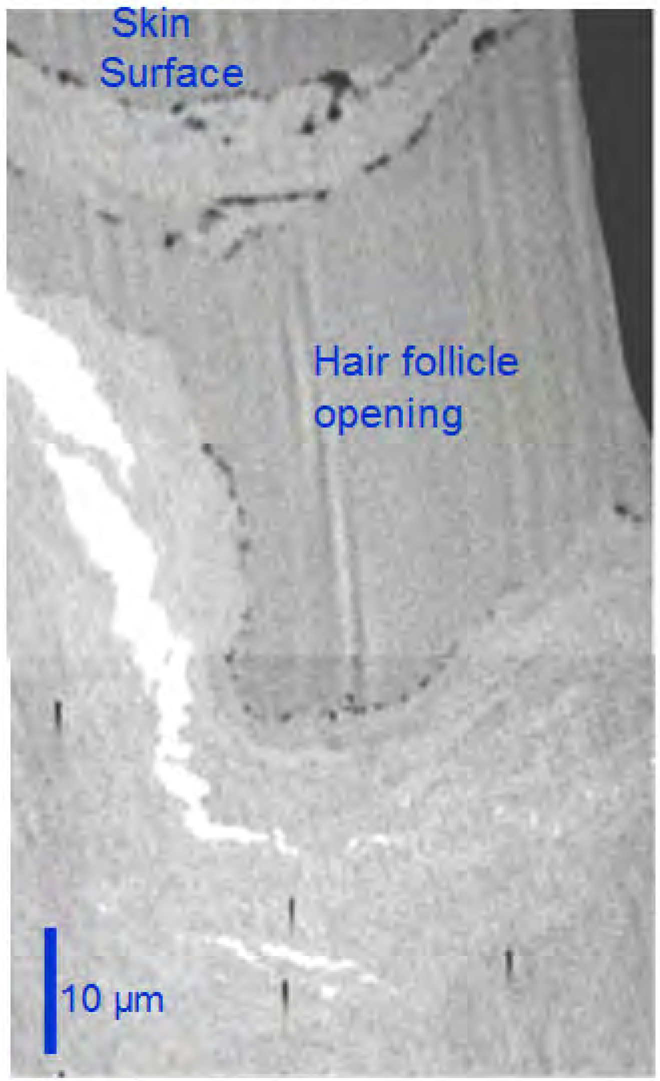
- Element-selective
- Site-selective
  (probes the chemical contrast)

Penetration of Slica Nanoparticles into Human Skin

Particle diameter: 161±13 nm

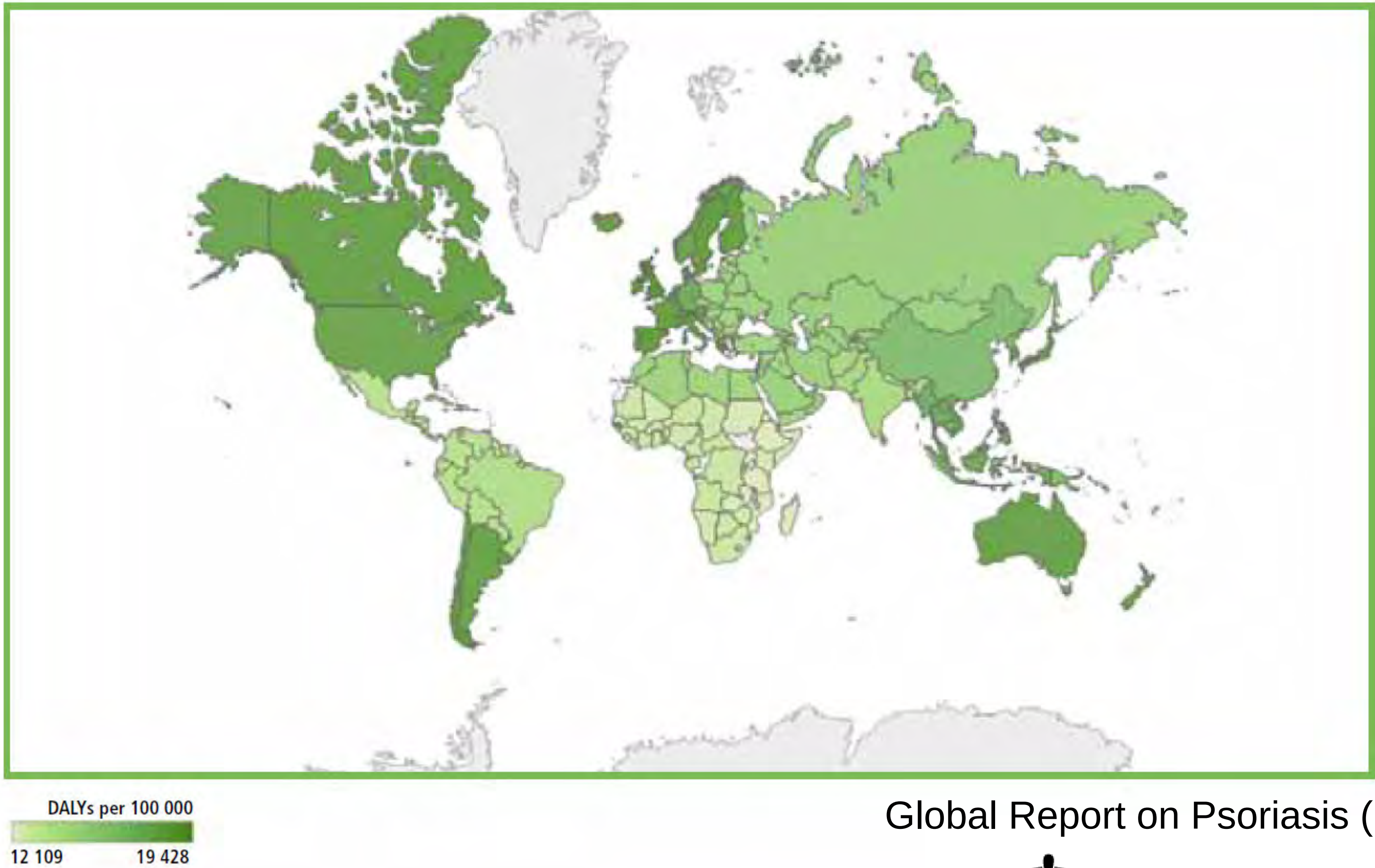


STXM, E = 270 eV, 350 nm section



C. Graf et al., J. Biomed. Opt. **14**, 021015 (2009).

Psoriasis: Prevalence in Population



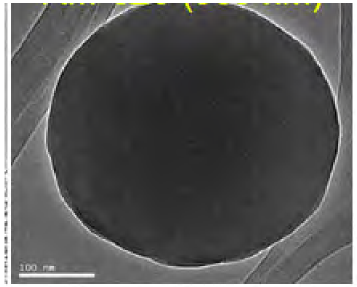
Global Report on Psoriasis (2016)

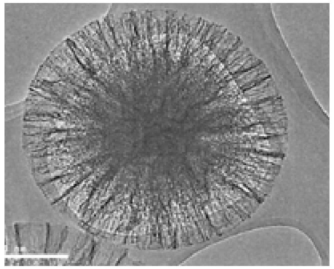
World Health Organization

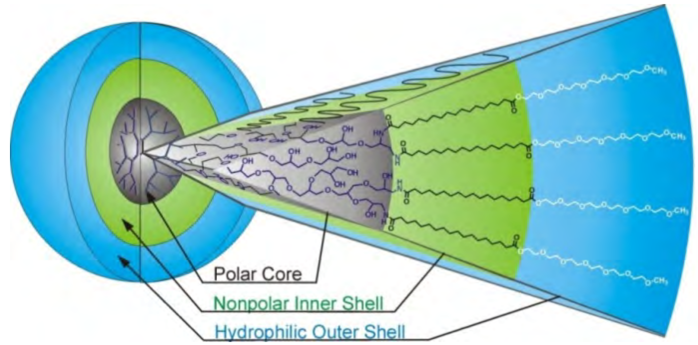
DALY: disability-adjusted life years

Inorganic Particles

Polymer Particles







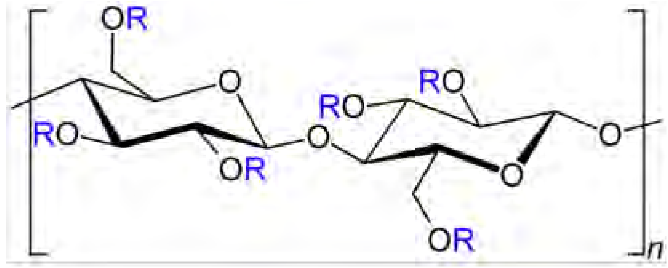
Important issues:

- Medical need
- Efficient drug delivery:
  protection of fragile drugs or overcoming bio barriers
- Degradation and metabolisms
- Model environment of testing the use of nanoparticles

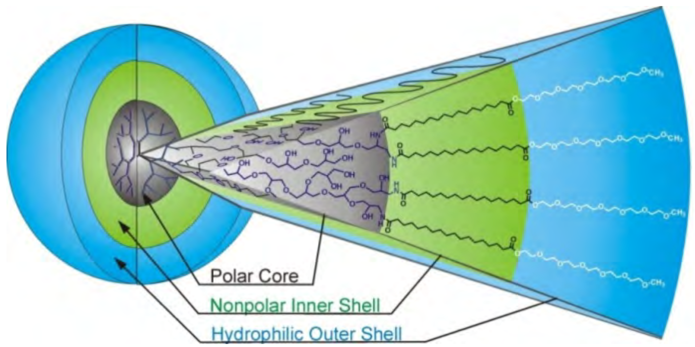
Topically Applied Formulations

Ethanolic drug solutions

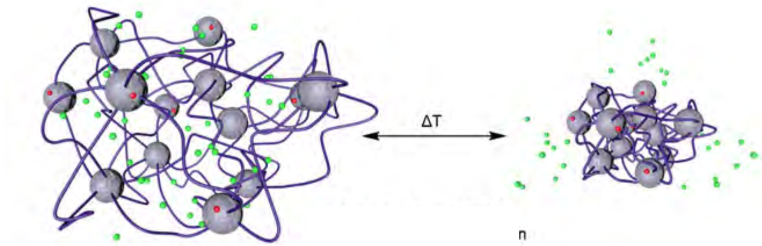
Hydroxyethyl cellulose (HEC) gel



Core-multishell nanocarriers
R. Haag, FU Berlin



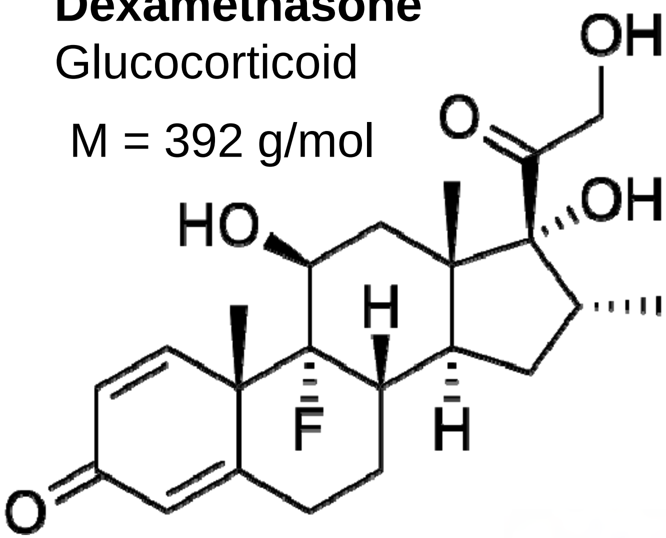
Thermoresponsive nanogels
M. Calderon, FU Berlin



Micelles
R. Gurny, Apidel SA, Geneva

Dexamethasone
Glucocorticoid

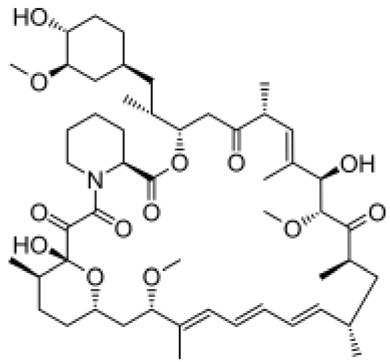
M = 392 g/mol

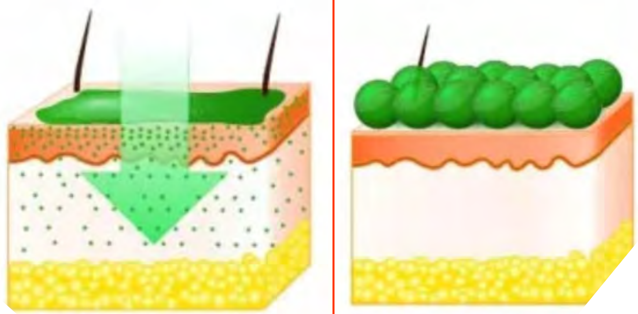


500 Dalton-Rule

Rapamycin
mTOR inhibitor

M = 914 g/mol





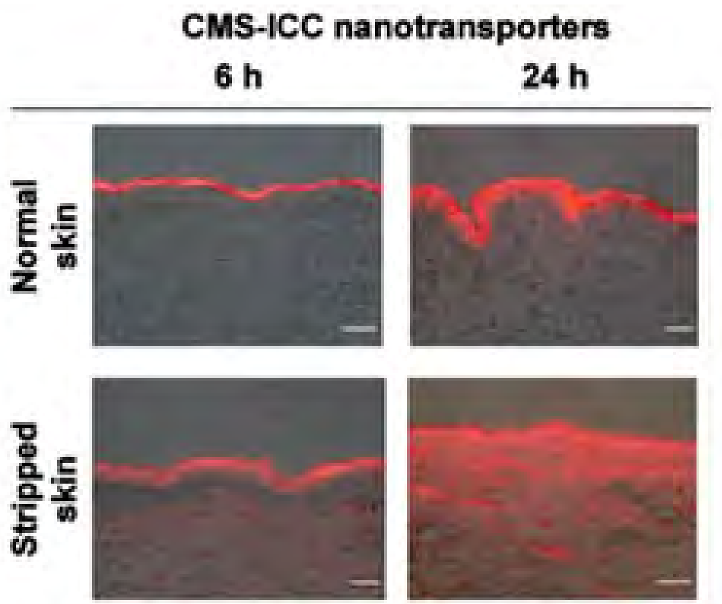
Fluorescence Microscopy

Formulation of dyes

Requirement:
Labeling by a fluorescent probe

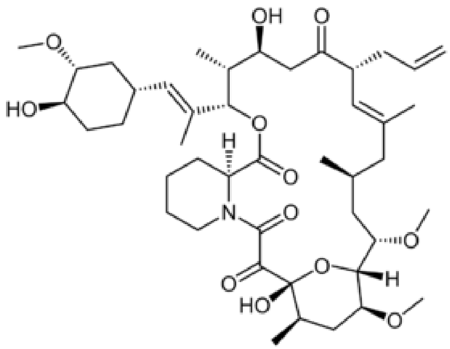
Advantage:
Sensitive detection

Limitation:
Spatial resolution: Diffraction limited
Most drugs are non-fluorescent



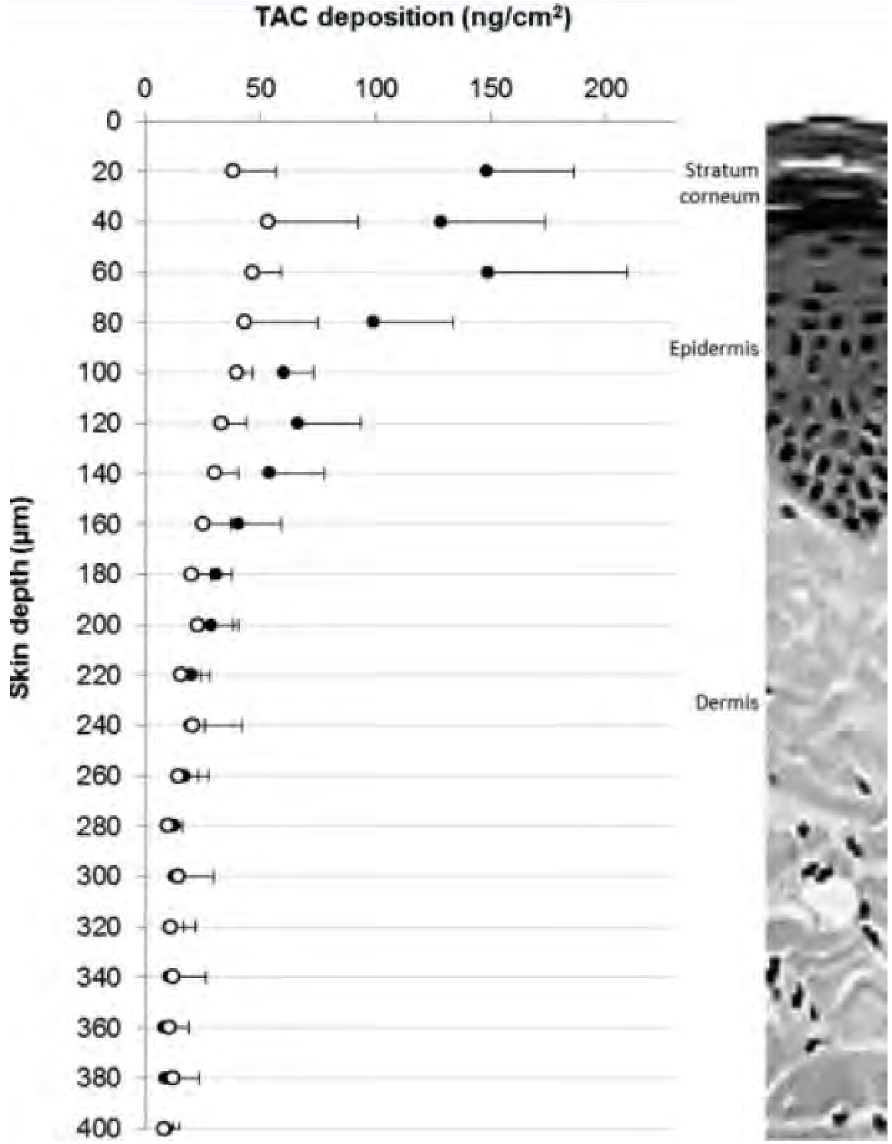
100 μm

Analytical Approaches: UHPLC-MS/MS



Tacrolimus
Calcineurin inhibitor (CNI)

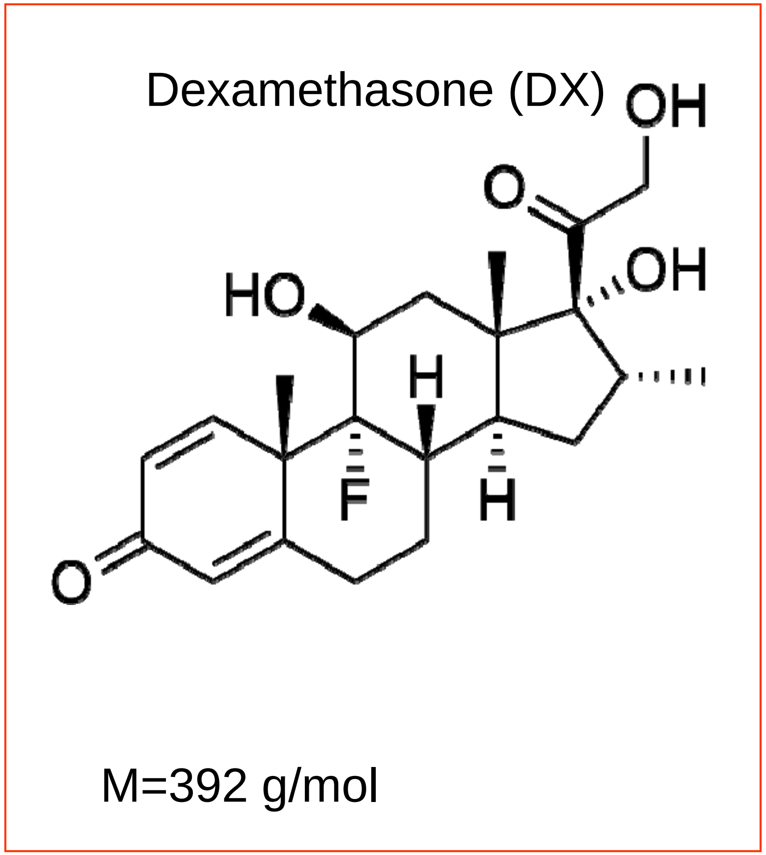
Label-Free
Quantitative Approach
Depth resolution: 20 μm

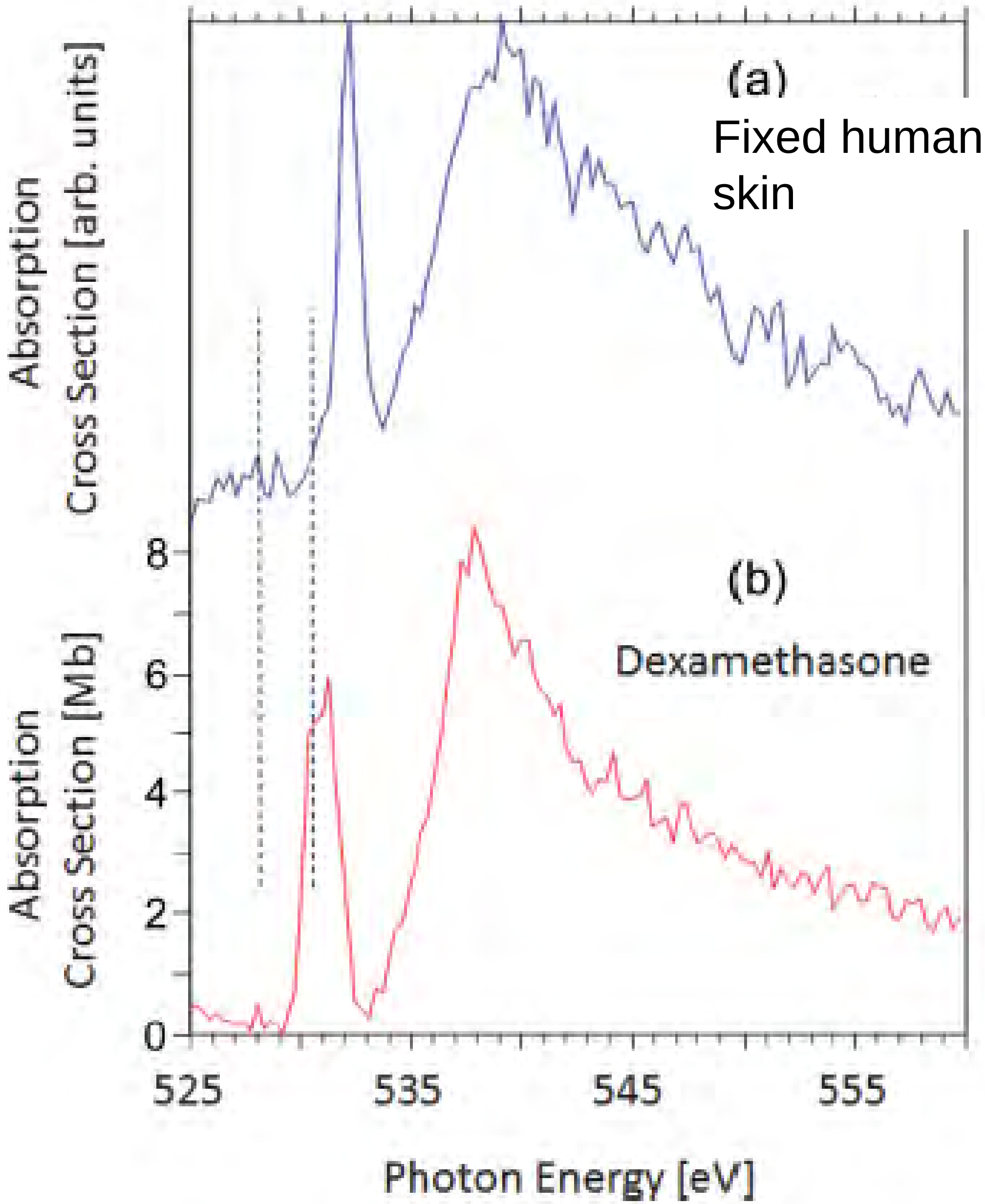


M. Lapteva et al., Mol. Pharm. (2014)

Label-Free Detection of Dexamethasone

X-ray microscopy





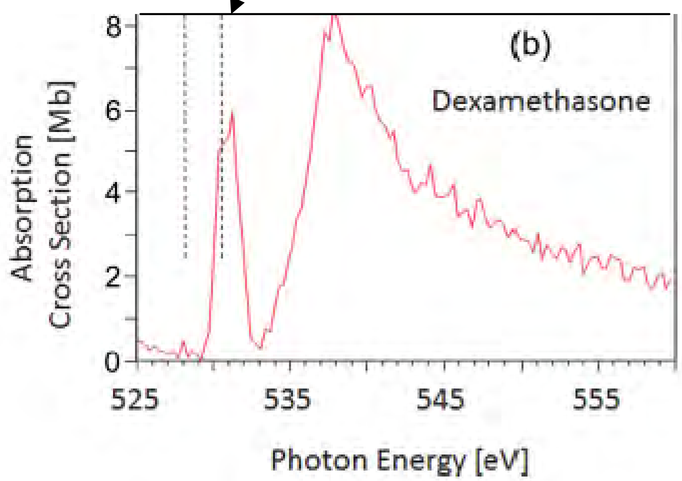
K. Yamamoto et al., Anal. Chem. **61**, 6173 (2015).

Beer Lambert Law

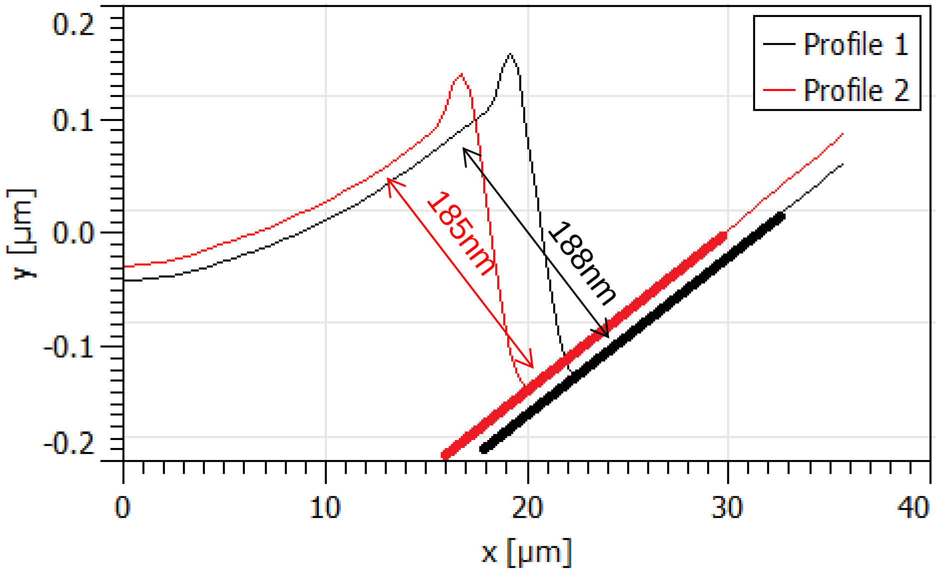
$$\ln\left(\frac{I_0(528.3\ eV)}{I(530.6\ eV)}\right) = \sigma \cdot \frac{N}{V} \cdot d$$

Minimum: Use of two photon energies

Absorption cross section of O 1s→π*: 5.1 ± 0.2 Mb

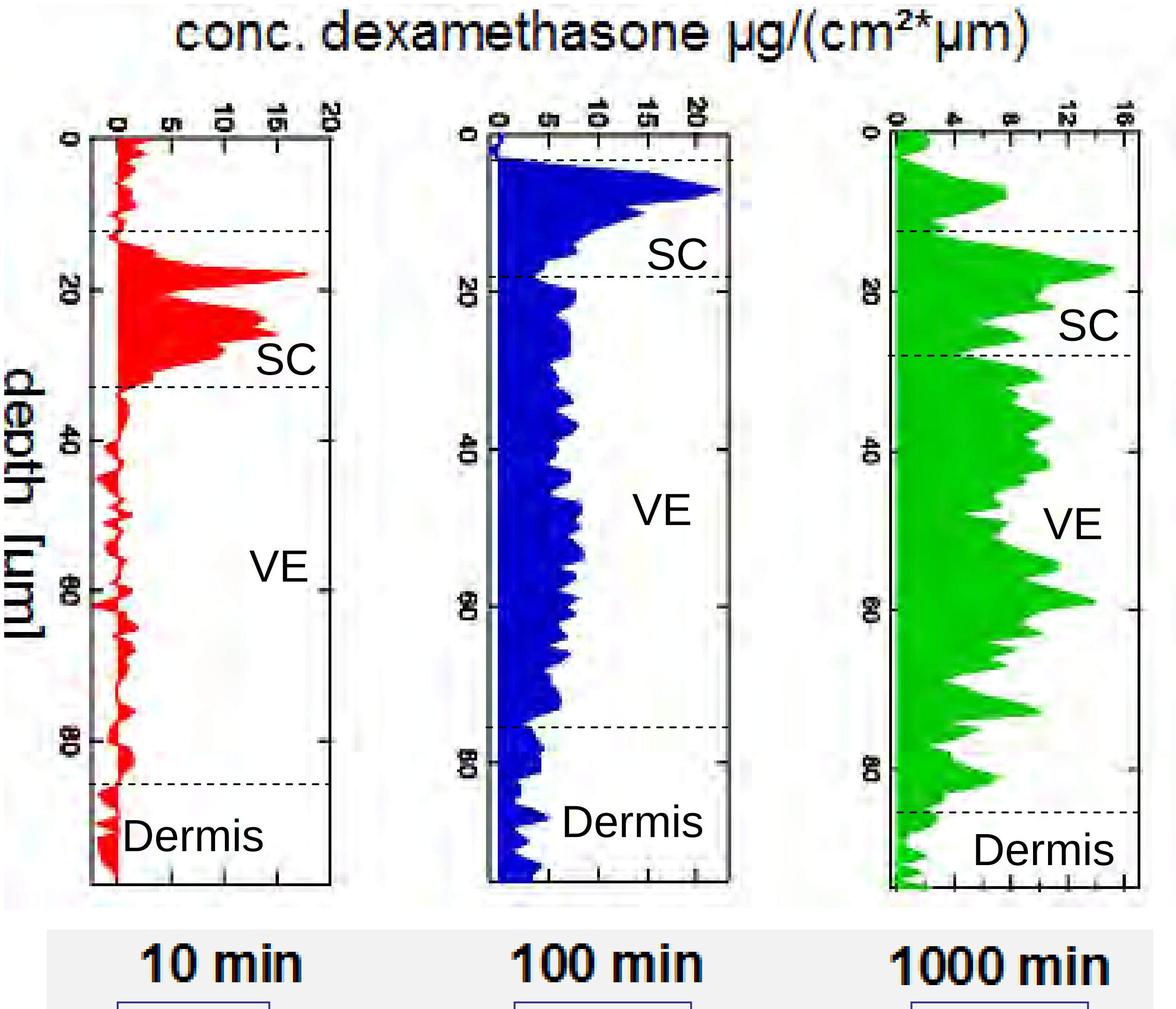


Atomic Force Microscopy



Applied: 600 μg/cm²

Eur. J. Pharm. Bioppharm. **118**, 30 (2017)



80 μg

390 μg

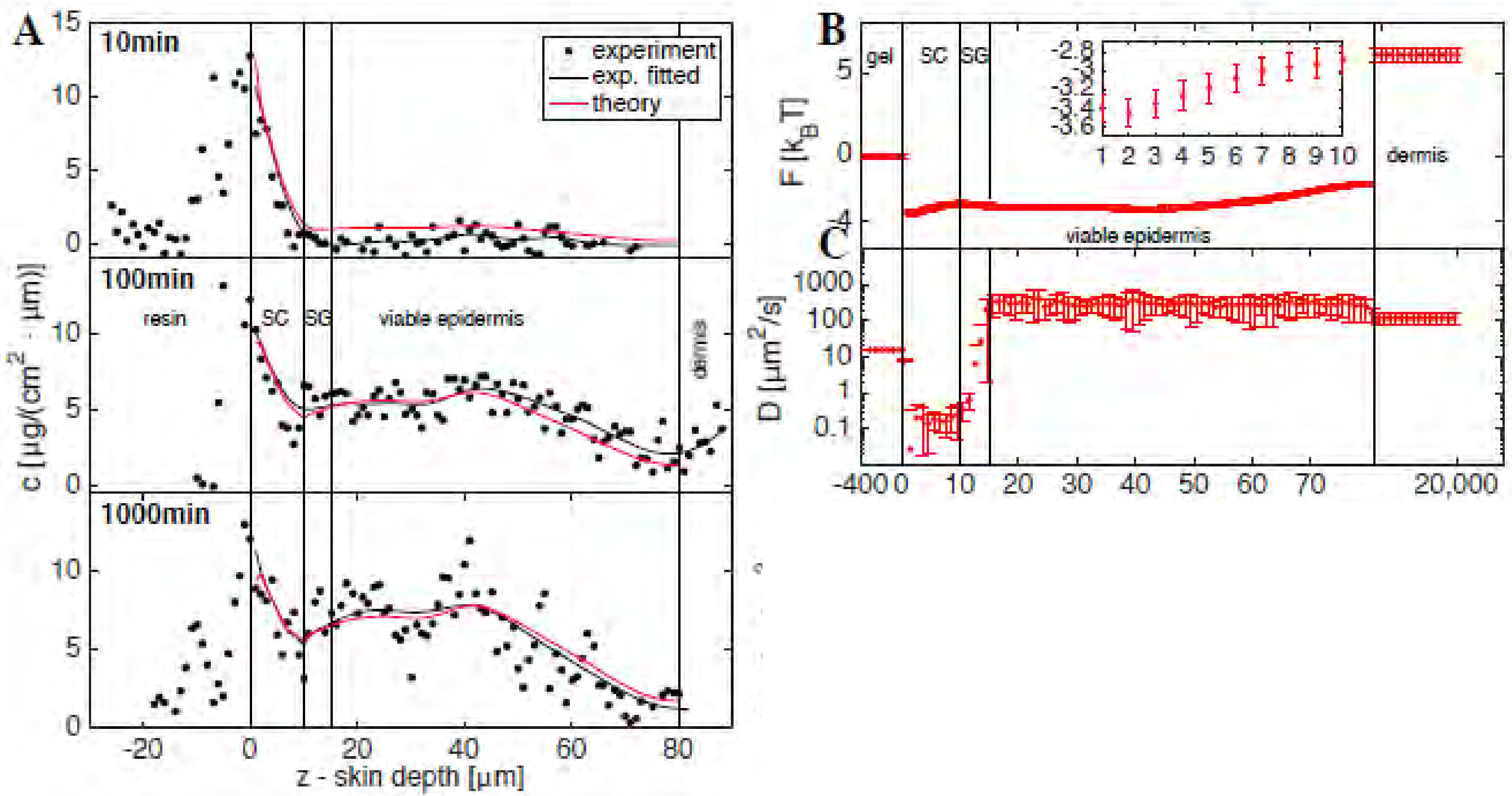
450 μg

Viable Epidermis (VE)

1D-Diffusion Model

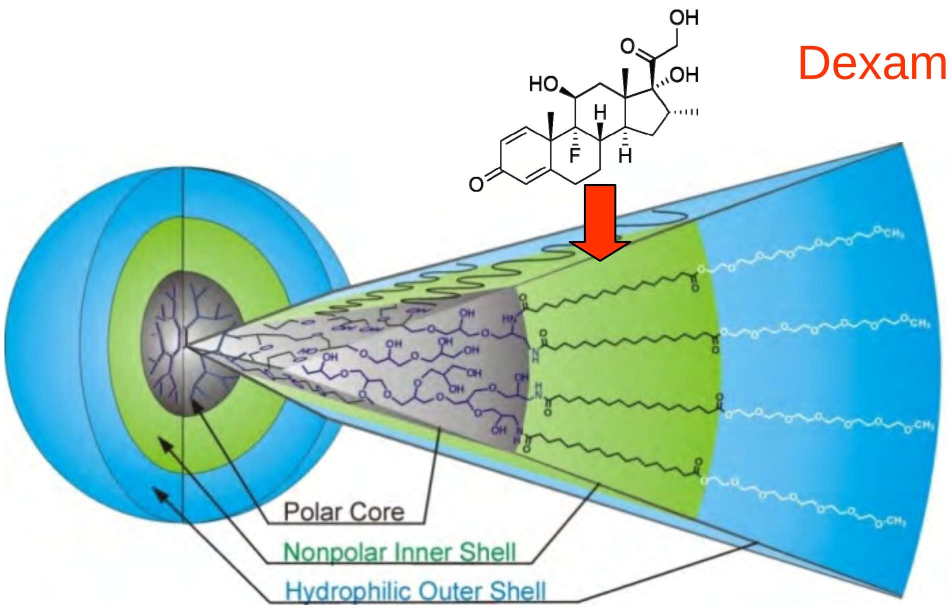
$$\frac{\partial}{\partial t}c(z,t) = \frac{\partial}{\partial z}\left(D(z)e^{-\beta F(z)}\frac{\partial}{\partial z}c(z,t)e^{\beta F(z)}\right)$$

β=1/kT



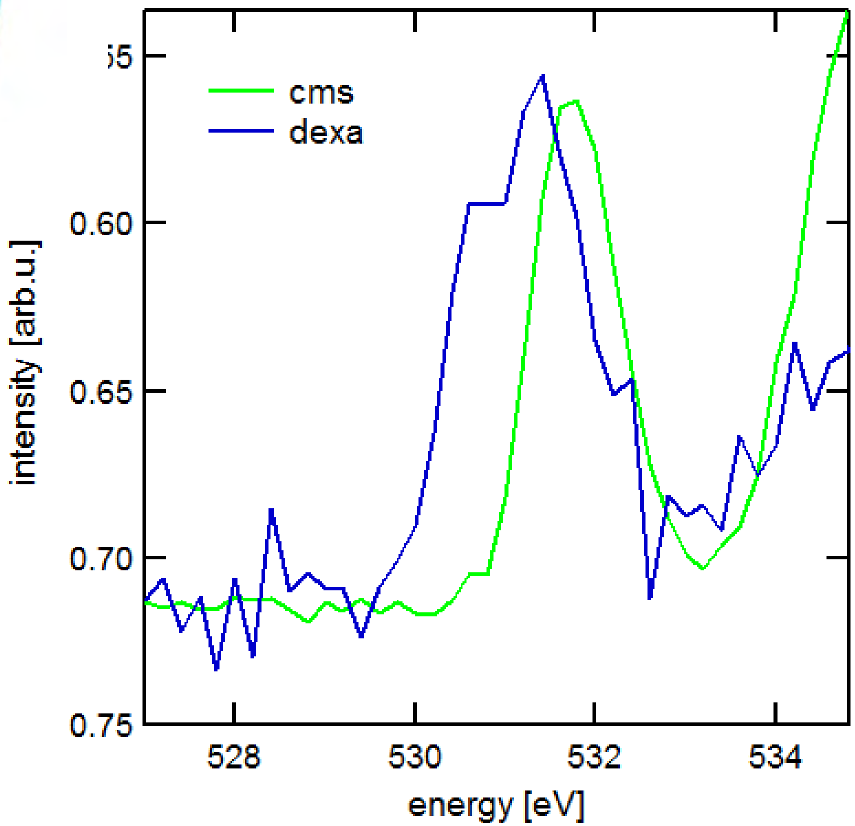
R. Schulz et al., Proc. Nat. Acad.Sci. **114**, 3631 (2017).
R. Schulz et al., Biophys. J. **117**, 998 (2019).

Dexamethasone (DX)



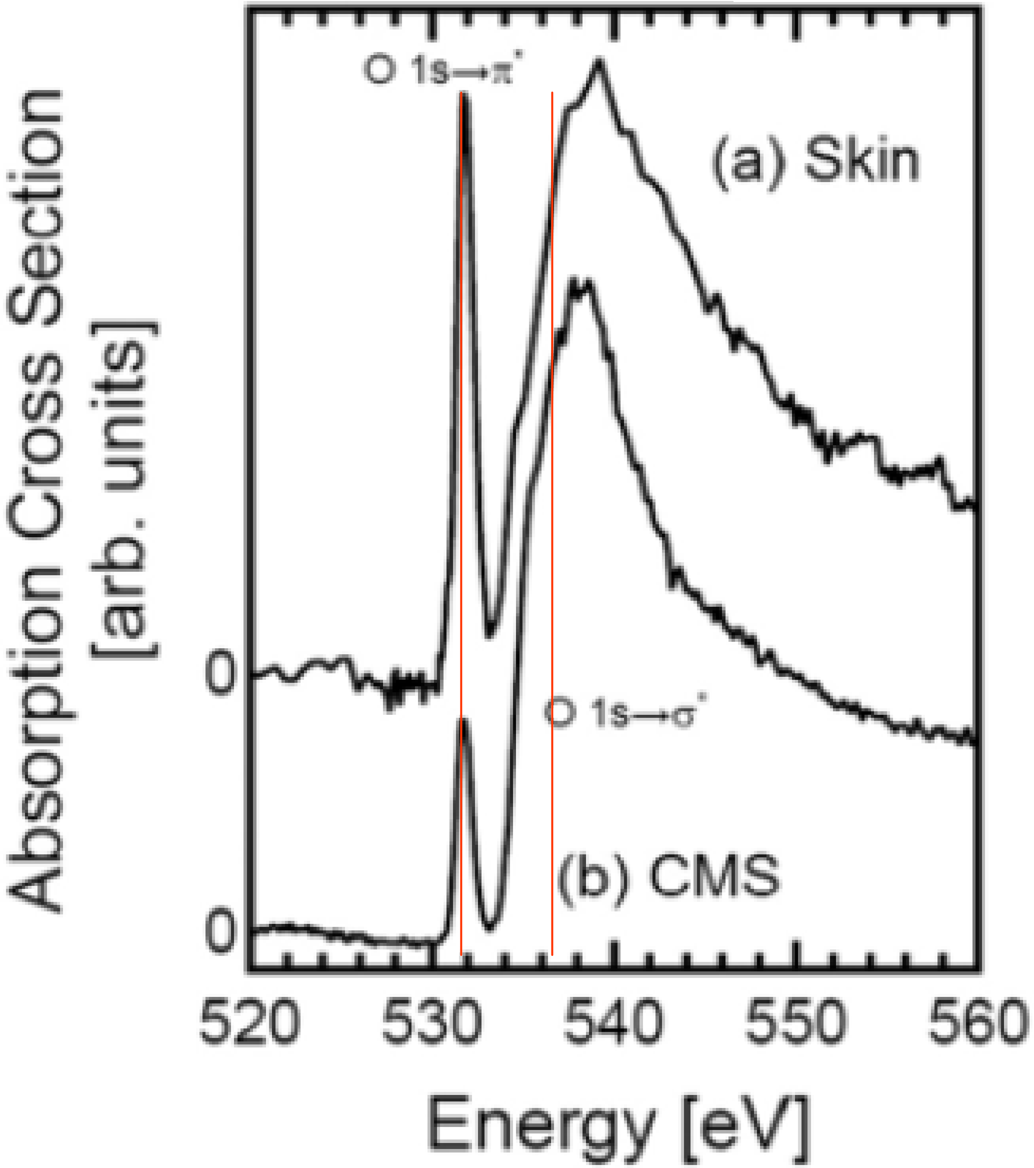
R. Haag et al.

O 1s→π*



- dendritic polyglycerol core
- inner hydrophobic alkyl shell
- outer hydrophilic poly(ethylene glycol) methyl ether shell

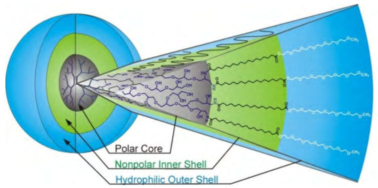
J. Control. Release **242**, 64 (2016)



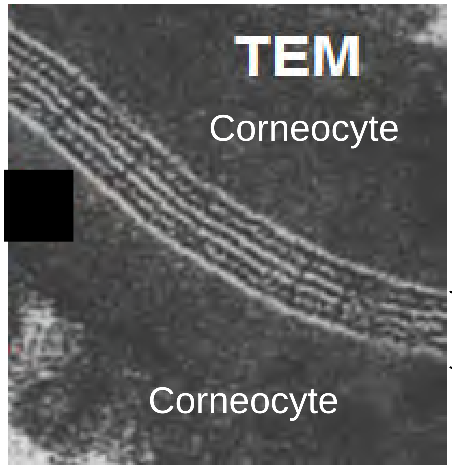
O 1s→π*
(a) Skin
O 1s→σ*
(b) CMS
0
0
Absorption Cross Section [arb. units]
520
530
540
550
560
Energy [eV]

Probing of CMS-Nanocarriers in Human Skin

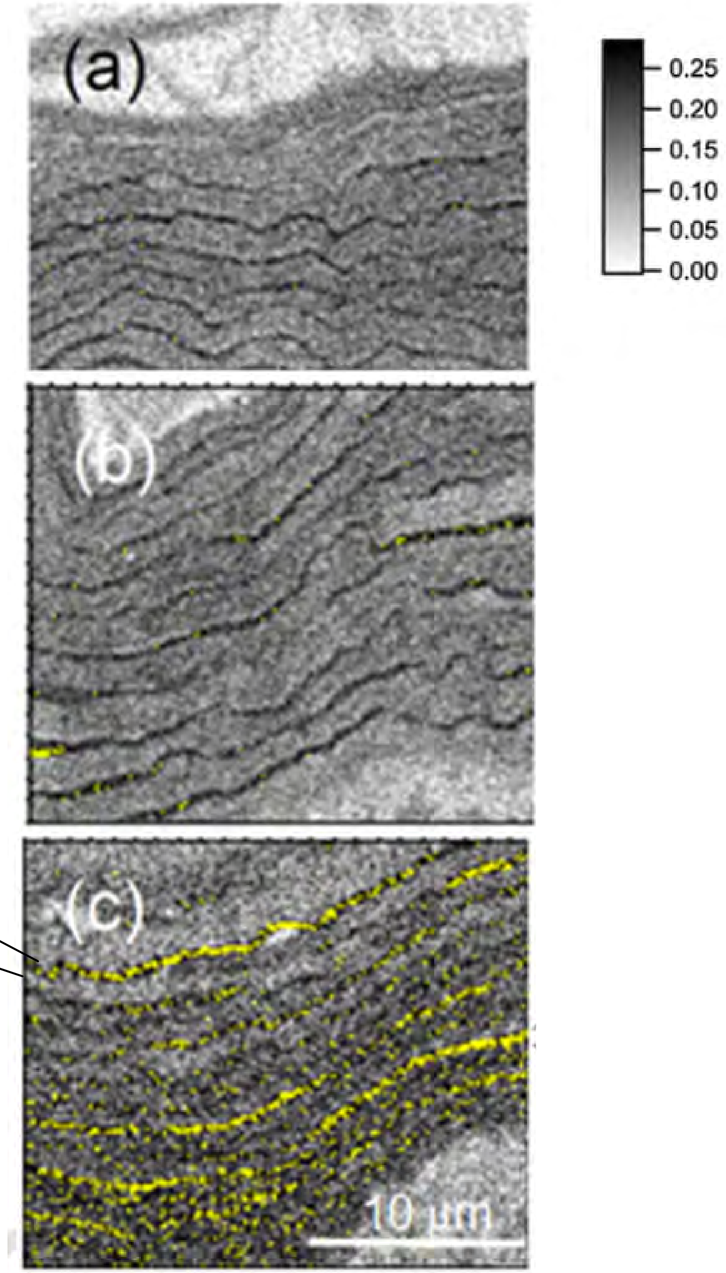
Reference

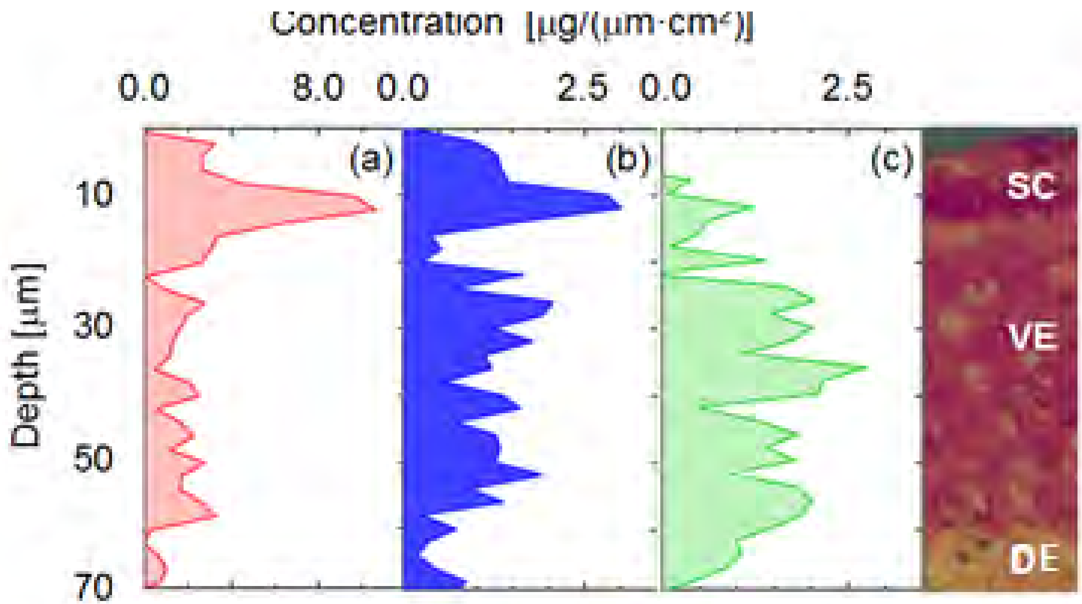


100 min



1000 min





Penetration of DX into Human Skin

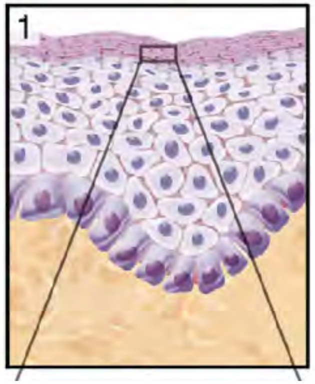
(a) DX in ethanol (4 h)

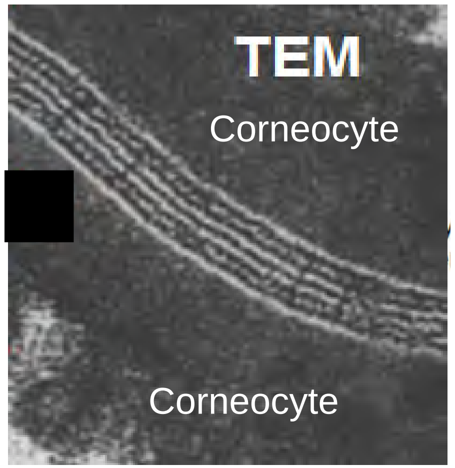
(b) DX in HEC gel (16 h)

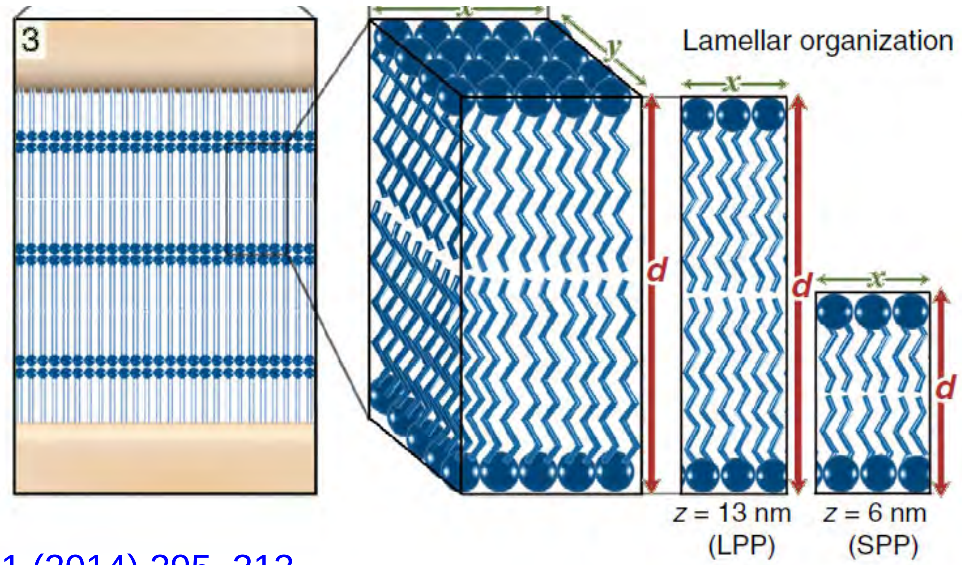
(c) CMS nanocarriers in HEC gel (16 h)

J. Control. Release **242**, 64 (2016)

Human epidermis



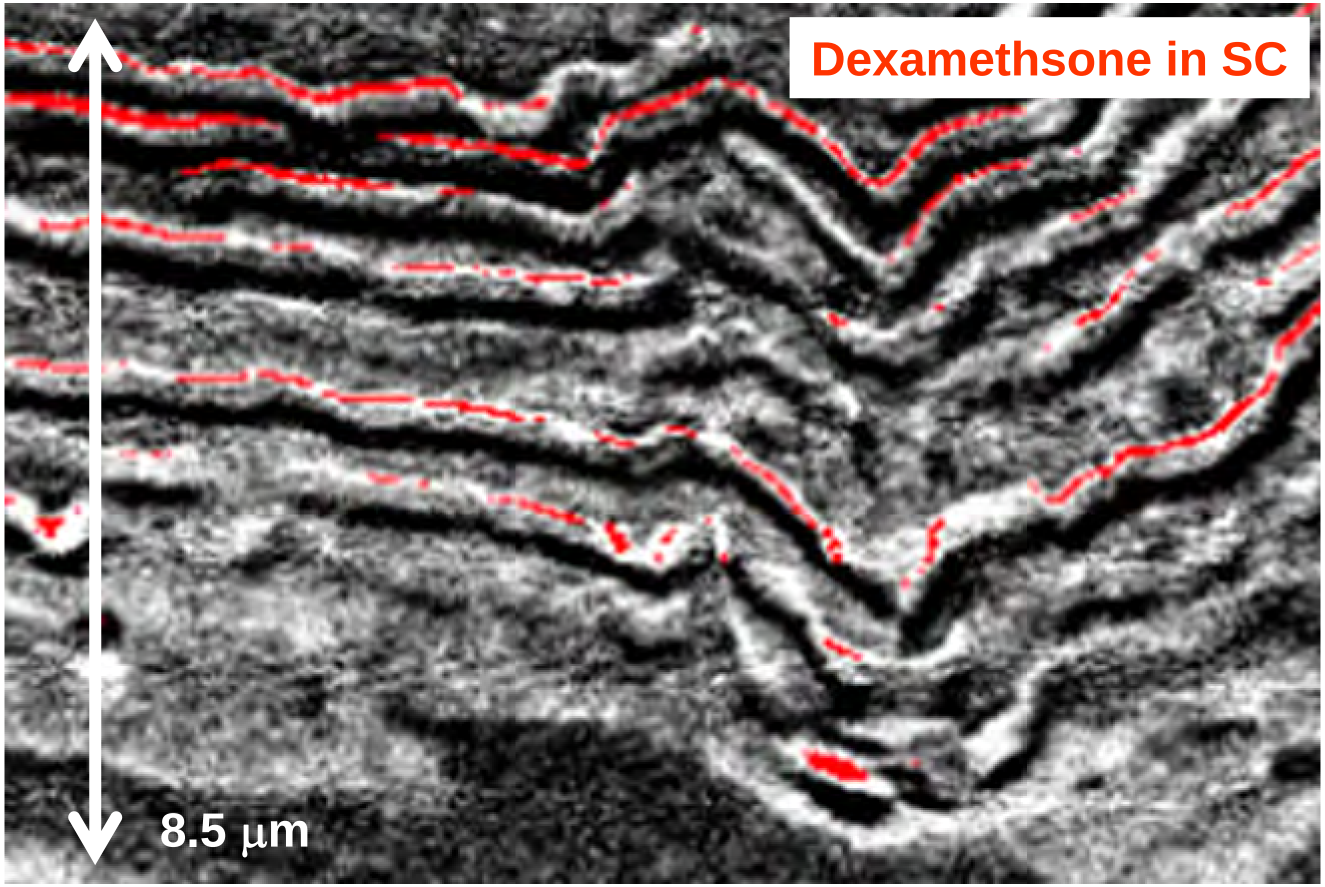


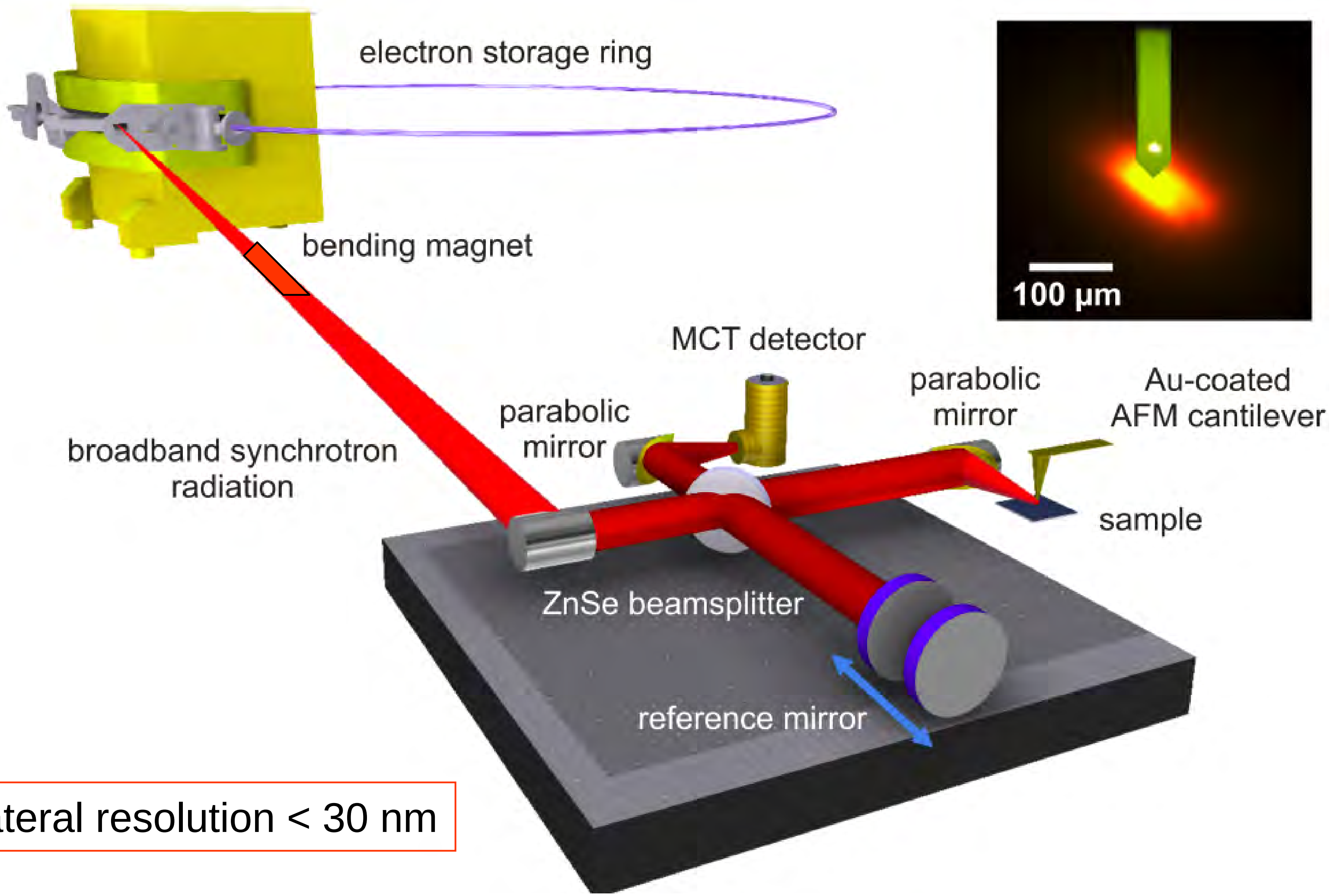


Biochimica et Biophysica Acta 1841 (2014) 295–313

High Spatial Resolution X-Ray Microscopy Studies

High resolution imaging (50 nm step width)





Lateral resolution < 30 nm

P. Herrmann et al., Opt. Express 2013, 2014

Summary and Conclusions

Part I: Isolated Nanoparticles Prepared in Beams

- Universal preparation scheme for nanoscopic matter
- Unique and size-dependent processes beyond the local scale of photoionization
- Novel photoionization processes leading to the emission of fast electrons
- Femtosecond dynamics of surface melting and Coulomb explosion
- Attosecond dynamics of elastic and inelastic scattering processes

Part II: Nanoparticles in Life Sciences

- **Label-Free Detection:** Drug penetration profiles in skin change as a function of time, damage of the skin barrier, and drug formulation.
- **Drug nanocarriers** modify the drug penetration properties, by overcoming the skin barrier(s).
- **High spatial resolution** along with chemical selectivity leads to a detailed understanding of the drug penetration by label-free X-ray microscopy and AFM-based techniques.