

PAUL SCHERRER INSTITUT



Rafael Abela

Structure and Function

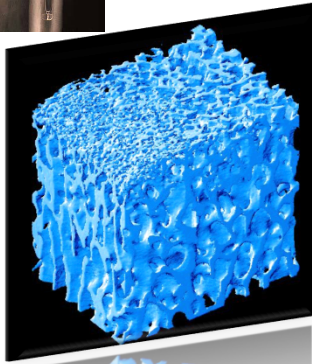
SYMPOSIUM SCHWEIZER SPITZEN MEDIZIN, October 5th, 2017

1. Introduction: static and dynamic
2. Seeing atoms through diffraction
3. FEL in a nutshell
4. Scientific impact: results and “dreams”
5. PSI and Industry

Symposium Schweizer Spitzenmedizin 2017

Materials (in a very broad sense)

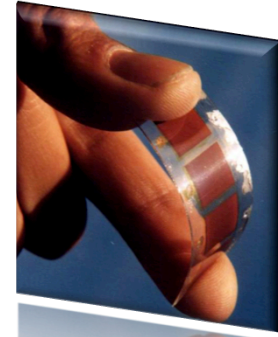
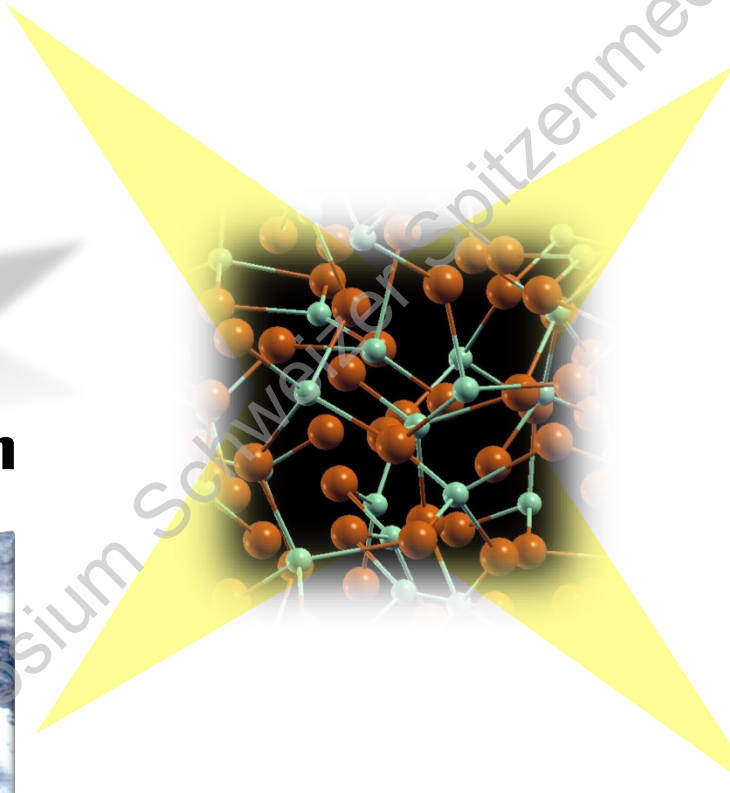
Which are their constituents,
properties, functions?



Medicine/Health

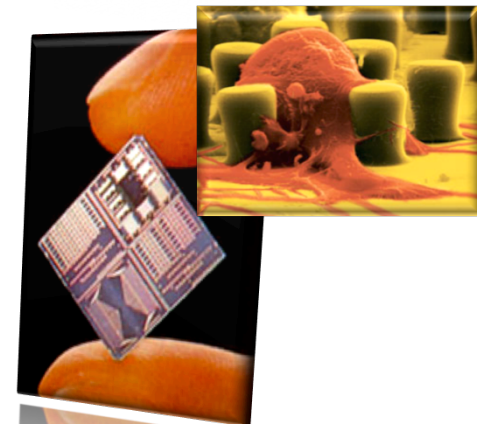


Transport



Energy/

Environment



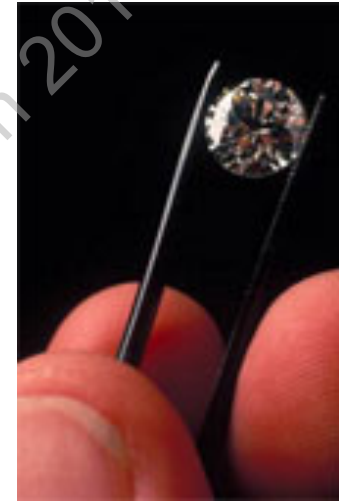
Information/

Communication

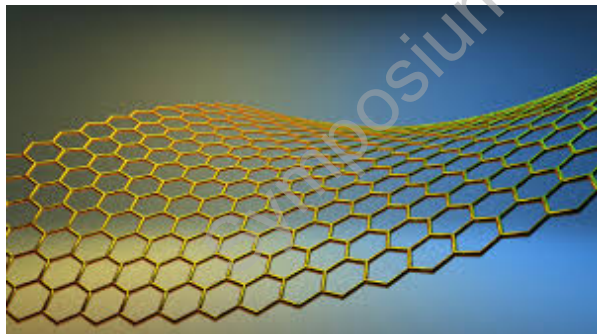
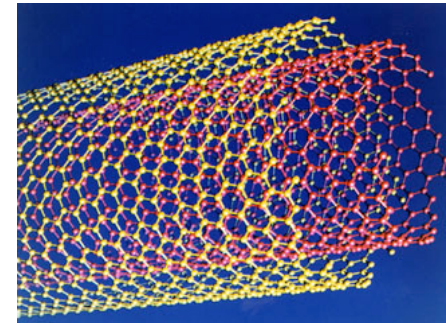


Graphite

Diamond

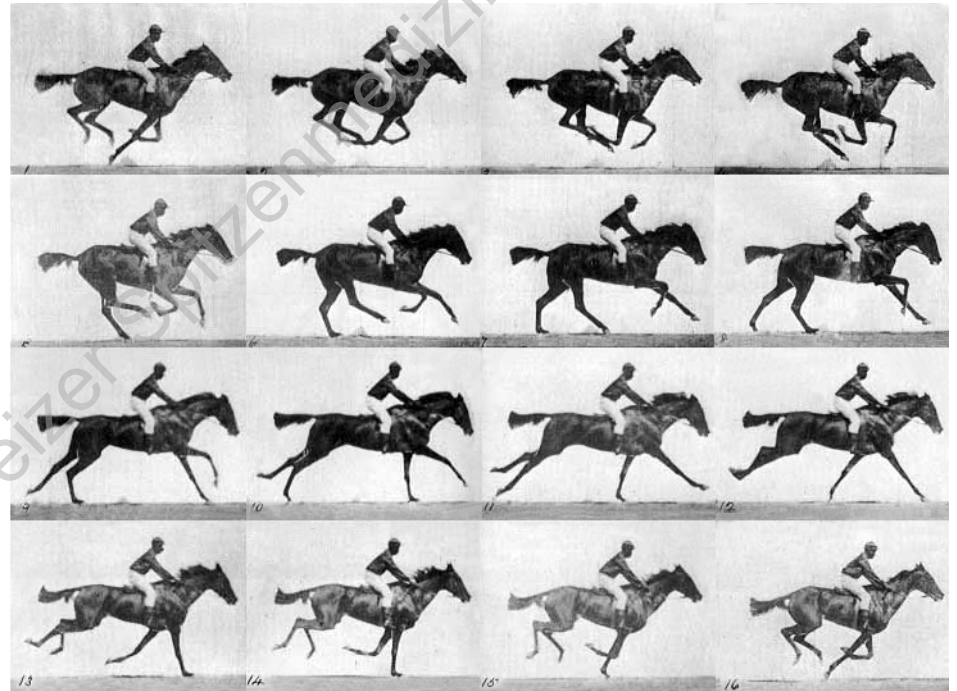
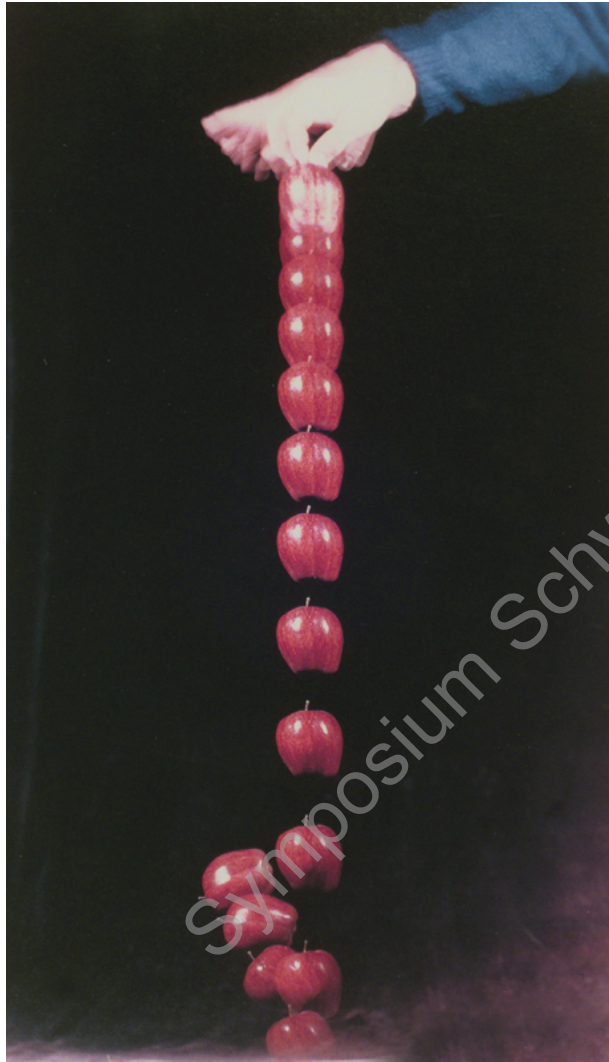


Carbon Nanotubes

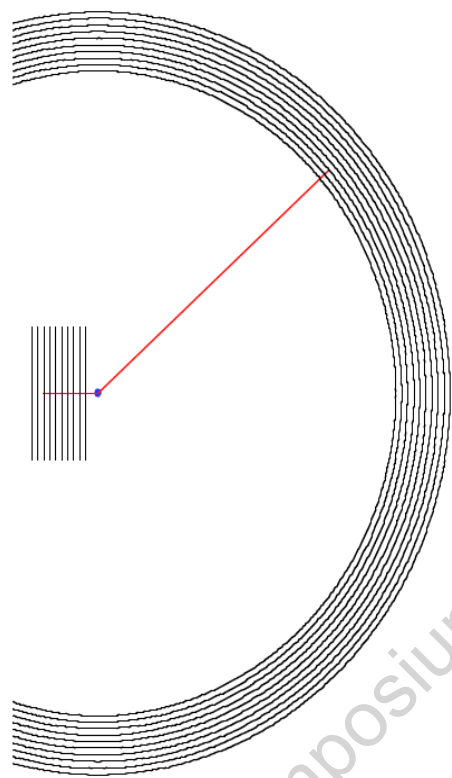


Graphene

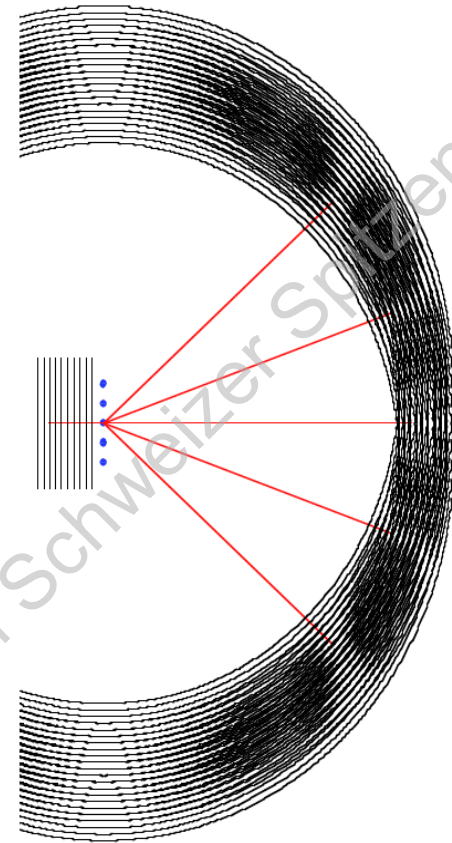
Snapshots with 1- μ second resolution



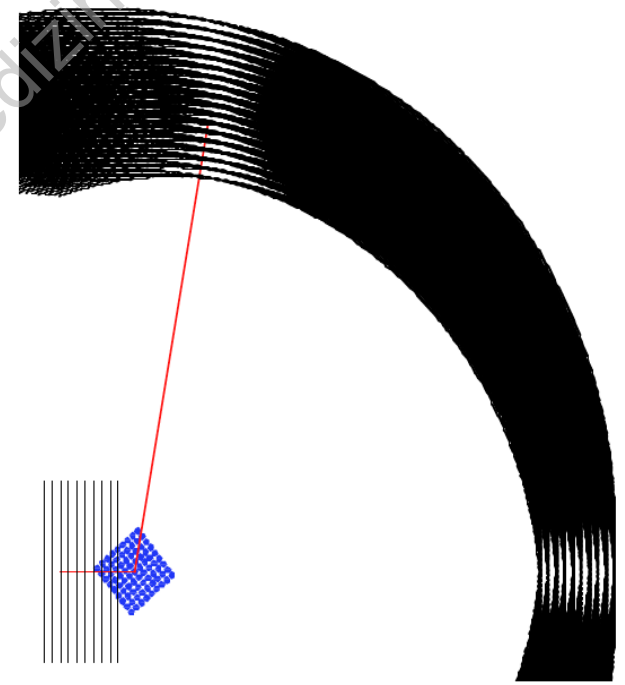
Aside: "seeing" atoms with diffraction: periodic sample



1 atom



5 x 1 atoms



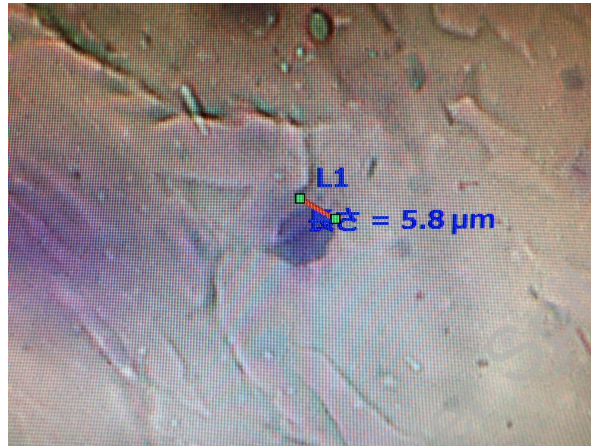
9 x 9 atoms

Bragg's Law (1912):

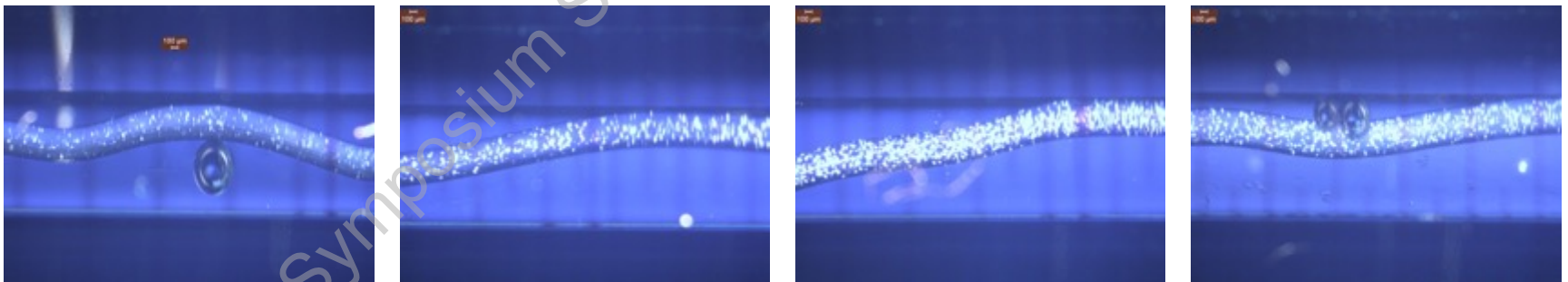
$$\lambda = 2d \sin \theta$$

Fundamental step 1 : produce a „periodic sample“

28%

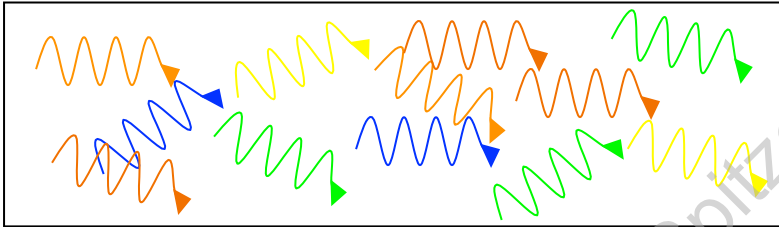


LCP grown crystal optimization for serial crystallography in syringes

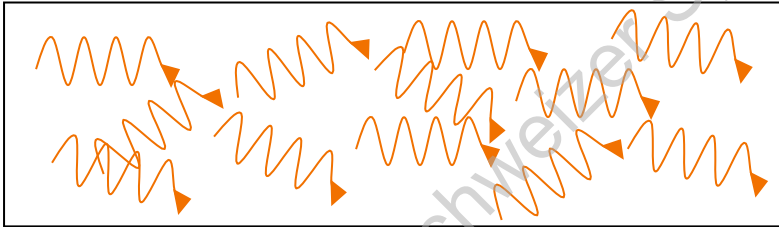


Fundamental step 2 : produce a „powerful light source“

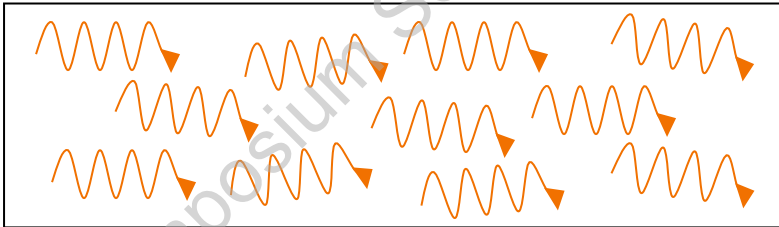
High photon
flux



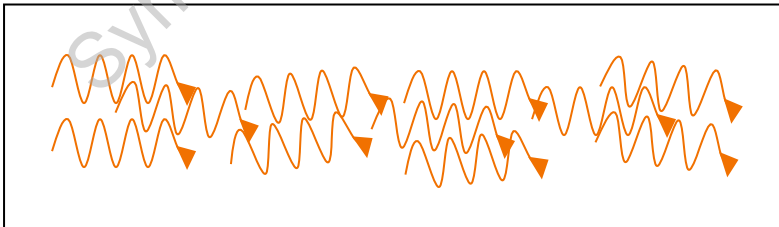
Small freq.
bandwidth



Low
divergence



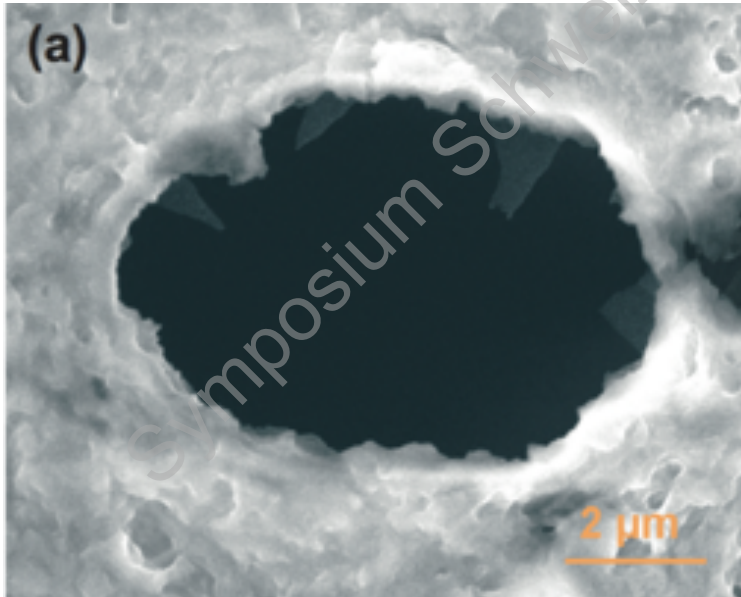
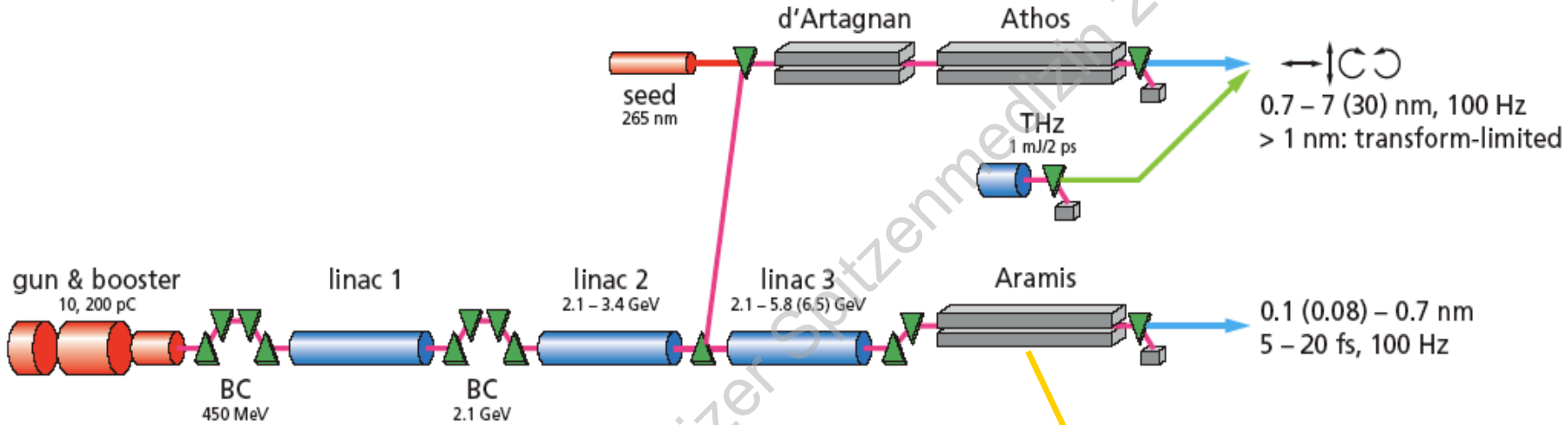
Small source
size



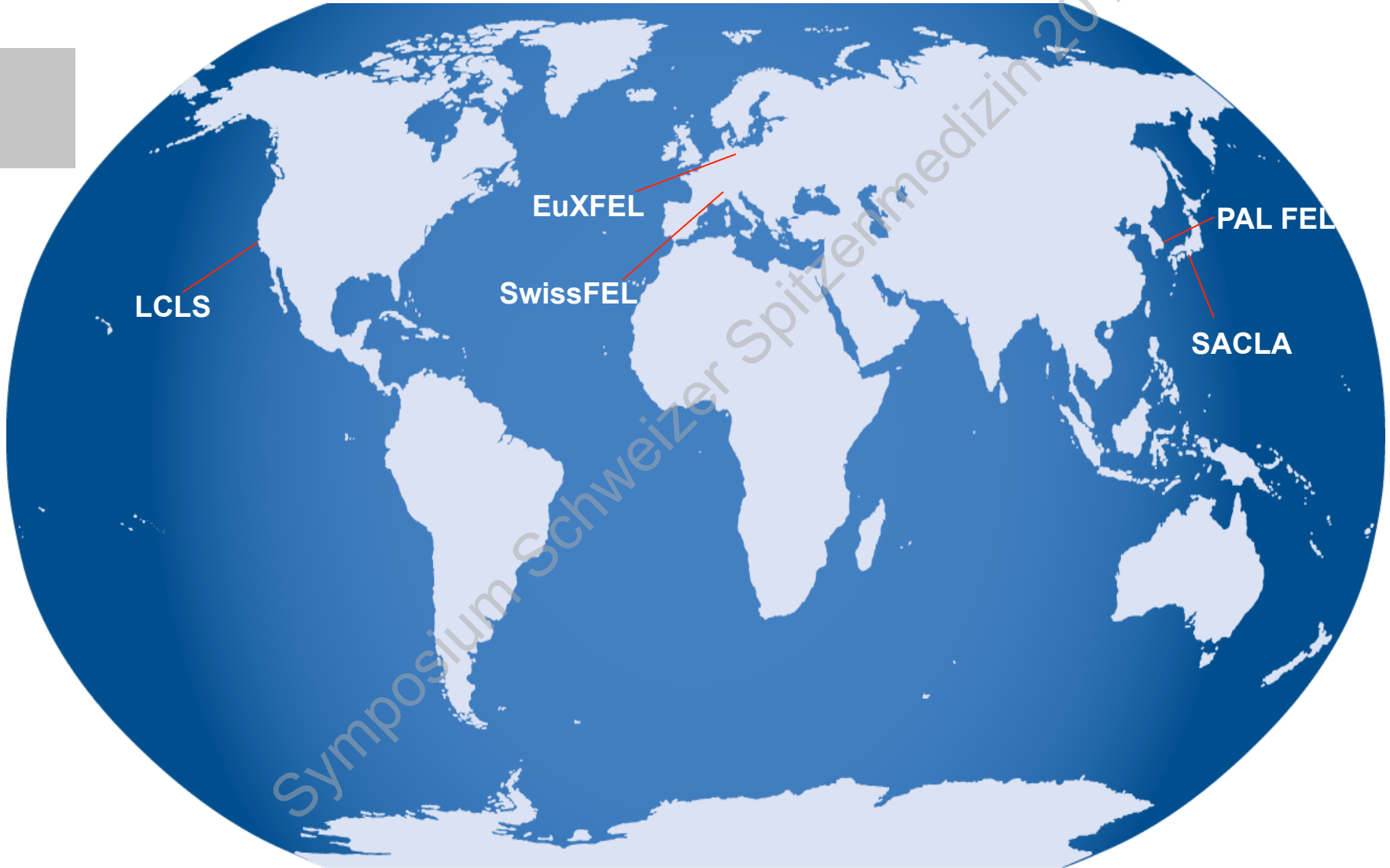
Ultrashort pulsed source

Size = 1 micrometer
Duration = 10 fsec
Photons/pulse = 10^{11}

SwissFEL: Schematische Darstellung



X-ray FEL Projects Around the World



LCLS

SwissFEL

EuXFEL

SACLA

PAL FEL

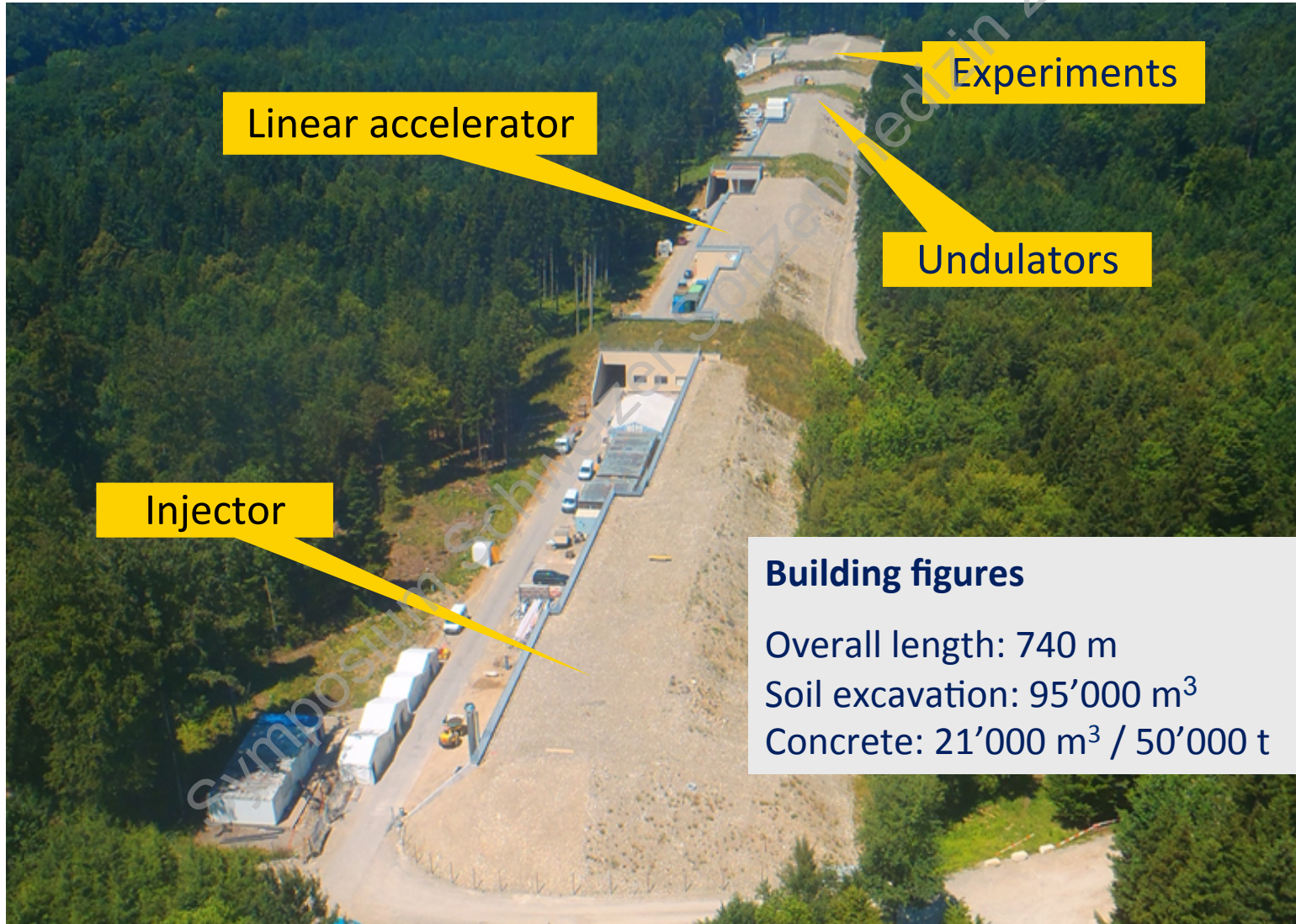
Fundamental step 3: Advanced technologies for sample delivery



SwissFEL: in the forest



SwissFEL construction site



Injector

Linear accelerator

Undulators

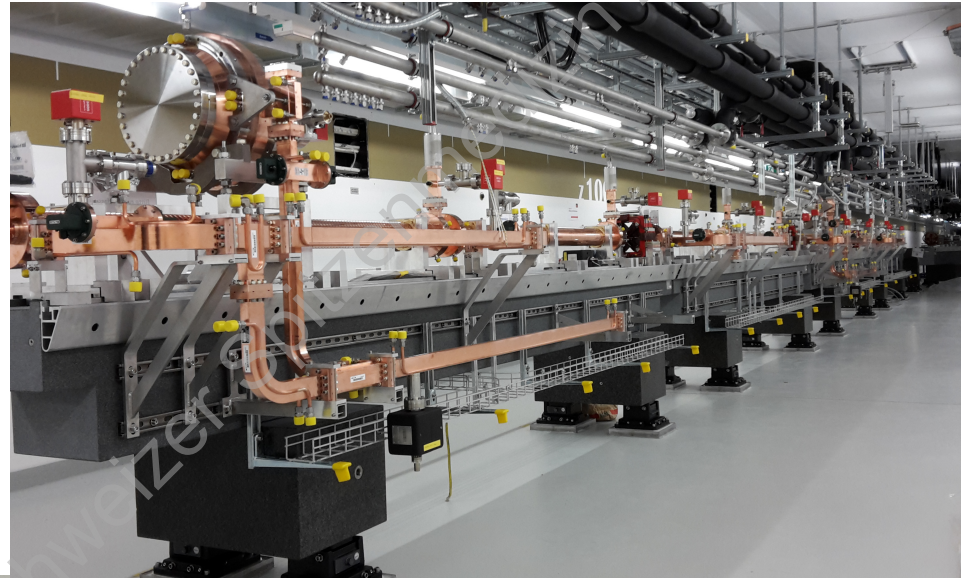
Experiments

Building figures
Overall length: 740 m
Soil excavation: 95'000 m³
Concrete: 21'000 m³ / 50'000 t

First Users at SwissFEL

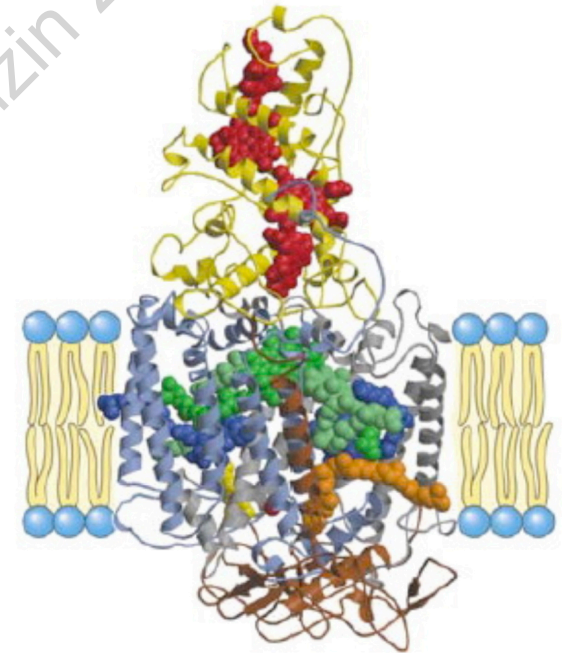


Accelerator / Undulators



Membrane protein drug targets

- **Membrane proteins** targets make some of the most successful medicines to date.
- Most tractable membrane targets have been successfully mined leaving the most **challenging targets yet to be addressed**
- **Structure based drug design** will unlock challenging membrane protein targets (GPCR, ion channel, transporter)



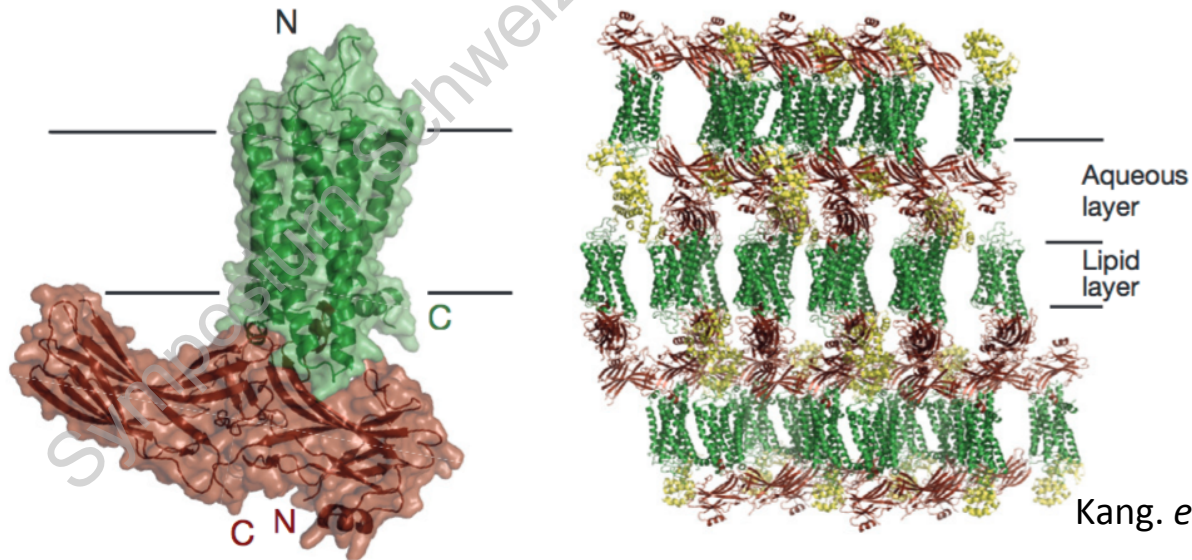
Difficult membrane protein complexes

ARTICLE

doi:10.1038/nature14656

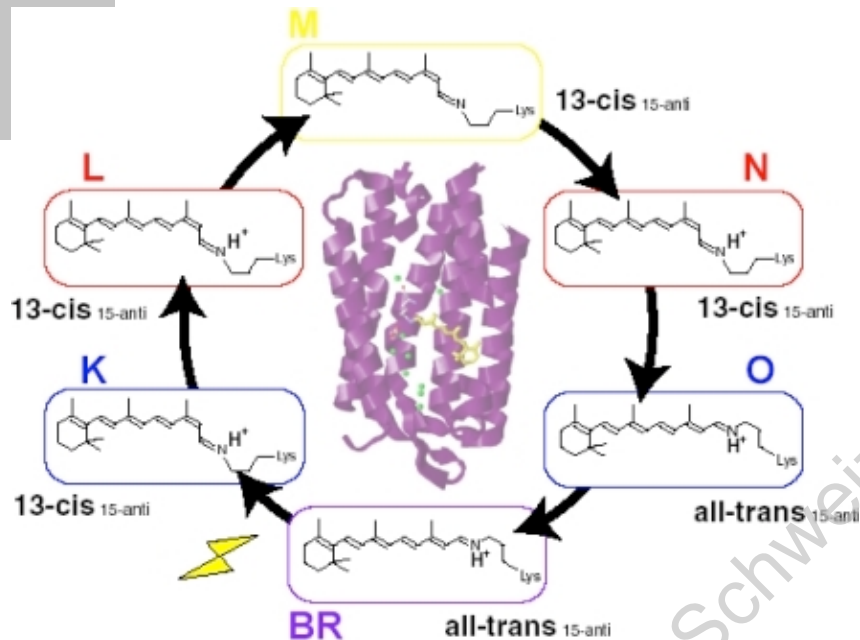
Crystal structure of rhodopsin bound to arrestin by femtosecond X-ray laser

Yanyong Kang^{1*}, X. Edward Zhou^{1*}, Xiang Gao^{1*}, Yuanzheng He^{1*}, Wei Liu², Andrii Ishchenko³, Anton Barty⁴, Thomas A. White⁴, Oleksandr Yefanov⁴, Gye Won Han³, Qingping Xu⁵, Parker W. de Waal¹, Jiyuan Ke¹, M. H. Eileen Tan^{1,6}, Chenghai Zhang¹, Arne Moeller⁷, Graham M. West⁸, Bruce D. Pascal⁸, Ned Van Eps^{9†}, Lydia N. Caro¹⁰, Sergey A. Vishnivetskiy¹¹, Regina J. Lee¹¹, Kelly M. Suino-Powell¹, Xin Gu¹, Kuntal Pal¹, Jinming Ma¹, Xiaoyong Zhi¹, Sébastien Boutet¹², Garth J. Williams¹², Marc Messerschmidt^{12,13}, Cornelius Gati⁴, Nadia A. Zatsepin^{2,14}, Dingjie Wang^{2,14}, Daniel James^{2,14}, Shibom Basu^{2,14}, Shatabdi Roy-Chowdhury^{2,14}, Chelsie E. Conrad², Jesse Coe², Haiguang Liu^{2,15}, Stella Lisova², Christopher Kupitz^{2,16}, Ingo Grotjohann², Raimund Fromme², Yi Jiang¹⁷, Minjia Tan¹⁷, Huaiyu Yang¹⁷, Jun Li⁹, Meitian Wang¹⁸, Zhong Zheng¹⁹, Dianfan Li²⁰, Nicole Howe²⁰, Yingming Zhao^{13,21}, Jörg Standfuss²², Kay Diederichs²³, Yuhui Dong²⁴, Clinton S. Potter⁷, Bridget Carragher⁷, Martin Caffrey²⁰, Hualiang Jiang¹⁷, Henry N. Chapman^{4,25}, John C. H. Spence^{2,14}, Petra Fromme², Uwe Weierstall^{12,14}, Oliver P. Ernst^{10,26}, Vsevolod Katritch⁹, Vsevolod V. Gurevich¹, Patrick R. Griffin⁸, Wayne L. Hubbell⁹, Raymond C. Stevens^{3,19,27}, Vadim Cherezov³, Karsten Melcher¹ & H. Eric Xu^{1,28}

Kang. *et al.*, *Nature*, 2015

Light-triggered 7 TM proteins (LBR Proposals)

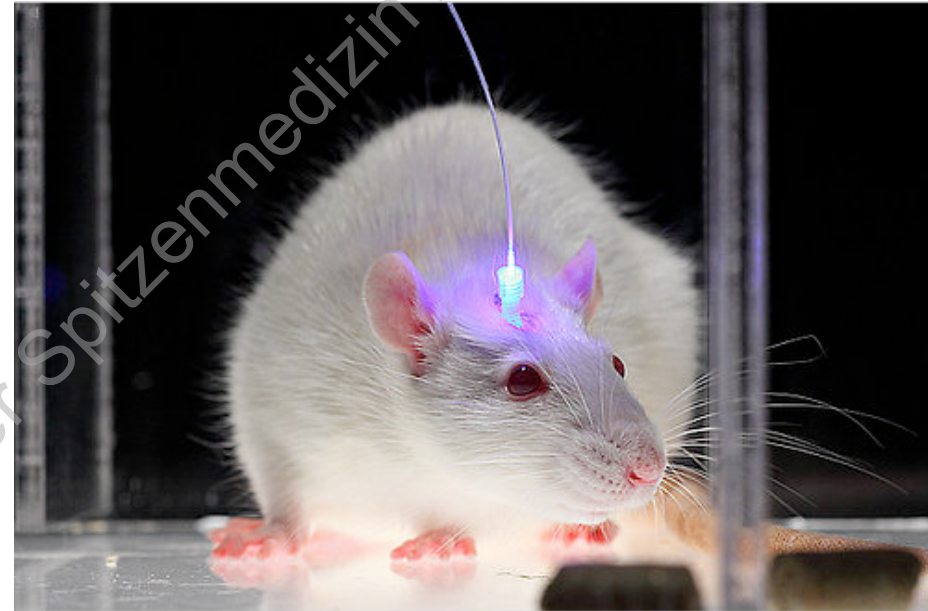
Structural Dynamics from fs to ms



Light-triggered 7TM proteins:

- G protein-coupled receptors
- Light-gated channels
- Light-driven ion pumps
- Light-driven proton pumps

Optogenetic Applications



Function of light-triggered 7TM proteins:

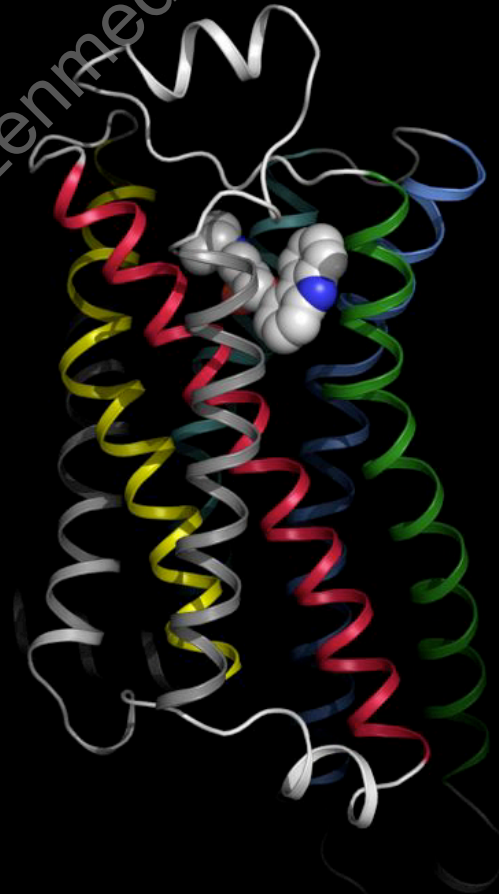
- Vision, Regulation of circadian cycle
- Phototaxis
- Preservation of ion gradients
- Generation of Energy

„Dream“

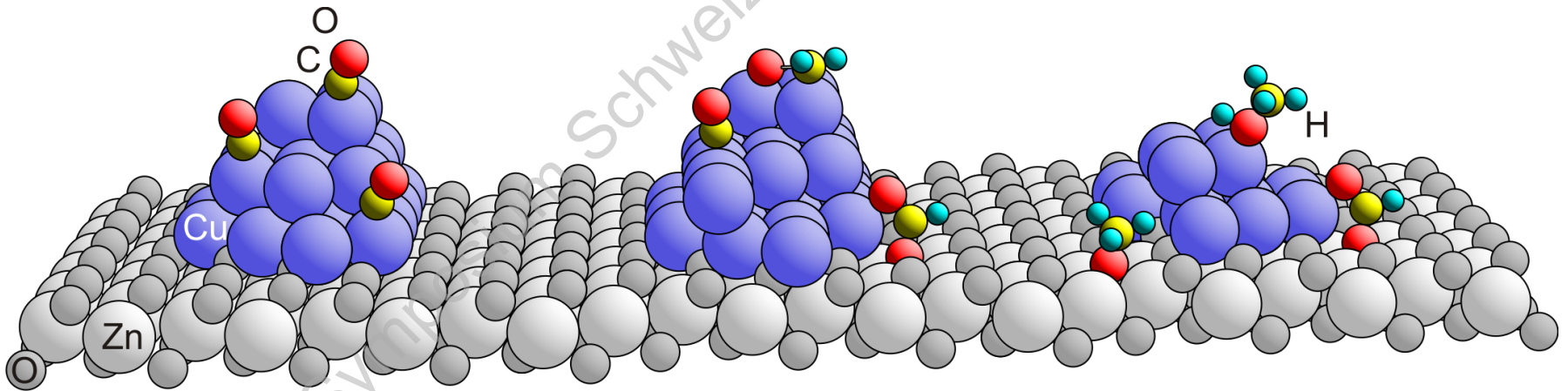
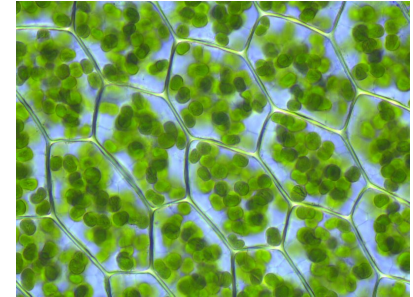
FEL enabled visualization of:

- Binding trajectory of ligands
- Binding intermediates
- Conformational changes upon signaling
- Structural basis of biased signaling

MD simulation b-adrenergic receptor and carvedilol by Xavier Deupi



Catalysis



PSI and Industry

Swiss Free Electron
Laser

SLS

LBR

lead:pro



LeadXpro AG – company at a glance



Single shot experiments are a speciality of Switzerland!

