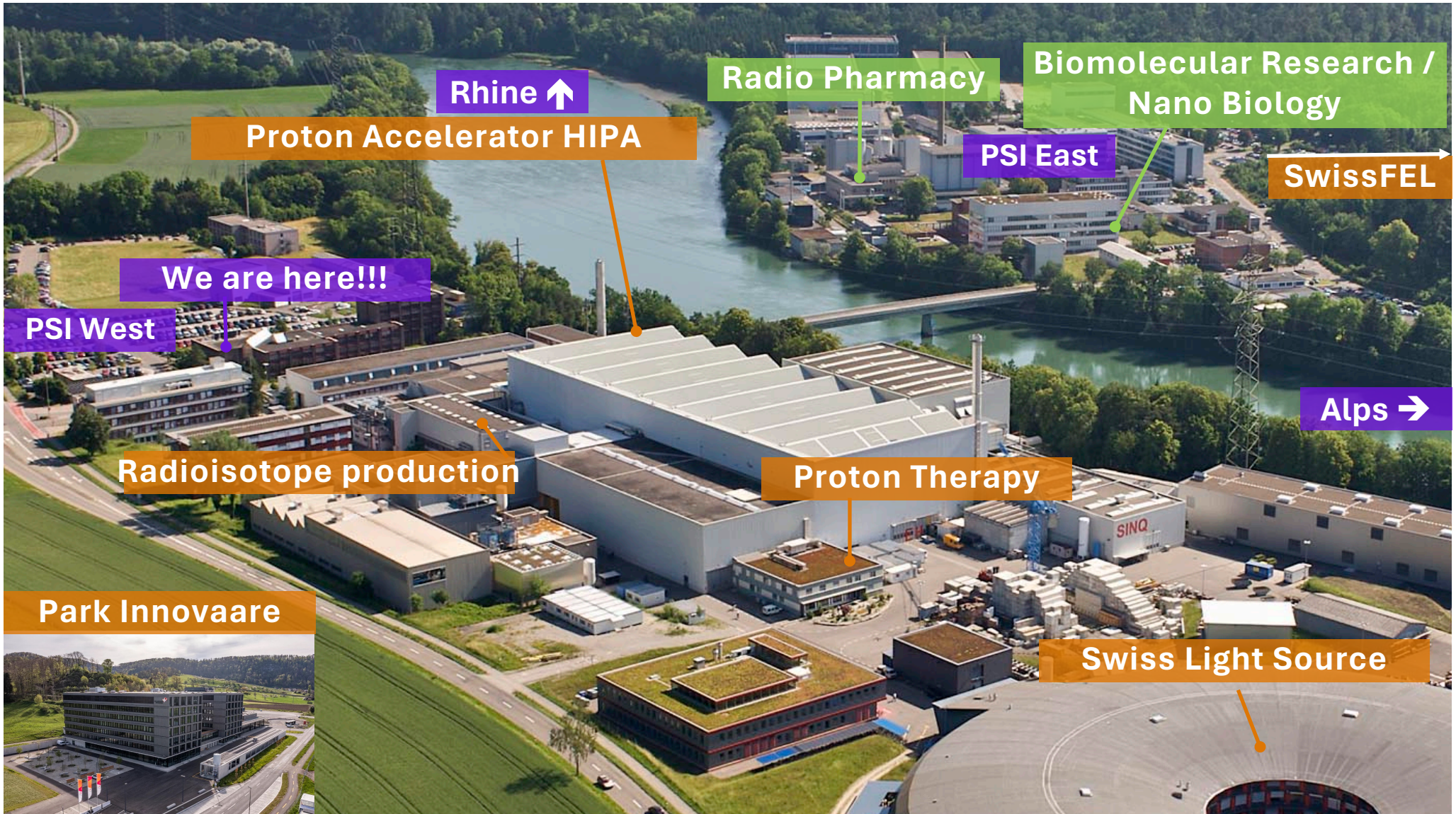
PSI Center for Life Sciences

Biomedical research in the PSI Center for Life Sciences

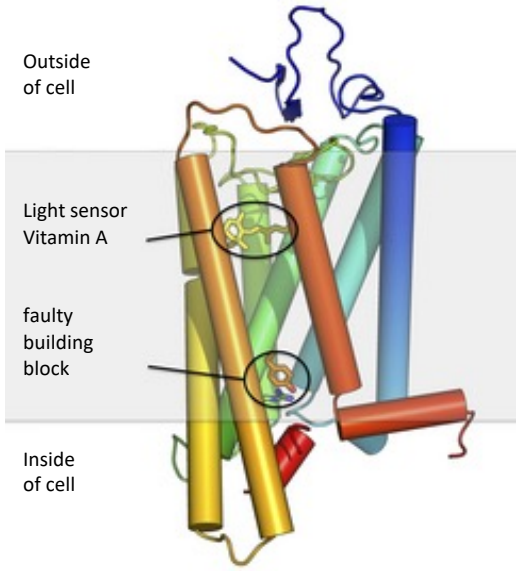
Dr. Jörg Standfuss::Laboratory Head and Group Leader
10.07.2024

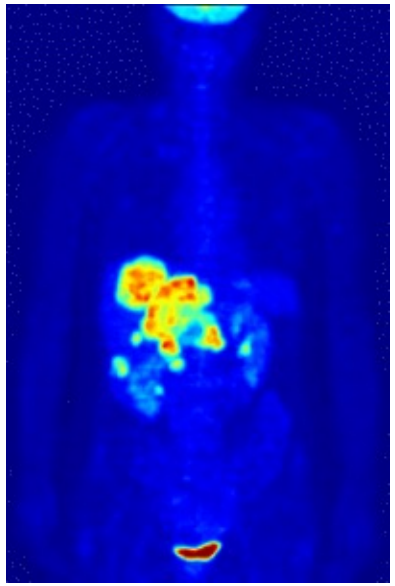
PSI Center for Life Sciences and relevant Large-scale Infrastructure



Biology and Health at the PSI Center for Life Sciences

Three laboratories take advantage of accelerator-based technologies to analyze biological samples





Biomedical Research

Structural biology and the targeted development of new drugs

Jörg Standfuss

⇒ Accelerators: **SwissFEL, SLS**

Nanoscale Biology

Sub-cellular structures and cell states and their relevance for disease.

G.V. Shivashankar

⇒ Accelerators: **SLS**

Radio Pharmaceuticals

Diagnosis and therapy of tumours

Roger Schibli

⇒ Accelerators: **HIPA, SINQ**

Proton Therapy

Destruction of tumours and protection of healthy tissue

Damian Weber

⇒ Accelerators: **COMET**

The PSI Center Life Science

highly competitive research center with a strong fundamental research program with potential for clinical applications

Primary mission of the center:

The research activities at CLS is to demonstrate the value of the unique infra-structure at PSI for ***curiosity-driven*** *and* ***translational*** *research in the areas of* ***structural biology, molecular pharmacology, radiopharmaceutical sciences****. The division is also taking into consideration the increasing relevance of novel* ***imaging and computational approaches*** *in biomedical research.*

Multi-scale biology at the PSI Center Life Sciences

Three laboratories bridge biological scales from molecules over cells to patients

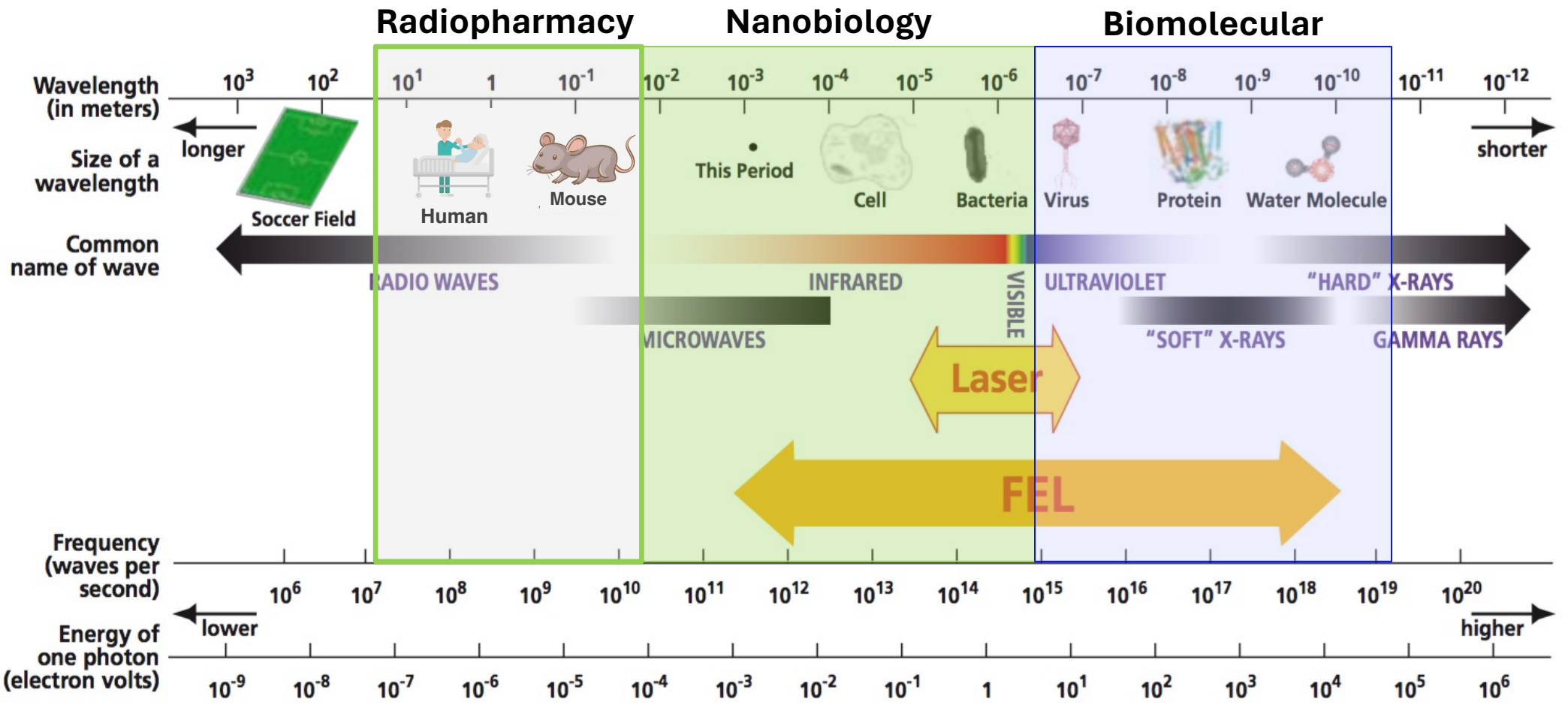


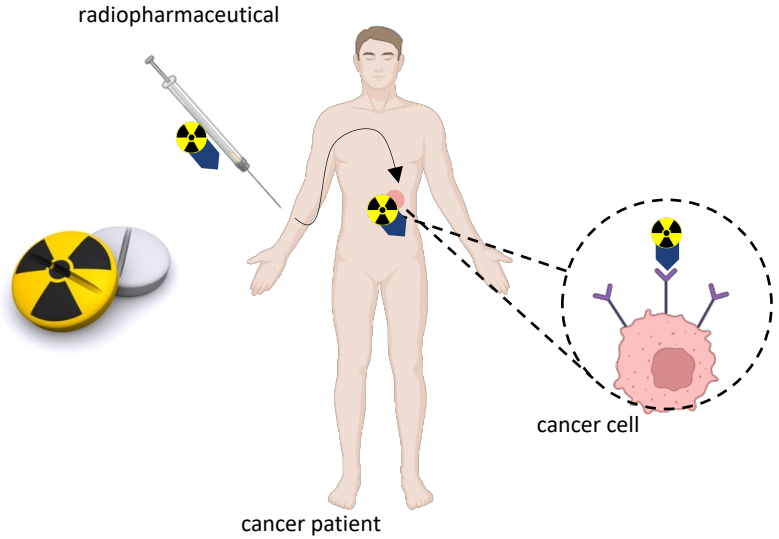
Fig. M.2. The wavelength range of a FEL vs. a quantum laser. Source: Advanced Light Source, Berkeley.

Radiopharmacy and Health

Radioisotopes are everywhere:
Bananas contain Potassium-40. **But** you would have to eat **600 bananas per second** before you have to worry about radiation. The lab journal's from Marie Curie will be poisonous for the **next 1600 years** due to Radium-226.

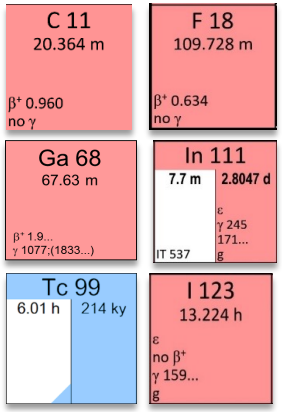
Radiopharmacy finds:
➔ Right kind of radioisotopes
➔ Methods to get them to the right spot
to affect specific tissues

Radiopharmaceuticals: A Special Class of Drugs Offering Unique Opportunities in cancer diagnosis and therapy

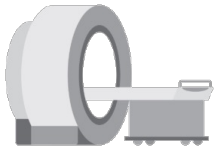


Diagnosis

γ, β^+



Non-invasive *in vivo* imaging



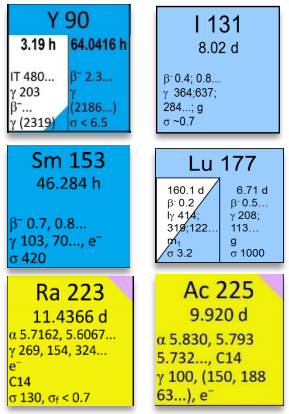
PET or SPECT

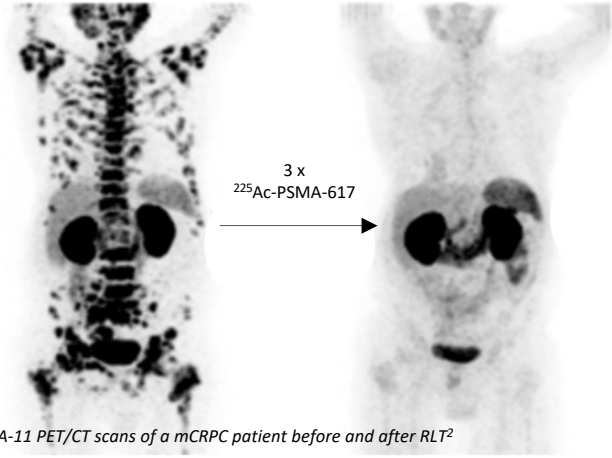
^{68}Ga-DOTATATE PET/CT of a duodenal NET patient[1]

Therapy

α, β^-

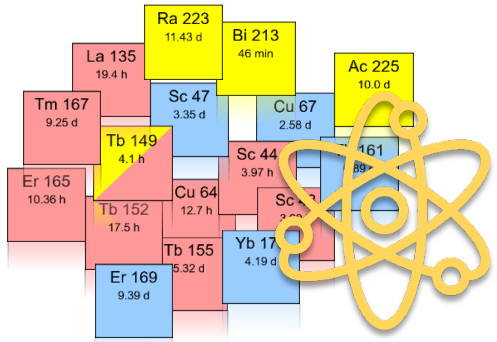
Radioligand therapy (RLT)





^{68}Ga-PSMA-11 PET/CT scans of a mCRPC patient before and after RLT[2]

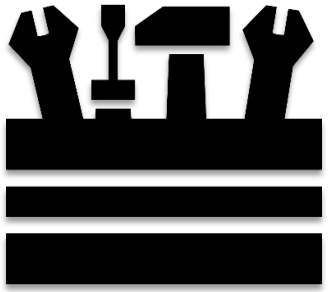
Strategy of RP@CLS: Expand the *Toolbox* in Radiopharmacy



Radionuclide diversity

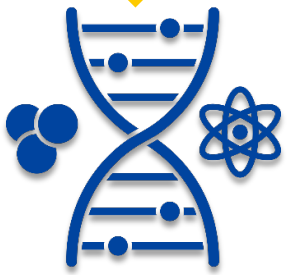
Synthetic versatility and efficiency ligand design

Medical Need



Medical solution

Combination therapies



Understanding radiobiology

PSI hosts the leading Swiss competence center in radiopharmaceutical sciences

Swiss-wide unique capabilities for medically relevant *on-site* radionuclide production and assessment for *clinical applications*.

→ *Bench-to-bedside capabilities* for radio-pharmaceuticals for diagnosis and therapy

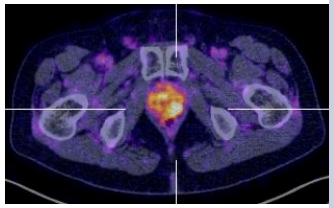
- Leading research expertise in *cancer diagnosis and treatment* using radionuclides
- Animal and GMP facility in radioactive zone

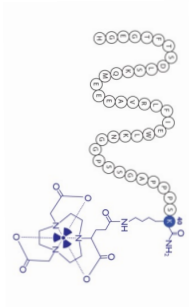
→ Production of tracers for *local hospitals* (Ga68 PSMA)

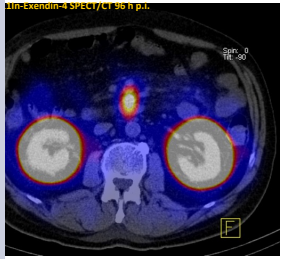
→ *PSI generated IP* is used to generate Spin-Offs and/or licence income

Kantonsspital Aarau

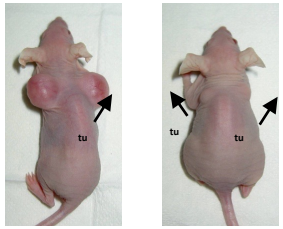
Ga-68 PET/CT

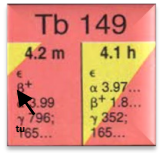




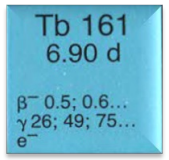


Control Treated

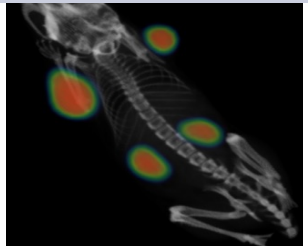


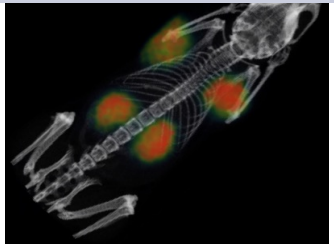


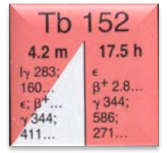
therapy with alpha particles



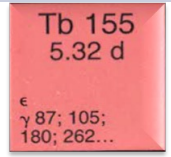
therapy with beta particles





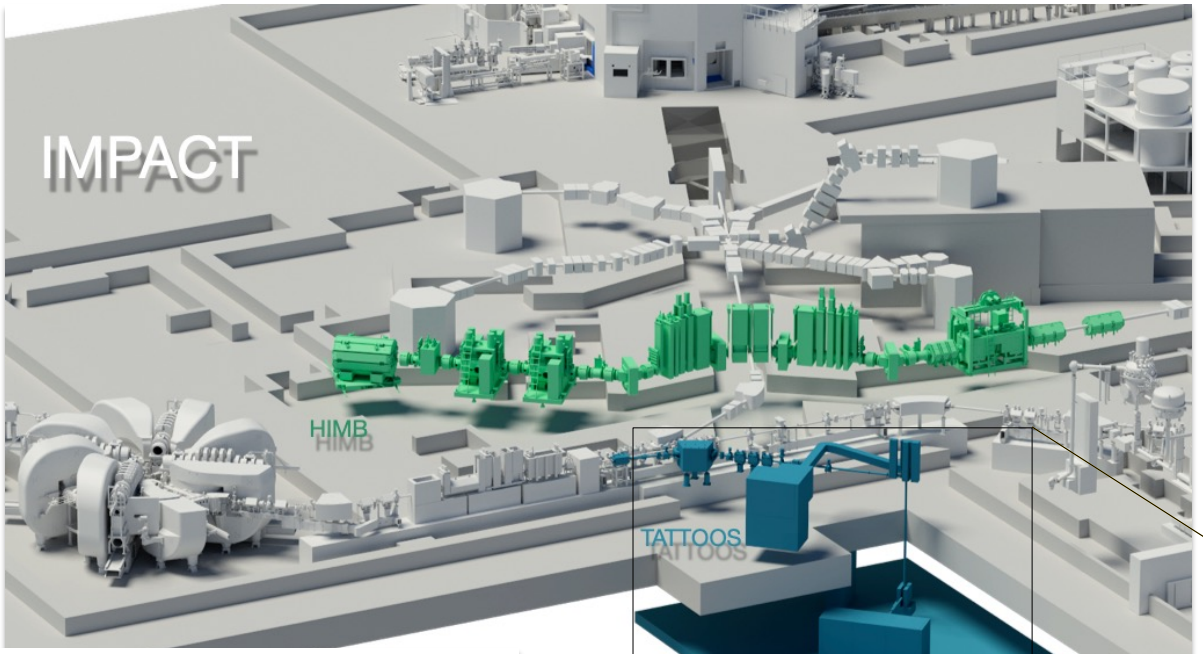


PET imaging



SPECT imaging

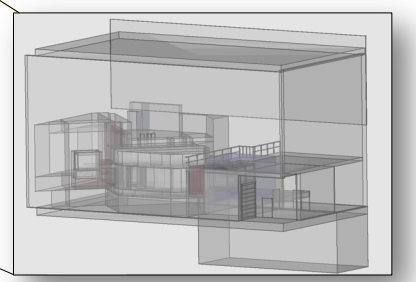
PSI/UZH/USZ “Large National Research Infrastructure Project”: IMPACT*



The High Intensity Proton Accelerator (HIPA) at PSI offers **world-record proton intensities**

IMPACT will comprises the two new installations:

- **TATTOOS:** Targeted Alpha Tumor Therapy and Other Oncological Solutions → ***Increasing radionuclides yield by a factor 50*** Radionuclides for diagnosis and therapy of cancer (and more)
- **HIMB:** High-Intensity Muon Beams → ***Increasing muon rate by up to a factor of 100***
- approx. 70 MCHF total investment
- approx. 35 MCHF for subproject TATTOOS



https://www.psi.ch/en/impact

*Isotope and Muon Production using Advanced Cyclotron and Target technologies

Multi-scale biology at the PSI Center Life Sciences

Three laboratories bridge biological scales from molecules over cells to patients

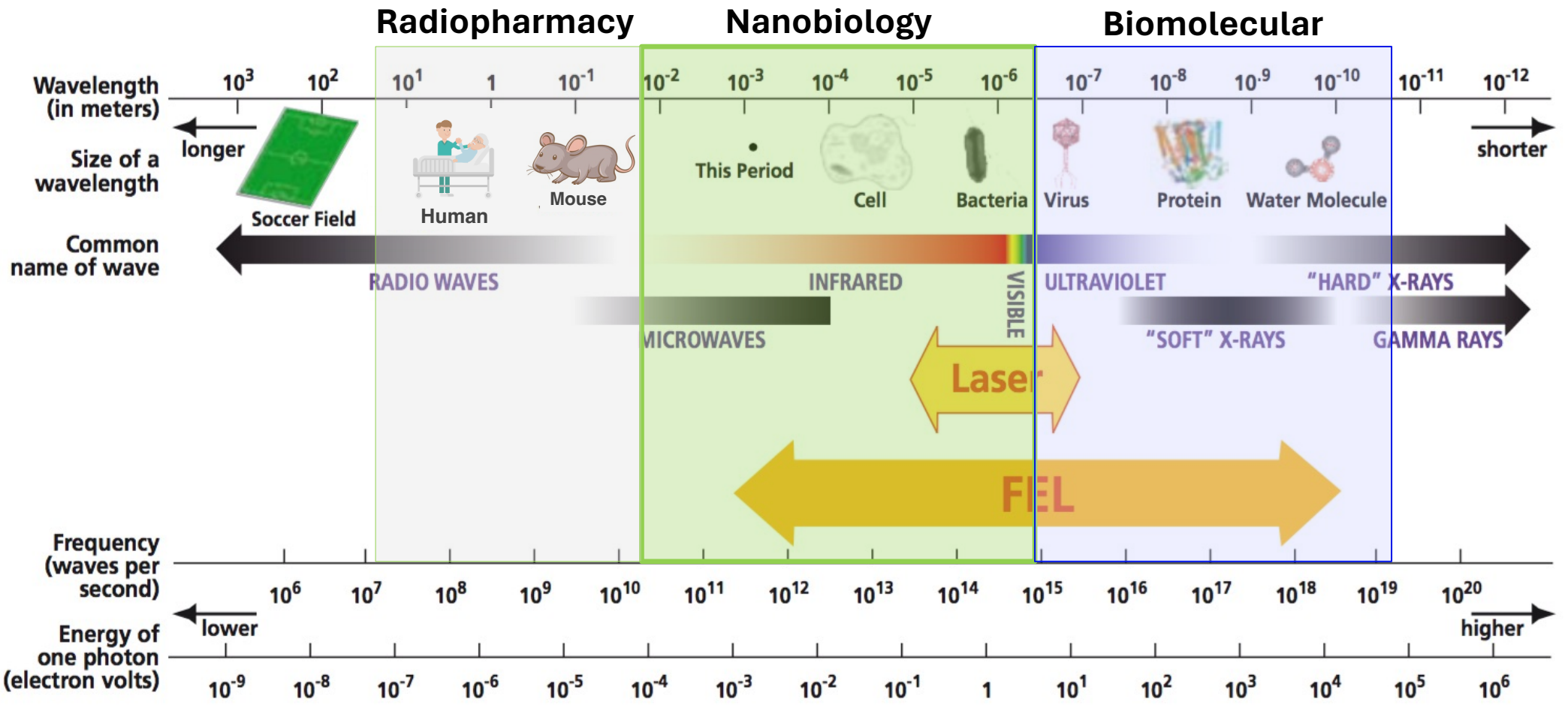
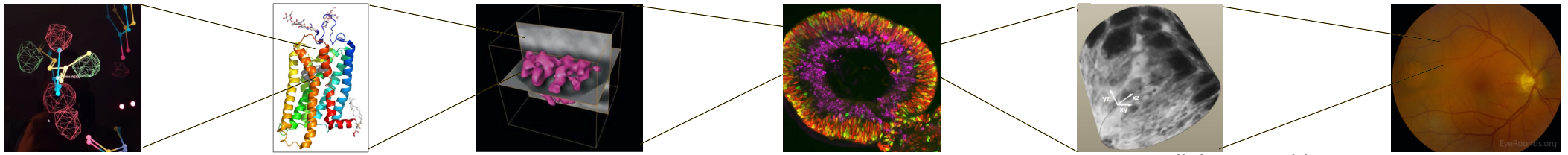


Fig. M.2. The wavelength range of a FEL vs. a quantum laser. Source: Advanced Light Source, Berkeley.

Correlative multi-scale analysis in biology and medicine

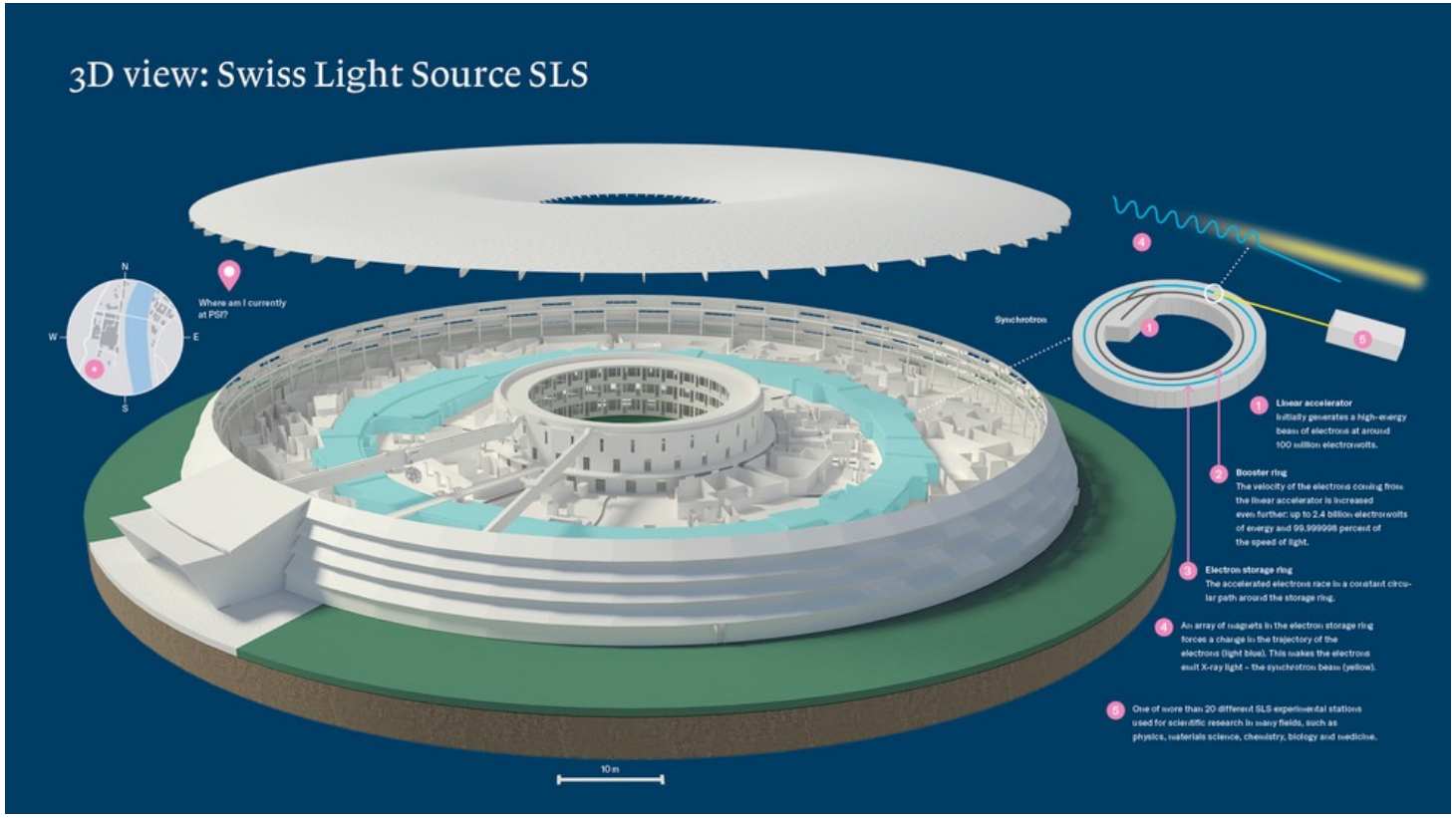
Integrating atomic scale and low-resolution structural and dynamic information into a complex physiological context at cellular and multicellular level

- ETH domain institutes with Swiss-wide leading expertise in photon- and electron-based imaging methods
- High relevance for basic and applied biomedical activities
- High relevance for development of non-invasive diagnostics and therapies for cancer, neurodegenerative and infectious diseases.
- Opportunity for intensive collaboration with Swiss hospitals, Biotech and Pharma as well as opportunities for generation of start-up companies.



Reaction dynamics | Structure-function | Multi-protein complexes | Organoid | Native cellular assembly | Organ

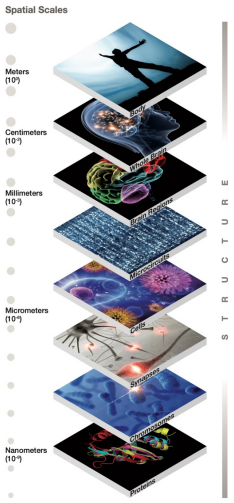
The Swiss Light Source 2.0 Project

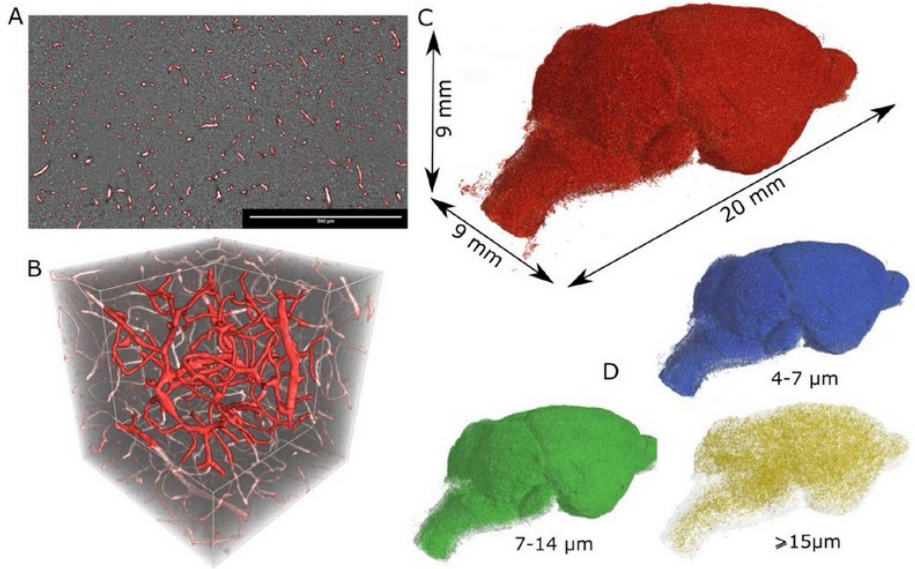


The synchrotron Swiss Light Source is the main **“work horse” for structural analysis** of proteins at PSI**. X-ray imaging capacities** play a critical role for the strategic goal of CLS and the Center for Photon Science for establishing PSI as a center for **multi-scale imaging.**

X-ray imaging at SLS: the microvascular architecture of the mouse brain

Same data set: 3D visualization of the segmented vessel network
The whole brain to contain approximately 5.0 million vessel branches. The whole-brain vascular length (295 m), and of the average vessel branch length (53 ± 3 µm).

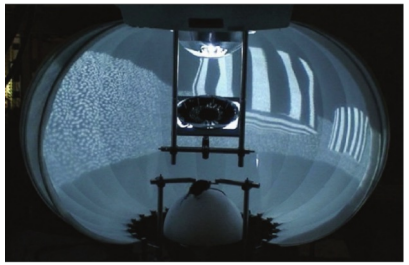


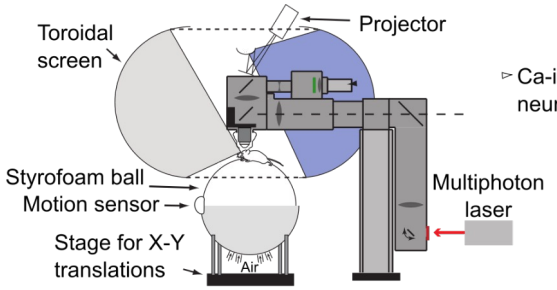


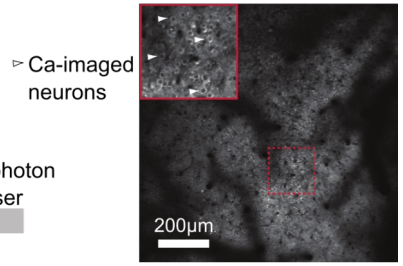
Miettinen *et al.,* BioInformatics 2019

Miettinen A. et al., unpublished, bioRxivv, March 16, 2021. https://doi.org/10.1101/2021.03.16.435616

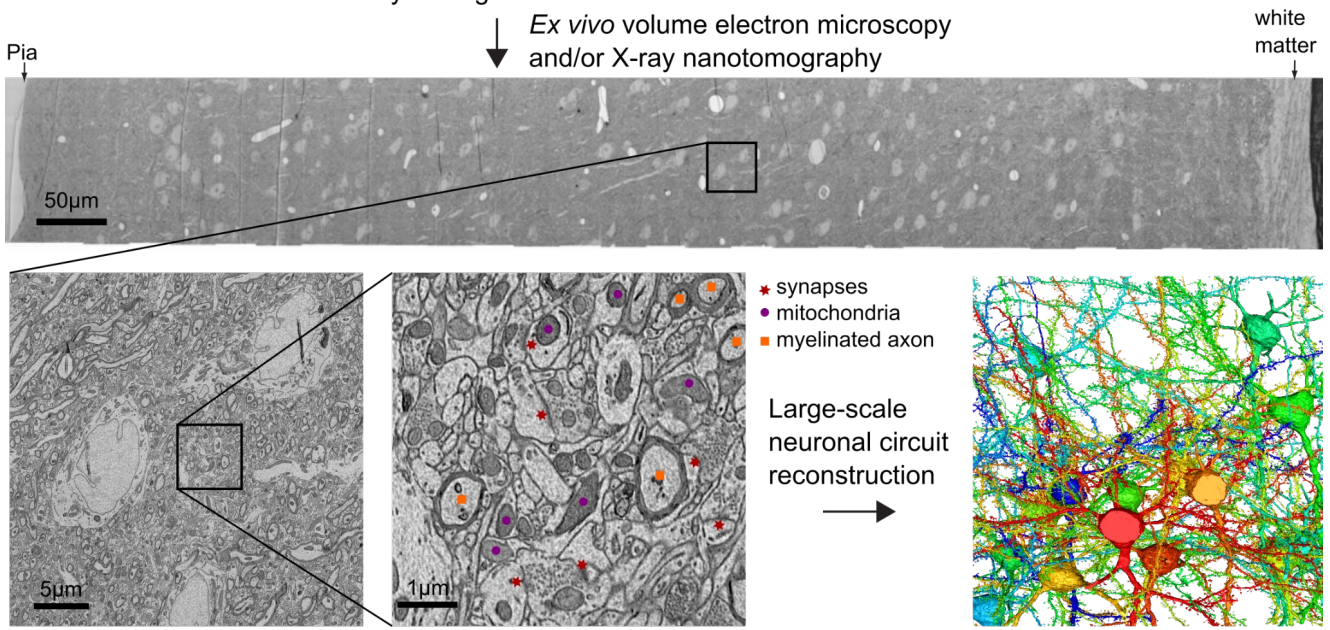
Correlative Imaging @ CLS: Dynamic structural and functional organization of neurons in healthy and diseased brains





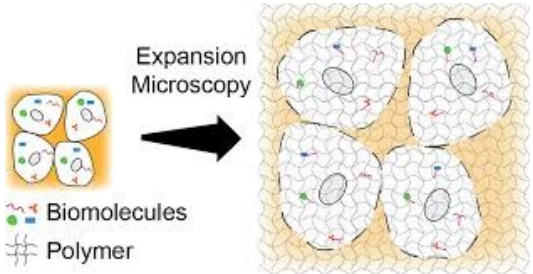


In vivo calcium imaging of hundreds of neurons simultaneously while the mouse performs navigation-based behavioral tasks in a virtual reality setting.



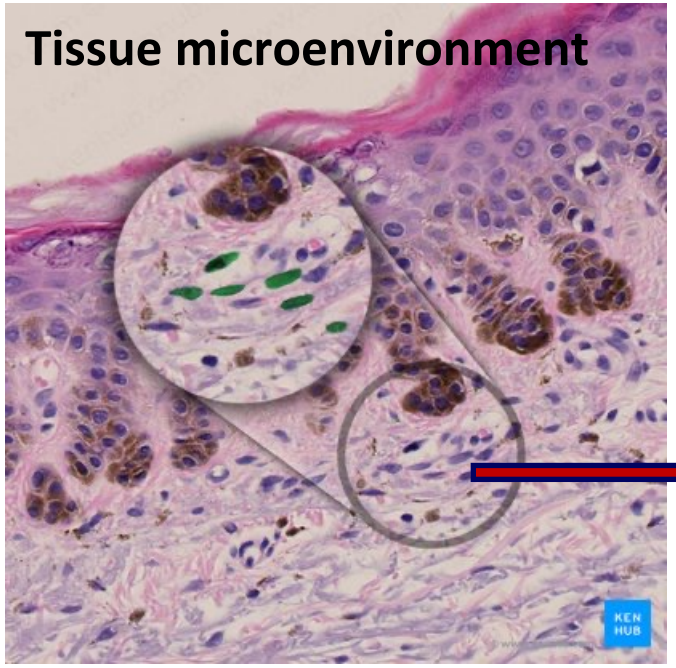
1. Building a two-photon calcium imaging pipeline to record neuronal activity in behaving mice (light microscopy)

2. Establishing an expansion X-ray nanotomography pipeline with PSD for imaging the brain ultrastructure at synaptic resolution (~20nm).



3. Functional and anatomical characterization of working memory-related neuronal network dynamics in retrosplenial cortex of healthy and Alzheimer's disease model mice (Electron Microscopy)

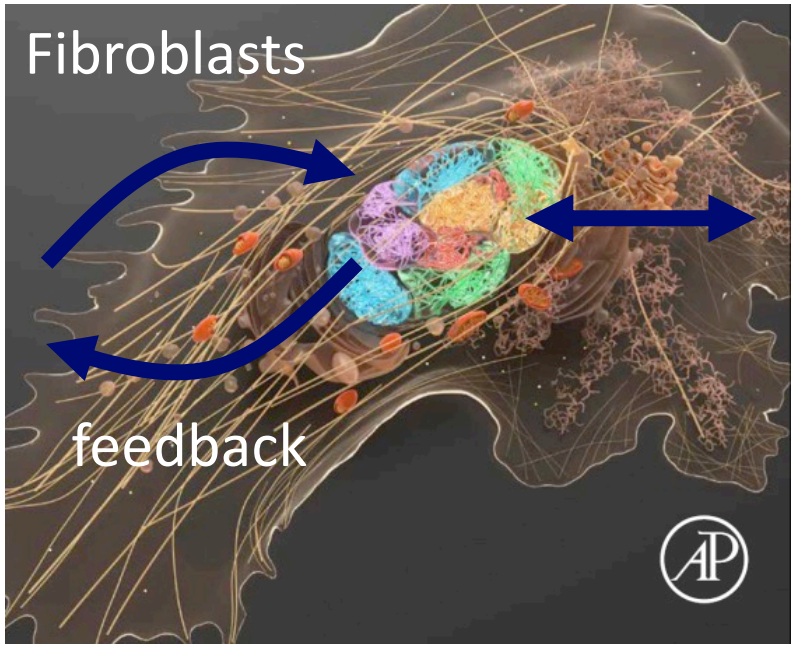
Cellular microenvironment and genome regulation: Mechano-Genomics



Micro-environmental Stimulus

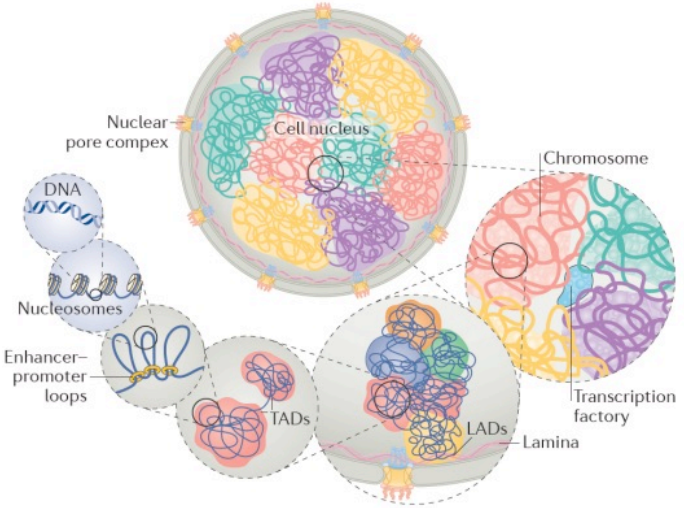
- **Forces:**
(Stretch, Compression, Shear)

- **Soluble signals:**
(TNFα, TGFβ, etc.)



Nuclear mechanotransduction

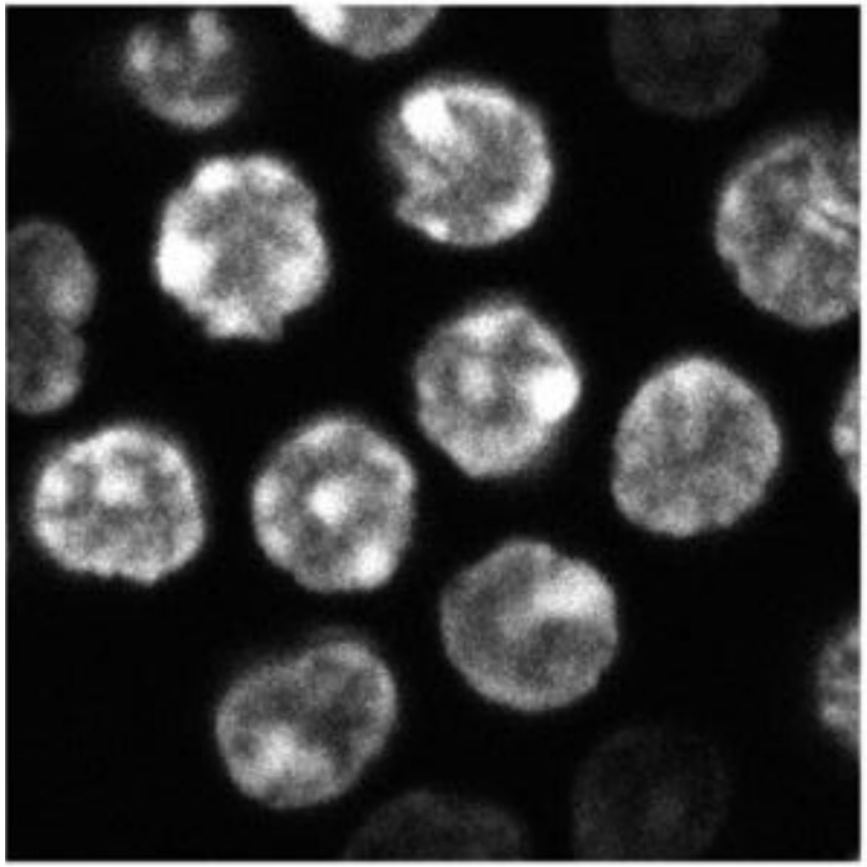
3D genome organization & gene expression

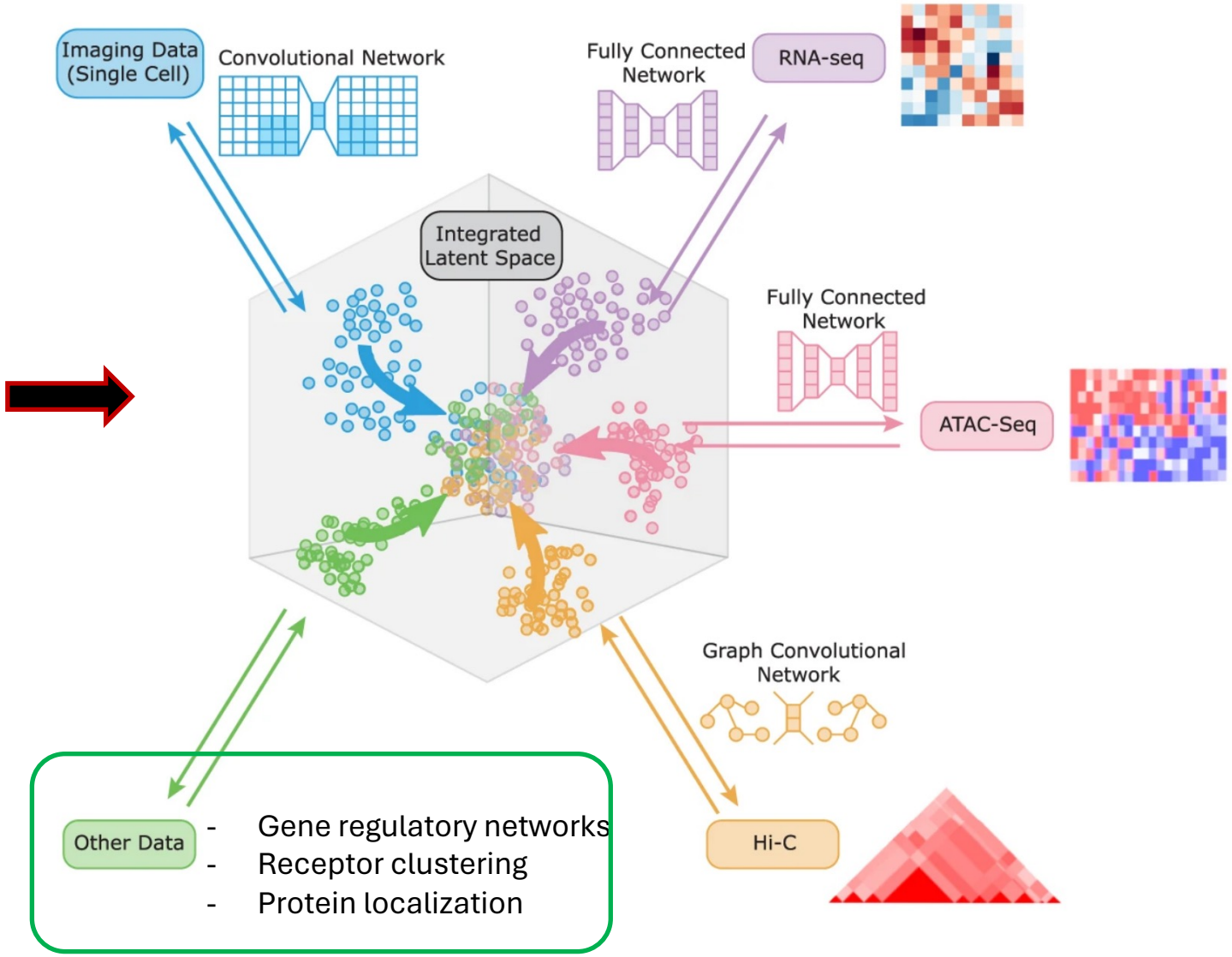


Shivashankar, Annual Reviews of Biophysics (2011)
Uhler & Shivashankar, Nature Reviews Molecular Cell Biology (2017)
Uhler & Shivashankar, Nature Reviews Molecular Cell Biology, (2020)

Multi-domain data integration/translation to link chromatin imaging and function

PSI

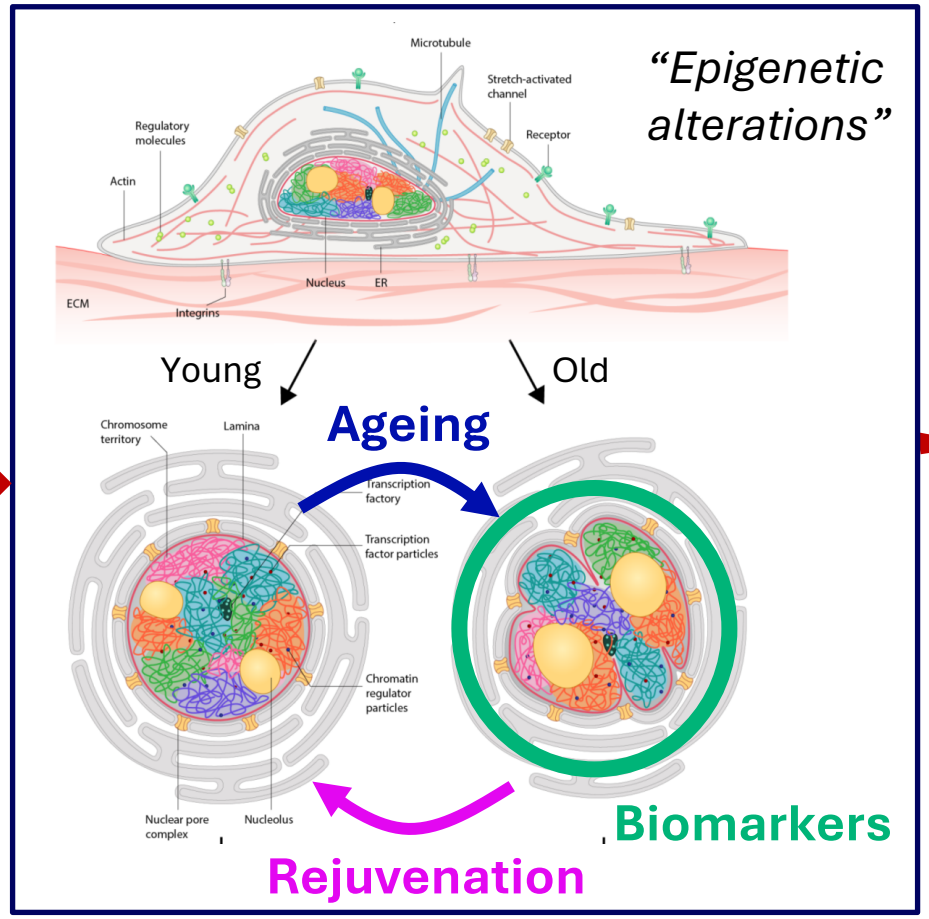




Yang, KD., et al., *Nature Communications*, *12, 31, 2021*
Belyaeva, A., *Nature Communications*, *12,* 1024, 2021
Paysan, et al., *(under review, 2024)*
Cammarata, et al., *(under review, 2024)*

Research themes:

"...ageing is inevitable...."



Mechano-Genomics of Cellular Rejuvenation & Cell-based Therapies *

(*Spin-off: FOCAL Bioscience AG)

AI-based Chromatin Imaging Biomarkers for Ageing-related Diseases *

(*Clinical trials & a public health project)

Multi-scale biology at the PSI Center Life Sciences

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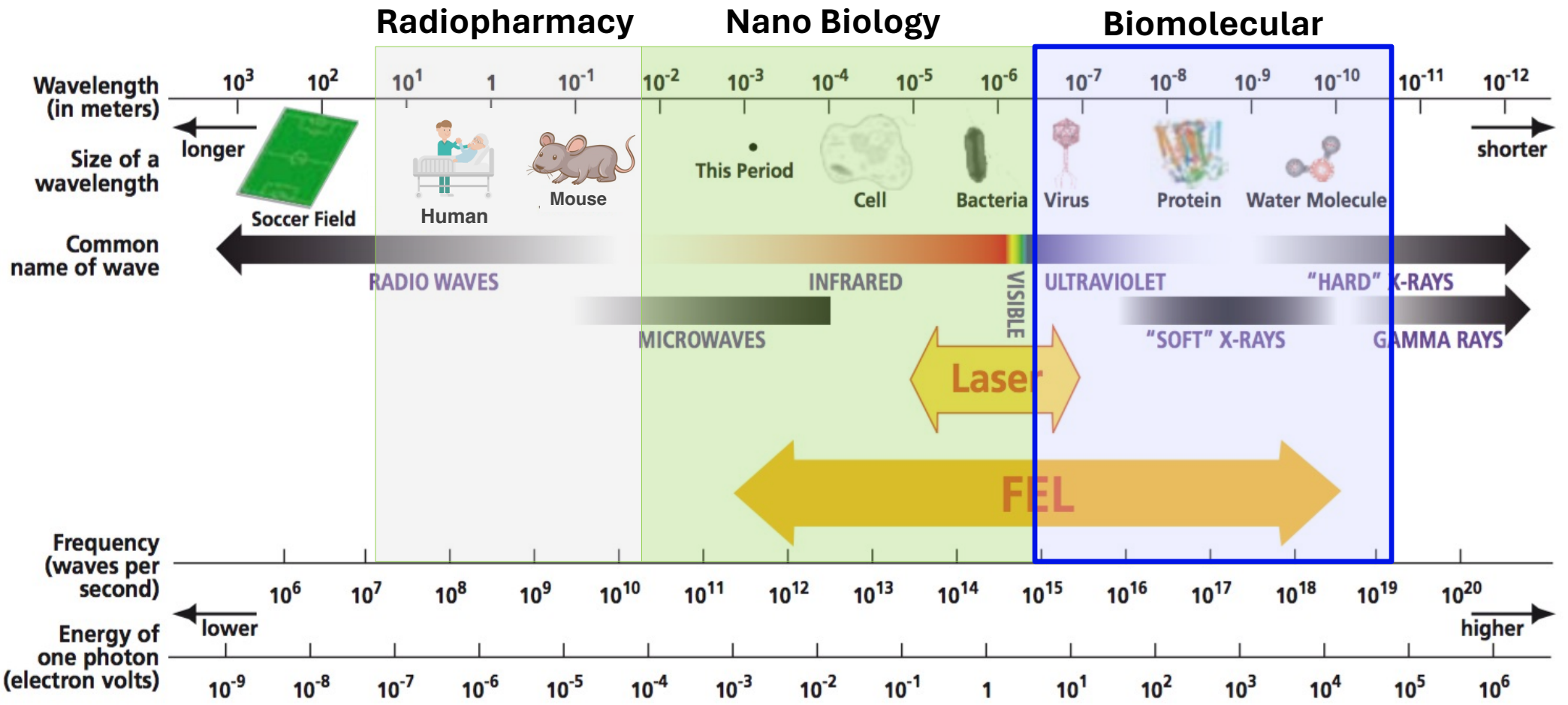
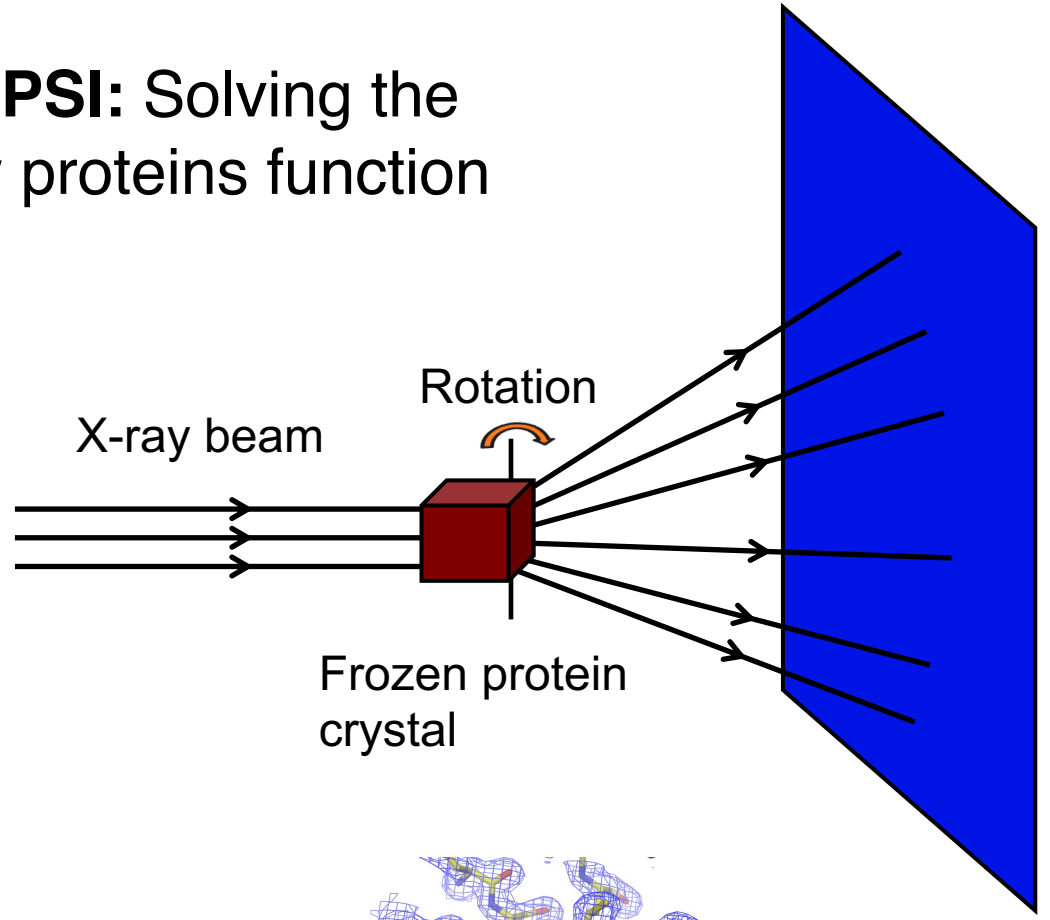


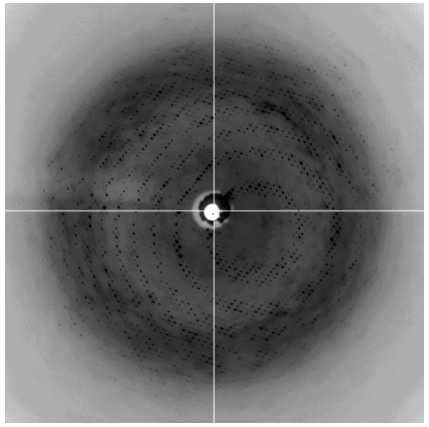
Fig. M.2. The wavelength range of a FEL vs. a quantum laser. Source: Advanced Light Source, Berkeley.

Structural Biology@PSI: Solving the atomic secrets of how proteins function

PSI

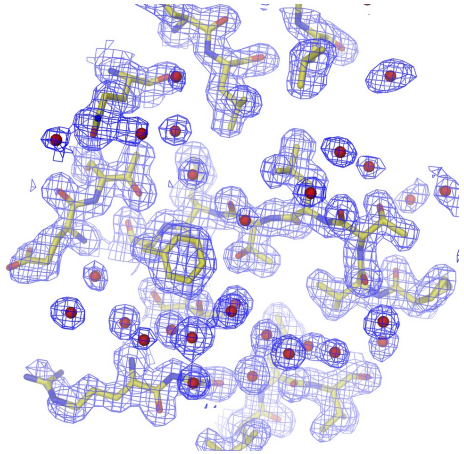
Synchrotron Source





Diffraction Image

Fourier Transformation



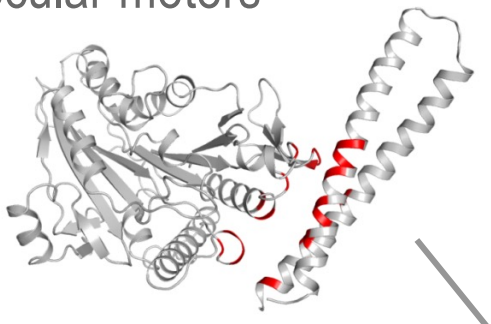
Electron Density

Atomic information on biological macromolecules!!

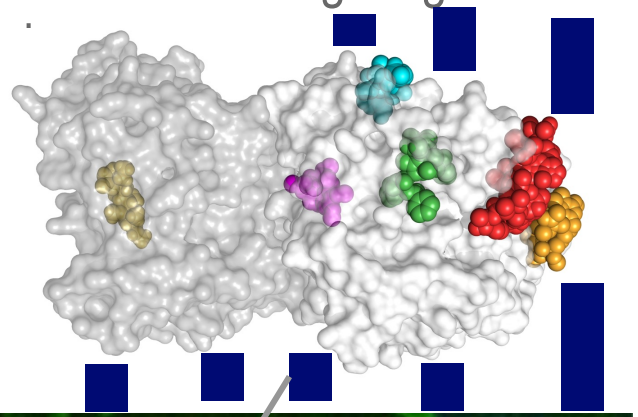
Biomolecular Complexes

"We investigate how proteins and drugs regulate microtubule structure, function, and dynamics during cell division"

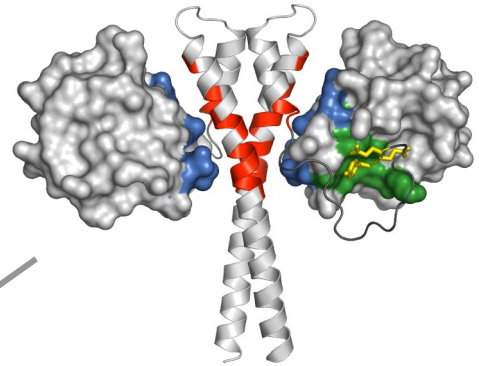
Molecular motors



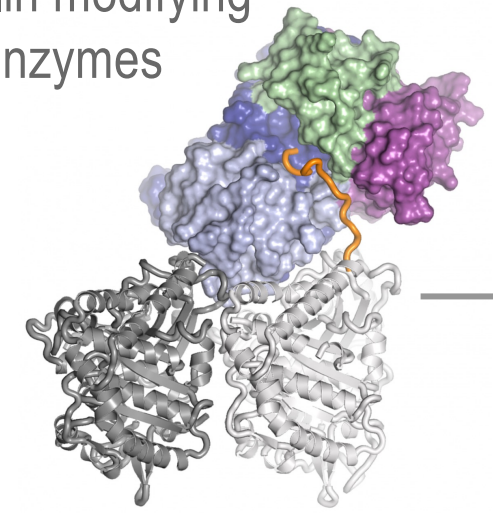
Microtubule-targeting

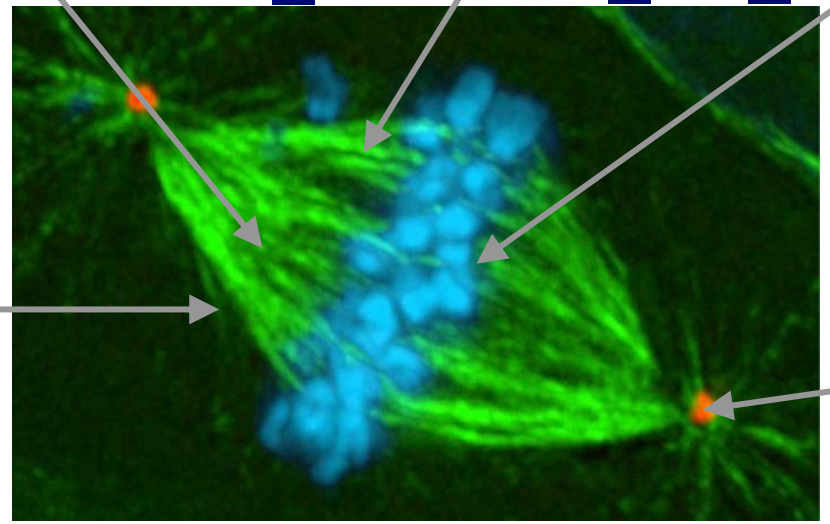


Microtubule-tip binding proteins



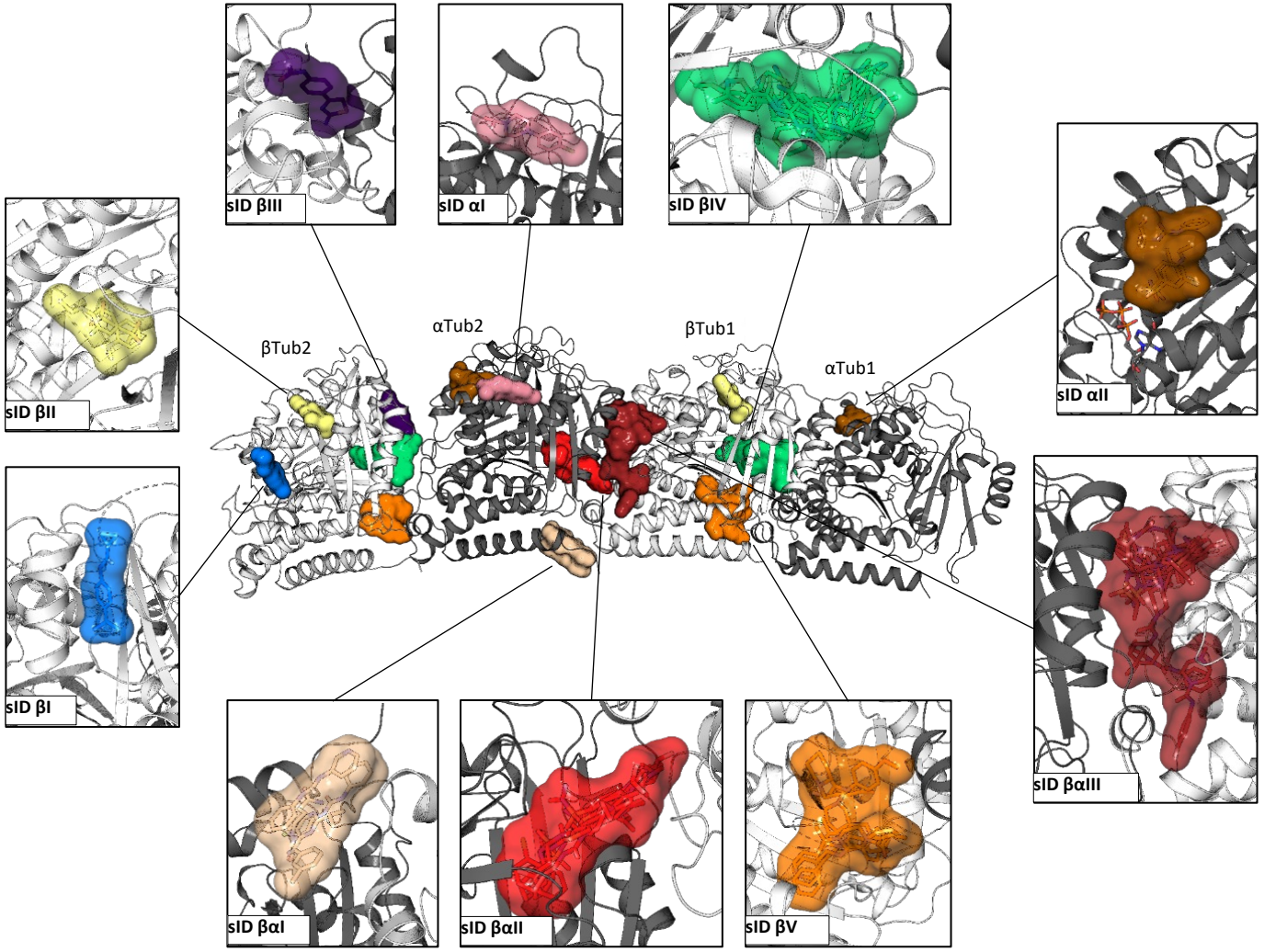
Tubulin modifying enzymes





Centriolar proteins

A comprehensive structural analysis of tubulin cancer drug binding sites



- XChem facility, Diamond
- Diamond Light Source Poised Fragment Library
- T_2R-TTL crystal system
- 708 fragments soaked
- 672 data sets collected
- 503 structures solved

➢ 56 fragments

➢ 10 binding sites, 6 novel

➢ 6 common binding motifs

Mühlethaler, Gioia et al. Angewandte Chem. 2021

Structural Biology is rapidly developing

- **Structural biology has been a tremendous success.**

-> 220.130 structures of biological macromolecules and over 10 Noble prizes

- **The molecular structures of most biologically relevant proteins have been solved.**

-> Acurate structure prediction by artificial intelligence

- **Protein structure is important but ultimately protein motions determine function.**

-> New frontier in time-resolved structural biology

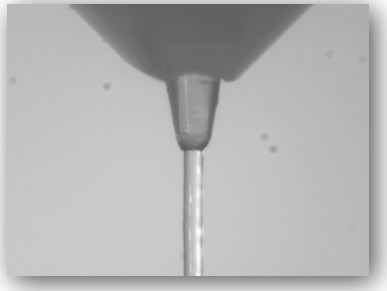
New X-ray sources for new Biology

PSI

Swiss Light Source 2.0

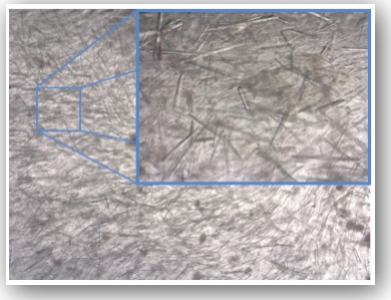
CLS/CPS Team

HVE Injector



Swiss Free Electron Laser

Microcrystals

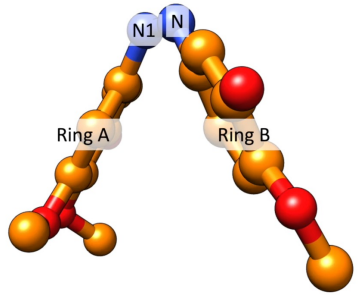


Time-resolved Structural Biology

"We include time as a fourth dimension in structural biology to understand how protein dynamics relate to protein function"

Femtosecond dynamics

Photochemical reaction of *azo*-Combretastatin A4



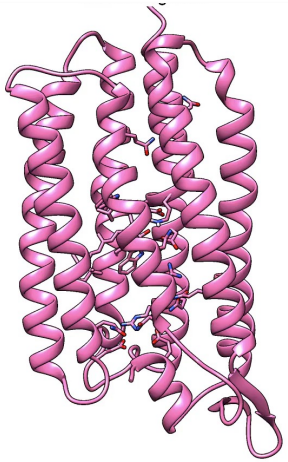
Δt = dark
C5-N1=N-C4 torsion = 0°

X-ray Laser **Synchrotron** **CryoEM**

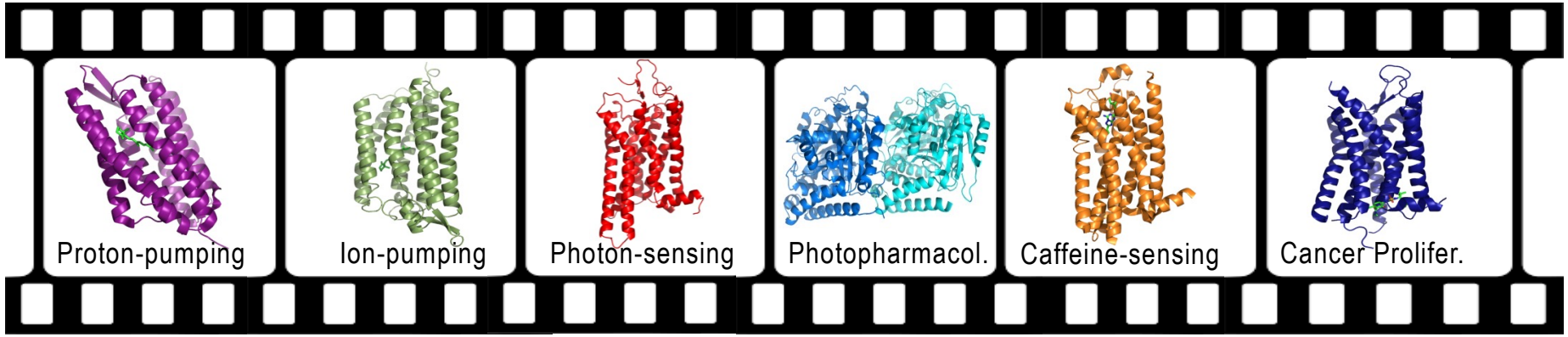
Time-resolved Spectroscopy

Computer Simulations

Millisecond dynamics

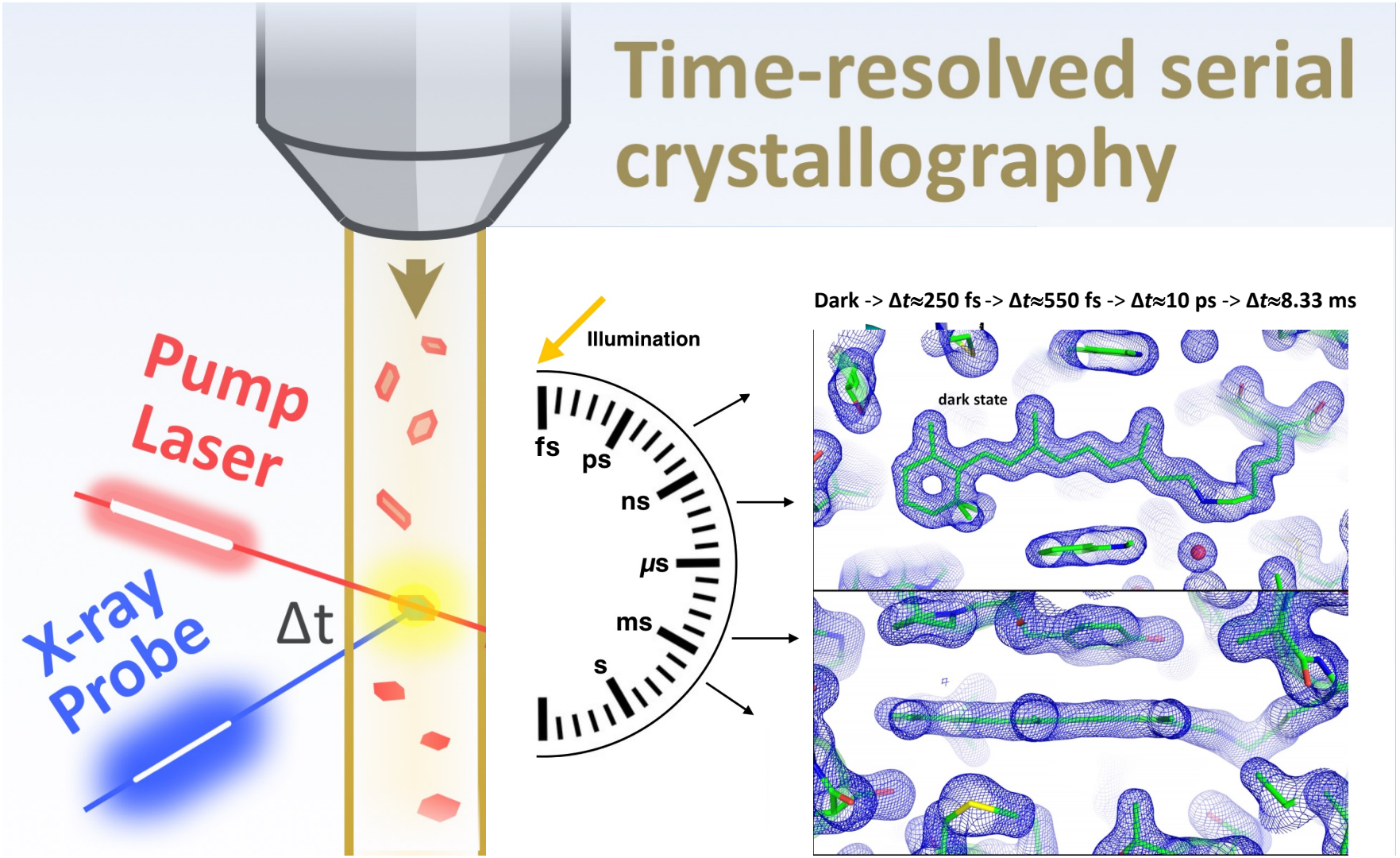


Molecular movies of proteins in action from SLS and SwissFEL



From Structures to Molecular Movies

Bringing time-resolved measurements to the molecular scale



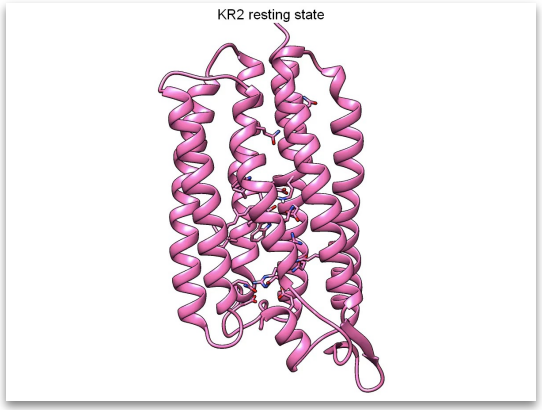
Standfuss, *Curr. Opin. Struc. Biol.*, 2019

Nogly *et al.*, *Science*, 2018

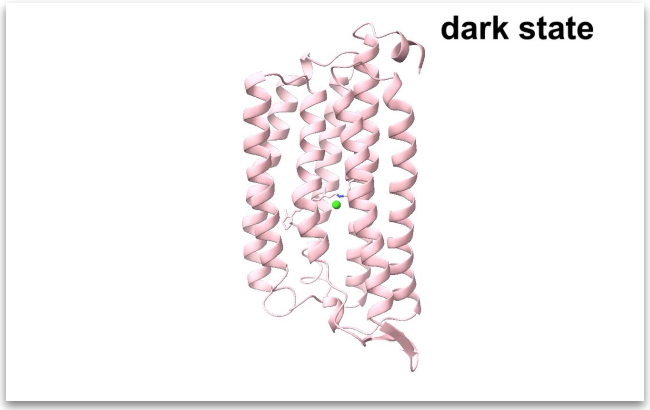
Early user experiments from the CLS

Retinal proteins pave the way into a dynamic future for structural biology

Nogly et al., 2018, Science



Skopintsev *et al.*, 2020, Nature



Mous *et al.*, 2022, Science

Proton pump

- First **"molecular movie"** of retinal protein with **atomic resolution and femtosecond resolution**
- Simple **Photosynthetic system**

Sodium pump

- Ten molecular snapshots of **sodium** transport **out of the cell**
- Potential as **optogenetic tool**

Chloride pump

- SwissFEL and **SLS** resolves **chloride** transport **into the cell**
- Electrostatic gates **explain transport**

X-ray lasers allow us to observe structural changes in a wide temporal window

PSI

Blink of an eye = 0.1 s

Photocycle = 0.01 s

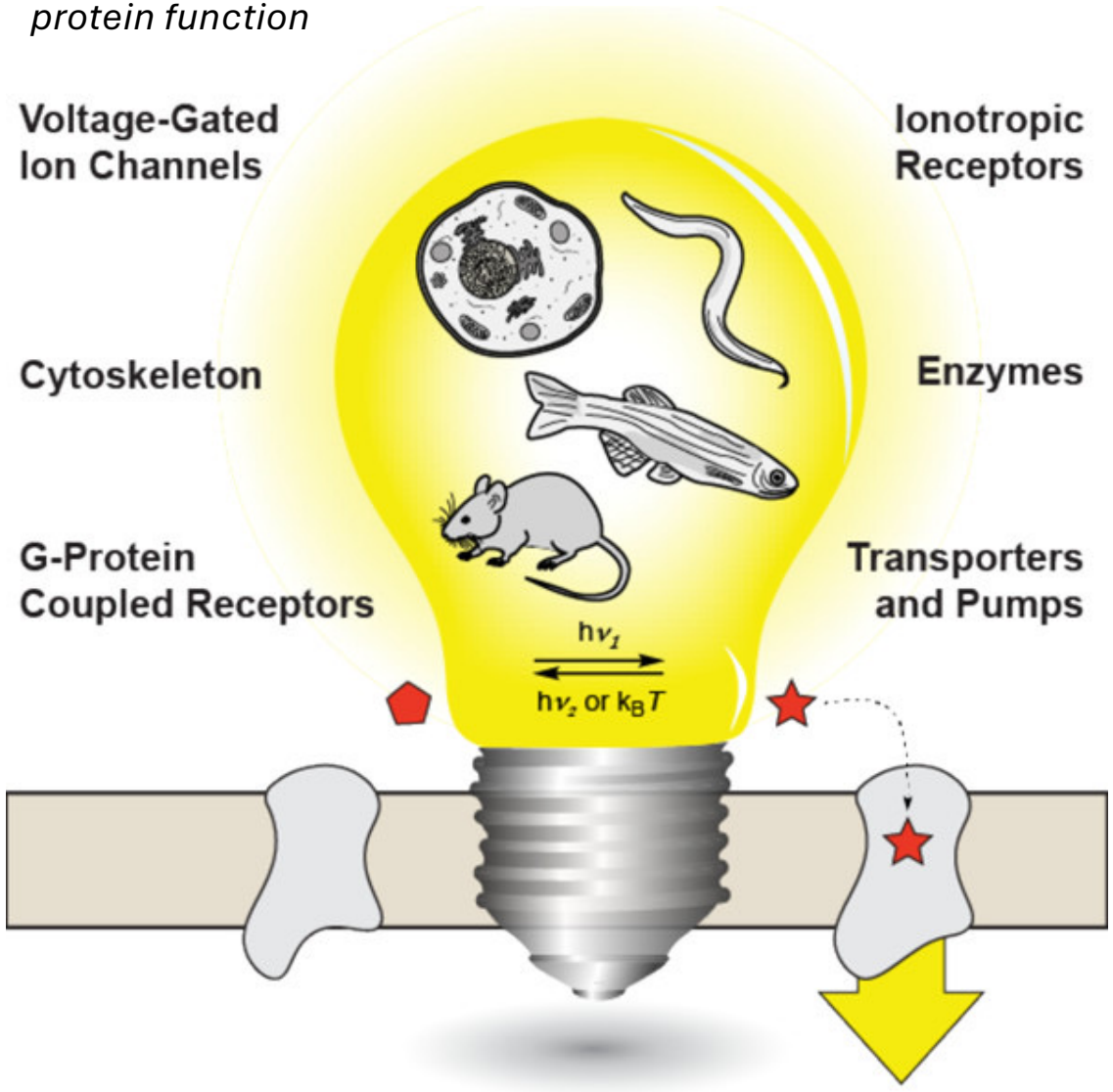
Retinal excitation = 0.000 000 000 000 1 s

-> **But most proteins don’t have photoswitches!**

…or do they?

Photopharmacology – Range of Targets

Chemists are developing a large variety of light-switches to manipulate protein function



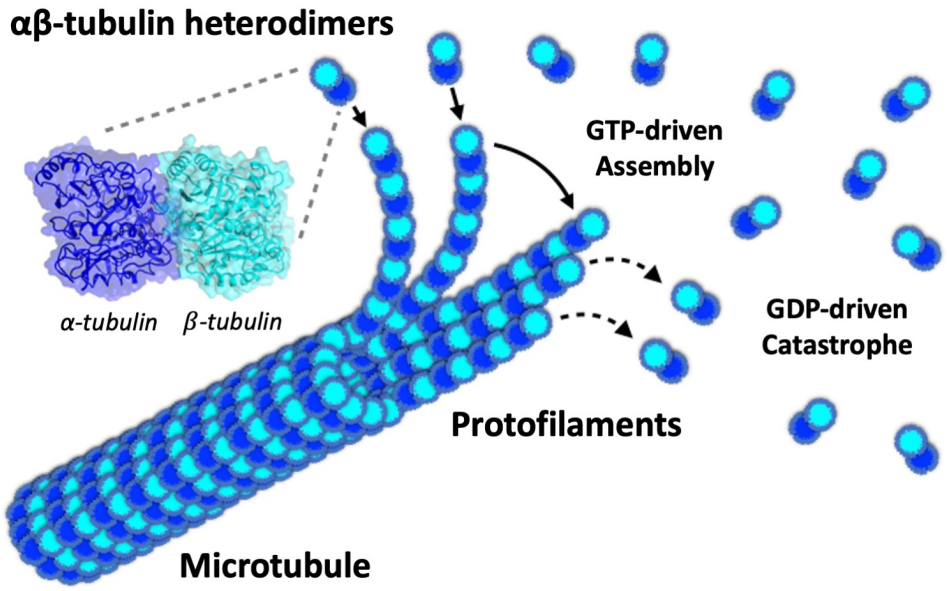
From: K. Hüll, J. Morstein, and Dirk Trauner, *Chem. Rev.,* 2018

Photoswitchable Inhibitors of Cell Mitosis

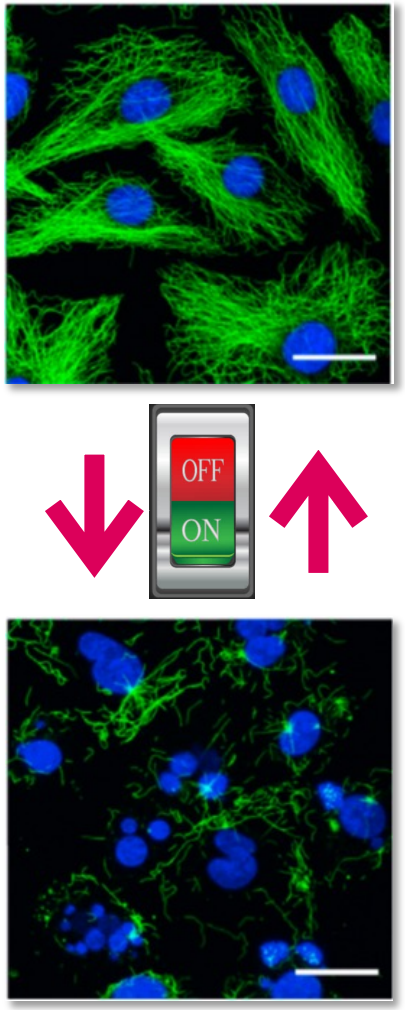
Photocontrol of microtubule formation

PSI

Target of interest:



Photopharmacology:



Tubulin binding drugs:

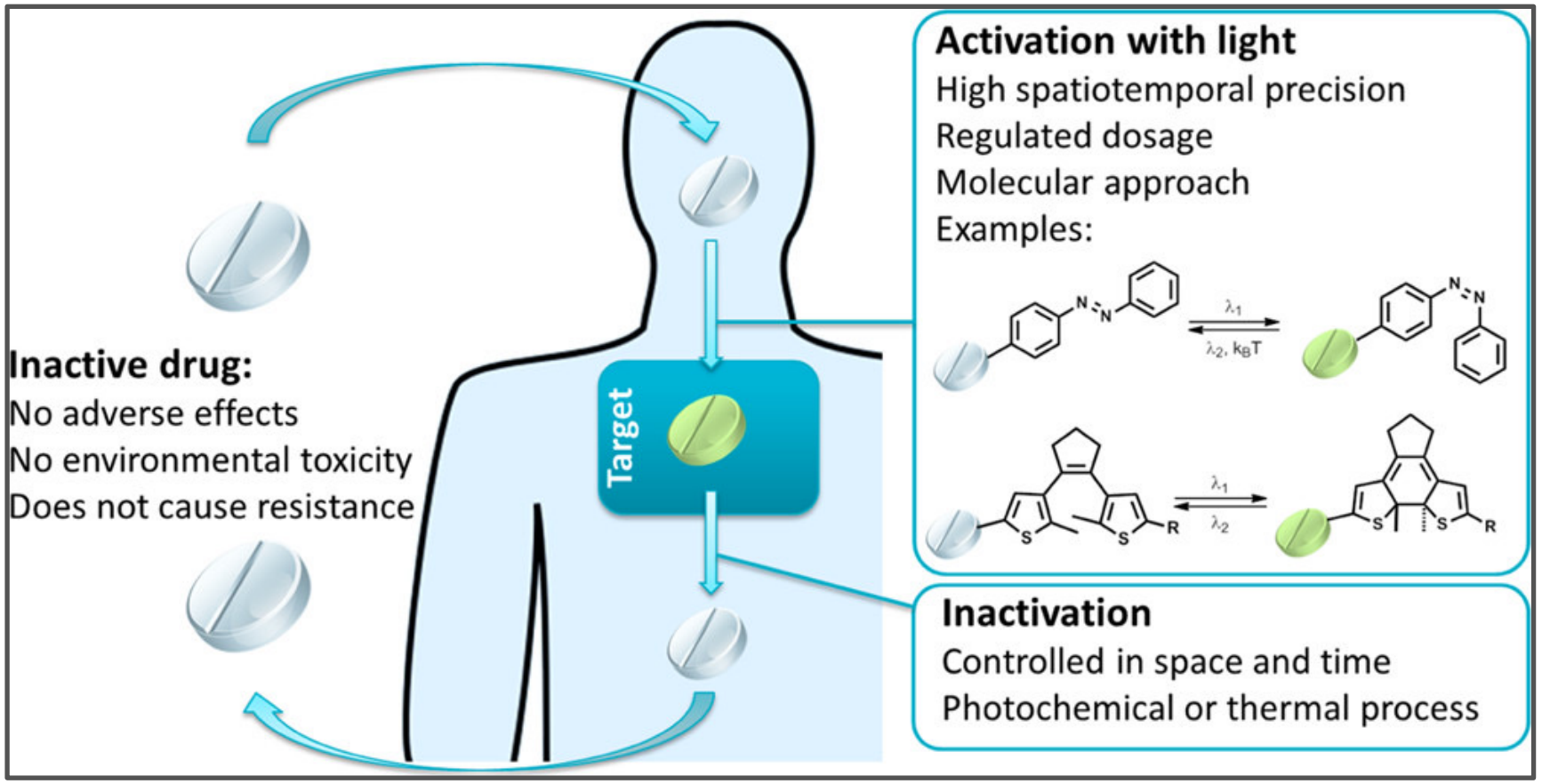
- Kill cancer cells (Taxol chemotherapy)
- Reduce inflammation (Colchicine)
- Lower Covid-19 death rate (Sabizabulin)

Collaboration Steinmetz Group (PSI)

From: Borowiak *et al.*, *Cell*, 2015

Photopharmacology – The basic principle

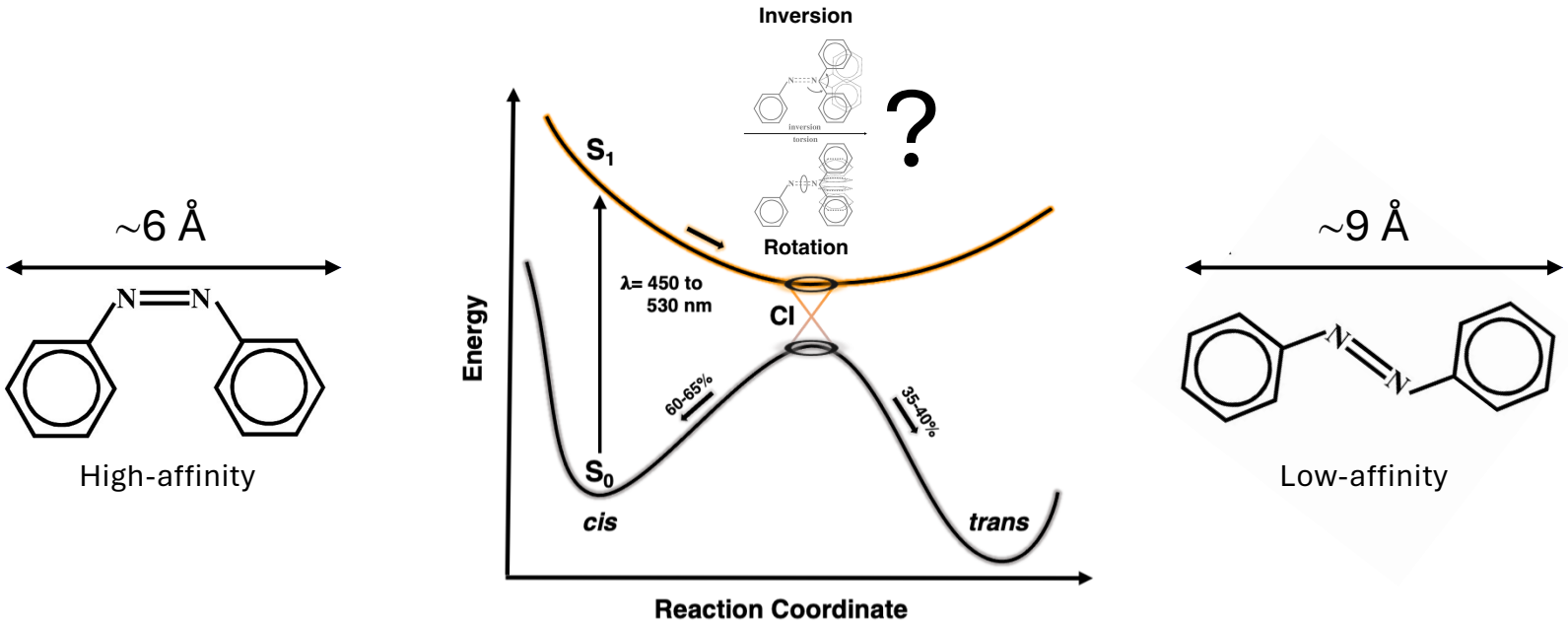
Allows for remote spatial and temporal control of bioactivity by light



From: W. Velema, W. Szymanski & B. Feringa (2014)

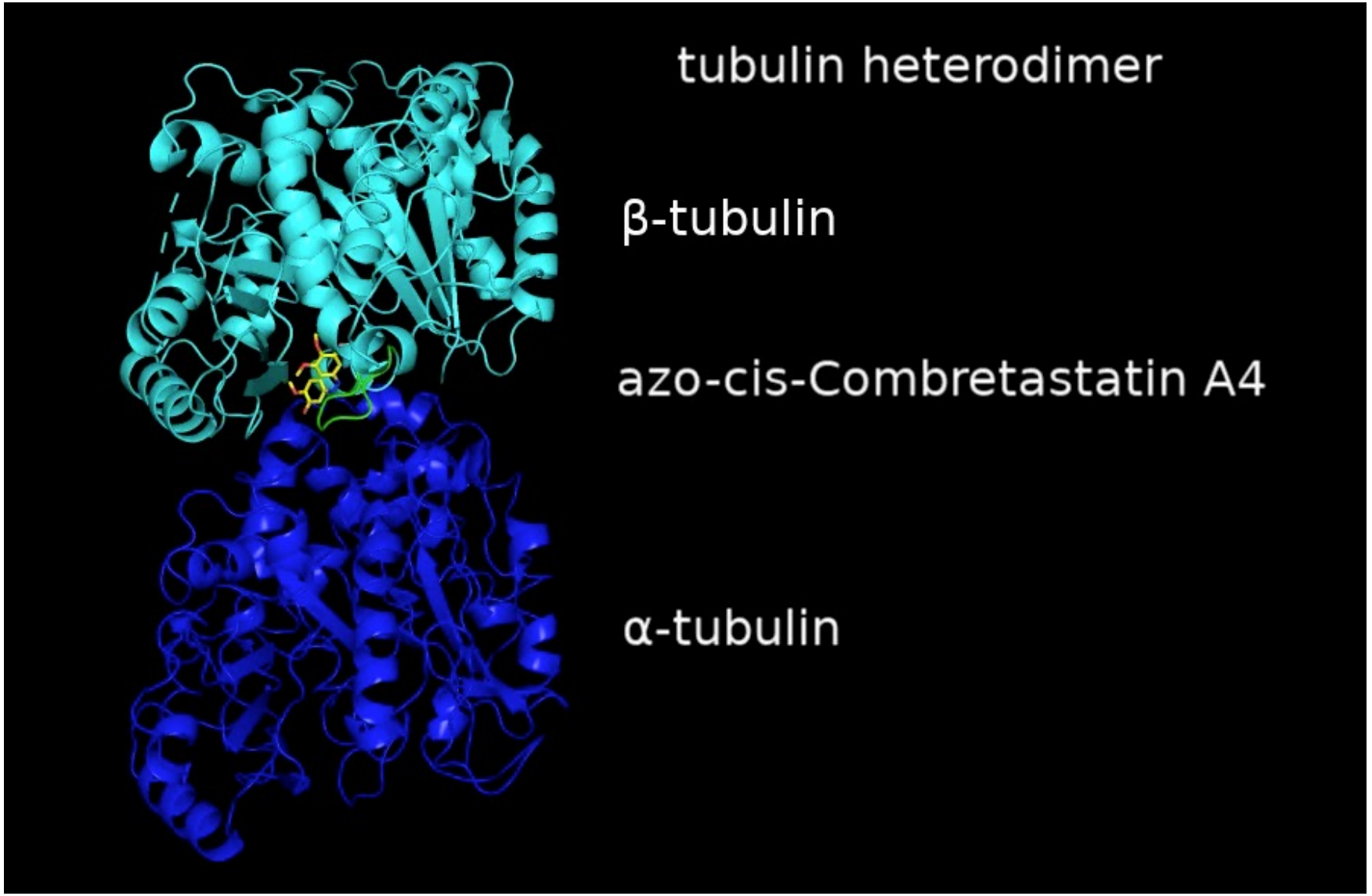
Photon energy is translated into mechanical energy via a transition in molecular shape!

… but the mechanisms remain controversial



Photopharmacology “The Movie”

Dynamics within the colchicine site targeted by gout, cancer and covid-19 drugs



Wranik *et al.*, *Nature Comm, 2023*

Structural Biology of Membrane Proteins

PSI

"G protein-coupled receptors (GPCRs) and their signaling complexes are the target for >30% of small molecular drugs"

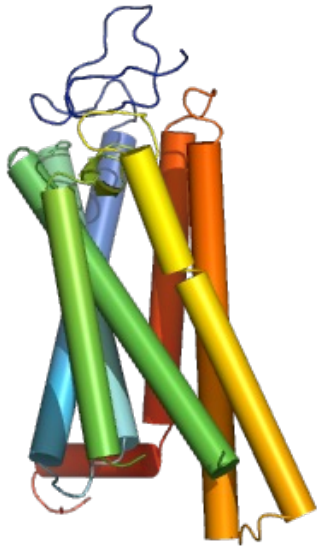
Vision

Taste

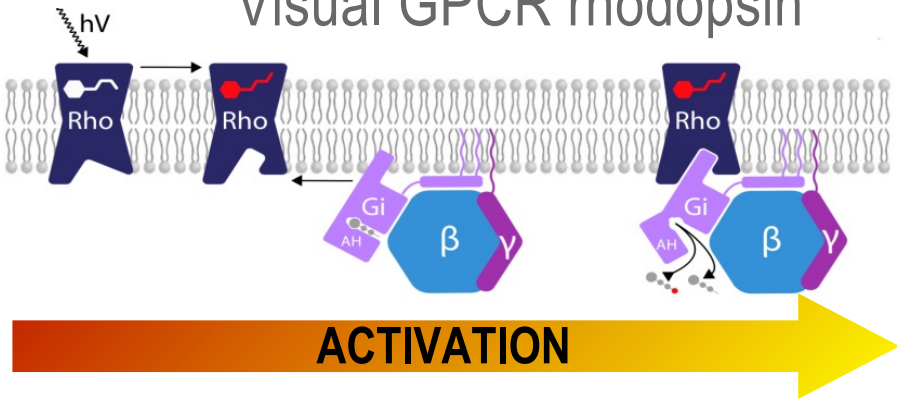
Blood pressure

Hormone

GPCR

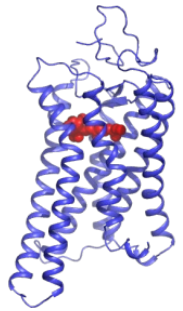


Visual GPCR rhodopsin

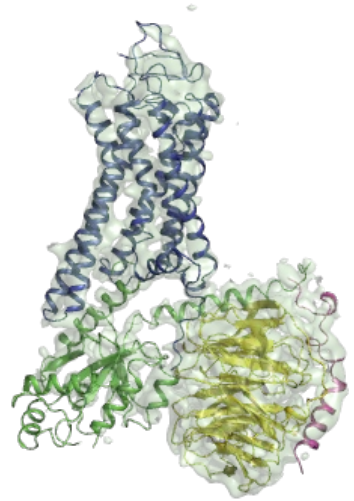


Inactive

Active



Signaling complex



Biomedical activities in a nutshell

PSI

large infrastructure @ PSI

SLS

SwissFEL

SinQ

Injector 2

Gantries

enables

Unique expertise in biology and medicine

- structural analysis of critical cellular systems (signal transduction, microtubule system)
- structural analysis of protein dynamics
- development of radio-nuclide based small molecules and biologicals for diagnosis and therapy
- World leading expertise in proton therapy
- Establishing multi-scale imaging technologies to address biological questions

fosters

Collaborations

ETHZ, EPFL, Swiss universities and hospitals, International partners (e.g. MRC-LMB Cambridge, Stanford University, Humboldt University, Kyoto University and many others)

Translation

Bench to bedside program, structure based drug discovery, industry collaborations, Spin-Off activities

enables

enables

requires

Novel methods and technologies

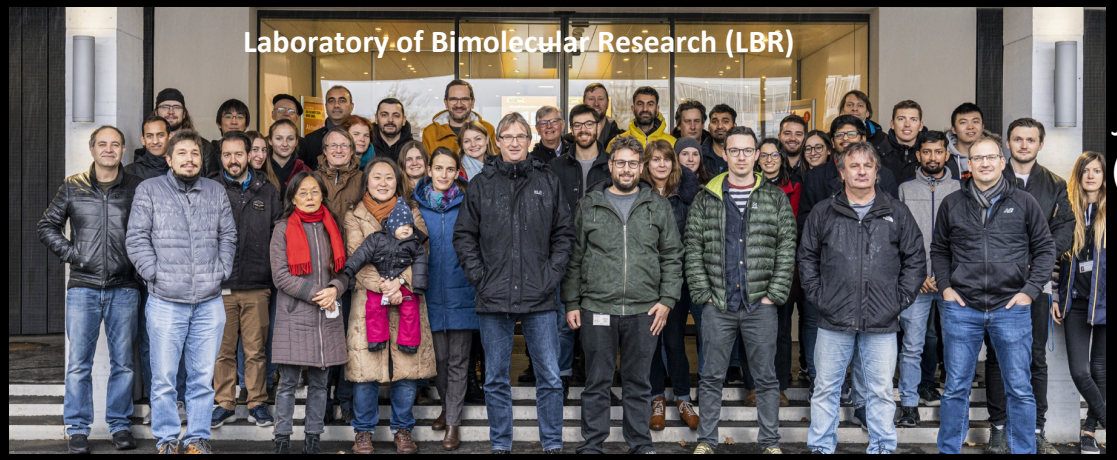
Electron diffraction, single molecule electron imaging, sample delivery, quantum mechanics-based analysis.

Additional expertise and infrastructure

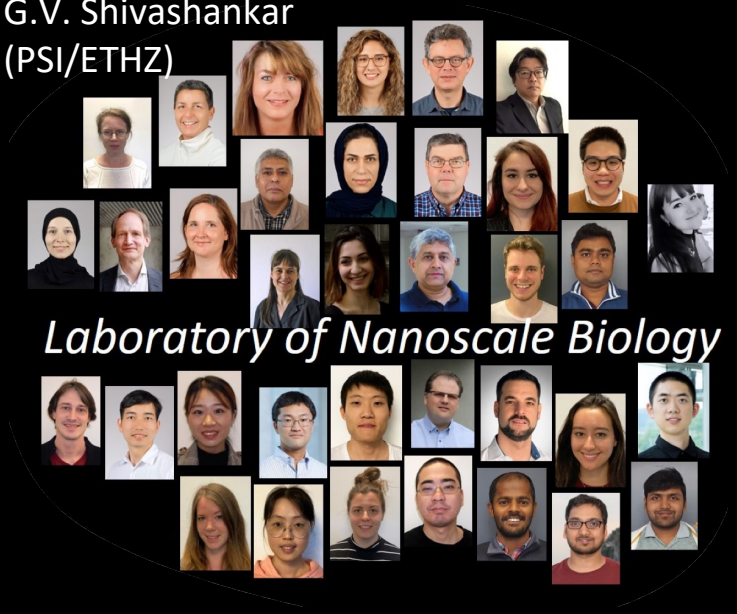
Electron & light microscopy, GMP-facilities, cell & molecular biology, advanced computation, radiobiology

Michel Steinmetz
(PSI/Uni Basel)

Jörg Standfuss
(PSI/UZH)



G.V. Shivashankar
(PSI/ETHZ)



Roger Schibli
(PSI/ETHZ)