

PAUL SCHERRER INSTITUT



# Life Science Research at Paul Scherrer Institute



**ETH**

Eidgenössische Technische Hochschule Zürich  
Swiss Federal Institute of Technology Zurich

## **Prof. Gebhard F. X. Schertler**

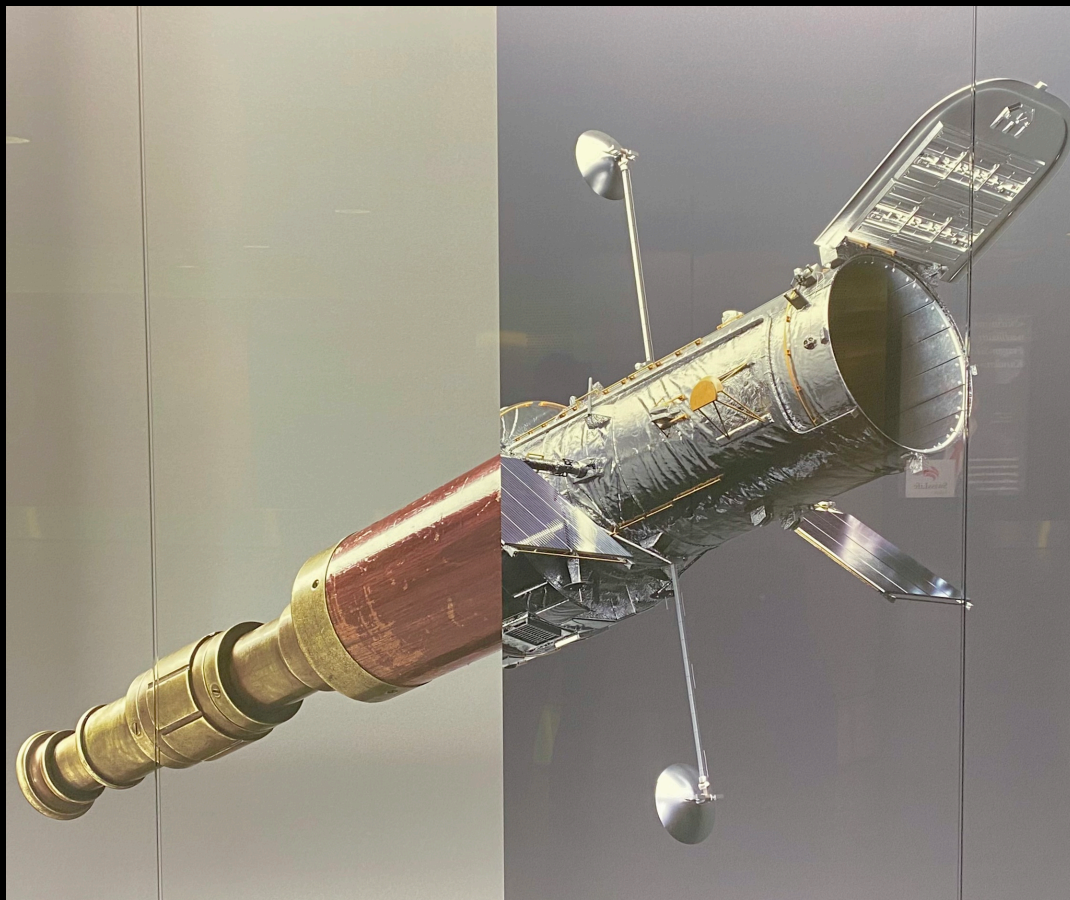
**Head, Division of Biology and Chemistry, PSI**

**Professor for Structural Biology ETH Zürich**

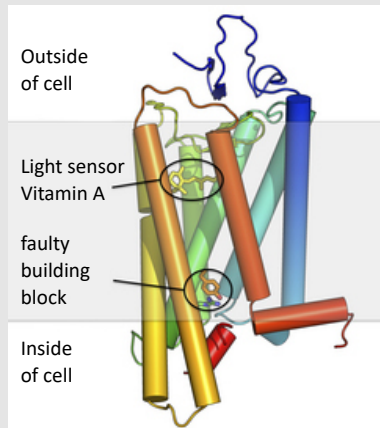
**Laboratory of Biomolecular Research**

**Switzerland**

# Technology Drives Science and Science Drives Technology







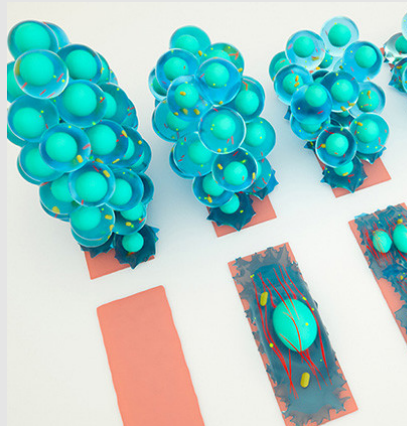
## Structure of Proteins

for the targeted development  
of new drugs

**Prof. G. Schertler**

**Prof. M. Steinmetz**

⇒ Accelerators: SwissFEL, SLS



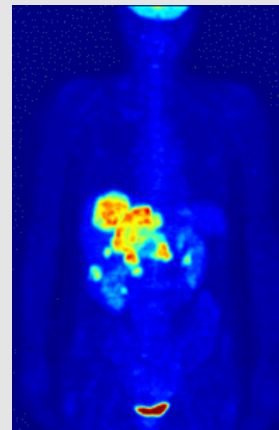
## Nanoscale biology

of  
molecular structure and  
dynamics in the living cell

**Prof. G. Shivashankar,**

**Prof. J.P. Abrahams**

⇒ Detectors: EM



## Radio Pharmaceuticals

for the diagnosis  
and therapy of tumours

**Prof. R. Schibli, Dr. R. Eichler**

⇒ Accelerators: HIPA, SINQ  
⇒ Isotopes, Radiochemistry,  
CRS



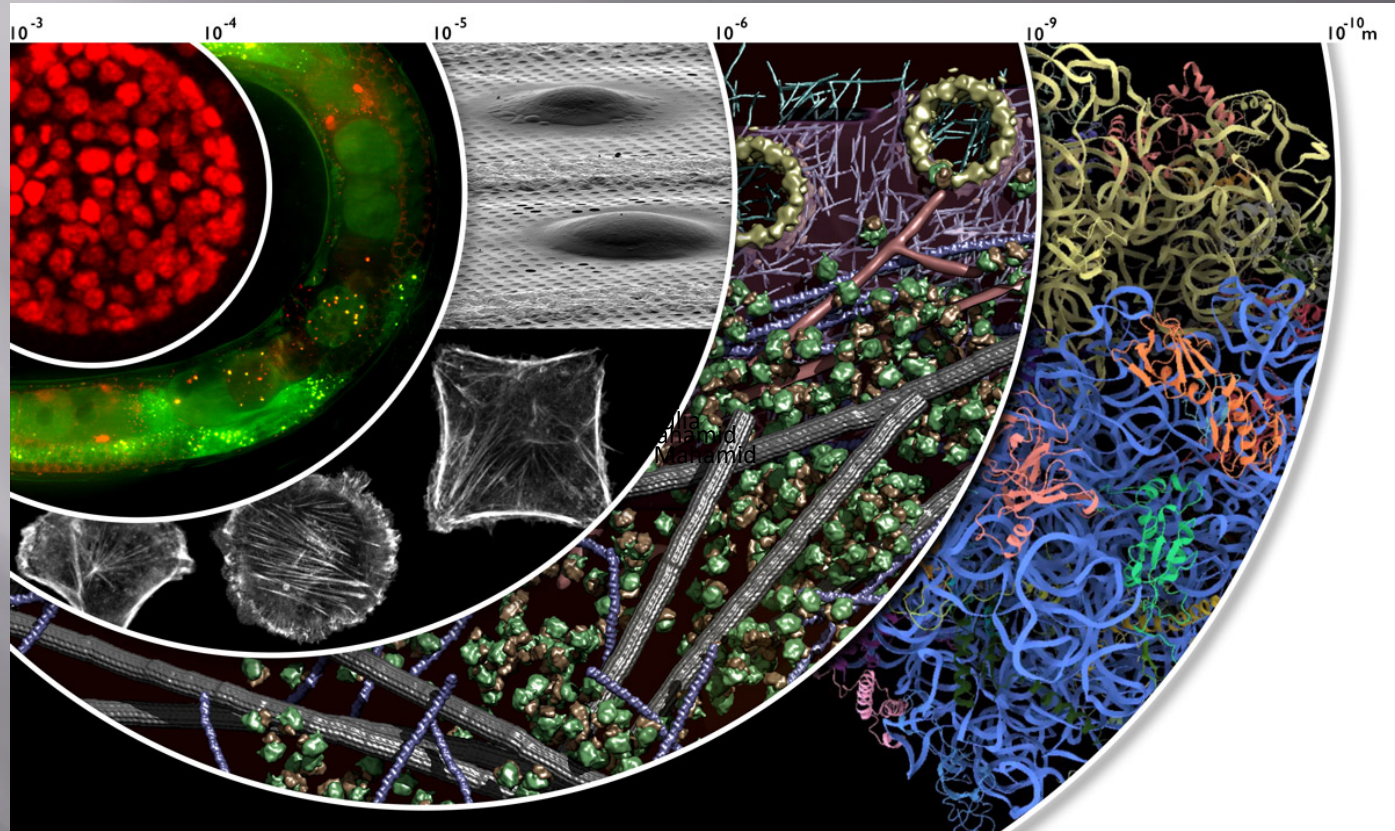
## Proton Therapy

for  
destruction of tumours and  
protection of healthy tissue

**Prof. D. Weber**

⇒ Accelerators: COMET

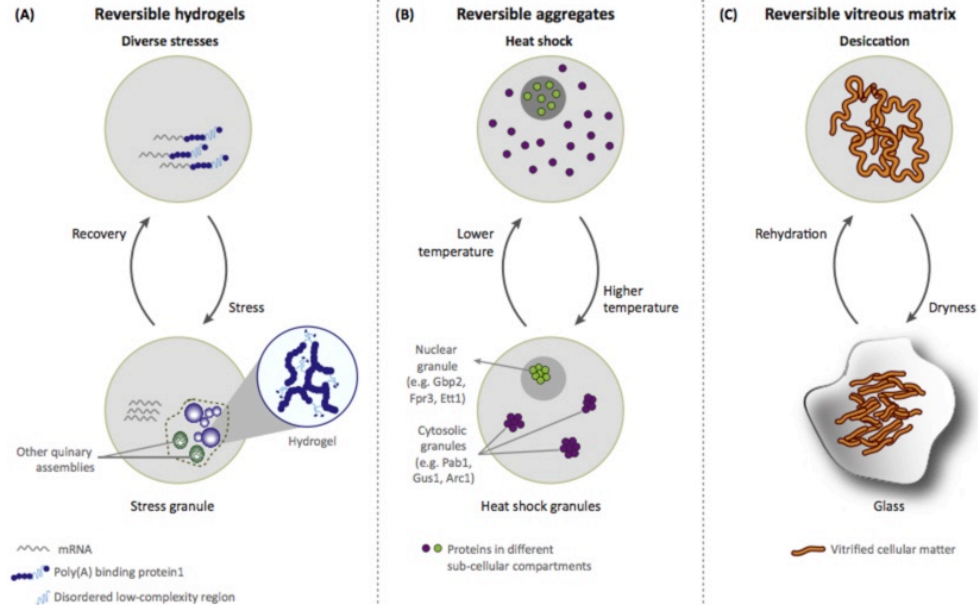
# The Complexity of Biology



# Intrinsically Disordered Proteins Adaptively Reorganize Cellular Matter During Stress

Intrinsically disordered proteins (IDPs) can protect cells from diverse stresses by forming higher order assemblies such as reversible aggregates or granules. Recently, Boothby et al. show that IDPs protect tardigrades against desiccation by forming a glass-like amorphous matrix, highlighting that material properties of disordered proteins can confer adaptation during stress.

The paper by Chavali et al can be found [here](#).

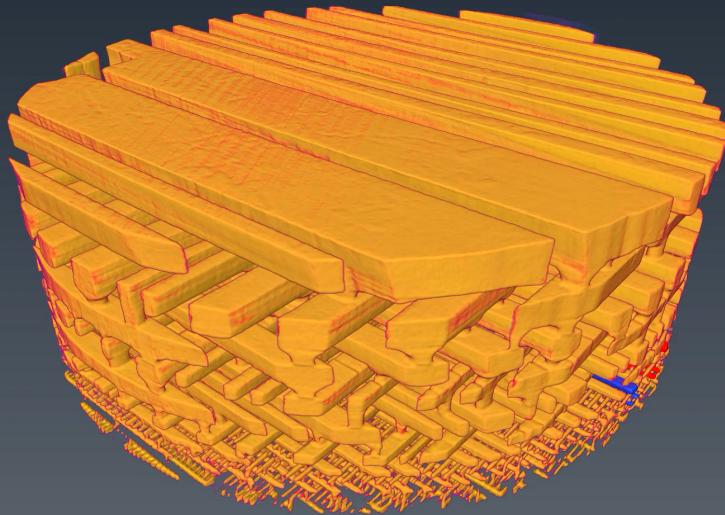




# Large-volume, high-resolution tomography

## 22-nm & 100-nm Intel processor

Holler *et al.*

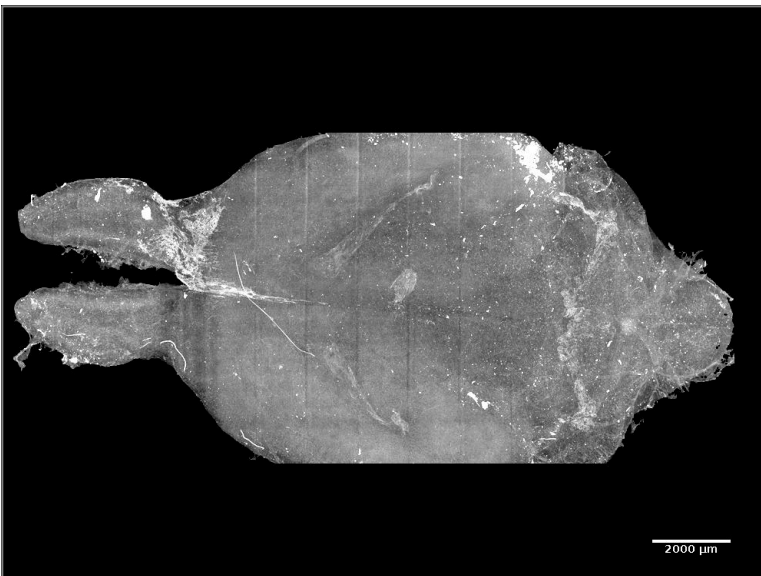
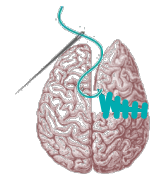


## 3D mouse brain

Miettinen *et al.*



Human Brain Project



5000 nm

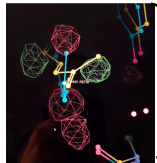
Integrating atomic scale and low-resolution structural and dynamic information in physiological context at cellular and multicellular levels to understand living systems

- Expertise in photon- and electron-based imaging methods across multiple length scales, as well as *in silico* modelling of biological and biochemical processes, is highly relevant for basic and applied biomedical research.
- These approaches help the development of non-invasive diagnostics and therapies for cancer, neurodegenerative states and infectious diseases. Collaboration is fostered with Swiss hospitals, biotech, big pharma and with institutes involved in biomedical research.

**ETH zürich**  
D-ITET; D-HEST  
D-BIOL; D-BSSE

**EPFL**  
BIOP; LBEM; LBP

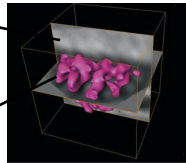
**Empa**  
Materials Science and Technology  
Empa Platform for Image  
Analysis; Biomedical Imaging  
Technologies



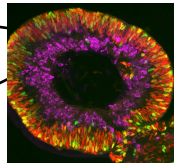
Reaction dynamics



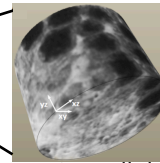
Structure-function



Multi-protein  
complexes



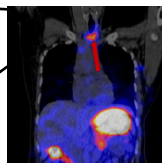
Organoid



Native cellular assembly



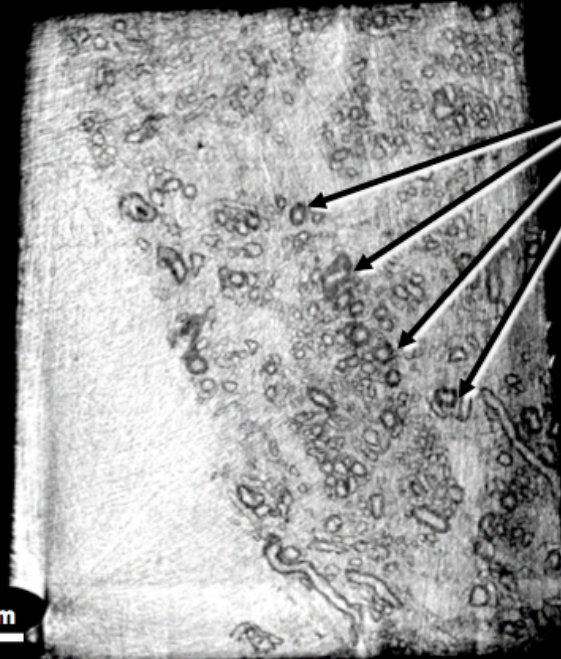
Organ



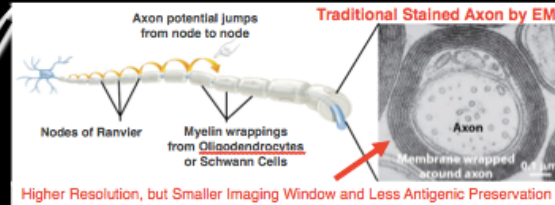
Patient

## OMNY (tOMography Nano crYo) Technology Developed at PSI Delivers Unmet Need for **Efficient Nanoscale Imaging** of Large Windows of **Unstained Cryo Tissues**

**Unstained cryo-preserved mouse brain**  
Reconstructed OMNY Tomogram – Movie



**Example of Identifiable Structures:**  
“**Highways of Communication**”  
Myelinated Axons in Brain



**“Non-Destructive Approach”**

No cutting, no milling; unique to others.  
**Imaging does not destroy specimen.**

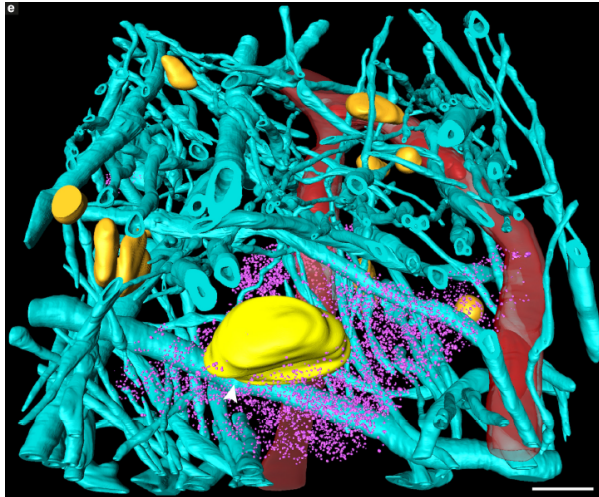
**“Precise Navigation System”**

Localise elusive cellular hallmarks for  
correlative imaging to reveal higher  
resolution **ultrastructural details** and  
**molecular identities** (as for disease).



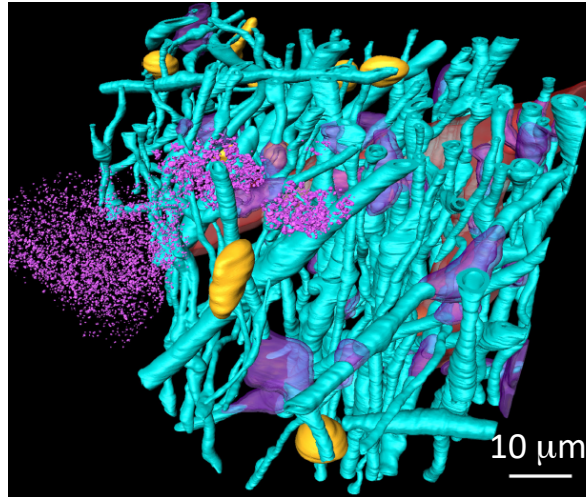
# Human brain tissue

healthy



5 specimens imaged from a healthy individual as control

Parkinson-diseased

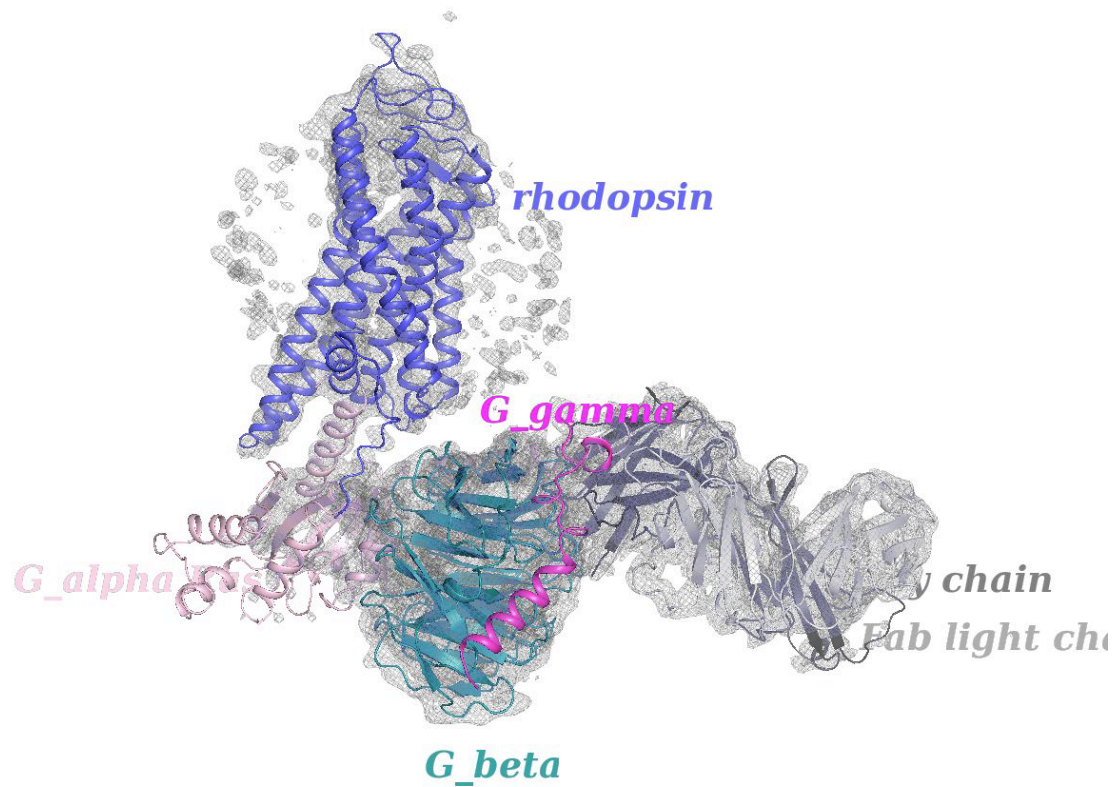


4 specimens imaged from a Parkinson-affected individual

Myelinated axons  
Swellings along axons  
Cell nuclei  
Neuromelanin-containing organelles  
Blood vessels  
Blood cells

*H.Tri Tran et al.,  
Front. in Neuroscience*

# Cry0-EM Rhodopsin Gi Protein Complex isolated from a living tissue



ChingJu Tsai



Filip Pamula





The structural biology work was performed at the macromolecular crystallography beamline **X06SA-PXI** at the **SLS** during the "**PRIORITY COVID-19 Call**". The crystallographic **data were collected on 9 April 2020**.

The planned **Easter shutdown of the SLS was cancelled for this specific experiment**. The paper was submitted within one month after answering the proposal call and **published in Nature on 29 July 2020**.

**nature** <https://doi.org/10.1038/s41586-020-2601-5>







**Accelerated Article Preview**

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**Papain-like protease regulates SARS-CoV-2 viral spread and innate immunity**

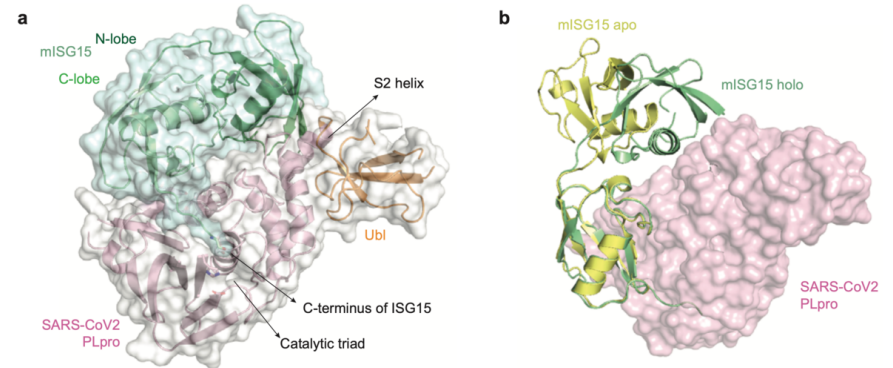
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**Online attention**

 517 tweeters	 1 blogs	 3 Facebook pages
 22 news outlets	 3 Redditors	 1 Video uploaders

**Access & Citations**

51k  
Article Accesses

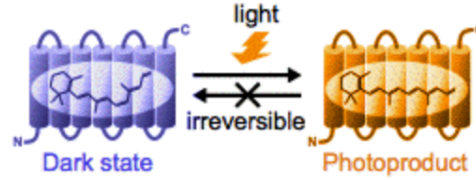


Shin, D., Mukherjee, R., Grewe, D. *et al.* Papain-like protease regulates SARS-CoV-2 viral spread and innate immunity. Nature (2020). <https://doi.org/10.1038/s41586-020-2601-5>

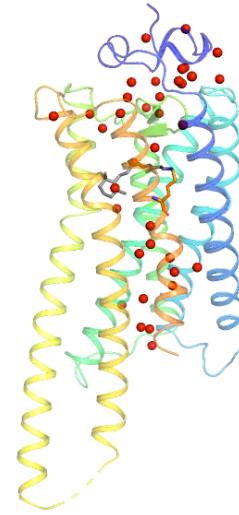
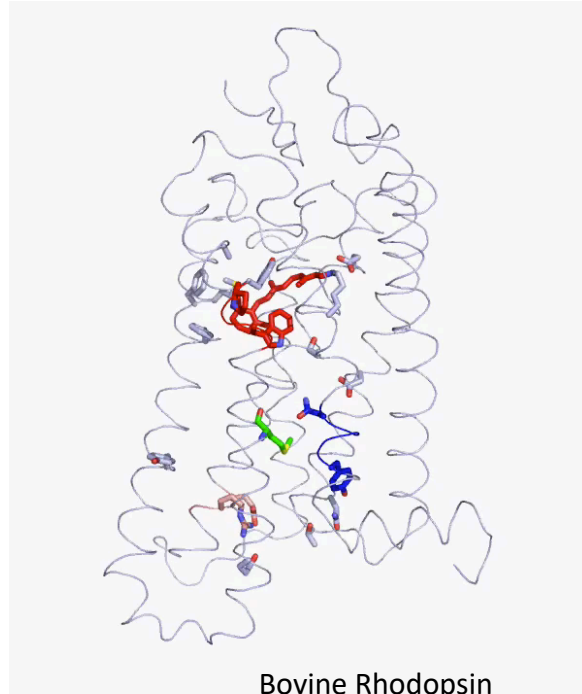
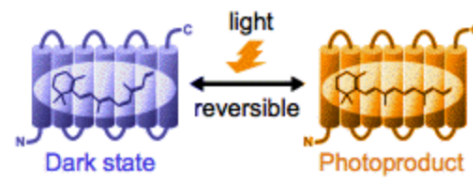
Structural analysis of SARS-CoV-2 PLpro in complex with full length ISG15

# Visual Pigments

## Bleaching pigment



## Bistable pigment



Eshita Mutt

Elena Leska

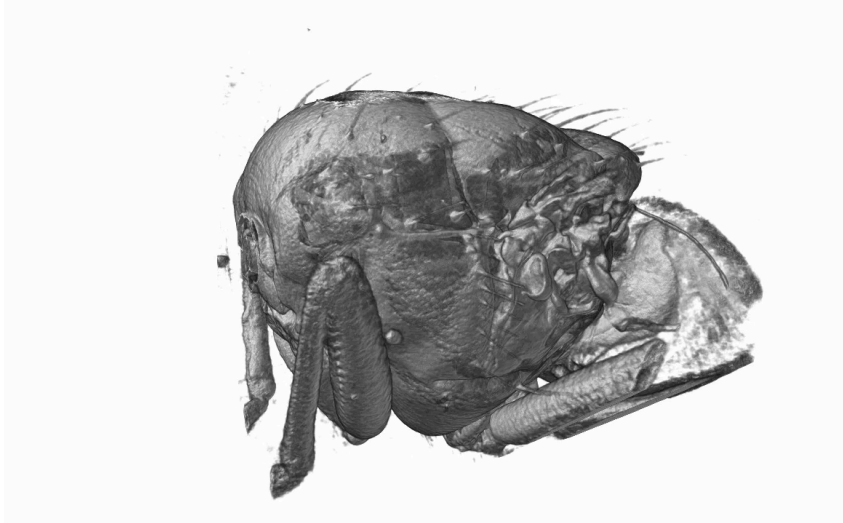
Niranjana Varma

- Imaging methods are dominating all of life science.
- Atomic structure drives mechanistic understanding and drug discovery.
- Large multicomponent molecular «machines» drive many cellular processes
- Intrinsically disordered protein domains are at the centre of nano and cellular organisation Optical readouts have been developed for signaling dynamics
- Computational methods for networks describe non linear responses in regulated processes
- Life sciences are inherently interdisciplinary and depend on novel method development



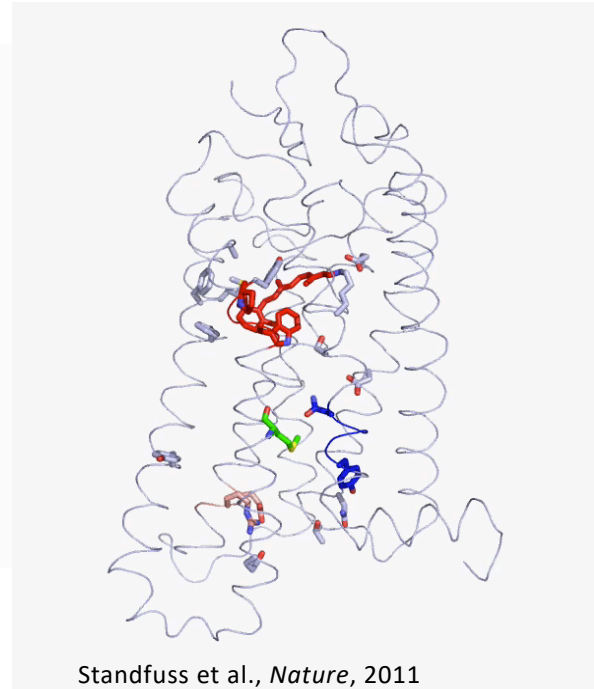
Visualizing the motion of an object helps to understand its function

## 4D *in vivo* X-ray imaging



Mokso et al., *Sci. Rep.*, 2015

## X-ray crystallography



Standfuss et al., *Nature*, 2011

# Time-resolved Structural Biology

*Driving Structural biology from molecular snapshots towards molecular movies*

Femtochemistry

Protein Dynamics

Multi-domain Protein

Structural element

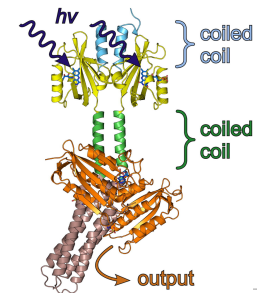
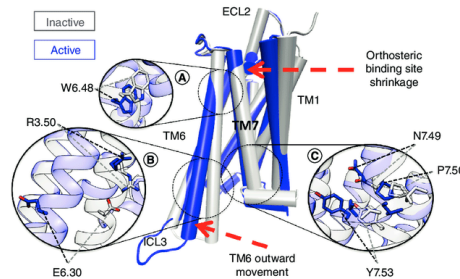
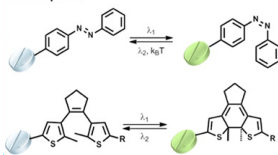
Activation with light

High spatiotemporal precision

Regulated dosage

Molecular approach

Examples:



Time

fs

ps

ns

μs

ms

s

Process

bond formation  
and breakage

concerted atom  
motions

small to medium scale  
conformational changes

large scale changes /  
complex formation

Structure

X-ray laser

Synchrotron

cryo-EM

Spectroscopy

Time-resolved spectroscopy

Simulation

Quantum Mechanics to Steered Molecular Dynamics

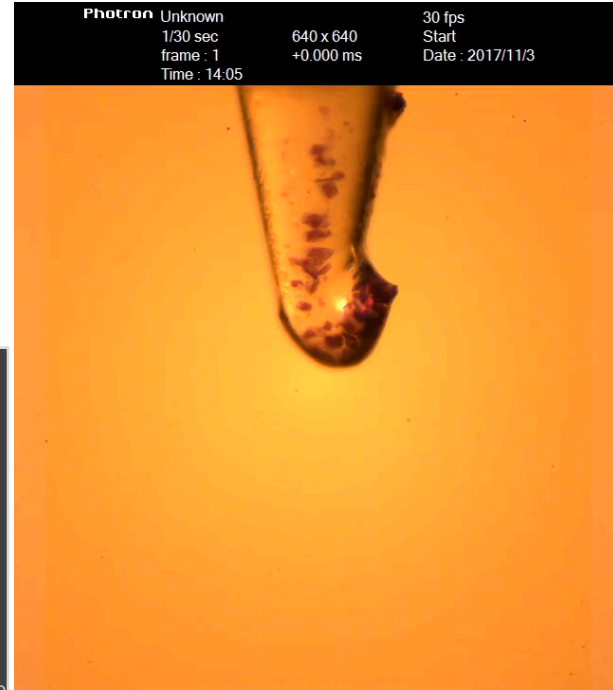
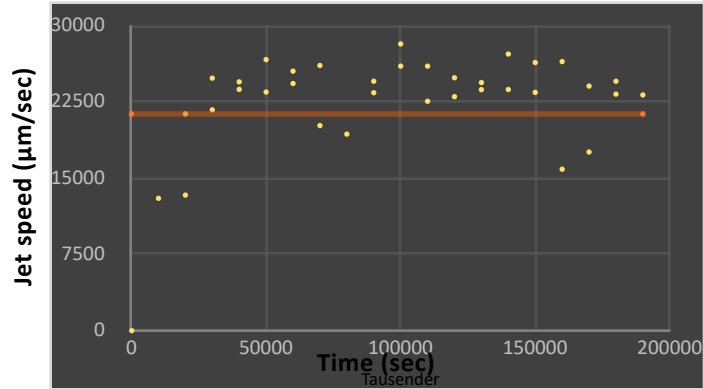
# Jetting tests with high speed camera

*A smooth injection improves data quantity and quality*

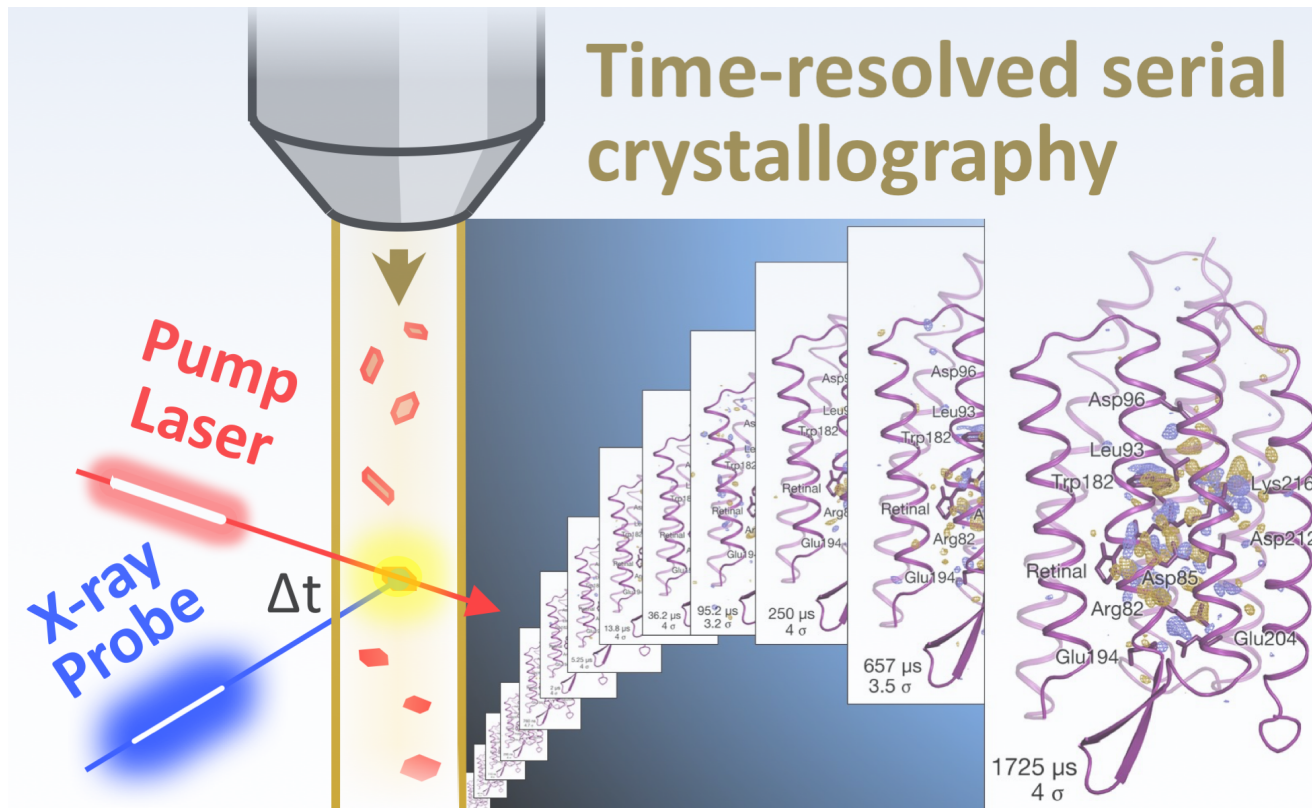


Dan  
James

- Video of the jet is taken at 1000-2000 fps
- The video is analysed by measuring the distance a crystal (or other feature) travels over a given number of frames



# Bringing time-resolved measurements to the molecular scale : Swiss FEL





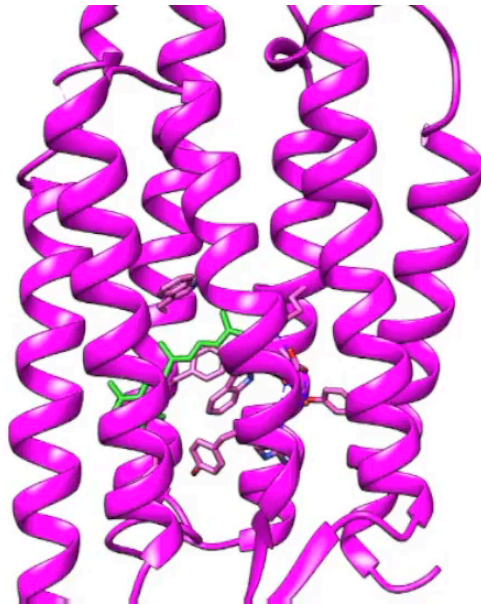
## Time resolved structural analysis of bacteriorhodopsin: Structural basis of **photocatalysis**



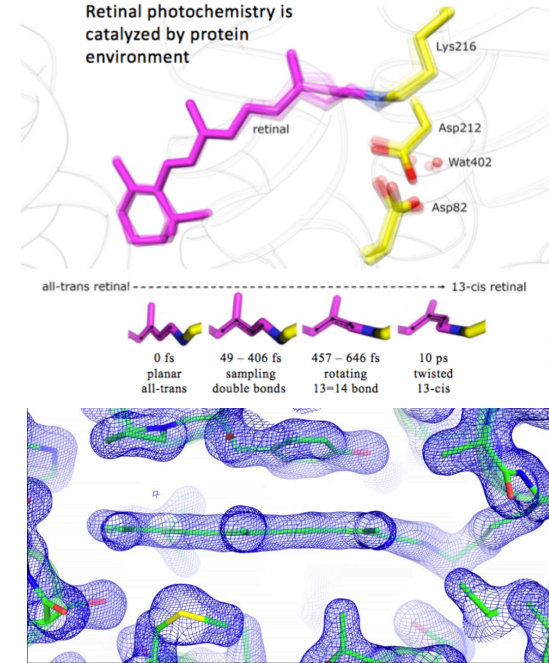
Joerg Standfuss



Przemek Nogly

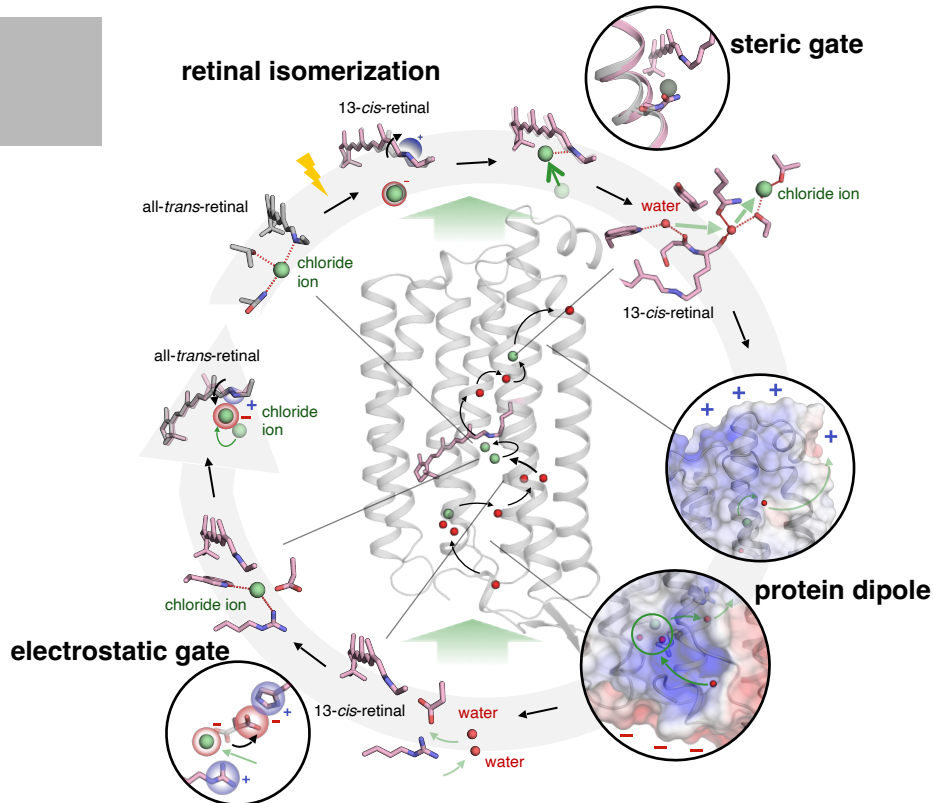


The chemical basis of **optogenetics**



Nogly et al. Science 2018; DOI: 10.1126/science.aat0094

# Movie of Chloride Pump through Cell Membrane



S. Mous *et al.*, *Science* 10.1126/science.abj6663 (2022).

Molecular analysis of **full activation cycle of light-driven chloride pump mechanism** using time resolved, serial X-ray crystallography and multiscale simulation.

- **Time-resolved** detection of **transient anion binding** across the cavity (time range: 10 ps to 55 ms).
- **Light-induced isomerization of retinal** provides energy for chloride transport.
- **Driving force** created by **protein dipole moment**.
- **Unidirectional transport** ensured by steric and electrostatic **molecular gates**.



Sandra Mous, ETHZ



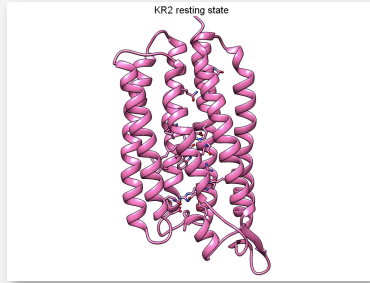
G. Gotthard, PSI



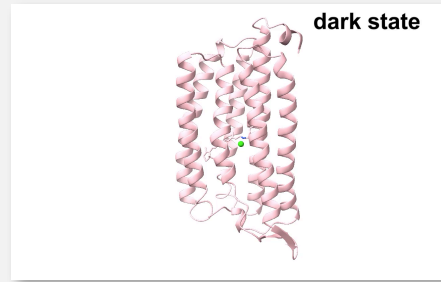
P. Nogly, ETHZ

# Examples of biological experiments at SwissFEL

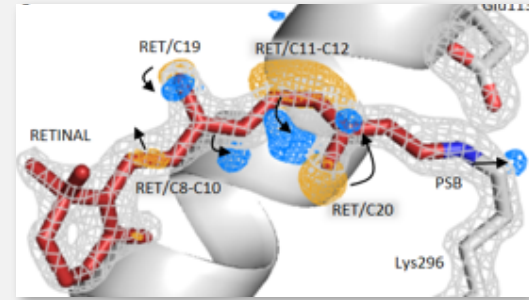
## Rhodopsins pave the way into a dynamic future for structural biology



Skopintsev *et al.*, 2020, Nature



Mous *et al.*, 2022 Science



Gruhl *et al.*, 2022, Nature, accepted

### Sodium pumping rhodopsin

- Ten molecular snapshots of **sodium** transport **out of the cell**
- Next-generation **optogenetic tool**

### Chloride pumping rhodopsin

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

### Visual GPCR rhodopsin

- Molecular snapshots of **early events in vision**
- **GPCR** activation

## Potential applications in pharmacology

Dynamic atomic information is necessary for understanding pharmacology

This includes fundamental processes like induced-fit, conformational selection or lock-and-key mechanisms of ligand binding

Understanding catalytic effect of proteins requires measuring the changes to the energetic landscapes introduced by the bound substrate or ligand

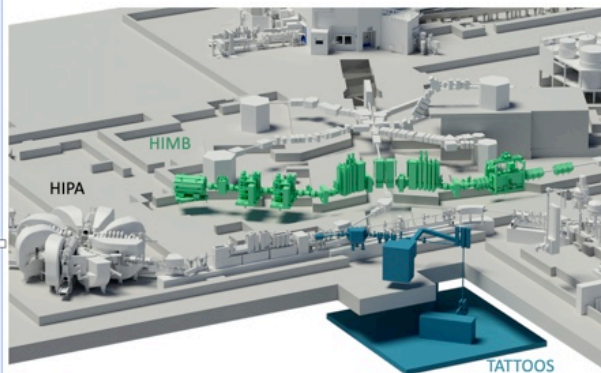
Quantification of the dynamic mixture of different conformations of Receptors, Channels and Transporters in solution can explain drug action

Using the right kind of experiments all these questions can be addressed

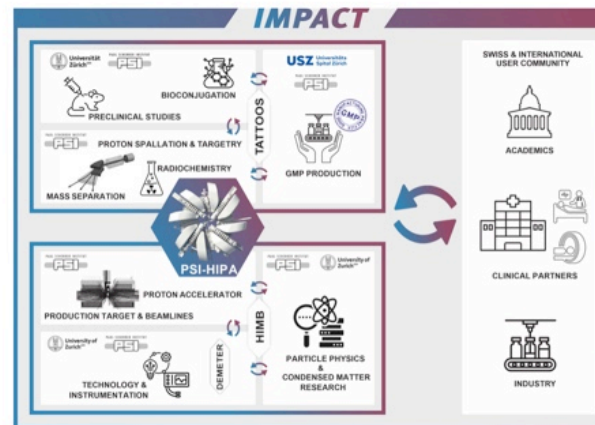


# IMPACT: TATTOOS

Das Ziel von **IMPACT** (engl.: Isotope and Muon Production using Advanced Cyclotron and Target technologies) SBF-Infrastrukturprojektes (Periode 2025-2028) ist der Aufbau von zwei neuen Target-Stationen sowie Strahl-  
linien an der Protonenbeschleunigeranlage HIPA (Eng.: High Intensity Proton Accelerator) des Paul Scherrer  
Instituts. Dies wird zu einer Erhöhung der Myonen-Intensität um einen Faktor 100 führen (HIMB) und neue  
Radionuklide für die fortgeschrittene Krebsbehandlung verfügbar machen (TATTOOS).

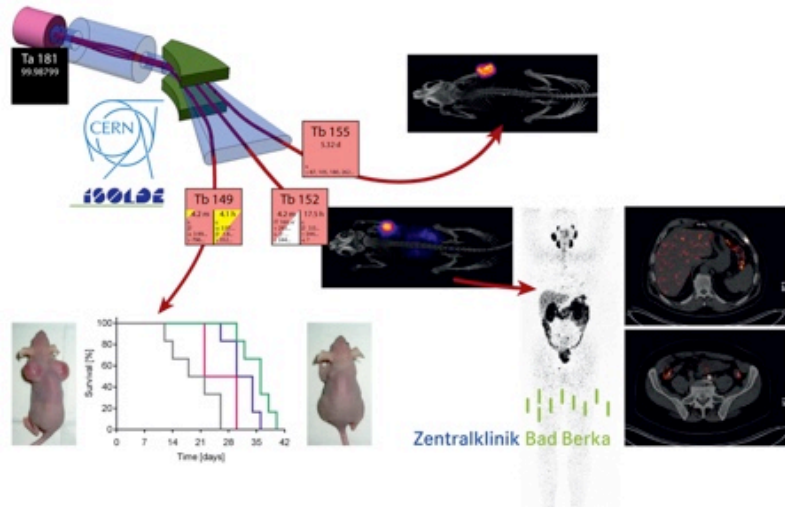


**IMPACT@HIPA** Die geplante Erweiterung der bestehenden Protonenbeschleunigerinfrastruktur zu Gunsten von HIMB (in grün; engl.: High-Intensity Muon Beams) und TATTOOS (in blau; engl.: Targeted Alpha Tumor Therapy and Other Oncological Solutions).

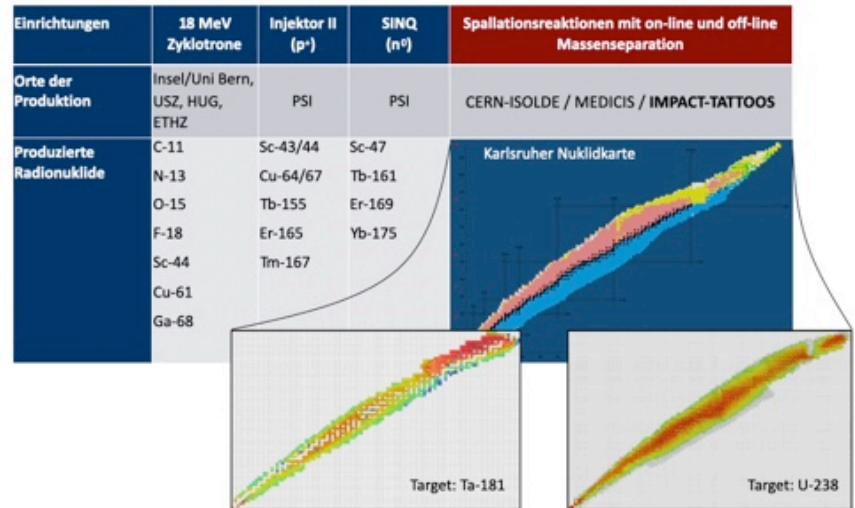


**Strategie IMPACT** Erklärtes Ziel ist eine substanzielle Erweiterung der bestehenden Protonenbeschleunigerinfrastruktur am PSI, die es erlaubt eine weltweit führende Anlage weiter auszubauen. Dies eröffnet eine Vielzahl einzigartiger Möglichkeiten für die weitere Erhöhung der Attraktivität des Forschungsstandortes Schweiz.

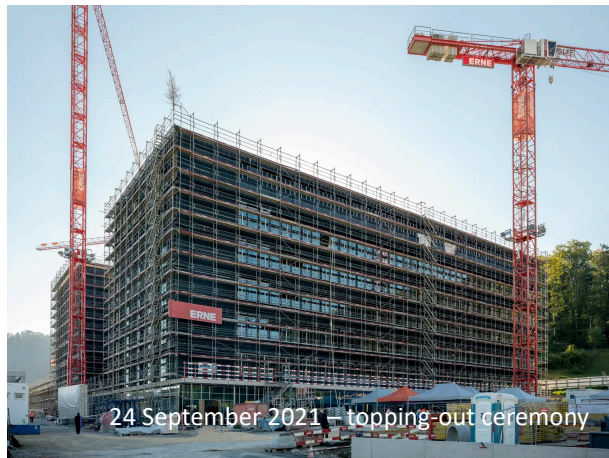
# IMPACT: TATTOOS



Die „Terbium-Schwester“ Die Terbiumisotope Tb-149 (Therapie), Tb-152 (Diagnose) und Tb-155 (Diagnose) wurden in Zusammenarbeit mit ISOLDE (CERN) am PSI auf deren radiopharmazeutische Anwendbarkeit erforscht. Diese Vorstudien waren äusserst vielversprechend und sind einer der entscheidenden Treiber hinter TATTOOS.



**Produktion von Radionukliden für die Radiopharmazie** Verschiedene Produktionsmöglichkeiten von Radionukliden für die Radiopharmazie (Bildgebung und Therapie) in der Schweiz. Mit TATTOOS wird die Anzahl verfügbarer Radionuklide (inkl. therapeutischen Dosen) schlagartig um ein Vielfaches vergrößert.



24 September 2021 – topping-out ceremony



**Combining cutting-edge research and an innovation ecosystem in one place:**

- talents and know-how (experts, Postdocs, PhD students, apprentices)
- large-scale research facilities (SLS, SwissFEL, SINQ, SμS)
- precision workshop
- vibration-free laboratories
- clean room for nanofabrication



# BIO/PSI Spin-Offs and Park Innovaare companies with high relevance for BIO

**lead:pro**

BIO Spin-Off, leading expertise in structural analysis of drug targets, important PSI partner for translational projects in sample preparation and delivery, tenant for Park Innovaare

Focal Bioscience

Upcoming LNB Spin-Off in 2022 on image-based diagnostics of disease related processes

**DECTRIS**<sup>®</sup>

PSI spin-off on detector development for X-rays and Electrons. Highly relevant collaboration partner for multi-scale imaging technology

**ELDIGO**  
SCIENTIFIC

Successful Start-up inspired by electron diffraction research at BIO with head quarter at Park Innovaare

**BIO Spinoff**

 **araris**

Successful BIO spin-off on site specific compound tagging of antibodies. Demonstrates wider impact of research activities at CRS outside of Radiopharmacy

**INTERAX**

BIO Spin-Off, AI-based lead compound validation, uses innovative approaches with high relevance for projects at BIO, tenant for Park Innovaare



## ● Life sciences are

- > Changing rapidly
- > Demand a very different user environment than large scale physics
- > Are inherently interdisciplinary and driven by method development
- > Need large facilities to catalyse these developments better

**Biology & Life Sciences are major drivers for large high energy facilities in Europe**

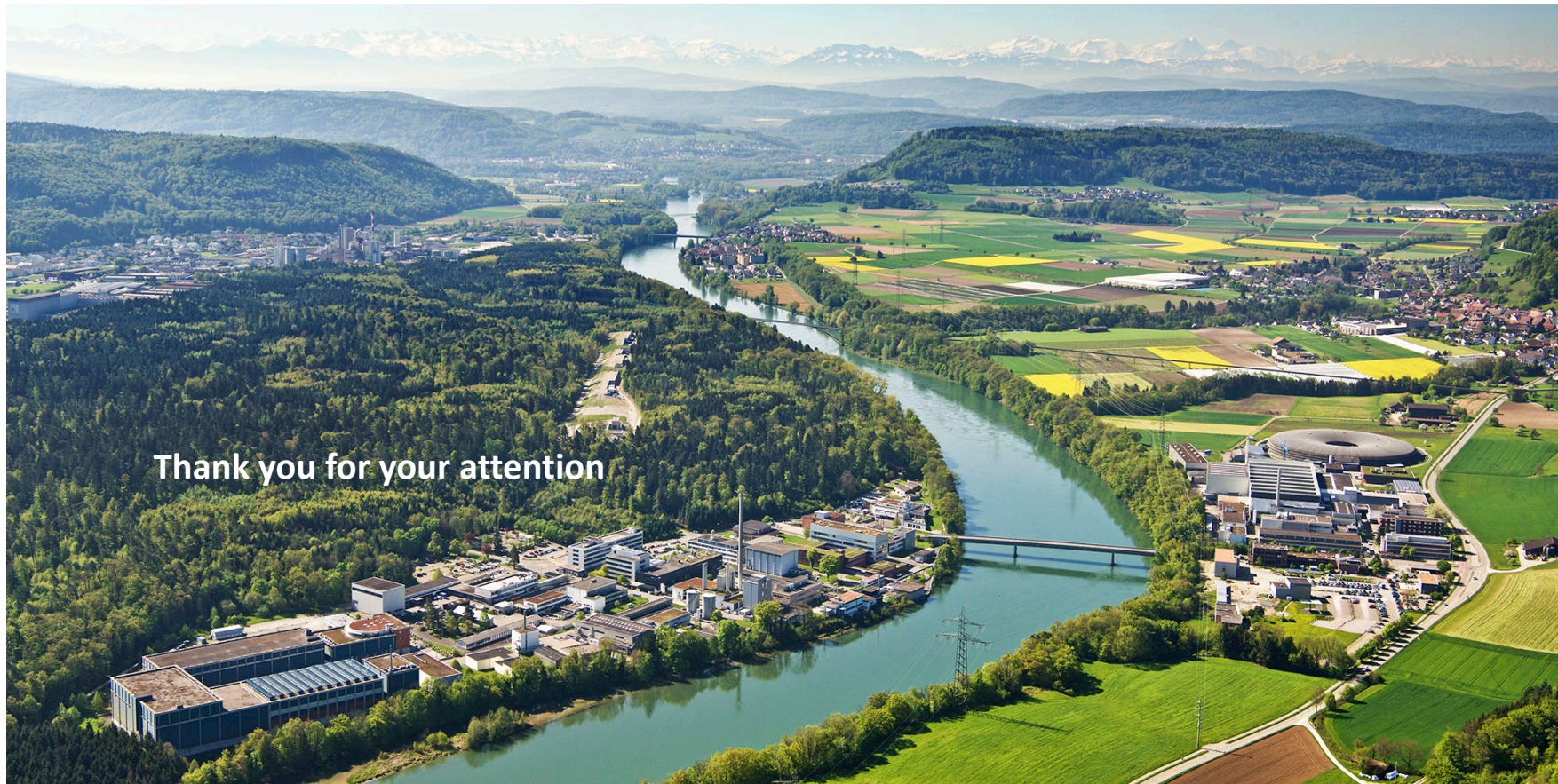
PSI offers a world-wide unique combination of large-scale facilities: X-ray sources SLS and SwissFEL, neutron source SINQ and muon source  $S\mu S$  and technology platforms for a broad range of research and development in science and medicine, education and collaboration with industry. **Infrastructure for science and innovation.**

Own science and technology program and combination with world-leading schools EPFL and ETH and three other Swiss national labs expands **know-how** and **talent pool**.

**Park Innovaare** of Switzerland Innovation is a new innovation park connected directly to the institute, setting the stage for much larger **economic impact**.



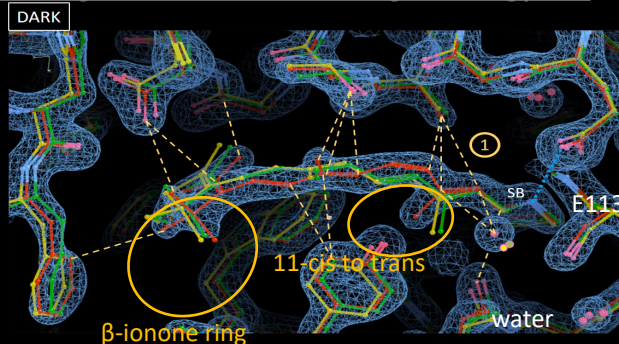
# Wir schaffen Wissen – heute für morgen



Thank you for your attention

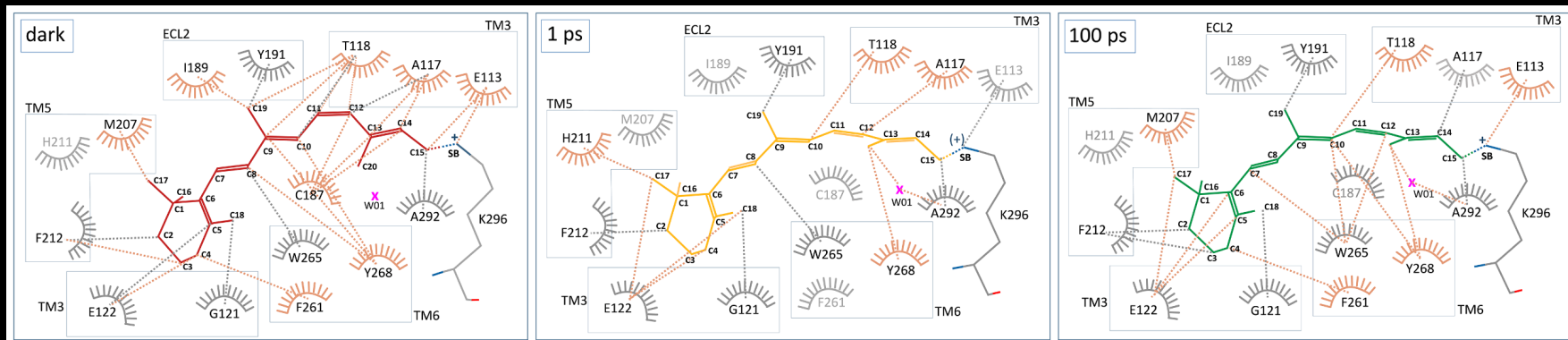
# Ultrafast changes in the rhodopsin binding pocket.

weakening of retinal interactions in the ligand binding pocket :



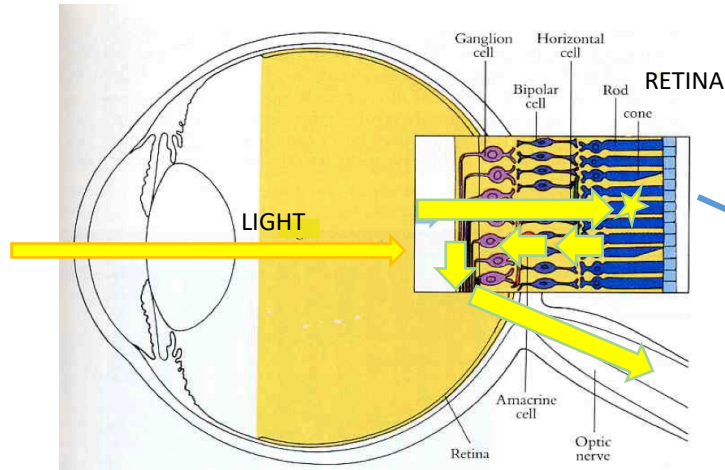
- dark state model
- 1 ps
- 100 ps

Environment distances < 3.7 Å





# Mammalian rhodopsin and the first step of vision



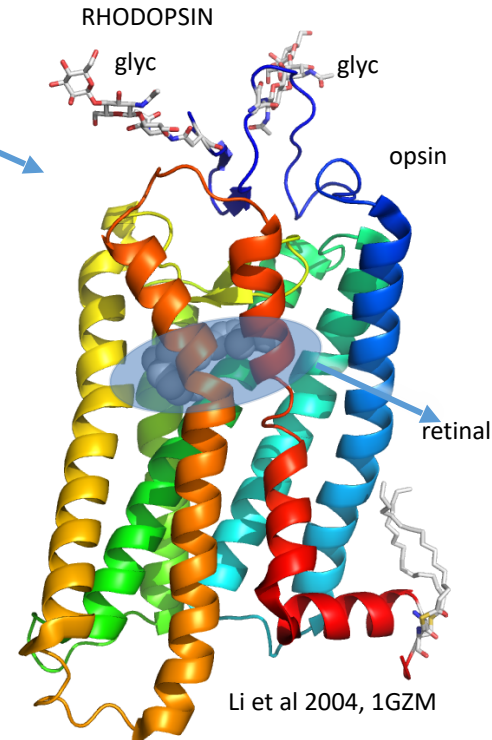
webvision.med.utah.com

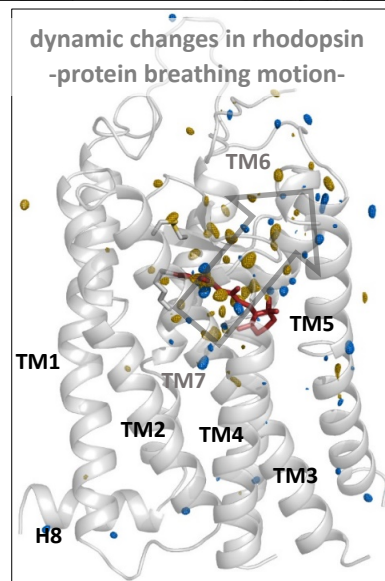
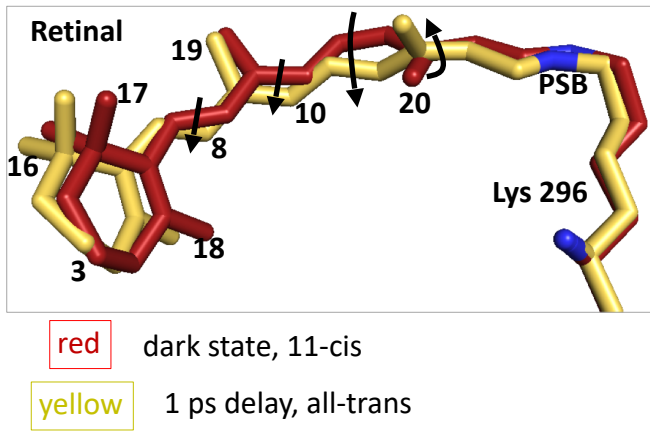
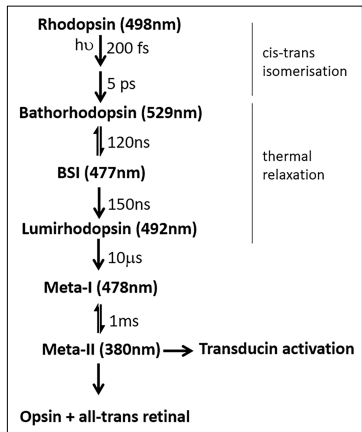
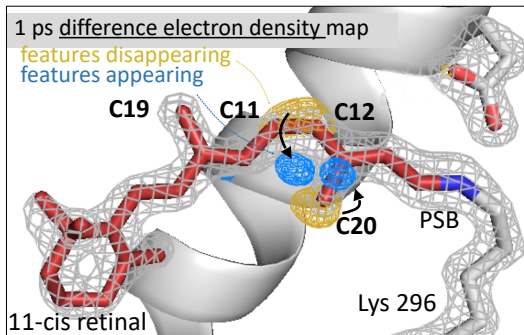
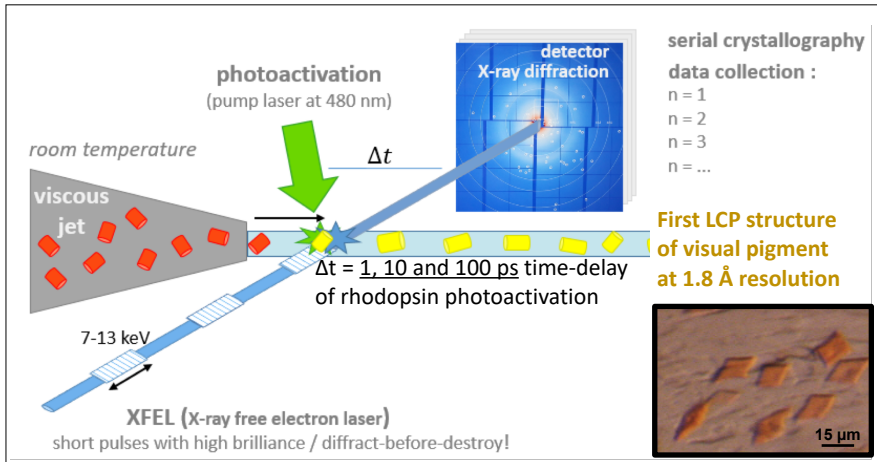
## GPCR (G protein-coupled receptor)

- 7 transmembrane segments
- monostable / bleaching
- coupled to the G protein transducin

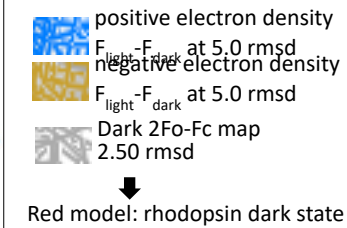
## Mutations in the opsin gene:

- > Retinitis pigmentosa
- > Night blindness





- Dynamics of the Switch for Vision
- Spatial and Temporal Resolution
- Complementary Characterization (solution scattering (XSS), quantum mechanics/molecular mechanics, molecular dynamics)
- Rhodopsin isomerisation is highly synchronised
- Steep conformational landscape is partially responsible for high quantum yield



Oct. 2022



Jan. 2023

**nature**  
Gruhl et al, IN PRESS