May 14 - 19, 2023
Elba Island, Italy

LEAPS League of European Accelerator-based Photon Sources

Meets Life Sciences

LEAPS and…

the Future of Life Sciences at Large Scale Facilities ?

Jean Susini
Synchrotron SOLEIL, France

A very personal view from the user facilities' perspective

Special thanks to Pierre Legrand, Andy Thompson, Frédéric Jamme, Sakura Pascarelli & Bárbara Machado Calisto

League of European Accelerator-based Photon Sources

Caterina Biscari – Welcome & Introduction May 15th

LEAPS is the largest consortium of analytical facilities worldwide and further expanding its service to an interdisciplinarity European user community.

19 facilities **16** institutions **10** countries

>300 operating End-Stations **>5.000** publications / year

>1.000.000 h beam time / year **>15** spin off companies

>35.000 user / year from all EU and beyond researchers from all research areas

SESAME LENS Canadian Light Source Centre canadien de rayonnement synchrotron ESUO EUROPEAN SYNCHROTRON AND FEL USER ORGANISATION

LEAPS and Life Sciences

Estimated number of endstations primarily dedicated to life sciences

- ~ 45 : XRD, MAD, SAD, SAXS, WAXS…
- ~ 35 : X-ray imaging & X-ray microscopy beamlines
- ~ 10 : IR and UV spectroscopy and micro-microscopy

Averaged over 5 (3.5) years

- > 3000 experiments / year
- ~ 6500 visits / year
- ~ 2215 publications / year

LEAPS LEAPS database

BioSync https://biosync.rcsb.org

WAY FOR LIGHT https://www.wayforlight.eu/

‘Synchrotron light’ techniques in life sciences

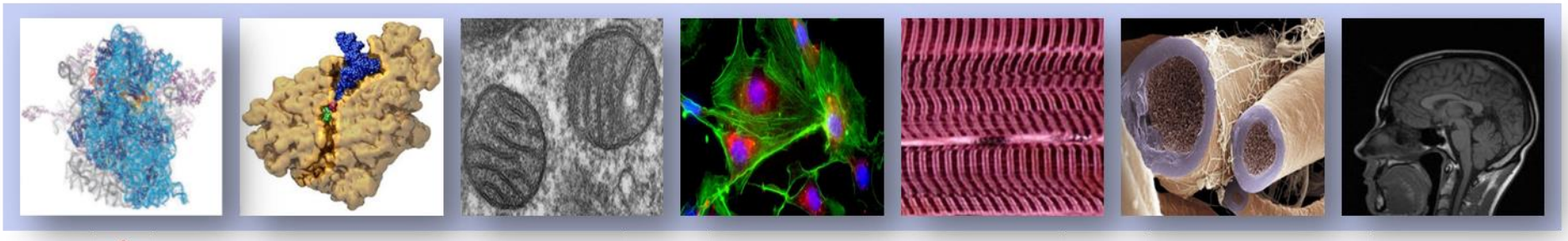
X-Ray Fluorescence

- Composition
- Quantification
- Trace element mapping

X-ray Diffraction & scattering

- Crystal structure
- Structural information
- High resolution

Increasing biological complexity and integrity



Å — nm — µm — mm

Increasing resolution

- High resolution
- Density mapping

FTIR & UV (micro)spectroscopy

- Molecular groups & structure
- High S/N for spectroscopy
- Functional group mapping

X-ray (micro)spectroscopy

- Short range structure
- Electronic structure
- Oxidation/speciation mapping

LEAPS and Life Sciences

We maintain the established discovery-driven **service** provision supporting and developing new, disruptive Ideas

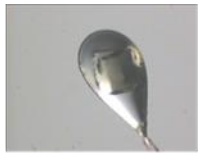
We implement a targeted challenge-driven **service** provision

We develop a new remote **service** provision

Free of charge

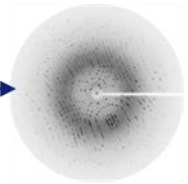
From sample preparation down to data processing

MX: Standardization for a production technique



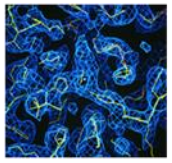
Crystal

X-rays



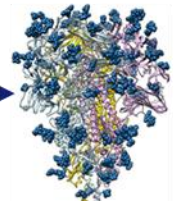
Diffraction pattern

Phase



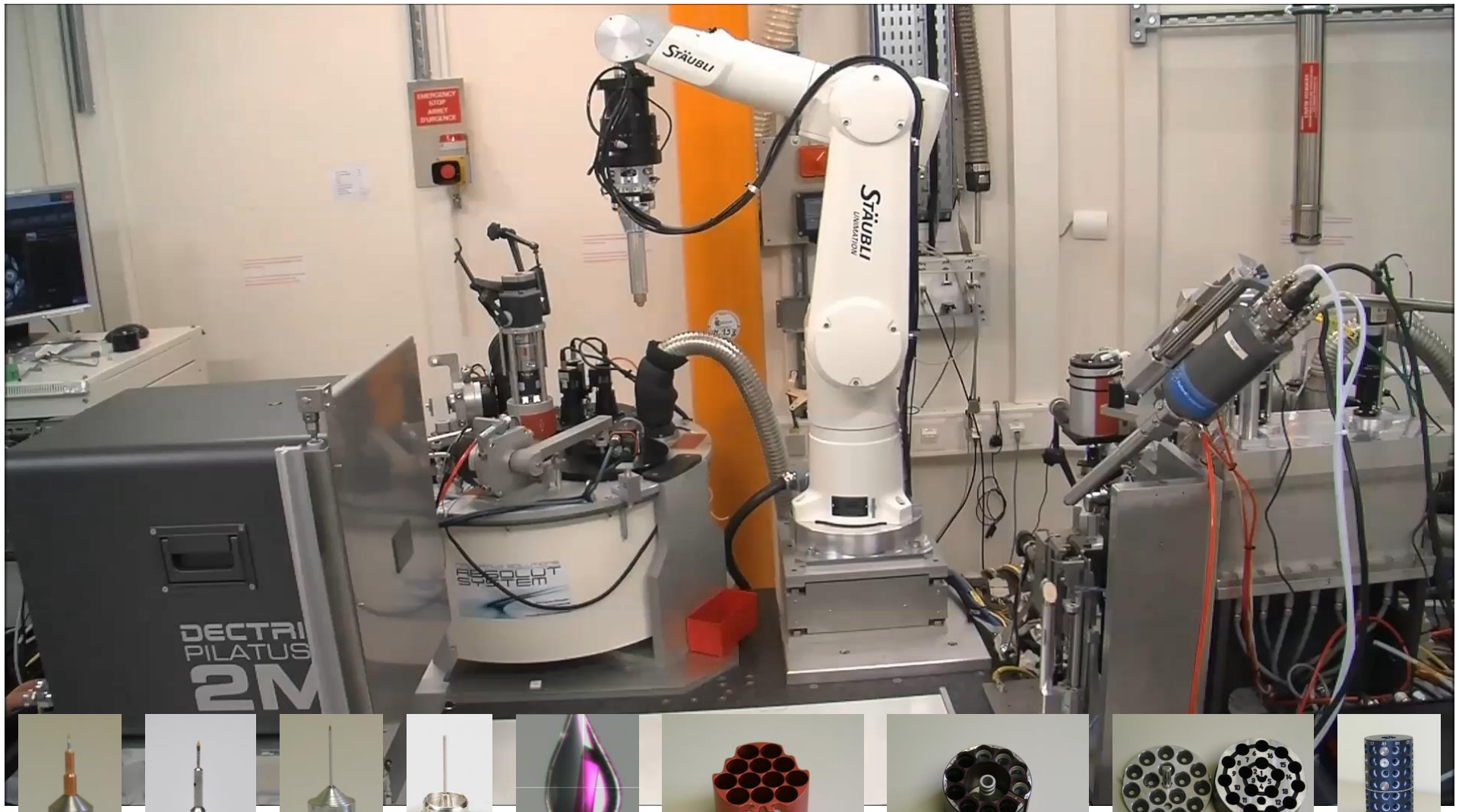
Electron density map

Fitting



Atomic model

refinement



…that was needed! one example…

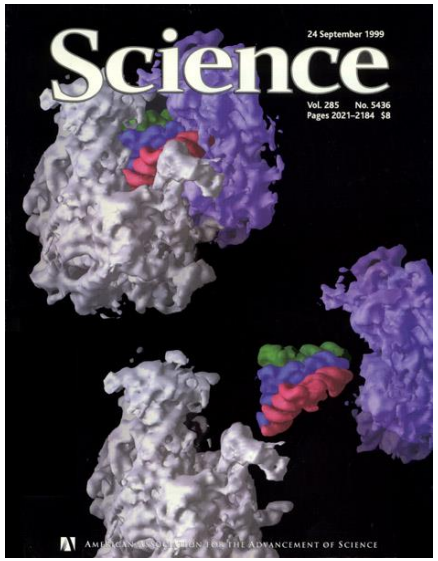
The Nobel Prize in Chemistry 2009

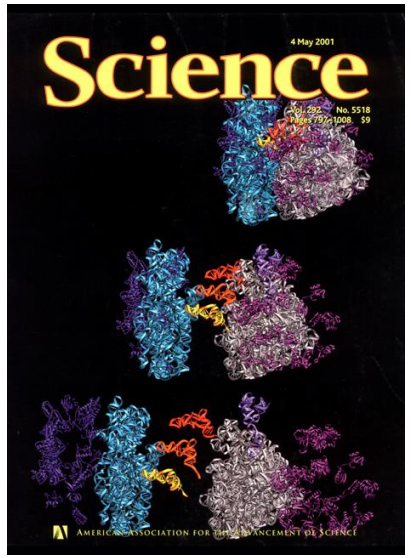
Photo: U. Montan
Venkatraman Ramakrishnan
Prize share: 1/3

Photo: U. Montan
Thomas A. Steitz
Prize share: 1/3

Photo: U. Montan
Ada E. Yonath
Prize share: 1/3

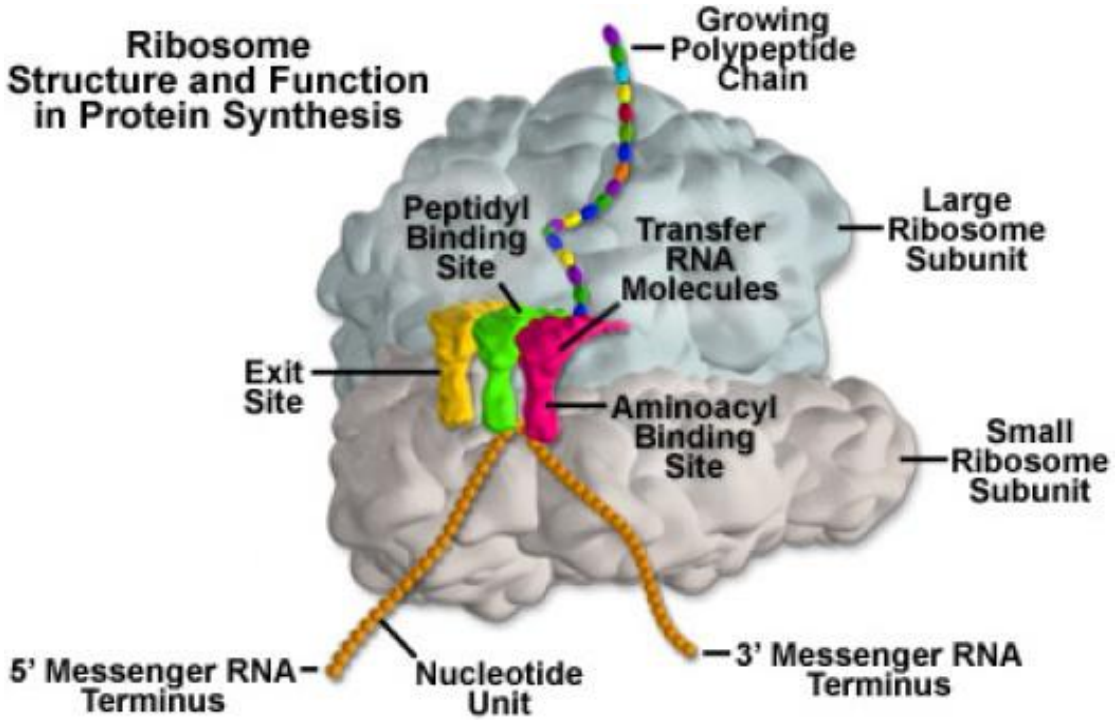
The Nobel Prize in Chemistry 2009 was awarded jointly to Venkatraman Ramakrishnan, Thomas A. Steitz and Ada E. Yonath *"for studies of the structure and function of the ribosome".*





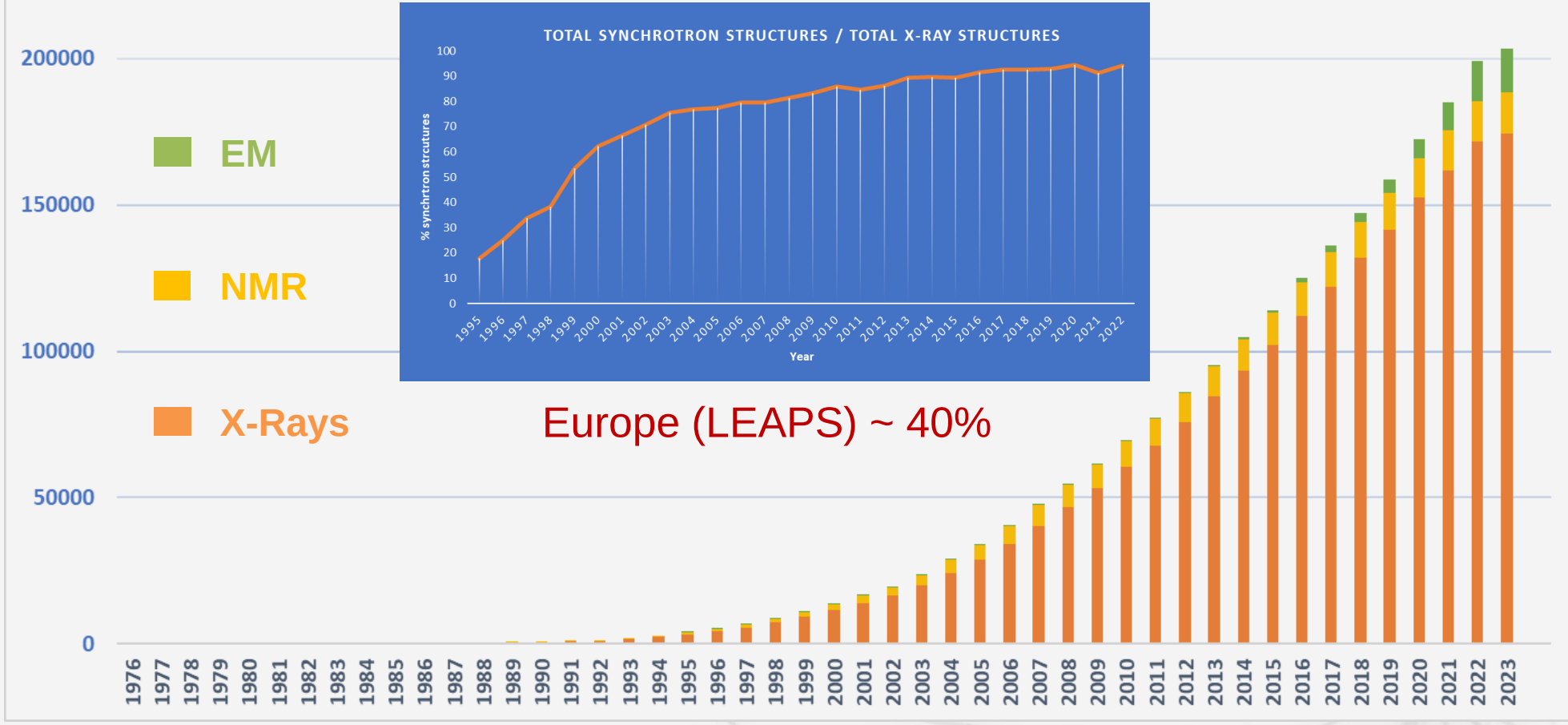
Over 5 years of use of ESRF beamlines

- Several 100s experimental sessions
- > 15,000 data collections



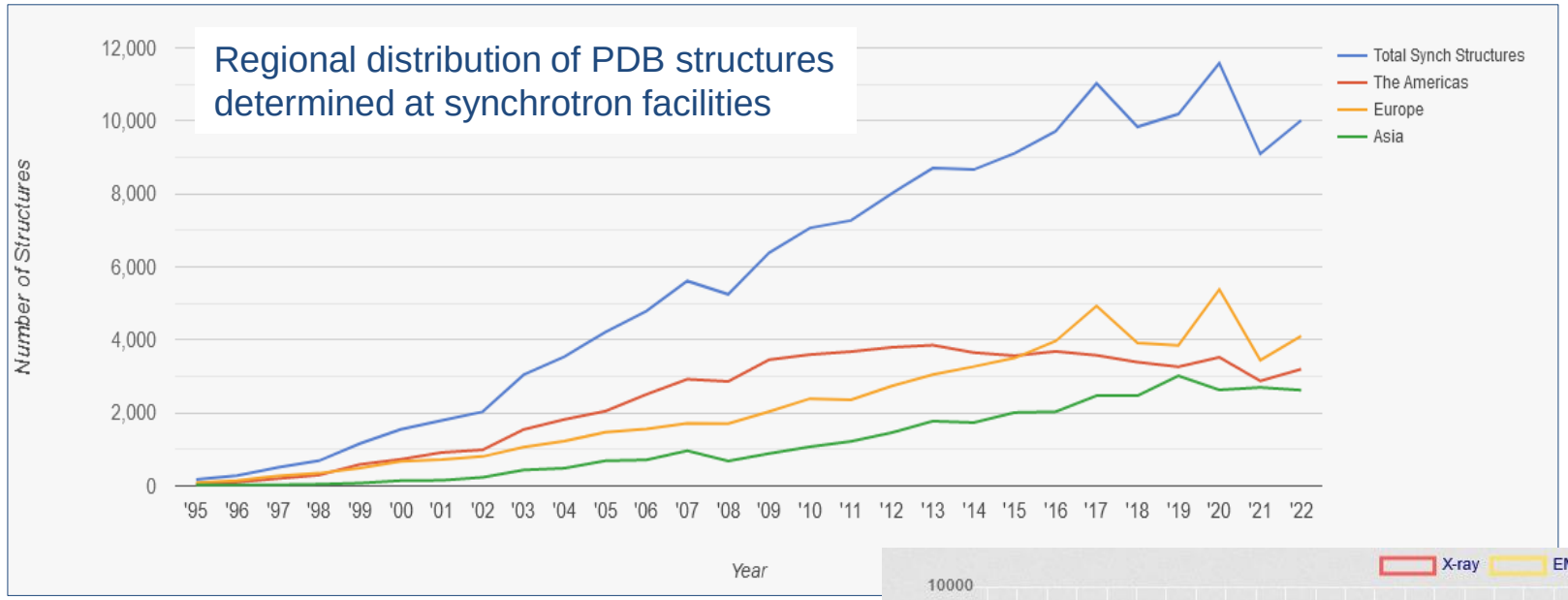
Structural Biology – some statistics (1)

PDB Statistics: Overall growth of released structures

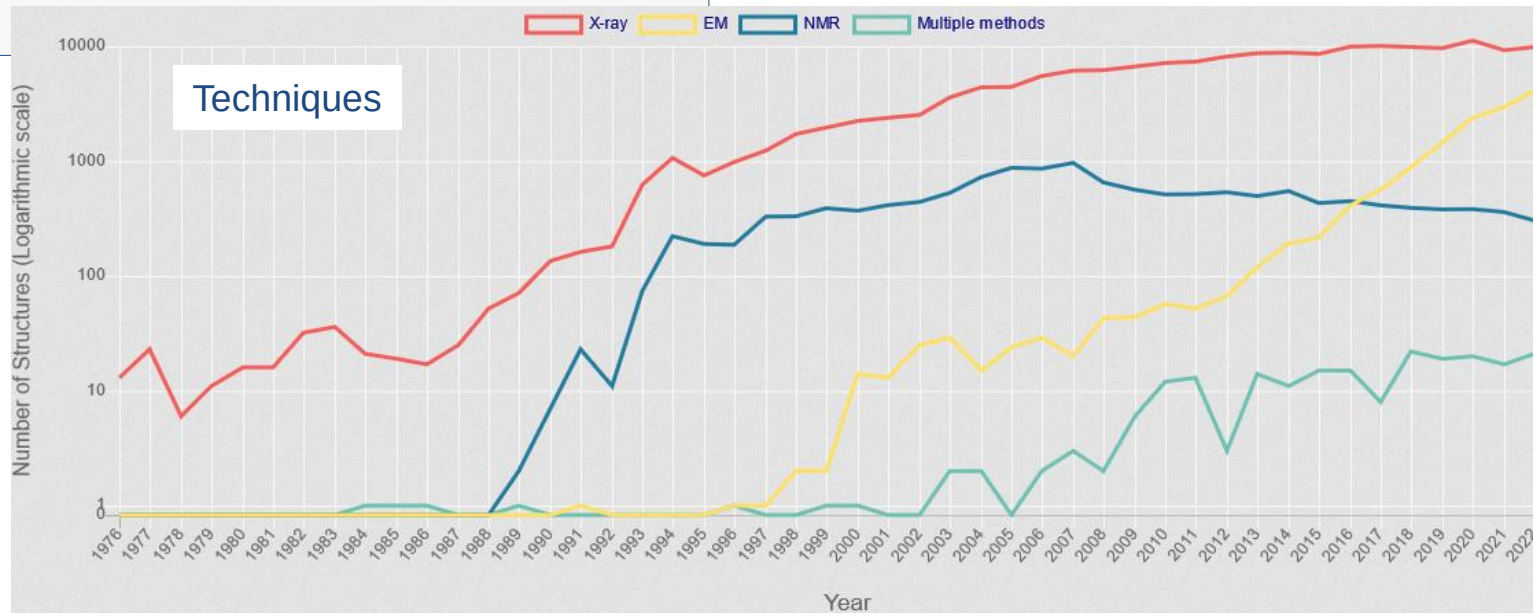


Europe (LEAPS) ~ 40%

Structural Biology – some statistics (2)



Number of structures released per year



“Running cryo-electron microscopes as beamlines”

2015 eBIC Diamond Light Source, Harwell, UK

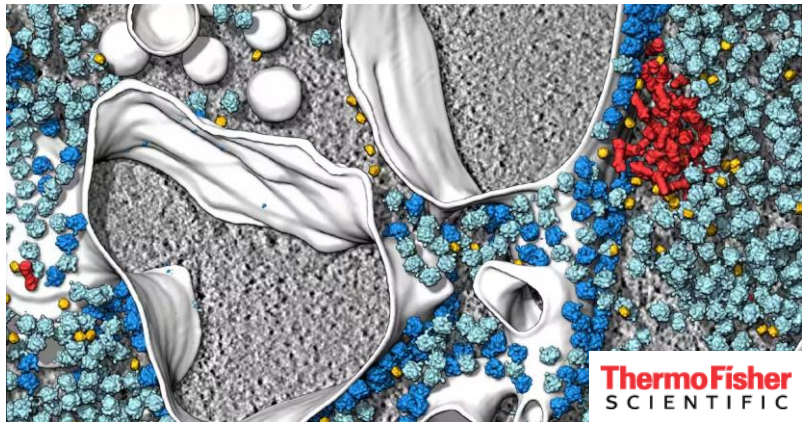
“… Synchrotrons are the best place to run cryo-electron microscopes…as user facilities”

Richard Henderson, EMBL Heidelberg 2017

As of today LEAPS partners run 17 (+2) cryo-EMs with access to the whole users’ community

Cryo-SPA ⟵ ? ⟶ Cryo-ET

2017 CM01 ESRF, Grenoble, France



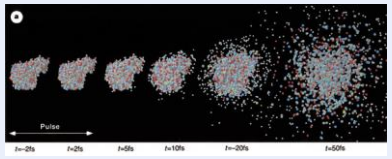
The three pillars of structural biology at photon source facilities

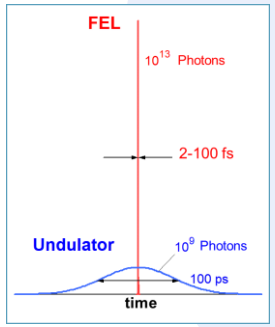
Sample
handling & management

Data
processing & management

X-FEL

"measuring before destroying"

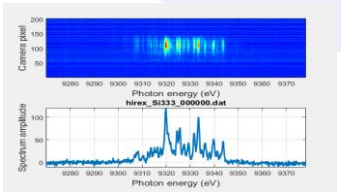




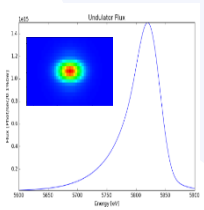
High expectation
very few instruments

From proof-of-concept
to science driven applications

R&D needed

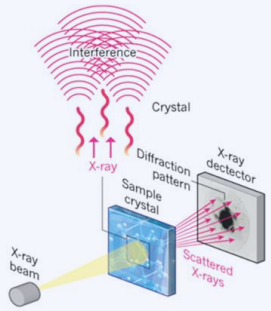


Serial
Crystallography
sample handling
room temperature
time resolution



Synchrotron

High throughput

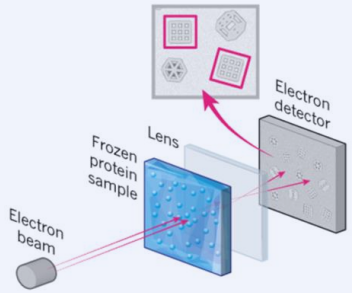


High but decreasing demand
High capacity

Data collection
Standardization
Automation

Cryo-EM

"no crystals"



High demand
increasing capacity
SPA & ET

Towards time-resolved
In-cellulo

dataset merging
samples handling
data processing
automated pipelines

Trends: multimodal and multi-facility experiments

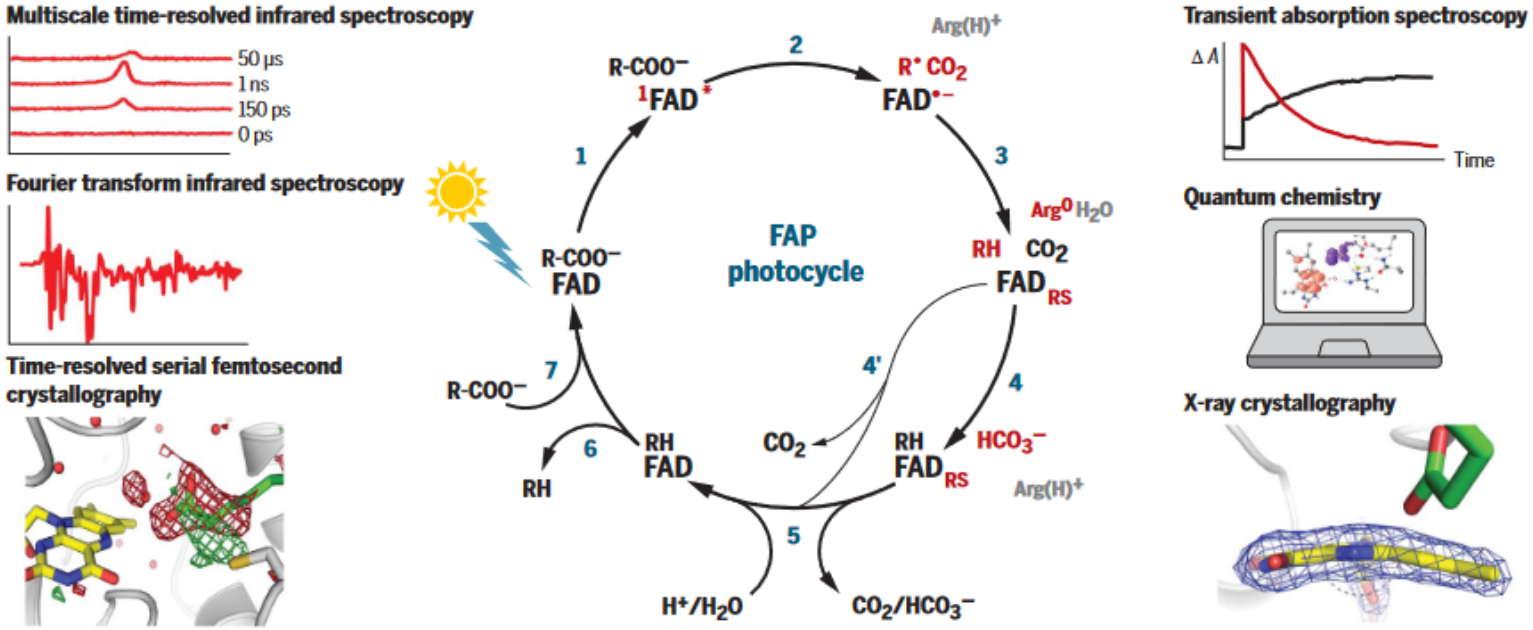
RESEARCH ARTICLE SUMMARY

PHOTOENZYMES

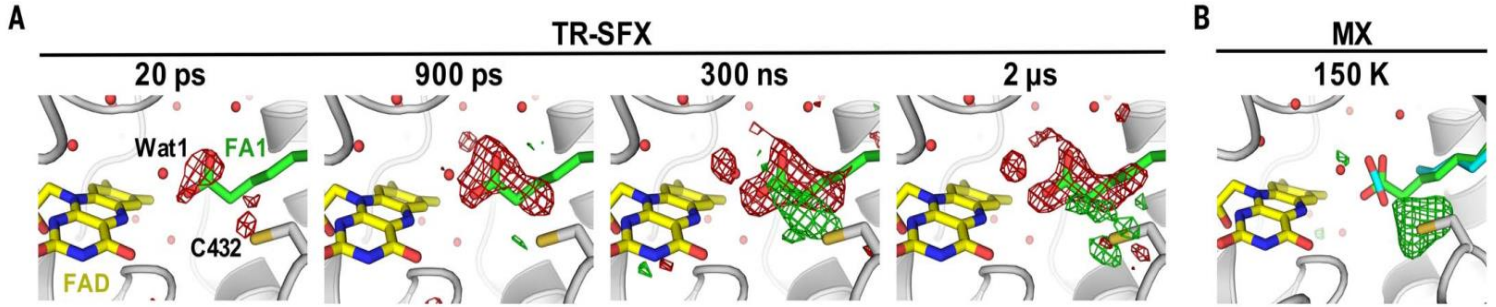
Mechanism and dynamics of fatty acid photodecarboxylase

D. Sorigué, K. Hadjidemetriou, S. Blangy, G. Gotthard, A. Bonvalet, N. Coquelle, P. Samire, A. Aleksandrov, L. Antonucci, A. Benachir, S. Boutet, M. Byrdin, M. Cammarata, S. Carbajo, S. Cuiné, R. B. Doak, L. Foucar, A. Gorel, M. Grünbein, E. Hartmann, R. Hienerwadel, M. Hilpert, M. Kloos, T. J. Lane, B. Légeret, P. Legrand, Y. Li-Beisson, S. L. Y. Moulin, D. Nurizzo, G. Peltier, G. Schirò, R. L. Shoeman, M. Sliwa, X. Solinas, B. Zhuang, T. R. M. Barends, J.-P. Colletier, M. Joffre, A. Royant, C. Berthomieu*, M. Weik*, T. Domratcheva*, K. Brettel, M. H. Vos*, I. Schlichting*, P. Arnoux*, P. Müller*, F. Beisson*

Science., ***372****(6538): art.n° eabd5687. (2021).*
doi.org/10.1126/science.abd5687



Elucidation of the FAP photocycle by combining spectroscopic, biochemical, crystallographic, and computational studies.



Complementarity in time scales

- IBS/ESRF - icOS
- ESRF - ID29
- ESF
- SLAC LCLS - CXI
- SLS - X10SA
- SOLEIL - PROXIMA 1

Trends: towards more challenging samples

nature COMMUNICATIONS

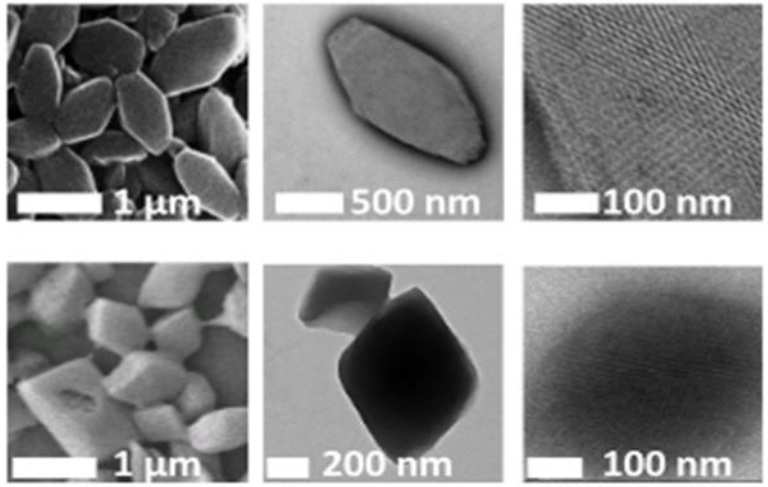
ARTICLE

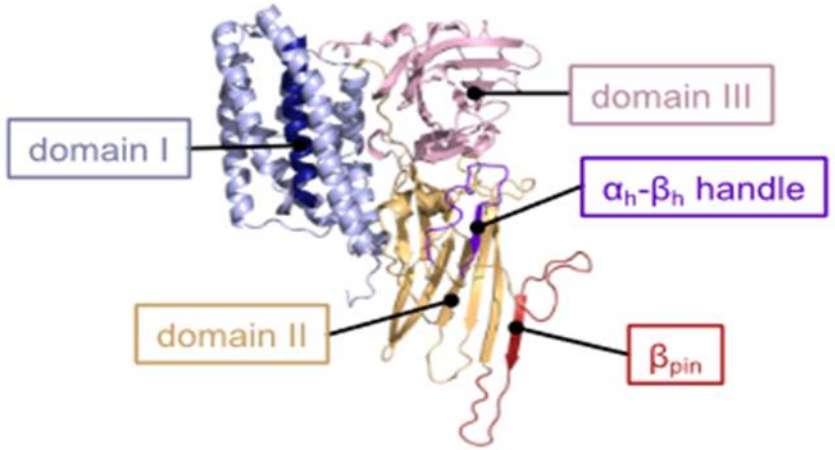
https://doi.org/10.1038/s41467-022-31746-x OPEN

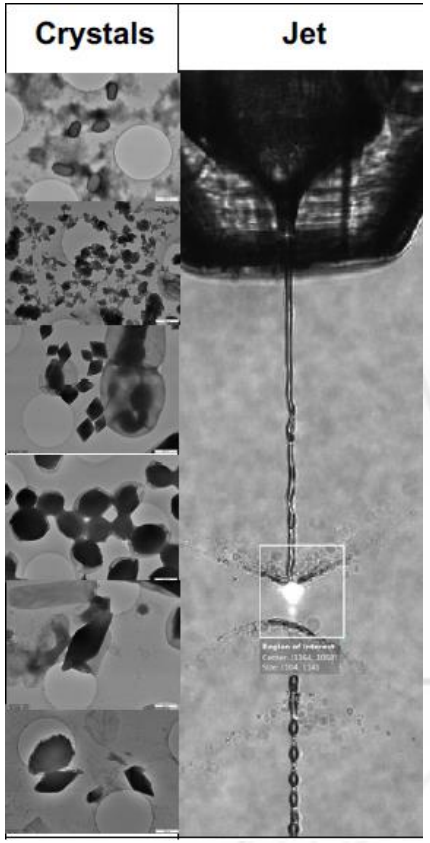
De novo determination of mosquitocidal Cry11Aa and Cry11Ba structures from naturally-occurring nanocrystals

Guillaume Tetreau[1,18], Michael R. Sawaya[2,18], Elke De Zitter[1,18], Elena A. Andreeva[1,3], Anne-Sophie Banneville[1], Natalie A. Schibrowsky[2,4], Nicolas Coquelle[5], Aaron S. Brewster[6], Marie Luise Grünbein[3], Gabriela Nass Kovacs[3], Mark S. Hunter[7], Marco Kloos[3,8], Raymond G. Sierra[7], Giorgio Schiro[1], Pei Qiao[9], Myriam Stricker[3], Dennis Bideshi[10,11], Iris D. Young[6], Ninon Zala[1], Sylvain Engilberge[1], Alexander Gorel[3], Luca Signor[1], Jean-Marie Teulon[1], Mario Hilpert[3], Lutz Foucar[3], Johan Bielecki[8], Richard Bean[8], Raphael de Wijn[8], Tokushi Sato[8], Henry Kirkwood[8], Romain Letrun[8], Alexander Batyuk[7], Irina Snigireva[12], Daphna Fenel[1], Robin Schubert[8], Ethan J. Canfield[13], Mario M. Alba[14], Frédéric Laporte[15], Laurence Després[15], Maria Bacia[1], Amandine Roux[16], Christian Chapelle[17], François Riobé[16], Olivier Maury[16], Wai Li Ling[1], Sébastien Boutet[7], Adrian Mancuso[8], Irina Gutsche[1], Eric Girard[1], Thomas R. M. Barends[3], Jean-Luc Pellequer[1], Hyun-Woo Park[10,11], Arthur D. Laganowsky[9], Jose Rodriguez[2,4], Manfred Burghammer[12], Robert L. Shoeman[3], R. Bruce Doak[3], Martin Weik[1], Nicholas K. Sauter[6], Brian Federici[10], Duilio Cascio[2], Ilme Schlichting[3] & Jacques-Philippe Colletier[1]✉

collected	hits	indexed	hitrate	indexing rate	Resolution
2610133	2474407	2307611	94.80	88.41	1.62
466741	378301	338153	81.05	72.45	1.73
707992	568035	450520	80.23	63.63	1.73
359061	324289	283638	90.32	78.99	1.65
1296717	1262648	1232801	97.37	95.07	1.8
430200	402334	196238	93.52	45.62	1.9
430200	402334	34686	93.52	8.06	2.2
634317	590155	484125	93.04	76.32	1.9

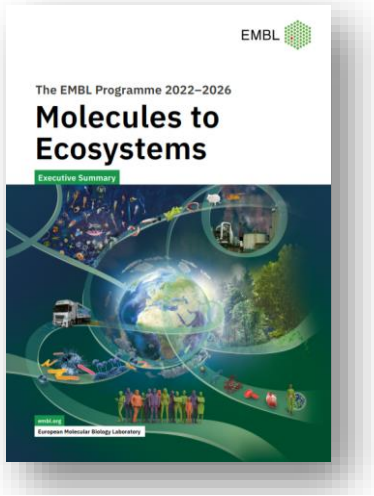






SPB-SFX@EuXFEL

From Biology to Life Sciences



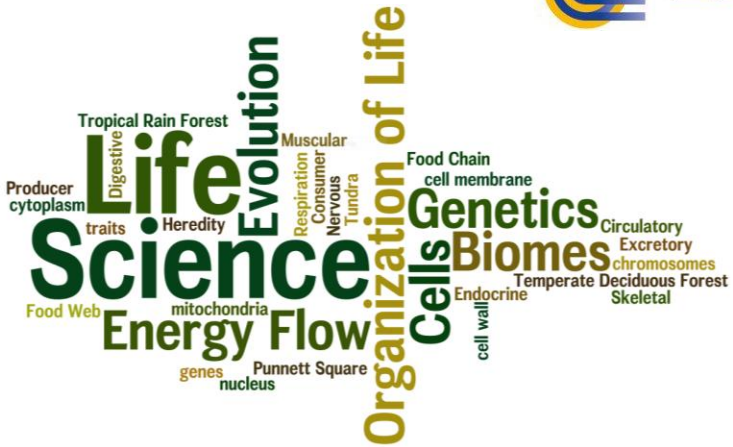
Structure

⇕

Biological / Physiological Functions

⇕

Interactions with interface boundaries



…to explore life in context by studying both classical and novel model organisms in the context of their real-world environment.

…to study life across interconnected scales (cells, tissues, organisms, populations) in different genetic and environmental contexts…

"…Improvements of microscopic and spectroscopic techniques towards ultra high spatial resolution will provide a better understanding of the cell's complex "machinery" in basic research…"

from "Vision Paper and Basis for Strategic Research Agenda for NanoMedicine", European Technology Platform on NanoMedicine, 2005.

XRF Imaging and correlative microscopy

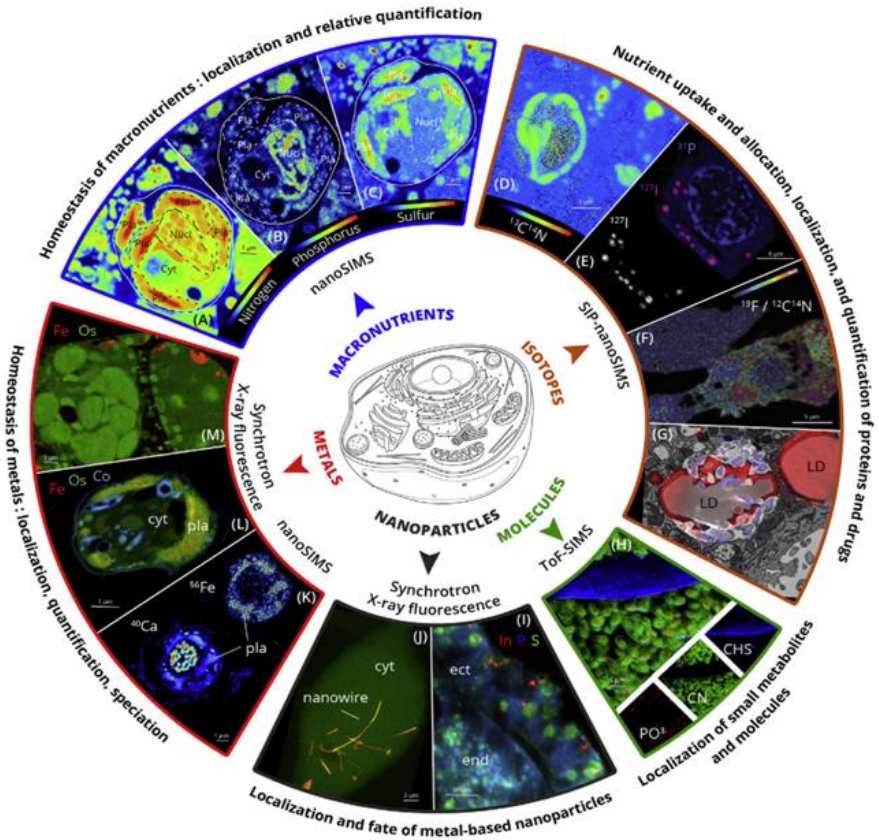
Trends in Cell Biology

CellPress REVIEWS

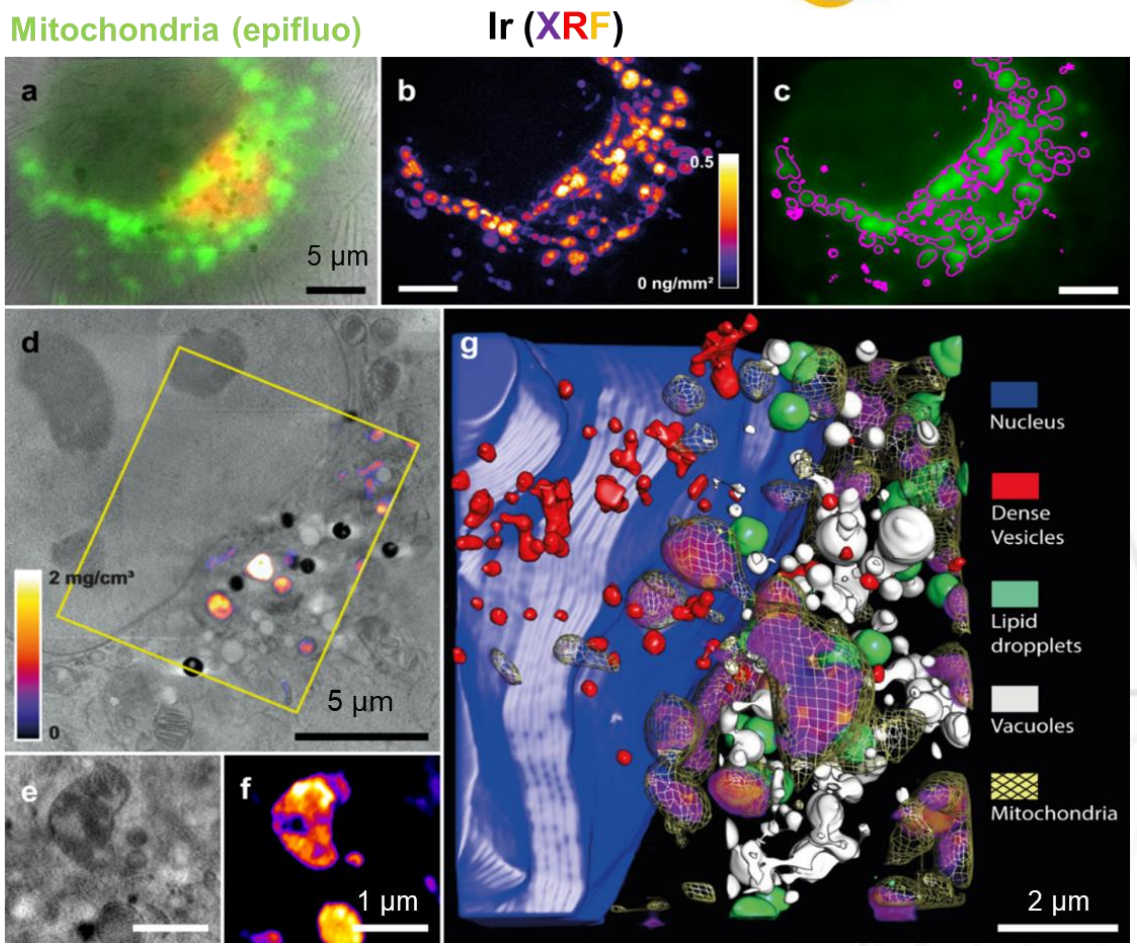
Review

Subcellular Chemical Imaging: New Avenues in Cell Biology

Johan Decelle,[1,*] Giulia Veronesi,[2,3] Benoit Gallet,[4] Hryhoriy Stryhanyuk,[5] Pietro Benettoni,[5] Matthias Schmidt,[5] Rémi Tucoulou,[3] Melissa Passarelli,[6] Sylvain Bohic,[3,7] Peta Clode,[8,9] and Niculina Musat[5]



Ir (XRF) + **Structure** (SoftXT)

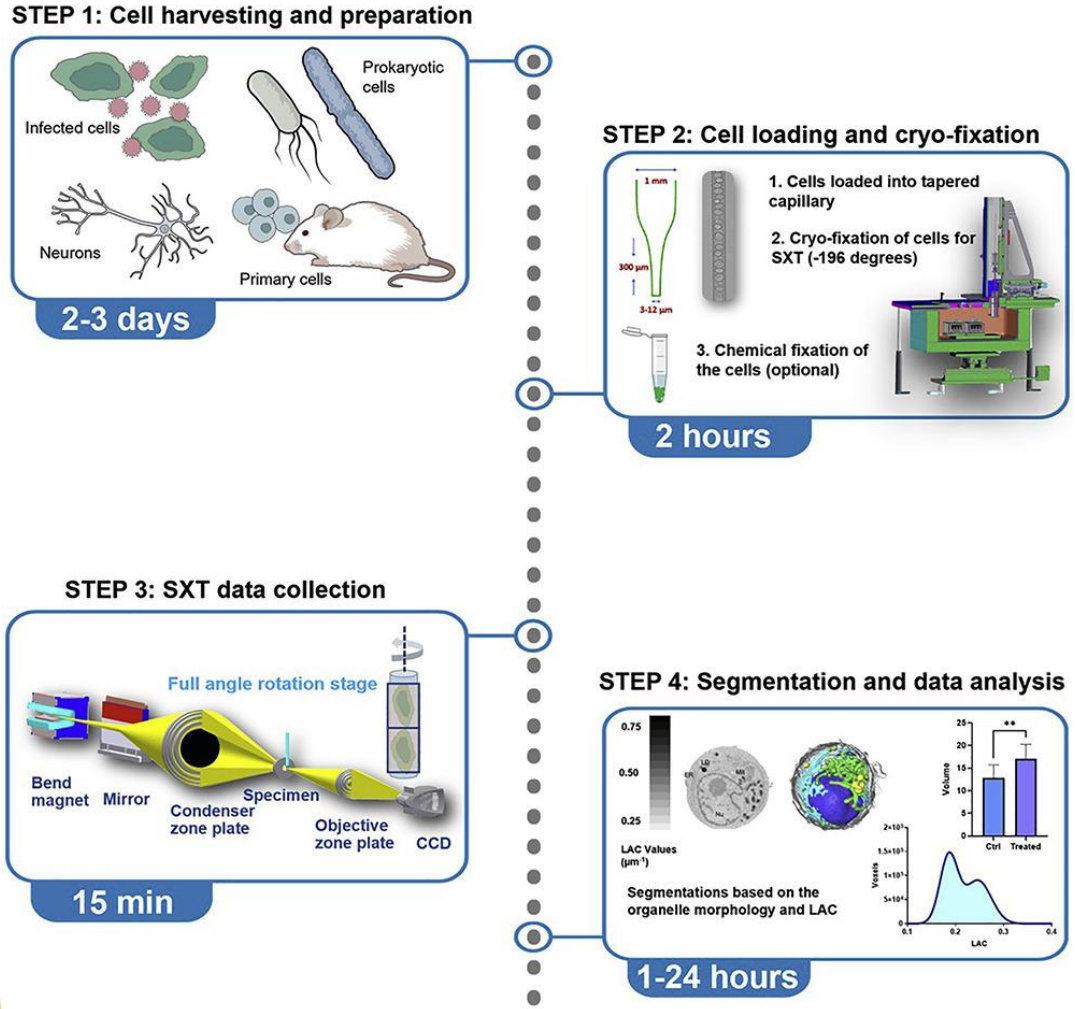


ESRF ID16A

ALBA MISTRAL

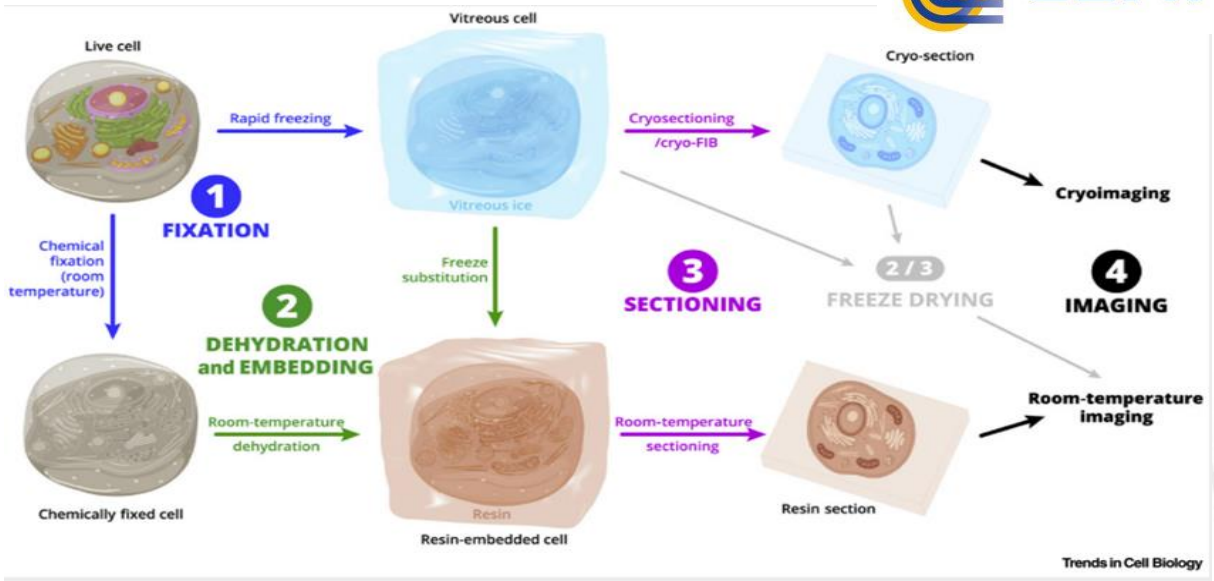
J. Conesa *et al.*, Angew. Chem., 59, 1270-1278 (2020)

New cryo preparation protocols in X-ray microscopies



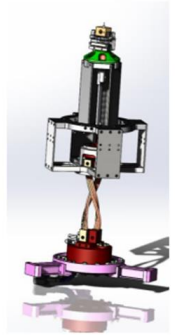
STARS Protocol : a protocol for full-rotation soft X-ray tomography of single cells

https://doi.org/10.1016/j.xpro.2022.101176



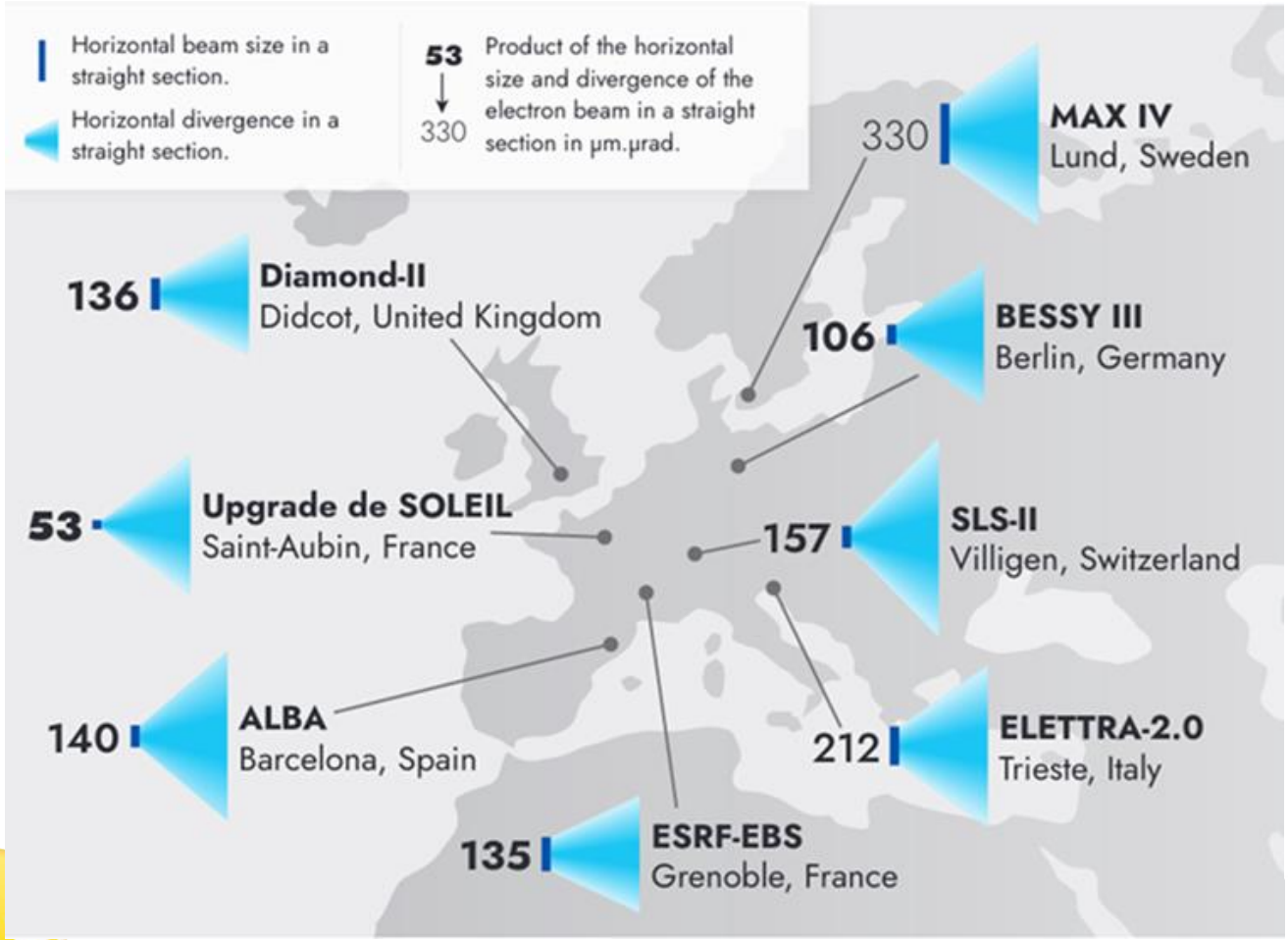
J. Decelle et al. *Trends in Cell Biology* 30(3), 2020,173-188
https://doi.org/10.1016/j.tcb.2019.12.007

Cryogenic sample preparation → **Cryo loading chamber and transfer system** → **Cryogenic cooling of the sample stage**

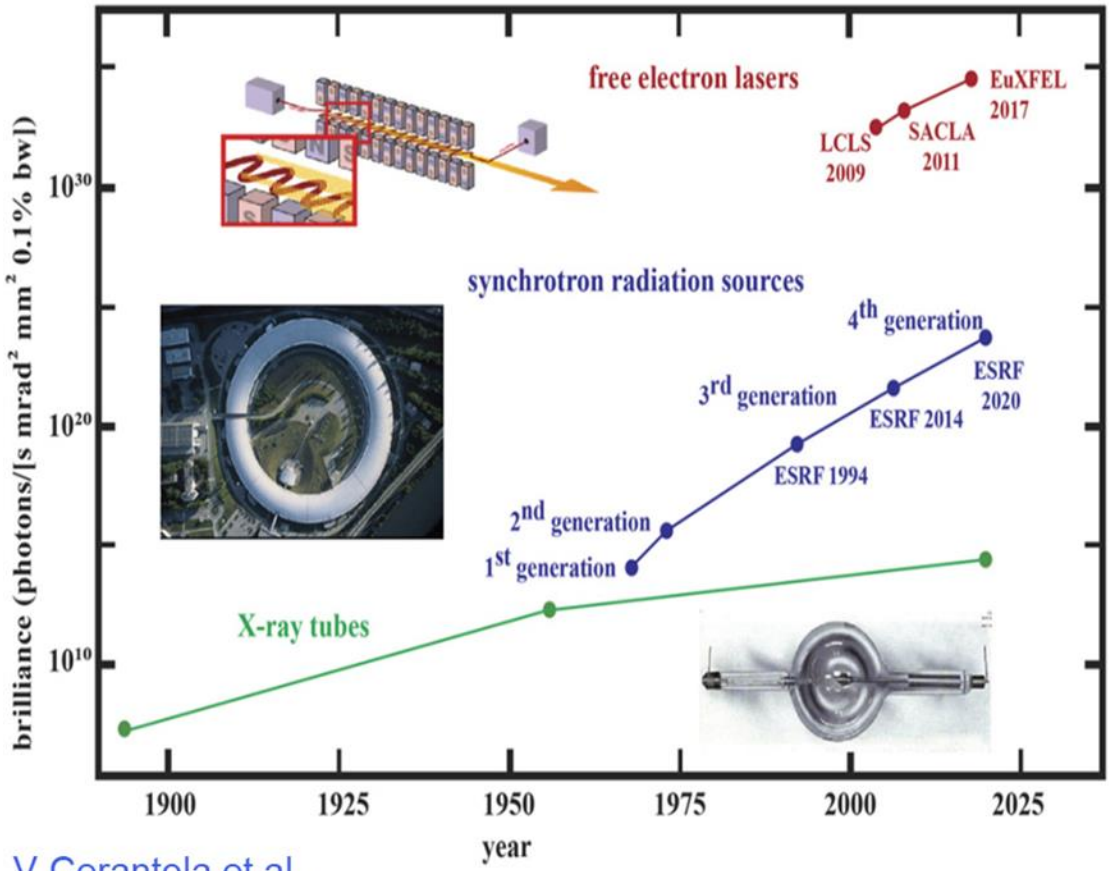


S. Bohic, P. Cleotens et al., ID16A, ESRF

Advent of the 4th generation SR sources

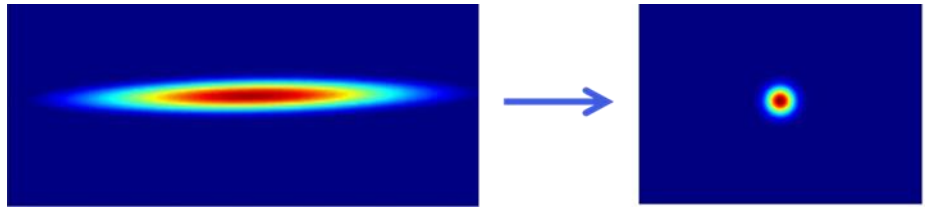


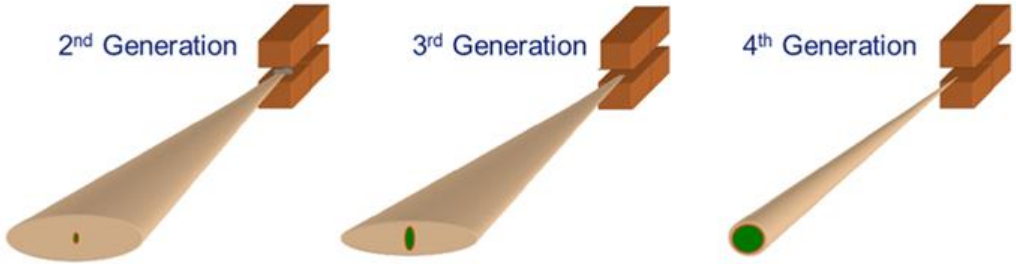
9 order of magnitude in 35 years !

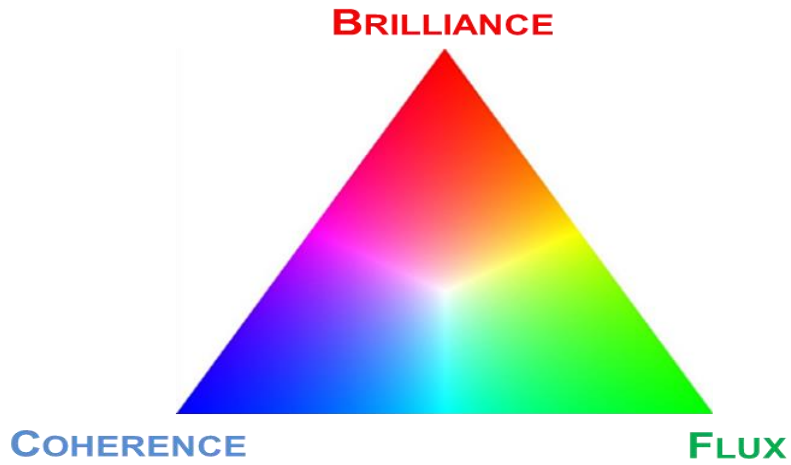


V Cerantola et al,
J. Phys.: Condens. Matter 33 (2021) 274003

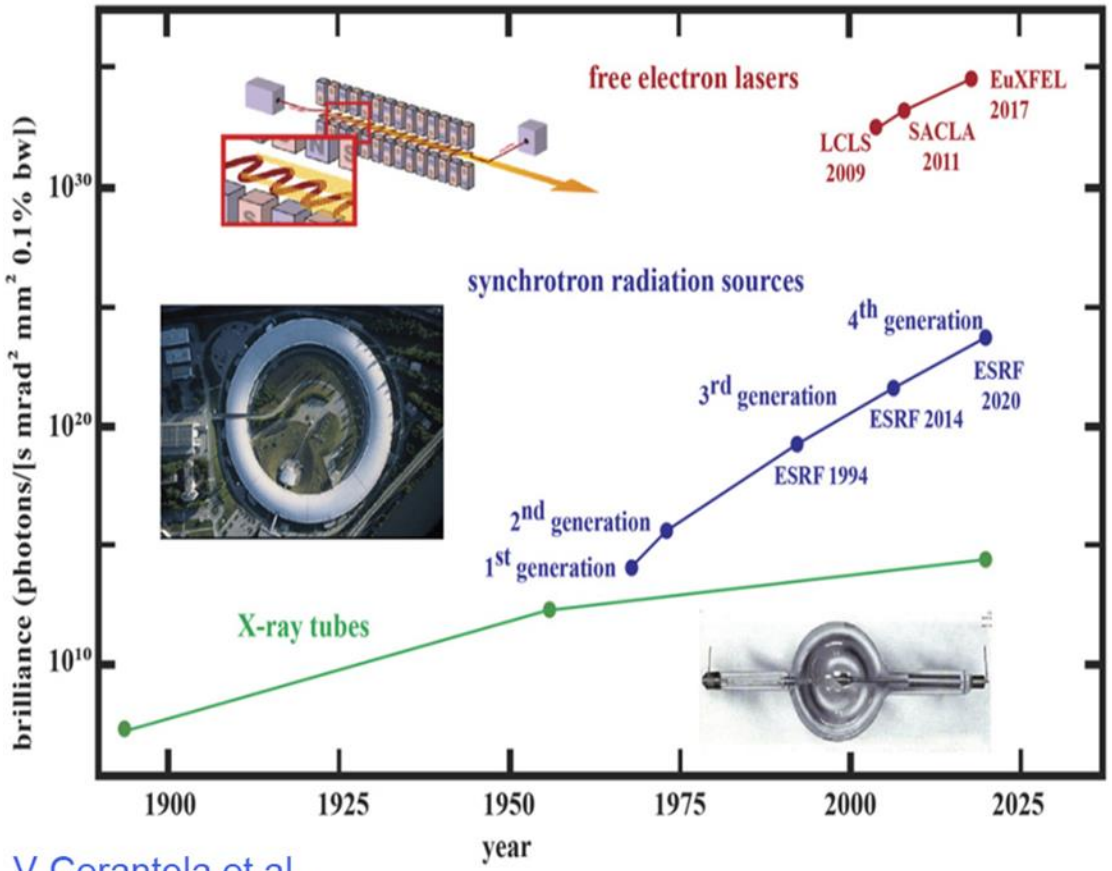
Advent of the 4th generation SR sources





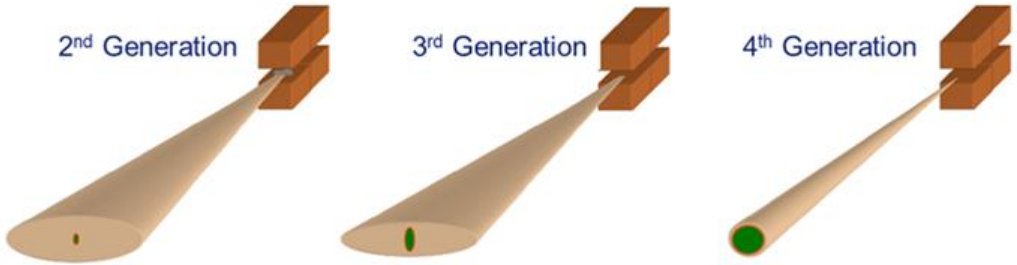


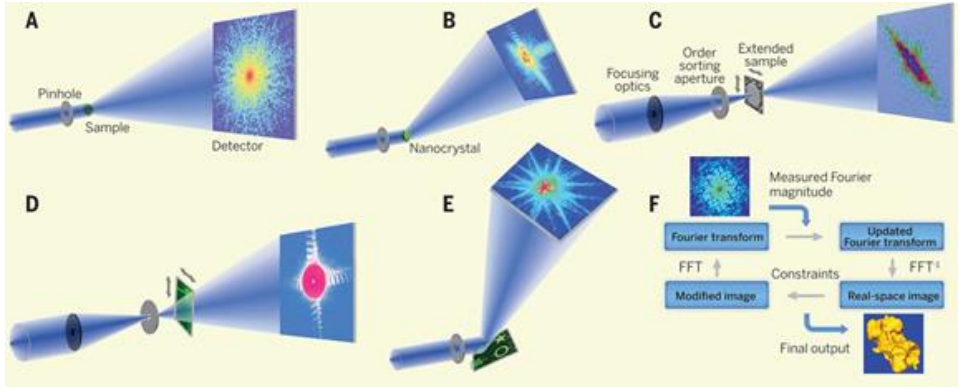
9 order of magnitude in 35 years !



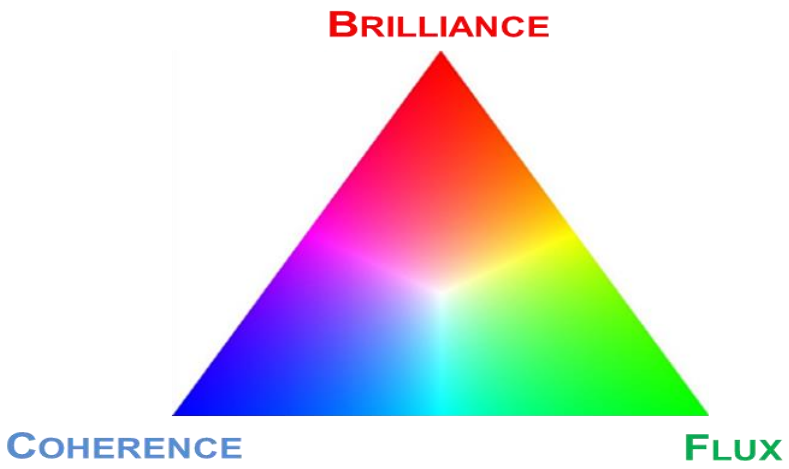
V Cerantola et al,
J. Phys.: Condens. Matter 33 (2021) 274003

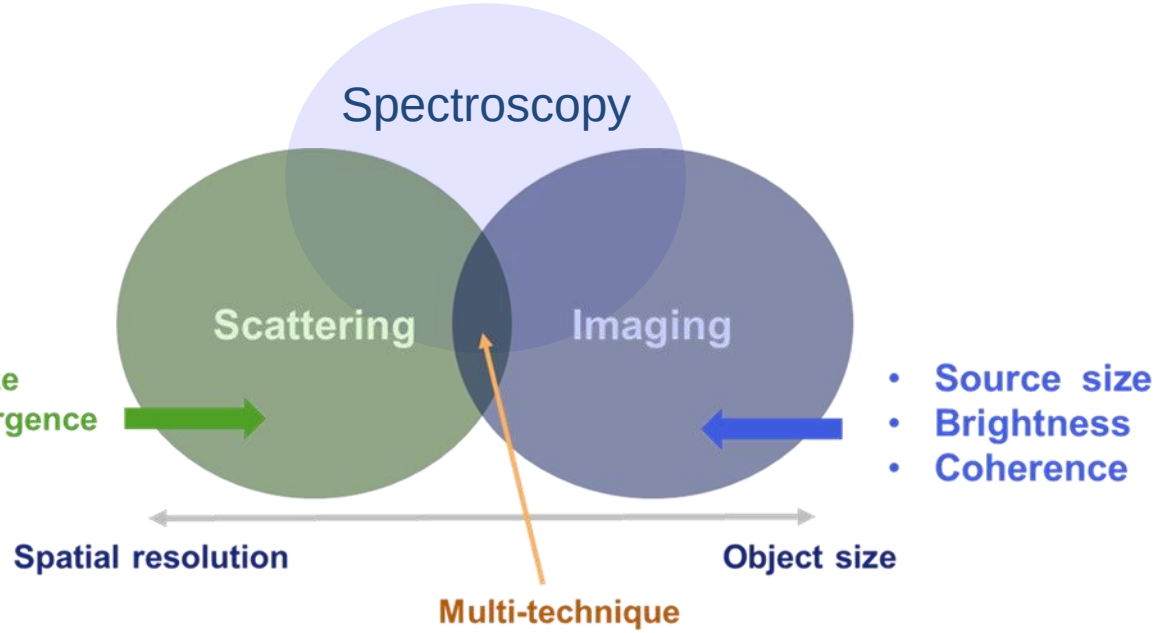
Impact of 4th generation SR sources ?





J. Miao et al. Science (2015), 348:530-535

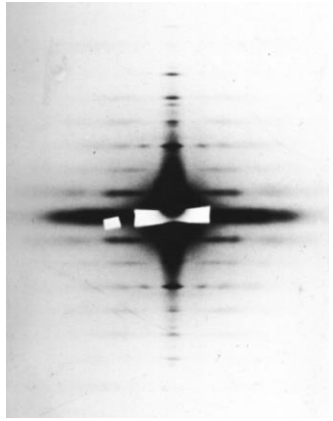




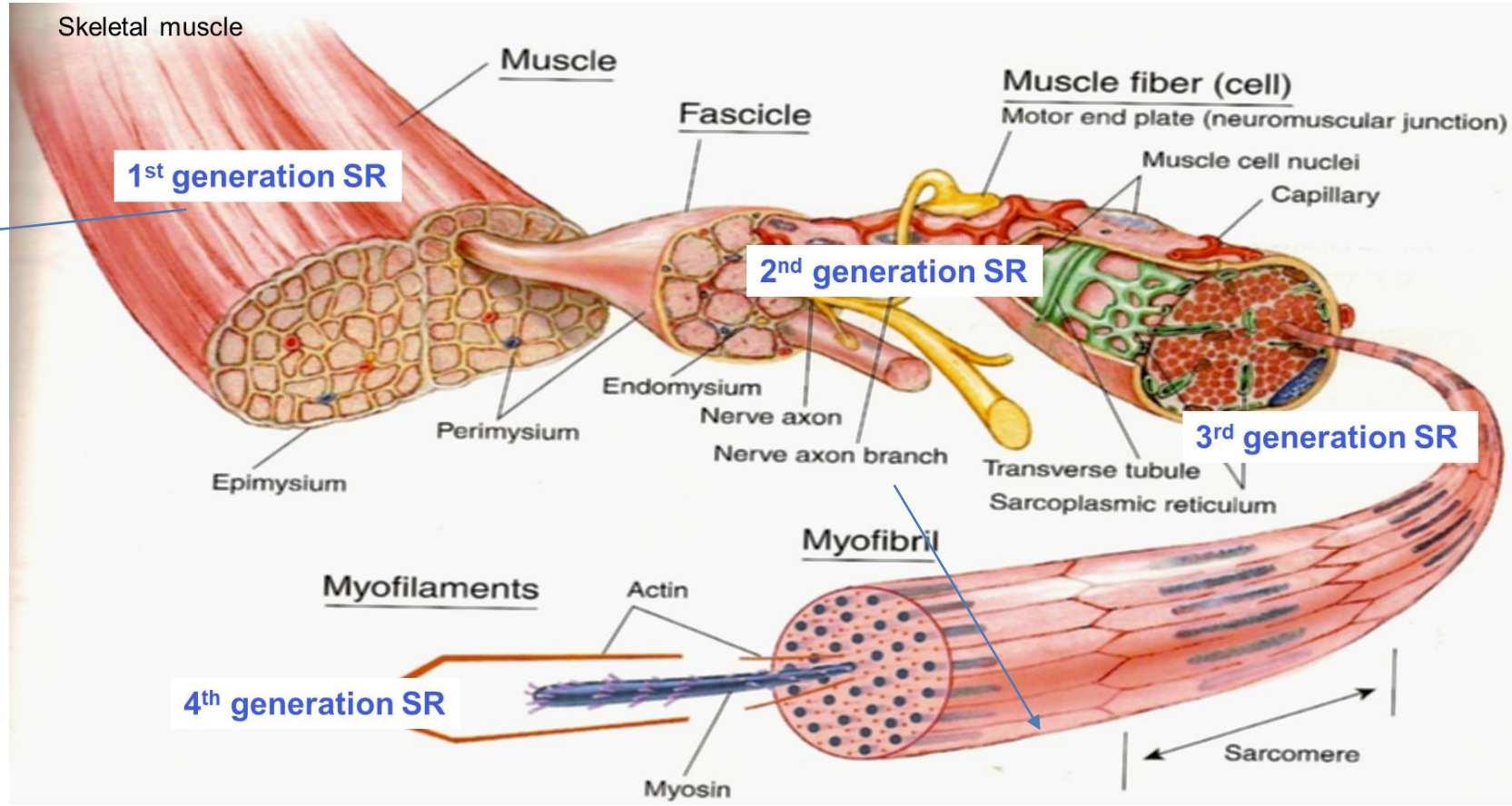
Temporal and spatial resolution
+
a boost for imaging techniques

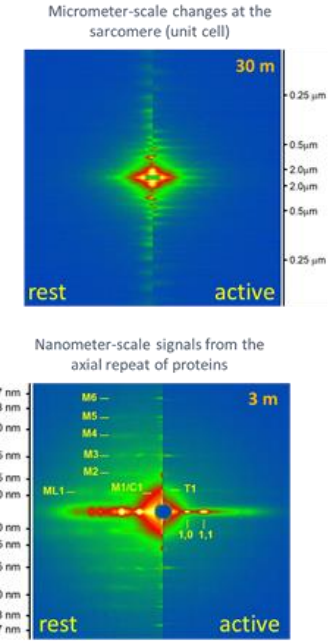
Impact of 4th generation SR sources ?

First X-ray diffraction experiments using synchrotron radiation, carried out by Holmes, Rosenbaum and Witz at DESY, **Hamburg, in September 1970**.



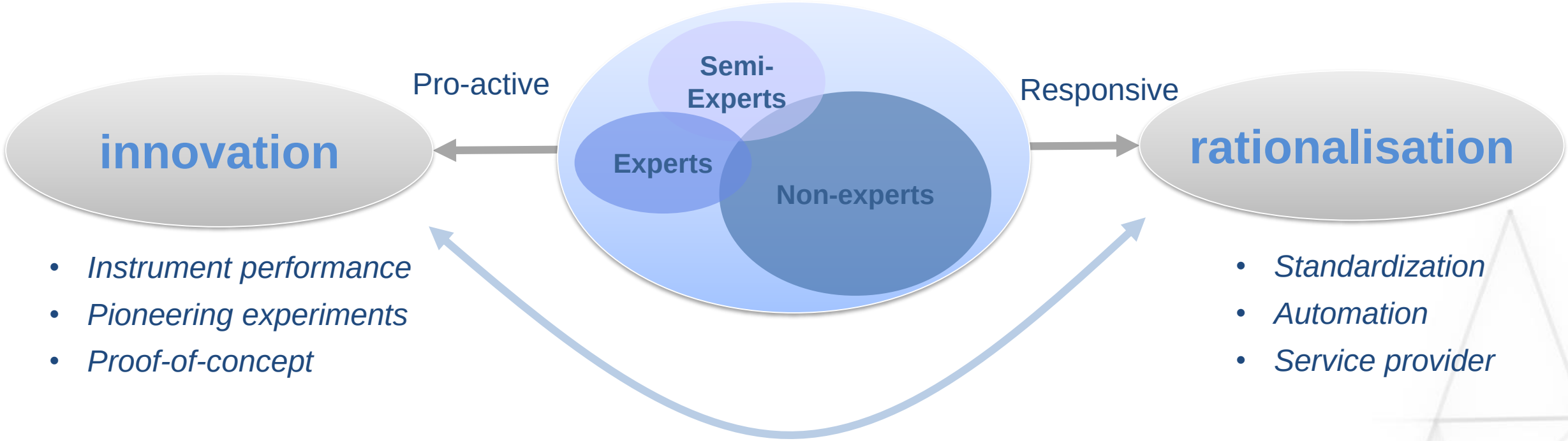
G. Rosenbaum et al., Nature 230, 434 (1971)





ID02-ESRF
Model of the structural dynamics of myosin filament domains during contraction
E. Brunello *et al.*, *PNAS* 117, 8177 (2020)

Facility paradigm in the Life Sciences

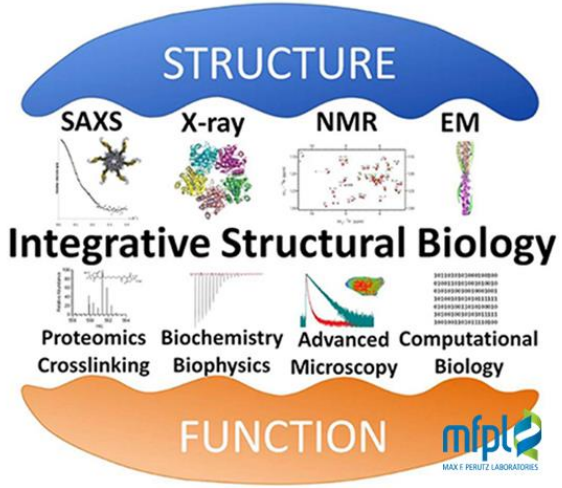


- *Instrument performance*
- *Pioneering experiments*
- *Proof-of-concept*

- *Standardization*
- *Automation*
- *Service provider*

- Cross-fertilisation and synergy between the two approaches
- Expectation management ?
- Perimeter of services (from sample handling down to interpretable data) ?

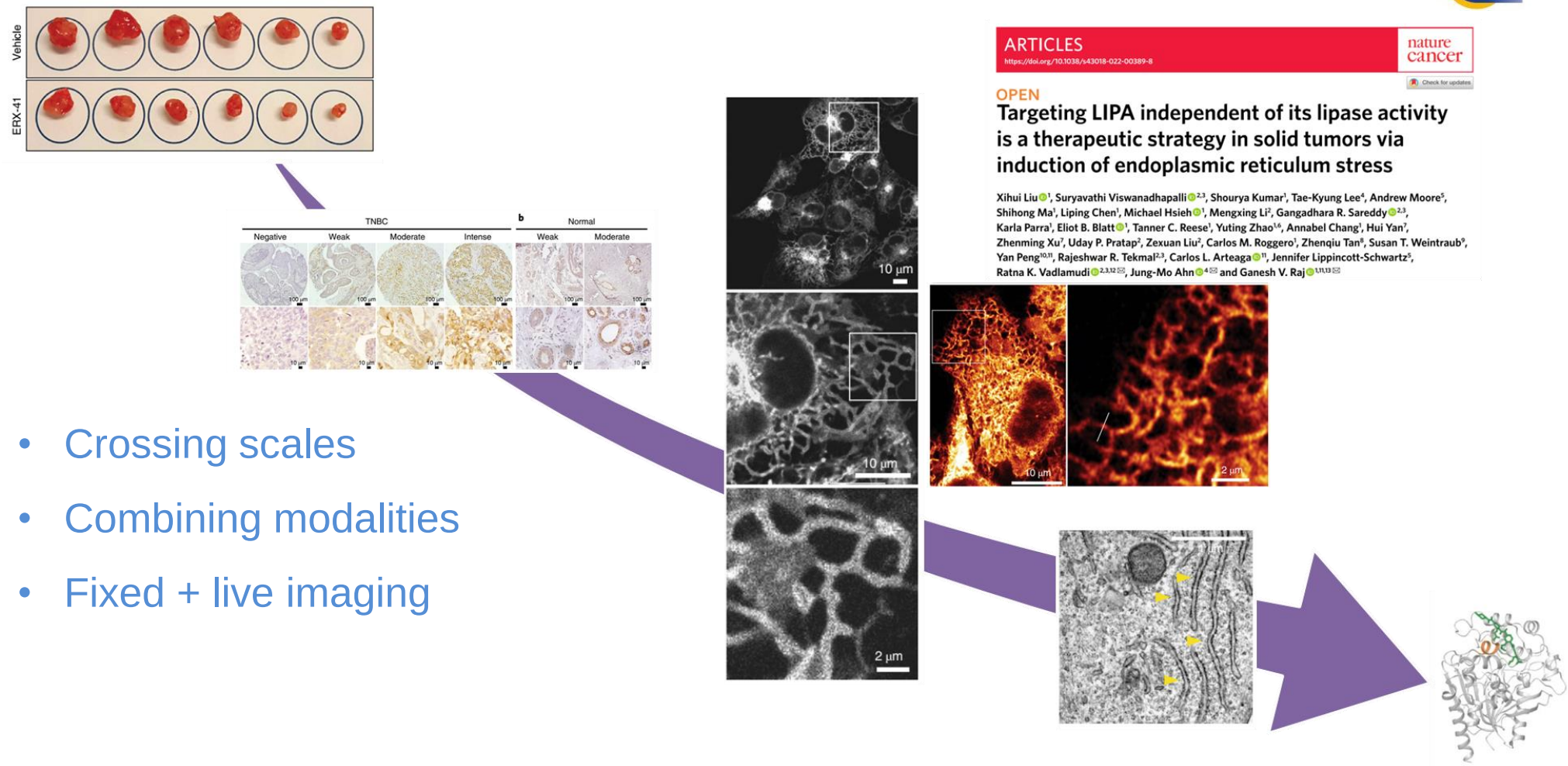
Strategic role of local ecosystems : X-ray based techniques are often one step in a long journey



Expert users

Institute for Integrative Biology of the Cell

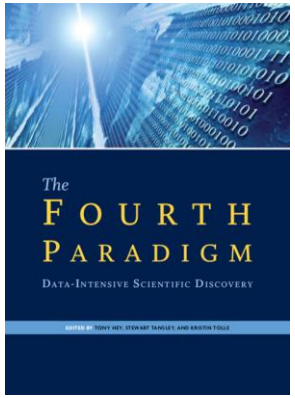
From individual projects to integrated programmes

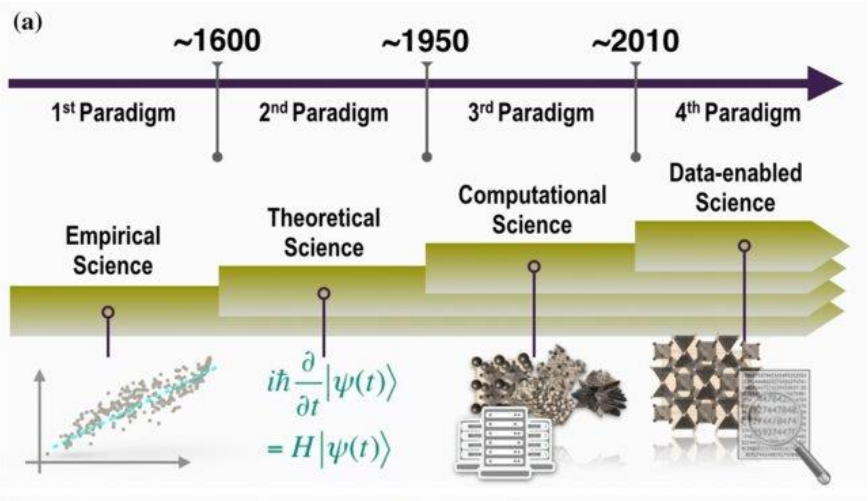


- Crossing scales
- Combining modalities
- Fixed + live imaging

- Expert users or facility experts as single entry point and chaperon
- Coordinated access to various instruments across one or several facilities

Databases are needed for drug design, preventive medicine, diagnosis & prognosis





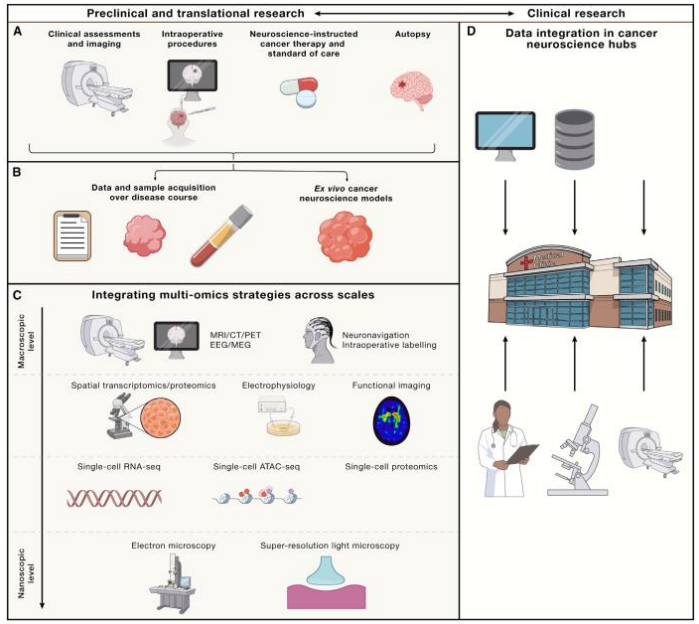
Cell

Leading Edge

Review

Cancer neuroscience: State of the field, emerging directions

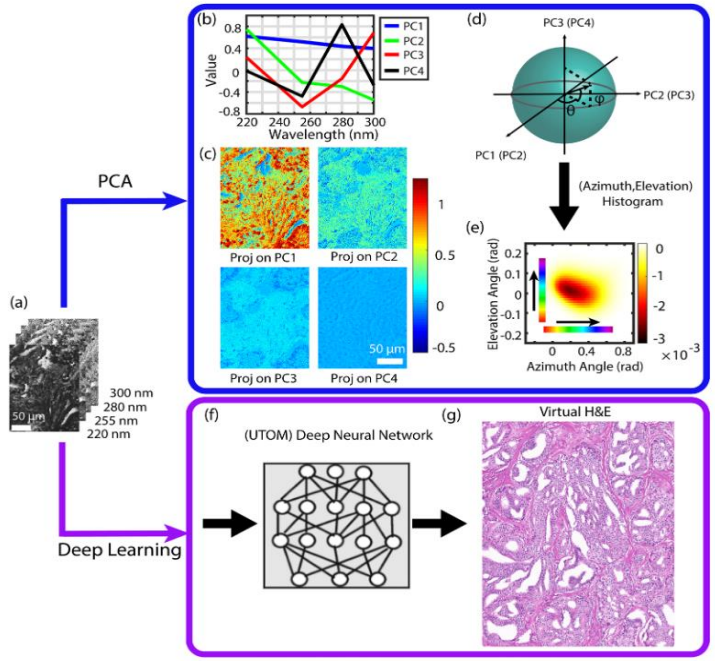
Frank Winkler,[1,16,*] Humsa S. Venkatesh,[2,16] Moran Amit,[3] Tracy Batchelor,[2] Ihsan Ekin Demir,[4] Benjamin Deneen,[5] David H. Gutmann,[6] Shawn Hervey-Jumper,[7] Thomas Kuner,[8] Donald Mabbott,[9] Michael Platten,[10] Asya Rolls,[11] Erica K. Sloan,[12] Timothy C. Wang,[13] Wolfgang Wick,[1] Varun Venkataramani,[1,8,16,*] and Michelle Monje[14,15,16,*]



Prostate cancer histopathology using label-free multispectral deep-UV microscopy quantifies phenotypes of tumor aggressiveness and enables multiple diagnostic virtual stains

Soheil Soltani, Ashkan Ojaghi, Hui Qiao, Nischita Kaza, Xinyang Li, Qionghai Dai, Adeboye O. Osunkoya & Francisco E. Robles

Scientific Reports **12**, Article number: 9329 (2022) | Cite this article



Nucleic acid circular dichroism database

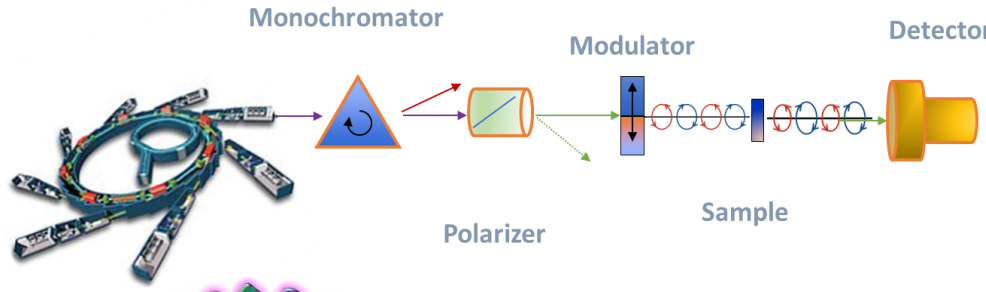
Nucleic Acids Research, 2022 1
https://doi.org/10.1093/nar/gkac829

NACDDB: Nucleic Acid Circular Dichroism Database

Andrea Cappannini[1,†], Kevin Mosca[2,†], Sunandan Mukherjee[1], S. Naeim Moafinejad[1], Richard R. Sinden[3], Veronique Arluison[2,4,*], Janusz Bujnicki[1,*] and Frank Wien[5,*]

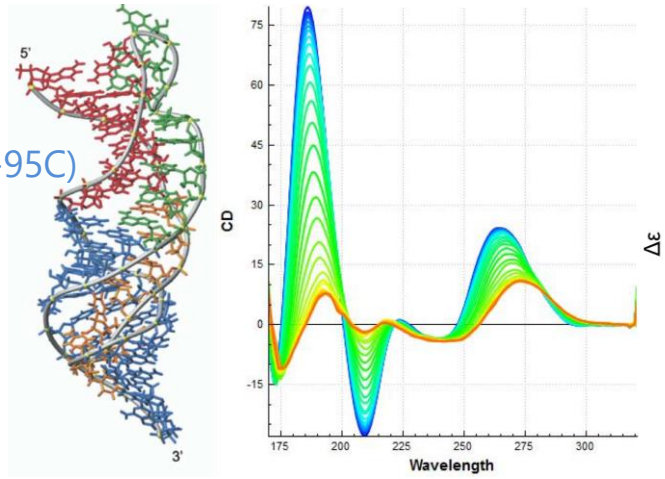
[1]Laboratory of Bioinformatics and Protein Engineering, International Institute of Molecular and Cell Biology in Warsaw, ul. Ks. Trojdena 4, PL-02-109 Warsaw, Poland, [2]Université Paris-Saclay, CEA, CNRS, LLB, 91191, Gif-sur-Yvette, France, [3]Department of Chemistry, Biology, and Health Sciences, South Dakota School of Mines and Technology, Rapid City, SD 57701, USA, [4]Université Paris Cité, UFR SDV, 75006 Paris, France and [5]Synchrotron SOLEIL, L'Orme des Merisiers, Saint Aubin BP 48, 91192, Gif-sur-Yvette, France

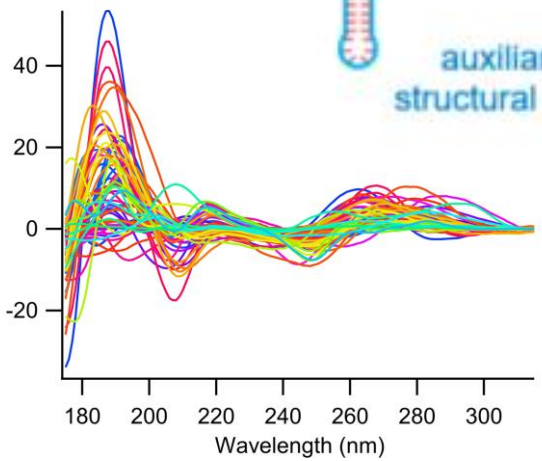
Received August 19, 2022; Editorial Decision September 04, 2022; Accepted September 15, 2022

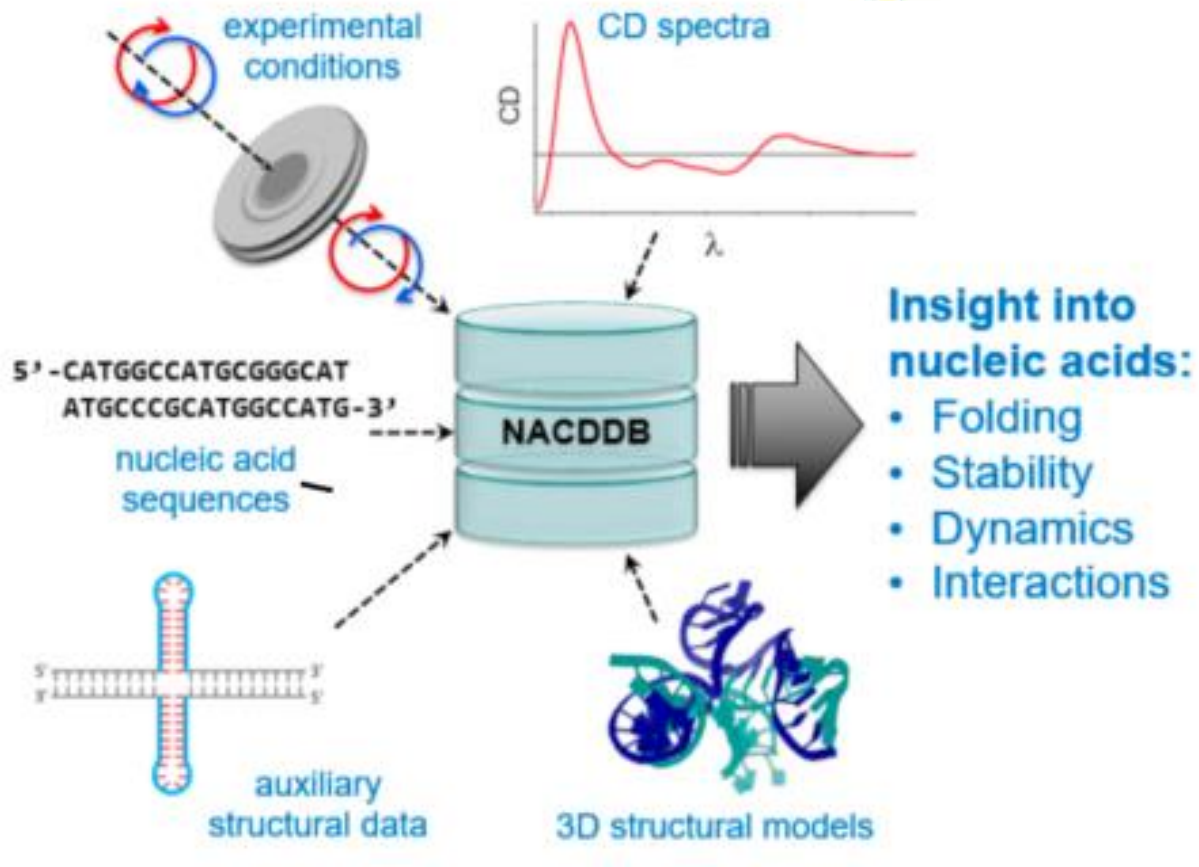


DISCO

Thermal denaturation (25-95C) of RNA pseudoknot







https://genesilico.pl/nacddb/

150+ spectra

Open source organ atlas

nature methods ARTICLES
https://doi.org/10.1038/s41592-021-01317-x
Check for updates

OPEN

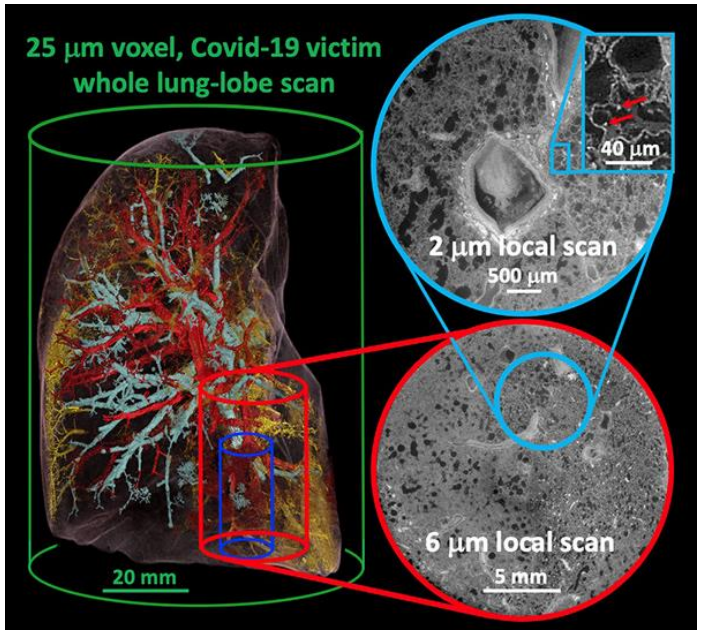
Imaging intact human organs with local resolution of cellular structures using hierarchical phase-contrast tomography

C. L. Walsh[1,2,17] ✉, P. Tafforeau[3,17] ✉, W. L. Wagner[4,5,17], D. J. Jafree[6,7], A. Bellier[8], C. Werlein[9], M. P. Kühnel[9,10], E. Boller[3], S. Walker-Samuel[2], J. L. Robertus[11,12], D. A. Long[6], J. Jacob[13,14], S. Marussi[1], E. Brown[2], N. Holroyd[2], D. D. Jonigk[9,10] ✉, M. Ackermann[15,16] ✉ and P. D. Lee[1] ✉

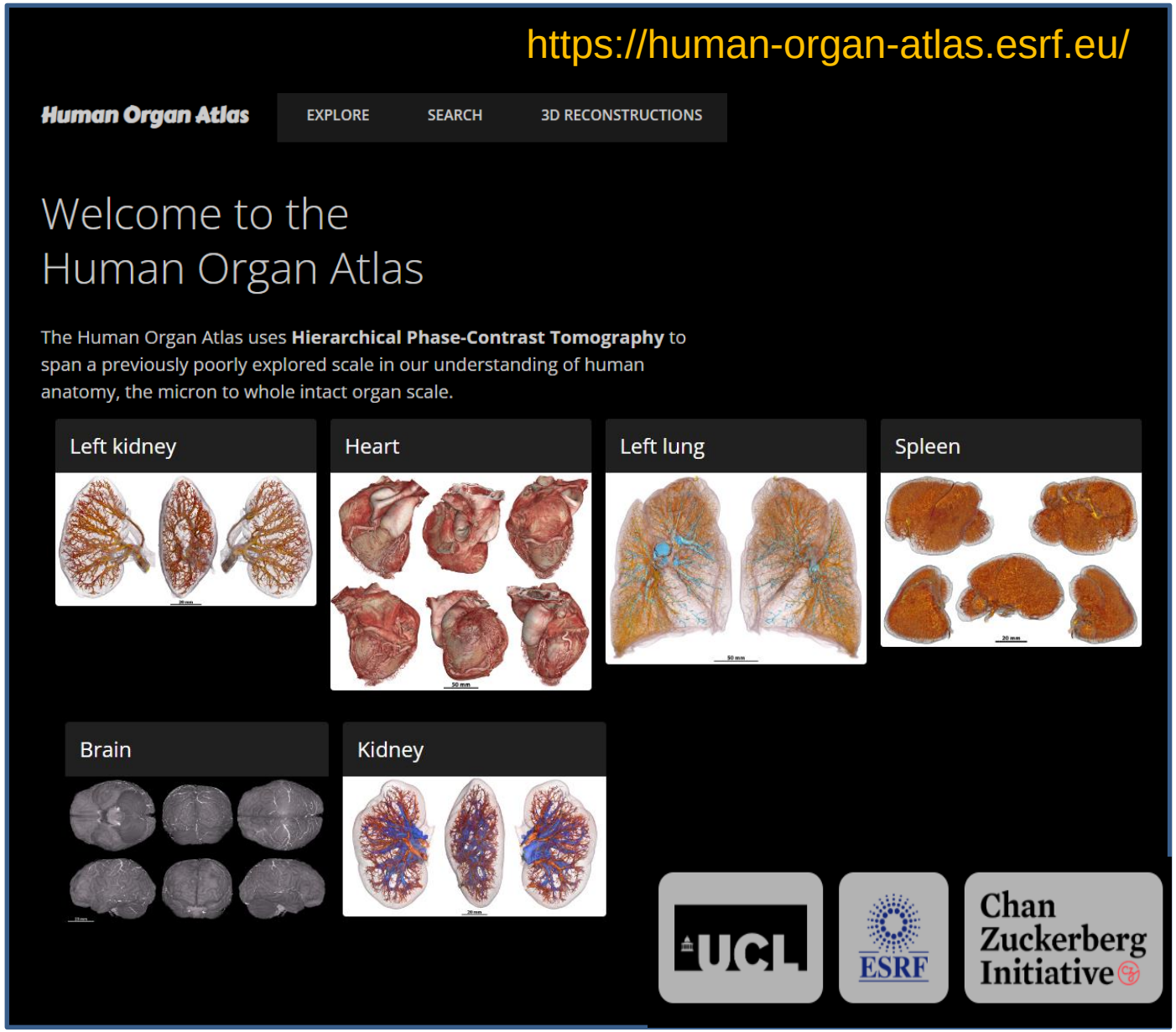
https://doi.org/10.1038/s41592-021-01317

ESRF The European Synchrotron

BM-18



https://human-organ-atlas.esrf.eu/



Virtual (digital) histology

Multi-modal (hyperspectral) imaging

- Find new fingerprints / molecules for classical histopathology
- Help for difficult or ambiguous diagnosis
- Transfer technology to clinical environments
- …..
- Develop histology pipelines on dedicated instruments

Complexity & investments

LEAPS Strategy in Life Sciences

"…Boosting existing capacities with adequate national and European funding programmes, places Europe´s Accelerator-based Photon Sources in a strong position to be a major player in addressing public health challenges such as cancer, neuro-degenerative diseases, resistance to antibiotics, or the emergence of infectious diseases. Preventive medicine will also need a wider range of topics to be addressed, such as food science, absorption of vitamins and minerals, which are possible to explore using Accelerator-based Photon Sources…"

Thank you very much for your attention !

A motto for LEAPS ?

“Alone we go faster, together we go further…”

Yes, but in which direction(s) ?