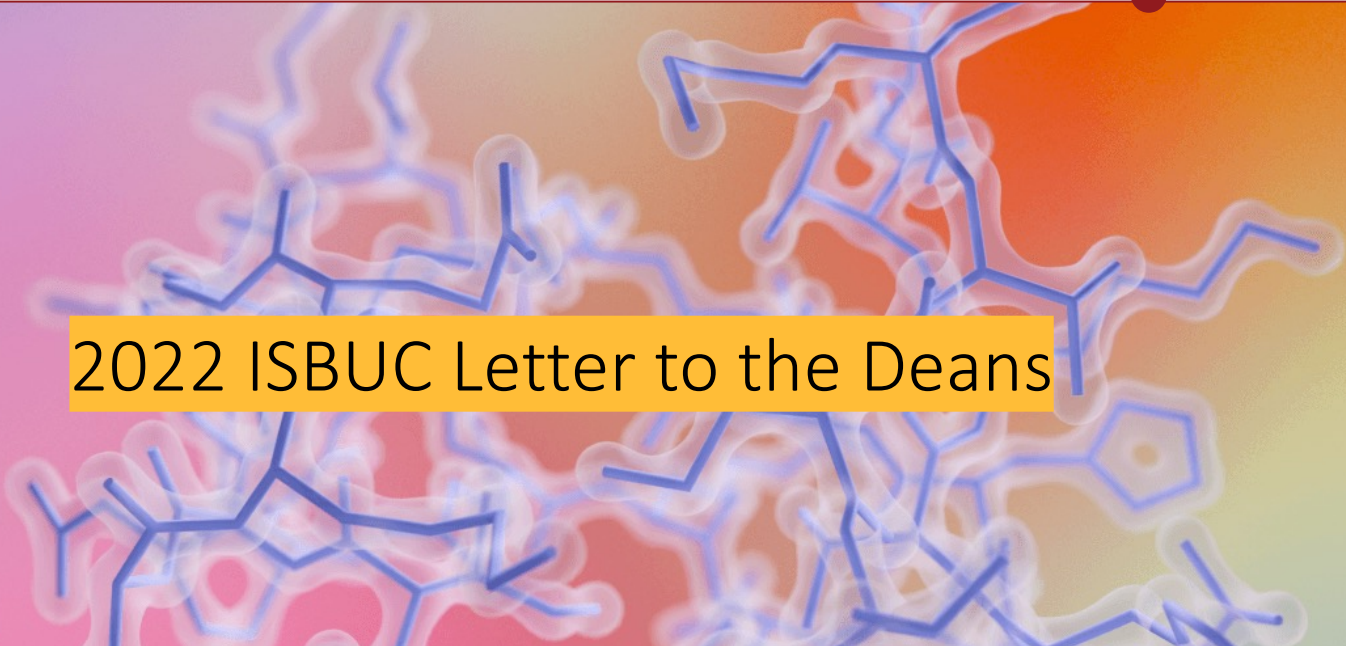




2022 ISBUC Letter to the Deans



Message from the ISBUC Steering Committee

2022 was a fantastic year for the structural biology community at the University of Copenhagen, filled with numerous scientific breakthroughs, a string of prominent awards and large prestigious grants for ISBUC researchers. Most memorably, it was wonderful to see the entire university come together to celebrate the fantastic achievements of Morten Meldal who was awarded the Nobel Prize in Chemistry 2022. This is a truly historical achievement which shines a light on the fantastic research being done here in Copenhagen.

Charged with fresh energy, ISBUC has spent time in 2022 reflecting on our priorities and have identified four key areas which ISBUC will work towards going forward. First and foremost, ISBUC's *raison d'être* is to strengthen internal networking and spearhead integration, innovation and interdisciplinarity here at the University of Copenhagen. After the disruptions of the pandemic, we have placed much emphasis in 2022 on achieving this goal. The ISBUC calendar has been filled with collaborative networking events and boundary pushing science meetings that have showcased and inspired new integrative approaches.

For the first time since Corona, ISBUC was able to host all three of its flagship events in the same year: the

ISBUC PI Day, the ISBUC Industry Day and the ISBUC Annual Meeting. In addition, thanks to a grant from the Novo Nordisk Foundation supporting the ISBUC Annual Meeting, ISBUC was also able to establish a new quarterly Structural Biology Seminar. ISBUC is using these seminars to showcase innovative structural biology research happening in the local region with the aim of strengthening regional connections and collaboration. In addition, in 2022, Junior ISBUC has launched its own Lunch Talk series featuring research presentations by newly established group leaders from both the University of Copenhagen and local industry. Through all these events, the ISBUC community is once again thriving.

Second, ISBUC aims to lead excellent education initiatives that will drive interest in structural biology as a field of study and help build the next generation of researchers. To this end, ISBUC has been busy laying the groundwork for numerous education initiatives which will come to fruition in 2023, including two PhD courses and one MSc course.

Third, building off our internal success here at the University of Copenhagen, ISBUC will aim to lead regional initiatives and assemble the critical mass necessary for realising

the full potential of integrative structural biology. Already, in 2022, the first steps have been taken towards realizing this aim through the Structural Biology Seminars. In addition, in 2022, ISBUC led an application to Nordforsk to establish a university cooperation between 26 universities that would allow us to build a Nordic network for integrative structural biology. After a successful pre-proposal, ISBUC has submitted a full proposal in 2023.

Fourth and finally, building off the communication and philosophy background of our coordinator, ISBUC is launching outreach initiatives that will try to overcome the many barriers for engaging the public with structural biology research. To this end, in 2022, ISBUC has initiated a collaboration with world leading artists and the PDBe to explore new ways of visualizing biomolecules that are both scientifically accurate and inspiring.

We look forward to sharing more news of all these initiatives in the years to come. Until then, we hope you enjoy reading about all of the inspiring structural biology research happening here at the University of Copenhagen.

Best regards,

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 Bithe B. Kragelund
 ISBUC Chair
 Faculty of Science



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 Claus J. Løland
 ISBUC Vice Chair
 Faculty of Health & Medical Sciences



Nikos Hatzakis
 SCIENCE



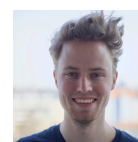
Michael Gajhede
 SUND



Guillermo Montoya
 SUND



Karen Martinez
 SCIENCE



Jacob Kæstel-Hansen
 SCIENCE

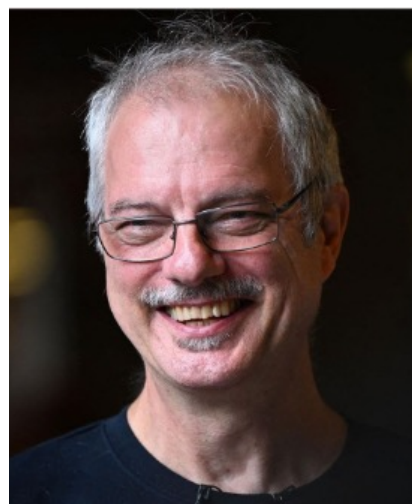


ISBUC researcher Morten Meldal receives the Nobel Prize in Chemistry

In 2022, Professor Morten Meldal (CHEM) was awarded the Nobel Prize in Chemistry for his groundbreaking work with click chemistry, a chemical reaction that makes it possible to “snap” molecules together in simply and quickly. The method is an extraordinarily useful tool for mapping DNA and creating new materials. Since its discovery, click chemistry has been widely deployed in pharmaceutical research. Morten Meldal shares the prize with two American researchers. Morten received his award for developing the chemical reaction *copper catalysed azide-alkyne cycloaddition*. During the click reaction, mo-



lecular groups, each carrying one part of a particular bond in the surface, are snapped together to create new constellations of molecules.



Heloisa Bordallo received KIF Prize & ISIS Impact Award

In 2022, Associate Professor Heloisa Bordallo (NBI) was awarded the Kvinder i Fysik Prize for her impressive scientific career together with inspirational and dedicated work with students and young scientists. This annual honorary award, which is supported with 5000 DKK from the Royal Danish Academy of Sciences and Letters, aims to raise awareness about the importance of women in physics and identify female physicists as role models. In addition, Heloisa Bordallo also received an ISIS Impact Award in 2022, which celebrates the scientific, social and economic impact of the members of Science and Technology

Facilities Council. She was awarded for her work developing smarter materials by tuning physico-chemical properties using TOSCA and IRIS.



Knud Jørgen Jensen becomes the first Scandinavian receiving the Max Bergmann Medal



In 2022, Professor Knud Jørgen Jensen (Chem) became the first Scandinavian researcher to receive the Max Bergmann Medal, which is awarded annually by Max-Bergmann-Kreis, a German-Swiss-Austrian scientific society for research into the biochemistry and chemistry of peptides. Knud’s research focuses on chemical modification of peptides and new synthetic methodologies, including reagents for solid-phase synthesis and for chemoselective chemistry on carbohydrates, peptides and proteins.

Nicholas Taylor awarded the Erhoff Fonden Talentpris

In 2022, Associate Professor Nicholas Taylor (CPR) received the Erhoff Fonden Talentpris for “demonstrating talent and a major commitment in original basic research within cellular and molecular membrane biology with translational potentials”. His team explores the basic biology and possible applications of molecular transport systems, using a combination of molecular biology, structural biology (cryo-EM) and protein design. Systems of interest are bacteriophages and related injection systems, the flagellar engine of bacteria and molecular mechanisms of multidrug transporters that possess physiological and pharmacokinetic functions.





Stamou leads collaboration that discovers an enzyme that enables brain signals to switch on and off at random

ISBUC researcher Dimitrios Stamou (CHEM) and collaborators have made an incredible discovery about the mammalian brain that got honored with the cover of the renowned scientific journal *Nature* (2022). Using groundbreaking methods, Stamou and collaborators are the first ever to isolate and study a mammalian brain enzyme. In doing so, they discovered that the enzyme, V-ATPase, which enables brain signals, is switching on and off at random. This contradicts previous theories which believed these enzymes to be active continuously. What's more, periods when the enzyme is switched off can last for hours, during which time synaptic vesicles are not able to function. This raises many interesting new questions about the functioning of neural communication as well as opportunities for anticancer drug development.

ISBUC research reveals lactic acid effects

Lactic acid is abundant in muscle cells after intense sport, and also in cancer cells, and leaves epigenetic marks that affect the way human DNA is read. Now, ISBUC researcher Christian Adam Olsen (ILF) has shown that specific enzymes can remove lactic acid marks from proteins and can potentially become targets for new drug candidates. This finding may increase our understanding of cancer medicine and how physical exercise, diet or sleep, among other things, can affect human epigenetics. The study was published in *Science Advances* (2022).

Using X-rays to optimize food taste and plant-based diets

ISBUC researcher Jacob Kirkensgaard (FOOD/NBI) and collaborators are using small-angle X-ray scattering to study food at the nanolevel, using the new Nano-inXider instrument that resides at FOOD. By understanding the structure of different food materials and how it relates to different tastes, textures and nutritional absorption, Kirkensgaard and collaborators hope to be able to develop food that help to prevent obesity, while also increasing sustainability. The Danish food producers and ingredient suppliers industry have already shown interest in this novel and promising approach.

The dopamine transporter depends on potassium gradient for regulating the dopamine uptake

An ISBUC collaboration between Claus Løland (IN), Nikos Hatzakis (CHEM) and Kasper D. Rand (IF) has revolutionized our understanding of the dopaminergic uptake in the brain: instead of solely depending on the differences in sodium concentration across cell membranes, it also depends on differences in potassium. The discovery expands our knowledge of how the brain regulates the availability of dopamine, and perhaps also other neurotransmitters. This may allow for a better comprehension of many conditions, such as schizophrenia and ADHD, and it represents a new target for developing drugs to treat mental disorders more efficiently, selectively regulating the neurotransmitters' uptake. The research was published in *Nature Communications* (2022).

Cryo-EM may help treat some of the deadliest cancer forms

ISBUC researcher Guillermo Montoya (CPR) and his colleagues have used cryo-electron microscopy to investigate a complex of three proteins (RAF-1, HSP90 and CDC37) that causes cancer cells to divide and spread. This has unveiled key information that can help interfere and destroy the association of these proteins to stop uncontrolled and potentially deadly cell division. Thus, their work in collaboration with the Barbacid Group at CNIO may open new therapeutic avenues to treating cancers that are otherwise fatal. The results were obtained in mice, and their translation into humans has still to be assessed, but if it works equally well in both species, this better understanding of how this complex works could be a clear advantage when treating cancers where the stabilization of RAF-1 is a driving force in proliferation. This research was published in *Molecular Cell* (2022).

ISBUC collaboration uses social media to assess AI applications in structural biology

ISBUC researchers Amelie Stein (BIO) and Kresten Lindorff-Larsen (BIO) have taken part in an international collaboration which demonstrated the accuracy of AlphaFold by using social media as a tool for scientific collaboration. In this project, researchers tested the utility of protein structures predicted by AlphaFold for use in a broad range of applications. The collaboration was led by Pedro Beltrao (ETH Zürich), who aimed to round up results that had been shared on social media by numerous research groups since AlphaFold was first presented. The work of researchers from 18 institutes in 11 countries showed that the AlphaFold predictions were as suitable as structures based on experimental data for many applications, emphasizing the enormous potential of artificial intelligence in structural biology as well as the power of social media as a means to share and benefit from each other's findings in such fast-moving fields. The research was published in *Nature Structural & Molecular Biology* (2022).

ISBUC research highlights

Mapping the 3D structure of human NALCN channelosome

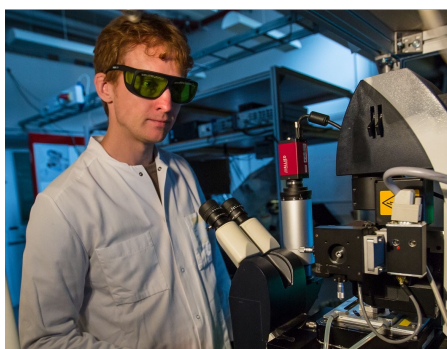
ISBUC researcher Stephan Pless (ILF), along with Genentech and other international collaborators have mapped the 3D structure of the final two of the four large proteins that make up the NALCN channelosome. This complex controls electrical currents in the body and is vital for survival in mammals. This fruitful study demonstrated the power of a truly integrative collaborative approach to structural biology involving

as well as functional characterization. Furthermore, the research found a fifth protein, calmodulin, that seems to be part of this massive complex, suggesting that there might also be other proteins involved. These findings open new doors for the assessment of how human mutations affect NALCN channelosome function and lead to severe, although rare, diseases. This research was published in *Nature* (2022).

Nano-scale insights define mechanical behavior of filopodia

Ultra-fine microscopical recordings from the lab of ISBUC researcher Poul Martin Bendix (NBI) have added to the world's understanding of how cells move and interact with each other: using filopodia, tentacle-like structures that rotate, twist and contract in a similar way to a rubber band. This mechanism appears to be found in all living cells. The discovery of this mechanism is an example of the relevance and potential of basic science, which could further translate into new findings and applications in fields such as, for instance, cancer

therapy. This research was conducted using the state-of-the-art optical tweezers at NBI and was published in *Nature Communications* (2022).

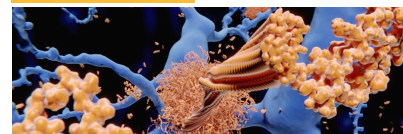


ISBUC researchers might have found a cue for early detection of Parkinson's disease in skin lipids

ISBUC researcher Céline Galvagnion-Büll (ILF) and collaborators have discovered that the lipids in fibroblasts seem to be significantly different in patients with a certain type of familial Parkinson's disease. This is the first time that anyone has been able to link changes in skin lipid makeup to Parkinson's, and could lead to an early detection method for people who might at risk for familial Parkinson's. In

further good news, a small molecule drug that is currently in clinical trial against Parkinson's seems to revert the changes of these lipids in the skin. It is hoped that the changes found in skin lipid makeup are mirrored in the brain – and represent an effective new strategy to counteract the disease. Future research will test this hypothesis using neurons grown from stem cells. This research was published in *Brain* (2022).

Using machine learning and biophysics to predict how molecules organise and interact



A new computer model developed by ISBUC researchers Giulio Tesei, Kresten Lindorff-Larsen and colleagues (BIO) can help predict how disordered proteins interact and collaborate on functional tasks. Until now, the highly dynamic nature of these proteins made this kind of predictions difficult. The new model combines biophysical measurements with a machine learning method to discover the rules of how disordered proteins interact, such as their propensity to come together in small droplets. The advancement could play a role in understanding for example autism, dementia, and cancer that can be caused by dysregulation of assemblies, and was published in *PNAS* (2021).

Nano-containers allow for first screenings of pharmaceutical candidates at much lower costs

A highly integrative research effort led by ISBUC researcher Nikos Hatzakis (CHEM) has led to a new tool that can speed up the development of vaccines and other pharmaceutical products by more than one million times while minimizing costs. The method works by using fluorescently barcoded soap-like bubbles as nano-containers, in which multiple ingredients can be mixed using DNA nanotechnology and identified using machine learning technologies. This tool provides results within just seven minutes, very close to a live read-out, and could revolutionize the synthetic development and evaluation of pharmaceuticals. It was published in *Nature Chemistry* (2022).

Montoya lab is honoured with the cover of Nucleic Acids Research

ISBUC researcher Guillermo Montoya (CPR) has been honoured with the cover of the prestigious journal *Nucleic Acids Research* for the article: [Mechanics of CRISPR-Cas12a and engineered variants on λ-DNA](#). In this article, Montoya and collaborators uncover molecular mechanisms of these endonucleases and their binding events that suggest the possibility of generating new variants with biomedical and biotechnological applications.



ISBUC funding news

Mette Rosenkilde awarded ERC advanced grant

In 2022, Professor Mette Rosenkilde (BMI) was awarded a prestigious ERC Advanced Grant worth DKK 18 million for innovative research over the next five years. Mette’s research focuses on the study of G protein-coupled receptors and other membrane proteins, with the aim to develop medications targeted at these, as they are involved in multiple body processes. Hopefully, her new insights into these receptors may one day lead to treatments in areas that are difficult to assess today.



Sapere Aude grant for Weria Pezeshkian

Weria Pezeshkian (NBI) was awarded the coveted Sapere Aude grant for his project “Coupling Architectures of the Cellular Powerhouse to Energy Production States Using Computational Microscopy”. This project will provide key insights into how cellular powerhouse organize to function and delivers a computational framework to provide a realistic mechanistic picture of such processes.



Lundbeck Foundation Professorship grant to further support Danish neuroscientific projects

In December 2021, Professor Ulrik Gether (IN) received a Lundbeck Foundation Professorship worth DKK 40 million to continue his research on neurotransmitters and receptors in the brain. This grant aims to support some of the extremely strong profiles within Danish neuroscience to conduct research with ground-breaking potential, while also committing to train the next generation of researchers by involving younger colleagues in their projects. Gether’s research explores the impact of neurotransmitters and receptors in the brain on disease, and how they may be influenced by drugs. In this project, he will study the basic role of dopamine in behaviour and brain disease by using highly sophisticated molecular research techniques.



NFF Emerging Investigator grant to study genome replication processes and the reparation of DPCs

Thomas Miller (ICMM) received an NNF Emerging Investigator Grant for the project “Defining the molecular mechanisms of replication-coupled DPC repair using EM-based visual biochemistry”. This research will help reveal how the proteins involved in genome replication (replisomes) overcome obstacles that can prevent faithful duplication of the DNA before cell division, as well as why a failure in these processes causes human disease. To do this, Thomas will use electron microscopy to image replisomes as they encounter and coordinate the repair of DNA-protein crosslinks (DPCs), a common and highly toxic obstacle to DNA replication. The results will provide insights into how our cells maintain genome stability and may identify opportunities for enhancing current chemotherapies that kill cancer cells by forming DPCs on DNA.



ISBUC IN PRINT

232

Publications by ISBUC researchers in 2022

Publications by 2+ ISBUC researchers in 2022

31

9

Publications by 3+ ISBUC researchers in 2022

Villum Experiment grant to predict protein structure, mutations and dynamics



ISBUC researcher Thomas Hamelryck (DIKU) has been awarded a Villum Experiment grant for his project “Predicting protein structure, mutations and dynamics with deep generative models”. Currently, protein structure prediction methods, successful as they are, assume that a protein adopts a single, fixed structure. Using state-of-the-art machine learning algorithms, based on deep generative models and Stein variational inference, this project plans to tackle the prediction of protein ensembles.

ISBUC welcomes two new group leaders: Azadeh Shahsavari and Weria Pezeshkian

In 2022, we welcome two new group leaders to the ISBUC community: Azadeh Shahsavari (ILF) and Weria Pezeshkian (NBI). Both are stand-out young researchers who have pioneered innovative new structural biology methods. During her short career, Azadeh has developed the serial synchrotron method and used it to solve the structure of GlyT1. This protein sits in the brain and regulates NMDA receptors. It has been suggested as a target for treating

neurological diseases and its structure had been unsolved for 20 years before Azadeh spent 5 years studying this molecule during her postdoc and finally cracked it. Weria has developed a multi-scale simulation method which allows researchers to zoom in and out between the atomic level, the coarse-grain level and also the meso-scale. Weria uses this approach to study membrane proteins and how Shiga toxins are able to cross them.



ISBUC activities



ISBUC welcomes new Chair and Vice-Chair

In 2022, there has been some seat-shuffling in the ISBUC Steering Committee and we are very happy to announce our new Chair Professor Birthe B. Kragelund (BIO) and Vice-Chair Claus Løland (IN). Birthe and Claus will serve for the next two years before the chairs shuffle again.

We would also like to say a huge thank you to our outgoing Chair Guillermo Montoya (CPR), who has played a huge role in getting ISBUC up and running. Happily, Guillermo will remain in the ISBUC Steering Committee, helping to shape and drive our community forward.

ISBUC Annual Meeting

The 2022 ISBUC Annual Meeting was a day filled with inspiring science, cross-discipline networking and thought-provoking discussions. The day featured four exceptional keynote speakers including Kristina Djinović-Carugo (EMBL Grenoble), James Fraser (UCSF), Martha Sommer (ISAR Bioscience Institute) and Poul Nissen (Aarhus University). These fantastic presentations all demonstrated the power of truly integrative structural biology and raised the bar for scientific excellence. As always, the Annual Meeting featured a



stimulating panel discussion, this year about the opportunities for integrating neutron scattering with other structural biology methods. Led by Instrument Scientist Esko Oksanen, the discussions shone a light on the potential of the coming neutron source at ESS for ISBUC researchers.

In addition, the day featured flash talks by junior researchers and two very-full poster sessions. Special congratulations go to Andreas Haahr Larsen and Solveig Gaarde Schmidt for winning the 2022 Junior ISBUC Best Talk and Best Poster Prize.

ISBUC PI Day



On 14th March, ISBUC held its first in-person PI Day since the pandemic. Over 30 senior researchers came together to hear presentations by nine ISBUC group leaders. The ISBUC PI Day provides a platform where group leaders from different departments and faculties can present their current and future research directions and identify potential areas of collaboration. The event led to many fruitful interchanges and discussions between researchers.

ISBUC activities

ISBUC Industry Day

The 2022 ISBUC Industry Day was a great success. Over 70 people turned up in force on the day to see the latest research happening right here at UCPH, including researchers from Novo Nordisk, Novozymes, Lundbeck and LEO Pharma. In addition to a showcase of industry-relevant structural biology being done here at UCPH, the day also featured talks by industry researchers and several

ISBUC group leaders who have started their own spin outs. We would particularly like to congratulate PhD student Felix Kummer who took home the Industry prize for best poster. Feedback has been hugely positive and plans are underway for a similar event in 2024.

Read the full write up by Copenhagen Science City:

<https://copenhagensciencecity.dk/industry-introduced-to-business-ready-research-instruments/>



Nordforsk University Cooperation Application

In 2022, ISBUC has led an application to the Nordforsk call for University Cooperation to establish a Nordic network for integrative structural biology. The proposed network would bring together 26 university partners as well as ESS and MAXIV and aims to scale-up the ISBUC model for spurring interdisciplinary, innovative and integrative structural biology research across all five Nordic countries. After a successful pre-proposal, ISBUC submitted a full proposal to Nordforsk in 2023.

Structural Seminars

In 2022, ISBUC launched the Structural Seminars. These quarterly seminars shine a light on envelope-pushing integrative structural biology research happening in Copenhagen and the surrounding regions. And they provide a space where ISBUC researchers can get together on a regular basis to catch-up and network across departments and faculties. Speakers in 2022 included Guillermo Montoya (UCPH), Pétur Orri Heiðarsson (UICE), Azadeh Shahazar (UCPH) and Gerhard Schütz (TU Wien).

Junior ISBUC Takes Off!

In the fall of 2022, Junior ISBUC started its own Lunch Talk series. A space for junior researchers to connect with newly established group leaders working in structural biology at UCPH. Each month, we invite either an academic or industry researcher to discuss their research. This provides a



great forum for junior researchers to learn about structural biology research happening outside their own departments. In addition, researchers talk about their careers, giving guidance and advice for junior researchers interested in securing a permanent position. Speakers in 2022 included Martin Gustavsson (BMI), Weria Pezeshkian (NBI), Sune Christensen (Novozymes), Céline Galvagnion-Büll (ILF). Also in 2022, Junior ISBUC organized a Find Your Structural Biology Lab day for MSc students interested in doing a thesis project in structural biology. The event included flash talks by junior researchers from ISBUC labs and was a great success.

Structures of Life communication program

In 2022, ISBUC started a collaboration with the Danish artists Dark Matters to explore new ways of visualizing biomolecules that are both scientifically accurate and beautiful. The ultimate aim is to work with different artists each year to develop an open access image library for molecular and structural biology based on actual PDB data. In addition, ISBUC aims to organise public installations of biological structures and various activities for Kulturat.

