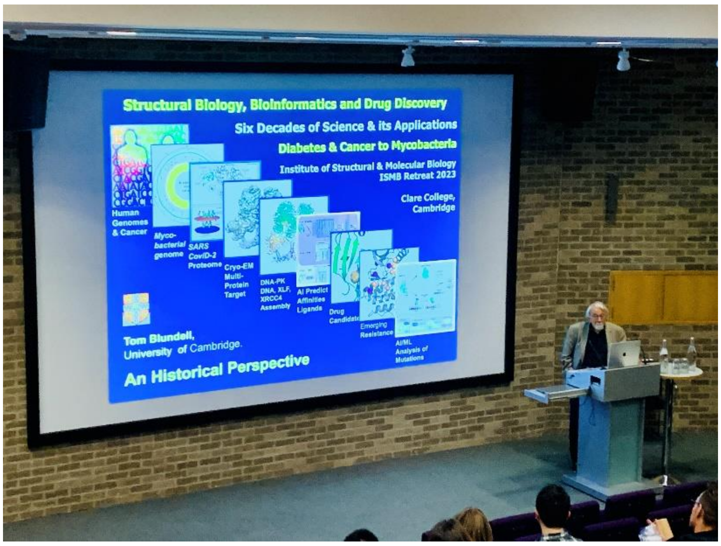
10th ISMB Retreat
4th – 5th July, 2023
Clare College Cambridge

The 10th ISMB Retreat, the first to take place at Clare College in Cambridge, was held on 4th-5th July 2023. Over a hundred delegates from the ISMB attended the two-day event, which featured five keynote speakers, ten students and postdoctoral researchers presenting talks on diverse areas of research, and a lively poster session.

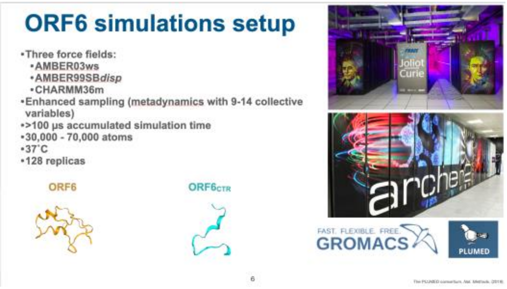
This year's retreat was also the first to be organised under the leadership of the recently appointed ISMB Director, Professor Franca Fraternali, who took over the role from interim director Professor Finn Werner in 2022.



Following a warm welcome from Fraternali, the very first session of the ISMB Retreat 2023 kicked off with a keynote presentation from renowned structural biologist **Professor Sir Tom Blundell** of the University of Cambridge. Sir Tom has enjoyed a distinguished career spanning crystallography, biochemistry, bioinformatics and computational biology, drug discovery, politics, entrepreneurship, and science policy, and his presentation reflected this wealth of experience. His insightful talk covered a broad range of topics, starting with his early efforts on solving the first crystal structure of insulin and revealing its beautiful symmetry. Sir Tom also discussed his travels across Asia and Africa and his work in science outreach, his early contributions to computational bioinformatics and structure-based drug design, and his co-founding of Astex Therapeutics, a biotechnology company which later sold for $900 million.

The session continued with talks from ISMB postdoctoral researchers, starting with **Abhinav Koyamangalath Vadakkepat** from Professor Gabriel Waksman's group at Birkbeck. Vadakkepat presented his recent work on solving a high resolution cryoEM structure of a bacterial secretion system complex. This newly solved structure contains over 90 polypeptide chains and it illustrated a novel, never-before-seen mechanism of assembly for a bacterial secretion complex, which has important implications for the fight against antimicrobial resistance. Next, **Vaishali Waman** of Professor Christine Orengo's group at UCL presented her work on the structural diversity of ATPase enzymes. Waman spoke about a new computational pipeline for understanding the structural diversity in different families of enzymes, using ATP-pyrophosphatases as a case study. Her work on the substrate specificity and evolutionary history of these enzymes has potential applications for the development of drugs against pathogens such as *Mycobacterium tuberculosis*.

The session concluded with a talk from **Alice Pettitt**, a PhD student in Professor Flemming Hansen's group at UCL. Pettitt presented her work on characterizing a disordered protein from SARS-CoV2, using both molecular dynamics simulations and NMR experiments. Her fascinating talk covered a mixture of computational and experimental methods, winning her a well-deserved prize for the joint best talk of the retreat.



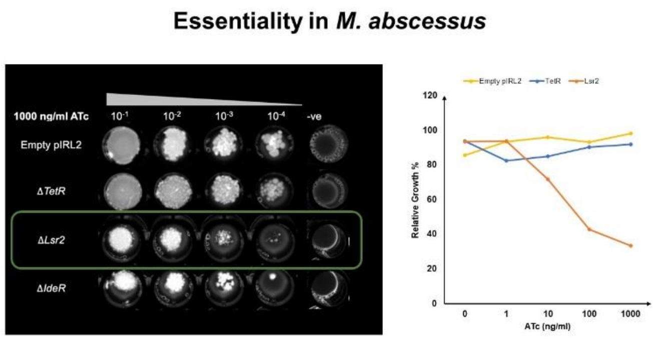
ORF6 simulations setup

- Three force fields:
  - AMBER03ws
  - AMBER99SB*disp*
  - CHARMM36m
- Enhanced sampling (metadynamics with 9-14 collective variables)
- >100 μs accumulated simulation time
- 30,000 - 70,000 atoms
- 37˚C
- 128 replicas

The second session on the first day started with two keynote speakers. The first was structural bioinformatician **Professor Charlotte Deane** from the University of Oxford. Deane took us through her impressive academic career, focusing on modelling and comparing the binding sites of immune receptor proteins to enable their design. She demonstrated her many of the software products that her group had contributed to the field and illustrated a beautiful use of AI and machine learning for drug discovery and understanding protein networks.

The second keynote speaker was **Dr. Stacey Southall**, Associate Director and head of the Biophysics platform at Sosei Heptares. Southall shared the story of how scientists at Sosei Heptares had stabilised G-coupled protein receptors using StaR technology, which has resulted in an impressive amount of structural data and the development of new drugs targeting GPCRs. Their work is an excellent example of their StaR technology's synergy with recently advanced cryo-EM and MS methods to unlock structure-based drug design.

This session included three talks by young scientists. Postdoctoral researcher **Georgina Charlton** from the Thalassinos Lab at UCL, gave a visually impressive talk whereby she explained how crosslinking mass spectrometry can increase our understanding of the structures of proteins implicated in Huntington's disease. She focused mainly on two proteins that are part of a large, flexible protein complex and are known as FAN1 and MLH1.


Essentiality in *M. abscessus*

The second student talk was given by **Chris Daniel**, a postdoctoral researcher in Professor Sanjib Bhakta's Mycobacteria Research Laboratory at Birkbeck. Daniel's prize-winning presentation demonstrated how mutations silenced by CRISPR interference are used to understand how the opportunistic pathogen *Mycobacterium abscessus*, known to cause tuberculosis-like lung disease, is regulated.

The last talk of the session was from an invited speaker, **Luigi Martino** from the Wellcome Trust. Martino is an expert on research careers and career development and gave an overview of two funding schemes from Wellcome: Career Development Awards and Wellcome Early-Career Awards. The talk was very informative, and his extended Q&A session was very insightful and helpful for the many early career scientists in the room.

As the first day drew to a close, ISMB members as usual participated in an activity to encourage team building. This year, around sixty delegates went punting, and despite the rain, it was enjoyed by all. The evening closed with a formal dinner at the Great Hall, and a toast by Sir Tom to the ISMB's continued excellence in science.

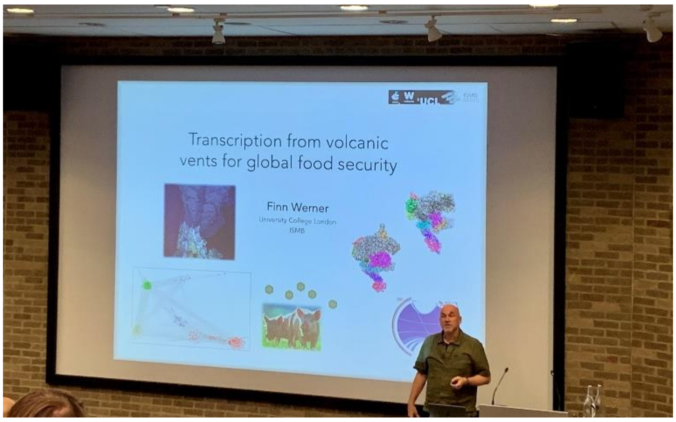
The second day began with talks from two distinguished speakers. The first was **Dr Jan Lowe** from the MRC Laboratory of Molecular Biology in Cambridge. Lowe gave an overview of his impressive career studying cytoskeletal filaments and how properties intrinsic to their polymerisation achieve complex cellular organisation and regulation across both prokaryotes and eukaryotes. By studying cytoskeletal conservation across all known life, Lowe pioneered the term "cytomotive switch" to describe the ubiquitous conformational changes which accompany polymerisation to enable filament formation in the absence of other factors.

The second speaker was **Professor Sonia Gandhi** from the Francis Crick Institute and UCL QS Institute of Neurology. With a strong medical background Gandhi showcased the strength of combining molecular and computational biology with clinical research. She gave an overview of the combined approach she has taken to map Parkinson's disease development from analysis of alpha-synuclein oligomerisation in patient -derived induced pluripotent stem cells, to brain scans from patients living with Parkinson's. Professor Gandhi wrapped up the presentation by sharing a striking preview of an interactive fully mapped brain allowing in-depth interrogation of how a brain is affected by alpha-synuclein in the developing stages of the disease.

Javier Carbello Garcia, a postdoctoral researcher from Professor Stefan Howarka's group at UCL, enthused us by describing his elegantly designed experiments using inducible DNA origami scaffolds to slow down vesicle formation for subsequent visualisation by direct stochastic optical reconstruction microscopy (dSTORM).

The next young scientist to speak was **Kamila Kamuda**, a PhD student from David Lomas' group at UCL. Kamuda presented her PhD research investigating the genetic disorder alpha1-antitrypsin deficiency (AATD). Combining live-cell functional experiments such as flow cytometry with nifty computational analysis of electron microscopy data, Kamuda characterised the broad impact that a variant of Alpha1-anti trypsin protease inhibitor can have on the cellular landscape, and critically linked mitochondrial function to disease progression.

The final talk of this session was from **Luyao Yang**, a PhD student from Saul Purton's group at UCL. Yang's research investigated how shrimps could be fed with genetically modified Chlamydomonas for both delivery of fish growth hormones, and more importantly to vaccinate the shrimp against the deadly viral infections that are catastrophic to food security in Thailand.



The last session of the retreat commenced with a keynote speaker, **Professor Finn Werner** from the RNA polymerase lab at UCL and acting director of the ISMB from 2019-2022. Werner demonstrated the high impact of the African Swine Fever Virus (ASFV) and how the virus machinery expresses its own RNA polymerase. The group's multidimensional approach, involving transcriptomics, mass spectroscopy, and cryoEM, has provided compelling insights into the evolution of the virus' proteins and is an invaluable tool for developing protein inhibitors as candidates for antiviral drugs to combat ASFV.

The session continued with a talk by **Joseph Ng**, a postdoctoral researcher in the Fraternali Lab at UCL. Ng demonstrated how he uses single-cell transcriptomic data to infer the dynamics and direction of class-switch recombination for germline B-cells. The computational work uses processes specific to B cells and gives insights into the regulation of class-switching and the dynamics of B cell maturation during an immune response.

The retreat ended with a talk by **Tianyang Liu**, a postdoctoral researcher from Professor Carolyn Moores' lab at Birbeck. Liu presented her work on molecular visualization of cortactin using cryoEM. These small proteins stabilize actin filament branches by interacting with the Arp2/3 complex. Regulation of the assembly and turnover of branched actin filament networks nucleated by this complex is essential during many cellular processes including cell migration and membrane trafficking.

All that remained was for Fraternali to close a successful retreat by presenting prizes for the best talk and poster and thanking all who had been involved in making it go so well. This year, the talk and poster judging process was open to all delegates who could vote for their favourites using the Mentimeter app. The competition was tight, with a tie for the best talk and the following students and postdocs emerging as winners:

Best Talk (tied 1st Place)

Alice Pettitt, "Biophysical characterisation of ORF6 from SARS-CoV-2"

&

Chris Daniel, "Regulatory Trifecta: Characterisation of CRISPRi-silenced mutants of iron acquisition in Mycobacterium abscessus"

Best Poster

1st Place

Anushandan Navaratnarajah, "Modified HT-SPOTi: *An in vitro* antimicrobial susceptibility testing to evaluate formulated therapeutic combinations against microbial infection".

2nd Place

Vilde Leipart, "Understanding the structure-function relationship of honeybee Vitellogenin".

3rd Place

Karan Kanwar, "Characterisation of ATP-dependent Mur ligases from *Mycobacterium abscessus*".

Congratulations to all.

The next biennial ISMB retreat will take place in summer 2025; before then, there will be another ISMB symposium – the 11th – in June 2024.

Thank you to the contributors who have put together this report: Naail Kashif-Khan, Vilde Leipart, Lucy Troman, and Clare Sansom.