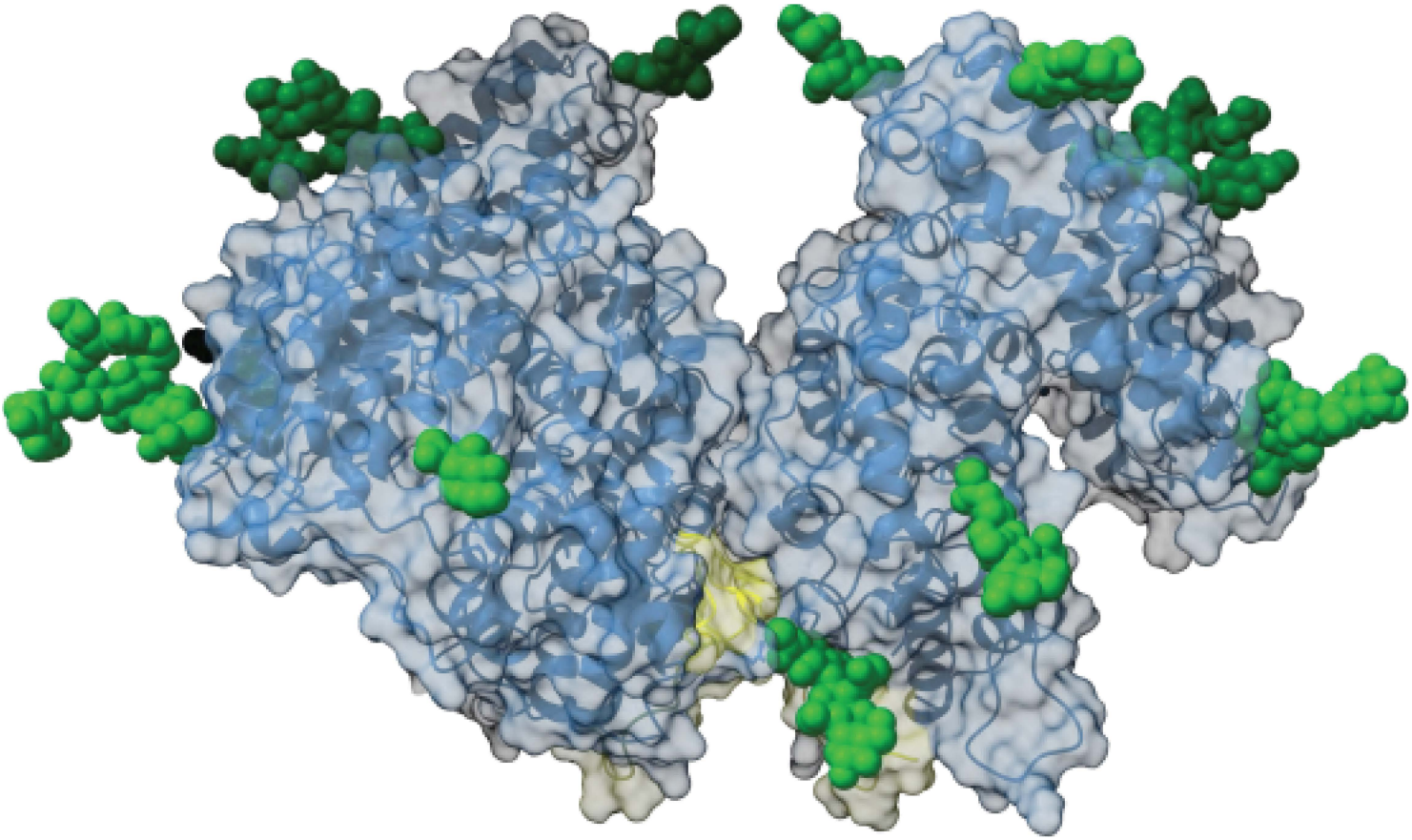
Inside the Researcher's Mindset Workshop

CRYO-EM IN DISCOVERING NEW DRUGS AND VACCINES



A dimer of Angiotensin Converting Enzyme, the key to blood pressure control - drawn by Lizelle Lubbe - UCT - https://doi.org/10.15252/embj.2021110550

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EMU
Electron Microscope Unit

IDM
INSTITUTE OF INFECTIOUS DISEASE AND MOLECULAR MEDICINE

AFRICAN RESEARCH SOCIETY

Inside the Researcher's Mindset Congress
17- 20 August 2024

Saturday 17 Aug: ***"Inside the Researcher's Mindset" lecture***
Sunday 18 Aug: ***Social Event***
Monday 19 Aug: ***"The role of CryoEM in discovering new drugs and vaccines" hybrid workshop***
Tuesday 20 Aug: ***VC's lecture "Cryo-electron microscopy, a new foundation for molecular medicine and drug design"***

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Meet our speaker

JOACHIM FRANK

Prof. Joachim Frank is the inventor of the key underlying technology that has led to the “Resolution Revolution” in cryogenic electron microscopy (cryo-EM), a major driver of innovation in medicine, biotechnology, and agriculture.

He is a noteworthy structural biologist, and among his major works are the structure of the ribosome and calcium release channel.

In 2017, Joachim shared the Wiley Prize in Biomedical Sciences with Richard Henderson and Marin van Heel. Later in the same year he was awarded the Nobel Prize in Chemistry together with Richard Henderson and Jacques Dubochet.

He is an important innovator in the field and is currently developing techniques for time-resolved cryo-EM – making atomic-resolution movies of life processes.

The role of single-particle cryo-EM in discovering new drugs and vaccines

Single-particle cryo-EM, in being able to capture an entire spectrum of states of a biomolecular complex, is uniquely suited for drug discovery as well as development of vaccines. Increasingly the capacity of a biomolecule to “breathe” and change its structure dynamically in the thermal bath is recognized as key in understanding drug efficacy and, more generally, the propensity of its interaction with antibodies and other ligands. We anticipate that this aspect is further illuminated in the development of powerful time-resolved cryo-EM methods.

WORKSHOP SCHEDULE 19 AUG 2024

Institute for Infectious Diseases and Molecular Medicine: Wolfson Lecture Theatre

	TIME	SPEAKER	TITLE	ALLOCATION
	9:00 AM - 9:15 AM	Digby Warner Trevor Sewell	Welcome Introduction	15 minutes
1.	9:15 AM - 10:10 AM	Joachim Frank	The role of single-particle cryo-EM in discovering new drugs and vaccines	45 minutes presentation 10 minutes Q&A
2.	10:10 AM - 10:40 AM	Michael Lawrence (Zoom from Melbourne)	Unwrapping Insulin Signalling by Cryo-EM	30 minutes presentation and Q&A
	10:40 AM - 11:20 AM	Coffee Break		40 minutes
3.	11:20 AM - 11:50 AM	Constantinos Kurt Wibmer	Structure-guided immunogen and immunotherapeutic design	30 minutes presentation and Q&A
4.	11:50 AM - 12:20 PM	Jason van Rooyen (Zoom from Didcot)	Supporting the Adoption of Cryo-EM by Industry at Diamond Light Source	30 minutes presentation and Q&A
	12:20 PM - 1:20 PM	Luncheon		1 hour
5.	1:20 PM - 2:00 PM	Ed Sturrock	Cryo-EM structure of angiotensin-converting enzyme: Novel structural and mechanistic insights into cooperativity, dimerization and allostery	30 minutes presentation and Q&A
6.	2:00 PM - 2:30 PM	Katerina Naydenova (Zoom from Cambridge)	Structure Determination by Cryo-EM at 100 keV	30 minutes presentation and Q&A
7.	2:30 PM - 3:00 PM	Jeremy Woodward	Development of a two-component nanoparticle vaccine displaying an HIV-1 envelope glycoprotein that elicits Tier 2 neutralising antibodies.	30 minutes presentation and Q&A
	3:10 PM - 3:25 PM	Coffee Break		15 minutes
8.	3:25 PM - 3:40 PM	Danielle Martin	Design of soluble HIV-1 Env trimers from highly neutralization-resistant HIV-1 strains for the isolation of broadly neutralizing antibodies.	10 minutes presentation 5 minutes Q&A
9.	3:40 PM - 3:55 PM	Paige Mackenzie	Using Cryo-EM to Investigate Mycobacterial Pilin	10 minutes presentation 5 minutes Q&A
10.	3:55 PM - 4:10PM	Lauren Coulson	Target-based drug discovery at the Holistic Drug Discovery and Development Centre	10 minutes presentation 5 minutes Q&A
11.	4:10 PM – 4:25 PM	Veneshley Samuels	A new look at an old target: towards Cryo-EM elucidation of bioaerosol-captured *Mycobacterium tuberculosis*	10 minutes presentation 5 minutes Q&A
12.	4:25 PM - 5:00 PM	Bridget Carragher (Zoom from the Chan Zuckerberg Imaging Institute)	Tools and Technologies for Cryo-Electron Tomography	30 minutes presentation 5 minutes Q&A
	5:00 PM - 5:20 PM	Closing Remarks and Discussion		20 minutes

Zoom link: https://uct-za.zoom.us/j/91408209640?pwd=4dYOes4op2uM31nYb8aGMqKNfAM7CI.1

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MIKE LAWRENCE

Prof. Mike Lawrence has honorary appointments within WEHI (the Walter and Eliza Hall Institute of Medical Research, Parkville Melbourne) and within the Department of Medical Biology, University of Melbourne (Parkville, Melbourne).

His undergraduate and doctoral studies were within the Department of Physics at the University of Cape Town (UCT; 1974 - 1980). He then transitioned his research into structural biology, spending two post-doctoral years at the MRC Laboratory of Molecular Biology in Cambridge, UK.

Upon return to South Africa, he worked at the SAMRC Institute of Electron Microscopy and was subsequently Director of the Electron Microscopy Unit at UCT.

He migrated to Australia in 1988 to join initially CSIRO. Since 2001, his research has centered almost entirely on the structural biology of the insulin receptor system.

Unwrapping insulin signalling by cryoEM

The atomic structure of insulin has been known since the late 1960s, but it is only relatively recently that molecular detail has been obtained of the insulin receptor and of the way in which insulin and its receptor interact and effect signal transduction into the cellular interior. These advances have been dependent both on the use of synchrotron x-ray sources for crystallographic study and on the use of cryo-EM for single-particle reconstruction. The talk will discuss the complementary nature of these technologies in the context of these discoveries.

CONSTANTINOS KURT WIBMER

Dr. Constantinos Kurt Wibmer is Director of the Wits Health Consortium's ViPER (Venom & Vaccine Immunotherapeutics & Immunogens Protein Engineering Research) division.

He received his PhD in 2016 from the University of the Witwatersrand, and began his training in protein x-ray crystallography with Drs. Peter Kwong and Jason Gorman at the Vaccine Research Center (NIH, Bethesda, USA) during a Fogarty AITRP traineeship. He further developed these skills as a postdoctoral research associate with Prof Ian Wilson at Scripps Research (La Jolla, USA). More recently, Kurt has trained in cryo-EM at EPFL (Lausanne, Switzerland).

Dr. Wibmer is developing novel antivenom to treat snakebite envenoming and novel immunogens for Africa's neglected pathogens by coupling mAb discovery with structural biology to design extremely broad, potent, and thermostable biologics for use in the developing world.

Structure-guided immunogen and immunotherapeutic design

Structural biology is essential for the rational design of novel vaccines, drugs, immunotherapeutics, or other biologics. Stabilised HIV-1 envelope antigens have facilitated the discovery of rare broad and potently neutralizing antibodies, and structure-guided stabilisation of coronavirus spikes facilitated the rapid design of SARS-CoV-2 spike vaccines. Similarly, snakebite envenomation, which kills >135,000 people annually, remains a Neglected Tropical Disease, with the only effective antivenom (polyvalent animal plasma) made through outdated technology. Our work in mAb discovery and structure-guided design has impacted HIV-1 and SARS-CoV-2 vaccine development, and has led to next-generation monoclonal antivenom antibodies for the treatment of bites by African mambas and cobras.

JASON VAN ROOYEN

Dr. Jason van Rooyen is the scientific lead of Diamond's industry-dedicated "tube-to-structure" platform, eBIC for Industry. He completed his MSc and PhD studies in Structural Biology at the University of Cape Town and did his post-doctoral studies at the EMBL in Grenoble. He has spent several years in EM-focused scientific computing, deploying automated acquisition systems and HPC processing pipelines. Currently, as, he is helping pharma and bio-tech companies apply next-generation EM in their challenging research problems.

Supporting the Adoption of Cryo-EM by Industry at Diamond Light Source

The electron Bio-Imaging Centre (eBIC) at Diamond Light Source offers a unique service to pharma and biotech companies to rapidly advance their discovery and development of lead compounds, biologics, or drug carriers whilst uncovering valuable information regarding biomolecule structure, stability and domain flexibility by using cryo-EM. By offering flexible access to worldclass cryo-EM facilities, including dedicated Glacios and Krios microscopes, and highly-experienced scientists, eBIC for Industry lowers the barrier to entry for a technique traditionally requiring large capital and training investments.

ED STURROCK

Prof. Ed Sturrock is a Professor in the Department of Integrative Biomedical Sciences (Head of Department 2015-2020) and a founding member of the Institute of Infectious Disease and Molecular Medicine (IDM) at UCT. He received his PhD from the University of Cape Town and postdoctoral fellowship at Harvard Medical School with Jim Riordan where he started his research on angiotensin-converting enzyme. Together with colleagues from the UK and USA, he founded AngioDesign Ltd, a spinout company that focuses on the rational design of enhanced next-generation drugs for proven cardiovascular disease targets, such as ACE and neprilysin.

Cryo-EM structure of angiotensin-converting enzyme: Novel structural and mechanistic insights into cooperativity, dimerization and allostery

Angiotensin-converting enzyme (ACE) is a zinc metallopeptidase that plays a critical role in blood pressure, and fluid and electrolyte homeostasis. ACE can cleave angiotensin I, bradykinin, and many other peptide substrates. Until recently, little was known regarding the specific role of each of the two ACE domains, their 3D structural orientation, dynamics and dimerization. In this talk I describe the first cryo-EM structures of full-length, glycosylated somatic ACE. Mechanisms are proposed for domain hinging, cooperativity, and homodimerization. Furthermore, the observation that both domains were in the open conformation has important implications for the design of allosteric modulators of ACE.

KATERINA NAYDENOVA

Dr. Katerina Naydenova is a career development fellow in the group of Felix Randow at the MRC Laboratory of Molecular Biology, Cambridge, UK.
She completed her PhD with Chris Russo also at the MRC LMB, where she worked on the development of new specimen supports for cryoEM and on improving microscope technology. Now, she is applying cryo-EM to study the innate immune response to bacterial infections.

Structure determination by cryoEM at 100 keV

Electron cryomicroscopy can, in principle, determine the structures of most biological molecules, but is currently limited by access, specimen preparation difficulties and cost. We present a purpose-built instrument operating at 100 keV (instead of the widely-used 300 keV instruments) - including advances in electron optics, detection and processing - that makes structure determination fast and simple at a fraction of current costs. We demonstrate the capabilities of this new microscope by determining the structures of eleven different biological specimens, using a fraction of the time and data normally required. Microscopes designed specifically for high-efficiency, on-the-spot imaging of biological molecules will help drive the continuing exponential growth in the number of structures determined by cryoEM.

JEREMY WOODWARD

Dr. Jeremy Woodward is a Research Officer in the Electron Microscope Unit, Principal Investigator in the Structural Biology Research Unit and the convenor of the Structural Biology Honours degree programme at the University of Cape Town.

He completed his PhD in Structural Biology at Ruhr University and the University of Cape Town and Postdoctoral studies in the Department of Medical Biochemistry at the University of Cape Town before being awarded an NRF Research Career Advancement Fellowship.

He administers the cryo-EM block Allocation Group for South Africa at the electron Bio-Imaging Centre (eBIC) at Diamond Light Source and currently holds a three-year grant from the Chan Zuckerberg Initiative for his project: “Cryo-EM training for Southern Africa”.

Development of a two-component nanoparticle vaccine displaying an HIV-1 envelope glycoprotein that elicits Tier 2 neutralising antibodies.

Despite treatment and other interventions, an effective prophylactic HIV vaccine is still an essential goal in the control of HIV. Inducing robust and long-lasting antibody responses is one of the main targets of an HIV vaccine. Delivery of HIV Env using nanoparticle (NP) vaccines has been shown to elicit better immunogenicity than soluble HIV Env. In this talk I describe the development of a nanoparticle-based vaccine decorated with HIV Env using the SpyCatcher/SpyTag system and its characterisation by cryo-EM. Rabbits primed with two doses of DNA vaccines and a mosaic subtype C Gag and boosted with three doses of the NPs developed autologous Tier 2 neutralising antibodies.

BRIDGET CARRAGHER

Dr. Bridget Carragher is the founding Technical Director of the Chan Zuckerberg Imaging Institute since January 2023.

She received a PhD in Biophysics from the University of Chicago in 1987 and worked in a variety of positions, both in industry and academia before moving to the New York Structural Biology Center in 2015 to lead the Simons Electron Microscopy Center (SEMC), together with Clint Potter.

While at SEMC, Bridget and Clint directed the National Resource for Automated Molecular Microscopy (NRAMM), the National Center for CryoEM Access and Training (NCCAT), the National Center for *In-situ* Tomographic Ultramicroscopy (NCITU), and the Simons Machine Learning Center (SMLC). They also founded the company NanoImaging Services in 2007.

Tools and Technologies for Cryo Electron Tomography

The mission of the Chan Zuckerberg Imaging Institute (CZII) is to enable deep insights into the architecture of complex biological systems at the molecular level, through the development and application of novel imaging technologies. The initial grand challenge for CZII is to develop technologies and methodologies to image the molecular architecture of the cell to near atomic resolution using cryo-electron tomography. I will describe our plans and progress on the platforms, technologies and driving biological projects that have been initiated towards these goals.

DANIELLE MARTIN

Design of soluble HIV-1 Env trimers from highly neutralization-resistant HIV-1 strains for the isolation of broadly neutralizing antibodies

PAIGE MACKENZIE

Using CryoEM to Investigate Mycobacterial Pilin

LAUREN COULSON

Target-based drug discovery at the Holistic Drug Discovery and Development Centre

VENESHLEY SAMUELS

A new look at an old target: towards CryoEM elucidation of bioaerosol captured Mycobacterium tuberculosis