MOLECULAR ARCHITECTURE OF LIFE

Seeks to untangle the details of the complex molecular processes that underlie all living systems, with implications for everything from our understanding of evolution to our ability to treat disease.

The program aims to understand the fundamental structure-function relationships and dynamics of biomolecules in living organisms. It focuses on three subclasses of molecular machinery within the cell that are the key to life: DNA self-replication and compaction, the role of ribosomes and proteasome in regulating proteins, and the regulation of protein expression and cell function through G-protein-coupled receptors (GPCRs). More than 50 per cent of current drug targets in the human body are related to functions of GPCRs, which bridge protein expression and cell function, and for the most part have remained elusive. Major advances in single-molecule imaging over the past year now allow us to watch these molecular processes in action.

Two program meetings were held in 2016/2017. The first took place in November 2016 in Shanghai in partnership with the Chinese Academy of Sciences (CAS), the National Centre for Protein Sciences (NCPSS), the Institute of Biochemistry and Cell Biology and the iHuman Institute of ShanghaiTech. This meeting laid the groundwork for Making a Molecular Map of the Cell, a global effort that rivals the Human Genome Project in scope and impact. Program members connected with researchers in China, at NCPSS and at a one-day joint session at the 4th International iHuman Forum at ShanghaiTech University, to begin exploring how the program can understand the molecular architecture of the cell at scale.

The second program meeting, held in Montreal in April 2017, explored the latest results from program members on single molecule imaging and GPCR signalling of protein complexes and provided brainstorming opportunities to foster collaboration among program members. Members also visited McGill University's imaging facility, led by Fellow **Paul Wiseman** (McGill University). As part of the meeting, Fellow **Michel Bouvier** (Université de Montréal) hosted members at the Institute for Research in Immunology and Cancer.

Three new fellows were also added to the program: **Michel Bouvier** (Université de Montréal), Sihyun Ham (Sookmyung Women's University) and **Tanja Weil** (Max Planck Institute for Polymer Research).

RESEARCH HIGHLIGHTS

The advent of ultrafast, highly brilliant, coherent X-ray free-electron laser sources is driving novel approaches for determining protein structure and promises visualization of protein dynamics on a sub-picosecond timescale with full atomic resolution. A collaboration between Program Co-Directors **Oliver Ernst** (University of Toronto) and **Dwayne Miller** (University of Toronto, Max Planck Institute for the Structure and Dynamics of Matter) and Advisory Committee Chair **David Stuart** (University of Oxford) is developing a sample delivery system to exploit these unique X-ray sources in the most efficient manner for high-throughput crystallography. Using this approach, atomic-level insights into key biological processes under native conditions will one day be resolved. Several publications highlight results and progress to date:

- Owen RL et al. 2017. Low-dose fixed target serial synchrotron crystallography. *Acta* Crystallogr D Struct Biol. 73(Pt 4): 373-378.
- Oghbaey S et al. 2016. Fixed target combined with spectral mapping: approaching 100 per cent hit rates for serial crystallography. Acta Crystallogr D Struct Biol. 72(Pt 8): 944-955.
- Ginn HM et al. 2016. TakeTwo: an indexing algorithm suited to still images with known crystal parameters. Acta Crystallogr D Struct Biol. 72 (Pt 8): 956-965.

Program Co-Director **Oliver Ernst** (University of Toronto) is collaborating with Autodesk Life Sciences to demonstrate the latest advances in visualizing and communicating biomolecular structures, which are essential to understanding biological processes on the most fundamental level. Autodesk's Molecular Viewer enables users to explore, customize and share interactive 3D biomolecular models in an immersive virtual reality environment that is far superior to current 2D representations

Time is an essential component of biological processes. The primary clock is in the brain, with secondary clocks present in other cells. For instance, many of the biological processes in the eye are circadian-regulated processes such as the removal of toxic compounds naturally formed in the retina.

AT A GLANCE

FOUNDED: 2014

PROGRAM DIRECTORS: R. J. Dwayne Miller, Max Planck Institute for the Structure & Dynamics of Matter and University of Toronto, and Oliver P. Ernst, University of Toronto

FELLOWS, ADVISORS AND CIFAR AZRIELI GLOBAL SCHOLARS: 16

INSTITUTIONS REPRESENTED: 14, in 6 countries

FIELDS AND SUBFIELDS REPRESENTED: biophysics; biochemistry and molecular biology; structural biology; genetics; neuroscience; basic medicine, including pathology, pharmacology and toxicology; analytic and organic chemistry; optics

MEETINGS: 2; in Shanghai, China, and Montreal, Canada

RELEVANT KNOWLEDGE USERS: industry (e.g., pharmaceuticals, medical devices, surgical technologies, etc.)

SUPPORTERS: Government of British Columbia

TO LEARN MORE: www.cifar.ca/research/molecular-architecture-of-life/

Fellows **Daniel Figeys** (University of Ottawa) and Krzysztof Palczewski (Case Western Reserve University) are currently exploring this fundamental process and its circadian regulation. With the help of postdoctoral fellows **Brian Keveny**, **Aleksander Tworak** and **Kerwin Chiang**, the team is examining the dynamic mechanisms involved in vision and identifying signalling cascades involved in the regulation of the early stages of this process.

Other Notable Publications and Outputs

- Johnson PJM, Ernst OP, Miller RJD et al. 2017. The primary photochemistry of vision occurs at the molecular speed limit. J Phys Chem B. 121(16): 4040-4047.
- A technique developed this past year for single protein detection using laser ablation and mass spectrometry has also shown promise for in situ pathology for cancer detection and as a way of performing scar-free surgery. While not related to the program's scientific objectives, the work is going to clinical trials in the coming year, and a proof-of-principle device for surgeons is being developed.

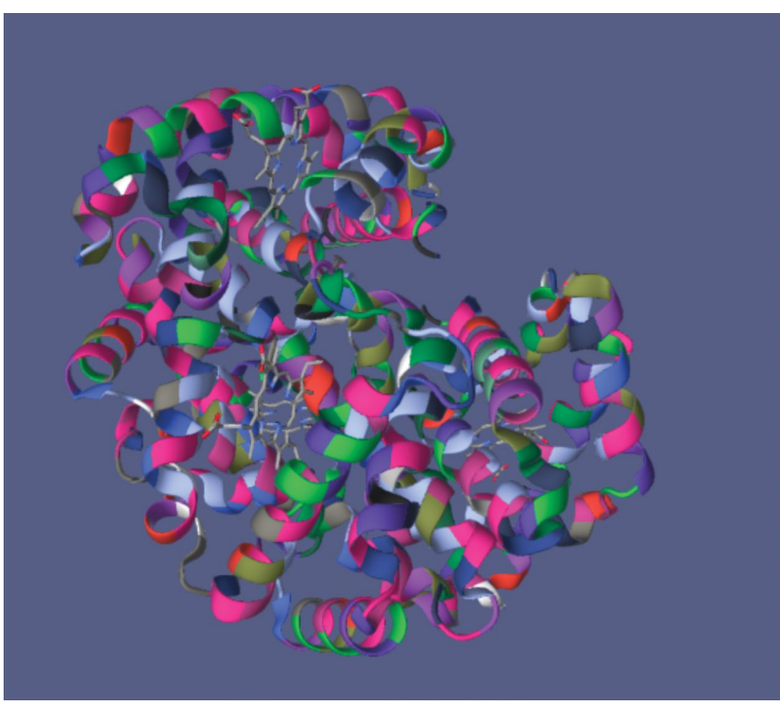
IDEAS EXCHANGE

The program refined its knowledge mobilization strategy and started to develop plans to engage with the pharmaceutical sector. A workshop exploring how systems pharmacology can be applied to drug design is being developed for next year.

GLOBAL ACADEMY

In 2016/2017 **Mikko Taipale** (University of Toronto) became the program's first CIFAR Azrieli Global Scholar, presenting his latest research at the November 2016 program meeting.

The program also engaged two postdoctoral fellows as program meeting reporters to provide written summaries of presentations.



Program Co-Director Oliver Ernst used the Autodesk Molecular Viewer to create and share molecular images like the one at right.