



McGill

# From bench to patients: how structural biology transforms medicine

**CRBS Bench-to-bedside workshop** – Inaugural session

**Jean-François Trempe**

Associate Professor  
Dept Pharmacology & Therapeutics  
McGill University

**CRBS**  Centre de  
Recherche  
en Biologie  
Structurale



# Objectives of *Bench-to-bedside* workshop series

1. Bring awareness of the power of structural biology to the greater biomedical community
2. Foster collaborations between clinicians and basic scientists

## Format:

- Research talks by 1 structural biologist and 1 clinician/biomedical scientist
- Open discussion
- Frequency: every 3-6 months?





# Program

14:00 – 14:20	Introduction – Dr Jean-François Trempe Title: <i>History of structural biology &amp; biophysics and ties to medicine</i>
14:20 – 15:00	Guest speaker, Dr Edward Fon Title: <i>Insight into Parkin function in biology and disease or why clinicians should care about protein structure</i>
15:00 – 15:35	Discussion 1 Topic: Bridging the gap between clinicians and basic scientists
15:35 – 15:55	Discussion 2 Topic: Ideas for future bench-to-bedside seminars
15:55 – 16:00	Conclusion



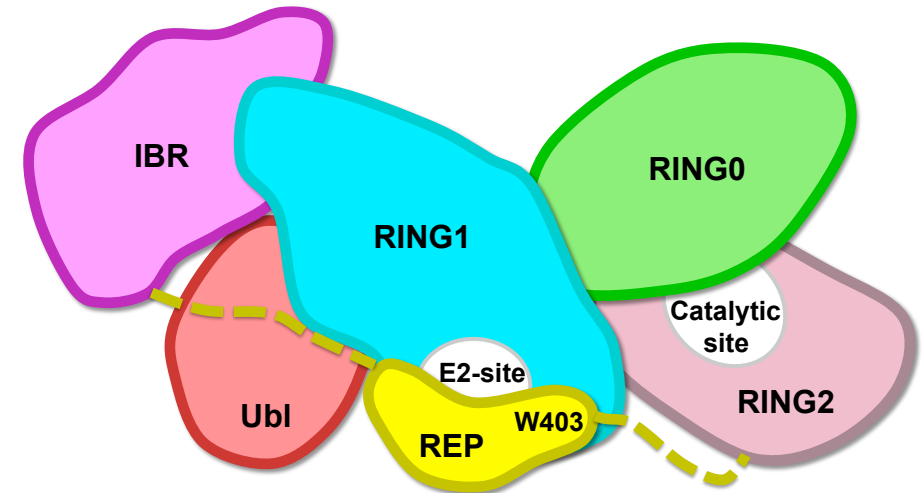
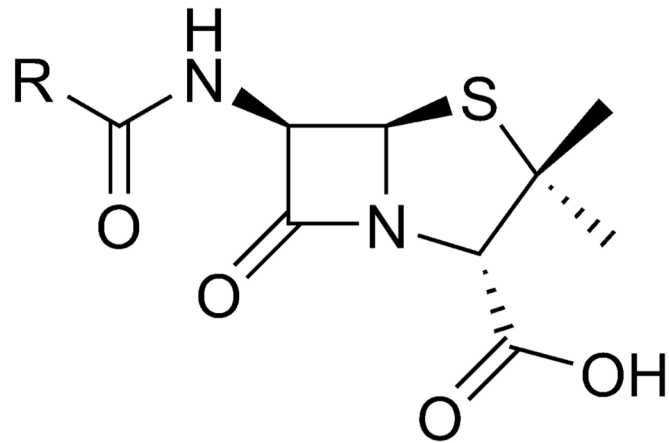
**Chair:** Jean-François Trempe, PhD  
Canada Research Chair in Structural Pharmacology  
Director, Proteomics platform of the RI-MUHC  
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**Guest speaker:** Edward A. Fon, MD, FRCP(C)  
Scientific Director, Montreal Neurological Institute  
Director, FRQS Quebec Parkinson Network  
Canada Research Chair in Parkinson's Disease  
Professor of Neurology and Neurosurgery  
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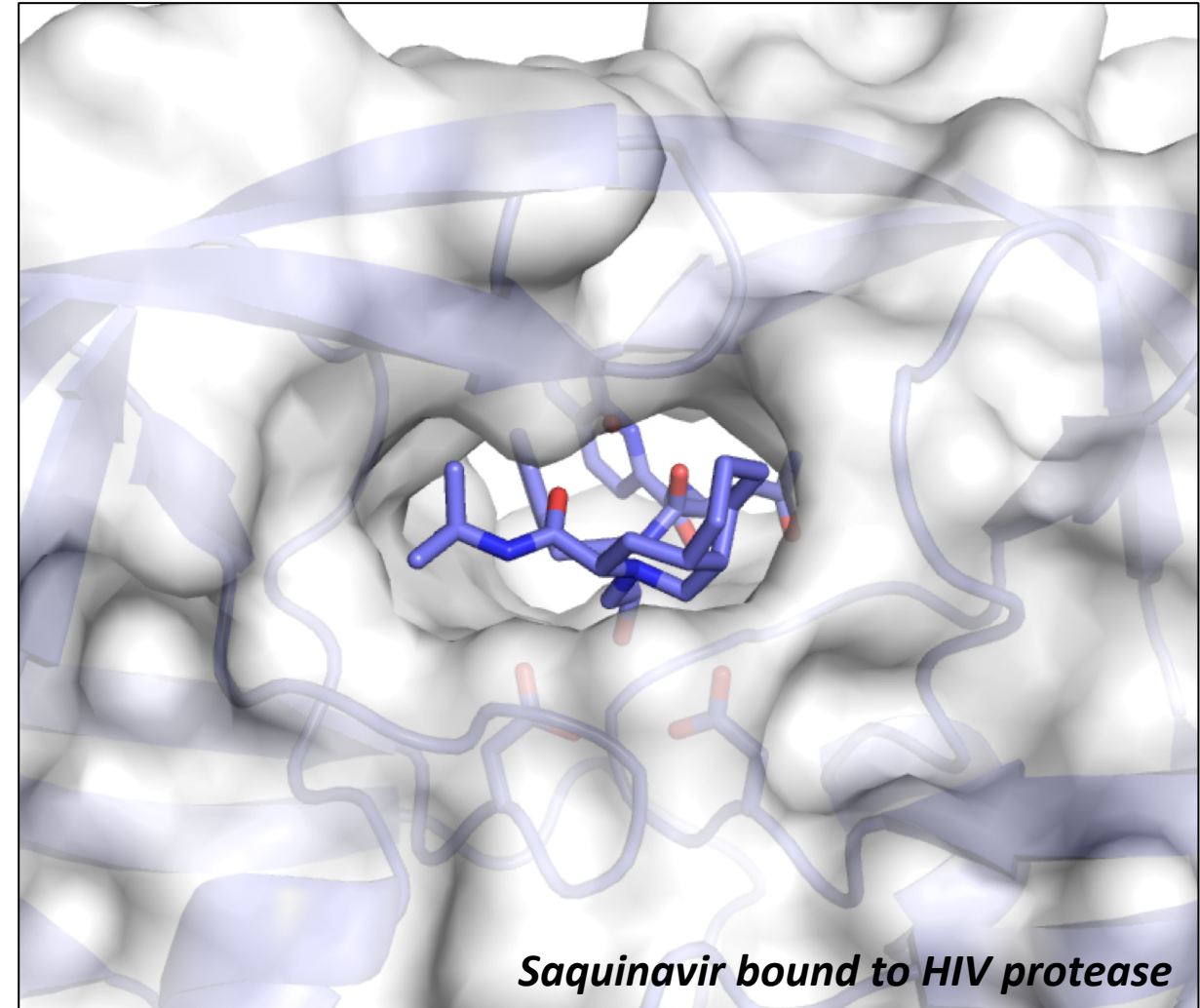
# History of structural biology & biophysics and ties to medicine





# What is structural biology and why do we care?

- A branch of biology concerned with the **molecular** structure of biological molecules.
- Structures **reveal** features of molecules and allow new hypotheses/concepts
- This discipline is responsible for major **conceptual advances** in biology:
  - Enzyme mechanisms
  - Receptor-ligand interactions
  - DNA replication
  - Drug action and design





# Nobel prizes in structural biology

1915	Physics	Bragg/Bragg	Analysis of structure with X-rays
1946	Chemistry	Sumner/Northrop/Stanley	Enzyme crystallization
1954	Chemistry	Pauling	Chemical bond/protein structure
1962	Chemistry	Perutz/Kendrew	Structure of globular proteins
1962	Medicine	Watson/Crick/Wilkins	Structure of nucleic acids
1964	Chemistry	Hodgkin	Structure of biochemical substances
1972	Medicine	Edelman/Porter	Structure of antibodies
1982	Chemistry	Klug	Electron microscopy of DNA:protein
1985	Chemistry	Hauptman/Karle	Direct X-ray phasing methods
1988	Chemistry	Deisenhofer/Michel/Huber	Photosynthetic reaction centre
1991	Chemistry	Ernst	NMR methods
1997	Chemistry	Walker/Boyer/Skou	ATP synthase
2002	Chemistry	Wüthrich/Fenn/Tanaka	Biological NMR and mass spectrometry
2003	Chemistry	Agre/MacKinnon	Water and ion channels
2006	Chemistry	Kornberg	Transcription machinery
2009	Chemistry	Ramakrishnan/Steitz/Yonath	Ribosome and transfer RNA
2012	Chemistry	Lefkowitz/Kobilka	G-protein coupled receptor (GPCR)
2017	Chemistry	Dubochet/Frank/Henderson	Cryo-electron microscopy

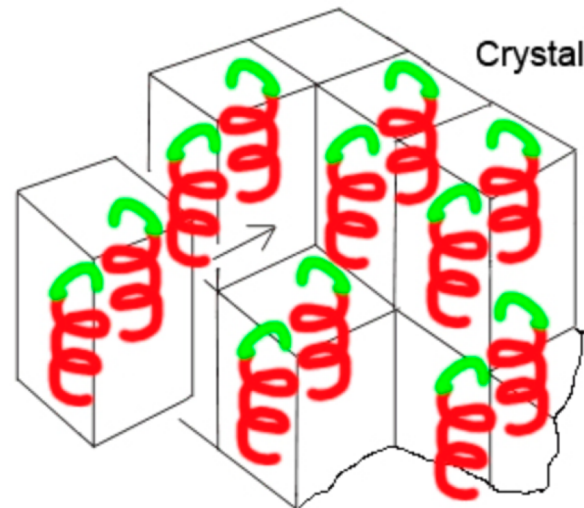
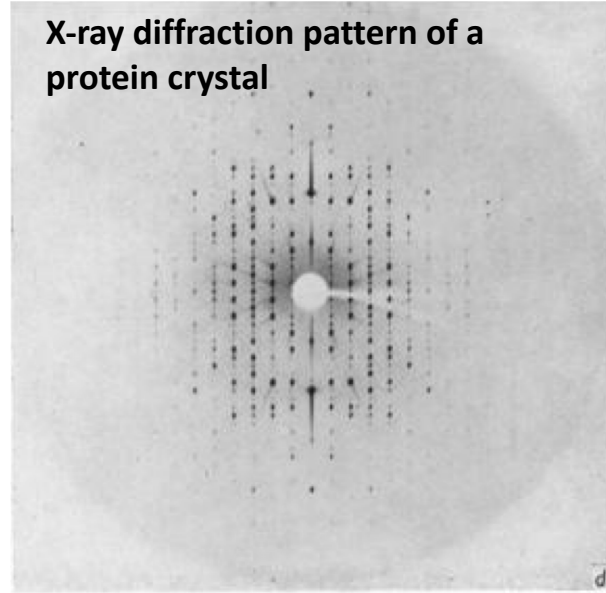


# How did it start? In the 1920-30s...

Dorothy Crowfoot Hodgkin  
Nobel Prize, Chemistry 1964



X-ray diffraction pattern of a  
protein crystal

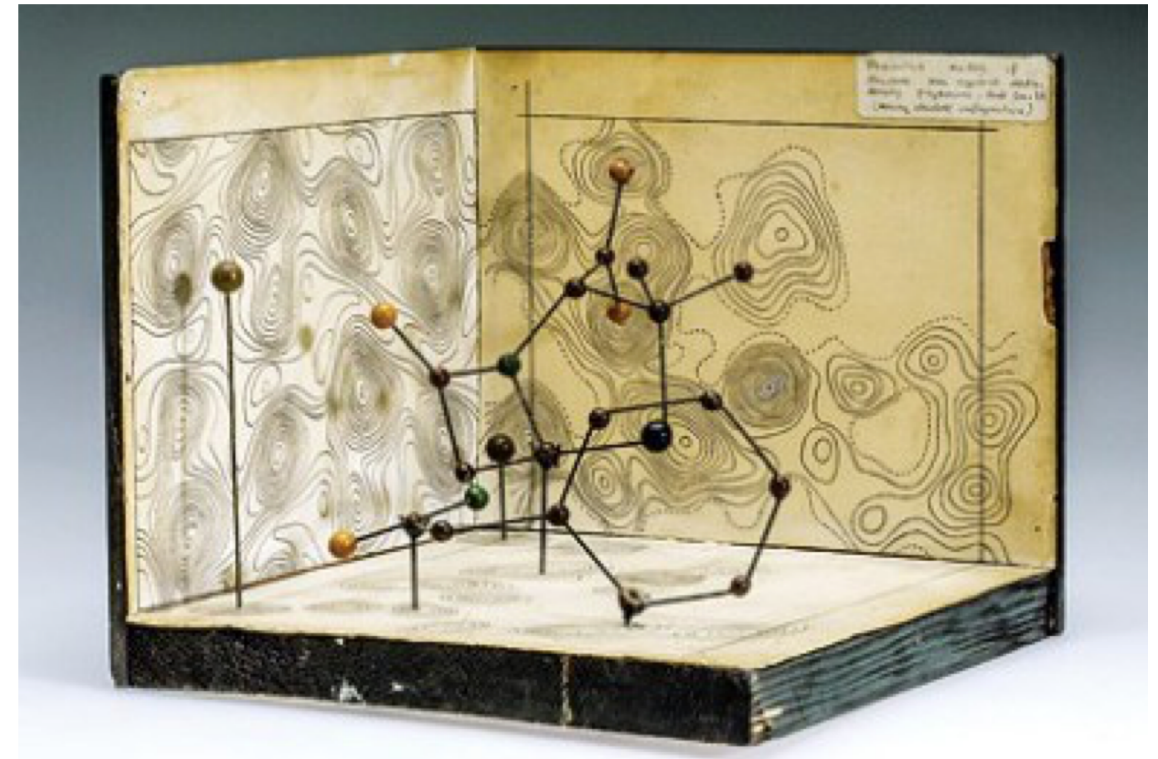
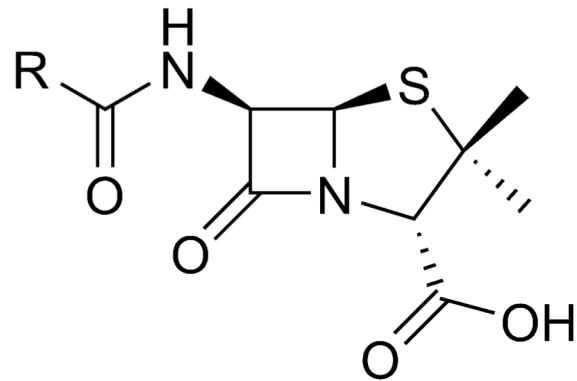


High-resolution crystal structure of pepsin bound to inhibitor  
(1995, PDB 1PSO)





# Penicillin, the first biological X-ray structure (1945)



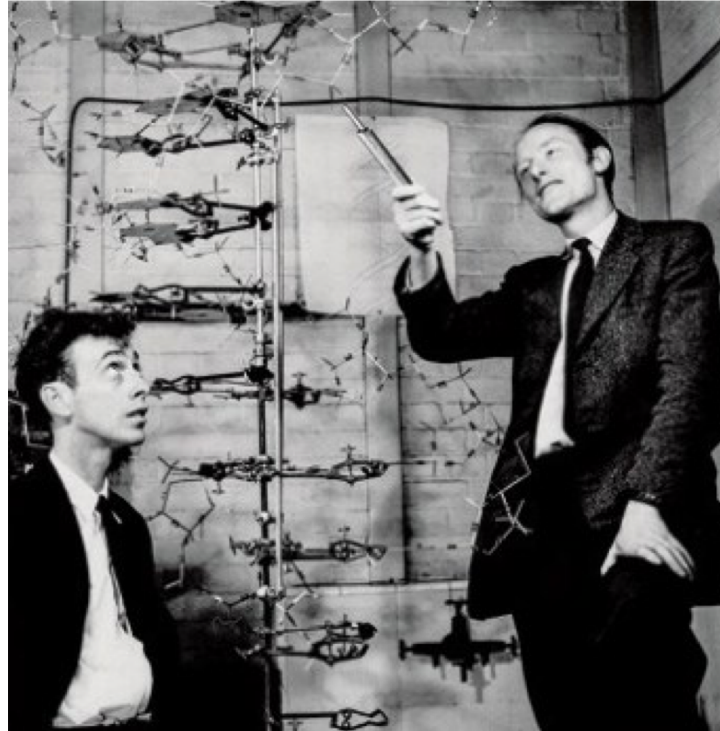
London Science Museum



# Structure of the DNA double-helix (1953)



Rosalind Franklin &  
Maurice Wilkins

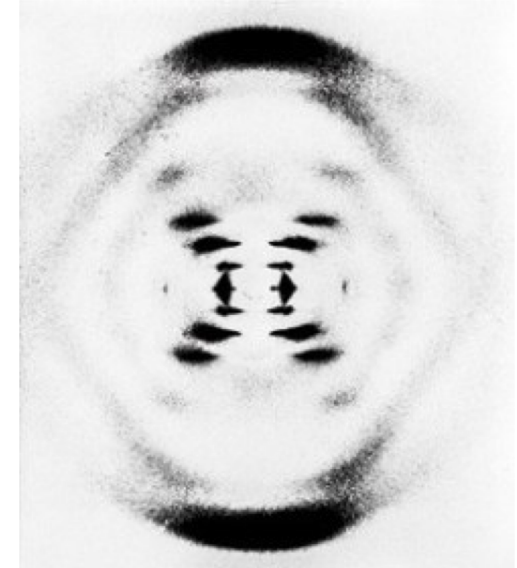


James Watson & Francis Crick



This figure is purely diagrammatic. The two ribbons symbolize the two phosphate—sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

Watson & Crick  
(1953) *Nature*, **171**,  
737-738



B-DNA fiber X-ray diffraction



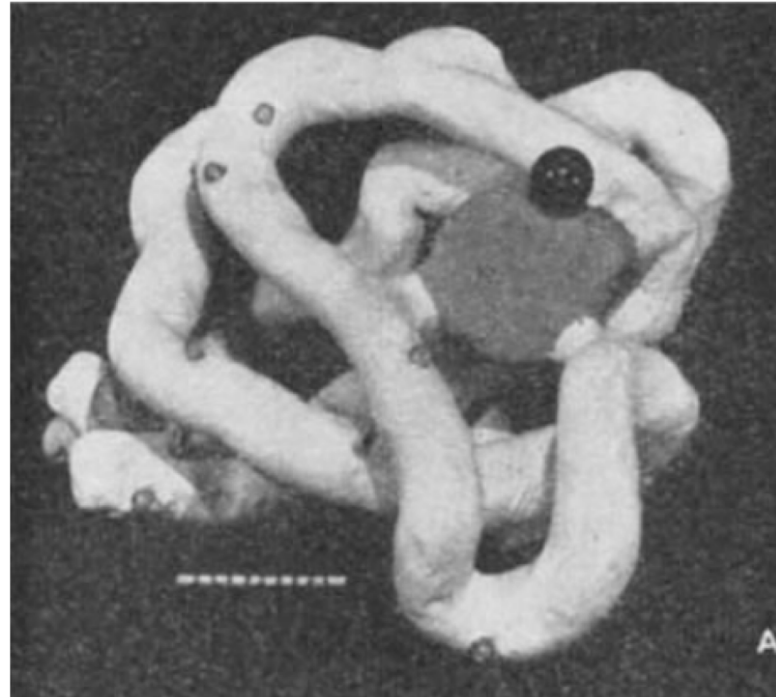


# Myoglobin, the first protein structure (1958)

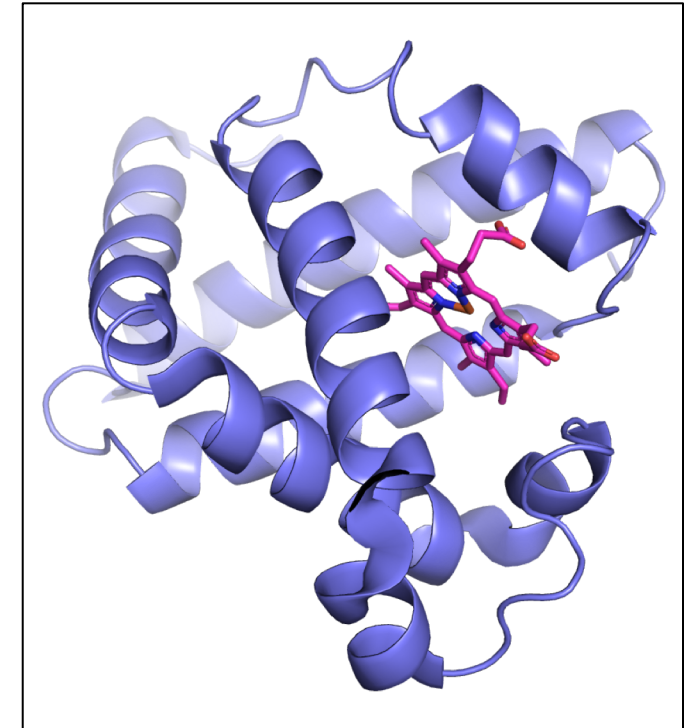


Figure 1 | **Max Perutz (1914–2002) and John Kendrew (1917–1999)**. Photograph taken in 1962 of Max Perutz with his balsa-wood model

Kendrew J et al . (1958) *Nature*, 181, 662-666



High-resolution structure of myoglobin (1982)







# Modern structural biology

- Recombinant DNA technology – Protein production
- X-ray crystallography – synchrotron
- High-field NMR
- Cryo-electron microscopy
- Super-resolution microscopy
- **In other words: we can now do more, with less**
- 165,117 structures @ [www.rcsb.org](http://www.rcsb.org)

Canadian Light Source (synchrotron, X-rays)



Electron microscope for cryo-EM

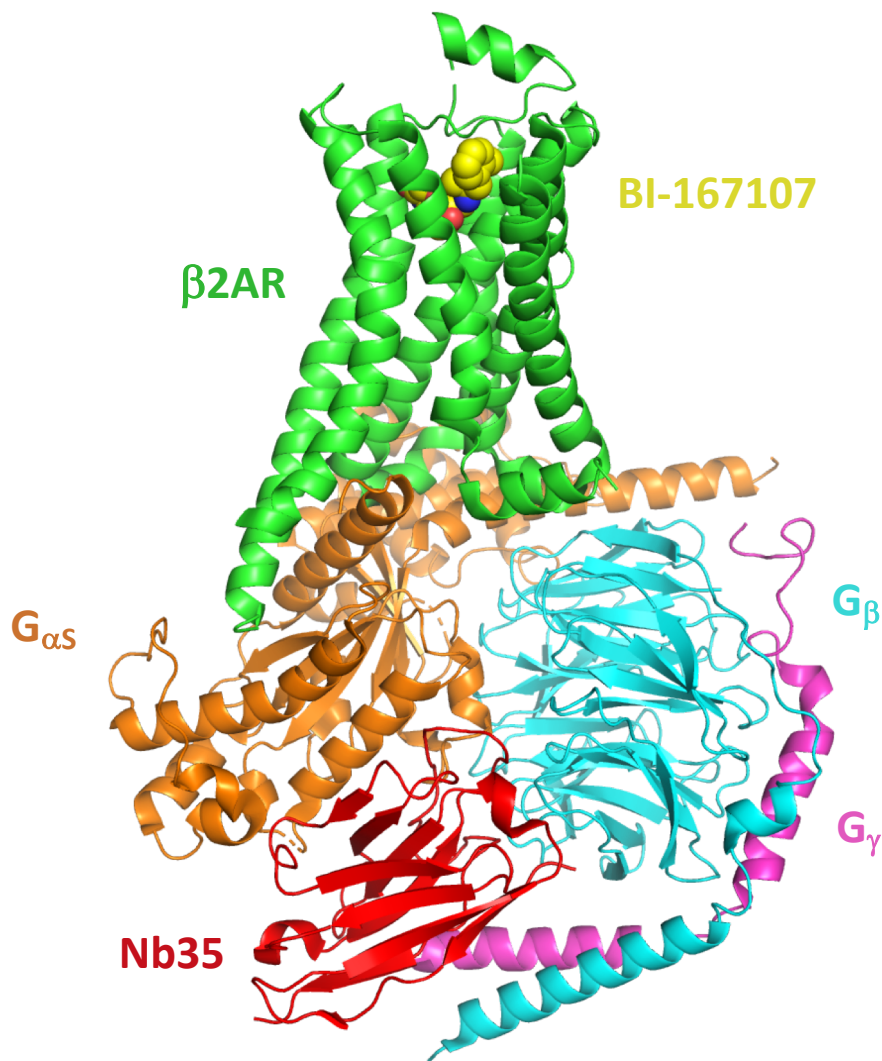


800 MHz NMR  
with cryoprobe



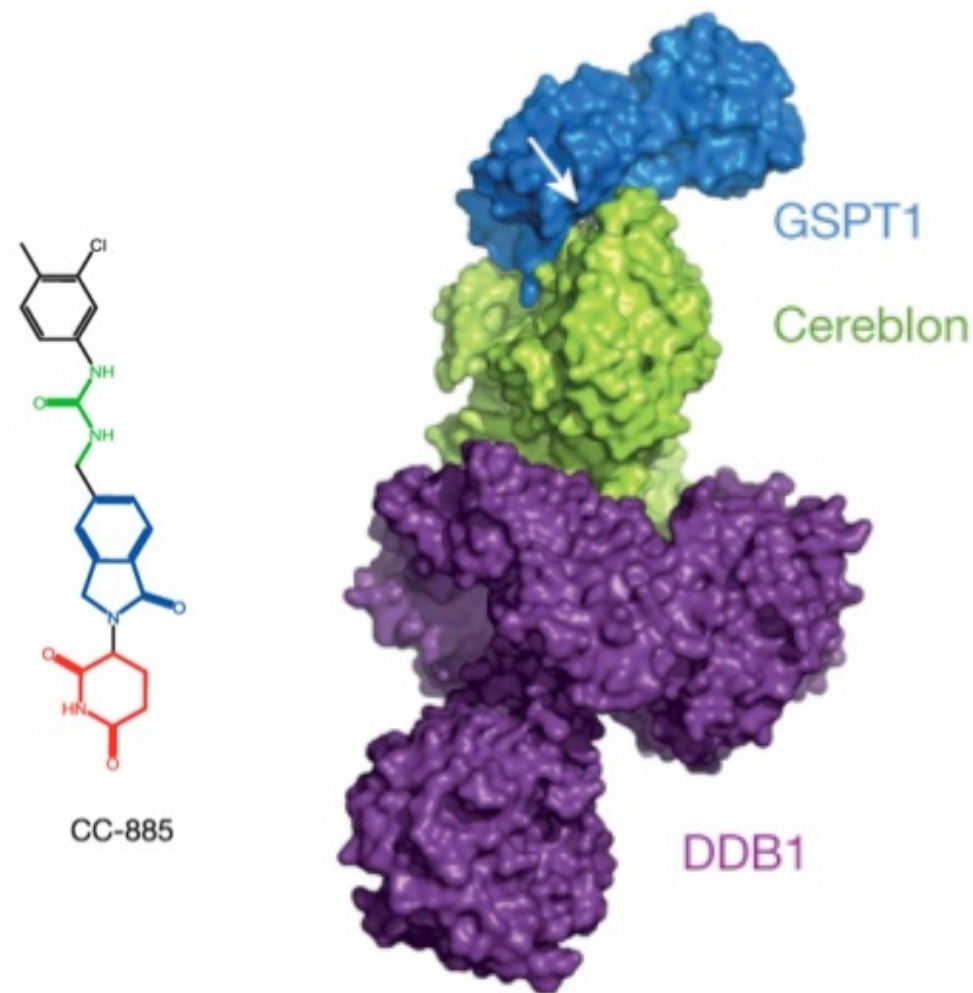
# Ties to medicine: examples

GPCR structures and drug design



Rasmussen et al. (2011) Nature 477:549

Mechanism of action of thalidomide and design of novel immunomodulatory drugs



Matyskiela et al. Nature 535, 252-7 (2016)



# History of structural biology @ McGill



McGill

- **Mirek Cygler** @ BRI (now at U Saskatchewan)
  - Montreal Structural Biology Meetings (2006-2008)
- **Kalle Gehring** @ Biochemistry
  - FRQ-S *Groupe de Recherche Axé sur la Structure des Protéines* (GRASP) 2008-2018
  - Québec/Eastern Canada High Field NMR Facility (QANUC)
- **Other early pioneers:**
  - **James Coulton** @ MIMM
  - **Masad Dahma** @ Chemistry
  - **Albert Berghuis** @ Biochemistry
- **Joaquin Ortega** @ Anatomy & Cell Biology
  - Facility for Electron microscopy research (FEMR)
- **Martin Schmeing & Alba Guarné**
  - FRQ-S *Centre de Recherche en Biologie Structurale* (CRBS) since 2019





# CRBS: the premier structural biology center in Quebec

- *Director: Martin Schmeing                      Assoc. director: Alba Guarné*
- *38 McGill researchers using structural biology and biophysical techniques to address important biological questions*
- *State-of-the-art facilities for structural biology and biophysics, including the largest electron microscopy platform in Canada*
- *Promote scientific excellence, interdisciplinary research, and collaborative training*
- *~350 graduate students in 14 departments* {

*Research-intensive graduate programs*  
*Access at MSc and PhD levels*  
*Focused on student success*

# What do we do?

*Cellular and  
protein networks*

*Protein processing,  
transport and folding*

*Protein synthesis  
and disease*

Kalle Gehring  
Susanne Bechstedt  
Gary Brouhard  
Khanh Huy Bui  
Allen Ehrlicher  
Adam Hendricks  
Gergely Lukacs  
Gerhard Multhaup  
Bhushan Nagar  
Joaquin Ortega  
Jerry Pelletier  
Alvin Shrier  
Nahum Sonenberg  
David Thomas  
Jean-François Trempe  
Youla Tsantrizos  
Javier Vargas  
Jason Young

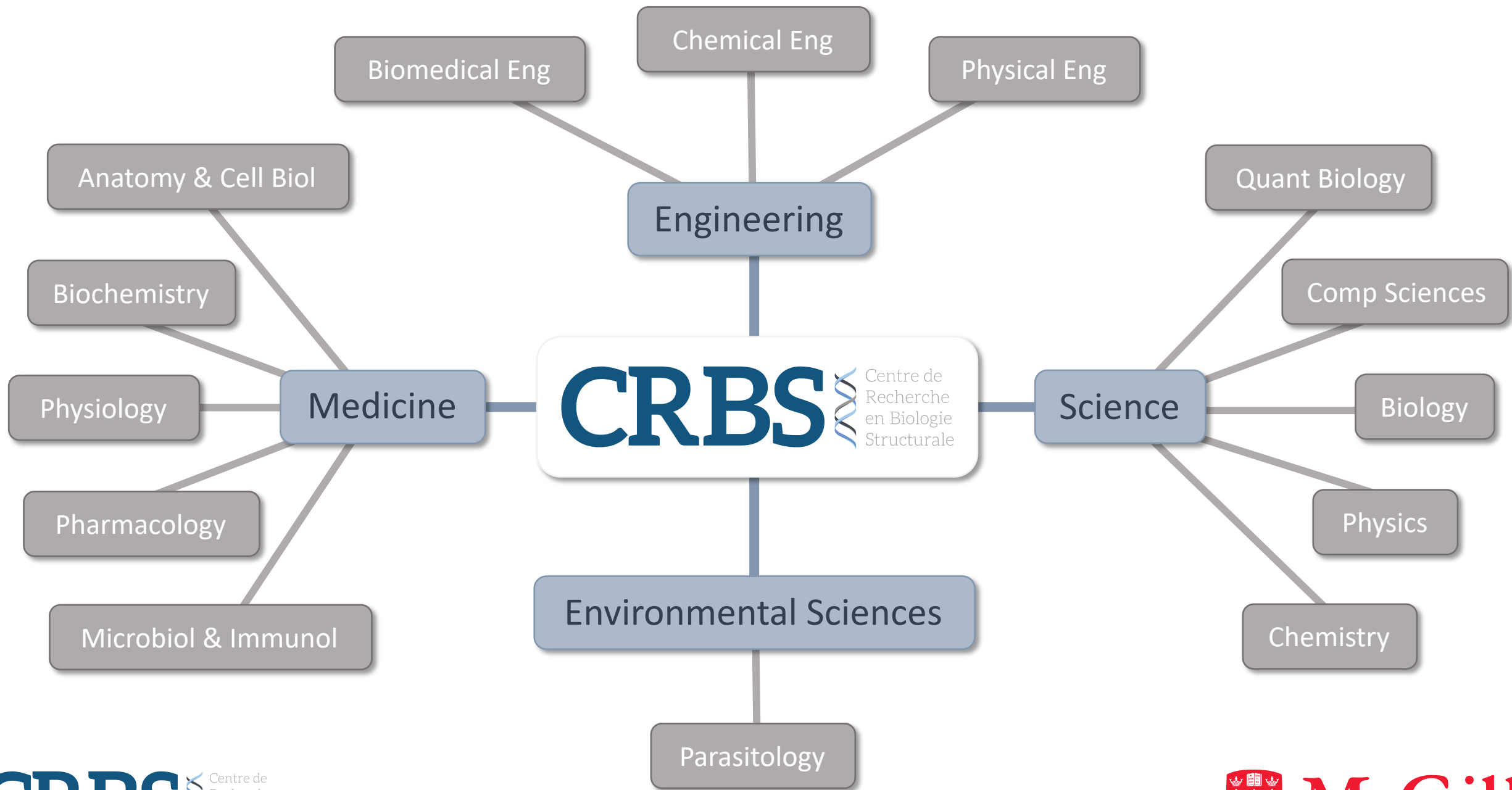
Masad Damha  
Karine Auclair  
Albert Berghuis  
Gonzalo Cosa  
Alba Guarné  
Armando Jardim  
Sabrina Leslie  
Nathan Luedtke  
Maureen McKeague  
Tony Mittermaier  
Rodrigo Reyes-Lamothe  
Reza Salavati  
Martin Schmeing  
Hanadi Sleiman  
Michael Strauss  
Christopher Thibodeaux  
Paul Wiseman  
Brandon Xia  
Natalie Zeytuni

*Synthetic biology and  
bacterial infection*

*Parasite and  
viral infections*

*DNA repair, replication  
and DNA biomaterials*

- *Molecular basis of disease and treatments*
- *Biophysical, chemical and synthetic biology*

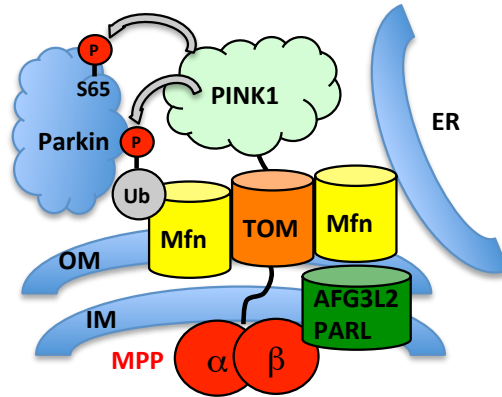




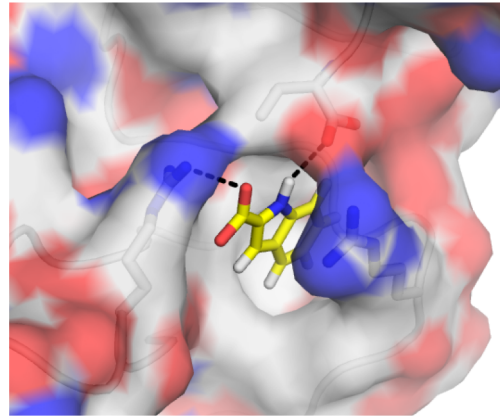
# Trempe lab: mitochondrial QC and neurodegeneration



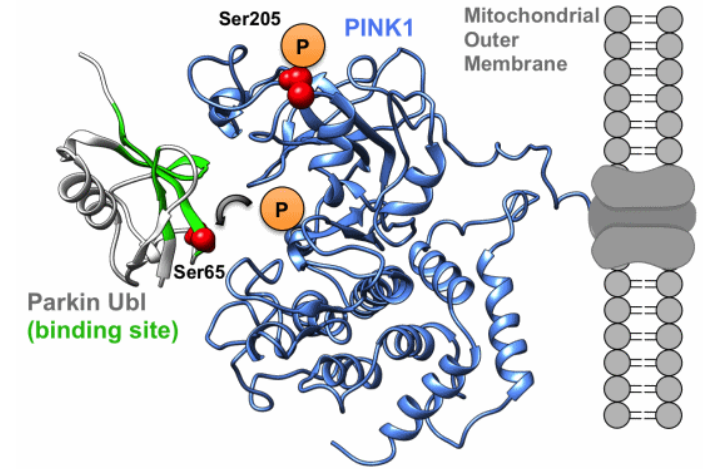
[www.trempelab.org](http://www.trempelab.org)



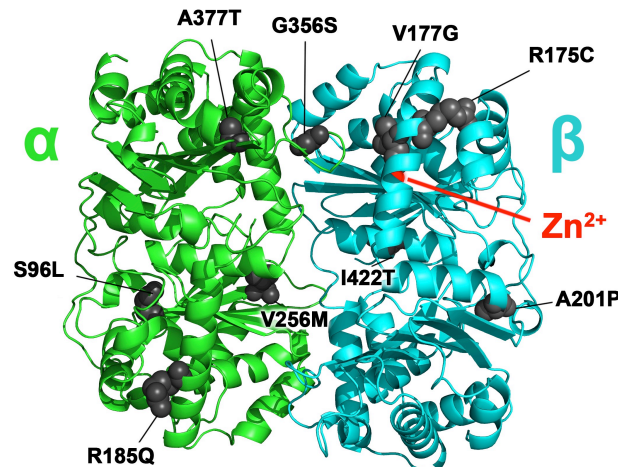
Mechanism of substrate selectivity by Parkin (Lu, Vranas, Levi)



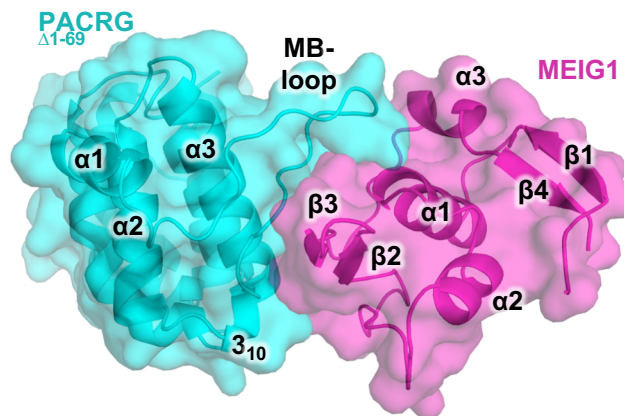
Small-molecule activators and activating mutations of Parkin (Veyron, Croteau, Yi, Eldeeb, Gehring, Sauv , Sung)



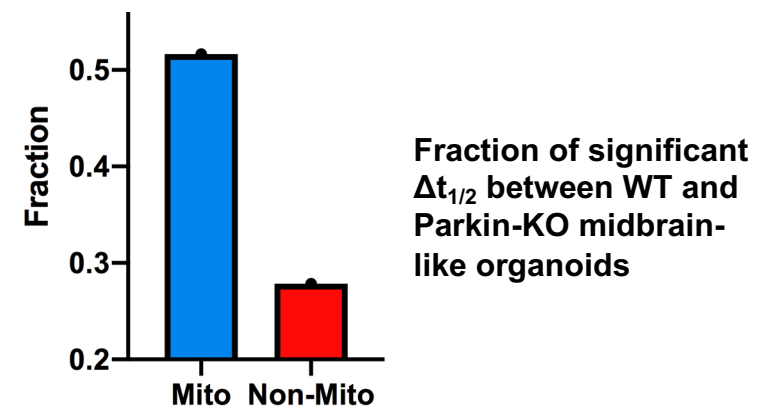
Structure of PINK1 and mechanism of activation (Rasool, Truong, Shomali)



Structure and function of MPP in neurodegeneration (Bayne, Dong)



Structure of human PACRG:MEIG1 (Khan, Pelletier, Croteau, Veyron, Bui, Black, Bechstedt, McAlear)



Measuring mitochondrial turnover in organoids and mice (Duchesne, Vi-Nguyen, Pellitero, Taylor)



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# Discussion

To facilitate discussion, we will randomly split participants in breakout rooms:

- Introduce yourselves
- Nominate spokesperson
- Brainstorm ideas for 10 min
- Each spokesperson summarizes highlights in less than 2 min



# Discussion 1:

## Bridging the gap between clinicians and basic scientists

- Funding opportunities? joint studentship between CRBS and MI4/GCRC
- Networks and training programs? MI4, QLS, FEMR, Regenerative medicine, IPN
- At what stage should initiate a collaboration?
- How long do structural biology projects take?
- Role of basic research on proteins not linked to specific diseases?
- Contacting structural biologists: <http://csbmcmcgill.ca>



# Discussion 2:

## Ideas for future bench-to-bedside seminars

- **Medical genetics:** the relationship between pathogenic mutations and structure
- **Drug design:** how structure can help design better small molecule drugs
- **Biologics:** the role of macromolecular structure in optimization of therapeutic antibodies.
- **Computational approaches:** In silico modeling of proteins and interactions
- **Structural studies of membrane proteins**
- **Hydrogen-deuterium exchange mass spectrometry**
- **Quantitative analysis of biological processes**
- **Structural basis of Proteolysis targeting chimeras (PROTACs)**
- **By specific disease area:** kinases implicated in cancer, Parkinson's, cardiomyopathies, etc.



# Upcoming CRBS events : CRBS bootcamps

## **Exploring Protein Structures and Interactions using PyMol**

Instructors: Jean-Francois Trempe and Martin Scheming

Date: Tuesday, June 30, 2020

Time: 1 – 4 PM

## **Probing Protein Dynamic Structure with Hydrogen-Deuterium Exchange Mass Spectrometry**

Instructor: Christopher Thibodeaux

Date: Tuesday, July 21, 2020

Time: 1 – 4PM

## **Learning to do Map Segmentations and Make Movies in Chimera and Chimera X**

Instructor: Joaquin Ortega

Date: Tuesday, August 11, 2020

Time: 1 – 4 PM

<https://forms.gle/LXenrnKbpcjyRfbM7>



# Upcoming CRBS events : seminar

## **SPECIAL ONLINE SEMINAR ANNOUNCEMENT**

**Natalie Zeytuni, PhD**

**Assistant Professor  
Department of Anatomy and Cell  
Biology, McGill University**



***Title: Unravelling the Molecular Secrets of Bacterial  
Secretions Systems by Hybrid Approaches***

Join Zoom Meeting

<https://mcgill.zoom.us/j/93945238785>

Meeting ID: 939 4523 8785