McGill | Faculty of Medicine

Annual Report for Faculty of Medicine Funded Centres, Core Facilities and Networks

The Annual Report should be set in the context of the Centre's, Core facility's and Network's overall goals and objectives, programs and research priorities, performance indicators outlined in the application (or subsequently developed), activities and strategies.

Please provide the following:

1. Name of Centre, Unit or Institute: Groupe de Recherche Axé sur la Structure des Protéines (GRASP)

2. Name and contact information of the Director and/or Administrative Assistant:

   Director: Prof. Kalle Gehring
   kalle.gehring@mcgill.ca
   phone: 514-398-7287

   Coordinator: Dr. Annick Guyot
   grasp.med@mcgill.ca
   phone: 514-398-2293

3. Is the centre recognized as an official Senate approved McGill Research Centre?

   Yes No X

   We are preparing a dossier for official Senate recognition in the next academic year.

4. The date the centre received Senate approval as an official McGill Research Centre N/A

5. A summary of the overall goals and objectives, programs and research priorities and any changes to these that may have occurred during the past year. Please indicate the extent to which the objectives have been met. (**limit 200 words**)

   The last year has seen outstanding progress in our goals of improving the infrastructure, faculty and funding for research on conformational diseases. Despite an extremely difficult funding environment, GRASP's FRSQ *Groupe de recherche* funding ***was renewed for 4 years with a 35% increase in funding and a global score of 4.6/ (see appendices)***.

   Renovations for the Cystic Fibrosis Translational Research Centre on the 10th floor of the McIntyre Building have been completed. The new CFTR Centre, lead by GRASP associate member, John Hanrahan, was inaugurated in October 2011. GRASP supported the hiring of Justin Kollman, a

talented structural biologist from the University of California at San Francisco. Dr. Kollman started in the Dept of Anatomy and Cell Biology in March 2012. In support of our junior faculty members, GRASP has led a joint McGill-UdM CFI round 7 application for $12 M in new X-ray, NMR and imaging infrastructure.

Despite the increase in funding from the FRQS, our global funding level has gotten worse as our NSERC Major Resources Support grant for Quebec/Eastern Canada High Field NMR Facility was not renewed. ***NSERC canceled the entire program.*** The continued and vigorous support of the Faculty of Medicine is therefore essential.

6. Please document **the major achievements** resulting from the use of the Funds from the Faculty, including any advances in knowledge, relevant publications, or international collaboration. You may select from the menu of reporting items/performance indicators in appendix 1 that may be relevant, noting that the menu list is not exhaustive. (Please limit your response to a maximum of **1 page**)

New member recruitment:
-Justin Kollman at McGill
-Gerhard Multhaup at McGill
-Nicolas Doucet at INRS Armand Frappier
-Rafael Najmanovich at Université de Sherbrooke
-Pascale Legault at Université de Montréal
-James Omichinski at Université de Montréal

Graduate and post-graduate student funding:

$43,000 in GRASP Recruitment Awards:
1 M.Sc. Student
2 Ph.D. Students
1 Post-Doc Fellow

$19,500 in GRASP Travel Awards:
12 Graduate Students
1 Post-Doc Fellows

Workshops, conferences or seminars:

4th Annual GRASP Symposium (McGill New Residence Hall, November 21, 2011)
5 invited speakers, ~ 200 attendees.

Close to one hundred visits by members to National or International destinations, events, and short and long term visits by visiting scientists to McGill

Over 100 publications with high impact such as:

Rabeh WM, Bossard F, Xu H, Okiyoneda T, Bagdany M, Mulvihill CM, Du K, di Bernardo S, Liu Y, Konermann L, Roldan A, **Lukacs GL**. Correction of both NBD1 energetics and domain interface is required to restore ΔF508 CFTR folding and function. ***Cell***. 2012 Jan 20;148(1-2):150-63.

-Girard M, Larivière R, Parfitt DA, Deane EC, Gaudet R, Nossova N, Blondeau F, Prenosil G, Vermeulen EG, Duchen MR, Richter A, Shoubridge EA, **Gehring K**, McKinney RA, Brais B, Chapple

JP, McPherson PS. Mitochondrial dysfunction and Purkinje cell loss in autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS). ***Proc Natl Acad Sci USA***. 2012 Jan 31;109(5):1661-6.

-Lin YS, Park J, De Schutter JW, Huang XF, Berghuis AM, Sebag M, Tsantrizos YS. Design and synthesis of active site inhibitors of the human farnesyl pyrophosphate synthase: apoptosis and inhibition of ERK phosphorylation in multiple myeloma cells. ***J Med Chem***. 2012 Apr 12;55(7):3201-15.

-Fabian MR, Cieplak MK, Frank F, Morita M, Green J, Srikumar T, **Nagar B**, Yamamoto T, Raught B, Duchaine TF, Sonenberg N. miRNA-mediated deadenylation is orchestrated by GW182 through two conserved motifs that interact with CCR4-NOT. ***Nat Struct Mol Biol***. 2011 Oct 7;18(11):1211-7.

-Hambleton, S., Salem, S., Bustamante, J., Bigley, V., Boisson-Dupuis, S., Azevedo, J., Fortin, A., Haniffa, M., Ceron-Gutierrez, L., Bacon, C.M., Menon, G., Trouillet, C., McDonald, D., Carey, P., Ginhoux, F., Alsina, L., Zumwalt, T.J., Kong, X.F., Kumararatne, D., Butler, K., Hubeau, M., Feinberg, J., Al-Muhsen, S., Cant, A., Abel, L., Chaussabel, D., Doffinger, R., Talesnik, E., Grumach, A., Duarte, A., Abarca, K., Moraes-Vasconcelos, D., Burk, D., **Berghuis, A.**, Geissmann, F., Collin, M., Casanova, J.L., Gros, P. (2011) IRF8 Mutations and Human Dendritic-Cell Immunodeficiency. ***New Eng. J. Med.*** 365, 127-138.

-Freiburger, L.A., Baettig, O.M., Sprules, T., **Berghuis, A.M.**, Auclair, K. & **Mittermaier, A.** (2011) Competing allosteric mechanisms modulate substrate binding in a dimeric enzyme. ***Nat. Struct. & Mol. Biol***. 18, 288-294.

-Quan, S., Koldewey, P., Tapley, T., Kirsch, N., Ruane, K., Pfizenmaier, J., Shi, R., Hofmann, S., Foit, L., Jakob, U., Xu, Z., **Cygler, M.** and Bardwell, J.C.A. (2011). Genetic selection designed to stabilize proteins uncovers a chaperone called Spy. ***Nat. Struct. Mol. Biol.*** 18 (3), 262-9.

- Yang, R., Gaidamakov, S.A., Xie, J., Lee, J., Martino, L., Kozlov, G., Crawford, A.K., Russo, A.N., Conte, M.R., **Gehring, K**. & Maraia, R.J. (2011) "La-related protein 4 binds poly(A), interacts with the poly(A)-binding protein MLLE domain via a variant PAM2w motif, and can promote mRNA stability", ***Mol. Cell. Biol.*** **31**(3):542-56.

-Guillet V, Knibiehler M, Gregory-Pauron L, Remy M-H, Cemin C, Raynaud-Messina B, Bon C, **Kollman JM**, Agard DA, Mourey L, Merdes A (2011) Insight into γ-tubulin complex assembly from the crystal structure of GCP4. ***Nat. Struct. Mol. Biol***. 18, 915-919

1 patent:

-**Youla S. Tsantrizos**, Joris W. De Schutter anf Yih-Shyan Lin. Heterocyclyl-pyridinyl-based bisphosphonic acid, pharmaceutically acceptable salt thereof, composition thereof and method of use thereof. US Provisional Application filed on May 28, 2010; Serial No: 61/349,442. US Patent Application No 61/487,323; filed May 18, 2011 and PCT/CA2011/050322; filed on May 27, 2011.

7. Please provide a **List of Members** (Full, Associate, Trainee noting whether graduate student or post-doctoral fellow) **if not already on your website** and all institutional affiliations current up to the date of the Annual Report. Add rows as necessary.

See website and appendices

8. Please describe how your activities align with the Academic or Research mission of the Faculty of Medicine and/or other Faculties at McGill focusing on the activities for the current year and strategic plans for the subsequent year (**limit 200 words**)

GRASP supports numerous research activities that are central to the Faculty's mission of health science research. Established in April 2008, GRASP's mission is to promote excellence in research in conformational diseases and structural biology. The support from McGill VPRIR and Faculty of Medicine allowed us to leverage $260 K per year from FRSQ for the first 4 years. GRASP has been renewed in April 2012 with a global score of 4.6/5 and a 35% increase in the funding with $350K per year from the FRSQ to support research in cystic fibrosis, structural biology, and infectious diseases.

GRASP held its annual high-profile symposium in the McGill New Residence Hall on Parc Avenue on Nov. 21, 2011 with ~200 attendees and 6 internationally renown speakers.

GRASP has two student stipend programs – recruitment awards and travel awards – that support the recruitment and retention of high quality students to McGill. GRASP also manages four equipment platforms in Bellini and across campus for QANUC, X-ray analysis, protein-protein interactions, protein crystallization. In addition, we provide $20K to the McGill Facility for Electron Microscopy Research to support the salary of a cryoelectron microscopy manager, Mihnea Bostina. These platforms have contributed to the success of faculty members and the large number of high impact publications from GRASP.

9. Please provide the ***URL* of the Research Centre's, Core Facility's or Network's web site**.

Note: The Research Centre's, Core Facility's or Network's *website should contain the following information:*

- all sources of funding support,
- the List of Members and their institutional affiliation,
- the activities supported by the Research Centre, Core Facility of Network, and
- the Annual Report.

URL: http://grasp.mcgill.ca

10. Other information:

Please indicate how the Research Centre, Core Facility or Network has:

- Tackled or plans to tackle issues in a manner that may not otherwise have been achievable without the financial support of the Faculty of Medicine
- Increased or is planning to increase the scale and focus of research activities
- Facilitated multidisciplinary, multi-institutional or international collaborations

(Please limit response to **200 words**)

The successes of the past year would not have been possible without the support from the Faculty of Medicine. First and foremost, the financial support from the faculty has allowed us to leverage 350K from the FRSQ and lead to the renewal of the FRSQ *Groupe de recherche,* GRASP, at McGill University. This increased visibility and funding allowed us to recruit talented young faculty members such as Drs. Schmeing and Kollman and to retain others such as Dr. Bhushan Nagar. Training and travel awards to GRASP students and trainees has promoted international exposure and contributed to the Faculty of Medicine's training mission for the next generation of health researchers. McGill University signed a memorandum for putting into place an international student exchange agreement with the University of Strasbourg.

Support from the Faculty of Medicine has contributed to all these aspects of GRASP's mission and is essential for our future success.

The Year End Financial Report reports on:

- Expenditure of funding provided by the Faculty of Medicine and other sources, towards meeting the objectives of the Research Centre, Core Facility or Network; and
- Details of any in-kind contributions provided to the Centre, Core Facility or Network.
- See **Appendix 2** for the "Year End Financial Report" form to complete

A.4.2 – TABLEAU RÉSUMÉ DES EFFECTIFS					
	2008-2009	2009-2010	2010-2011	2011-2012	**MOYENNE**
Chercheurs					
Nombre de chercheurs réguliers	26	29	29	31	**28.75**
Nombre de chercheurs-boursiers	15	17	16	17	**16.25**
Nombre de EPT	23	25.5	25.5	27	**25.25**
Nombre de chercheurs associés	13	14	14	16	**14.25**
Étudiants et stagiaires					
Nombre en maîtrise et au doctorat	171	206	224	219	**205**
Nombre au postdoctorat	73	75	66	67	**70.25**
TOTAL	**244**	**281**	**290**	**286**	**275.25**
Nombre d'étudiants boursiers	78	93	96	96	**90.75**

A.4.3 – TABLEAU DES OCTROIS					
	2008-2009	2009-2010	2010-2011	2011-2012	**MOYENNE**
Du groupe*					
Subventions ($)	330,000	319,000	318,000	320,000	**321,750**
Bourses ($)	0	0	0	0	**0**
TOTAL	330,000	319,000	318,000	320,000	**321,750**
Des membres réguliers**					
Subventions ($)	12,238,706	15,969,705	6,645,849	6,264,829	**10,279,772**
Bourses ($)	1,153,319	1,313,250	1,387,556	1,595,833	**1,362,490**
TOTAL	13,392,026	17,282,955	8,033,405	7,860,662	**11,642,262**

** Octrois d'organismes subventionnaires reconnus émanant directement des activités du groupe*

***Octrois d'organismes subventionnaires reconnus attribués aux membres réguliers du groupe et ne découlant pas directement des activités du groupe. Calculés au prorata selon le nombre d'EPT déclaré.*

A.4.4. Tableau des publications, mémoires, rapports et brevets					
	2008	2009	2010	2011	**MOYENNE**
Avec comité de lecture	65	92	106	106	92.25
Sans comité de lecture	0	0	0	0	0
Chapitre ou volume parus	7	4	4	16	7.75
Rapports et mémoires	1	0	0	1	0.5
TOTAL	**73**	**96**	**109**	**123**	**100.25**
TOTAL des copublications*	**1**	**8**	**12**	**7**	**7**
Brevets	2	5	1	1	2.25

Nombre de publications émanent directement des activités du groupe par ses membres réguliers
** On entend par « copublication » une publication où au moins deux membres réguliers du groupe sont co-auteurs.*

A.4.5. Tableau des conférenciers invités*				
	2008	2009	2010	2011
Nombres d'invités provenant du Québec	1	2	3	1
Nombre d'invités provenant du reste du Canada et des États-Unis	6	4	4	7
Nombres d'invités internationaux	1	2		
TOTAL	**8**	**8**	**7**	**8**

** conférenciers ayant présenté à votre groupe*

A.4.6. Tableau des conférences ou congrès internationaux organisés par le groupe			
Titre	Année	Nombre d'invités	Nombre de participants*
1er Symposium Annuel du GRASP	2008	7	175
2ème Colloque Annuel du GRASP/MSBM	2009	8	225
3ème Colloque Annuel du GRASP/MSBM	2010	7	200
4ème Colloque Annuel du GRASP	2011	6	200

***** *approximatif*

SECTION A.5 – ACTIVITÉS DU GROUPE DE RECHERCHE

AVIS IMPORTANT

Cette section doit être **soumise sur clé USB dans son entier SAUF la section A.5.1** ci-dessous.
Voir le guide à la page 2 du guide pour la liste complète des documents à fournir électroniquement.

A.5.1. Liste des membres en 2011-2012

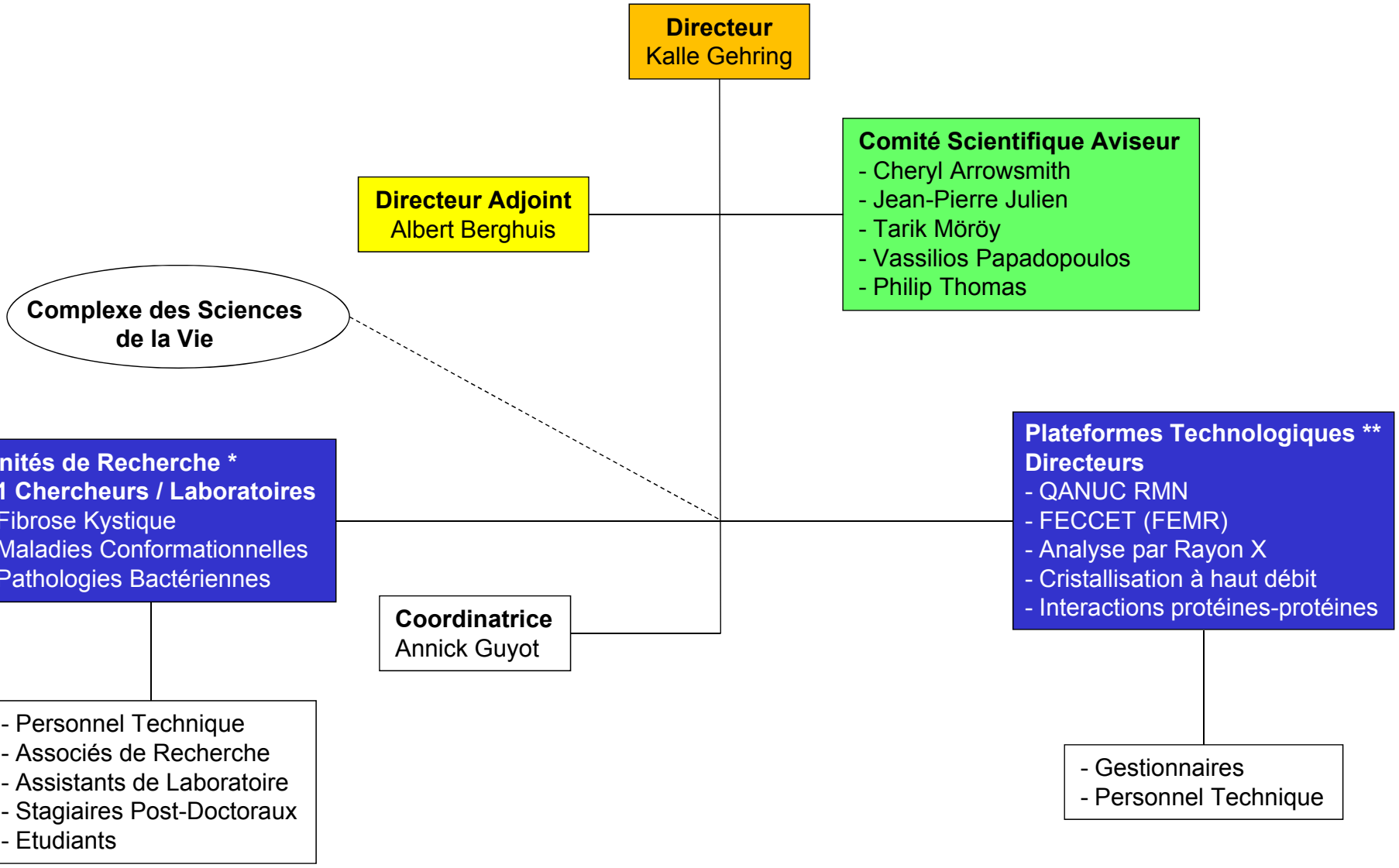
Vous référez à la page 8 du guide pour compléter ce tableau.

% de temps en recherche	NIP	Nom du chercheur	Source salariale	Nombre d'années d'expérience	Date d'arrivée	% activités de recherche avec le groupe	ETP
>75% *entre 0.5 et 1 ETP*	BERAL0102	Albert Berghuis	CRC Tier I/McGill	16	01-Jan-08	100	1
	BORKA0502	Katherine Borden	CRC Tier I/UdM	15	01-Jan-08	50	0.5
	CYGMI0001	Mirek Cygler	CRNC-IRB	27	01-Jan-08	100	1
	DOUNI9901	Nicolas Doucet	Institut Armand-Frappier	1	26-Oct-11	100	1
	ENGAN9801	Ann English	Concordia Res. Chair	26	17-Dec-09	100	1
	GEHKA9801	Kalle Gehring	Université McGill	17	01-Jan-08	100	1
	HALMI0003	Michael Hallett	Université McGill	11	01-Jan-08	50	0.5
	JENSA0701	Sarah Jenna	UQAM	5	14-Jan-09	100	1
	LAVPI8901	Pierre Lavigne	Sherbrooke	12	24-Sep-08	50	0.5
	LUKGE0701	Gergely Lukacs	CRC Tier I/McGill	26	01-Jan-08	100	1
	MARIS9502	Isabelle Marcotte	UQAM	5	01-Jan-08	100	1
	MCKMA9501	Marc McKee	James McGill Prof	21	17-Dec-09	50	0.5
	MILGR0601	Gregory Miller	IRSC/McGill	5	01-Jan-08	100	1
	MITAN0501	Anthony Mittermaier	Université McGill	6	01-Jan-08	100	1
	MOINI0301	Nicolas Moitessier	Université McGill	8	01-Jan-08	100	1
	NAGBH0501	Bhushan Nagar	CRC Tier II/McGill	6	01-Jan-08	100	1
	NAJRA0801	Rafael Najmanovich	FRSQ/Sherbrooke	2	01-Dec-11	50	0.5

	PAQJO9101	Joanne Paquin	UQAM	22	14-Jan-09	100	1
	PAWPE9701	Peter Pawelek	Université Concordia	5	01-Jan-08	100	1
	PUREN9801	Enrico Purisima	CRNC-IRB	24	01-Jan-08	100	1
	ROUIS0701	Isabelle Rouiller	IRSC/McGill	5	01-Jan-08	50	0.5
	ROYRE9901	René Roy	CRSNG/CRC TierI/UQAM	26	01-Jan-08	100	1
	SACMI0702	Michael Sacher	IRSC/Concordia	5	01-Jan-08	100	1
	SALRE0601	Reza Salavati	Université McGill	6	01-Jan-08	100	1
	SCHTH0951	Thomas Martin Schmeing	CRC Tier II/McGill	1	17-Dec-09	100	1
	SHRAL0001	Alvin Shrier	Université McGill	32	01-Jan-08	50	0.5
	SILJO9201	John Silvius	Université McGill	30	01-Jan-08	50	0.5
	SLELE0101	Lekha Sleno	CRSNG/UQAM	3	04-Jan-09	100	1
	THODA0001	David Thomas	CRC Tier I/McGill	34	01-Jan-08	100	1
	TSAYO9801	Youla Tsantrizos	Université McGill	20	20-Mar-09	100	1
	YOUJA0501	Jason Young	CRC Tier II/McGill	7	01-Jan-08	100	1
Membres Associés		Gonzalo Cosa					
		Jean-François Couture					
		Masad Damha					
		Gregory De Crescenzo					
		John Hanrahan					
		Armando Jardim					
		Maria Kilfoil					
		Robert Kiss					
		Justin Kollman					
		Roger Prichard					
		Joe Schrag					
		Philippe Séguéla					
		Hojatollah Vali					
		Christopher Wilds					
		Simon Wing					
		Paul Wiseman					

Section A.2.1.a

ORGANIGRAMME DES EFFECTIFS DE RECHERCHE ET ADMINISTRATIFS DU GRASP



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*** Voir organigramme des équipes scientifiques**

**** Voir organigramme des plateformes technologiques**

ORGANIGRAMME DES EQUIPES SCIENTIFIQUES DU GRASP

Directeur
Kalle Gehring

Directeur Adjoint
Albert Berghuis

McGill Cystic Fibrosis Translational Research Centre
Directeur: John Hanrahan

Montreal-Kingston Bacterial Structural Genomics Initiative
Directeur: Mirek Cygler

Fibrose Kystique

Dr Ann English	**Dr Kalle Gehring**	**Dr Michael Hallett**
Dr Sarah Jenna	**Dr Gergely Lukacs**	**Dr Enrico Purisima**
Dr Lekha Sleno	**Dr David Thomas**	**Dr Jason Young**

M Baek **E**
A Clarke **E**
M Kathirsean **E**
D Jr Martins **E**
M Shadrina **PD**
Z Stoyanova **E**

C Baran **E**
S Bastos **E**
D Calles **E**
E Matta **E**
M Ménade **PD**
J Munoz **E**
H Pande **E**
N Safaee **E**
M Seirafi **E**
J Xie **E**

S Fourati **E**
R Lesurf **E**
E Paquet **E**
I Paylypenko **E**
S Saleh **E**
S Suderman **PD**
A Tofigh **PD**

B Boucher **E**
G Lacoste-Caron **E**
E Martin **E**

P Apaja **PD**
G Veit **PD**

S Acoca **E**
V Campagna **PD**
J Li **PD**
A Shaneh **E**
V Vivcharuk **PD**

S Ben Haddou **E**
Y Boudhekimi **E**
FL Chu **PD**
A Leblanc **E**
V Plante **E**

S Anjos **PD**
Y Chen **E**
RT Lis **E**

I Baaklini **PD**
C Hantouche **E**
P Kim Chiaw **PD**
Y Patel **E**

Maladies Conformationnelles

Dr Katherine Borden	**Dr Pierre Lavigne**	**Dr Marc McKee**
Dr Gregory Miller	**Dr Bhushan Nagar**	**Dr Rafael Najmanovich**
Dr Joanne Paquin	**Dr Isabelle Rouiller**	**Dr Michael Sacher**
Dr Alvin Shrier	**Dr John Silvius**	

M Arguello **PD**
B Culjkovic **PD**
F Hariri **E**
V LaFlamme **E**
M Osborne **PD**
N Siddiqui **PD**
M Talebzadeh **PD**
L Volpon **PD**
H Zahreddine **E**

M Bédard **E**
D Bernard **E**
J Cabana **E**
V Frappier **E**
Y Guedri **E**
F Lacroix **E**
D Létourneau **PD**
M Montagne **PD**

D Athanasiadou **E**
F Chicatun **E**
B Hoac **E**
S Solanki **E**

E Andrews **E**
V Gosein **E**
G Machkalyan **E**

Y Abbas **E**
F Frank **E**
A Gorelik **E**
G Virgili **E**

M Chartier **E**
D Duchene **E**
V Frappier **E**
F Gaudreault **E**
IU Nlend **E**
MI Zylber **PD**

F Bouchard **E**
P Ducharme **E**
H Salmi **E**

K Basu **PD**
B Beckett **E**
M Bonar **E**
L Fabre **E**
D Mountassif **PD**

S Brunet **E**
D Duarte **E**
M Milev **PD**
N Shahrzad **E**

B Foo E
T Quail E
S Thamara PD
C Valinsky E

P Bhagatji **E**

Pathologies Bactériennes

Dr Albert Berghuis	**Dr Mirek Cygler**	**Dr Nicolas Doucet**
Dr Isabelle Marcotte	**Dr Anthony Mittermaier**	**Dr Nicolas Moitessier**
Dr Peter Pawelek	**Dr René Roy**	**Dr Reza Salavati**
Dr Martin Schmeing	**Dr Youla Tsantrizos**	

S Caldwell **E**
D Rodinov **E**
N Sabet-Kassouf **E**
K Shi **E**
B Yachnin **E**

A Grishin **PD**
S Kalynych **E**
R Shi **PD**
D Yao **PD**

H Carlettini **E**
B Folch **PD**
D Gagné **E**
A Ndoti-Nembe **E**
N Nguyen Thi **E**

M Beaugrand **E**
P Brisebois **E**
F Byette **E**
A Gravel **E**
R Hennebicq **E**
S Nirasay **E**
M-O Seguin-Heine **E**
C Tardy-Laporte **E**
S Zaraa **E**

M Butkiewicz **E**
S de Cesco **E**
E Habib **E**
J Harris **E**
E Meneses **E**
T Miletti **E**
S Zhu **E**

R Arreola **E**
M Bezanson **E**
S De Cesco **E**
S Deslandes **PD**
D Kaldre **E**
L Lim **E**
Z Liu **E**
R Mendoza **E**
J Pottel **E**
S Rocheleau **E**
P Schiavini **E**
E Therrien **PD**

D Alonzo **E**
F Bergeret **PD**
K Bloudoff **E**
J Reimer **E**
M Tarry **PD**

D Foshag **E**
I Jaworski **E**
P Pakarian **E**

L Abassi **E**
N Arya **E**
YM Chabre **PD**
F Héroux **E**
J Martel **E**
A Moheb **E**
V Placide **E**
G Pognon **PD**
C Saucier **E**
R Sharma **E**
S Tremblay **E**

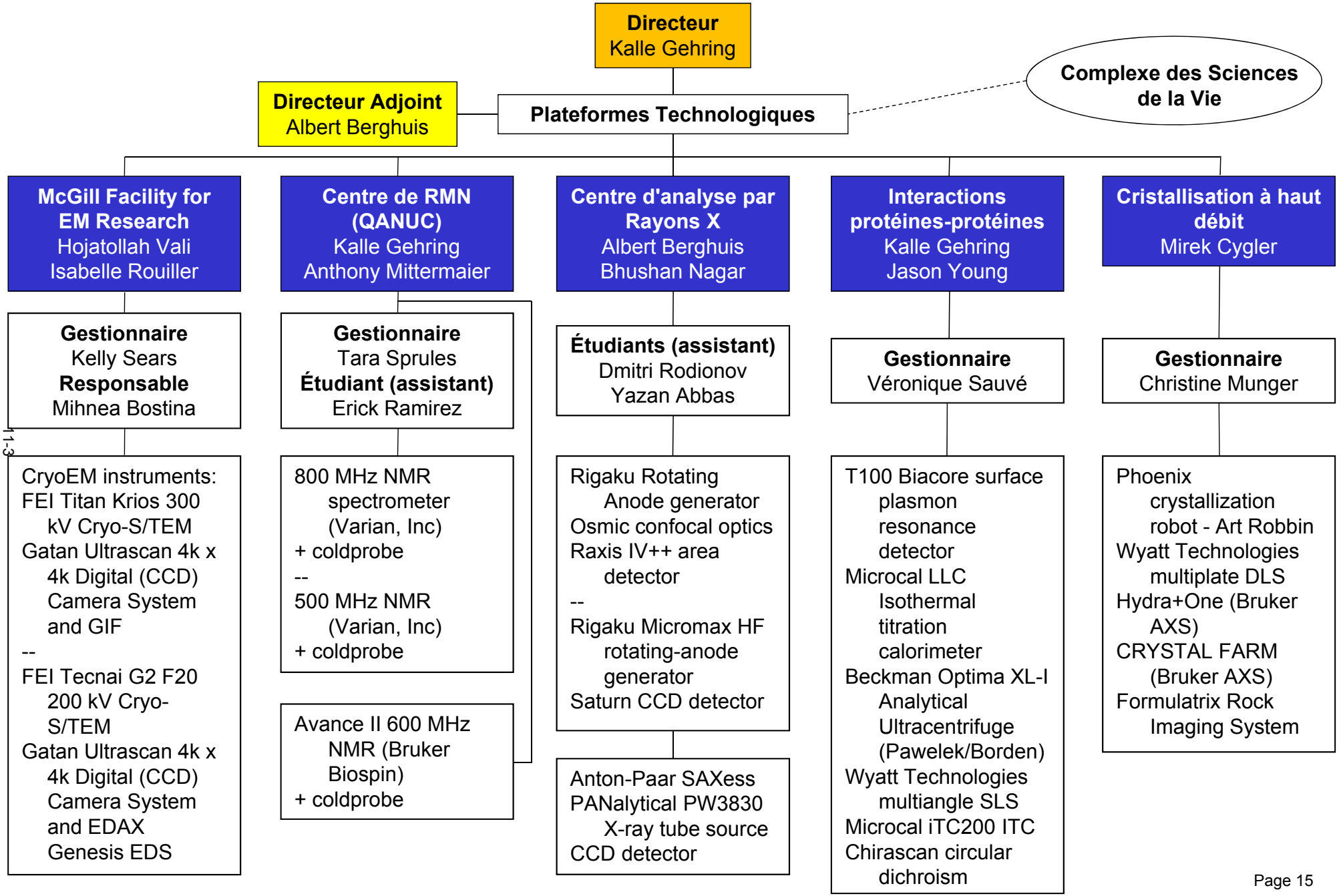
S Kala **E**
H Moshiri **E**
HS Najafabadi **E**
A Shaneh **E**

J De Schutter **E**
C Lacbay **E**
A Langille **E**
O Leogane **PD**
CY Leung **E**
Y-S Lin **E**

Légende: E: étudiants; PD: post-docs

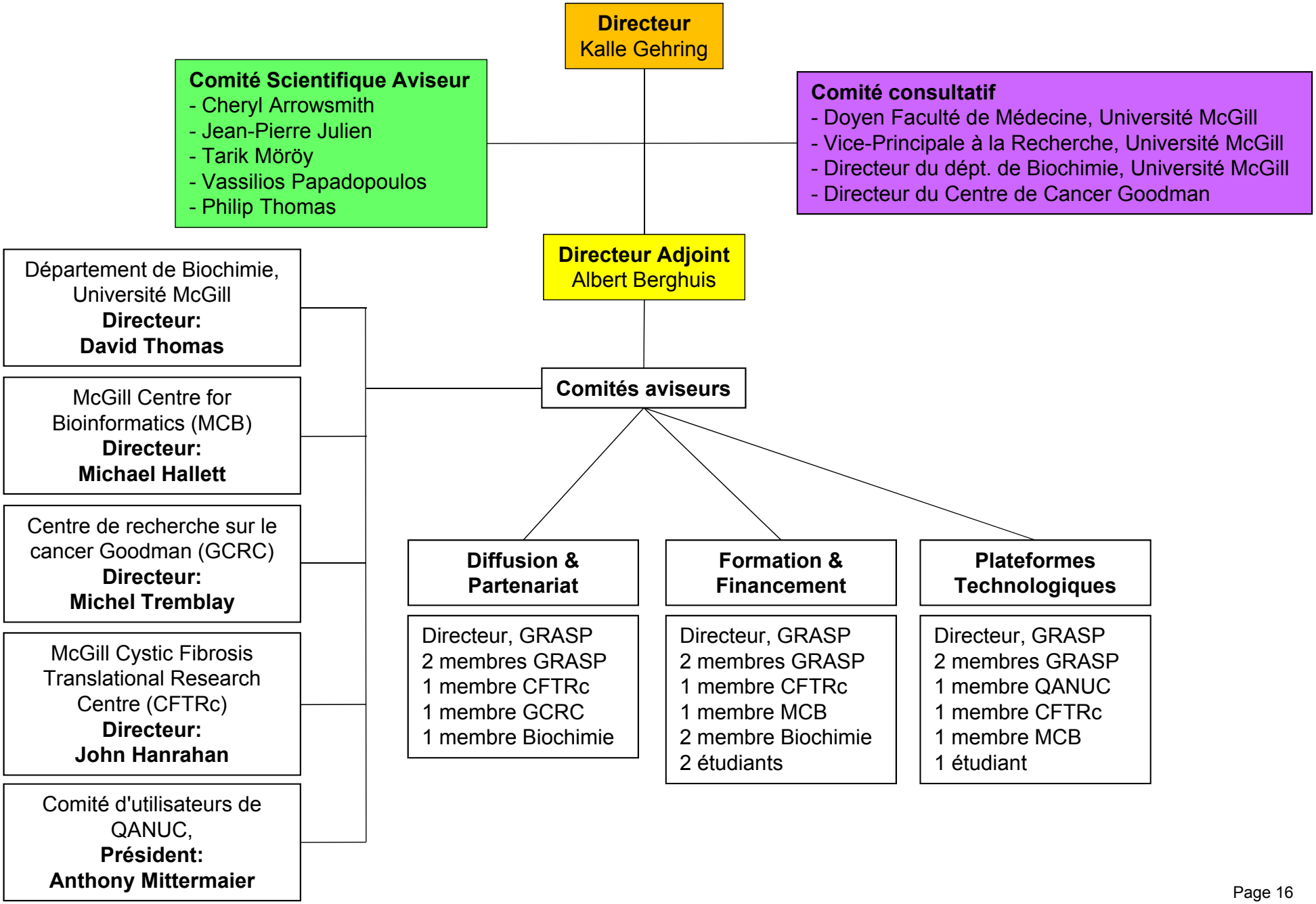
Section A.2.1.a

ORGANIGRAMME DES PLATEFORMES TECHNOLOGIQUES DU GRASP

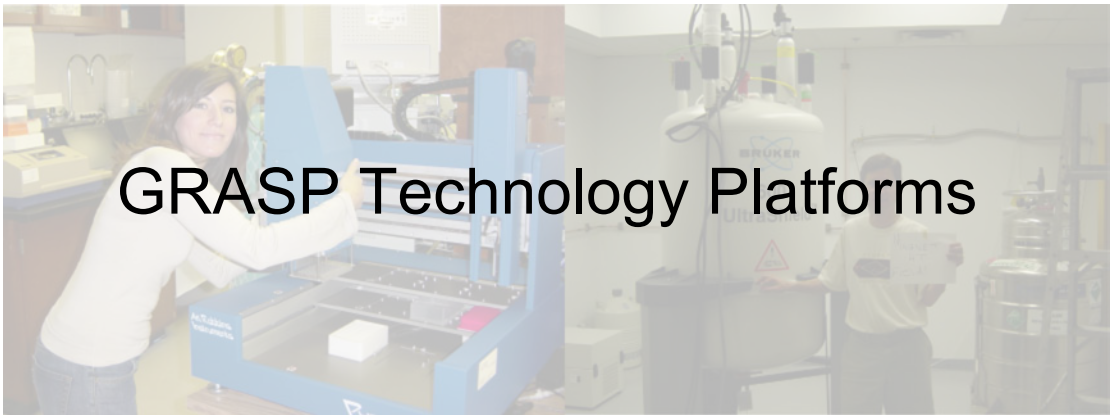


Section A.2.1.a

ORGANIGRAMME DU PROCESSUS DECISIONNEL DU GRASP



11-4



GRASP Technology Platforms

Quebec / Eastern Canada High Field NMR Facility

Directors: Dr. Kalle Gehring & Anthony Mittermaier
Manager: Dr. Tara Sprules

Website: http://www.nmrlab.mcgill.ca

The Quebec / Eastern Canada High Field NMR Facility, better known as QANUC, was established in 2004. It is located in a newly renovated laboratory adjacent to the Department of Chemistry at McGill University. The facility includes two spectrometers: a Varian INOVA 500 MHz and 800 MHz, and an adjacent laboratory for sample preparation. These allow the facility to provide users access to state-of-the art NMR instruments and expertise in biomolecular NMR. The high resolution spectra obtained from these high-field magnets, coupled with the increased sensitivity of cryogenic probes, allow researchers to determine structures of proteins, nucleic acids and complexes involved in a multitude of diseases.

In addition to being an indispensable tool for solving protein structures, NMR is a technique that complements well the other platforms available in the group. While crystal structures provide static images at atomic resolution of enzyme mechanisms and links between ligands and proteins, specialized NMR experiments can be used to probe the dynamic properties of proteins on time scales ranging from few picoseconds to several hours. The perturbations of chemical shifts in ^{15}N-^{1}H HSQC spectra ("fingerprint" of the protein NMR) are used to quickly determine which specific amino acids are assigned to an interaction with a ligand. The titration of proteins with ligands can provide an estimate of the kinetic parameters of interaction and the association constant. These parameters can be compared and used in combination with results from isothermal titration calorimetry and surface plasmon resonance. The synergy between these techniques has been demonstrated repeatedly in recent publications of the group.

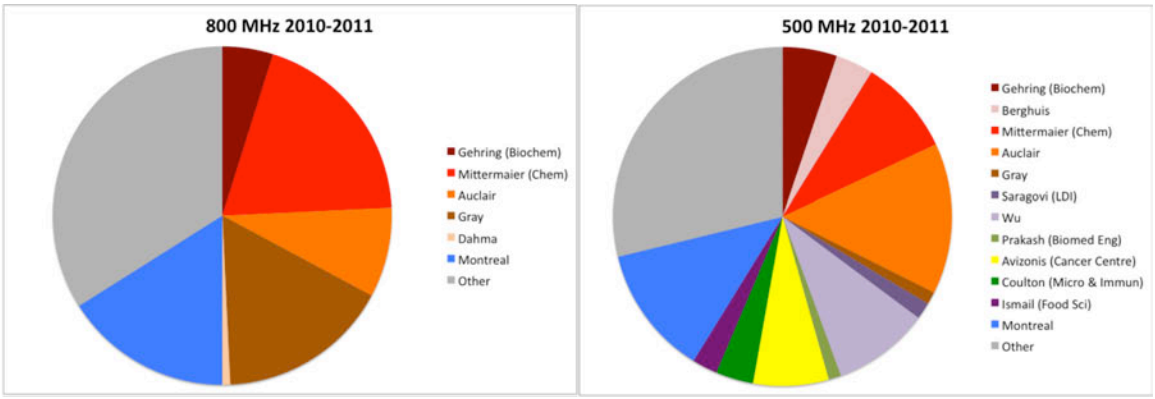
Funding

The facility is funded by an NSERC Major Resources Support grant ($72,000), user fees ($35,000) and support from McGill University ($18,000). The total operating budget is roughly $125,000 per year, which covers cryogens costs of $35,000 per year and salaries (~$90,000).

Usage of QANUC

As the facility has matured, the usage of the spectrometers has settled into a fairly consistent pattern, with approximately 30-35% of the time on the 500 and 800 MHz spectrometers being used by research groups located outside of the Montreal metropolitan area. The 800 MHz spectrometer is further split with 20% of the usage coming from other Montreal-region universities, and 45% of the time used by McGill researchers, mainly from the Chemistry and Biochemistry Departments. The 500 MHz spectrometer is heavily used by McGill researchers about 65% of the time, and a further 5% of the

usage is from small companies and university labs in Montreal.



Representative recent publications:

Frank, Sonenberg & Nagar (2010) Structural basis for 5'-nucleotide base-specific recognition of guide RNA by human AGO2. *Nature*. **465**, 818-822.

Liu, Moldoveanu, Sprules, Matta-Camacho, Mansur-Azzam, & Gehring (2010) Apoptotic regulation by MCL-1 through heterodimerization. *J. Biol. Chem.* **285**, 19615-19624.

Tong, Gagnon, Sprules, Gilbert, Chowdhury, Meerovitch, Hansford, Purisima, Blankenship, Cheung, Gehring, Lubell & Saragovi (2010) Small-molecule ligands of GD2 ganglioside, designed from NMR studies, exhibit induced-fit binding and bioactivity. *Chemical Biology* **17**, 183-194.

Freiburger, Baettig, Sprules, Berghuis, Auclair & Mittermaier (2011) Competing allosteric mechanisms modulate substrate binding in a dimeric enzyme. *Nature Struct. Mol. Biol.* **18**, 288-294.

Volpon, Osborne, Capul, de la Torre & Borden (2010) Structural characterization of the Z RING-eIF4E complex reveals a distinct mode of control for eIF4E. *Proc. Natl. Acad. Sci. U S A*. **107**, 5441-6446.

Dikeakos, Di Lello, Lacombe, Ghirlando, Legault, Reudelhuber & Omichinski (2009) Functional and structural characterization of a dense core secretory granule sorting domain from the PC1/3 protease. *Proc. Natl. Acad. Sci. U S A*. **106**, 7408-7413.

McGill Macromolecular X-ray Facility

Directors: Albert Berghuis & Bhushan Nagar

Diffraction infrastructure

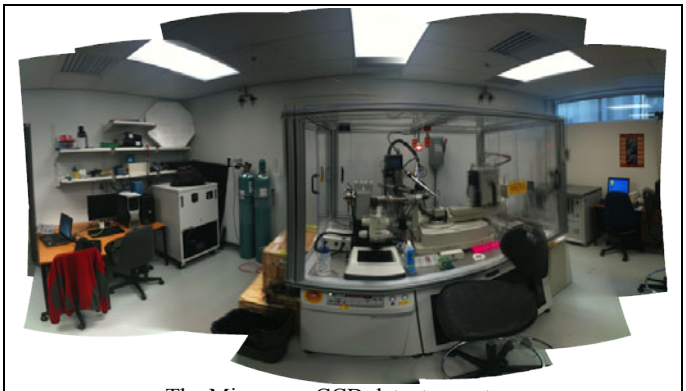
The GRASP-supported macromolecular X-ray facility is located in the Bellini Life Sciences Building, room 445, in close proximity to several of the principal users, and was officially established in January of 2009. The facility consists of two independent setups for collecting single crystal X-ray diffraction data, under cryogenic conditions, from biological samples (Table 1). Both setups were acquired through support from the Canadian Foundation for Innovation, with the first setup being purchased in 2003 and the second in 2008. Acquisition of the second setup became necessary because of McGill's implementation of its *Strategic Plan,* which emphasized an expansion in structural biological research. This led to the recruitment of three additional faculty members, i.e. Drs. Bhushan Nagar (2005), Greg Miller (2006), and Martin Schmeing (2010), who all use X-ray crystallographic methods in their research.

Table 1. Infrastructure of the GRASP Macromolecular X-ray Diffraction Facility

	Image plate	***CCD detector***
In service since	October 2003	January 2009
Generator	*Rigaku* RU-H3R Copper rotating anode	*Rigaku* MM-007HFM Copper rotating anode
Optics	*Osmic* confocal blue	*Rigaku* VariMax HF
Goniometer	Inverted Phi axis	Kappa geometry
Detector	*Rigaku* Raxis IV++ image plate area detector	*Rigaku* Saturn 944 HG CCD camera
Cryo-control	*Rigaku* X-stream 2000 low temp. system	*Rigaku* X-stream 2000 low temp. system
Computer control	1 PC	2 PCs

The two diffraction systems at the GRASP Macromolecular X-ray Facility, with in the foreground the CCD system and in the background the R axis image plate system.

The two setups present in the GRASP macromolecular X-ray diffraction facility are both capable of measuring high-quality diffraction data from macromolecular crystals. While many structural biology groups routinely use synchrotron radiation for data collection, and use the in-house diffraction facilities only for monitoring of optimization procedures for crystallization and/or crystal screening prior to synchrotron data collection, the GRASP facilities are such that final data collection can often be done in-house. Given that the two setups are composed of different elements (i.e. different generators and different detectors), experience has shown that they function complementary. The *Image plate* system is frequently used for collection of publication quality diffraction data, while the *CCD detector system* has found extensive use for screening of crystal quality for either optimization of crystal conditions or prior to synchrotron data collection visits.



The Micromax CCD detector system

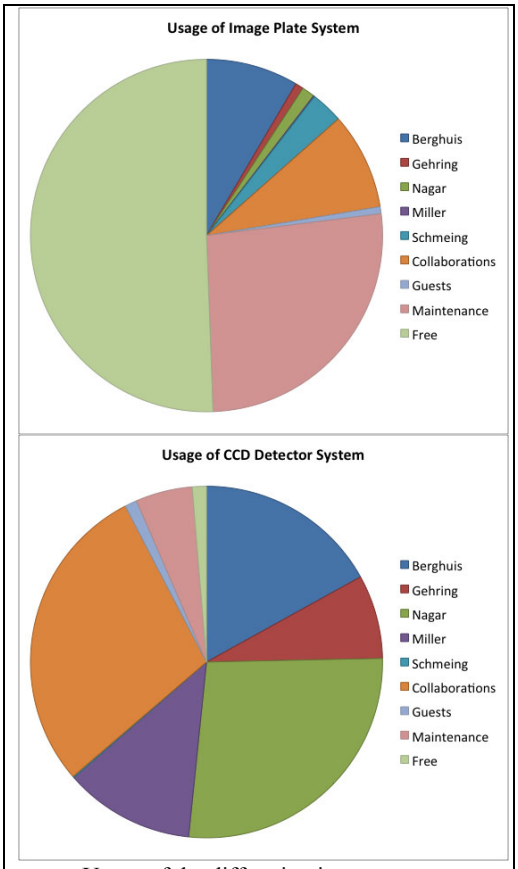
Management of facility

The X-ray diffraction equipment is managed by Dr. Albert Berghuis, who has more than 25 years of experience in protein crystallography. Dr. Berghuis oversees the overall operations of the facility, including maintenance of infrastructure and training of users. The day-to-day operations of the facility are being overseen by Mr. Dmitry Rodionov, under the supervision of Dr. Berghuis. Mr. Rodionov is one of Dr. Berghuis' senior graduate students, and he has been extensively trained in the use of the equipment. Furthermore, he has also received training by *Rigaku* (the manufacturers of the X-ray diffraction equipment) to perform various maintenance tasks. Mr. Rodionov instructs new users of the facility on proper operating procedures, and monitors adherence to these procedures together with Dr. Berghuis. Furthermore, in consultation with *Rigaku* and Dr. Berghuis, Mr. Rodionov performs preventative maintenance of the infrastructure.

Usage of the infrastructure

Usage of the macromolecular X-ray diffraction facility has steadily increased since its establishment in January of 2009. At present, the facility is predominantly used by five structural biology groups located at McGill University (i.e. Berghuis, Gehring, Nagar, Miller and Schmeing). However, a respectable portion of the available time is also used by other groups through collaborations. Examples of collaborators are: Drs. Peter McPherson (Montreal Neurological Institute), Joelle Pelletier (Université de Montréal), and Youla Tsantrizos (McGill University). The number of guest users is at present very limited, and include people such as Drs. Mirek Cygler (formerly NRC-BRI), Peter Pawelek (Concordia University), and Sheng-Xiang Lin (Université Laval).

It is not surprising that of the two systems available, the *CCD detector system* is most heavily used (see Figure 3). The higher intensity X-ray beam produced by this setup greatly facilitates rapid examination of crystal quality. Also, the older *Image plate system* has, due to its advanced age, been subjected to substantial down-time this past year, which has discouraged extensive usage. Fortunately, repairs have been performed and the *Image plate system* is currently being used again. However, given that the older system is approaching the end of its expected lifetime (~10-12 years), we hope to use future CFI opportunities to make upgrades to this system.



Usage of the diffraction instruments.

Small-angle X-ray scattering infrastructure

The SAXS facility, located in the Bellini Building of the Life Science Complex, was established at McGill in 2008. The system was purchased from Anton-Paar, an Austrian-based company that markets SAXS based on the Kratky geometry (Table 2).

Table 2. Infrastructure of the GRASP SAXS Facility

Anton Paar SAXSess mc2	
X-ray Source	Sealed tube, Panalytical PW3830 X-ray Generator
X-ray optics	Line Collimated
Sample Holder	TCS 120 temperature controlled sample unit
Sample Holder	Quartz Capillary for liquids; u-Cell for small sample volume
Detectors	CCD Detector (Princeton Instruments); Imaging Plates (Perkin Elmer)
Typical Measurement time	30m (for Concentrated samples) - 2h (Buffer and dilute Samples)
Useful Concentration Range	1mg/ml protein - 10mg/ml
Accessories	
Haskris system	Refrigerated pump to cool the X-ray Tube
Julaba F25 Water Bath	Maintain CCD Detector Jacket temperature
Perkin Elmer Cyclone Plus	Phosphorimager for Image Plate readings
Dell Workstation	SAXSQuant data acquisition and analysis software

SAXS is a biophysical technique that can be used to analyze properties of macromolecules in the solution state. Because SAXS can be performed directly on protein solutions, the only requirement is a homogeneous solution of the protein of interest. Exposure of the solution to X-rays yields an isotropic scattering pattern that falls off with increasing resolution (Figure 1a). The fall-off of this scattering intensity varies for differently shaped proteins, and hence contains information on the shape of the particle. Information directly obtainable from this primary data are the scattering at zero angle (I(0)) which can be correlated with the molecular weight of the protein, and the radius of gyration (Rg) by vanalysis of the Guinier region. The Rg is the distance at which the average mass of the particle is concentrated and can be correlated with how relatively extended or compact a particle is in solution.

It is exquisitely sensitive to even minute conformational changes in proteins and can be used to monitor ligand binding or extracting binding constants. Fourier transformation of the scattering data results in the distance distribution function (P(r)), which is a plot of the interatomic vectors present in the protein (Figure 3b). From this function, the maximum dimension of the protein (Dmax) can be determined. Perhaps the most interesting information that can be derived from SAXS data is shape reconstructions of the protein.

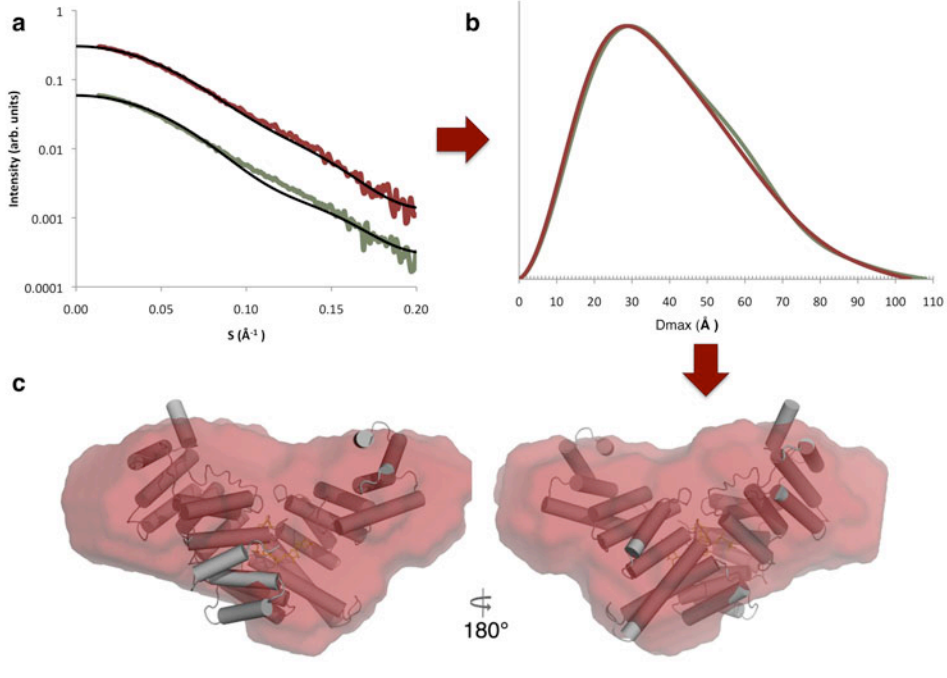
SAXSess instrument from Anton-Paar

Typically, shapes are recapitulated with the use of a large number of close-packed beads whose positions are adjusted iteratively such that the scattering calculated from the bead assembly matches the observed scattering profile optimally. SAXS is useful for providing low-resolution structural information and is an indispensable tool for probing the overall shapes of large complexes and gross structural changes that take place in

dynamic systems. In a manner similar to that used in electron microscopy structures, SAXS envelopes can be used for docking in high-resolution subunits or domains obtained from techniques such as NMR or X-ray crystallography. Thus, the SAXS facility in combination with the X-ray crystallography and NMR facilities offers a powerful approach for deducing the structures of biologically important large macromolecular complexes.

Management of SAXS infrastructure

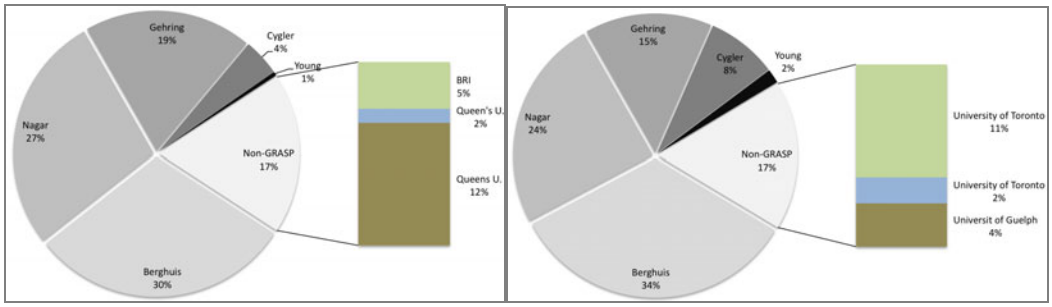
Dr. Bhushan Nagar, who brought SAXS expertise to McGill University, manages the SAXS instrument. Dr. Nagar has published several papers using the SAXS technique. He oversees the overall operations of the facility, including maintenance of infrastructure and training of users. The direct operations of the facility were initially performed by Dr. Jean-Francois Trempe, who has since left the facility. Currently, day-to-day operations are being overseen by Mr. Yazan Abbas, under the supervision of Dr. Nagar. Mr. Abbas is one of Dr. Nagar's graduate students and he has been extensively trained in the use of the equipment. Mr. Abbas instructs new users of the facility on proper operating procedures, and monitors adherence to these procedures together with Dr. Nagar.



Sample SAXS data. a, primary scattering data. b, distance distribution function. c, shape restoration.

Usage of the SAXS infrastructure

Since its establishment, the SAXS facility has become very popular amongst researchers from both within GRASP and outside. The facility is used by several groups within GRASP at McGill University (i.e. Berghuis, Gehring, Nagar, Young) and at the Biotechnology Research Institute (Cygler – now located at the U. of Saskatchewan). Additionally, a number of groups not affiliated with GRASP have formed collaborations to incorporate SAXS data into their research. These include: Dr. Irena Ekiel (BRI), Dr. Steve Smith (Queens U.), Dr. Zongchao Jia (Queens U.), Dr. Mitsu Ikura (Ontario Cancer Institute), Dr. Julie Forman-Kay (U. of Toronto) and Dr. George Harauz (U. of Guelph).



SAXS usage by GRASP and other groups. Left panel, November 2008 - November 2009 (212 days). Right panel, July 2010 - October 2011 (122 days)

Research output

In the less than 3 years that the GRASP macromolecular X-ray facility has been operational, the facility has already enhanced the research productivity of its users. This is perhaps best illustrated by the quality of the publications that have resulted from usage of this infrastructure. Below is given a small sample of some of the publications that have benefitted from this GRASP platform.

Representative recent publications:

Frank, Sonenberg & Nagar (2010) Structural basis for 5'-nucleotide base-specific recognition of guide RNA by human AGO2. *Nature*. **465**, 818-822.

Mirza, Yachnin, Wang, Grosse, Bergeron, Imura, Iwaki, Hasegawa, Lau & Berghuis (2009) Crystal structures of cyclohexanone monooxygenase reveal complex domain movements and a sliding cofactor. *J. Am. Chem. Soc.* **131**, 8848-8854.

Kozlov, Pocanschi, Rosenauer, Bastos-Aristizabal, Gorelik , Williams & Gehring (2010) Structural basis of carbohydrate recognition by calreticulin. *J. Biol. Chem.* **285**, 38612-23860.

Matta-Camacho, Kozlov, Li & Gehring (2010) Structural basis of substrate recognition and specificity in the N-end rule pathway. *Nature Struct. Mol. Biol.* **17**, 1182-1187.

Shi, Houston & Berghuis (2011) Crystal structures of antibiotic-bound complexes of aminoglycoside 2''-phosphotransferase IVa highlight the diversity in substrate binding modes among aminoglycoside kinases. *Biochemistry*. **50**, 6237-6244.

Frank, Fabian, Stepinski, Jemielity, Darzynkiewicz, Sonenberg & Nagar (2011) Structural analysis of 5'-mRNA-cap interactions with the human AGO2 MID domain. *EMBO Rep.* **12**, 415-420.

Trempe, Shenker, Kozlov & Gehring (2011) Self-association studies of the bifunctional N-acetylglucosamine-1-phosphate uridyltransferase from Escherichia coli. Protein Science 20, 745-752.

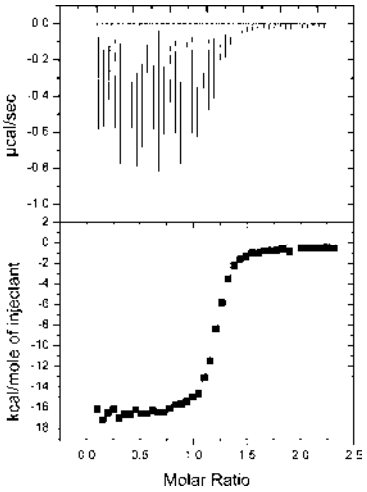
Shi, Proteau, Villarroya, Moukadiri, Zhang, Trempe, Matte, Armengod & Cygler (2010) Structural basis for Fe-S cluster assembly and tRNA thiolation mediated by IscS protein-protein interactions. PLoS Biol. 8, e1000354.

Kozlov, Määttänen, Schrag, Hura, Gabrielli, Cygler, Thomas & Gehring (2009) Structure of the noncatalytic domains and global fold of the protein disulfide isomerase ERp72. *Structure* **17**, 651-659.

Two examples of research output from the GRASP platform.

Protein-protein interaction platform

Directors: Kalle Gehring & Jason Young
Manager: Veronique Sauvé



Characterization of interactions between biological macromolecules is an essential step in the structural analysis of complexes between biomolecules, whether for a preliminary characterization of affinity or a thorough analysis of thermodynamic parameters of a reaction. To achieve these measures, the platform includes tools isothermal calorimetry, differential scanning calorimetry, surface plasmon resonance, circular dichroism and analytical ultracentrifugation. In addition, several of these techniques provide additional structural information such as stoichiometry and the hydrodynamic radius of complex macromolecules.

Isothermal calorimetry (ITC) is a technique that measures the heat released during a reaction. For the case of interaction between molecules, this technique allows one to evaluate not only the association constant but also the entropy and enthalpy of a specific binding reaction. This technique has the advantage of using proteins in solution without resorting to chemical changes. In addition to the current instrument MicroCal LLC located in the laboratory of Dr. Gehring, a newer instrument ITC200 MicroCal funded by MDEIE and McGill University is also available. Differential scanning calorimeter (differential scanning calorimetry, DSC) allows one to measure the heat capacity of a sample as a function of temperature and to estimate the enthalpy associated with a phase transition as a cooperative unfolding protein in the presence of a ligand.

Surface plasmon resonance (SPR) allows the observation of intermolecular interactions in real time. The ligand is first immobilized on a gold metal surface and a solution of binding molecules is injected on this surface. The interactions are detected through an optical system of high sensitivity. This technique allows one to measure the association constant at equilibrium, the kinetic constants of association and dissociation, as well as the entropy and enthalpy of a biomolecular association. The platform is equipped with a Biacore T-100 an instrument (GE Healthcare), which even allows the observation of interactions with small molecules, an incomparable research tool for screening for pharmacological inhibitors. The automation of this technique permits one to test several types of ligands at a high throughput. In addition, this technique requires minimal amounts of material, an important asset for studying molecules that are expensive and difficult to produce.

All of the research groups use the techniques mentioned above in a routine manner and GRASP

funding is absolutely essential for its proper functioning. Examples of applications of these techniques are included in the publications cited in other sections.

Representative recent publications:

Fan, Kozlov, Hoegl, Marcellus, Wong, Gehring & Young (2011) Interaction between the human mitochondrial import receptors Tom20 and Tom70 in vitro suggests a chaperone displacement mechanism. *J. Biol. Chem.* **286**, 32208-32219.

Okiyoneda, Barrière, Bagdány, Rabeh, Du, Höhfeld, Young & Lukacs (2010) Peripheral protein quality control removes unfolded CFTR from the plasma membrane. *Science* **329**, 805-810.

Townshend B, Aubry I, Marcellus RC, Gehring & Tremblay (2010)
An RNA aptamer that selectively inhibits the enzymatic activity of protein tyrosine phosphatase 1B in vitro. *Chembiochem*. **11**, 1583-1593.

Plesa, Kim, Paquette, Gagnon, Ng-Thow-Hing, Gibbs, Hancock, Rosenblatt & Coulton (2011) Interaction between MMACHC and MMADHC, two human proteins participating in intracellular vitamin B_{12} metabolism. *Mol. Genet. Metab.* **102**, 139-148.

High-throughput crystallization

Director: Mirek Cygler
Manager: Christine Munger

The determination of 3-D structures of proteins is crucial for the discovery of protein function and mechanism of action at the molecular level. X-ray crystallography is a key element in the determination of molecular structures. However, a critical step in this technique is the generation of crystals of the protein of interest, a rate-limiting non-trivial step. Despite the significant progress made in the methods of crystallization, the generation of crystals remains a trial and error process that requires analysis of hundreds of conditions. It is a process that requires expertise and specialized know-how and benefits greatly from automation and miniaturization.

The platform provides the infrastructure for high performance analysis of hundreds of simultaneous crystallization conditions. The operation of the platform is provided by a team of experienced technicians who perform crystallization on a routine basis and have access to equipment at the cutting edge of technology. These technicians have many years of experience and have crystallized a large number of proteins. The platform can provide professional assistance in optimizing the behavior of the protein and crystal growth.

The equipment of the platform currently includes:
• A robot Hydra + One (Art Robbins) for the distribution of crystallization drops from 0.2 µL to 1-10 µL in 96-well plate format.
• Phoenix robot (Art Robbins) for the distribution of crystallization drops from 50 nL to 10 µL in 384-well plate format.
• A station storage Crystal Farm (Bruker AXS) of crystallization plate at 20 ºC and visualization with Internet access to the database
• A dynamic light scattering device for detection of protein aggregates in the 384-well plate format.
• A fluorescence plate reader with temperature control to test the influence of additives on the thermal stability of proteins.

Crystallization robots greatly facilitate the exploration of the chemical conditions of crystallization such as pH, buffers, salts and precipitants. The robot Hydra + one station and storage and imaging Crystal Farm are part of the service of crystallization of the Biotechnology Research Institute (NRC-CNRC), while the Phoenix robot is located in the Bellini Pavillon of the Life Science

Complex. To complement the Phoenix robot, a RockImager imaging instrument (Formulatrix) was purchased to automate the crystal identification process. The presence of two sets of robot / imaging systems will significantly increase the rate of generation of crystals.

The dynamic light scattering (DLS) system is used to determine the hydrodynamic radius of particles in solution, the relative abundance of each population and the polydispersity. This information is very useful for optimizing crystallization from protein solutions by enabling the identification of conditions where a single species of particle is present in solution. Solutions with a low polydispersity have an increased likelihood of crystallization. The DLS also helps determine the approximate size of a particle in solution. These measurements are currently performed using a DLS instrument from Wyatt Technologies. A related technique, multi-angle static light scattering MLS) provides additional information on the absolute mass of the particles in solution, which can then be used to evaluate the stoichiometry of protein complexes. The MLS instrument was funded by MDEIE and McGill University.

Representative recent publications:

Matte, Kozlov, Trempe, Currie, Burk, Jia, Gehring, Ekiel, Berghuis & Cygler (2009) Preparation and characterization of bacterial protein complexes for structural analysis. *Adv. Protein Chem. Struct. Biol.* **76**,1-42.

Quan, Koldewey, Tapley, Kirsch, Ruane, Pfizenmaier, Shi, Hofmann, Foit, Ren, Jakob, Xu, Cygler & Bardwell (2011) Genetic selection designed to stabilize proteins uncovers a chaperone called Spy. *Nat Struct Mol Biol.* **18**, 262-269.

Grishin, Ajamian, Tao, Zhang, Menard & Cygler (2011) Structural and functional studies of the Escherichia coli phenylacetyl-CoA monooxygenase complex.
J. Biol. Chem. **286**,10735-10743.

Shi, Munger, Asinas, Benoit, Miller, Matte, Maier, Cygler (2010) Crystal structures of apo and metal-bound forms of the UreE protein from Helicobacter pylori: role of multiple metal binding sites. *Biochemistry* **49**, 7080-7088.