LYSOSOMAL STORAGE DISEASE TWO-YEAR FELLOWSHIP

Overview

The Division of Medical Genetics offers 2 Fellowship training programs to residents successfully completing their medical genetics residency or other applicable post-graduate training; one is of 1 y duration and the other is 2 years. The description that follows is for the two year program. This additional time is generally used to complete a further specialization in treatment and diagnosis of lysosomal storage disease and clinical research projects, under staff supervision. Trainees will spend most of their time involved in the management and follow up of patients with these complex disorders. This contact will not dilute the clinical exposure of any of the more junior house staff. The fellows will not be involved in any on-call activities except during rotations in biochemical genetics.

Dependent on fellow interest, opportunity exists to participate in a number of didactic educational activities including teaching of junior house staff. The trainee is invited to participate in all Department of Pediatrics or Department of Medicine academic activities including those within the Division. See below for a schedule of the usual activities.

Prior to the onset of the fellowship, the fellow and program director will together predetermine an individualized set of training goals. Goals of the fellowship and trainee performance will be reviewed quarterly. The trainee will have reciprocal opportunities to assess their supervisors and the training program.

General information

The duration of this training will be a minimum of 18 months but typically 24 months.

Trainees will only be eligible for this training if they are deemed eligible if they have or will soon have completed training in medical genetics, pediatric neurology or internal medicine; this assures that they would be eligible to receive a training card from the *College des Medecins du Quebec.*

The Lysosomal Fellowship Director and the Training Committee will supervise the Fellowship program. They will be responsible for implementation, recruitment and supervision of the Fellowship, and will ensure that the Genetics residents or medical students will continue to experience adequate clinical exposure, supervision and educational content.

Clinical activities

Generally, the trainees will be responsible for managing the supervision and follow up of patients with lysosomal storage disease. The trainee will be expected to be involved in the longitudinal multidisciplinary management of patients with lysosomal storage disease including clinic visits, planning of surgeries and organization of regular follow up in other disciplines. Involvement in clinical trials management will be provided and options for participation in these trials will be available. Responsibilities will also include the management of enzyme replacement therapy whether it takes place within the hospital or outside the hospital. Depending on experience, a biochemical genetics rotation of 1-2 months will be mandatory. Trainess will provide call servie during this time. During the biochemical genetics rotations, trainee will also attend biochemical genetics clinics on Mondays and Tuesdays with one of the 4 staff working in the biochemical genetics clinic to see relevant patients. If the program director deems that the clinic has been assigned very few house staff, the Fellow can attend additional clinic and work in parallel with the usual house staff. Additional fixed one month rotations will occur at the Montreal Neurological institute, the Jewish General Hospital , and the biochemical genetics laboratory. Optional rotations will include lysosomal laboratory at Ste Justine, Fabry management at Sacre Couer, and biochemical genetics lab at Sherbrooke.

Additional pedagogic activities

All trainees are encouraged to attend at least one conference per year; this is often the World Lysosomal Meeting, the Society for the study of inborn errors of metabolism, the Garrod Association annual meeting or Society for inherited metabolic disorders. Our division has adequate funding to assist with registration costs and some travel costs for lysosomal fellows residents. The Fellows are also able to be granted additional funds from the MCH research institute, if their abstracts have been accepted for presentation.

Lab:

Fellows will be expected to spend 2 months in the provincial laboratories that are involved in the testing and diagnosis of lysosomal diseases (CHUS, CHUM) There will be an option for the fellow to spend time in Dr Mitchell's research laboratory and learn techniques related to mass spectrometry in addition to measurement of cytokines.

Research Activities:

Dr Mitchell's main research interests revolve around the treatment and follow up of lysosomal storage disorders. He is extensively involved in clinical trials in cutting edge therapies for these orphan disorders including natural history studies, enzyme replacement therapies, cofactor therapies, substrate reduction therapies and gene therapies. His laboratories main interest is in the development of biomarkers for lysosomal storage disorders.

Administrative responsibilities

Fellows will be responsible for the coordination of their clinical activities. Additionally, they will be involved in the teaching schedule for house staff and may help to select topics and then supervise the Friday morning sessions.

Evaluation

The Program Director will meet with the Fellow at least quarterly; the progress with the course work, research project and possible clinical exposure will be explored. Evaluation forms will be reviewed at this time. If issues arise prior to these meetings, the Fellow may approach the Program Directors, the Training Committee members or any member of the staff to discuss issues.

At the end of the Fellowship, a final written evaluation will be completed and placed in the Fellow's file.

The Fellow will have the opportunity to provide feedback to the Training Committee and Fellowship Program Director anonymously. The Training Committee will assess the quality of the curriculum of the Fellowship, at least on an annual basis.

The Fellow will receive a signed certificate outlining the duration of their training at McGill University.

If the trainee is involved in clinical outpatient care, the specific objectives and evaluation form for this type of exposure will also be completed on a quarterly basis

General competencies

Medical Expert-

1. To apply relevant clinical or basic science information to research development
2. To demonstrate medical expertise in situations other than direct patient care
3. To provide advice and education to other health care providers with respect to patient care, and legal opinions.

Communicator

1. To document research ideas as a protocol, manuscript or lecture
2. To develop good communication skills with research subjects, supervisor, trainees and/or team members.

Collaborator

1. To contribute effectively to other interdisciplinary team activities, particularly those most often associated with endocrinology
2. To acquire the skill of identifying potential collaborators locally, nationally or internationally and the skill of proposing a mutually beneficial academic collaboration

Manager

1. To appropriately allocate time to research education, and other professional commitments
2. To utilize resources effectively when designing and implementing a research project
3> To manage a research operating budget

Health advocate

1. To identify determinants of health that affect a patient
2. To use research as a tool to advocate for health changes and to disseminate health information

Scholar

1. To formulate a clinical/research question and research protocol.
2. To complete a project based on this question
3. To contribute to the development of new knowledge
4. To critically appraise medical literature
5. To undertake and complete advanced course work (in epidemiology, public or community health, or educational programs).

Professional

1. To exhibit appropriate personal and interpersonal professional behaviour
2. To demonstrate responsibility and self-discipline
3. To recognize one's own limitations
4.To demonstrate a willingness to accept peer and supervisor reviews of professional competence.
5. To demonstrate an understanding of the principles of medical ethics as they relate to clinical research
including autonomy, beneficence/ nonmalificennce, justice and confidentiality

APPLICATION FORM FOR FELLOWSHIPS

Name of institution: McGill University

Location: Montreal

Type of Fellowship: Clinical research or basic research- in conjunction with graduate school degree

- Program Information:
- Number of fellowship positions requested There will only be one lysosomal fellow at a time. If there is a fellow doing a two year program, there will only be one fellow every two years. If there is a fellow in the one year program, a fellow can be recruited for the following year
- Academic affiliation- McGill University
- Name of hospitals involved in training- Montreal Children's Hospital, Royal Victoria Hospital, Montreal Neurological Institute, Jewish General Hospital
  - % time spent by the fellow in each institution
  - 85% MUHC (75% Glen; 5% MNI; 5% JGH)
  - Specific rotations in laboratories or clinics of non-affiliated hospitals (to complete 2/4):
    - CHU Ste-Justine (Lab/clinic)
    - CHU Sherbrooke (Lab)
    - Halifax (Clinic)
    - CHUM (clinic)

- Background:

The Division of Medical Genetics offers a Fellowship training program to residents who have completed a medical genetics residency or other equivalent training. This additional training aims to provide structured individually tailored academic training; most trainees will use this time to enhance their clinical skills in management of lysosomal storage disorders. However, there is also the opportunity to complete a graduate degree in Epidemiology, Education, or Public Health or Ethics. Additionally, this time is generally used to complete basic science or clinical research projects, under staff supervision.

Trainees will spend more than 90% of their time involved in these activities; All clinical activities will be arranged according to the trainee's interest.

Dependent on fellow interest, opportunity exists to participate in a number of didactic educational activities including teaching of junior house staff and didactic lecture for the different services that may be involved in the management of patients with lysosomal storage diseases. The trainee is

invited to participate in all Department of Pediatrics and Department of Medicine academic activities including those within the Division.

Prior to the onset of the fellowship, the fellow and program director will together predetermine an individualized set of training goals. Goals of the fellowship and trainee performance will be reviewed quarterly. The trainee will have reciprocal opportunities to assess their supervisors and the training program.

- Research activity- see above

- Mission-

To train medical geneticists in specialized management of lysosomal storage disorders and become academicians, which may entail clinical management, combined research training and/or graduate degrees in either Epidemiology, Public Health or Education.

- Outline how intended fellowship will enhance residency training

The Fellows will act as role models and provide some mentorship for the residents. They will likely be able to provide some insight into the rationale for extra training, the process of application for an academic position. On a daily basis, they may provide some academic and clinical insights.

Name of the Fellowship Program Director: Dr John Mitchell

Names of the Teaching Faculty: this includes the entire faculty

- Roles

Our division has 8 staff at the MUHC (Dr. John Mitchell, Dr. Daniela Buhas, Dr. Nancy Braverman, Dr. Yannis Trakadis, Genevieve Bernard, Dr Isabelle Debie, Dr Laura Russel and Dr. Daneilla D'Agostino) that are involved in many academic endeavours including patient care, research and education. We see a wide range of pathologies and run several specialized clinics. The staff have a broad base of knowledge, as well, most have focused areas of clinical and basic research and patient care. Lina Moisan is also a full time nurse that works with the lysosomal storage clinic in both a research and clinical capacity. She has a vast breadth of knowledge on enzyme infusion therapies and long term management of these patients.
Dr. Sarit Assouline (Hematology) is involved in the management of Gaucher adults at the Jewish General Hospital. Follow up of these patients is done 4 times per year with an annual review of treatment goals.
Dr. Angela Genge (Neurology) is involved in the management of late onset Pompe disease. She follows these patients at the Montreal neurological institute.
Many of the lysosomal storage patients have significant bone pathology and these patients are jointly followed at the MUHC and the Shriner's Hospital.

- Summary of clinical practice-please see above for clinic details

- Major strengths

Our division has been recognized for a long time as being one that provides outstanding clinical teaching, mentoring skills as well as fulfills the academic mandate of being involved in both basic and clinical research.

Academic facilities

Our genetics clinic has a busy outpatient service and there are currently 4 full time staff that are involved in the follow up and management of biochemical genetics patients. This includes the management and work up of patients referred for developmental delay, developmental regression, abnormal imaging, muscle pathology and other symptoms compatible with inborn errors of metabolism. Dr Mitchell follows the majority of the patients with lysosomal storage disorders but some of the other staff are also involved in the work up and follow up of these patients. In addition, the Jewish General Hospital (Dr. Sarit Assouline) has an adult Gaucher disease program and is involved in the long term follow up and management of these patients. The Montreal Neurological Institute (Dr. Angela Genge) follows patients with adult onset Pompe disease (a lysosomal storage disorder).

With respect to clinical research, our center operates a number of clinical trials through the center for innovative medicine. This facility allows for resource heavy clinical studies to be offered to patients across a provincial or National basis. This is one of the top facilities in Canada with respect to support and research based platforms. Dr Mitchell currently has natural history studies, enzyme replacement therapy trials, gene therapy trials and post marketing registries for follow up of innovative therapies. Dr Angela Genge is involved in a number of cutting edge clinical trials and is an expert in enzyme replacement therapy. Genevieve Bernard has an extensive research experience in the management of patients with leukodystrophy.

Clinical Laboratory Facilities

Biochemical Genetics Laboratory:

- CHU Sherbrooke--P. Waters and C. Aurais-Blais: biochemical laboratory test methods and interpretation
- CHU Ste-Justine--P. Allard and C. Brunel-Guitton: biochemical laboratory test methods and interpretation

Research Institute: There are three separate metabolic research laboratories within the structure of the MCH Research Institute. These are:

a) Braverman laboratory for peroxisomal disorders
b) Mitchell Laboratory for lysosomal storage disease
c) Bernard Laboratory for leukodystrophies

Summary of Adequacy of Resources

We are indeed fortunate to have the one of the largest lysosomal services in Canada . As mentioned above, there are also opportunities to see patients at other McGill institutions and non-affiliated institutions.

Basic Science Laboratory of Dr Mitchell :

My laboratory at the Research Institute of the McGill University Health Center (Montreal Children's Hospital site), is primarily focused on the development of biomarkers that are used for follow up and treatment targets for lysosomal storage disease. Dr Farah El-Turk is a full time PhD biochemist that runs the laboratory.
Our current research projects are

1. Cytokines in lysosomal storage disease: Aim at further characterizing the mechanism of GAGs mediated lesions in MPS disorders by examining the levels of pro-inflammatory cytokine and chemokines in the serum of MPS patients. Specific cytokines and chemokines levels in serum of MPSs patients will be quantified using biochemical tools. We will evaluate the levels of TNF-α, IL-1β, IL-6, IL-8, IL-10, MCP-1, MIP-1a and MMP-9 using Quansys (Q-PlexTM) kits. The kit performance is optimised for analysis of precise proteins in human samples. The method provided by this kit is based on ELISA (enzyme-linked immunosorbent assay) concept. Our ultimate aim is to probe the inter-relationship between serum inflammatory markers (cytokine), the serum level of ceramides
2. Ceramides in mucopolysaccharidoses: Sphingolipid metabolites, particularly ceramide, are lipid mediators that regulate varieties of cellular functions which include cell growth, survival, angiogenesis and inflammation. Direct disruption of their metabolism (such as in Gaucher disease) results in organ involvement similar to that seen in MPSs. Preliminary work has demonstrated ceramide accumulation in organs of MPS patients, and speculated the role of these molecules in organ dysfunction in MPSs. Ceramides are known to be increased by lipopolysaccharide stimulation of the toll like receptor. This receptor is also stimulated by accumulation of glycosaminoglycans that are seen in MPS patients. In order to understand the role of inflammation in disease progression, part of our research at the laboratory of Dr. John Mitchell at the MUHC, aims at elucidating the role of ceramides in metabolic and signaling processes pertinent to MPSs disorders. The ceramide quantification method employs an electrospray tandem mass spectrometry approach coupled to reverse phase liquid chromatography. Interesting results have been obtained as per the levels of glucosylceramide and dihydroceramide species. Ultimately, we aim to determine how abnormalities of the blood ceramide profile relate to the pathogenesis in MPS disorders, and whether ceramide could be used as a biomarker for diagnosis, follow up and potential therapeutic target.

- Library access, materials relevant to fellowship training
  - McGill University: world-class with broad range of electronic journal subscription, Uptodate.com.
  - MCH Paediatric Library: well stocked, with on-line searching capability
  - Staff offices - wide range of textbooks and articles.

- Multimedial learning materials available- quote hospital details please

  There are eight computers with hardwire connections to allow for on-line searches, for downloading of articles and Internet and email in the two trainee offices. As well, all ward computers and support staff computers can be used for these activities, if needed because the computers are networked and allow multiusers.

- Availability of a skills lab, if applicable- not applicable

Fellow Duties and Responsibilities

- Call responsibilities to cover service- During BCG rotation (1-2 months)
- Include whether the fellow is the senior supervisor of residents- No
- Outline whether there are fixed rotations at various institutions- yes
- Outpatient clinic responsibilities need to be outlined-

Generally the trainees are expected to be involved in the overall management of patients with lysosomal storage diseases. These are extremely complex patients who have follow up with most services in the hospital. Dr Mitchell currently follows 50 patients with lysosomal storage disorders. There are also adult Gaucher patients followed at the Jewish General Hospital and Pompe patients followed at the Montreal Neurological Institute. The fellow will act as the primary contact person for the treatment and management of these patients. Duties will include planning and supervision of the treatments being offered to the patients. This will include development of protocols for infusion of enzyme, prevention of infusion related reactions, determination of immune response and follow up of outcome measures. Outcome measures include both biochemical and clinical assessment of long term outcomes. The fellow will also have the opportunity to attend the biochemical genetic clinic. If the Fellow wishes to attend this clinic, then patients, who need to be seen more urgently and have been triaged to attend an 'office' visit by only the staff, could be seen by the Fellow. The staff, who would have evaluated the patient by themselves, can attend the clinic to review the case. If this staff is already booked in the clinic, then they will arrange their time to attend the clinic earlier than usual to review the Fellow's case/s. We have experience with this and have found that the house staff attending the usually scheduled clinic is given the usual amount of attention, while allowing the Fellow to see patients.

If the clinic has very few house staff assigned to it, as deemed by the Program Director, then the Fellow can attend and work in parallel with the usual house staff.

Weekly schedule

Monday morning- Biochemical genetics clinic 9:00- 1700 (LSD patients only)*

Tuesday morning Biochemical genetics clinic 0800- 1200 (LSD patients only)*

Thursday AM BCG Adult clinic, one Thursday per month (During BCG rotation).

Thursday afternoon Biochemical genetics service review 14:00-16:00

Friday morning- medical genetics half day (Fellow may be the facilitator, if interested)

Variable time – 2-3 patients/week in hospital receiving enzyme replacement therapy (over 6 hours duration)

- Outline role of the fellow towards residents on service- None
- Teaching responsibilities towards residents-see above
- Outline participation in academician activities involving the residents: seminars, outcome assessment (morbidity and mortality rounds etc)

- Describe any support staff available to the fellow: program coordinator, nurse, clinician, secretarial

Our administrative secretary assists in coordinating all rotations, the application and acceptance process. If the Fellow participates in clinics, then he/she has access to our secretaries, who are in charge of the clinics.

- Proposed meetings to be attended by the fellows

Additional pedagogic activities

All trainees are encouraged to attend at least one conference per year; this is often the World Lysosomal Meeting, the Society for the Study of Inborn Errors of Metabolism (SSIEM), the Garrod Association annual meeting or Society for inherited Metabolic Disorders (SIMD). There are often other meetings individually directed at the lysosomal storage disorders. Our division has adequate funding to assist with registration costs and some travel costs for endocrine residents and Fellows. The Fellows are also able to be granted additional funds from the MCH research institute, if their abstracts have been accepted for presentation.

- Research productivity and publications expected by the Fellow

Most Fellows would be expected to present, prepare and present an abstract/manuscript that reflects their academic activities during the Fellowship. Some trainees may be capable of additional manuscripts. If she/he is enrolled in a graduate program, then their thesis would be expected to be completed during the Fellowship or shortly thereafter, depending on the course or research load in that particular period.

Curriculum

- Intended case load- none
- Intended percentage of varieties of cases- The fellow will have exposure to management of mucopolysaccharidoses, Gaucher disease, Fabry disease and Pompe disease. Rotations at the Jewish General Hospital, and the Montreal Neurological Institut will add to the clinical exposure. As the lysosomal disorders are individually rare and we may be lacking patients with some specific individual disorders, external rotations at specialized centers across Canada will be offered as an option to supplement exposure.
- Regular reading materials provided- none
- Conference weekly schedules-none
- Development of institutional guidelines for management of patients with mucopolysaccharidoses, Pompe, Gaucher and Fabry disease
- Review and development of enzyme infusion protocols including enzyme administration, management of infusion related reactions, prevention of antibody development,

  Conferences/ Service Rounds:

  1. Biochemical genetics service rounds, Thursday 14:00-16:00
  2. Medical genetics academic half day Friday 9:00-12:00
  3. Pediatric/medical grand rounds (as applicable)
  4. Research institute rounds Monday 12:00 (as applicable)

- Role of fellow in attending, presenting, supervising, organization

The Fellow is involved in presenting her/his research work, works to organize the year and weekly schedule and is involved in some supervisional activities but these are mostly related to her/his research.