CLINICAL FELLOWSHIP PROGRAM IN
HISTOCOMPATIBILITY AND IMMUNOGENETICS

The Department of Laboratory Medicine and Pathology
University of Alberta, Faculty of Medicine and Dentistry and
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Guidelines and Objectives
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CLINICAL FELLOWSHIP IN HISTOCOMPATIBILITY AND IMMUNOGENETICS

INTRODUCTION and BACKGROUND

The fellowship is designed to provide comprehensive training in the areas of histocompatibility and immunogenetics. Both areas support multiple transplant programs that exist at the University of Alberta Hospitals as well as other clinical programs where diagnosis relies on immunogenetics.

PROGRAM OBJECTIVES

Diagnostic objectives

To provide training and knowledge in the areas of Histocompatibility and immunogenetics testing, HLA antibodies, and transplantation immunobiology.

Educational objectives

1. To prepare the fellow for a successful challenge of the required examination administered by the American Board of Histocompatibility and Immunogenetics as well as for certification by the American Society of Histocompatibility and Immunogenetics Directors’ Training Review and Credentialing committee.

2. To ensure that the fellow acquires the skills and knowledge required to assume the responsibilities of a Histocompatibility laboratory director.

Research objectives

To familiarize the fellow with the clinical applications of Histocompatibility and immunogenetics testing through involvement in research projects.

PROGRAM CURRICULUM

The Histocompatibility and Immunogenetics Fellowship program curriculum will include details of the training outlined for each of the two years of training.

YEAR 1

The first year will focus on the technical aspects of histocompatibility testing and transplant immunology. On-the-bench training will be provided in each area of the laboratory testing. The fellow will be expected to keep a log of all testing performed and will be expected to successfully perform assays using internal proficiency testing samples once training in each bench is successfully completed. Quarterly reports will be made to document short-term goals and accomplishments.

The training will consist of the following components for each rotation:

1. Educational -
   • reading and discussing principles and concepts of laboratory procedures and testing method technologies
• tutorials with the laboratory directors and supervisors to discuss new technologies, novel findings from conferences, and recent literature
• attending journal clubs, seminars, teleconferences, and all clinical rounds involving the Histocompatibility laboratory

2. Practical –
• performing the laboratory procedures
• documentation of tests performed
• successful mastery of all assays performed by the Histocompatibility laboratory

3. Quality and Accreditation Standards –
• Understanding what quality control (QC) is necessary for each assay performed, why it is done and actual performance of the QC when possible
• Understanding the measures instituted by the laboratory to monitor quality assurance
• Understanding the laboratory and technologists' performance expectations as dictated by the American Society of Histocompatibility and Immunogenetics (ASHI) standards, including external proficiency testing

4. Interpretation and Application –
• interpretation of assay results and reporting of results, apply troubleshooting principles for failed QC and unexpected/ discordant patient results within the assays
• troubleshooting the technical problems that may be encountered by any of the instruments used to acquire data to generate reports in the Histocompatibility laboratory
• Clinical Laboratory Environment

The fellow will be instructed on all techniques used in the Histocompatibility laboratory with a focus on how they adhere to the ASHI standards for testing.

General Histocompatibility      Duration - 2 months

History of clinical histocompatibility
Inheritance of HLA antigens and relevance in transplantation
Nomenclature of HLA antigens (past and current)
Understanding of cross-reactivity and shared epitopes

Serological Assays      Duration - 4 months

• Cell isolation techniques
• Cryopreservation and thawing of cells
• Complement-dependent cytotoxicity
• Theory of serological typing
• Luminex-based HLA antibody testing (Screen, Phenotype, and Single Antigen beads)

Flow based assays      Duration - 2 months

• Flow cytometry crossmatch and corresponding cell isolation methods
• Flow cytometry-based bead testing (FlowPRA)

Molecular assays      Duration - 2 months

• Luminex-based Reverse Sequence Specific Oligonucleotide testing
• Sequence Specific Primer testing
• Theory of sequence based typing (SBT) and Next Generation Sequencing

Rotation in affiliated transplant programs

Renal transplant Duration - 1 week
Thoracic transplant (heart and lung) Duration - 2 weeks
Other non-renal transplant (islet, liver, small bowel) Duration - 2 week
Transfusion Medicine Duration - 1 week

Note: The above training components will not necessarily be completed sequentially.
Report generation and assay interpretation

Reporting of clinical cases

Duration – final 3 months of the first year
Reporting performed at the senior technologist level prior to final review and sign-off by a director. Focus will be on quality assurance of assay results, result interpretation, and generation of reports. This rotation will also include instruction on reagent budget, ordering and quality control associated with reagent shipments.

YEAR 2

The second year of training will concentrate more on the director's responsibilities and management skills. At this time, the fellow will be placed on the Director On-Call schedule for first call with decisions still being made by the scheduled (Director On-Call) and continue to train for Donor Workups. The following components will be stressed during the second year of training:

1. Review of worksheets and co-signing reports
2. Review of Proficiency Testing results including documentation of corrective actions
3. Detailed analysis of HLA antibody screens and identification
4. Research and Development projects, including test method validation
5. Developing management skills
6. Completion of portfolio for documentation of training
7. External rotation at a center with expertise in Bone Marrow and Stem Cell transplantation
8. Preparation for American Board of Histocompatibility and Immunogenetics Diplomate examination
9. Preparation for ASHI Director Training Review Committee oral examination

DOCUMENTATION OF TRAINING EXPERIENCE

The fellow will maintain a Case Book of personally studied patient work-ups and follow-up studies that include demographic, pre- and post-transplant clinical information, serum screening analysis, crossmatching evaluations, HLA typings and degree of matching, any other patient data (e.g. transplant biopsy data), appropriate literature references, and the program director's signature indicating review for:

60 deceased donor transplants – percentages of cases for each organ type should reflect the number of transplants performed for each transplant program.
10 of these will be selected with help from the directors and senior laboratory staff to document in detail as required for inclusion into detailed cases for portfolio submission.
60 living related transplants - percentages of cases for each organ type should reflect the number of transplants performed for each transplant program (currently only Renal and Liver Transplant). 10 of these will be selected with help from the directors and senior laboratory staff to document in detail as required for inclusion into detailed cases for portfolio submission.

60 Cases of Non-Transplant related cases (e.g. HLA Disease Association) 10 of these will be selected with help from the directors and senior laboratory staff to document in detail as required for inclusion into detailed cases for portfolio submission

Provide a listing of cases reviewed by the applicant for each technology. Include a brief description of the case or reference the case from a category of testing where the technology is used:

50 tests using serology - complement dependent and solid phase methods
50 tests using molecular methods – primarily rSSO assays
50 tests using flow cytometry – primarily flow cytometry crossmatches

**DETAILED SPECIFIC CURRICULUM**

**I. HLA antibody detection** – Solid phase and serological assays

**A. Practical (Solid Phase)**

1. Algorithm for assessing HLA antibody screen and phenotype results
2. Algorithm for determining HLA antibody specificities using single antigen beads
   - Analysis of epitope reactivity patterns
   - Incorporation of antigen density variability
3. Proficiency in operation of vacuum wash station and Luminex 200 instrument
4. Proficiency in use of vendor software for assays such as HLA Fusion and Match IT! Software programs

**Practical (Serology)**

1. Use of frozen lymphocyte cell trays for serological antibody screening
2. Proficiency in operation of Lambda Jet dispenser and serology syringes for assays using Terasaki plates.

**B. Quality Control**

1. Quality control of allowable NC and PC bead values for bead interpretation
2. Quality control of microvolume dispensers
3. Room temperature recording
4. Complement quality control (QC)

**C. Equipment**

1. Use, maintenance, and QC of Luminex 200 Analyzer and fluidics
2. Use, maintenance, and QC of the flow cytometers (also see Flow Cytometry section below for more detail)
3. Use and maintenance of pipettes
4. Operation and maintenance of the Lambda Jet dispensers
5. Operation, maintenance and QC of the waterbath
6. Other miscellaneous QC practices in the laboratory such as temperature charts for fridges and freezers
D. Reagents

1. Reagent receipt and control
2. Complement thawing and storage
3. Reagent preparation and labeling
4. General reagent shipment quality control as part of the reagent receiving process

E. Application

1. Organ transplantation
2. Platelet transfusion
3. HLA antibody detection by serology
   • Algorithm for detection and analysis of reactions
   • Analysis of private and public epitope specificities
   • Methods – NIH, anti-human globulin enhanced

II. Flow Cytometry

A. Practical

1. Instrument set-up and calibration
2. Source, type and use of reagent antibodies (monoclonals)
3. Data acquisition
4. Test methodologies
5. Analysis on the flow cytometer
6. Proper gating parameters
7. Data analysis
8. Interpretation of all relevant parameters, including interfering immunotherapies
9. Correlation to virtual crossmatch
10. Troubleshooting

B. Quality Control

1. Instrument maintenance and operation
2. Reagent QC

C. Application

1. Flow cytometric crossmatch
   • Selection of positive and negative controls
   • Interpretation of negative control values
   • Establishment of thresholds for interpretation
   • Interpretation of positive crossmatch – B and/or T cell reactions
2. Flow PRA HLA antibody screen
   • Analysis of results
   • Interpretation of results
III. DNA Technology

A. Practical

• PCR-SSOP method
• SSP method

1. DNA extraction
2. PCR amplification
3. Hybridization, washing and detection of dot blots
4. Interpretation of HLA SSOP and SSP data

B. Quality Control (QC)

1. Reagent QC
2. Equipment QC and maintenance
3. Control cell lines for Class I and Class II alleles

C. Application

1. Use of DNA typing in bone marrow transplantation
2. Use of DNA typing in solid organ transplantation
3. Disease associations/ drug sensitivity testing with HLA Class I and Class II alleles
4. HLA polymorphism and human anthropology
5. Mutation detection

IV. Management

The fellow will be given basic management principles together with specific skills unique to histocompatibility and transplantation laboratories. These skills will be learned by:

• Attending selected management meetings
• Participating in daily problem solving in the laboratory
• Attend and participate in weekly laboratory meetings with technologists, supervisors, laboratory manager and director.
• Reading of training manuals
• Attending management seminars and workshops
• Rotating in pertinent AHS departments (e.g. purchasing, finance, HR)

The following topics are incorporated in the training:

A. Regulations and standards governing Histocompatibility/clinical laboratories in Canada

1. Inspections and accreditations (ASHI, CAP)
2. WHMIS standards
3. Have an awareness of Occupational Health and Safety requirements in the laboratory
4. Federal and Provincial regulations, including the Alberta College of Physicians and Surgeons
5. Legal/professional liability
6. Be aware of required safety training for clinical laboratories using local resources

B. Accounting principles applied to the laboratory
1. Budget preparation and monitoring of test volumes
2. Developing charges, cost accounting, billing
3. Have an awareness of how new technologies are funded in the laboratory

C. Personnel Management

1. Recruitment, salaries and benefits
2. Defining job descriptions, objectives, responsibilities
3. Training and continuing education
4. Personnel evaluations

D. Laboratory organization and management principles

1. Developing structure and lines of authority
2. Logistics of laboratory operation-laboratory organization
3. Inventory and ordering
4. Evaluation of laboratory efficiency, distribution of workload
5. Evaluation of workload and turnaround time
6. Develop an understanding of the laboratory’s interaction with other laboratory departments and relevant external programs

V. Research and Development

Duration - 2 years
Recommend 10-20% allocation of training time

The fellow will be expected to engage in research projects throughout the training period. These projects are related to histocompatibility and HLA antibodies in transplantation and possibly HLA typing in disease associations.

Seminars, Rounds and Teaching Sessions

Histocompatibility Laboratory General Meeting – Held once a month with additional meetings scheduled as required. Topics include, but are not limited to, general operational issues, laboratory safety, feedback from external proficiency testing, changes to SOPs, etc. Minutes are taken and circulated.

Histocompatibility Laboratory Senior Staff Meeting – Held once a month. Review of high level laboratory business, discussion of changes to be implemented into the laboratory, review of laboratory performance. Budget and management issues will also be discussed. Strategic planning is also incorporated into these meetings. Minutes are taken and circulated.

Histocompatibility Laboratory Teleconference Seminar – Held once a month. Presentations selected from the most current Georgetown Teleconference seminar series. These teleconferences are recorded and historic presentations are available for continuing education.

Transplant Fellows Lecture Series – Weekly, between August to May. Presentations by University of Alberta faculty on multiple topics related to transplantation.
Alberta Transplant Institute Lecture Series – ATI Lectures are weekly, between September to June. Presentations are given by University of Alberta faculty or invited speakers on multiple topics related to transplantation.

Laboratory Medicine Rounds – LMP Rounds are weekly, between September to June. Presentations are given by University of Alberta faculty, LMP graduate students, or invited speakers on multiple topics related to laboratory medicine.

SPECIALTY TRAINING REQUIREMENTS

Eligible candidates must have completed a Ph.D. from an accredited institution in the field of Immunology followed by a 2-3 year post-doctoral fellowship in Transplant Immunology and/ or Histocompatibility.

DURATION AND LOCATION

Two years of full time training in the Histocompatibility laboratory. The fellow will be primarily located at the UAH Histocompatibility laboratory with a short rotation (3-4 weeks) in a center where bone marrow/ stem cell transplants are performed and is supported by a well-respected Histocompatibility laboratory. The preference would be to rotate through a larger center where the fellow can experience the management of larger sample volumes and staff.

EVALUATION

The fellow’s learning will be evaluated on an ongoing basis through weekly meetings with the director on service. Performance at the bench will be evaluated based on the fellow’s performance in assessing proficiency testing samples. Further feedback will also be obtained from the Quarterly reports made to document short-term goals and accomplishments.

RESOURCES AND PERSONNEL

Space and Workload

The fellow will be allocated a desk and a computer in an office that is to be shared with the laboratory scientist. All bench work will be performed at the respective areas of the laboratory. The workload may vary from day to day but the fellow will be expected to be present for regular workdays: Monday to Friday between 9 am and 5 pm unless otherwise indicated.
Faculty responsible for Histocompatibility and Immunogenetics Fellow

Members of Histocompatibility and Immunogenetics Subspecialty Practice at the UAH sites:

Dr. Patricia Campbell
Dr. Luis Hidalgo

ACCREDITATION AND CERTIFICATION

Upon successful completion the fellow will be issued a certificate from the office of Post Graduate Medical Education, Faculty of Medicine, University of Alberta, affirming that 24 months of subspecialty training have been successfully completed.

RECOMMENDED READING and EDUCATION RESOURCES