

## AMERICAN SOCIETY FOR HISTOCOMPATIBILITY & IMMUNOGENETICS

### REQUIREMENTS FOR HISTOCOMPATIBILITY & IMMUNOGENETICS TRAINING PROGRAMS

(Board Approved: 08/25/2011)

**Duration:** Two Years

**Pre-requisites:** Completion of pathology residency or other eligibility requirement for post-graduate medical studies

Post-graduate MD: Board-eligible in Clinical Pathology or Anatomic/Clinical Pathology

Post-graduate PhD: Two years of postdoctoral training or experience in Immunology or equivalent, as defined by the Center for Medicare and Medicaid Services (CMS), and as reflected in the ASHI Standards

#### **Learning Objectives and Expectations**

##### **Patient Care:**

Candidates must demonstrate a satisfactory level of diagnostic competence and the ability to provide appropriate and effective consultation in the context of histocompatibility testing for solid organs, transplant immunology, and bone marrow or human stem cell transplantation (BMSC). These skills will be determined by formal and informal evaluation, taking and successfully passing the American Board of Histocompatibility & Immunogenetics (ABHI) and/or other Histocompatibility and Immunogenetics specialty Board examination(s) (optional for AP/CP or CP board eligible MD candidates), and the development of the requisite training portfolios for evaluation by the American Society for Histocompatibility & Immunogenetics' Directors' Training Review & Credentialing Committee.

##### **Candidates will be expected to:**

- Competently perform, utilizing the necessary technical skills, diagnostic services under faculty/technologist supervision.
- Gather essential information about patients from their medical records, personal physicians, and test interpretation.
- Develop familiarity and understanding of the principles of histocompatibility testing, high and low resolution molecular typing techniques, flow cytometry and the technical aspects necessary for determining donor-recipient compatibility for solid and hematopoietic cell transplant, as well as gain skills in assessing a patient's immune status and competency.
- Review and interpret testing results for presentation to faculty, prior to final sign out and release of information.
- Develop an in depth knowledge of the action of common immunosuppressive agents, most widely used immunosuppression protocols for solid organ and stem cell transplant management, and of the laboratory tests used in determining the effectiveness of those agents and protocols in managing graft rejection.
- Make informed decisions about specimen testing based on patient or potential donor demographics, type of tests available in the respective laboratories, local and international transplant/histocompatibility databases and clinical judgment.
- Understand and participate in the development of antibody monitoring and treatment protocols for the pre- and post-transplant management of highly sensitized patients.
- Counsel and educate patients and their families, physicians, nurses, allied health professionals, pathology assistants, and other medical professionals when necessary.
- Develop understanding of laboratory information systems for acquiring patient clinical information applicable to organ and hematopoietic cell transplantation.

##### **Clinical and Immunological Knowledge:**

Candidates must demonstrate knowledge about established and evolving biomedical and clinical advances as they pertain to histocompatibility and transplant immunology, and the application of this knowledge to pre- and post-transplant management of individual patients.

**Candidates will be expected to:**

- Develop understanding of the disease processes involved in end stage organ disease and hematologic malignancies, as well as recognizing and monitoring for rejection of graft vs. host disease in the appropriate setting through formal lectures, seminars, professional meetings, and extensive reading of textbooks and primary literature.
- Understand the theoretical considerations of histocompatibility testing and transplant immunology, as well as the relationship of human histocompatibility with certain diseases, and in determining parentage.
- Read and understand given reference materials including selected textbook chapters, papers, testing manuals, and other literature pertinent to solid organ and BMSC transplantation.
- Develop a working knowledge of histocompatibility testing for solid organ and BMSC transplantation, principles of transplant immunology, mechanism of action of the major classes of immunosuppressive agents and their use in various regimens for rejection management in solid or BMSC transplantation.
- Develop a theoretical and practical knowledge base of the basic and clinically supportive sciences appropriate to histocompatibility testing, including pathophysiology, hematopathology, transfusion medicine, and molecular pathology.
- Formulate diagnoses based on these correlations.
- Participate in the diagnostic routine of the laboratory, including cadaveric donor call and testing.
- Rotations through the administrative transplant center, the local Organ Procurement Organization, hematopathology, transfusion medicine, and molecular pathology services are recommended.
- Develop and complete at least one research project that leads to both a presentation at a national meeting and a peer-reviewed publication

**Practice Based Learning and Improvement:**

Candidates must be able to demonstrate the ability to investigate and evaluate their diagnostic and consultative practices, appraise and assimilate scientific evidence and improve their patient care practices.

**Candidates will be expected to:**

- Apply immunological knowledge and information from the current literature to resolve current cases.
- Be able to utilize library, web-based, and other educational sources to work up cases and develop a differential diagnosis.
- Organize workload and clinical cases for optimal turn-around-time.
- Participate in weekly conferences for each of the programs serviced by the laboratory, i.e., renal, heart-lung, and bone marrow/stem cell; liver is optional.
- Analyze practice experience, and practice-based improvement, using the defined quality assurance program for the histocompatibility laboratory and transplant center specific continuous improvement and risk assessment committees as warranted.
- Utilize performance evaluations to improve practice.
- Acquire skills to engage in "lifelong" learning through appraisal and assimilation of scientific studies related to specific problems in histocompatibility testing and transplant immunology.
- Facilitate learning of medical students, residents, pathology fellows, new HLA director-in-training candidates and other health care professionals as requested.

**Systems Based Practice:** Candidates must demonstrate an awareness and responsiveness to the larger context and system of health care and the ability to call on system resources to provide optimal histocompatibility/transplant immunology services.

**Candidates are expected to:**

- Be involved with the management issues of the histocompatibility laboratory, specific to the effects of this management of other health care professionals, organizations, and societies.
- Develop a plan to arrive at an accurate, timely, cost-effective diagnosis (typing, antibody screening and identification, assessment of rejection or graft vs. host disease, etc.) that best serves the patient and does not compromise patient care.

- Understand the transplant immunologist's role and professional practices in relation to other health care professionals.
- Demonstrate ability to access, understand, and utilize, the resources, providers and systems necessary to provide optimal care. Advocate for quality patient care
- Develop a solid understanding of business practices related to the management of a transplant immunology/histocompatibility laboratory that includes, but is not limited to, developing a capital budget, assessing the laboratories technical and personnel needs, basics of human resource evaluation, and the basics of reimbursement for hospital-based and stand alone laboratories.

### **Interpersonal and Communication Skills:**

Candidates must be able to demonstrate interpersonal and communication skills that result in effective information exchange and learning with other health care providers, patients, and patient's families.

#### **Candidates are expected to:**

- Exhibit effective listening skills, the ability to follow standard operating procedures and verbal instructions.
- Interact with consultants, laboratory personnel and administration in an appropriate manner.
- Attend and participate in weekly histocompatibility laboratory meetings.
- Actively participate in clinical pathology grand rounds and clinical pathology call conferences.
- Present conferences in an organized, coherent fashion, with well planned audiovisual materials – both to the laboratory staff, and possibly as a conference for other transplant professionals.
- Provide effective and professional consultation to other clinicians and other health care professionals, demonstrating caring and respect for them.
- Develop and sustain ethically sound professional relationships with peers, colleagues, patients and patient's families.
- Work effectively as a team with the respective laboratory personnel, faculty, other director-training candidates, physicians, house staff, and all other health care providers.

### **Professionalism**

Candidates must demonstrate a commitment to fulfilling professional responsibilities and ethical principles and to sensitivity to a diverse patient population.

#### **Candidates are expected to:**

- Demonstrate sensitivity and responsiveness to patients, colleagues and laboratory personnel's culture, age, gender, sexual orientation and disabilities.
- Demonstrate commitment to ethical principles pertaining to confidentiality of patient information, informed consent, and business practices.
- Demonstrate respect, compassion and integrity.
- Demonstrate adherence to guidelines and regulations set forth by regulatory and accrediting agencies.
- Demonstrate ability to recognize and identify deficiencies in peer performance.

**Conferences: Candidates are expected to attend and actively participate in all specialty case conferences, lectures and other didactic experiences as requested by the program.**

### **Evaluation**

- The Candidate will be evaluated on a formal basis using a Program Evaluation form. Formal evaluations will assess the candidate's specific area(s) of competency including testing procedures, analytical skills, results interpretation, research development, patient care, medical knowledge, practice-based learning and improvement, interpersonal and communication skills, professionalism and systems-based practice.
- Formal evaluations will be augmented by assessment of the Candidate's daily performance, input from technologists and support staff as appropriate, and discussion throughout the specific rotations.

- Daily informal evaluation of performance will also be obtained through daily diagnostic activities, which will include but are not limited to consultations with attending physicians and house staff, test interpretation, interaction with laboratory personnel, and teaching.
- Candidates will be expected to evaluate all faculty members they worked with during each rotation and to evaluate the rotation itself. These evaluations will be submitted to the HLA Program Director(s) upon completion of a rotation.
- All formal evaluations (candidate, faculty, rotation) will be reviewed with the candidate on a quarterly and yearly basis with the program directors. The latter date will coincide with the candidate's anniversary date for entering the program and will be considered part of the candidate's yearly competency evaluation.
- Upon completion of the program, the candidate will have completed a research project in the area of histocompatibility testing, transplant immunology, or bone marrow transplantation and either has presented their findings at a national meeting, submitted it for publication in a major peer reviewed journal, or both.
- Upon completion of the program, the candidate will be expected to sit for the American Board of Histocompatibility & Immunogenetics (ABHI) and/or any other Histocompatibility and Immunogenetics specialty Board examination(s) (optional for AP/CP or CP board eligible MD candidates).
- Upon completion the candidate will have fulfilled all criteria set forth by the American Society for Histocompatibility and Immunogenetics Director Training Review Committee and/or other deeming agencies to qualify the candidate as a director for each of a HLA and Immunogenetics laboratory. These activities will be documented by the requisite case portfolios demonstrating their expertise in evaluating the technologies and categories during the training period a director training verification document signed and notarized by the program director(s).

### **Organizational structure of the program and teaching method**

- *Objective.* The Program is structured to fulfill the two-year requirement for histocompatibility and immunogenetic training over and above that required under 42CFR 493.1441 and by the United Network for Organ Sharing (UNOS).
- *Goal.* Upon completion of the program and with appropriate certification, the candidate will be able to function in the capacities of Director, Technical Supervisor, and Clinical Consultant as specified by CMS and the OPTN/UNOS Charter and Bylaws. The candidate will have developed the requisite portfolios according to the ASHI Director Training and Review Committee's guidelines (DTRC, Exhibit B) for each category and technology for which the associated institutions are accredited and will be ready for an oral interview by members of the DTRC.
- *Structure.* The development and maintenance of the program and the final evaluation of each candidate will ultimately be the responsibility of Training Program Directors. A complete 360° program evaluation will be done each year by the respective directors and changes will be incorporated as needed or as technologies change. Any amendments made to the program will be submitted to the DTRC for reference and approval.
- *Method.* The training curriculum will consist of three broad areas: a) lectures on immunology and immunogenetics, histocompatibility, solid organ transplantation, stem cell transplantation, theories of immunosuppression, and post transplant monitoring; b) practical experience in the Program's respective Histocompatibility and Immunogenetics laboratories; and, 3) by development and completion of at least one translational research project within the scope of human histocompatibility and stem cell or solid organ transplantation.

### **Selection of candidates**

1. Advertisements will be placed in the appropriate Histocompatibility, Transplantation, and Pathology periodicals announcing the program and requesting interested parties to apply.
2. The best qualified candidate(s) will be asked in for an interview with the faculty.
3. The combined faculty will vote on the interviewees and the final candidate(s) will be chosen.

## **Specific Curriculum (See Timeline - Appendix A)**

### **1. Serological Assays**

#### **a. Practical**

- Isolation of T lymphocytes from donor samples using Fluorobeads
- DTT treatment of serum for reduction of IgM antibodies
- The use of frozen lymphocyte cell trays for antibody screening
- Class I and II typing by serology using fluorescent dyes
- Reading and interpretation of registry class I and class II typing using fluorescence microscopy
- HLA typing tray preparation
- HLA typing tray production
- Sources of cells: Peripheral blood, lymph node, spleen, cell line

#### **b. Quality Control**

- Quality Control of Microvolume Dispensers
- Room Temperature Recording
- Quality Control of HLA Typing Trays
- Quality Control of Immunomagnetic Beads
- HLA: Complement Quality Control

#### **c. Equipment**

- HLA: Use and Maintenance of Microvolume Syringes
- Use and Maintenance of the Mettler Analytical Balance
- Use, Maintenance and Quality Control of Centrifuges
- Use and Maintenance of the Pipets
- Operation and Maintenance of the Dispenser
- Operation, Maintenance and Quality Control of Waterbaths

#### **d. Reagents**

- Reagent Receipt and Control
- Complement Thawing and Storage
- Reagent Preparation of Labeling

#### **e. Application**

- Organ and Bone Marrow Transplantation
- Platelet therapy
- Forensic medicine and Paternity testing
- Disease association
- Genotype analysis
- Crossmatching – evaluation of pattern of reactivity with different methods
  - (1) Methods – NIH, Amos modified, AHG, DTT
  - (2) Importance of autologous crossmatch
  - (3) Selection of appropriate target cell
  - (4) HLA antibody detection
  - (5) Algorithm for detection and analysis of reactions
  - (6) Construction of Panels
  - (7) Analysis of private and public epitope specificities
  - (8) Alternate target cells – platelets, cell lines, monocytes, endothelial cells
- Management of the highly sensitized patient

## 2. Flow Cytometry

### a. Practical

- Instrument Set-up and Calibration
- Source, Type and use of Reagent Antibodies (Monoclonals)
- Data Acquisition
- Principles of cell sorting
- Test methodologies
- Analysis on the flow cytometer
- Proper gating parameters
- Data Analysis
- Proper interpretation
- Clinical correlation
- Management of the highly sensitized patient
- Troubleshooting

### b. Quality Control

- Machine maintenance and operation
- Reagent QC

### c. Application

- Flow cytometric crossmatch
  - (1) Selection of positive and negative controls
  - (2) Interpretation of negative control values
  - (3) Establishment of "cut-off"
  - (4) Interpretation of positive crossmatch – B and/or T cell reactions
- Lymphocyte subset analysis for immunological monitoring
  - (1) Selection of antibody panel
  - (2) Analysis of results
  - (3) Analysis of % recover, viability and QC parameters
  - (4) Interpretation of results
  - (5) Clinical correlation
- Additional Flow Applications
  - (1) ATS quality control assessment
  - (2) Use in antibody identification
  - (3) OKT 3 monitoring
  - (4) Anti-OKT3 monitoring
  - (5) HLA-B 27 analysis

## 3. DNA Technology

### a. Pre-analytical preparation

- DNA extraction
- Preparation of DNA for typing
  - (1) SSP – Sequence Specific Priming
  - (2) SSOP – Sequence Specific Oligonucleotide Priming/Hybridization
  - (3) SBT – Sequence-Based Typing
  - (4) STR – Short Tandem Repeat sequencing as an engraftment monitor
- Hybridization, Washing and Detection of dot blots
- Dot blotting
- Oligonucleotide probe labeling
- PCR amplification

- Electrophoresis
- b. **Practical application to HLA**
- PCR-SSP method
  - PCR-SSOP method
  - Reverse dot blot method
  - Sequencing
- c. **Quality Control**
- Reagent QC
  - Equipment QC and maintenance
  - Control cell lines for class I and class II alleles
- d. **Application and analysis**
- Use of DNA typing in Bone Marrow transplantation
  - Use of DNA typing in Solid Organ transplantation
  - Interpretation of HLA SBT, SSP, and SSOP data
  - Disease associations with HLA class I and class II alleles
  - HLA polymorphism and human anthropology
  - Forensic use
  - Mutation detection

#### 4. **Management**

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

- Attending weekly laboratory meeting with administrator
- Participating in daily problem solving in laboratory
- Attend and participate in monthly laboratory meeting with technologists, supervisors, lab managers and director.
- Reading of training manuals
- Attending management seminars and workshops
- The following topics are incorporated in the training:
  - (1) Regulations and Standards governing Histocompatibility Laboratories
  - (2) Inspections and Accreditations
  - (3) OSHA Standards
  - (4) ESRD regulations, fee schedules, cost reports
  - (5) Legal/professional liability
- Accounting principles applied to the laboratory
  - (1) Budget preparation and monitoring
  - (2) Developing charges, cost accounting, billing
  - (3) Computing break-even point (BEP)
- Personnel Management
  - (1) Recruitment, salaries, and fringe benefits
  - (2) Defining job descriptions, objectives, responsibilities
  - (3) Training and continuing education
  - (4) Personnel evaluations
- 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

## 5. **Optional Ancillary Rotations**

- Hematopathology
- Transfusion Medicine
- Molecular Pathology

## 6. **Research**

Candidates will be involved in research projects throughout the training period. These projects must be related to immunogenetics, histocompatibility, immunopathology of transplant patients, hematopathology (stem cell transplantation), molecular pathology, and/or transplant patient management. The goal of a least one of these projects is to present a poster or podium presentation at a national meeting and submit a written manuscript to a peer-reviewed journal.

## 7. **Training Conclusion**

- a. Papers and/or abstract submitted for peer-review
- b. Completion and submission of case portfolios
- c. Registration for the ABHI and/or other Histocompatibility and Immunogenetics specialty Board examination(s) (optional for AP/CP or CP board eligible MD candidates)

### **Regularly Scheduled Lectures and Meetings**

- a. **Solid Organ Transplant Meeting** – Review of cases by Transplant Surgeons, Nurses, Pathologists, Social Workers and other transplant professionals.
- b. **Bone Marrow Meeting** – Review of cases by Transplant Surgeons, Nurses, Pathologists, Social Workers and other transplant professionals.
- c. **Management and Supervisor Meeting** – Progress reports and troubleshooting issues are discussed in these meetings.
- d. **Test Results Review** – The candidate will discuss the results of clinical tests with the laboratory director or manager.
- e. **Research Meeting/Journal Club** – The candidate will meet with the scientific mentors to discuss the progress of the research projects.

### **On-going Activities Throughout the Training**

- a. Lectures, seminars in clinical and basic immunobiology (See suggested topics - Appendix B)
- b. Clinical research/development project(s): Clinical research is encouraged, but primary emphasis should be on clinical testing. Ongoing research might be about 20-25% of the trainee's time.
- c. Additional responsibilities, eg. provision of "on-call" coverage, assistance to lab director, etc., may be designated by individual training programs, particularly if the institution is funding the training fellowship equivalent to a resident or "house staff" position.

### **Continuing Education**

- ASHI Annual Meetings
- ASHI Regional Workshops
- AFDT Specialist Course

- UNOS Regional Meetings
- Transplantation-related Meetings
- Other meetings pertinent to candidate's research interests

### **Program Funding.**

Funding includes the following:

- Trainee stipend
- Material needed for research projects
- Additional continuing education and training for the following:
  - ASHI Annual Meetings
  - ASHI Regional Meetings
  - AFDT Specialists Course
  - UNOS Regional Meetings






### **Institutional Approval.**

A letter of commitment from the institutional official to the trainee must be attached. This purpose of this letter is not only to affirm the institution intent to fund the program but also its commitment to policies of non-discrimination, institutional review board policies, and other policies, which may affect candidate selection.

**Appendix A  
Timeline of Histocompatibility & Immunogenetics Training**

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12	
<b>1<sup>st</sup> Year</b>	Basic Human and Transplant Immunology	Specimen Processing and Serological Techniques	Basics of PRA and Crossmatching	DNA isolation and SSP-Low Resolution Typing	SSP – High Resolution Typing	SSP – High Resolution Typing	Solid Organ Clinical Rotation	Sequence-Based Typing II and Engraftment Monitoring	Sequence-Based Typing II and Engraftment Monitoring	Stem Cell TSP Rotation	Flow cytometry I	Flow cytometry II	
	Quality assurance & Quality control	Flow Cytometry	Flow Cytometry	SSP-Low Resolution Typing	Sequence-Based Typing	Sequence-Based Typing	Flow Cytometry				Single antigen analysis	Single antigen analysis II	
	<b>Test result review</b>												
				<b>Case portfolio development</b>									
			<b>Management</b>										
											<b>Intro to Research</b>		

**Appendix A  
Timeline of Histocompatibility & Immunogenetics Training**

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12	
<b>2<sup>nd</sup> Year</b>	Immuno-suppression	Hematopath. Rotation	Hematopath. Rotation					Molecular pathology Rotation	Molecular pathology Rotation	Stem Cell TSP Rotation II	Preparation for ABHI Director's examination	Completion portfolios	
	Test validation	Cell mediated immune analysis	Cell mediated immune analysis								Written discussion of cases		
	Post-transplant monitoring	Densensitization Protocols	Desensitization Protocols	Solid Organ Clinical Rotation II							Completion outstanding projects	Submission to ASHI	
				Research								Submission of manuscripts	
	Test result review												
	Case portfolio development												
Management													

## **Appendix B**

### **Suggested Topics For Lectures and Seminars in Clinical and Basic Immunobiology**

#### **Basic immunobiology topics**

- Overview of cell interactions in the immune system
- Cells and organs of the immune system
- Antibody structure - isotypes, idiotypes, allotypes
- Immunoglobulin genes and gene expression
- Antigen-antibody reactions
- Major histocompatibility genes and proteins
- Mapping of the MHC genes by function and gene product
- Antigen recognition by T-cells
- The thymus in the development and differentiation of T-lymphocytes
- T cell receptor genes and proteins
- Adhesion/accessory molecules
- CD markers and nomenclature
- Antigen processing/presentation
- Cytokines and other regulatory molecules

#### **Immunogenetics**

- Review of basic principles of genetics
- Population genetics
- Immunoglobulin allotypes and other genetic matters
- Biostatistics including: Bayes theorem, probability analysis, chi square, correlation coefficient
- MHC genetics and polymorphism
- Immunoglobulin and TCR gene rearrangement; generation of diversity

#### **Basic Principles of Molecular Biology**

- Chemistry of DNA, RNA
- Gene regulation
- Transcription, translation
- Recombinant DNA technology
- Gene therapy

#### **Clinical Topics in Histocompatibility and Transplantation**

- Mechanisms of organ allograft rejection
- Immunologic tolerance to allogeneic tissue; specific and nonspecific immunosuppression
- Clinical aspects of solid organ transplantation
  - Diseases leading to specific organ failure
  - Recipient selection and preparation
  - Donor selection
  - Post-operative management
  - Follow-up procedures and outcomes
- Clinical aspects of bone marrow transplantation
  - Diseases treated by bone marrow transplantation
  - Recipient selection and preparation
  - Donor selection
  - Post-operative management
  - Follow-up procedures and outcomes
- Clinical manifestations and management of rejection
- Graft versus Host Disease
- Pathology of human allograft rejection
- Molecular basis for HLA/Disease associations
- Engraftment
- Genetic identification