International Summer School 2013

The History of HLA (I was there..)

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The History of Transplantation Immunology: Sir Peter Medawar (1915 – 1987)

- 1940s – Skin graft rejection studies - WWII
- Second graft rejected faster than first
- Tolerance to grafts after fetal exposure
- Nobel Prize in 1960
  (With Sir Frank Macfarlane Burnet)

“The human mind treats a new idea the way the body treats a strange protein – it rejects it”.
The History of Organ Transplantation: Joseph E Murray

• MD Harvard, 1943; Surgical Residency PBB
• Successful Skin Grafts, Identical Twins (WWII)
• Experimented with kidney transplants in dogs
• 1954-First Successful Living Donor Kidney Transplant (Identical Twins, Ronald and Richard Herrick)
• Immunosuppression experiments
• 1962-first unrelated Tx (1964-first deceased donor transplant
• Nobel Prize in 1990 (with E. Donnall Thomas)

Author of: "Surgery of the Soul: Reflections on a Curious Career" (2001)
Milestones in the History of Organ Transplantation and Transplantation Immunology

- **1954** First successful kidney transplant performed
- **1964** First International Histocompatibility Workshop
- **1966** First simultaneous kidney/pancreas transplant
- **1967** First successful liver transplant performed
- **1968** First successful isolated pancreas transplant and First successful heart transplant performed
- **1983** First successful single-lung transplant performed; Cyclosporine introduced
History of Histocompatibility (HLA) Testing

• 1958 - van Rood – 2 Loci; Payne – antibodies ← Pregnancy
• 1960-64 – First non-twin human kidney transplants – limited success
• 1964 - Amos – 1st Intl. Histocompatibility Workshop at Duke - Terasaki – Microlymphocytotoxicity Test – crossmatch test = prediction of immediate rejection (Class I HLA)
• 1964 – Mixed Leukocyte Culture (MLC) Test (Class II HLA)
• 1970’s HLA Typing Sera NIH Trays – not commercially available
• 1978– First AACHT (AACHT-NIAID) Standards and Lab Accreditation (Transplantation Proceedings)
• 1980s – Molecular HLA typing; flow cytometry for crossmatching
• 2000+ Single Antigen methods for Antibody Identification
• 2013 – Widespread use of “Virtual” Crossmatching
The First International Histocompatibility Workshop (IHW) June 1964

- Dr. Amos’ Laboratory, Durham, North Carolina, 23 Investigators
- Comparison of Methods
  - Agglutination, cytotoxicity, C’ dependent cytotoxicity, MLC, grafts
- Comparison of Reactions
  - HU-1 (Dausset and Ivanyi), LA (Payne and Bodmer) Four (van Rood)

The Second IHW – Leiden (van Rood) – 1965

- 77 participants, standard cell panel (JJvR), different sera and methods
- No standard nomenclature but one genetic system

The Third IHW – Torino (Ceppellini) – 1967

- 110 participants (16 teams), cells from 11 families, 476 sera
- 13 specificities identified – 2 Loci – named HL-A

The Fourth IHW – Los Angeles (Terasaki) - 1970

- Lymphocytotoxicity Test Standarized
- Sera mailed to labs for pre-workshop testing
- 11 “official” specificities (1,2,3,5, 7,8,9,10,11) + 8 workshop specificities (e.g., W27); a third locus identified (HLA-C)

The Fifth IHW – Evian (Dausset) – 1972

- HLA antigen frequencies in different ethnic/racial populations
- 10 new specificities identified (→ W32)
Early Efforts to Test Histocompatibility: Workshops, Exchanges of Sera, Comparisons of Test Methods
THE MICROLYMPHOCYTOTOXICITY TEST METHOD

- Optimum use of limited reagents (Terasaki Trays)
- Reproducibility and standardization of test conditions
Microcytotoxicity Test

Cells + Serum + C’
- Known cells – ID antibody
- Known sera – Cell typing
- Donor Cells, PT Serum = crossmatch

Elements of a good lab test
- Simple & compact
- Inexpensive/Reproducible
- Prognostic: rejection speed
  - Antibody quantity
  - Degree of match
- 1:1 relation w/ pathology
Role of HLA in Kidney Transplant Outcome (Terasaki, 1968) - (only HLA-A,B,C (Class I) known then)
PARALLEL HISTORIES of our SOCIETIES:

**ASHI:** 1972-1974 – NIH Tray Users – Serum **Exchange**
• 1975 – Incorporation/First Meeting (Birmingham AL) of the American Association of Clinical Histocompatibility Testing (AACHT); Name changed to include **Immunogenetics**
• 2013 – 1400 members, 33 countries –

**EFI:** Late 1970s, Committee of Experts in Histocompatibility (Council of Europe); founded 1985 as European **Foundation** Im. Changed to European Federation of Immunogenetics

**APHIA:** 1976 first meeting in Perth; ATTA 1977; AOH 1979
• 1983-89 name change, ASEATTA; 2009 – APHIA

**Missions:**
Exchange of Ideas, Advance Science, Education
The Sixth IHW – Arhus (Kissmeyer-Nielson) - 1975
• Genetics of the MLR (HLA-”D” – homozygous typing cells
• Relationships between HL-A loci now called HLA-A,B,C
• Antigens found on B-cells, NOT T-cells (“Ia-like”, “D-region associated)

The Seventh IHW – Oxford (Bodmer) - September 1977
• Relationship between la sera and HLA-D → HLA-DR officially defined
• More B-cell/not T-cell loci -“MT” (later DRB3/4/5) or “MB” (later DQ)

The Eighth IHW – Los Angeles (Terasaki) February 1980
• More clarifications of the MT and MB specificities
• Extensive HLA-Disease Risk associations (RA, etc.) and transplantation

The Ninth IHW – Munich and Vienna (Albert/Mayr) – May, 1984
• HLA-DQ locus formally defined; HLA-DP locus defined by PLT only
• First molecular typing (by RFLP methods)

The Tenth IHW – Princeton and New York (Dupont) 1987
• Molecular (RFLP) typing, first DNA based nomenclature (alleles)
• Reference B-cell lines
• The 11th IHW – Yokahama (Tsujii) 1991 – PCR with SSP and SSOP typing
• The 12th IHW – St. Malo/Paris (Charron) - 1996 – SBT introduced
• The 13th IHW– Princeton and New York (Dupont) 1987
• The 14th IHW – Melbourne (McCluskey) 2005
• The 15th HW – Rio de Janaro (Gerbase-DeLima/Moraes) 2008
• The 16th IHW – Liverpool (Middleton/Marsh) 2012
• The 17th IHW – San Francisco (Fernandez-Viña) 2017 – NGS, SNP, KIR
The Mixed Leukocyte Culture (MLC) Test
Typing for HLA-D using “homozygous” cells
Check for (HLA-Class II) Compatibility (early crossmatch test)
KINETICS OF MLC PROLIFERATION

Proliferation (Thousands)

Mitogen Induced Proliferation

Time course kinetics of a primary MLC response. Incorporation of tritiated thymidine by proliferating cells usually reaches a maximum at day 6-7.
MSP – “I was there”

1968 – Postdoctoral fellowship at the Institute de Pathologie Moleculaire, Paris (genetics)
1972 - Ortho Diagnostics Institute (CD3 company) – Attempts to make commercial HLA reagents
1977 – Sloan Kettering Inst. with Bo Dupont, Soo Young Yang, Malek Kamoun, Frank Christianson (John Hansen’s office) – Oxford Histocompatibility Workshop – first prenatal HLA typing – CAH, Transplant

Pollack MS et al., Prenatal diagnosis of congenital adrenal hyperplasia (21-hydroxylase deficiency) by HLA typing. Lancet 1979

1980-81 – First Description of the HLA-DP (DPB1) locus (SB = “Secondary B”)


1980s – First HLA laboratory standards
1983 – Baylor/Methods Houston (DeBakey) – also Chris Amos
Paul Terasaki (and MSP (and Paul Casperson) at the 2006 ATC
Dr. Terasaki was originally recognized as the “father” of tests to eliminate Acute AMR and
Is now known for tests to predict chronic rejection – all testing for HLA antibodies
MSP at the 2013 APHIA–HKSHI meeting (with Bill Canady & Dr. Chang (St.Petersberg) – (Bill was the source of the first HLA-A3 antibody - History of HLA personified!!)