



Gwasanaeth Gwaed Cymru
Welsh Blood Service

Significance of H&I and Impact on Organ Recipients

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Histocompatibility & Immunogenetics (H&I)



Solid Organ Transplantation



Stem Cell (Bone Marrow) Transplantation



Genetic Testing for Disease Diagnosis & Pharmacogenetics



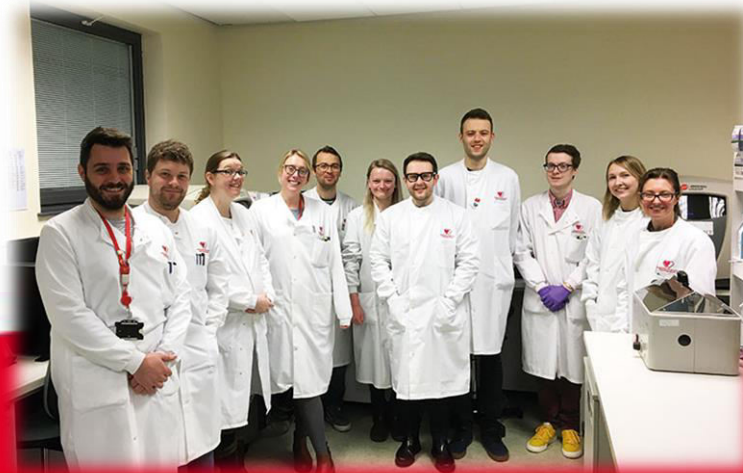
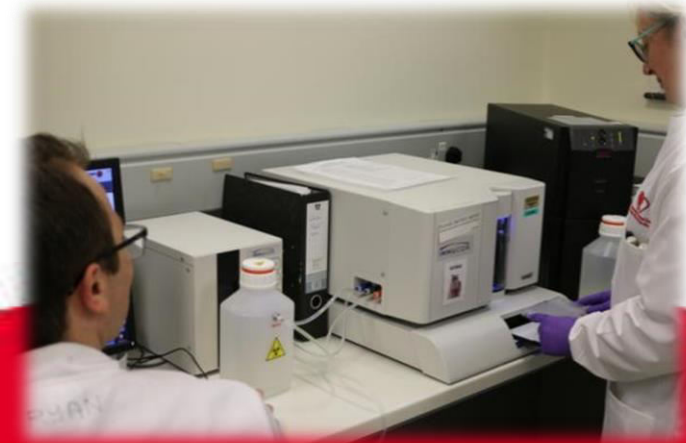
Platelet/Granulocyte Immunology



Specialist laboratories

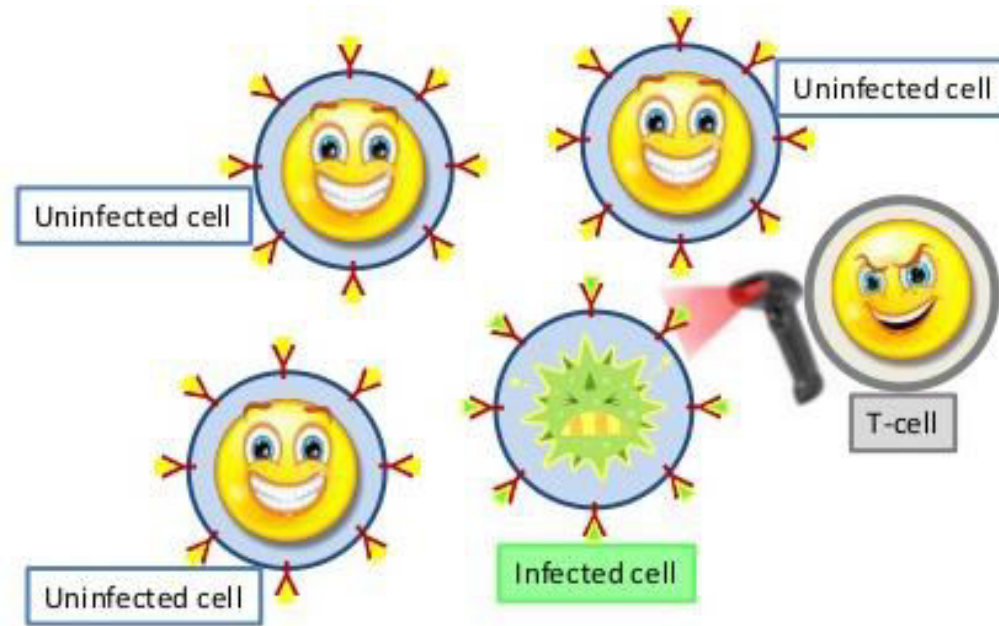
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Focus on Kidney
Transplantation



HLA Types

- HLA types (tissue types) are markers found on almost all cells of the body
- Includes cells that make up your tissues and organs
- In blood they are found on white blood cells and platelets, but not on red blood cells
- Play an important role in the immune system – signal infections



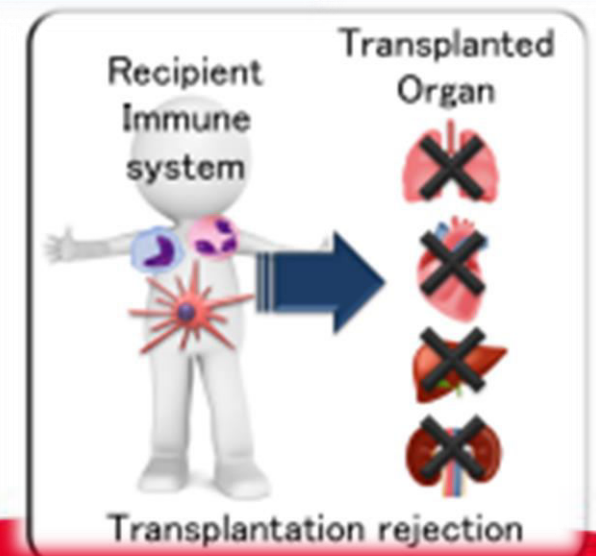
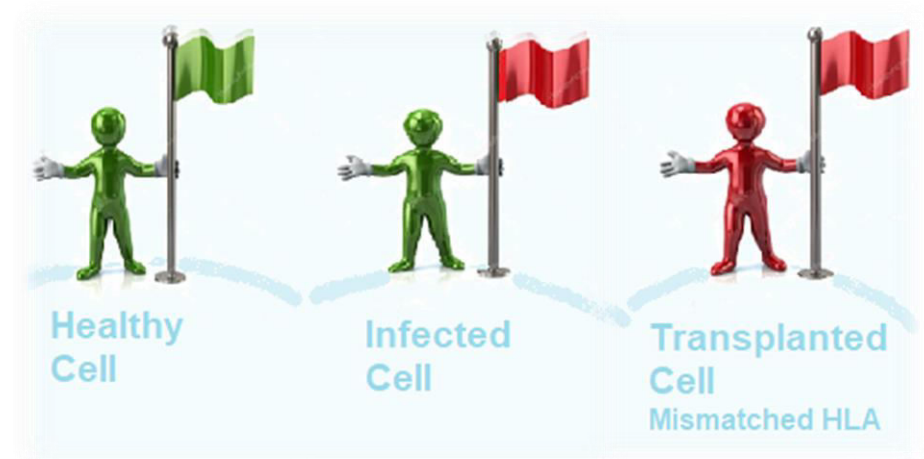
What are HLA Types for?

- Signal potential infection to produce immune response
- Acts like a flag on the cell surface
 - Indicate to the immune system whether a response is needed

Healthy cell - No response

Infected cell - Immune Response

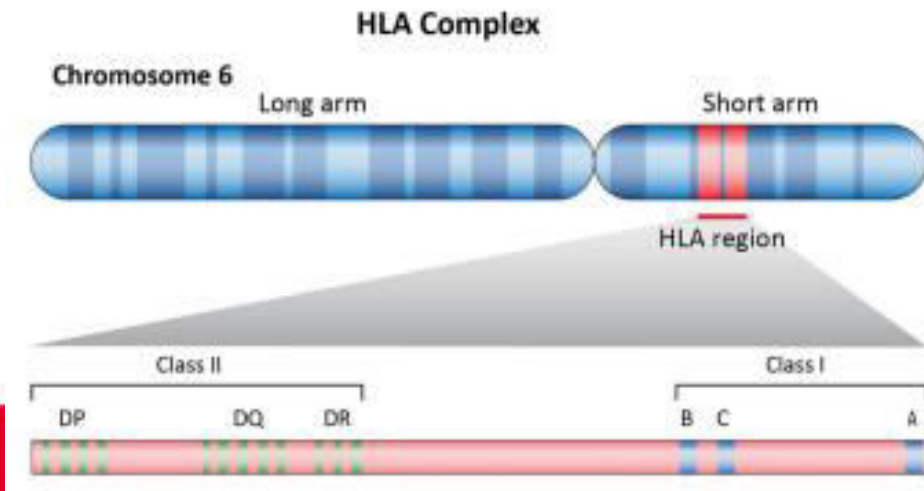
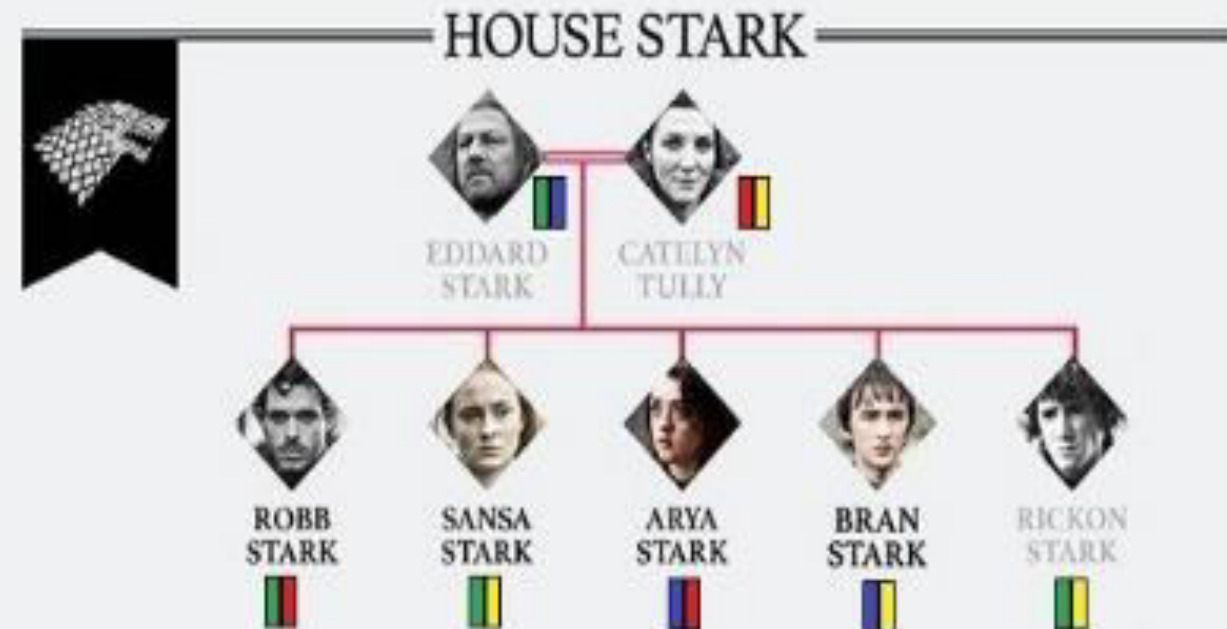
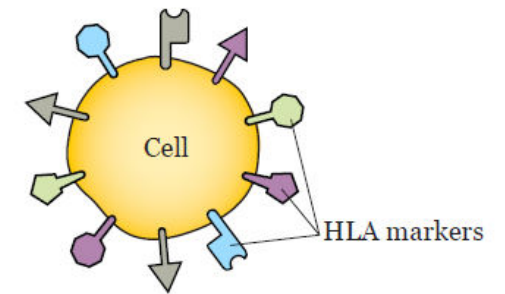
- Transplant situation
 - Differences in patient and donor tissue types = immune response = rejection
 - Need for immunosuppressive drugs



What determines HLA Type?

- HLA markers are determined by DNA
- Everyone has two sets of HLA markers
- Inherit 1 set from each parent
- 1 in 4 chance of siblings being matched

A2	A2
B51	B62
Cw1	Cw9
DR7	DR13
DQ7	DQ6



HLA types



- HLA types can be defined at different levels

- Resolution

- Dog

Broad Specificity- Dog

HLA-A2, A3; B5, B15; Cw1, Cw3; DR6, - DR52, -; DQ1,

- Spaniel

Split Specificity - Spaniel

HLA-A2, A3; B51, B62; Cw1, Cw10; DR13; DR52, -; DQ6,

- Cocker Spaniel

Allele - Cocker Spaniel

HLA-A*02:01, A*03:01; B*15:01, B*51:01; C*01:02, C*03:04;

DRB1*13:01, DRB1*13:02; DRB3:03:01, - DQA1*01:02

DQA1*01:03; DQB1*06:04, DQB1*06:03; DPA1*01:03

DPA1*02:01;DPB1*04:02, DPB1*02:01

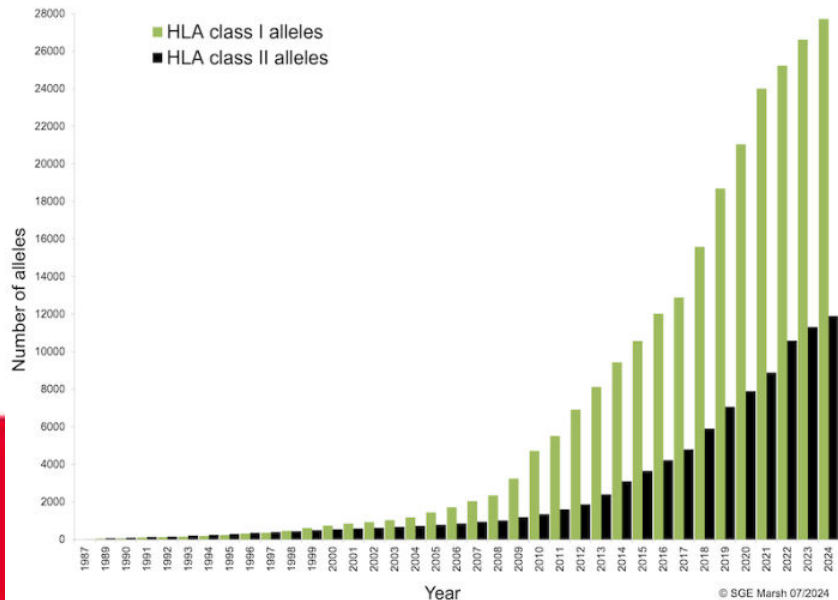
- Blue Roan



There are many different forms of HLA Types

HLA Gene	Alleles (Cocker)	Split HLA (Spaniel)	Broad HLA (Dog)
A	8,381	28	11
B	10,080	60	30
C	8,454	18	16
DRB1	3,714	20	11
DQB1	2,602	9	4
DPB1	2,607	-	-

A	B	D	C	DR	DO
A1	B5	B50(21)	Cw1	DR1	DQ1
A2	B7	B51(5)	Cw2	DR103	DQ2
A203	B703	B5102	Cw3	DR2	DQ3
A210	B8	B5103	Cw4	DR3	DQ4
A3	B12	B52(5)	Cw5	DR4	DQ5(1)
A9	B13	B53	Cw6	DR5	DQ6(1)
A10	B14	B54(22)	Cw7	DR6	DQ7(3)
A11	B15	B55(22)	Cw8	DR7	DQ8(3)
A19	B16	B56(22)	Cw9(n3)	DR8	DQ9(3)
A23(9)	B17	B57(17)	Cw10(n3)	DR9	
A24(9)	B18	B58(17)		DR10	
A2403	B21	B59		DR11(5)	
A25(10)	B22	B60(40)		DR12(5)	
A26(10)	B27	B61(40)		DR13(6)	
A28	B2708	B62(15)		DR14(6)	
A29(19)	B35	B63(15)		DR1403	
A30(19)	B37	B64(14)		DR1404	
A31(19)	B39(16)	B65(14)		DR15(2)	
A32(19)	B39(16)	B67		DR16(2)	
A33(19)	B3901	B70		DR17(3)	
A34(10)	B3902	B71(70)		DR18(3)	
A36	B40	B72(70)			
A43	B4005	B73		DR51	
A66(10)	B41	B75(15)		DR52	
A68(28)	B42	B76(15)		DR53	
A69(28)	B44(12)	B77(15)			
A74(19)	B45(12)	B78			
A80	B46	B81			
	B47	B82			
	B48				
	B49(21)				



Approx. figures
June 2024



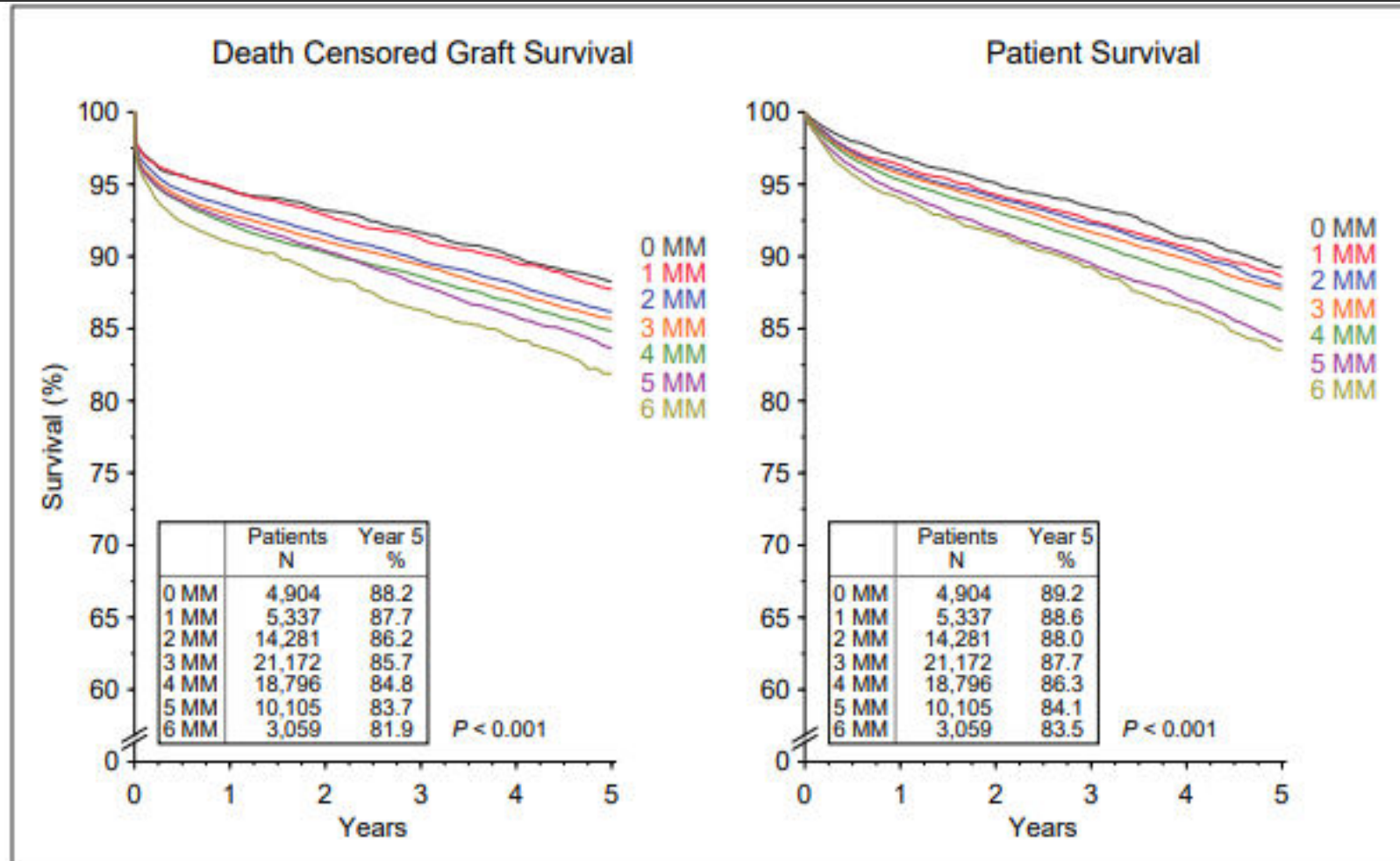
HLA Type Matching / Mismatching

- HLA matching reduces the number of differences between donor and recipient

Donor	A1	A2	B7	B8	DR3	DR4	A, B, DR Mismatch Grade
Recipient							
A	A1	A2	B7	B8	DR3	DR4	000
B	A1	A3	B7	B8	DR3	DR4	100
C	A1	A9	B5	B8	DR3	DR4	110
D	A3	A9	B5	B8	DR3	DR7	211



Collaborative Transplant Study Data – HLA matching 2005-2014

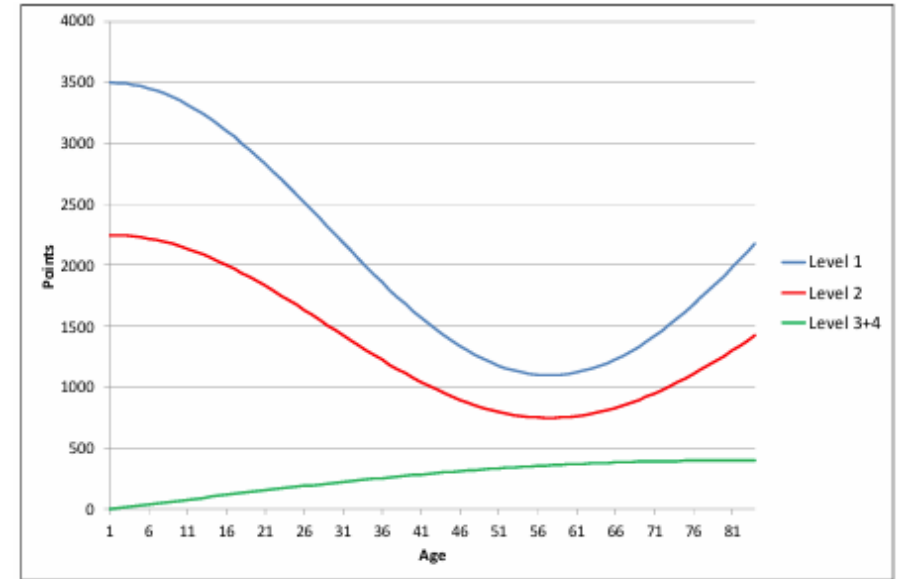


We observed a 71% increase in death censored graft failures from 0 to 6 HLA mismatches and Cox multivariate analysis showed a mean hazard ratio of 1.09 per HLA mismatch (95% CI 1.07–1.10, $P < 0.001$). The corresponding hazard ratio for patient survival was 1.04 (95% CI 1.03–1.06, $P < 0.001$).



HLA Matching in Kidney Allocation

- HLA not the only factor important in graft survival e.g. donor type, age
- Kidney allocation scheme: prioritises well matched organs for younger patients
- Due to the number of different HLA types, 000 is difficult outside of family.
- Frequency of HLA types varies in different ethnic/geographic populations
- Kidney allocation scheme: patients with rare HLA types get 'defaulted' to more common HLA types (e.g. A36 to A1) to match with more donors.

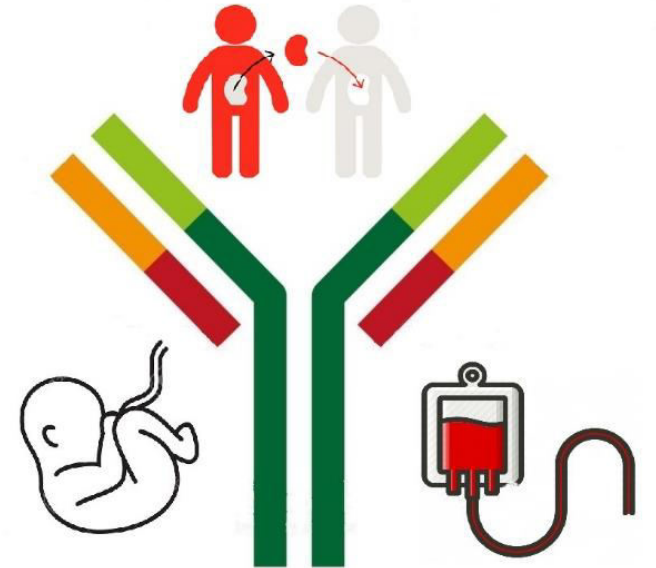


- HLA mismatched transplants are successful (immunosuppression)



Transplant Compatibility - Antibodies

- Antibodies play a crucial role in our immune system
 - Help destroy bacteria and viruses
- Individuals can make HLA antibodies if exposed to different HLA types:
 - Pregnancy
 - Transfusion
 - Transplantation
- HLA antibodies are very significant in transplantation
- Antibodies can cause rejection (even with immunosuppression) in worst case can cause irreversible damage to the transplant
- Patients with antibodies are “sensitised”



Transplant Compatibility

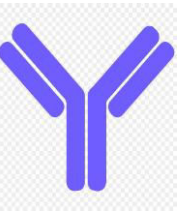
- Individuals with HLA antibodies can not receive a transplant from a donor with that HLA type
- The more HLA antibodies a patient has, the more difficult it will be to find a compatible donor
- If a patient is highly sensitised they become very difficult to transplant
- Calculated Reaction Frequency (cRF) –percentage of donors in pool of 10,000 with whom the donor is antibody incompatible (0% - 100%)



H&I Laboratory Testing



- HLA Typing
 - Patients and donors



- Antibody testing
 - Regular testing of patients

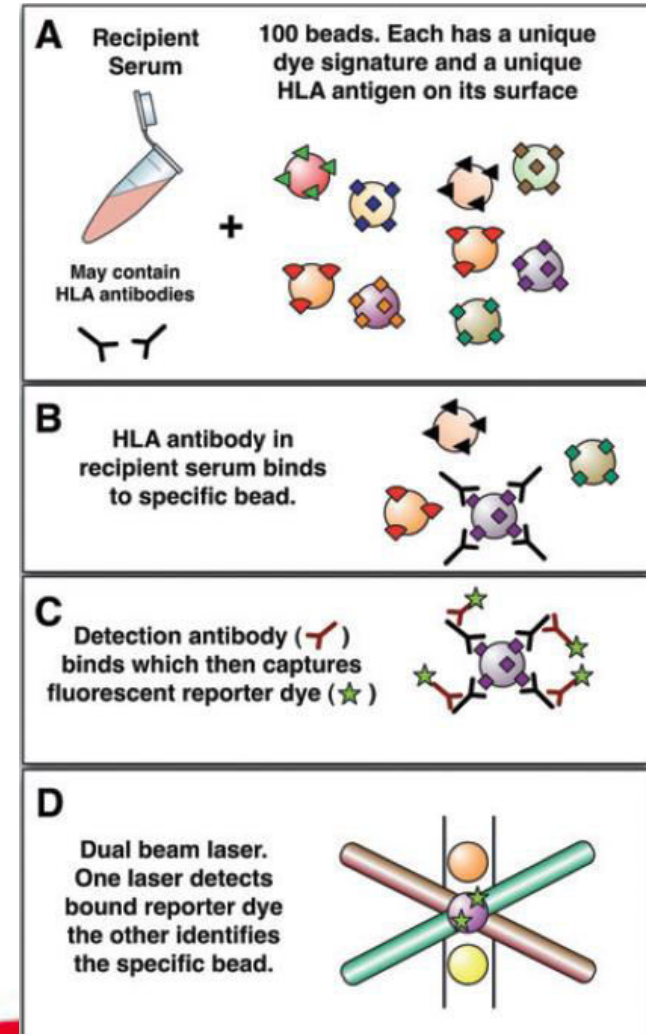


- Crossmatching
 - At time of (live/deceased) donor offer, to determine compatibility and immunological risk



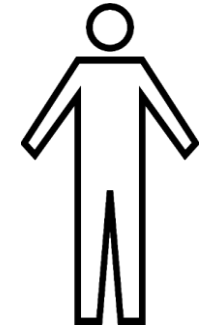
HLA Antibody Testing

- Luminex
 - Sensitive technique (Single Antigen Beads)
 - Detects “weak” and “strong” antibodies (MFI)
 - Not all detected antibodies are equal: “Weak” antibodies increase risk of transplant but it may still be possible to transplant
- Define HLA antibodies and list with OTDT as ‘unacceptable antigen’ to prevent offers from incompatible donors
- Monitor regular intervals to check for increase or decrease
- Check after sensitisation events e.g. transfusion, graft nephrectomy, reduction of immunosuppression
- Avoid **unexpected** positive crossmatches
- Determine cRF (calculated reaction frequency) – predict likelihood of receiving transplant

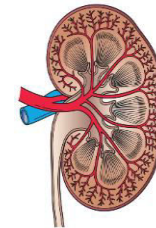


Crossmatching

- Specific test between a recipient and donor to determine compatibility
- Inform whether the transplant can go ahead
- Physical Laboratory Crossmatch
 - Mix donor cells and recipient serum to see if antibodies bind donor cells - mimics the transplant in the laboratory
 - CDC
 - Detects strong antibodies to prevent hyperacute rejection
 - Flow Cytometry
 - Able to detect strong and weaker antibodies
 - Not HLA-specific
- Virtual Crossmatch
 - Use donor HLA-type and recipient antibody results to predict crossmatch result
 - Quicker results - Reduces cold ischaemic time
 - Reduces laboratory workload on-call
 - Initial compatibility test for live donors

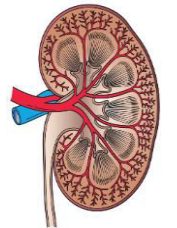


Recipient
HLA Antibodies
A2, A68, A69, B62



Donor 1
HLA Type
A1, A2, B8, B44, DR15, DR17

POSITIVE



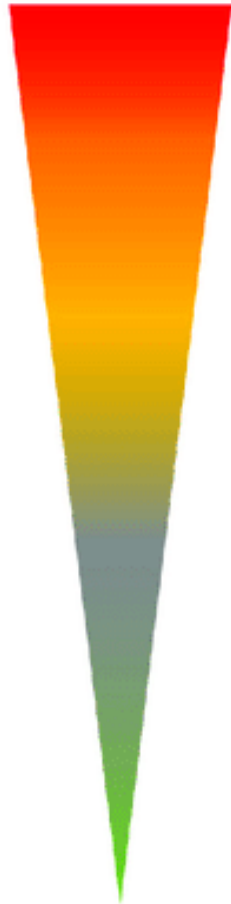
Donor 2
HLA Type
A1, A3, B7, B51, DR1, DR4

NEGATIVE



Immunological Risk

HUMORAL RISK



RISK CATEGORIES & MANAGEMENT

- 1. Day-zero DSA with positive CDC**
→ Tx impossible. Require desensitization before Tx
- 2. Day-zero DSA with positive flow and negative CDC**
→ Tx possible but very high risk for acute AMR and accelerated chronic AMR. Require adaptation of follow-up and maintenance IS
- 3. Day-zero DSA with negative flow**
→ Tx possible with risk for acute AMR, and acceptable medium-term graft survival. Require adaptation of follow-up and maintenance IS
- 4. Absence of day-zero DSA but potential cellular memory against donor HLA**
→ Tx possible with risk for AMR increased.
 - 4.a. Probably cellular memory if:**
 - historical DSA
 - pregnancy and/or previous transplant with repeat Ag
 - 4.b. Possible cellular memory if:**
 - transfusion(s) with no information on blood donors
- 5. No DSA and no cellular memory**
→ Tx possible lower risk for AMR but de novo DSA still possible
NB: patient with day-zero non DSA HLA antibodies are "good humoral responders" with possible increased risk for subsequent de novo DSA generation

HUMORAL MEMORY

SEROLOGICAL
MEMORY

CELLULAR
MEMORY

NAIVE



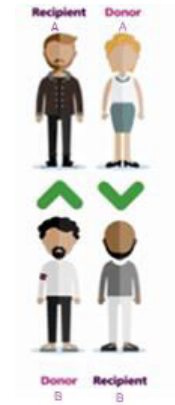
Deceased Donor Kidney Transplantation

- Patients are registered on the National Transplant Register (NHSBT-OTDT)
 - Any detected HLA antibodies are listed (Unacceptable Antigens) to ensure only compatible donors are offered to patients
 - Regular antibody testing while a patient is waiting for a transplant
- Deceased donors are HLA typed by the local tissue typing laboratory and reported to OTDT (24/7 service)
 - OTDT runs algorithm which identifies compatible recipients & kidney offered to the highest ranked patient
- Kidney is transported to patients transplant centre
 - Laboratory performs crossmatch as final compatibility check (24/7 service)
 - Provides clinical advice to medical team looking after patient

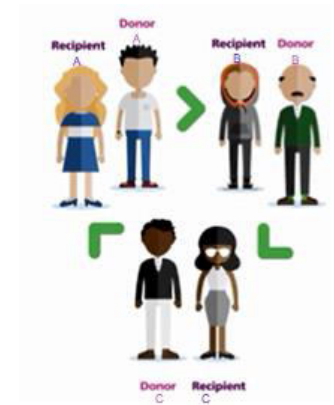


Live Donor Kidney Transplantation

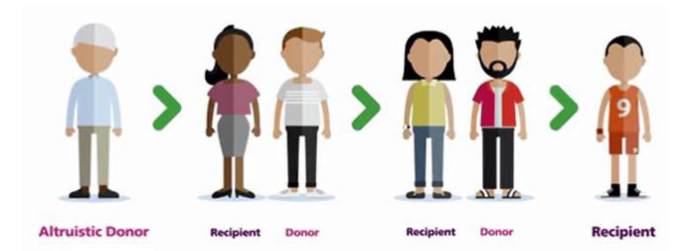
- HLA type any potential live donors
- Perform 'virtual' crossmatch to assess compatibility
- Compatible donor – proceed to laboratory crossmatch
- Incompatible live donors
 - Consider other live donors
 - Deceased donor
 - Blood group or HLA incompatible transplant – removal of antibodies prior to transplant
 - UK Living Kidney Sharing Scheme (LKSS)



2-way Exchange



3-way Exchange

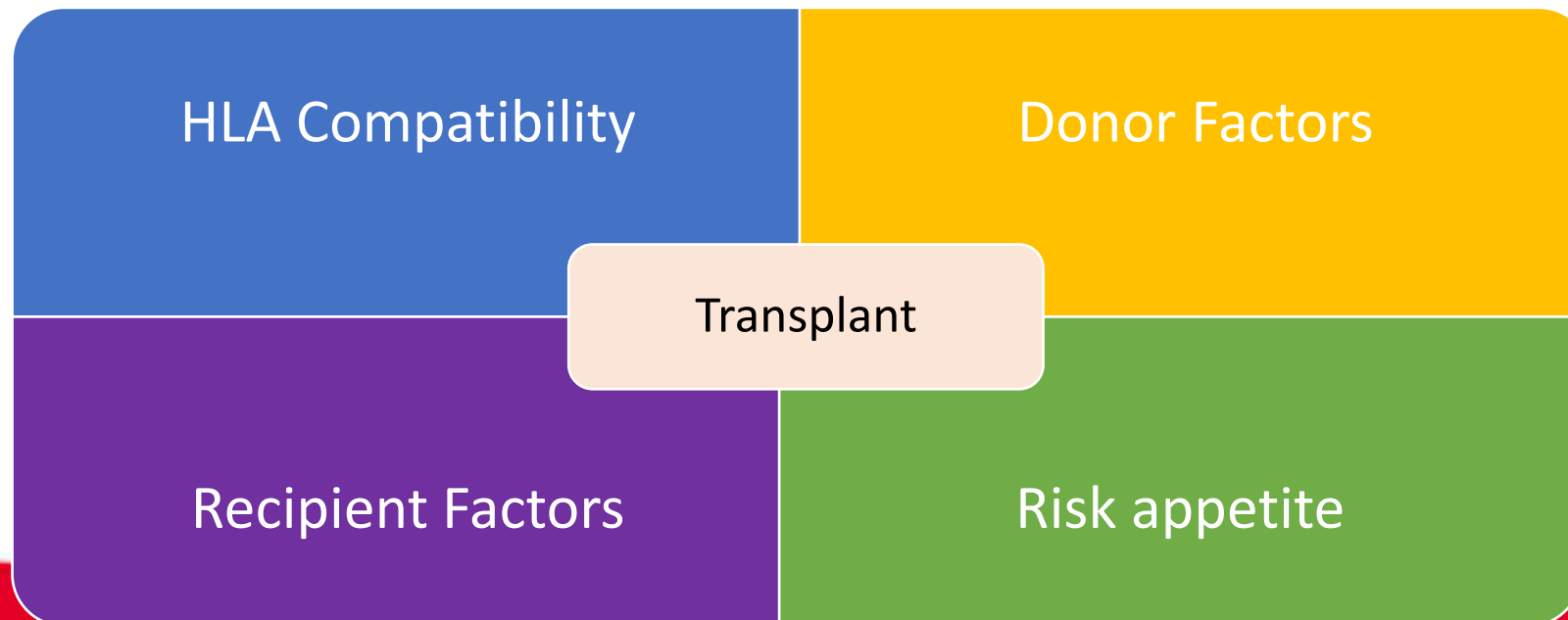


Altruistic donor chain



Individual Compatibility Assessment

- Interpretation of the laboratory results and clinical advice is very individual to specific recipient/donor
- Patients discussed in multi-disciplinary team meetings
- Our role is to advise on the immunological compatibility
- H&I testing is just one part of the decision to transplant



Summary

- HLA types are markers on the cell surface involved in the immune system - lots of different HLA types
- HLA matching is prioritised, but compatibility (avoid antibodies) is crucial to stop transplant rejection
 - HLA typing, HLA antibody testing and crossmatching
- Patients with lots of HLA antibodies are difficult to transplant (highly sensitised)
- Not all HLA antibodies are equal: different level of risk
- H&I Labs advise on compatibility and immune risk, which are important factors in the decision to transplant



Any Questions?



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