# HLA Complex

## *Clinical Utility*


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***February 23, 2012***

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# *Part I*

## Genetics & Biology

# *Part II*

## Clinical utility of HLA typing

- ✓FDA-approved uses of HLA typing
- ✓HLA matching for transplantation
- ✓HLA antibodies and transplantation

TISSUE ANTIGENS
IMMUNE RESPONSE GENETICS

Tissue Antigens ISSN 0001-2815

NOMENCLATURE UPDATE

# Nomenclature for factors of the HLA system, 2010

S. G. E. Marsh, E. D. Albert, W. F. Bodmer, R. E. Bontrop, B. Dupont, H. A. Erlich, M. Fernández-Viña, D. E. Geraghty, R. Holdsworth, C. K. Hurley, M. Lau, K. W. Lee, B. Mach, M. Maiers, W. R. Mayr, C. R. Müller, P. Parham, E. W. Petersdorf, T. Sasazuki, J. L. Strominger, A. Svejgaard, P. I. Terasaki, J. M. Tiercy & J. Trowsdale

| | | |
|---|---|---|
| *A*01010101* | becomes | *A*01:01:01:01* |
| *A*02010102L* | becomes | *A*02:01:01:02L* |
| *A*260101* | becomes | *A*26:01:01* |
| *A*3301* | becomes | *A*33:01* |
| *B*0808N* | becomes | *B*08:08N* |
| *DRB1*01010101* | becomes | *DRB1*01:01:01:01* |

(www)

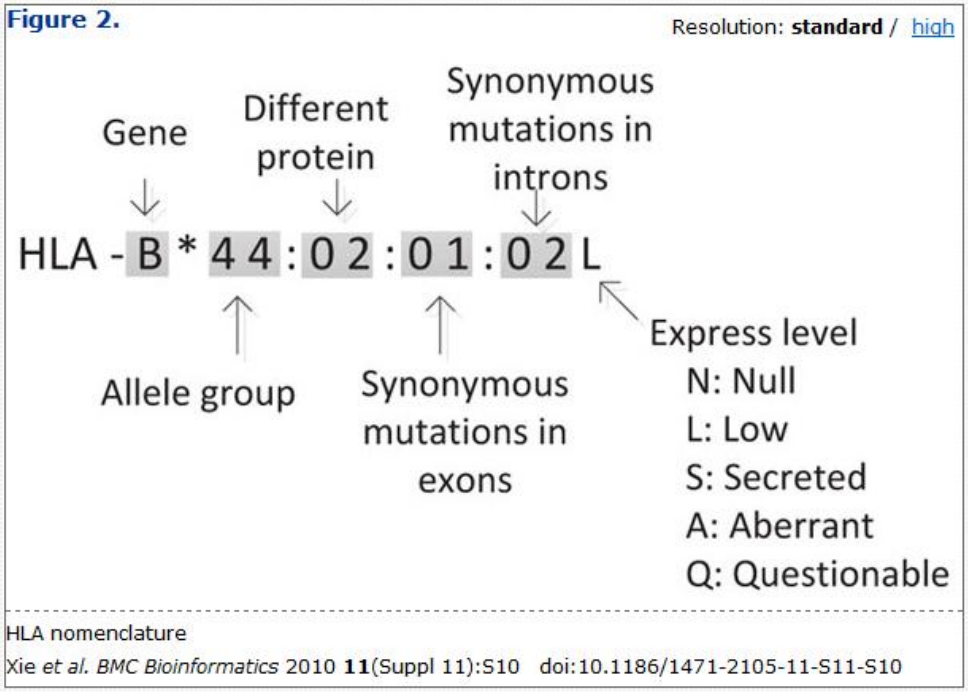
Xie *et al. BMC Bioinformatics* 2010, **11**(Suppl 11):S10
http://www.biomedcentral.com/1471-2105-11-S11

BMC Bioinformatics

RESEARCH Open Access

# Accurate HLA type inference using a weighted similarity graph

Minzhu Xie[1,2*], Jing Li[3], Tao Jiang[1*]



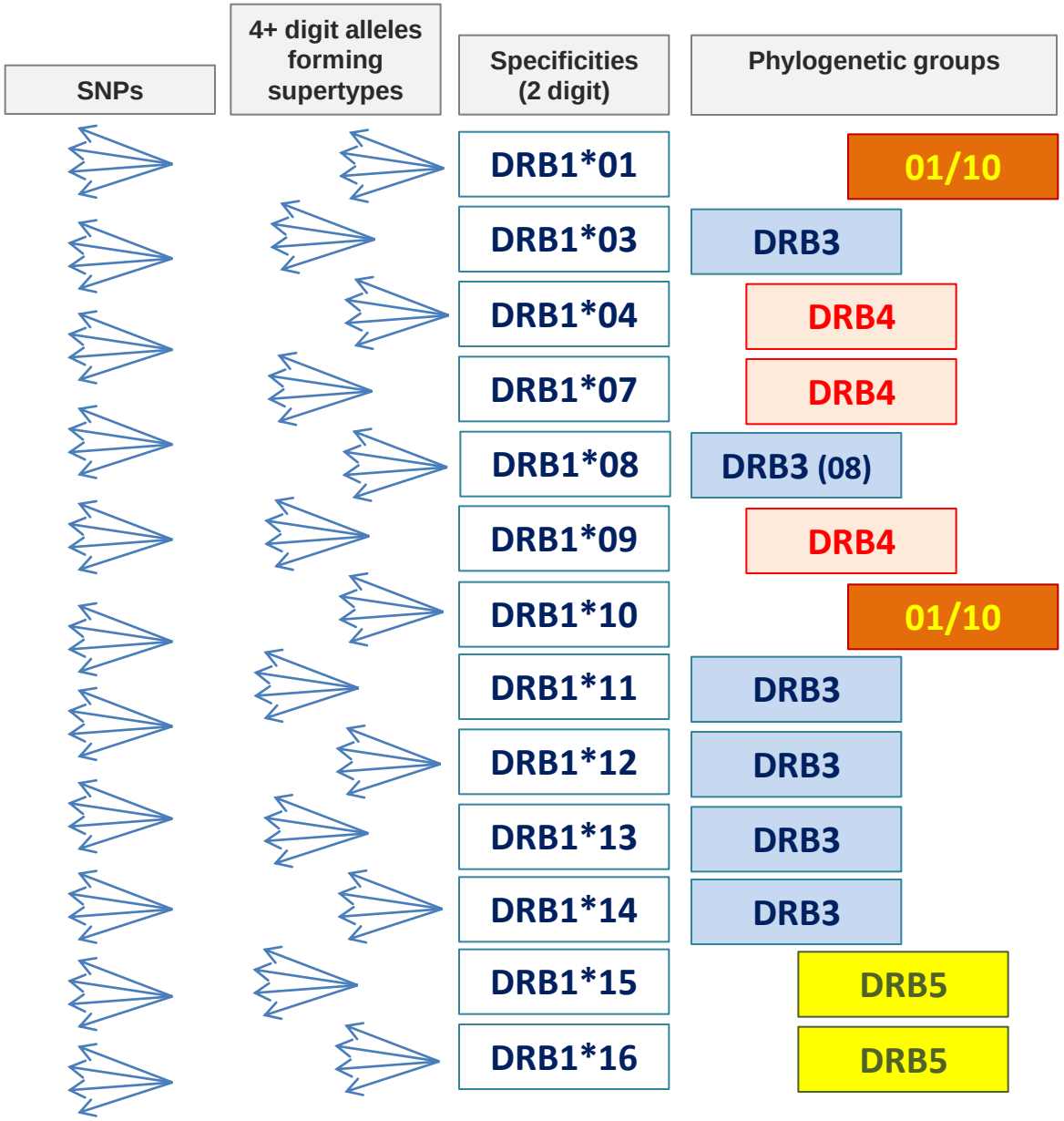

**Different levels of resolution:**

**HLA-B44 (serologic specificity / broad specificity)**

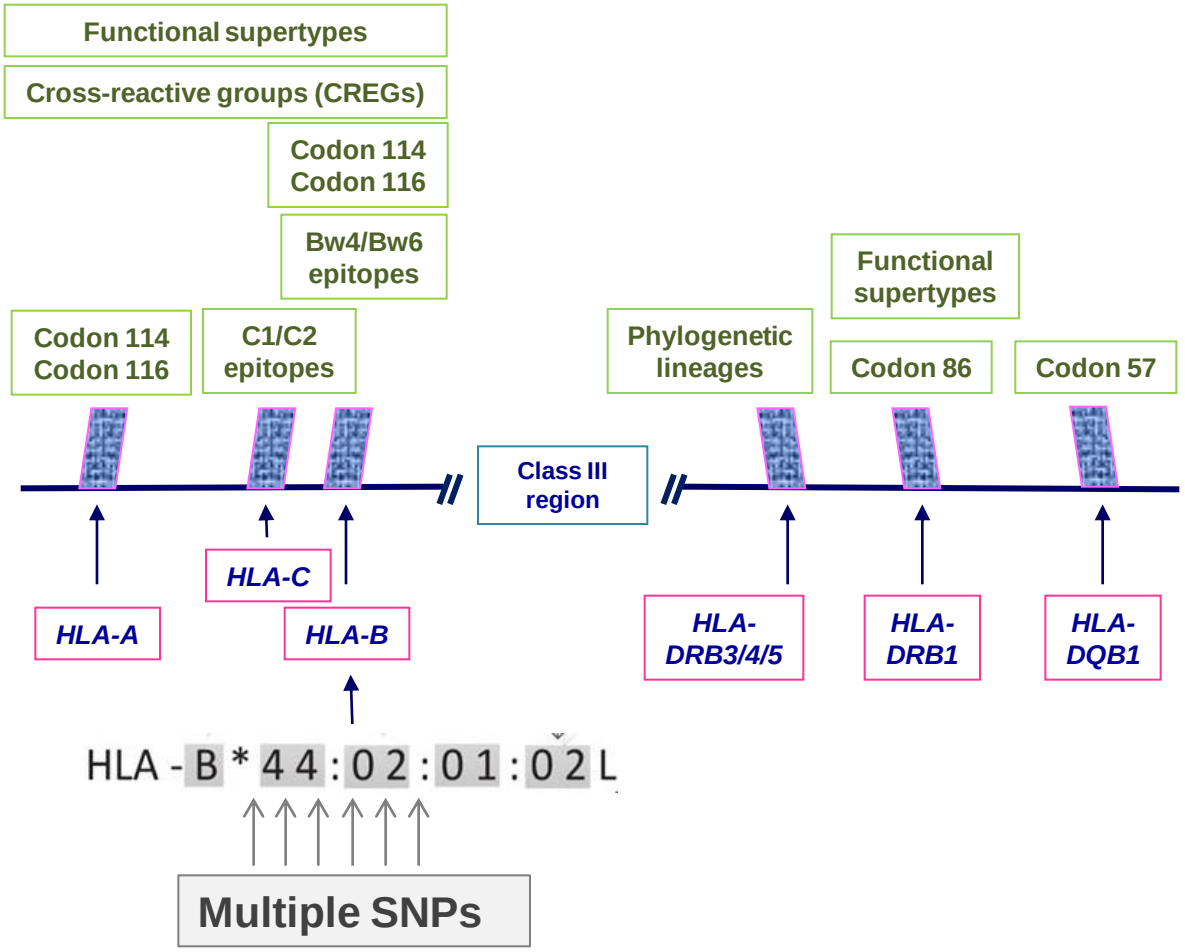
**HLA-B*44 > HLA-B*44:02 > HLA-B*44:02:04**

**two-digit four digits highest resolution**

# Functional multi-allelic HLA polymorphisms



# Functional multi-allelic HLA polymorphisms



# *Part I*

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# *Part II*

## Clinical utility of HLA typing

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- ✓HLA antibodies and transplantation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# HLA-B*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D., Jean-Michel Molina, M.D., Cassy Workman, M.B., B.S., Janez Tomažič, M.D., Eva Jägel-Guedes, M.D., Sorin Rugina, M.D., Oleg Kozyrev, M.D., Juan Flores Cid, M.D., Phillip Hay, M.B., B.S., David Nolan, M.B., B.S., Sara Hughes, M.Sc., Arlene Hughes, Ph.D., Susanna Ryan, Ph.D., Nicholas Fitch, Ph.D., Daren Thorborn, Ph.D., and Alastair Benbow, M.B., B.S., for the PREDICT-1 Study Team*

**CONCLUSIONS**

HLA-B*5701 screening reduced the risk of hypersensitivity reaction to abacavir. In predominantly white populations, similar to the one in this study, 94% of patients do not carry the HLA-B*5701 allele and are at low risk for hypersensitivity reaction to abacavir. Our results show that a pharmacogenetic test can be used to prevent a specific toxic effect of a drug. (ClinicalTrials.gov number, NCT00340080.)

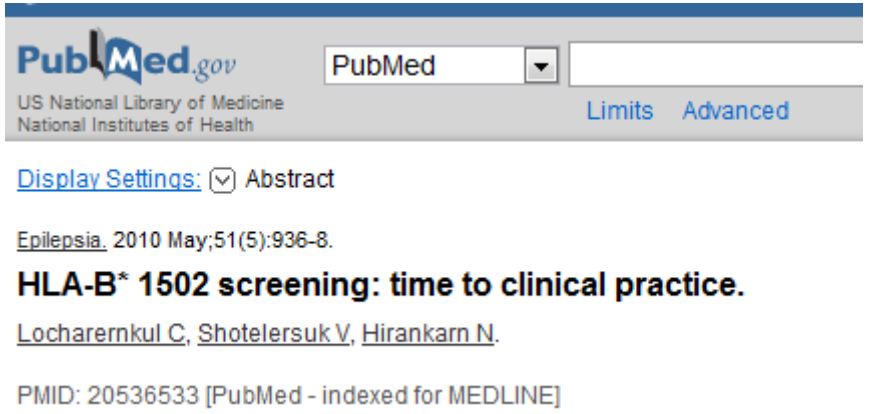
Published in final edited form as:
*Pharmacogenomics*. 2008 October ; 9(10): 1543–1546. doi:10.2217/14622416.9.10.1543.

# Carbamazepine, *HLA-B*1502* and risk of Stevens–Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations

**P Brent Ferrell Jr**[1] and **Howard L McLeod**[1,2,†]

1*University of North Carolina, Institute for Pharmacogenomics and Individualized Therapy, UNC Schools of Pharmacy and Medicine, and the Lineberger Comprehensive Cancer Center, USA*

2*University of North Carolina, Campus Box #7360, Chapel Hill, NC 27599−7360, USA Tel.: +1 919 966 0512; Fax: +1 919 966 0644; E-mail: hmcleod@email.unc.edu*



Somkrua *et al. BMC Medical Genetics* 2011, **12**:118
http://www.biomedcentral.com/1471-2350/12/118

BMC
Medical Genetics

RESEARCH ARTICLE Open Access

# Association of *HLA-B*5801* allele and allopurinol-induced stevens johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis

Ratchadaporn Somkrua[1], Elizabeth E Eickman[2], Surasak Saokaew[3], Manupat Lohitnavy[4] and Nathorn Chaiyakunapruk[1,4,5,6*]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## HLA-A*3101 and Carbamazepine-Induced Hypersensitivity Reactions in Europeans

Mark McCormack, B.A., Ana Alfirevic, M.D., Ph.D., Stephane Bourgeois, Ph.D., John J. Farrell, M.S., Dalia Kasperavičiūtė, Ph.D., Mary Carrington, Ph.D., Graeme J. Sills, Ph.D., Tony Marson, M.B., Ch.B,, M.D., Xiaoming Jia, M.Eng., Paul I.W. de Bakker, Ph.D., Krishna Chinthapalli M.B., B.S., Mariam Molokhia, M.B., Ch.B., Ph.D., Michael R. Johnson, D.Phil., Gerard D. O'Connor, M.R.C.P.I., Elijah Chaila, M.R.C.P.I., Saud Alhusaini, M.B., Kevin V. Shianna, Ph.D., Rodney A. Radtke, M.D., Erin L. Heinzen, Ph.D., Nicole Walley, B.S., Massimo Pandolfo, M.D., Ph.D., Werner Pichler, M.D., B. Kevin Park, Ph.D., Chantal Depondt, M.D., Ph.D., Sanjay M. Sisodiya, M.D., Ph.D., David B. Goldstein, Ph.D., Panos Deloukas, Ph.D., Norman Delanty, B.M., Gianpiero L. Cavalleri, Ph.D., and Munir Pirmohamed, Ph.D., F.R.C.P.

# HLA Alleles and Drug Hypersensitivity Reactions

Tracie Profaizer, *BS*

*Histocompatibility and Immunogenetics Laboratory*
*University of Utah Hospital*

**Table 1.** Drugs and their corresponding HLA alleles associated with a high-risk for SJS or TEN[15,20,44,45,46]

| Drug | Clinical Indication | HLA specificity |
|---|---|---|
| Abacavir | Antiviral | B*57:01 |
| Carbamazepine | Antiepileptic | B*15:02 |
| Allopurinol | Hyperuricemia | B*58:01 |
| Sulfonamides[a] | Antibacterial | A29, B12, DR7 |
| Oxicam[a] | Anti-inflammatory | A2, B12 |
| Nevirapine[a] | Antiviral | Cw8, DRB1*01:01 |

[a]*Weak predictive value*

# *Part I*

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## Clinical utility of HLA typing

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# What Goes on in an HLA Laboratory

**HLA typing**

**Detection of HLA antibodies**

- ✓**for transplantation**
- ✓**for blood transfusion**

**Disease association studies and other research**

# Transplantation/The HLA System and HLA Typing

< Transplantation

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# A New Era of Immunosuppression

**Full HLA matching is no longer required**

**Emphasis is on matching recipient antibodies against donor HLA antigens**

# The HLA system: immunobiology, HLA typing, antibody screening and crossmatching techniques

W M Howell,[1] V Carter,[1] B Clark[2]

[1]Department of Histocompatibility & Immunogenetics, NHS Blood and Transplant, Newcastle upon Tyne, UK
[2]Transplant Immunology, St James's University Hospital, Leeds, UK

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martin.howell@nhsbt.nhs.uk

**ABSTRACT**

The Human Leukocyte Antigen (HLA) system plays a critical role in regulating the immune response. As a consequence of its role in immune regulation and exquisite polymorphism, the HLA system also constitutes an immunological barrier which must be avoided or otherwise overcome in clinical transplantation. This introductory review provides a brief summary of the immunobiology of the HLA system and methodology for HLA typing, antibody screening and patient-donor cross-matching. This constitutes a basis for consideration of the importance of these procedures in the system-specific reviews which follow.

*J Clin Pathol* 2010;**63**:387–390

(www)

# HLA Typing

**Serological Typing**
**Using antiserum / monoclonal antibodies**

**DNA-based HLA typing**
**Conventional PCR methods: SSP, SSOP**
**Real-time PCR methods: TaqMan, SYBR Green**

**Sequence-based typing (SBT)**
**Next-generation sequencing**

My approach

The HLA system: immunobiology, HLA typing, antibody screening and crossmatching techniques

W M Howell,[1] V Carter,[1] B Clark[2]

*J Clin Pathol* 2010;**63**:387–390

**Table 1** Differences between the major PCR-based typing methods

| | PCR-SSOP | PCR-SSP | PCR-SBT gene specific | PCR-SBT group specific |
|---|---|---|---|---|
| Complete exon sequences | – | – | + | ++ |
| Definition of cis-linkages | – | + | – | ++ |
| Automation | + | – | + | ++ |
| Miniaturisation | + | ++ | ++ | ++ |

SBT = sequencing-based typing, SSOP = sequence specific oligonucleotide probing, SSP = sequence specific priming

Transfusions- und Tranplantationsmedizin Redaktion: Mariam Klouche

# HLA Diagnostic Sequencing – Conception, Application and Automation

Diagnostische HLA-Sequenzierung – Konzept, Anwendung und Automatisierung

R. Blasczyk

J Lab Med 2003; 27 (9/10): 359–368

# HLA Typing: SSP



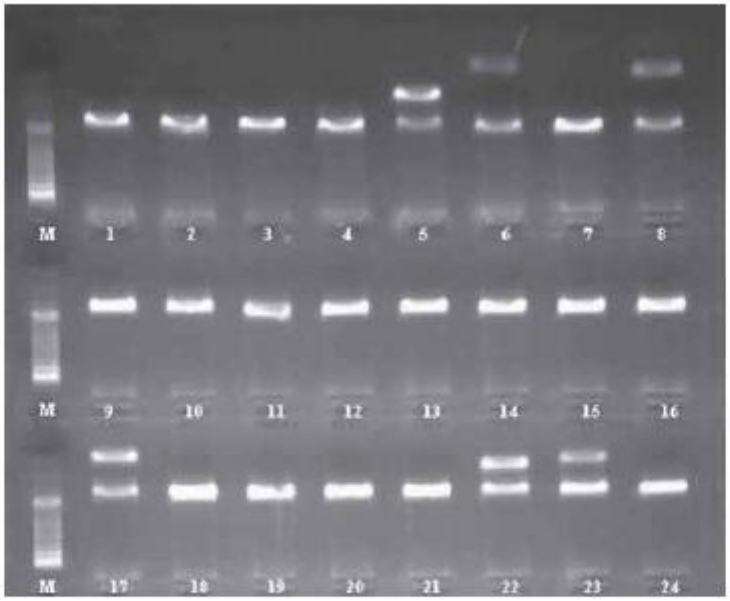



Fig. 1. HLA-DRB1 typing by PCR-SSP (low resolution).The presence of specific amplification bands in lanes 5, 6, and 17 indicates the presence of HLA-DRB1*03, and a positive reaction in lane 8 indicates the presence of DRB1*04. The specific amplification in lane 22 indicates the presence of DRB3* alleles, which are in linkage with DRB1*03 alleles. Lane 23 shows the presence of DRB4* alleles, in linkage with DRB1*04. M = size marker to identify size of amplified products (bp)

7

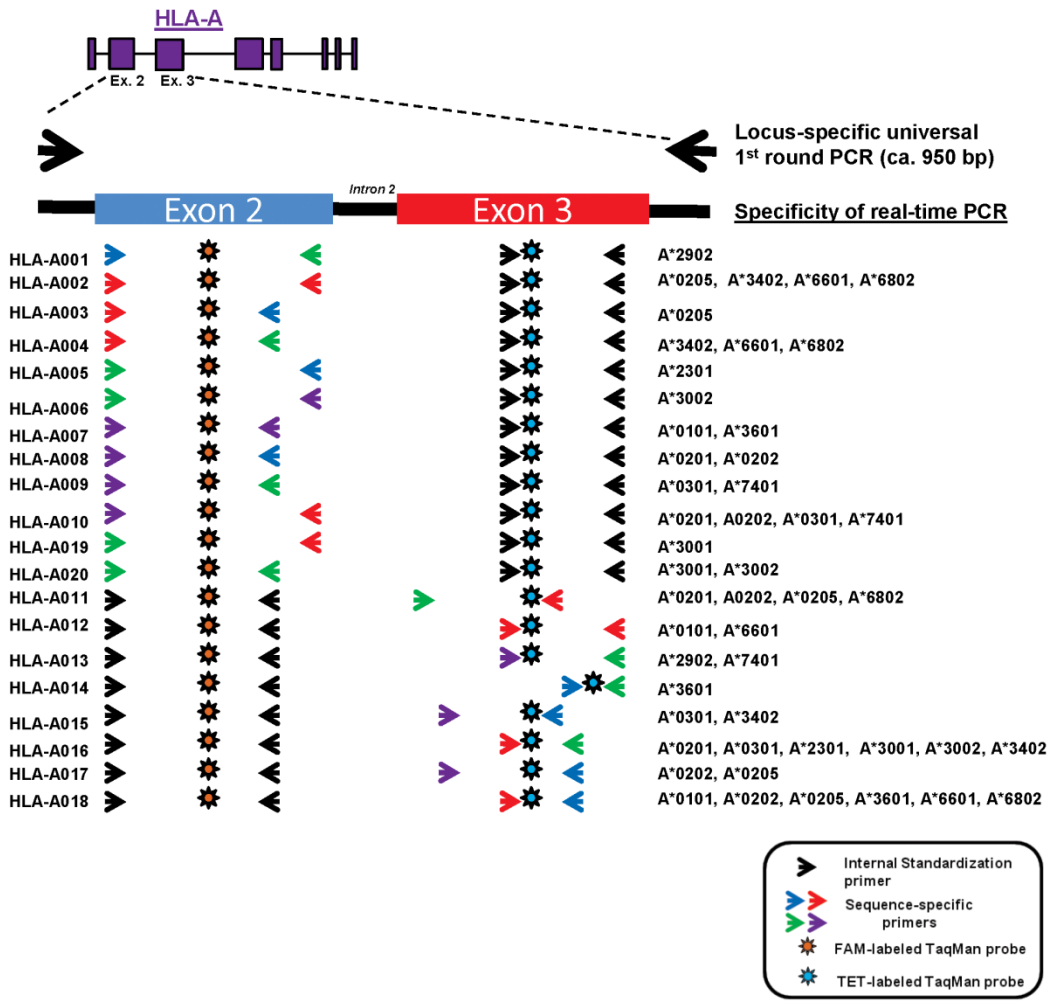
HLA Typing and Its Influence on Organ Transplantation

Stephen Sheldon and Kay Poulton

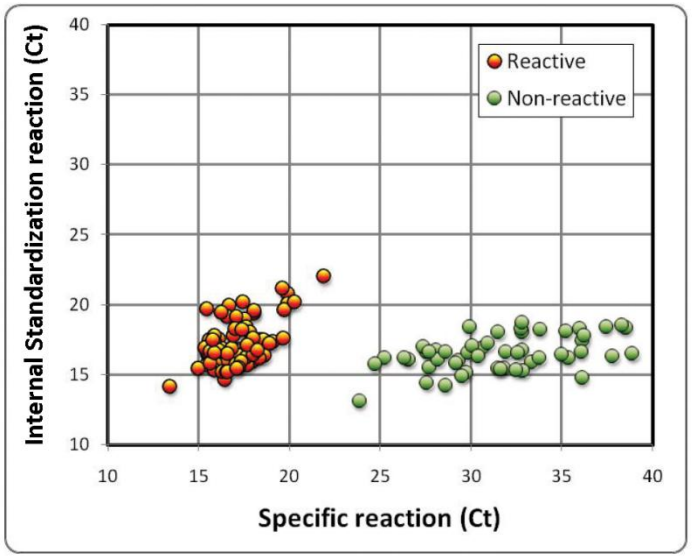
From: *Methods in Molecular Biology, vol. 333: Transplantation Immunology: Methods and Protocols*
Edited by: P. Hornick and M. Rose © Humana Press Inc., Totowa, NJ

# HLA Typing: SSP by TaqMan

a)




b)




OPEN ACCESS Freely available online
PLoS one

## High-Throughput High-Resolution Class I HLA Genotyping in East Africa

Rebecca N. Koehler[1], Anne M. Walsh[1], Eric E. Sanders-Buell[1], Leigh Anne Eller[2], Michael Eller[2], Jeffrey R. Currier[1], Christian T. Bautista[1], Fred Wabwire-Mangen[3], Michael Hoelscher[4,5], Leonard Maboko[5], Jerome Kim[6], Nelson L. Michael[6], Merlin L. Robb[1], Francine E. McCutchan[1¤], Gustavo H. Kijak[1*]

# HLA Typing: SSP by HRM

Linkage Biosciences™

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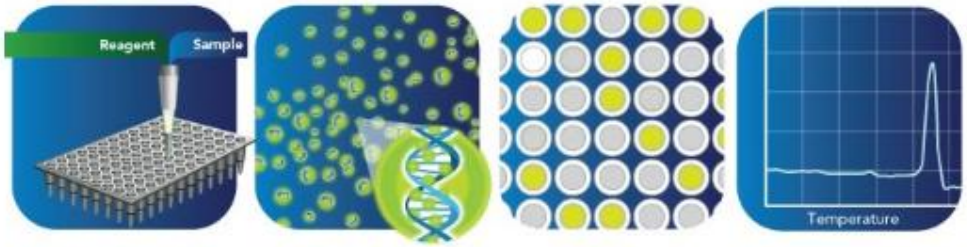
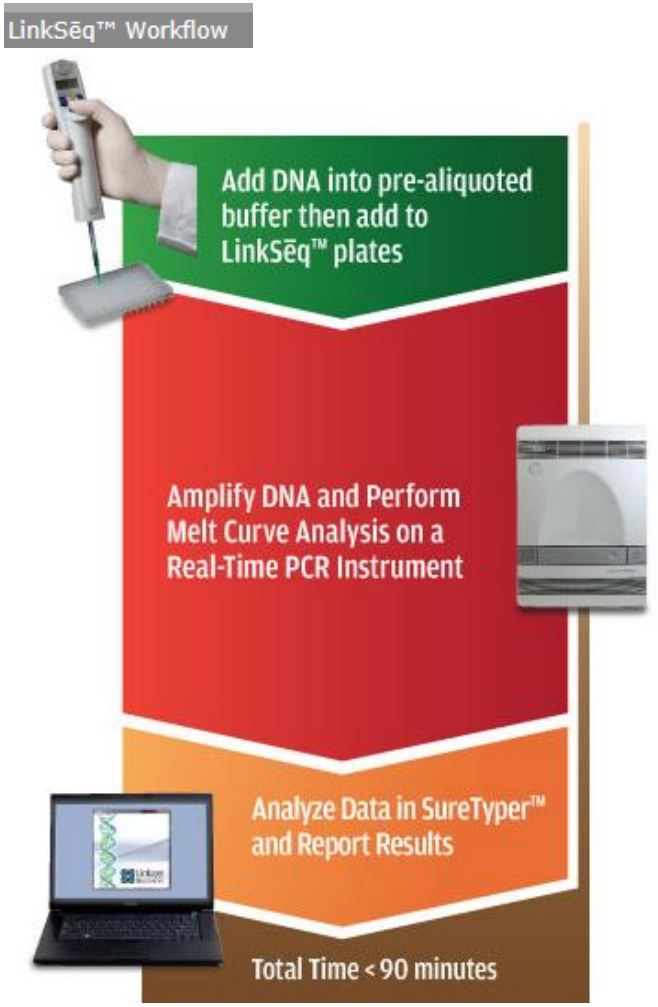
## Technology

**LinkSēq™ | Accurate, Fast, Easy HLA Typing**




LinkSēq™ is the first HLA typing chemistry developed for use on real-time PCR platforms (click here). This innovative chemistry, an end-point PCR process, uses allele specific amplification combined with SYBR® Green to detect PCR products on the instrument without electrophoresis or probing steps. Rather than separating DNA based on size, as in gel electrophoresis, melt curves identify specific DNA based on melting temperature (Tm). As double stranded DNA melts, SYBR® Green is released into solution, which causes a change in fluorescence. This change is recorded as a "melt curve". Once the PCR amplification process is completed, a melt curve analysis is performed to identify specific HLA alleles. SureTyper™ software identifies the HLA type by comparing the pattern of positive and negative reactions to known HLA sequences, simplifying the genotyping process. Linkage Biosciences tests are compatible with various plate-based real-time PCR systems.



# HLA Typing: NGS

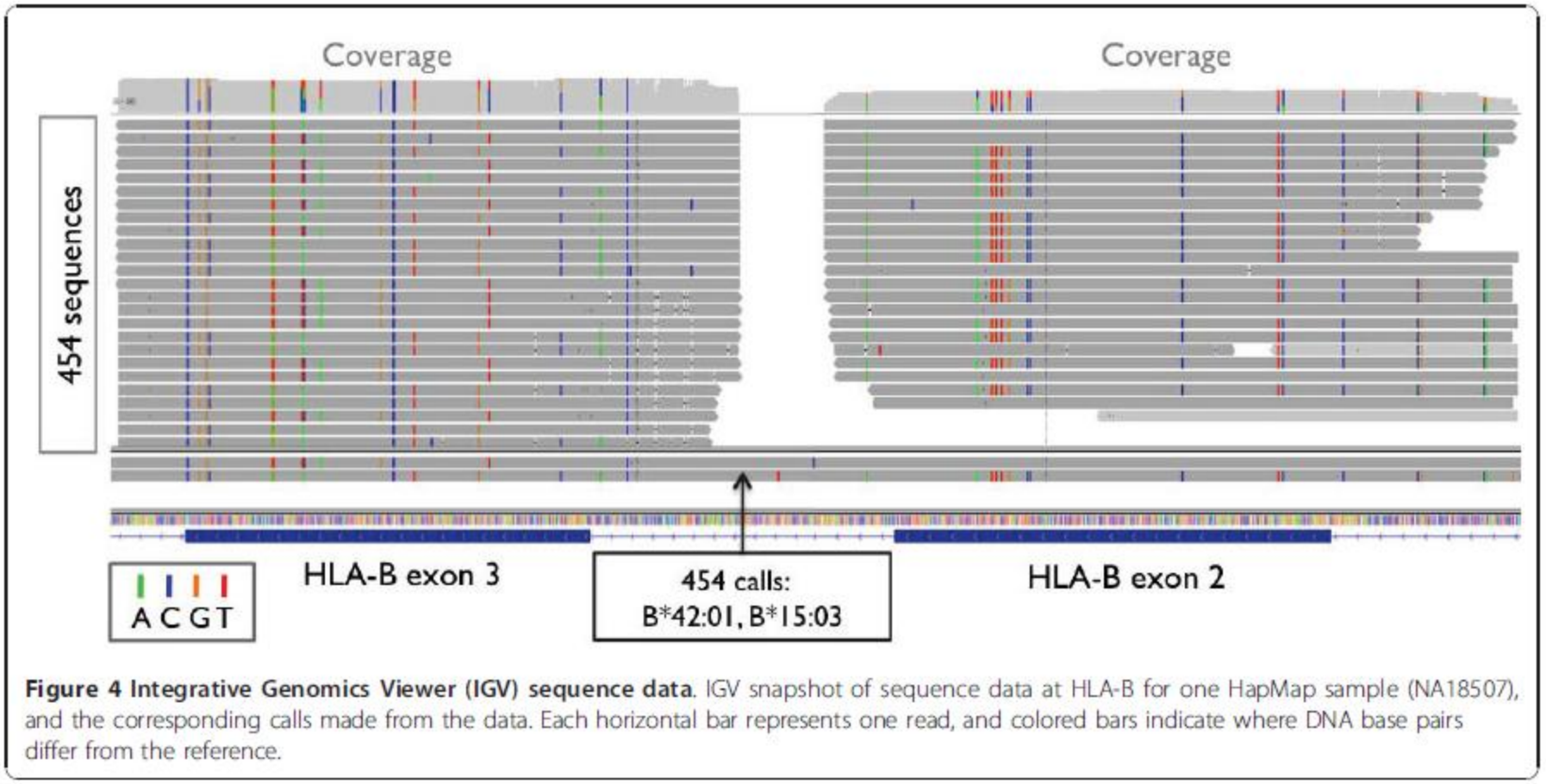



**Figure 4 Integrative Genomics Viewer (IGV) sequence data.** IGV snapshot of sequence data at HLA-B for one HapMap sample (NA18507), and the corresponding calls made from the data. Each horizontal bar represents one read, and colored bars indicate where DNA base pairs differ from the reference.

Erlich *et al. BMC Genomics* 2011, **12**:42
http://www.biomedcentral.com/1471-2164/12/42

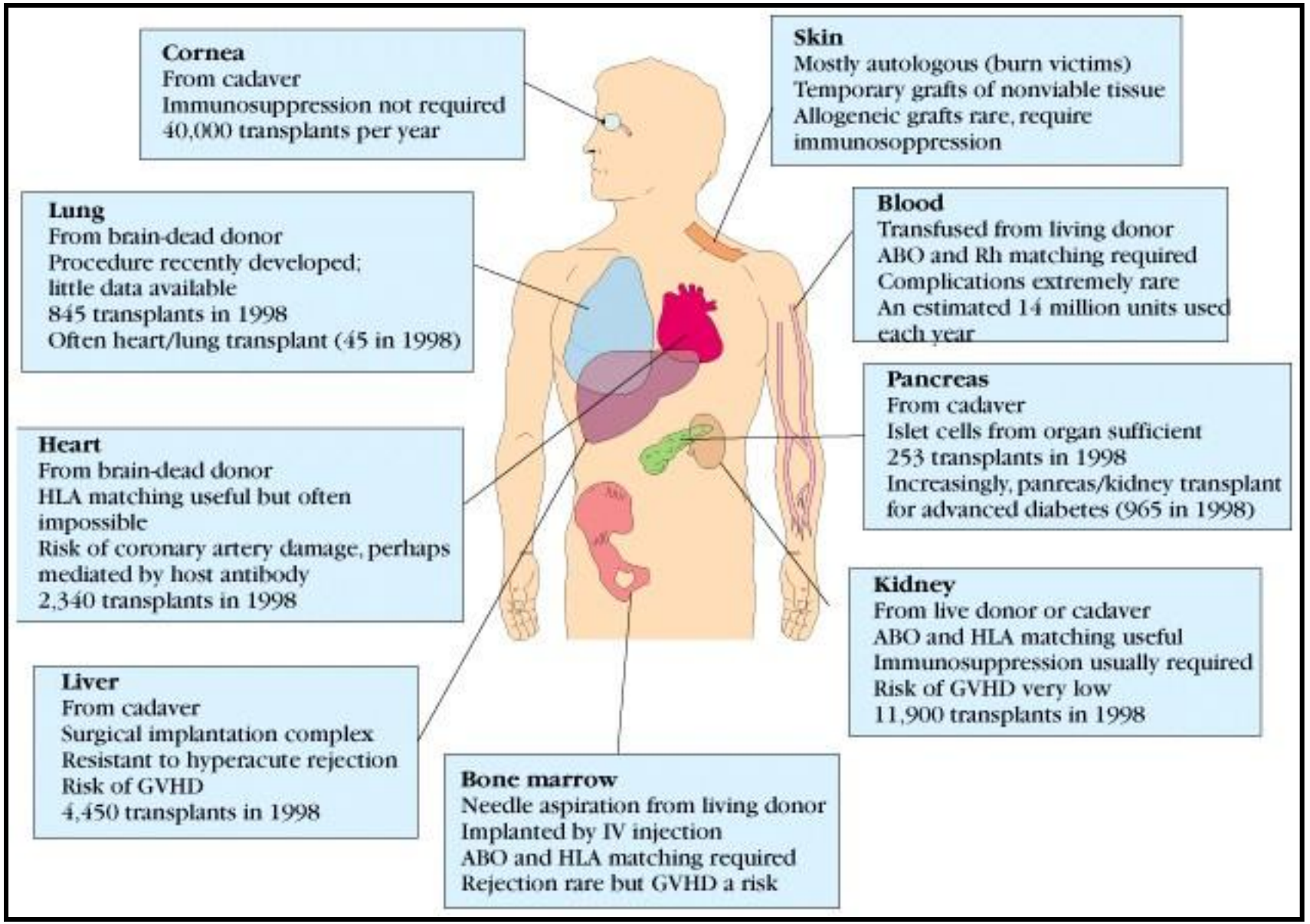
BMC Genomics

METHODOLOGY ARTICLE Open Access

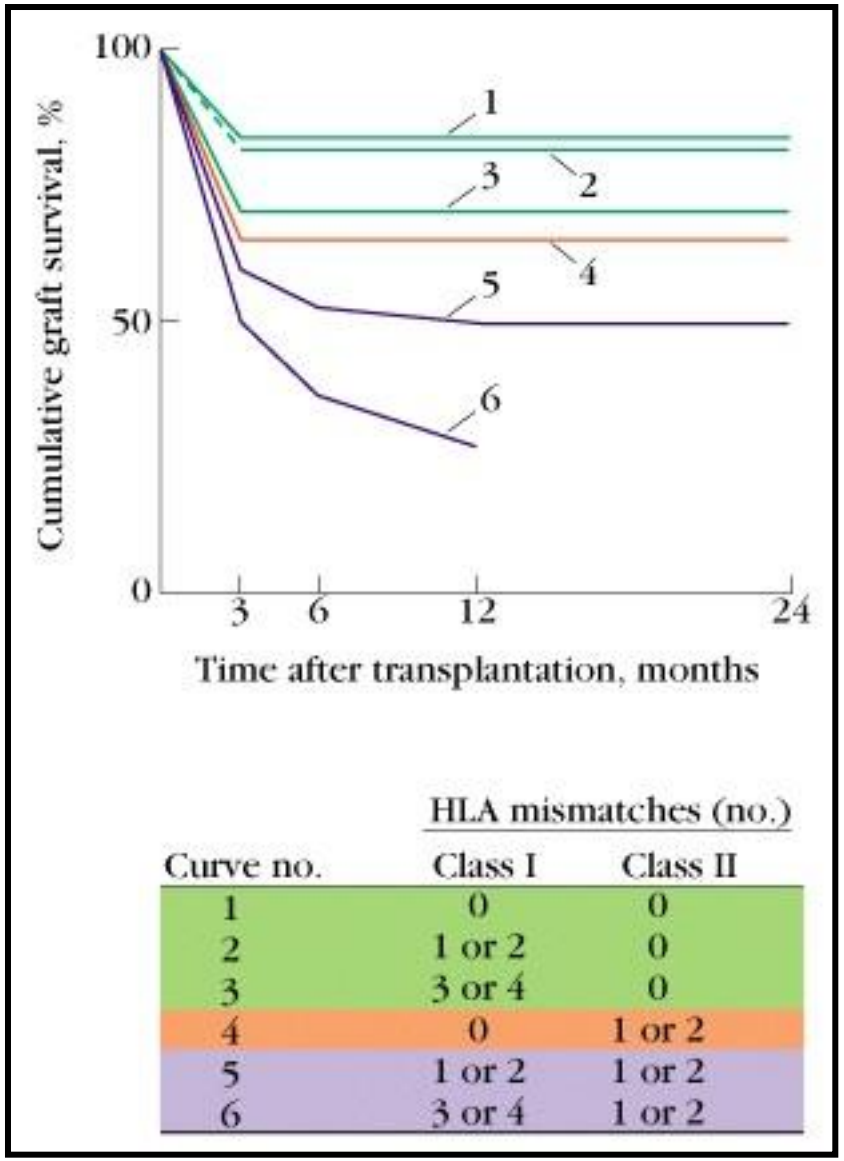
## Next-generation sequencing for HLA typing of class I loci

Rachel L Erlich[1†], Xiaoming Jia[1,2†], Scott Anderson[1], Eric Banks[1], Xiaojiang Gao[3,4], Mary Carrington[3,4], Namrata Gupta[1], Mark A DePristo[1], Matthew R Henn[1], Niall J Lennon[1], Paul IW de Bakker[1,5,6,7*]

# HLA Matching & Transplantation Success



# HLA Matching & Transplantation Success




| | HLA mismatches (no.) | |
|---|---|---|
| Curve no. | Class I | Class II |
| 1 | 0 | 0 |
| 2 | 1 or 2 | 0 |
| 3 | 3 or 4 | 0 |
| 4 | 0 | 1 or 2 |
| 5 | 1 or 2 | 1 or 2 |
| 6 | 3 or 4 | 1 or 2 |

# HLA Matching & Transplantation Success

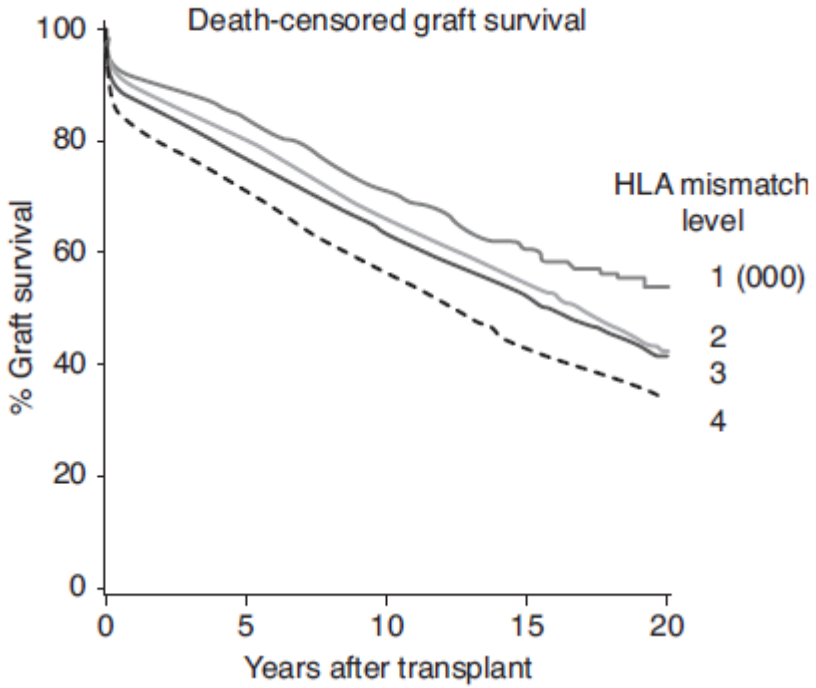



**Fig. 3.3** Effect of HLA mismatch on survival of deceased donor kidney transplants. Data from NHSBT deceased donor renal transplant database. Kaplan–Meier plot of 20-year, death-censored kidney graft survival according to level of HLA mismatch (mm) between donor and recipient where level 1 represents zero HLA mm; level 2 = 0 HLA-DR and 0/1 HLA-B mm; level 3 = 0 DR + 2 B mm, or 1 DR + 0/1 B mm; and level 4 = 1 DR + 2 B mm, or 2 DR mm, demonstrating the beneficial effect of HLA matching. HLA, human leucocyte antigen.

Chapter 3

## Transplantation immunology

Eleanor M. Bolton and J. Andrew Bradley

# HLA Matching & Transplantation Success

- HLA matching (ABO blood groups, six-antigen class I and II typing) is important in selection of suitable donors; a priority for kidney and bone marrow transplants, but less so for heart and liver transplants, and not established for small bowel and pancreatic transplants. Serological cross-match is done (donor lymphocytes and recipient serum) to detect circulating anti-HLA antibodies—likelihood of hyperacute rejection.
- Incompatibility between the donor graft and recipient for antigens encoded by genes of MHC is the most important cause of rapid graft rejection. Long-term (20 year post-transplant) graft survival correlates with level of HLA mismatch.

Chapter 3

## Transplantation immunology

Eleanor M. Bolton and J. Andrew Bradley

# HLA Matching & Transplantation Success

**Together with ABO, CMV compatibility and negative xM:**

**Absolute requirement in HSCT engraftment (but GvL?)**
**Other considerations:** donor age and gender, KIR matching
**Required for increased success of kidney Tx**

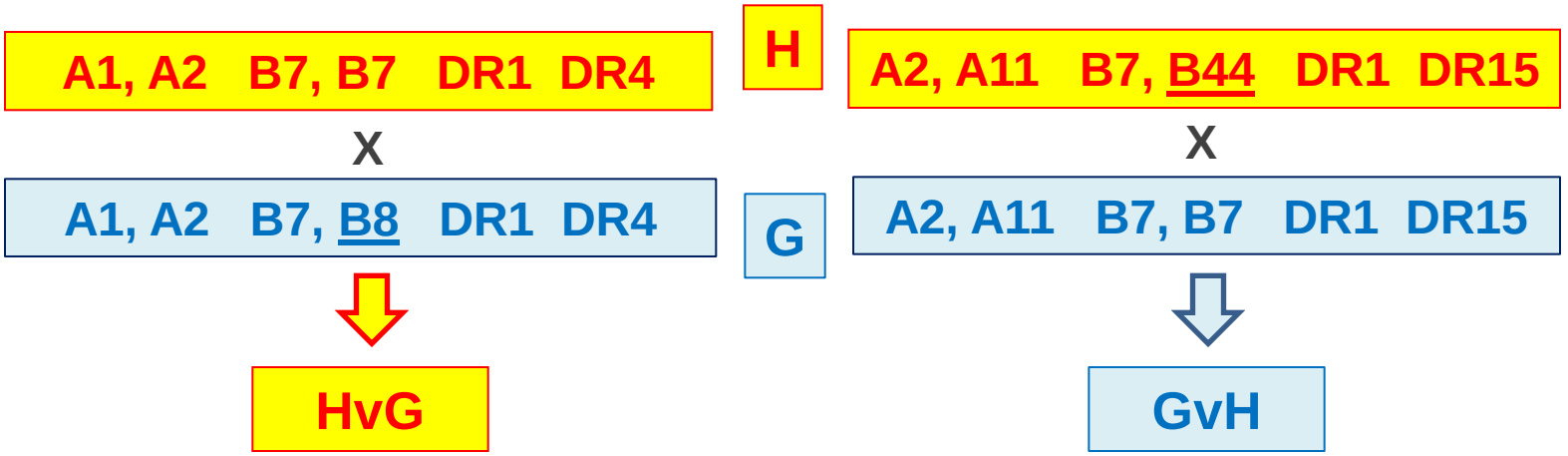
**Useful but not required for heart & lung, pancreas Tx**
**Other considerations are dominant**
(cold ischemia time, age- and size-matching)

**Not required for corneal transplantation success**
(except avoidance of first donor's HLA types in regrafting after rejection)

# HvG versus GvH

**HvG score: graft rejection**

**GvH score: graft-versus-host reaction**



# Sources of Anti-HLA Antibodies

**Multiparous women**

**Multiple blood transfusions**

**Previous rejection of HLA-mismatched transplant**

My approach

The HLA system: immunobiology, HLA typing, antibody screening and crossmatching techniques

W M Howell,[1] V Carter,[1] B Clark[2]

*J Clin Pathol* 2010;**63**:387–390

# Anti-HLA Antibodies in Transplantation

## Hyperacute rejection (<48h)
***preformed high-titer IgG complement-fixing Ab***

## Acute rejection (days-weeks after engraftment)
***CD4-mediated (lymphocyte infiltration) or***
***Ab-mediated (C4d deposition)***

## Chronic rejection (months-years)
**Multifactorial**

HLA and kidney transplantation

B Clark,[1] D J Unsworth[2]

*J Clin Pathol* 2010;**63**:21–25. doi:10.1136/jcp.2009.072785

My approach

The HLA system: immunobiology, HLA typing, antibody screening and crossmatching techniques

W M Howell,[1] V Carter,[1] B Clark[2]

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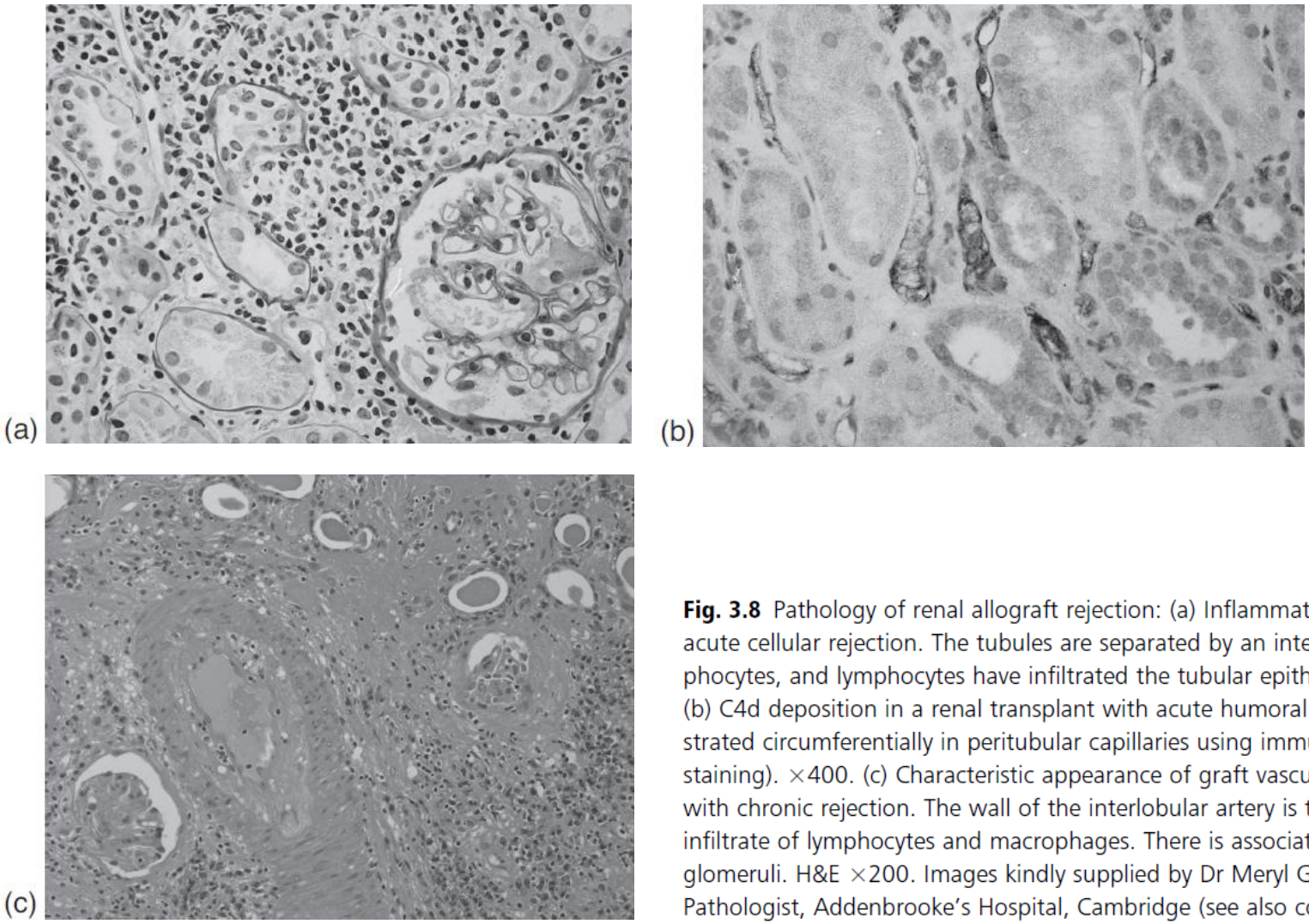

**Fig. 3.8** Pathology of renal allograft rejection: (a) Inflammatory infiltrate characteristic of acute cellular rejection. The tubules are separated by an interstitial infiltrate of lymphocytes, and lymphocytes have infiltrated the tubular epithelium (tubulitis). PAS ×400. (b) C4d deposition in a renal transplant with acute humoral rejection. C4d is demonstrated circumferentially in peritubular capillaries using immunohistochemistry (brown staining). ×400. (c) Characteristic appearance of graft vasculopathy in a renal transplant with chronic rejection. The wall of the interlobular artery is thickened by fibrosis and an infiltrate of lymphocytes and macrophages. There is associated atrophy of tubules and glomeruli. H&E ×200. Images kindly supplied by Dr Meryl Griffiths, Consultant Pathologist, Addenbrooke's Hospital, Cambridge (see also colour plate section).

Chapter 3

# Transplantation immunology

Eleanor M. Bolton and J. Andrew Bradley

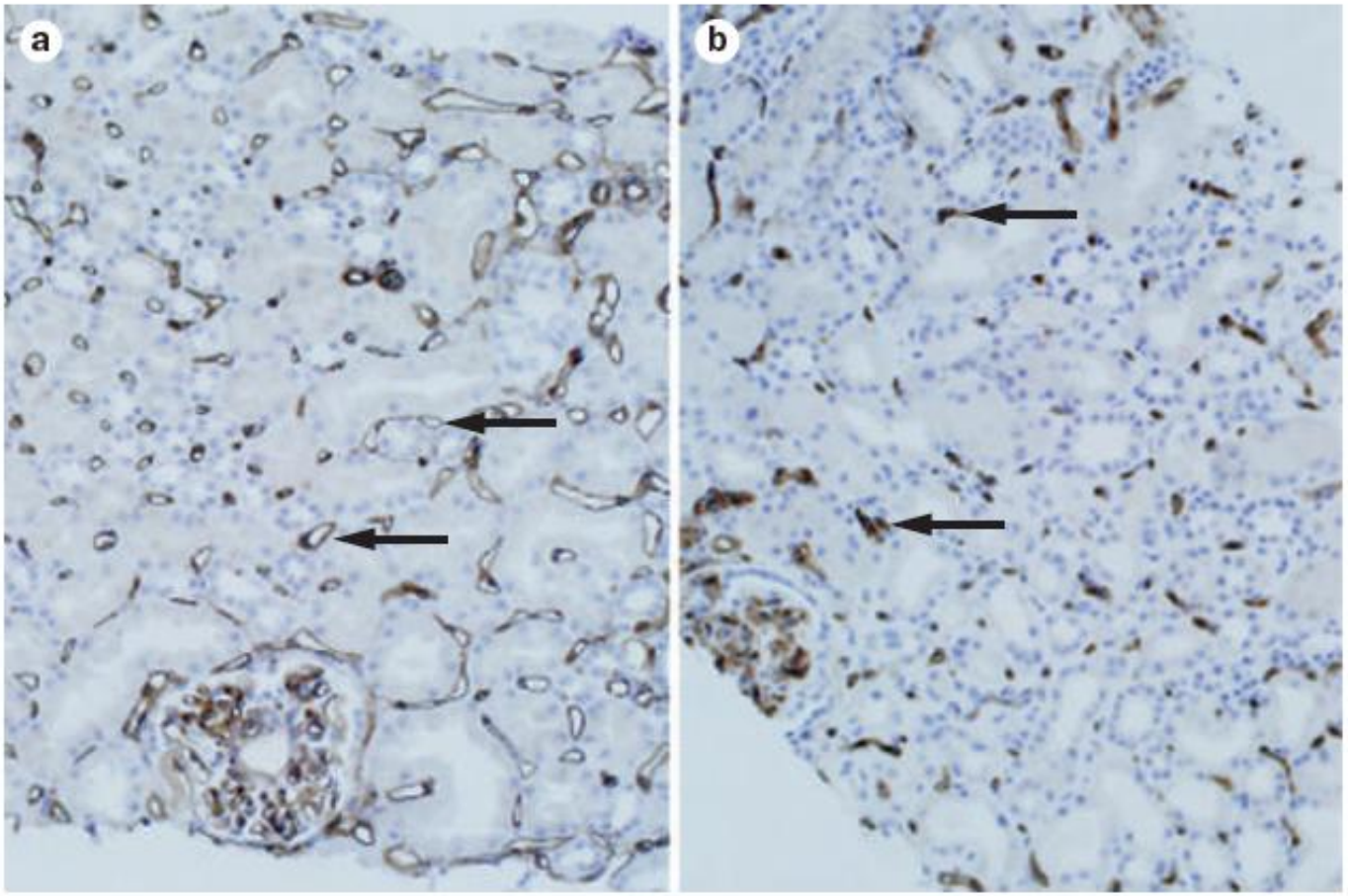


**Figure 1** | The effect of antibody-mediated rejection on peritubular capillaries. **a** | Normal peritubular capillaries (arrows). CD34 immunoperoxidase stain; original magnification ×20. **b** | Obliteration of peritubular capillaries (arrows) following chronic antibody-mediated rejection. CD34 immunoperoxidase stain; original magnification ×20.

## Sensitized renal transplant recipients: current protocols and future directions

*James Gloor and Mark D. Stegall*

*Nat. Rev. Nephrol.* **6**, 297–306 (2010)

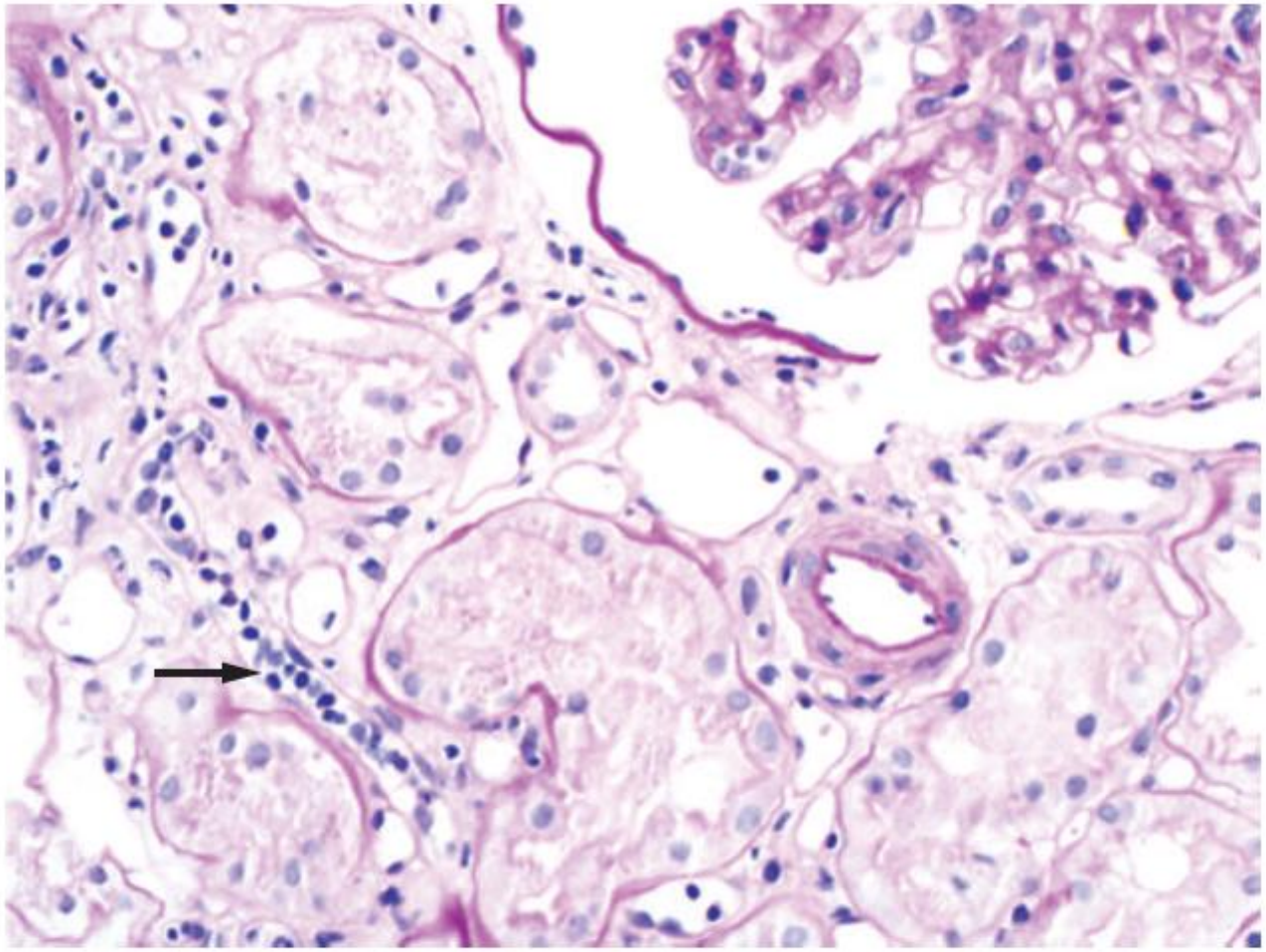

**Figure 2** | Infiltration of peritubular capillaries by mononuclear cells in subclinical chronic antibody-mediated rejection. Arrow shows infiltrated capillary. Periodic acid–Schiff stain; original magnification ×40.

## Sensitized renal transplant recipients: current protocols and future directions

*James Gloor and Mark D. Stegall*

*Nat. Rev. Nephrol.* **6**, 297–306 (2010)

# Anti-HLA Antibodies in Transfusion

**Hemolytic transfusion reactions**

**Platelet refractoriness**

**Non-hemolytic febrile reactions**

**Non-cardiogenic pulmonary edema**

My approach

The HLA system: immunobiology, HLA typing, antibody screening and crossmatching techniques

W M Howell,[1] V Carter,[1] B Clark[2]

*J Clin Pathol* 2010;**63**:387–390

# Anti-HLA Antibody Screening

## Panel-reactive Antibody Screening

**Complement-dependent cytotoxicity (CDC) Assay**

***using T-cells (class I) and B-cells (class II)***

**Flow cytometry-based assays**

***for non-complement-fixing antibodies***

**ELISA assays**

***for class I/II and for complement-fixing or nonfixing antibodies***

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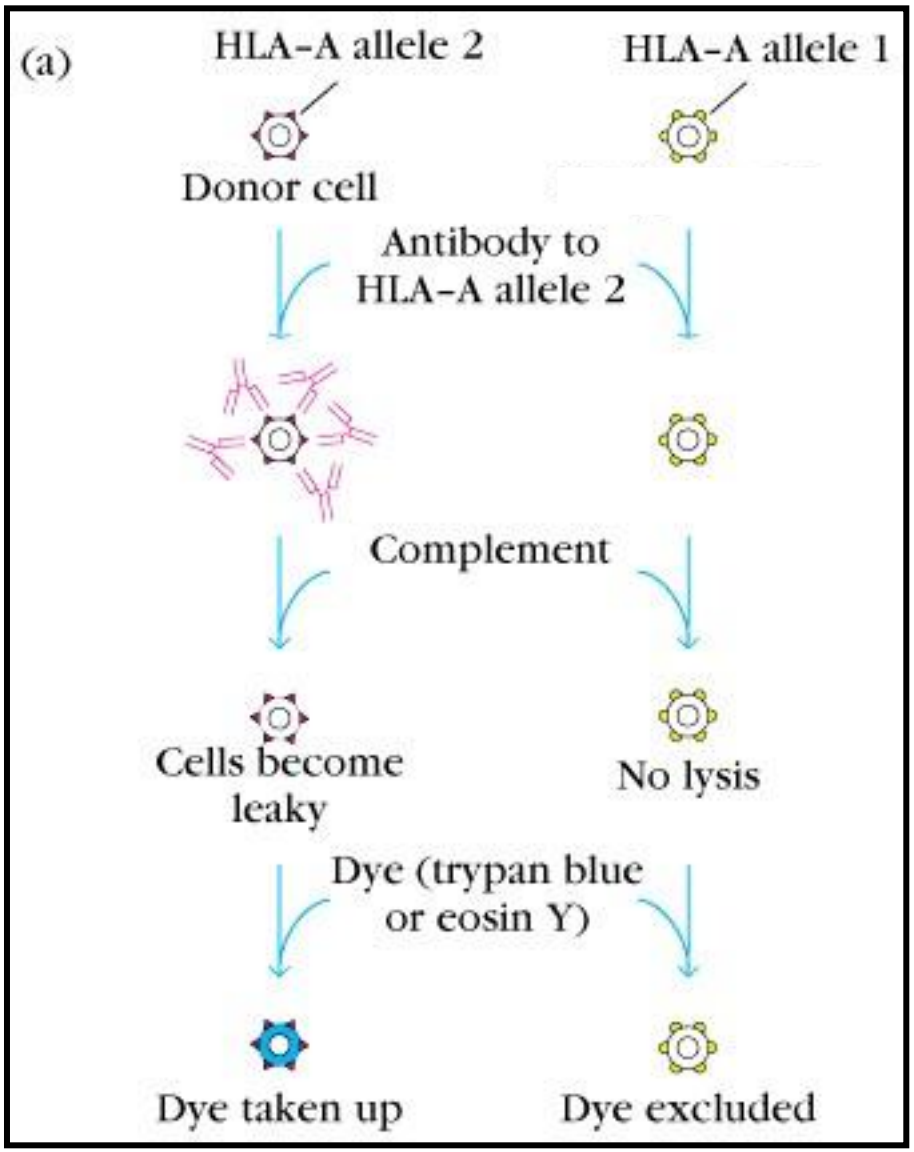
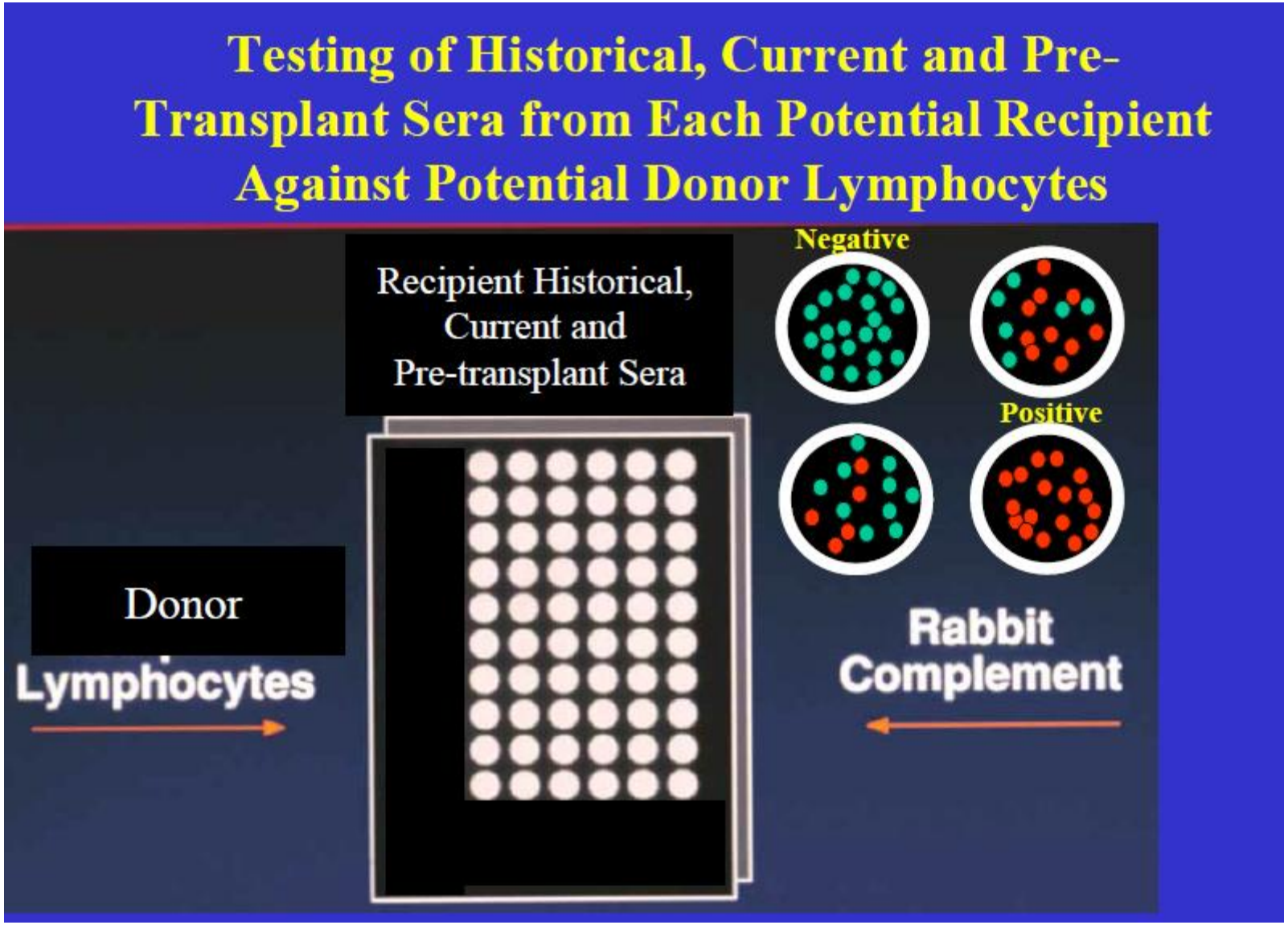
W M Howell,[1] V Carter,[1] B Clark[2]

*J Clin Pathol* 2010;**63**:387–390

# Anti-HLA Antibody Screening



# Anti-HLA Antibody Screening



# Anti-HLA Antibody Screening

## Donor x Recipient Crossmatch

***to detect preformed anti-HLA antibodies against a specific donor to avoid hyperacute rejection***

**1) CDC assay with (IgM) or without DTT (visual xMatch)**
**2) Flow cytometry: more sensitive; more effective against IgG antibodies**
**3) Solid phase methods: Donor cell HLA capture beads**

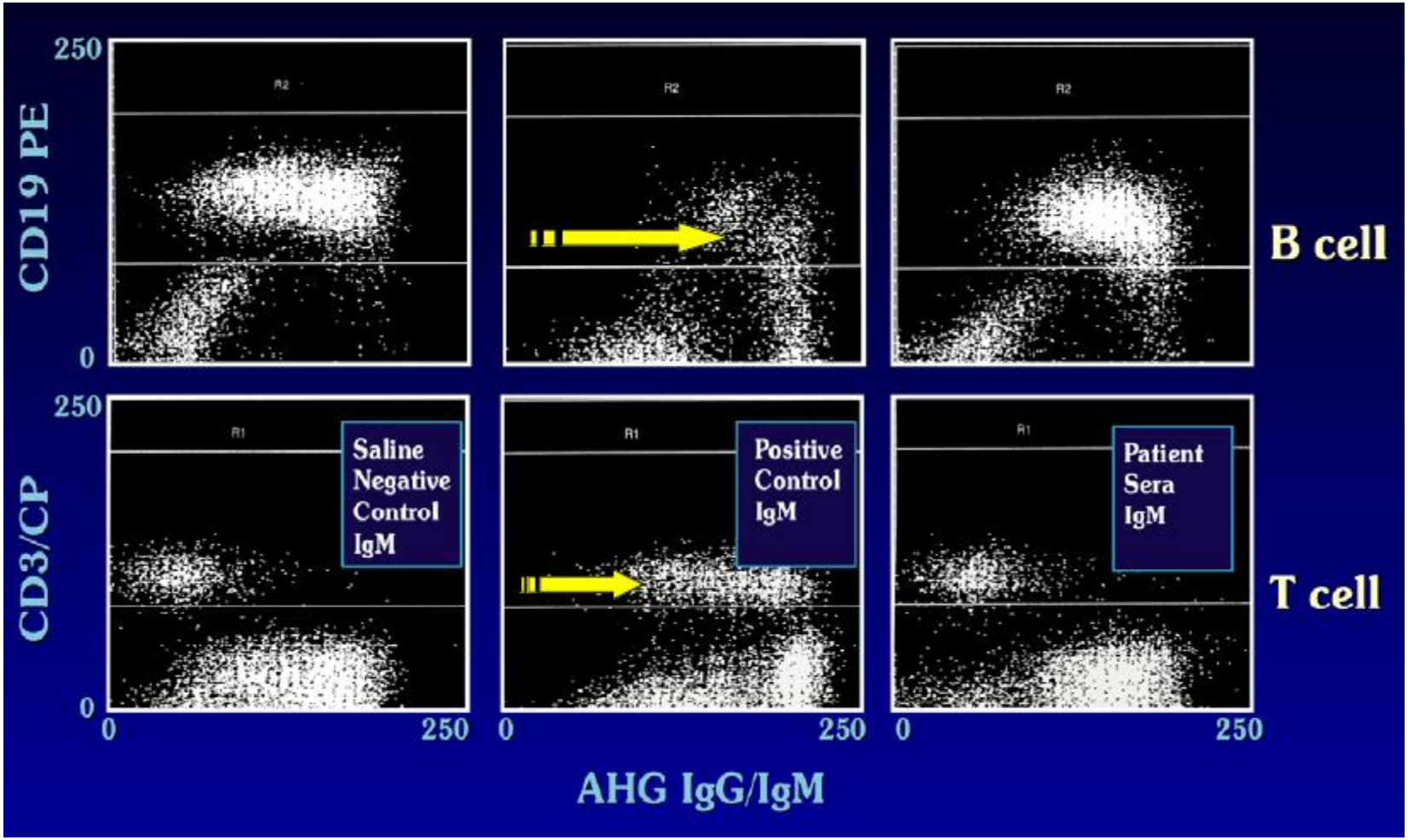
My approach

The HLA system: immunobiology, HLA typing, antibody screening and crossmatching techniques

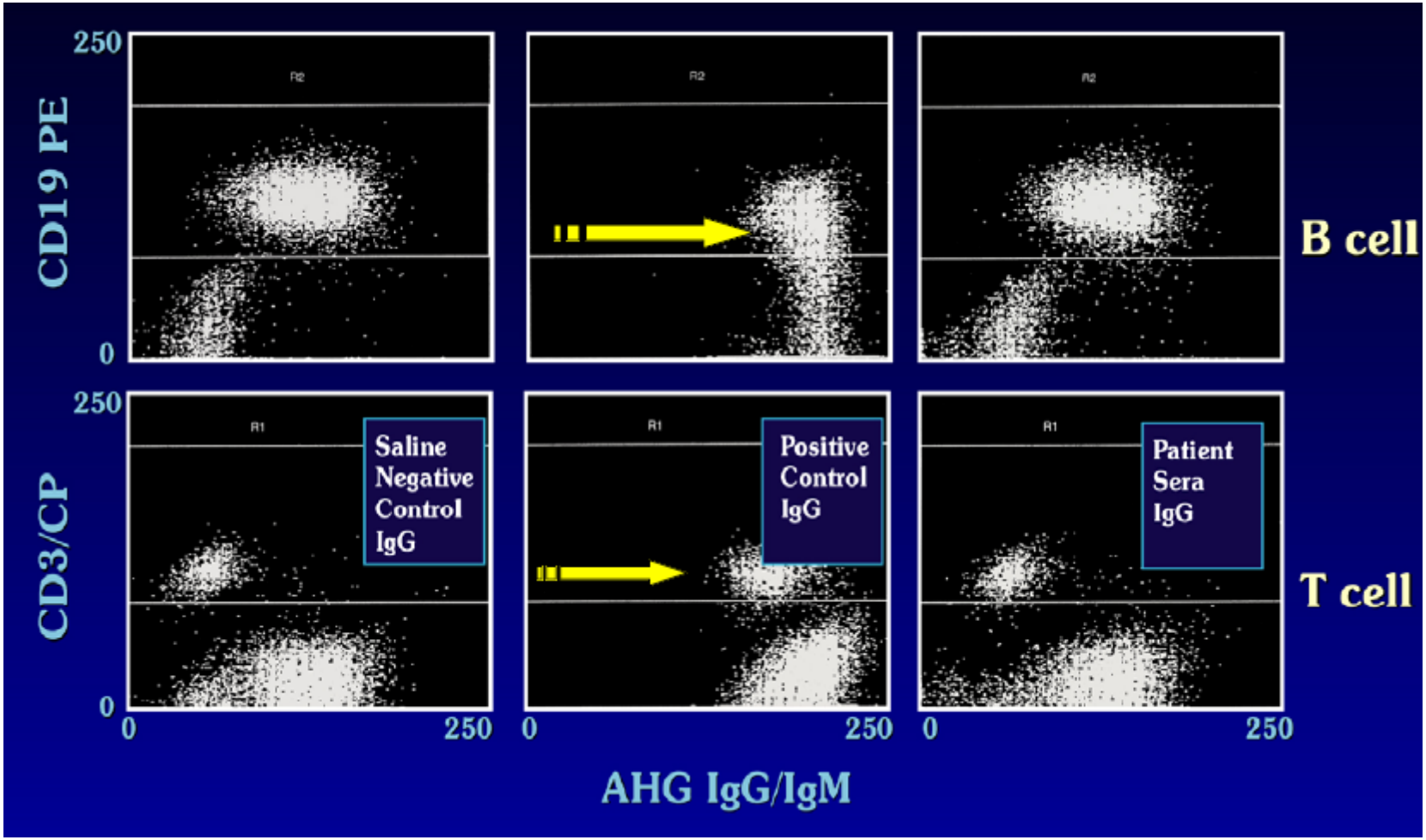
W M Howell,[1] V Carter,[1] B Clark[2]

*J Clin Pathol* 2010;**63**:387–390

# Anti-HLA Antibody Screening



# Anti-HLA Antibody Screening



# A New Era of Immunosuppression

**Full HLA matching is no longer required**

**Emphasis is on matching recipient antibodies against donor HLA antigens**

**Even antibody-positive recipients can be now be transplanted**

**Table 3.2** Immunosuppressive agents used to control rejection

| Category | Agent |
|---|---|
| Calcineurin inhibitors | Ciclosporin (cyclosporin A) |
| | Tacrolimus (FK 506) |
| Nucleotide synthesis inhibitors | Azathioprine |
| | Mycophenolate mofetil |
| | Leflunomide |
| Target of rapamycin (mTOR) inhibitors | Sirolimus |
| | Everolimus |
| Corticosteroids | Prednisolone |
| Depleting anti-T/B cell MABs | ATG (antithymocyte globulin) |
| | Anti-CD3 (orthoclone OKT3) |
| | Anti-CD52 (campath-1H) |
| | Anti-CD20 (Rituximab) |
| Blocking MABs, fusion proteins | Anti-CD25 (daclizumab, basiliximab) |
| | CTLA-4-Ig (belatacept) |

Chapter 3

# Transplantation immunology

Eleanor M. Bolton and J. Andrew Bradley

## Future directions

Although current protocols effectively prevent hyperacute rejection, acute AMR remains an important complication in positive-crossmatch kidney transplantation and carries a substantial risk of allograft loss. In addition, individuals with high DSA levels at baseline are often resistant to treatment and are unable to proceed to transplantation.[4,10,12] Although positive-crossmatch protocols have improved access to transplantation for highly sensitized candidates, further advances are clearly needed. Two potentially important innovations that are currently being explored are the prevention of antibody-mediated endothelial cell injury by complement blockade and the depletion of DSA-secreting plasma cells from the bone marrow using proteasome inhibition.

### Complement blockade

High levels of DSAs activate complement, thereby leading to the formation of membrane attack complex that injures donor endothelium and results in the histological abnormalities diagnostic of acute AMR. Eculizumab is a humanized monoclonal antibody that binds to the complement factor C5 with high affinity, inhibiting its cleavage to C5a and C5b, and preventing the formation of the membrane attack complex.

### Proteasome inhibition

In addition to physically removing or inhibiting of DSAs, decreasing DSA production is a goal for positive-crossmatch transplant protocols. Nevertheless, agents currently in use—such as anti-CD20 antibodies, anti-thymocyte antibodies, and intravenous immunoglobulin—are ineffective in depleting antibody-secreting plasma cells resident in the bone marrow, which has prompted investigators to consider other agents.[106]

In the past decade, proteasome inhibition has been recognized as a potentially important intervention with applications for enabling transplantation in allosensitized patients through its role in cell cycle regulation, cell–cell interactions, and apoptosis.[107] The proteasome inhibitor bortezomib is effective in the treatment of multiple myeloma, a plasma cell malignancy.[108,109] In 2008, Everly *et al.* reported that bortezomib use was associated with rapid improvement in allograft function and suppression of recurrent rejection over a 5-month period in six kidney transplant recipients with severe combined AMR and acute cellular rejection.[110]

**Sensitized renal transplant recipients: current protocols and future directions**

*James Gloor and Mark D. Stegall*

*Nat. Rev. Nephrol.* **6**, 297–306 (2010)

## NEW FRONTIERS: HIGHLY SENSITISED PATIENTS AND THE CASE FOR "DESENSITISATION"

Particularly in the context of re-transplants, previous allografting (or other sensitising events including pregnancy or transfusion) may lead to highly sensitised patients who are difficult to transplant because of the presence of HLA antibodies to a wide range of HLA types. Without extraordinary measures, these patients may never receive a further graft.

Strong pre-transplant immunosuppression followed by plasma exchange (or sometimes intravenous pooled human IgG) in the last few weeks immediately prior to transplant (to remove residual HLA or ABO antibody) can allow otherwise contraindicated transplants to proceed at reduced risk.[19 20] A range of immunosuppressant regimens have been tried. This approach is most practical where a live donor is available, because "desensitising" immunosuppression can be timed to coincide with live donation. The potential recipient must be judged healthy enough to undergo treatment with strong immunosuppressive agents pre-transplant. Ideally, immunosuppression continues until laboratory monitoring shows that ABO and/or HLA antibody titres have declined to acceptable levels. It is difficult to completely eradicate donor specific antibody, but generally accepted "minimum readouts" might include converting CDC positive cases to CDC cross-match negative cases, or reducing titres to levels associated with successful transplants in other patients.

In terms of outcomes, while global numbers to date are small, it appears that outcomes are better with ABO incompatible as compared with HLA antibody incompatible donor recipient pairs. Also, in terms of HLA antibody positive cross-matches, desensitisation is more effective when dealing with patients who have lower titre antibodies (ie, flow cytometry cross-match positive but CDC negative cross-match).

# HLA and kidney transplantation

B Clark,[1] D J Unsworth[2]

*J Clin Pathol* 2010;**63**:21–25. doi:10.1136/jcp.2009.072785

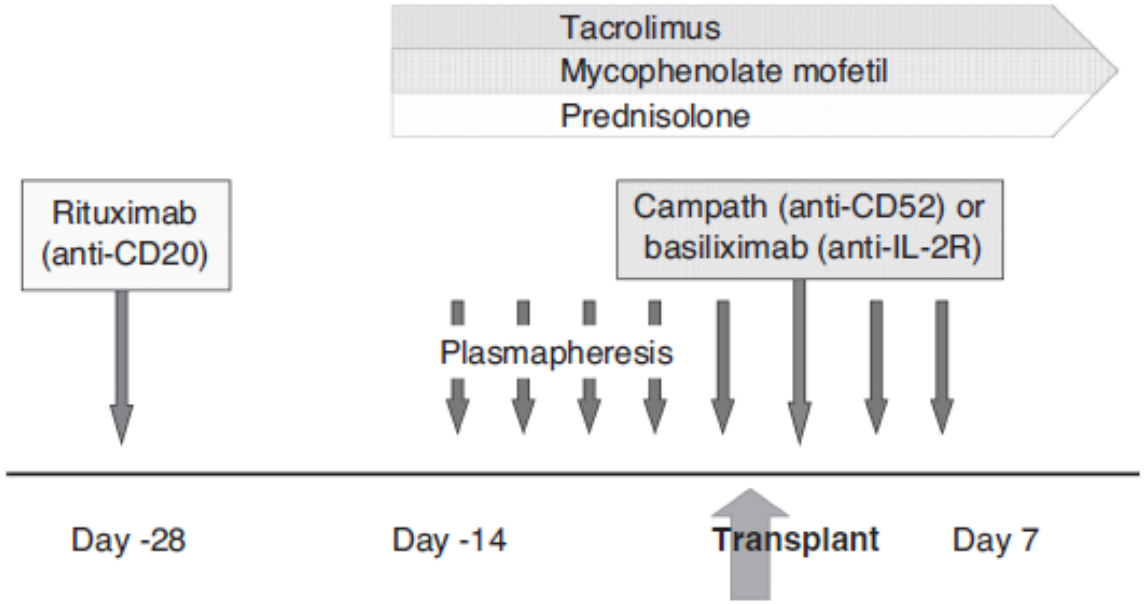



**Fig. 3.9** Desensitization protocol for ABO-i/HLAi living donor transplantation. The aim of desensitization protocols is to reduce the level of circulating anti-ABO or anti-HLA antibodies to a safe titre prior to transplantation and to prevent continuing and novel antibody production following transplantation. A typical protocol may involve treatment with rituximab to reduce the pool of B lymphocytes that might mature into plasma cells, together with multiple rounds of plasmapheresis to remove existing circulating antibodies. Patients receive immunosuppressive therapy to minimize continued antibody production, together with standard induction therapy at the time of transplantation, and additional episodes of plasmapheresis, with maintenance immunosuppression following transplantation. ABOi, blood group; HLAi, human leucocyte antigen; IL-2R, interleukin-2 receptor.

Chapter 3

# Transplantation immunology

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