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Characteristics, Detection, and Clinical Relevance of Alloantibodies in Kidney Transplantation

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1. Introduction

Almost four decades ago, Porter (Porter, 1970) and Edelman (Edelman, 1970) established the structure of antibodies (immunoglobulins). This discovery dramatically improved the understanding that antibodies function as both receptor and effector molecules. Humoral or antibody-mediated immunity requires noncovalent contact between antigens (ligands) and antibodies (receptors). Hypervariable regions of immunoglobulin light and heavy chains 1, 2, and 3, which are termed complementarity-determining regions (CDR), are primarily involved in the interaction with antigens (Figure 1).

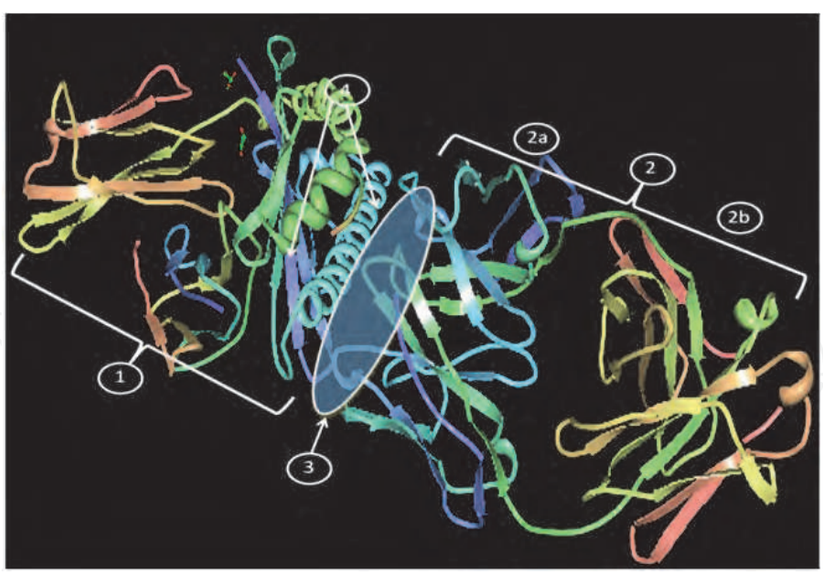

Fig. 1. Three-dimensional structure of HLA-I and alloantibody IgG complex.
1. HLA class I protein
2. IgG molecule.
   a. Variable regions of light and heavy chains
   b. Constant region of heavy chains
3. CDRs 1, 2, and 3 of heavy and light chains

The contact region of the antigen that the antibody binds to is called the epitope, or antigenic determinant. The portion of antibody that makes this contact is referred to as the paratope. Antibody effector functions are specified by the constant domains of heavy chains. Their most important function is the activation of the complement cascade, which is triggered by conformational changes in the hinge area after antigen binding. Complement activation results in the destruction of the cell membrane. An additional important effector function of immunoglobulins is their binding to pathogens, including bacteria and viruses. Pathogens that are coated with antibodies are recognized by Fc (constant fragment) receptors that are expressed on the surfaces of reticuloendothelial cells, including macrophages, monocytes, neutrophils, and dendritic cells. This event not only results in the elimination of the pathogen from the circulation and the tissues but also triggers additional functions of these cells, such as phagocytosis and degranulation. The latter ultimately results in the destruction of the invading pathogen. In contrast to strong and irreversible covalent bonds, antibody-antigen interactions are noncovalent. They strictly depend on temperature, pH, ionic strength, van der Waal's forces, hydrogen bonds and hydrophobic interactions. These weak bonds are formed by the interactions of many groups of biological molecules, including IgG, nominal protein antigens, and major histocompatibility complex (MHC) class I and class II proteins. In humans, the latter are called human leukocyte antigens (HLAs). A unique characteristic of genes that code HLAs is the extremely high occurrence of polymorphisms.

2. Role of alloantibodies in kidney transplantation

In kidney transplantation, graft outcomes critically depend on the degree of HLA matching between the donor and recipient (Abe et al., 1997; Akalin & Pascual, 2006; Balan et al., 2008; Bas et al., 1998; Claas et al., 2005; Scornik et al., 1992; Takemoto et al., 2004; Terasaki 2003; Terasaki & Cai, 2005, 2008;). Although the cellular component of the allogenic immune response to the transplanted tissue plays a key role in this matching, the contribution of antibodies should not be underestimated (Arnold et al., 2005; Bartel et al., 2007; Stegall et al., 2009; Sumitran-Holgersson, 2001; Vasilescu et al., 2004; Zeevi et al., 2009). Transplant candidates (TCs) with preexisting antibodies against HLA are called sensitized patients. The percent of reactive antibodies (PRA) is a major characteristic that defines the level of sensitization. Essentially, greater PRA values indicate greater numbers of anti-HLA antibodies in the patient, indicating a lower probability of receiving a kidney transplant. Indeed, donor-specific antibodies (DSAs) undeniably participate in hyperacute rejection (HAR), humoral acute rejection [also called accelerated antibody-mediated rejection (AMR)], and chronic rejection (CR) (Claas & Doxiadis, 2009; Gebel et al., 2003; Georgescu et al., 2007; Grandtnerova et al., 2008; Kerman et al., 1997; Lefaucheur et al., 2009; Poli et al., 2009; Scornik et al., 1989, 1992; Supon et al., 2001; Takemoto, 1995; Terasaki & Cai, 2008; Vasilescu et al., 2004; Ferry et al., 1997; Martin et al., 2003). HAR is frequently caused by preexisting DSAs that are directed at mismatched HLAs or by high concentrations of isohemagglutinins against major blood group antigens. Graft loss due to HAR has been shown to take place within hours after transplantation; however, in particular cases, wherein the recipient is exposed to multiple cycles of plasmapheresis (PP), post-transplant HAR may develop days later, and this condition is termed delayed HAR (DHAR). The pathological findings in both scenarios appear to be the same (Sugiyama, 2005). Today, HAR is a rare event owing to development of highly sensitive flow cytometry (FC) cross match (CM) technology, which

enables the prospective detection of low concentrations of DSAs (Bray, 1994; Shenton et al., 1995; Wang-Rodriguez & Rearden, 1995). Relatively low concentrations of preexisting DSAs are generally not a contraindication for transplantation (Bray, 1994, 2001; Gebel & Bray, 2000; Graff et al., 2009; Reinsmoen et al., 2008).

2.1 The development of alloantibodies against HLAs

In more than 30% of transplant cases, DSAs develop post-transplant, increasing the risk of AMR (Christiaans et al., 1998; Haririan et al., 2009; Martin et al., 2003; McKenna et al., 2000; Zachary et al., 2005). The development of these antibodies depends on multiple factors, including the immunogenicity of mismatched HLAs, HLA class II typing of the responder, immunosuppressive protocols, cytokine and chemokine production, and the hormonal background of the recipient (Adeyi et al., 2005; Claas et al., 2005; Fuller et al., 1999; Fuller & Fuller, 1999; Lachmann et al., 2008; Laux et al., 2003; Lobashevsky et al., 2002). Regulatory immune cells, such as NKT cells, T regs (CD4+/CD25+) (Tsang et al., 2007; Stasi et al., 2008 ; Bas et al., 1998; Jiang & Lechler, 2003; Levings & Thomson, 2009; Toyofuku et al., 2006) and B regs (so-called CD1d/CD5 B10 cells) (Amu et al., 2007), substantially contribute to the development of antibody-mediated immunity. Anti-HLA antibodies have been demonstrated in patients with a history of blood transfusion(s), pregnancy and previous transplant(s). In addition, serological cross-reactivity between HLA-B27 and the 60.0-80.0 kD protein of *Klebsiella pneumoniae* has been demonstrated (Husby et al., 1989; Ogasawara et al., 1986). Considerable effects on antibody profiles of pre-sensitized TCs may also be produced by vaccinations, including Hepatitis B/C and influenza. Indeed, Danziger-Isakov and R. Kennedy have reported bystander effects of vaccine immunization on humoral alloreactivity (Danziger-Isakov et al., 2010; Kennedy et al., 2010). The mechanism of vaccination-mediated sensitization in TCs has been described as follows. Antigen-specific CD4+ T helper cells are central components in naturally acquired and vaccine-induced immunity. These cells control the differentiation of HLA-specific B cells into plasma (antibody producing) cells and memory cells through the production of cytokines, such as interleukin (IL)-4, IL-5, IL-6, IL-2, IL-13, and IFNγ. Subsequent vaccination or infection triggers distinct groups of T helper cells to begin producing the cytokines mentioned above. These cytokines activate quiescent B memory and long-living plasma cells that reside in the bone marrow. These HLA-specific plasma cells then begin vigorously producing antibodies, resulting in changes in the PRA (Benson et al., 2009; Di Genova et al., 2010; Di Genova et al., 2006). Recently, the development of so-called "natural" anti-HLA antibodies has been reported by P. Terasaki's group. These investigators discovered that natural immunizing events, such as infection, protein ingestion and allergen exposure, result in the formation of HLA-A, - B, -C, and DQ loci-specific alloantibodies in non-alloimmunized healthy males. The "natural" antibodies are directed against rare HLA specificities, such as A80, B76, A82, and C17, and should not be ignored in clinical decisions for organ allocation (Morales-Buenrostro et al., 2008).

2.2 B lymphocytes and alloantibody production

After naïve CD20+/CD138-/CD38-/CD27- B cells interact with the HLA protein antigen, two key events occur. First, the naïve B cells become activated in lymphoid tissue, differentiate into short-lived CD20-/CD138-/CD38+/CD27- plasma cells (PCs), and secrete low-affinity antibodies. Second, another group of activated B cells rapidly divides and differentiates into long-term, high-affinity antibody-secreting CD20-

/CD138+/CD38+/CD27- PCs upon interaction with follicular dendritic cells after receiving signals, such as IL-4 and IL-5, that are produced by T helper cells (Stegall et al., 2009; Higgins et al., 2009). These cells often migrate back to the bone marrow, where they may continuously secrete antibodies for years. An additional important event in the process of alloantibody production is the formation of B memory CD20+/CD27+ CD138-/CD38- cells, which are able to transform into long-lived PCs after secondary stimulation by antigens or bystander T cells (Stegall et al., 2009; Bohmig et al., 2008; Cai & Terasaki, 2005; Armitage & Alderson, 1995) (Figure 2).

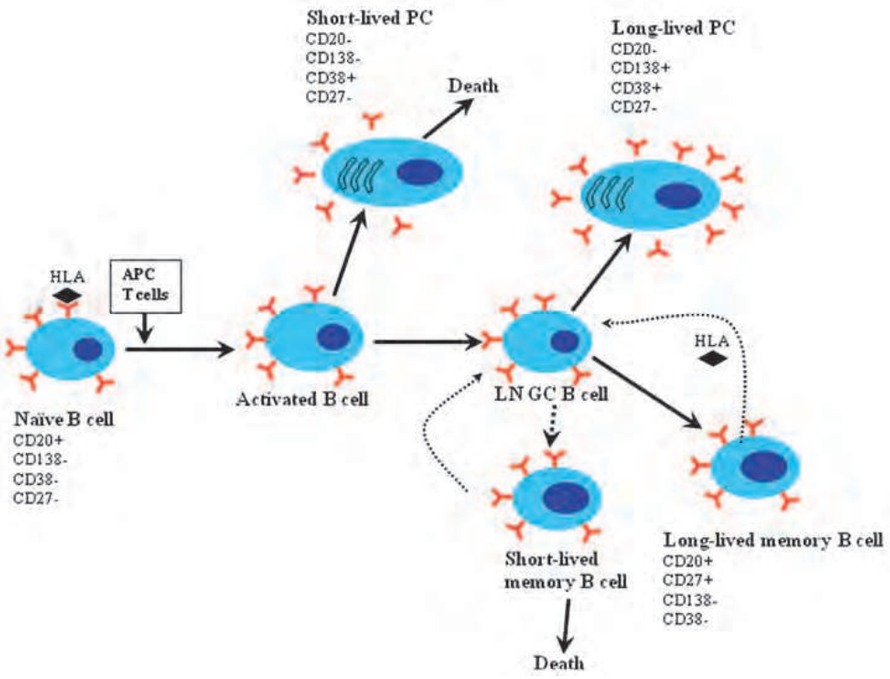

Fig. 2. Model for the generation of long-lived alloantibody-secreting plasma cells (PC) after recognition of HLA. APC, antigen presenting cells; LN, lymph node; GC, germinal center;

3. Some immunological factors determining alloantibody production

As mentioned above, the risk of AMR and kidney graft survival strictly depends on HLA matching between donor and recipient tissues. Highly sensitized TCs, i.e., those having a high PRA, have the highest risk of AMR-mediated graft failure. In addition, these patients are disadvantaged in comparison to those with a low PRA. They typically experience longer times on the waiting list (until a cross-match-negative donor is found) and dialysis. Numerous clinical studies since the 1990s have demonstrated various strategies for identifying donors for high PRA patients. Rodey's and Takemoto's groups have reported successful kidney graft outcomes and negative cross-matching when HLA matching was performed using cross-reactive groups (CREG) and/or public epitopes (Rodey & Fuller, 1987; Takemoto, 1995, 2004). Terasaki's method for analyzing donor and recipient compatibility applies the amino acid sequencing of HLA alleles (Cai et al., 2006; Deng, 2008; El-Awar et al., 2005, 2006a, 2006b, 2007; El-Awar & Terasaki, 2007).

3.1 Amino acids and the triplet/eplet concept of HLA matching

In 2002, Duquesnoy described a molecularly-based algorithm for histocompatibility determination called HLAMatchmaker (Duquesnoy, 2002). This approach considers a comparison of linear amino acid residue (AAR) sequences (or triplets) between donors and recipients to be elements of potential epitopes. Therefore, each HLA protein represents a linear sequence of triplets, and the degree of mismatch is assessed by the number of triplets that are not shared between the donor and recipient. There are two important points in this approach. First, the location of the particular triplet in the HLA protein is carefully examined. Only those AARs that are accessible to antibodies, i.e., triplets residing on α-helical coils and β-loops, are considered. In contrast, those triplets that are located on the β -pleated floor and beneath the α-chains are not available for antibody binding (Figure 3).

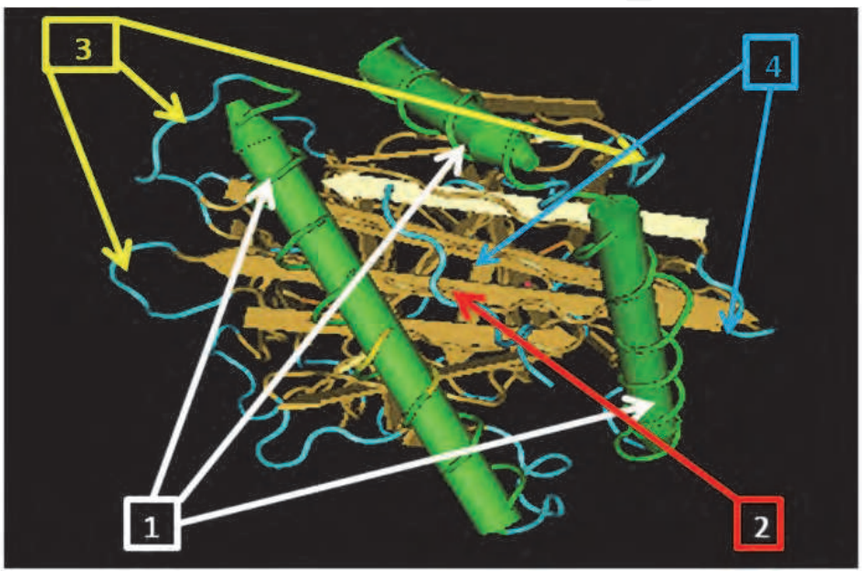

Fig. 3. Three-dimensional structure of HLA-I molecule (top view).
1. α helical coils
2. oligopeptide located in the antigen presenting groove
3. β loops
4. β pleated floor of antigen presenting groove

For this reason, the mismatched triplets residing on the bottom of the antigen-presenting groove of the HLA proteins are often not critical to antibody production and are not immunogenic. Secondly, alloantibodies can be produced only against non-self mismatched triplets. Subsequent clinical studies have proven the validity of the HLAMatchmaker algorithm as a method for finding cross-match compatible donors for TCs with PRA values above 80% (Claas et al. 2005; Claas et al. 2004; 2005; Doxiadis et al. 2005; Duquesnoy 2007, 2008a, 2008b; Duquesnoy & Claas, 2005; Lobashevsky et al., 2002). Furthermore, AAR triplet analysis has appeared to be capable of explaining or predicting the development of non-DSAs in kidney allograft recipients (Lobashevsky et al., 2002; Adeyi et al., 2005); however, subsequent clinical studies of alloantibody profiles in post-transplant nephrectomized TCs have demonstrated that the HLAMatchmaker computer algorithm provides an incomplete HLA epitope repertoire. Indeed, an inconsistency between mismatched triplets and the pattern of antibody reactivity has been reported. In 2005, Duquesnoy's group, using human

monoclonal antibodies, demonstrated reactivity against HLA-A3 (triplotype 62Qe, 142mI, 144tKr, and 163dT) owing to a unique 163dT triplet; however, other monoclonal antibodies also reacted with 62Qe, 142mI, or 144tKr triplets, although these triplets were present on different HLA-A locus antigens. Furthermore, the 62Qe triplet that is carried by A30 and A31; the 142mI triplet that is carried by A23, A24, A25, and A32; and the 144tKr triplet that is carried by A80 did not react with the monoclonal antibodies that were directed against the triplets mentioned above (Duquesnoy et al., 2005). Similar results were summarized in a report on the structural basis of HLA compatibility at the 14th International HLA and Immunogenetics Workshop (Duquesnoy & Claas, 2007). Further investigations of the three-dimensional structure of antibody-antigen complexes showed that functional HLA epitopes could be presented by a group of AARs that are not located beside one another, but rather represent a 3-Å to 5-Å radius patch. These patches have been defined as "eplets." Some of eplets include short sequences of AARs, which are equivalent to triplets, whereas, others contain residues that are located distally (apart). For instance, the presence of glycine in position 56 is required for reactivity of monoclonal antibodies specific for 62Qe triplet. The AARs of each eplet are clustered together on the surface of the HLA protein molecule that represents a functional immunogenic epitope (Marrari et al., 2010; Marrari & Duquesnoy, 2010; Duquesnoy et al., 2005; Duquesnoy & Askar, 2007) (Figure 4). Therefore, the eplet concept of the HLAMatchmaker algorithm appears to more accurately define functional HLA-A, -B, -C, -DR, -DQ (α andβ chains) and DP (α andβ chains) epitopes (Claas et al., 2005; Claas & Duquesnoy, 2008; Duquesnoy, and Marrari, 2010; Duquesnoy, 2006, 2008a, 2008b; Duquesnoy & Askar, 2007; Marrari et al., 2010; Lomago et al., 2010). Thus, HLA epitope- (eplet) matching using the HLAMatchmaker computer algorithm represents a robust and valid approach to finding compatible donors for highly sensitized TCs. It may also be used to analyze antibody reactivity patterns in sensitized patients by defining the mismatched eplets the patient has been exposed to. This information, in turn, facilitates the interpretation of antibody profiles in TCs. In addition, a comparative analysis of the HLA epitopes that were defined by Terasaki's group (amino acids that are unique to a group of alleles that react with mouse monoclonal antibodies) and HLA epitopes that are defined by eplets showed more than a 90% correlation (Marrari & Duquesnoy, 2010; Duquesnoy & Marrari, 2010).

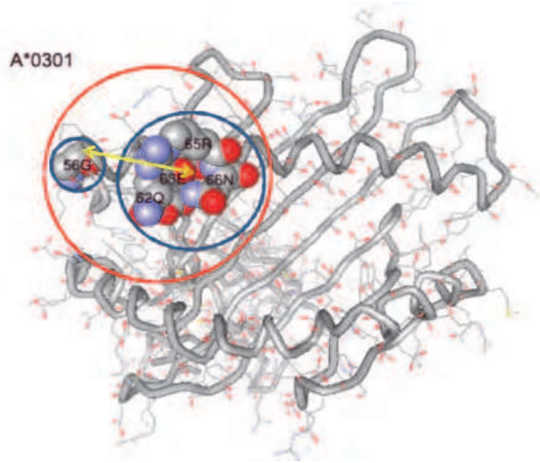

Fig. 4. Topography of 62Q eplet (red circle) of HLA-A*03:01 allele consisting of two patches (blue circles) 56G and 62, 63, 65, 66QERN. These patches are approximately 11Å apart (yellow arrow).

3.2 HLA class II typing of the responder

It is generally accepted that mismatched allogenic HLAs can be recognized by the immune system both directly and indirectly. In kidney transplantation, both of these processes take place simultaneously. The immunological response to non-self HLAs is MHC restricted. The phenomenon of MHC restriction postulates that non-self proteins, including HLAs, are recognized by the immune system after being processed and presented by host antigen presenting cells, in the context of self-MHC I and/or MHC II, to the responder's (host) T cells (Doherty and Zinkernagel, 2005). Although many factors influence the strength of the immune response, the affinity between the members of the tri-molecular complex, including self-HLA II, peptide, and T cell receptors (TCRs), is believed to be the most important. HLA class II proteins have six regions or pockets that participate in peptide binding. These pockets contain highly polymorphic amino acids, which interact with the motifs of the peptides that are being presented to the TCRs. The stronger the affinity between the peptide, HLA and TCRs, the stronger the stimulation signal the T cell receives. Anderson and colleagues have demonstrated that antibody production against tumor HEP-2 peptide was considerably stronger in an HLA-DR11 patient than in an HLA-DR14 individual (Anderson et al., 2000). Furthermore, a report by Fuller demonstrated increased antibody synthesis against HLA-Bw4 antigenic inclusions in HLA-DRB1*01 or HLA-DRB1*03 positive individuals in comparison to HLA-DRB1*04 recipients (Fuller & Fuller, 1999).

4. Role of alloantibodies directed against other than HLA determinants

4.1 Antibodies against A and B blood groups

The compatibility of HLA and the ABO blood groups, which are two antigenic systems in the human body, have a significant effect on graft outcome. Historically, ABO incompatibility has been considered to be an absolute contraindication for renal transplantation due to the high risk of HAR development that is caused by preexisting anti-A or anti-B antibodies. Unlike HLA, the A, B and O (H) blood group antigens are oligosaccharides that structurally differ via α-galactose (α-Gal) and N-acetyllactosamine (NAc). Adding these sugars to precursor backbones requires catalyzation by a group of enzymes that are called glycosyltransferases. The A blood group has two common subgroups, A1 and A2. There are quantitative and qualitative differences between A1 and A2; the A1 phenotype has 4 glycolipids, whereas the A2 phenotype contains very low levels or none at all. Immunological cross-reactivity between them has been reported (Gloor et al., 2006; Gloor & Stegall, 2007; Tyden et al., 2010). Furthermore, 8% of A2 individuals produce antibodies against A1. The ABO system also plays an important role in kidney allocation; donors and recipients must be either ABO identical or compatible (Futagawa & Terasaki, 2006). A/B antigens are known to be passively absorbed by different tissues of the kidney, including the glomerular endothelium and the tubular epithelium (Rivera & Scornik, 1986, Aikawa et al., 2003; Fidler et al., 2004; Rydberg et al., 2007). Endothelial and epithelial cell surface densities of A/B antigens are also different. For example, the A blood group antigen has higher expression levels than the B blood group antigen. Interestingly, immunohistochemical analysis has revealed that the A2 blood group has the lowest cell surface expression (Pober et al., 1997; Shimmura et al., 2004; Yung et al., 2007); however, data analysis of kidney transplants that has been performed across ABO barriers has not revealed statistically significant differences between the A (donor) →B (recipient) or B (donor) →A (recipient) groups (Squifflet et al., 2004; Sugiyama et al., 2005; Valli et al., 2009).

Anti-A/B blood group antibodies belong to the IgM and IgG isotypes, and their titers, which are determined by the direct agglutination test, vary from 1:2 to 1:256 (Issitt & Issitt, 1979). These titer differences are particularly meaningful in cases of ABO-incompatible kidney transplantation (see below).

4.2 Antiphospholipid antibodies

Phospholipids (PLs) are known to play an important role in regulating coagulation. They form complexes with plasma proteins, such as prothrombin, protein S, protein C, annexin, and β_2-glycoprotein (Forman et al., 2004; Wagenknecht et al., 2000). These proteins are known to be natural anticoagulants (Vaidya et al., 1998). Anti-PL antibodies (APLAs) are autologous antibodies, which can cause venous and arterial thrombosis. The binding of APLAs to PLs or plasma proteins results in the inhibition of natural anticlotting effects, which triggers thrombosis and subsequent fibrin deposition (Knight et al., 1995, Pierangeli, 2003). There are several groups of APLAs, including anti-cardiolipin antibodies (ACA), anti-β_2-glycoprotein and the lupus anticoagulant (Forman et al., 2004; Vella, 2004). High concentrations of APLAs, (as determined by ELISA) and particularly ACAs in association with vascular thrombosis or thrombocytopenia result in a clinical disorder that is called antiphospholipid syndrome (APLS) (Pierangeli, 2003, Harris & Pierangeli, 2000). An analysis of APLA levels in kidney transplant recipients has demonstrated that high titers could cause vascular thrombosis and subsequent graft loss. Tolkoff-Rubin's group, in a study that included 337 renal TCs, reported a 25% reduction in the glomerular filtration rate in post-transplant patients with low to medium ACA titers. Graft losses were observed in two cases where high concentrations of ACA were detected (Forman et al., 2004). Furthermore, Knight reported kidney transplant losses on the second day after transplantation due to vascular thrombosis that was caused by high concentrations of ACA (Knight et al., 1995; Vaidya et al., 1998). Similar results have been reported by Wagenknecht, who showed that of 56 failed renal transplant recipients who were maintained on hemodialysis prior to transplantation, 32 were positive for APLAs (Wagenknecht et al., 2000). In summary, preoperative testing for APLAs should be considered for renal TCs with a history of maintenance hemodialysis, particularly if the patients have a history of thrombotic events. If high concentrations of APLA are detected, the risk of post-transplant thrombosis is increased and anticoagulation therapy is a concern. In contrast, no significant difference in graft outcomes have been detected between TCs that tested positive or negative for APLA if the ACA titers were low (Forman et al., 2004). Anti- β_2-glycoprotein antibodies were shown to activate endothelial cells (ECs) by affecting NFκB. EC activation is accompanied by the upregulation of adhesion molecules, such as vascular cell adhesion molecules (VCAM)-1, which represents a potential pathogenic mechanism for cellular rejection and accelerated arteriosclerosis (Meroni et al., 2002).

4.3 Cold agglutinins

Cold agglutinins (CAs) are autologous antibodies that are usually of the IgMκ subtype but are occasionally of the IgG and IgA subtypes. CAs are specific to the Ii (N-acetyllactoseamine) red blood cells antigenic system. The components of this system present on the surfaces of adult human erythrocytes (Diaz et al., 1984; Roelcke, 1974). CA typically found at low titers in the peripheral blood of healthy individuals; however, their titers increase following infections by *Mycoplasma pneumoniae,* Epstein-Barr virus, and

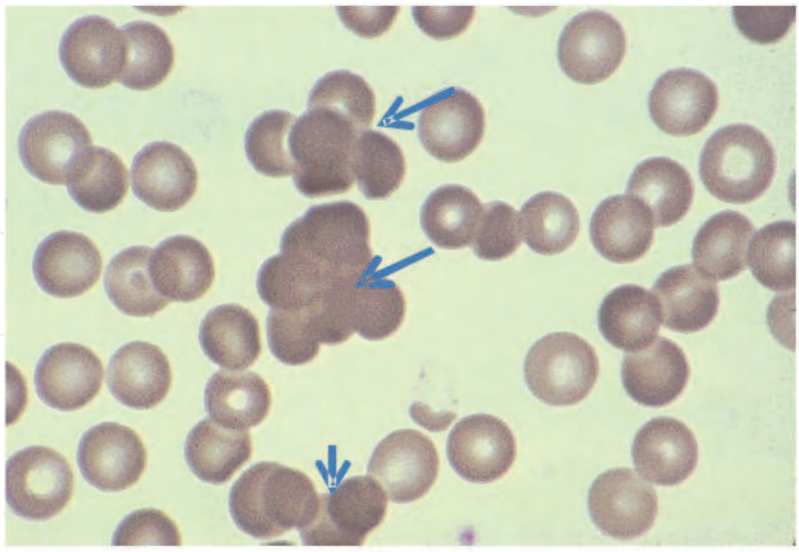

Fig. 5. Human blood smear. Blue arrows indicate agglutinated red blood cells

cytomegalovirus. These antibodies are termed CAs because they have a range of thermally-mediated activities, with the temperature of 0°C being the best (Zilow et al., 1994). CAs may also react with red blood cells at higher temperatures. The range of their reactivity is called the thermal amplitude. It has been demonstrated that the maximum thermal amplitude temperature is always less than the normal body temperature (37°C) because their activity ceases above this temperature (Diaz et al., 1984; Roelcke, 1989) (Figure 5). CAs destroy erythrocytes and can cause autoimmune hemolytic anemia through complement activation. In addition, they cause red blood cell aggregation, which, in turn, can lead to microcirculation failures (Izzat et al., 1993; Roelcke, 1974, 1989). Activation of the complement system at low temperatures can initiate the formation of microemboli and microthrombi, which may obstruct capillaries and cause organ ischemia (Roelcke, 1989; Diaz et al., 1984; Lobo et al., 1984). Carloss and Tavassoni have reported CA-mediated hyperacute kidney failure. They described a patient who developed oliguria and showed increased creatinine levels following stomach surgery. The autopsy revealed glomerulonephritis that was caused by immune complex deposition. In addition, high levels of CAs of the IgM isotype that reacted at 32°C were also detected (Carloss & Tavassoli, 1980). Sturgill and coworkers have reported hyperacute allograft failure in two diseased donor-kidney recipients. Both recipients did not have preexisting donor-specific HLA antibodies, and tissue typing indicated a six-antigen match. Kidney failure occurred immediately after the establishment of vascular anastomosis, and biopsies were performed. Marked red blood cell aggregation and fibrin thrombi in capillaries and small arteries were observed in both TCs. Elevated CA levels of the IgM isotype were also demonstrated in the serum from the recipients. The kidney from one of the recipients was removed 23 days after transplantation despite therapeutic intervention (Sturgill et al., 1984). Thus, CAs can cause irreversible changes after renal transplantation that may lead to graft loss. High concentrations of CAs in the serum may represent a potential explanation for hyperacute graft injury in non-HLA sensitized patients.

4.4 Anti-endothelial cells (EC) antibodies

The importance of DSAs for kidney allograft outcomes was documented many years ago. A strong correlation between the development of alloantibodies to mismatched HLAs and poor graft outcomes has been reported by many investigators (Adeyi et al. 2005; Baid-Agrawal & Frei, 2007; Bray & Gebel, 2008; Cai & Terasaki, 2005; Mujtaba et al., 2010; Terasaki & Cai, 2005). Recipients of perfectly matched kidney transplants generally survive longer and do not frequently develop rejection; however, 2-5% of zero HLA-mismatched kidney recipients lose their grafts due to HAR or AMR (Rodriguez et al., 2000). These graft failures can be caused by HLA allele-specific antibodies and/or non-HLA antibodies (Ferry et al., 1997; Grandtnerova et al., 2008; Lomago et al., 2010; Lucchiari et al., 2000; Perrey et al., 1998; Sumitran-Karuppan et al., 1997). In 1976, Moraes and Stastny described eight groups of non-HLA antigens that are expressed on monocytes and EC (Moraes & Stastny, 1976). Subsequent studies have demonstrated that anti-endothelial cell antibodies (AECAs) were directed against adhesion molecules, such as ICAM, VCAM, ELAM, PECAM, and vimentin (Le Bas-Bernardet et al., 2003; Lucchiari et al., 2000). Antibodies against the protein Tie2, which is one of tyrosine kinase receptors that is expressed on vascular endothelium, have also been described (Peters et al., 2004). Unlike MHC, the genes coding non-HLAs are not located on the 6th chromosome (Kalil et al., 1989). This fact offers an explanation for the rejection of HLA-identical grafts. Indeed, transplant recipients from HLA-identical siblings with no PRA had considerably longer graft survival times in comparison to those who had anti-HLA antibodies (Opelz, 2005). The vascular endothelium of transplanted kidneys and other organs is the first line of defense between the allograft and the host immune system. Similar to classical MHC antigens, the non-HLAs represent immune system targets, and AECAs appear to be clinically important as a potential risk factor for AMR (Han et al., 2009; Pober et al., 1996; Rodriguez et al., 2000; Vasilescu et al., 2004; Yard et al., 1993; Vanderwoude et al., 1995). FCCM analysis using peripheral blood EC for the detection of AECAs has been recently described. This method was shown to be reliable for identifying patients at risk for AMR that is mediated by non-HLA antibodies (Alheim et al., 2010; Breimer et al., 2009).

4.5 Antibodies against MHC class I chain-related antigens (MIC)

Another group of non-HLAs are represented by non-classical MIC antigens A (MICA) and B (MICB). These proteins are expressed on endothelial cells, fibroblasts, keratinocytes, and monocytes (Zwirner et al., 2006). In contrast to the non-HLAs described above, MICs are polymorphic (MICA has 40 alleles, MICB has 23 alleles), and their gene family is located on the 6th chromosome close to the HLA-B locus. The presence of antibodies against these antigens has been demonstrated to be associated with inferior kidney graft outcomes (Rebellato et al., 2006). Relatively high frequencies (26%) of anti-MICA antibodies have been reported in recipients with anti-HLA antibodies who lost their kidney grafts because of AMR (Mizutani et al., 2005; Mizutani et al., 2006). In summary, non-HLA antigens are expressed on graft EC but not on lymphocytes, which are routinely used for CM. Antibodies that are directed against these antigens, produce different types of rejection, including HAR, AMR, and chronic allograft nephropathy (CAN). Therefore, the detection of AECAs and anti-MIC antibodies in TCs may provide insight into unexplained graft rejection, particularly in recipients without DSAs and those who have received zero HLA-mismatched kidneys.

5. The significance of alloantibody concentration, isotype and subtype

When the initial work up of a potential renal TC is performed, the following important questions regarding humoral immunity must be answered. Does this recipient have anti-HLA antibodies? If so, what is the PRA? Are these antibodies donor-specific (DSAs)? What is the isotype of the DSAs? How much DSAs does this particular TC have? The rationale for obtaining this information is related to clinical studies, which have universally demonstrated that pre-existing DSAs can cause HAR, accelerated or AMR, and CAN (Al-Lamki, 2008; Bartel et al., 2007; Bishay et al., 2000; Bohmig et al., 2008; Cornell LD et al., 2008; Ghasemian et al., 1998; Grandtnerova et al., 1995; Lefaucheur et al., 2009; Lobo et al., 1995; Terasaki & Cai, 2008; Racusen et al., 1998). The earliest method that was used to routinely detect anti-HLA antibodies was the complement-dependent cytotoxicity assay (CDC). This technology has a relatively low sensitivity (see below), wherein it identifies anti-HLA class I antibodies using a panel of HLA-typed lymphocytes or DSA class I and class II antibodies, which are obtained from patient serum and donor lymphocytes at high concentrations. Transplanting kidneys to recipients that have been found to have DSAs by CDC generally results in irreversible HAR. The CDC assay is able to detect anti-HLA antibodies of both the IgG and IgM isotypes. Discrimination between the two isotypes is accomplished by using heating or reducing agents, such as dithiothreitol (DDT) or dithioerythritol (DTE). These compounds destroy disulfide bonds between heavy chains of IgMs and abolish their reactivity. The identification of the isotypes of DSAs is important because they differentially influence graft survival (Schonemann et al., 1998; Stastny et al., 2009). Indeed, DSAs of the IgM isotype are generally not believed to be detrimental to renal allografts (McCalmon et al., 1997; Schonemann et al., 1998; Fredrich et al., 1999); however, there have been reports of DSAs of the IgM isotype that mediate HAR and decrease the survival of kidney transplants (Demirhan et al., 1998; Stastny et al., 2009). Many investigators have reported the distribution of DSA isotypes/subclasses in kidney TCs. Arnold and colleagues have demonstrated the usefulness of ELISA in the detection of the IgG (IgG1, IgG2, IgG3, and IgG4) and IgA (IgA1 and IgA2) subtypes in kidney TCs (Arnold et al., 2005, 2008). These investigators have observed considerably higher frequencies of IgA1 and IgA2 alloantibodies in retransplant patients than in first-transplant recipients (Arnold et al., 2008). Kerman (Kerman et al., 1996) and Koka (Koka et al., 1993) have reported the non-complement fixing of IgG2/IgG4 and IgA antibodies to have a beneficial effect on kidney graft survival. Results from our transplant center have shown uneventful kidney graft outcomes in three recipients with high levels of pre-existing DSAs. Subsequent IgG subtype analysis revealed that more than 50% of these antibodies were of the IgG2/IgG4 isotype (Lobashevsky et al., 2010). It is generally accepted that low (CDC assay-negative) concentrations of DSAs of the IgG isotype are not a contraindication for transplantation, provided that pre- and post-transplantation desensitization (DS) (see below) and proper DSA monitoring are used (Bohmig et al., 2008; Bray, 1994; Christiaans et al., 1998, 2000; Graff et al., 2009; Martin et al., 2003; Patel et al., 2007; Reinsmoen et al., 2008; Vaidya et al., 2001). TCs with low DSA concentrations are considered to be medium risk patients due to higher AMR frequencies over a long-term (>5 years) follow up period in comparison to negative-DSA recipients (Gebel et al., 2009; Jordan et al., 2004, 2006; Reinsmoen et al., 2008; Vo et al., 2008).

6. Alloantibodies against HLA specificities and their impact on kidney graft outcomes

Because the deleterious effects of DSAs, which are directed against HLA-A, -B, -DRB1, and DQB1 molecules, on kidney transplant outcomes have been well documented (Abe et al., 1997; Adeyi et al., 2005; Baid-Agrawal & Frei, 2007; Billen et al., 2009a, 2009b; Bohmig et al., 2008; Cai et al., 2006a, 2006b; Christiaans et al., 1998; Dunn et al., 2010; Gebel et al., 2009; Ghasemian et al., 1998; Kerman et al., 1997; Lederer et al., 1996; Lefaucheur et al., 2009; McKenna et al., 2000; Schonemann et al., 1998; Scornik et al., 1992; Terasaki, 2003; Terasaki & Cai, 2005; 2008), this section of the review is focused on the role of antibodies against additional HLAs, such as C, non-DRB1 (DRB3, DRB4, and DRB5), DQA1, DPB1, and DPA1. This group of molecules are classical MHC antigens, meaning that, by definition, they are able to elicit cellular and humoral immune responses and present non-self antigens to CD8 (cytotoxic T lymphocytes) and CD4 (helper) T cells. In comparison to other classical HLAs, these proteins are less polymorphic (Marsh et al., 2000).

6.1 Anti-HLA-C locus alloantibodies

The immunobiology of the HLA-C locus is not well defined. One of the features of this MHC antigen is its low (~10%) cell membrane expression in comparison to HLA-A and HLA-B proteins. In addition, the products of HLA-C locus genes are not expressed on platelets (Zemmour & Parham, 1992). During the last decade, several reports have addressed their role in clinical transplantation. Kidney transplant failures and graft losses due to DSAs that are directed against mismatched HLA-C have been reported by Worthington (Worthington et al., 2003) and Qasi (Qasi et al., 2006). T cell-positive FCCM due to anti-HLA-C antibodies that have been detected by solid phase Luminex technology (see below) has been reported by Stastny (Stastny et al., 2006). These investigators have also discovered that, to produce a positive FCCM, the median fluorescence intensity (MFI) values of anti-HLA-C antibodies must be significantly higher that those produced by antibodies against HLA-A and –B. The considerable influence of anti-HLA-C antibodies on kidney allocation and graft outcomes has been noted in a recent review of Gebel and Bray (Gebel and Bray, 2010).

6.2 Anti-HLA-DRB3, -DRB4, -DRB5, -DQA1, and -DP loci alloantibodies

The immunological role of mismatches at HLA-non-DRB1, HLA-DQA, and HLA-DP loci in renal transplantation is currently under investigation. The impact of these mismatches on graft survival depends on the level of expression, immunogenicity and distribution within renal tissue. Kidney glomerular epithelium and mesangium constitutively express HLA-DRB determinants (Hart et al., 1981; Williams et al., 1980). Using an immunofluorescence technique, Fuggle and colleagues were able to detect the aforementioned antigens on glomerular endothelium, tubular capillaries and cortical and medullary tubules (Fuggle et al., 1983). They also found considerable variation in the expression of HLA-DR by proximal tubular cells. Interestingly, as was later reported by Müller, these cells lack HLA-DQ and HLA-DP antigens (Müller et al., 1989). Muczynski and colleagues, using three-laser multicolor FC analysis, have demonstrated the co-expression of HLA-DR, -DQ, and –DP proteins in renal microvascular cells (Muczynski et al., 2003). Subsequent studies have shown that all class II genes are expressed, whether constitutively or upon induction, at the

following levels in decreasing order: DR>DP>DQ (Guardiola & Maffei, 1993). In addition, the degree of cell surface expression largely depends on the cytokine milieu, particularly TNFα and IFNγ as well as the activity of the CIITA (class II, major histocompatibility complex, transactivator) transcription factor (Guardiola & Maffei, 1993; Muczynski et al., 2003). The impact of promoter activity on the haplotype expression of HLA class II DRB1-DRB3, DRB1-DRB4, and DRB1-DRB5 has been investigated by Vincent and colleagues. These investigators, using a competitive PCR methodology, analyzed the transcriptional levels of these genes and have shown that DRB1-DRB3 (serologically DR52) haplotypes have the highest levels of promoter activity, followed by DRB1-DRB4 (serologically DR53) and DRB1-DRB5 (serologically DR51) (Vincent et al., 1996). It is necessary to mention that the α chains of HLA-DQ and –DP heterodimers are polymorphic, which is unlike the α chain of DR (only two alleles have been reported thus far). This may have a significant impact on graft outcomes due to potential antibody production in cases where the donor and recipient are HLA-DQA and/or HLA-DPA mismatched. Johnson and colleagues have described the first case of anti-HLA-DP single-allele antibody development. These investigators have reported an increase in HLA-DP-specific alloantiserum in a recipient who received multiple immunizations of intradermal injections of mononuclear cells from a healthy donor (Johnson et al., 1986). Subsequent studies have not shown a significant effect of HLA-DP mismatches on graft outcomes in first transplant recipients; however, a considerable reduction in graft survival time was observed in retransplant patients (Arnold et al., 2005; Laux et al., 2003; Mytilineos et al., 1997; Qiu et al., 2005; Rosenberg et al., 1992). In kidney transplantation from deceased donors, a B cell-positive FCCM due to HLA-DP DSA was observed to result in adverse graft outcomes (Goral et al., 2008; Piazza et al., 2006; Vaidya et al., 2007). Kamoun and coworkers have reported successful kidney transplantation in a regraft patient, who showed positive FCCM due to HLA-DP DSAs, by using intensive immunosuppressive therapy (Kamoun et al., 2006). The role of pre-existing anti-HLA-DQA1 antibodies in kidney transplantation is still uncertain. Results from our transplant center have demonstrated uneventful graft outcomes in retransplant kidney recipients who had high concentrations of HLA-DQA1*05 DSAs (Lobashevsky et al., 2010). Paul Terasaki's group reported a rejection episode in a kidney transplant recipient due to HLA-DQA1*02:01 DSAs (Deng, 2008). These investigators used homozygous lymphoblastoid B cell lines for antibody absorption to demonstrate reactivity to a single DQA1/DQB1 epitope that is shared by multiple DQ determinants. Similar results were obtained by Tambur and coworkers, who reported the presence of antibodies in the pre-transplant serum of kidney TCs that were directed toward conformational changes that had been generated by a combination of DQα and DQβ-chains (Barabanova et al., 2009). In summary, the immunogenicity of HLA-non-DRB1, HLA-DQA, and HLA–DP antigens has been demonstrated by many investigators (Lobashevsky et al., 2011; Arnold et al., 2005a, 2005b; Barabanova et al., 2009; Duquesnoy et al., 2008; Duquesnoy & Askar, 2007; El-Awar et al., 2009; Laux et al., 2003; Qiu et al., 2005; Rosenberg et al., 1992). DSAs against these determinants have appeared to be less clinically significant in comparison to anti-class I and anti-DRB1 antibodies. They cause graft failure at significantly lower rates, and transplantation in individuals with a positive CM that was caused by antibodies against the aforementioned HLA determinants is less deleterious than that when a positive CM that is caused by anti-DRB1 antibodies is involved. One potential explanation for this is a lower complement binding activity in comparison to anti-DRB1 or anti-class I DSAs (Bartel et al., 2007; Fuller et al., 1999; Scornik et al., 1992); however, anti-HLA-non-DRB1, HLA-DQA, and

HLA-DP antibodies may need to be evaluated in retransplant recipients for matching and graft outcomes.

7. Methodological considerations of anti-HLA antibody detection

Antibodies against HLA can be detected by many techniques, which differ in sensitivity. This section of the review is devoted to highly sensitive FC and solid-phase methods, which employ live cells or purified HLA proteins, respectively. These methods are currently used worldwide for pre- and post-transplant alloantibody monitoring. Due to their high sensitivities, these techniques allow investigators to detect low concentrations of anti-HLA antibodies, which may be missed by low-sensitivity methods, such as CDC (Aubert et al., 2009; Fuggle & Martin, 2008; Fujita et al., 1997; Gebel & Halloran, 2010; Grandtnerova et al., 1995; Haririan et al., 2009; Jordan et al., 2006; Kerman et al., 1996; Lobo et al., 1995; Lucchiari et al., 2000; Susal & Opelz, 2002; Terasaki & Cai, J 2005, 2008; Yard et al., 1993).

7.1 Flow cytometry cell based alloantibody analysis

FC cell-based technology has been introduced in two variations: donor-specific CM (Garovoy et al., 1983) and anti-HLA antibody screening using a pool of Epstein-Barr virus (EBV)-transformed B lymphoblastoid cells or peripheral blood lymphocytes (Harmer et al., 1993; Shroyer et al., 1995). This assay uses a laser beam to detect alloantibodies. The intensity of the signal that is produced by secondary anti-human antibodies that have been conjugated to fluorochrome is proportional to the amount of bound anti-HLA antibodies and can be interpreted as the percent of reactive antibodies or PRA. The FCCM assay is the most important immunological test that is performed in transplantation because it allows for both the detection and quantification of DSAs (Bray, 1994, 2001, 2004; Bray et al., 1989; Christiaans et al., 1998; Dunn et al., 2010); however, the presence of autologous antibodies, non-HLA antibodies, or mono- and poly-clonal IgG antibodies that are used for immunosuppressive therapy in the recipient serum have significantly hampered the interpretation of the FCCM results (Lobashevsky et al., 2000; Rodriguez et al., 2000; Scornik et al., 1997). These problems were eliminated with the introduction of solid-phase assays.

7.2 Solid-phase alloantibody analysis

Solid-phase technology uses purified HLA class I and/or class II proteins that are attached to an artificial substrate or matrix. These assays offer significantly higher sensitivities and specificities than cellular methods (Fuggle & Martin, 2008; McKenna et al., 2000; Smith & Rose, 2009). The enzyme-linked immunosorbent assay (ELISA) was the first solid-phase analysis that was developed for antibody screening and specificity determination (Buelow et al., 1995). In this assay, HLA molecules are bound to the wells of plastic trays, and positive reactions are measured by the color signal intensity, which is produced by enzymes that have been conjugated to anti-human antibodies followed by the addition of substrate to the wells. Subsequent studies have shown that the ELISA methodology was less sensitive than FC methods (Arnold et al., 2004; Christiaans et al., 2000; Kerman et al., 1996; Lefaucheur et al., 2009; Schonemann et al., 1998; Smith & Rose, 2009). FC solid-phase assays use microspheres that have been coated with soluble HLA proteins, which can be extracted from a single cell line for specificity analysis or mixed for PRA analysis (Flow PRASpecific, FlowPRA, One Lambda) (Pei et al., 2003). LUMINEX bead technology incorporates

microparticles that have been conjugated to varying amounts of two dyes, which enables the identification of 100 sets of beads. HLA-specific alloantibodies are detected via addition to a reaction mixture of secondary PE-conjugated anti-human antibodies. Because each group of beads can be identified by the amount of conjugated fluorochrome, it is possible to identify which HLAs have bound antibodies. The original assay was introduced as a combination of beads that were coated with HLA proteins that had been extracted from individual cells. More recently, with the development of recombinant HLA proteins, LUMINEX technology produced microparticles that were covered with a single class I or class II HLA. This methodological approach revolutionized antibody specificity analyses, particularly in highly sensitized patients (Billen et al., 2009; El-Awar et al., 2005, 2006; Lobashevsky & Higgins, 2009; Mujtaba et al., 2010; Pei et al., 2003; Zeevi et al., 2009). The considerably higher surface density of HLAs on the microbeads in comparison to that achieved on lymphocytes (Jar How Lee, personal communication, 2010) makes the LUMINEX single-antigen (SA) methodology extremely specific and highly sensitive, enabling investigators to detect very low concentrations of HLA-directed antibodies. The latter is particularly important from a clinical point of view. Yet, how strong must the DSA signal that is produced by a SA Luminex assay be to generate a positive FCCM? In order to address this question, correlation analyses between MFI values that are detected by SA beads and signals that are detected by lymphocyte FCCM must be performed (Lobashevsky & Higgins, 2009; Martin et al., 2003; Mizutani et al., 2006; Ozawa et al., 2006; Poli et al., 2009; Qasi Y et al., 2006; Stegall et al., 2009; Terasaki & Cai, 2005; Zachary et al., 2005, 2009). At our transplant center, the positive MFI thresholds for anti-HLA class I and class II antibodies, which are detected via SA technology and produce positive FCCMs, are 2800 and 3500, respectively (predictive value >95%) (Figure 6).

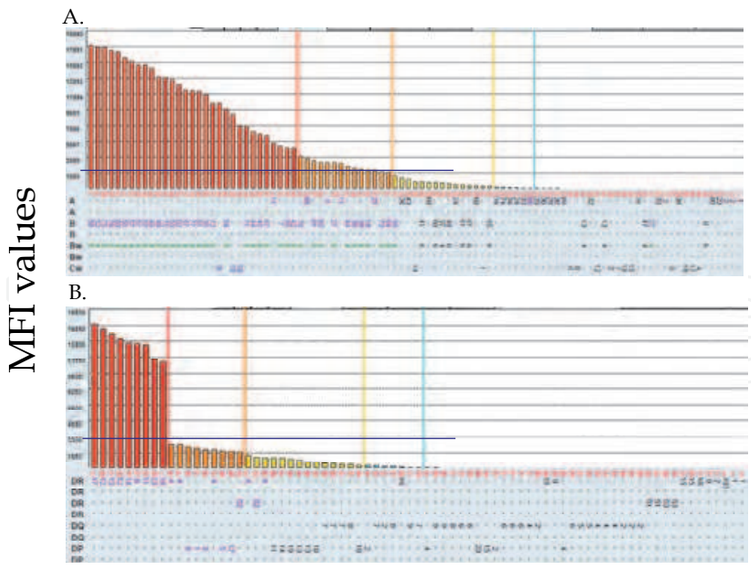

Fig. 6. HLA class I (A) and class II (B) antibody specificity determination using Luminex platform solid phase methodology. Vertical axis indicates mean fluorescence intensity (MFI), horizontal axis indicates single HLA class I and class II proteins conjugated to the beads. Blue lines determine positive cut-offs (i.e. MFI value levels producing positive FC CM results when donor lymphocytes are used) established by our laboratory.

This effect is cumulative when multiple DSAs are being considered (Lobashevsky & Higgins, 2009). There are a few caveats regarding the SA LUMINEX analysis. First, as mentioned above, the density of HLA molecules on the bead is significantly higher than that on lymphocyte (5×10^4 - 10^5 molecules per cell) or endothelial cells. Therefore, even a minor admixture of anti-HLA antibodies of the IgM isotype may cause false negative results. To overcome this obstacle, serum DTT-treatment is recommended (Zachary et al., 2009). More recently, discrepant results between negative FCCMs and highly reactive DSAs that have been determined by SA Luminex have been reported. In this study, strong DSA anti-B44 (high-resolution donor HLA-B locus typing confirmed DSAs) reactivity was determined in the recipient serum by SA beads; however, negative T- and B- cell FCCM was observed when donor lymphocytes were used. Biochemical modification (denaturing) of HLA proteins during the bead conjugation process can account for this discrepancy. In comparison to unmodified HLAs, denatured HLAs have a higher affinity for DSAs and, when present in large amounts, they produce strong false positive signals. To rule out antibodies against denatured HLAs, an acid treatment is used. Antibodies against denatured HLA proteins are likely present when no difference in MFI values is observed between treated and untreated beads (Gandhi et al., 2011). Several years ago, solid-phase bead-based CM assays were developed at the Tepnel Lifecodes Corporation. This technique utilizes synthetic micro-particles that have been labeled with different fluorochromes and coated with capturing antibodies that are directed to non-polymorphic domains of class I (α3) and class II (β2) HLA molecules. Donor HLAs (lysate) are extracted from lymphocytes and incubated with the beads. Recipient serum and anti-human antibodies are then added. Fluorescent signals identify each set of microparticles as well as the reporter dye that is linked to the secondary antibodies. In this way, it can be determined if the potential recipient has class I or/and class II DSAs. A comparative analysis of solid-phase and lymphocyte CM assays, which have been performed by our group, have demonstrated a 100% agreement when sera with anti-HLA-A, -B, and -DR antibodies were used (Lobashevsky et al., 2009).

Complement activation following antibody/HLA interactions is clinically important in two ways. First, the classical pathway of complement activation causes C4d deposition in peritubular capillaries and is usually associated with graft cell damage and poor graft outcomes. Second, high concentrations of pre-existing IgG DSAs (positive CDC CM) are a risk factor for HAR. Over the course of the last decade, the implementation of various DS protocols (see below) for highly sensitized patients has resulted in successful kidney transplantation in patients with positive FCCMs that have been caused by DSAs; however, the graft outcome and survival times appear to depend on several parameters, e.g., the amount of DSAs that are producing a positive FCCM, their isotype, the cytokine profile of the recipient and others (Akalin & Bromberg, 2005; Bray 1994; Christiaans et al., 1998; Graff et al., 2009; Horsburgh et al., 2000; Lobashevsky et al., 2010; Martin et al., 2003; Mujtaba et al., 2010; Qasi et al., 2006; Scornik et al., 1997; Worthington et al., 2003; Zachary et al., 2005). It has recently been demonstrated that some DSAs that are detected by FC, but not by CDC (FC pos/CDC neg), are able to activate complement. Bartel and colleagues demonstrated, using SA bead technology and antibodies against C4d, C1q and C3b, that inferior graft outcomes were observed more frequently in recipients whose DSAs were able to bind the complement (Bartel et al., 2007). Similar findings have been reported by others (Bohmig et al., 2008; Yabu et al., 2010). Saw and coworkers have developed a comprehensive procedure that determines cell death and antibody binding in a single assay by using TOPRO-3

staining for apoptotic cells (Saw et al., 2008). In summary, solid-phase analysis represents a powerful tool for anti-HLA antibody analysis and has several advantages over other assays. First, due to its superior sensitivity and specificity, low concentrations of DSAs pre- and post-transplant can be detected. Second, this technology does not require viable cells. Third, it detects only anti-HLA antibodies.

8. Desensitization is a method for the removal of pre-existing anti-HLA antibodies

The development of anti-HLA antibodies represents a significant barrier to transplantation for many patients because of the high risk of AMR-mediated graft failure (Adeyi et al., 2005; Zachary, 2009; Bray, 1994, 2001; Haririan et al., 2009; Yard et al., 1993; Zeevi et al., 2009). Historically, transplantation for such patients was possible only when a donor could be found whose tissues did not express any HLA that the recipient produced antibodies against.

8.1 Intravenous immunoglobulin (IVIG)

During the last two decades, however, protocols using pooled human IVIG and/or plasmapheresis (PP) have been shown to eliminate some or all DSAs (Jordan et al., 2004, 2006; Reinsmoen et al., 2008; Rogers et al., 2011; Thielke et al., - 2005; Claas et al., 2004; Gloor et al., 2004; Stegall et al., 2009; Leong et al., 2008). Furthermore, a beneficial effect of IVIG/PP treatment for AMR has been reported by many transplant centers (Akalin et al., 2008; Furth et al., 1999; Lehrich et al., 2005; Rifle & Mousson, 2003; Toyoda et al., 2004; Vo et al., 2010). More recently, it was reported that sensitized TCs require different DS regimens to reduce DSA levels, including varying the IVIG dose and the number of PP cycles (Cai & Terasaki, 2005; Thielke et al., 2005; Ferrari-Lacraz et al., 2006; Glotz et al., 2004; Rogers et al., 2011). Subsequent studies have demonstrated that susceptibility to IVIG/PP DS depends on immunoregulatory mechanisms, such as polymorphisms in cytokine genes, the frequency of regulatory cells, and hormonal backgrounds (Figure 7) (Glotz et al., 2004; Lobashevsky et al., 2009; Rogers et al., 2011; Zachary et al., 2003; Bas et al., 1998; Di Genova et al., 2006, 2010; Jiang & Lechler, 2003, Amu et al., 2007; Anderson et al., 2000; Hill & Sarvetnick, 2002; Kalil et al., 1989; Stasi et al., 2008; Stastny P et al., 2006; Yoo et al., 1995).

Furthermore, the efficacy of DS has been reported to be different for DSAs and third-party HLA antibodies. For example, Andrea Zachary's group reported a considerable reduction in DSAs in a TC that had been subjected to IVIG DS in comparison to the level of alloantibodies against a third party (Zachary et al., 2003). Higgins et al. observed similar results (Higgins et al., 2009). Our data are also in agreement with these findings; however, they did not reach statistical significance (Lobashevsky et al., 2009). IVIGs are commercially prepared products that contain IgGs (>90%) that are derived from human plasma that has been pooled from tens of thousands of healthy individuals. In addition, IVIGs contain antibodies against CMV, T cell receptor idiotypes, and some cytokines, including GM-CSF and IL-1β (Jordan et al., 2003). The primary mechanisms of IVIG-mediated immunomodulation are summarized as the following: first, the inhibition of complement binding through blockage of C3 convertase (Kazatchkine & Kaveri, 2001; Lutz et al., 2004; Watanabe & Scornik, 2005); second, the neutralization of circulating antibodies through idiotype-anti-idiotype interactions (Glotz et al., 2004; Jordan et al., 2004, 2006; Watanabe & Scornik, 2005); third, the inhibition of IL-2 and IFN–γ secretion (Glotz et al., 2004;

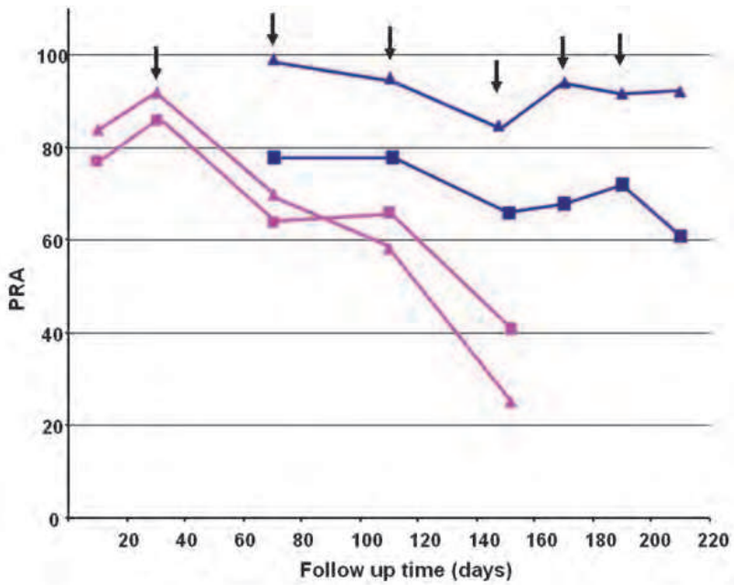

Fig. 7. PRA changes (—■— class I, —▲— class II) in susceptible (pink line) and resistant (blue line) to DS TCs after sequential courses of IVIG/PP. Black arrows indicate IVIG administration.

Kazatchkine & Kaveri, 2001); forth, the inhibition of T cell proliferation through anti-T cell receptor activity (Jordan et al., 2006; Klaesson et al., 1993); and fifth, the downregulation of antigen that presents cell (APC) activity, which causes the inhibition of T cell activation through Fc receptor-mediated interactions (Bayry et al., 2003). Clinically, IVIG are known to be well tolerated; however, adverse events, such as osmotic nephropathy and hemolytic anemia in non-O blood type patients, have been reported (Banerjee et al., 2003). Commercial preparations of IVIG contain different concentrations of anti-A and anti–B isohemagglutinins. The highest concentrations have been found in Privigen (1:64 and 1:32 titers of IgG anti-A and anti-B, respectively). In contrast, Carimune contains the lowest titers of anti-A and anti-B isohemagglutinins; however, this preparation is hyperosmolar, which limits its use in patients who are not on dialysis or present with an increased risk of thrombosis (Kahwaji et al., 2009). IVIG immunomodulation should be considered for treatment in non-O blood type TCs due to the increased risk of IVIG-induced hemolytic anemia. Anti-A and/or anti-B isohemagglutinin titers in IVIG preparations are particularly meaningful when AB blood type-incompatible kidney transplantation is an option due to the increased risk of anti-A/B antibody-mediated graft failure.

8.2 Rituximab

A combination of IVIG and Rituximab (Rituxan) (chimeric humanized monoclonal antibodies against the CD20 marker for B lymphocytes) DS has been shown to effectively reduce DSAs. The rates of the conversions of positive to negative CDC CMs and reductions of MCS in FCCMs were higher in comparison to cases where DS was used without Rituxan (Lefaucheur et al., 2009; Rogers et al., 2011; Vo et al., 2008; Vo et al., 2010). Rituxan affects mature B-cells (CD20+, IgG-, CD19+) and at lesser degree memory B cells (CD20+, CD27+, IgG+) and prevents the formation of plasma cells (CD20-, CD19- IgG-, CD38+, CD138+) *de*

novo. A beneficial effect of Rituxan and IVIG for AMR treatment in kidney transplantation was reported by Vo et al. (Vo et al., 2010) and Lefaucheur et al. (Lefaucheur et al., 2009). The IVIG/Rituxan treatment resulted in more effective DSA removal, likely by blocking the indirect pathway of mismatched HLA protein recognition. In this case, mature B cells function as APCs and present donor HLA-processed peptides to the host T helper cells. The latter become activated and stimulate the differentiation of B memory and mature B cells into antibody-producing short- and long-living plasma cells by secreting IL-4, IL-6, IL-1β, GM-CSF, and IL-17 (Yoo et al., 1995).

8.3 Plasmapheresis (PP) or therapeutic plasma exchange (TPE)

As mentioned above, PP [or therapeutic plasma exchange (TPE)] is a necessary component of immunomodulation/DS or AMR therapy because it physically removes anti-HLA antibodies from the circulation. This function can also be applied to paraproteins, polyclonal autoantibodies, or antibodies in immune complexes. Although PP implementation results in a considerable reduction of anti-HLA antibodies, the effect can only be achieved after multiple cycles of treatment in highly sensitized TCs. This is presumably because of IgG equilibration between the intravascular and extravascular spaces. For example, depleting the total body IgGs by 85% was observed to require five exchanges of 1.25 times the plasma volume (Weinstein 2003). In addition, the removal of immunoglobulins by PP may be followed by an increase in specific antibody titers (the rebound effect) to levels that are even higher than those at baseline. The mechanism of this phenomenon is through biofeedback stimulation to increase IgG synthesis (Dau P 1995).

8.4 The removal of anti-AB blood group antibodies

Historically, ABO incompatibility (ABOi) is considered to be a contraindication for kidney transplantation due to irreversible HAR of the graft. The shortage of kidney donors has led to an increasing gap between the number of patients who are waiting for kidney transplantation and the number of available kidney donors. An expansion of the kidney donor pool can be achieved by performing transplantations despite the immunological barrier of ABOi. Successful kidney transplantation from A2 (A2B or A2O) donors to B or O recipients was reported (Alkhunaizi, 2006; Bryan et al., 1998; Nelson et al., 1998). Bryan and colleagues demonstrated that the graft outcomes in A2 donor (deceased and living) kidney recipients were comparable to ABO-compatible transplants (Bryan et al., 1998). Subsequent investigations have shown that the success of A2 donor transplantation depends on anti-A1 and anti-A2 IgG isohemagglutinin titers in the recipient serum prior to transplantation. A1 and A2 blood group antigens differ qualitatively and quantitatively (see above). Indeed, for transplantation from A2 donors into B or O recipients, anti-A1 IgG titers that were above 1:128 have been shown to represent a significant risk factor for AMR (Squifflet et al., 2004; Tyden et al., 2010; Valli et al., 2009; Warren et al., 2004). In addition, Alkhunaizi reports that up to 8% of A2 individuals have anti-A1 IgG antibodies in their sera (Alkhunaizi, 2006). Anti-A1 IgG antibody titers of less than or equal to 1:8 have been considered to be a cut-off for assuming a low risk of AMR (Gloor & Stegall, 2007; Jordan et al., 2009; Rydberg et al., 2007; Warren et al., 2004). Additional therapeutic measures are required when titers of anti-A1 IgG antibodies are high, such as plasma exchange that is accompanied by a bimonthly monitoring of anti-A1 titers (Montgomery & Locke, 2007; Tobian et al., 2009; Tyden et al., 2010; Winters et al., 2004).

About a decade ago, more A1 to B, B to A1, and A1 or B to O ABOi kidney transplants were initiated to increase the potential donor pool. Reports from Europe, Japan and the United States have demonstrated successful ABOi kidney transplantation from both living and deceased donors. Tanabe reported a relatively high percentage of 1- and 2-year graft survivals (96% and 94%, respectively) after using 3-4 pre-transplant PPs along with splenectomy and/or Rituximab (Tanabe, 2007; Beimler & Zeier, 2007). A new protocol for ABOi kidney transplantation was introduced in Sweden in 2001. In this method, immunoabsorption columns that were filled with A/B oligosaccharides (Glycosorb, Glycorex Transplantation AB, Lund, Sweden) were used instead of PP in order to remove anti-A or anti-B antibodies. In addition, Rituximab was used instead of splenectomy in order to prevent rebound effects (Tyden 2007; Valli et al., 2009). These investigators demonstrated that anti-AB IgG antibody titers were reduced from 1:2 – 1:128 to 1:1-1:2 after 4-8 cycles of immunoabsorption. A rebound effect was observed in only one of eleven recipients after 36 months post-transplantation. Notably, no differences in graft survival time between ABOi and ABO-compatible transplantations were observed (Rydberg et al., 2007; Tyden et al., 2005). Five years ago, the John Hopkins Transplant Center established a DS protocol for ABOi transplantation, which consisted of PP, IVIG and Rituxan administration (Sonnenday et al., 2004; Tobian et al., 2009). This immunomodulating strategy included multiple cycles of pre-transplant PP so as to reduce anti-A/B antibody titers to <1:16 followed by a single dose of Rituximab. The post-transplantation treatment included an additional 3-4 PP/IVIG cycles. An analysis of graft outcomes in six ABOi donor/recipient combinations did not demonstrate any differences in either creatinine levels or the rate of humoral rejection (Sonnenday et al., 2004). More recently, several groups have reported successful implementations of the drug Bortezomib ($C_{19}H_{25}BN_4O_4$) (Velcade) for DS and AMR treatment in kidney transplantation (Everly et al., 2009; Raghavan et al., 2010; Walsh et al., 2010). Originally, Bortezomib was used for the treatment of multiple myeloma, which is a tumor consisting of plasma cells (PCs) (Cavo 2006; Mitchell 2003). The mechanism of action for this drug involves proteosome inhibition, which is accomplished by the binding of the 26S subunit and subsequent apoptosis, through caspase 3/7, in antibody-producing PCs (Diwan et al., 2011; Perry et al., 2009; Ruschak et al., 2010). The use of Bortezomib in clinical transplantation is advantageous for the specific targeting of long-living CD38+/CD138+/CD20- PCs in the bone marrow and secondary lymphoid tissue. Subsequent studies have shown that Bortezomib alone had little or no impact on DSA levels (Sberro-Soussan et al., 2010); however, when used in combination with PP, IVIG or Rituximab, a prominent reduction in class I and class II DSA concentrations were demonstrated (Diwan et al., 2011; Everly et al., 2009; Perry et al., 2009). In summary, removing DSAs or anti-A/B blood group antibodies expands the donor pool for highly sensitized or ABOi kidney TCs; however, these methods introduce several concerning issues. First, in the majority of cases, DS does not completely eliminate DSAs. Second, the DSA rebound effect presents considerable concern. The rate and intensity of alloantibody return depends on multiple factors, including the production of cytokines, hormones, frequency immunoregulatory cells, and infection. Third, desensitized patients require regular post-transplant DSA monitoring so as to determine if additional immunomodulating therapy is necessary. Finally, long-term kidney graft outcomes in desensitized recipients are beset with frequent humoral rejection episodes and graft loss when compared to DSA-negative TCs.

9. The association between post-transplant alloantibody production and rejection

9.1 Antibody-mediated rejection (AMR) or humoral rejection

AMR is a frequent complication in renal transplant recipients and may develop any time after transplantation (Abe et al., 1997; Christiaans et al., 1998; Cornell et al., 2008; Gloor et al., 2004; Lefaucheur et al., 2009; Matas et al., 2000; Patel et al., 2007; Perrey et al., 1998; Supon et al., 2001; Zeevi et al., 2009). Alloantibodies that are produced against donor tissues are usually directed against mismatched HLA class I and/or class II antigens, in addition to non-HLAs, including MIC and EC antigens (reviewed in Cornell et al., 2008; Smith & Rose, 2009; Smith, 2007). It is generally accepted that complement-mediated cytolysis is the major mechanism of kidney vascular endothelial and parenchymal cell damage. The clinicopathological presentation of AMR is characterized by peritubular capillary C4d deposition, which is characterized by a rapid rise in serum creatinine and the appearance of DSAs in the circulation. C4d is a component of the classical pathway of complement activation, which remains in the tissue for several days (Cornell et al., 2008; Haririan et al., 2009). Peritubular capillary C4d deposition has been demonstrated in 88%-95% of kidney transplant recipients who developed class I and class II DSAs (Colvin, 2007); however, AMR can occur even without detectable concentrations of DSAs in the circulation, which is likely due to their absorption by the kidney graft. The subsequent nephrectomy is usually accompanied by a rise in DSAs within several days (Cornell et al., 2008; Duquesnoy, 2008; Duquesnoy & Claas, 2007). The detrimental effects of non-HLA antibodies are also associated with complement fixing but at a lower degree; however, in the absence of complement, anti-MIC antibodies and AECA can activate graft ECs to proliferate, resulting in the upregulation of adhesion molecules, such as ELAM, ECAM, and neuropilin-2 receptor, as well as the production of TGF-β, which stimulates the growth of connective tissue fibroblasts [reviewed in (Smith & Rose, 2009)]. Recently, graft accommodation in experimental models was described (Aikawa et al., 2003; Jin, 2002; Tabata, 2003). The state of accommodation is defined as normal graft function and appearance, which is evaluated by light microscopy, in the presence of circulating DSAs (Cornell, et al., 2008). The mechanism of accommodation was found to be associated with the upregulation of anti-apoptotic genes, such as bcl-2, bcl-xL, and A20. The precise mechanism of accommodation is still under thorough investigation.

9.2 The role of aloantibodies in chronic rejection or chronic allograft nephropathy (CAN)

DSAs also participate in the development of chronic allograft changes, which can be seen in glomeruli, vessels, tubules and the interstitium (Cornell et al., 2008; Racusen et al., 1998). Their pathological effects therein are mediated by two major processes. First, DSAs cause EC damage by complement-dependent cytotoxicity, which is also a mechanism of humoral rejection; however, unlike AMR, C4d deposition has been reported in approximately 30% - 50% of cases (Colvin 2007). Second, the upregulation of fibroblast growth factor receptors has been demonstrated in elegant studies that were conducted by E. Reed's group (Jin, 2002). These investigators found that the antibody-mediated ligation of class I HLAs triggers an activation signal in ECs, resulting in arterial smooth muscle cell and basement membrane fibroblast proliferation. As a consequence, the lumen of glomerular arteries is decreased and subsequent fibrosis and tissue/organ ischemia develop.

10. Conclusions

1. HLA and non-HLA-specific DSAs play a critical role in the pre- and post-transplant monitoring of renal patients. High levels of anti-HLA (high PRA) antibodies are generally associated with longer periods of time on dialysis and/or on the transplant waiting list until a CM-compatible donor can be found. Post-transplant DSA development often leads to AMR, graft deterioration, or eventual loss.
2. AMR or humoral rejection is mediated by a multi-component mechanism that is associated with anti-HLA class I and class II alloantibodies, complement, and T cells whose primary targets are graft endothelial and tubular cells. Although complement-dependent cytotoxicity is the chief mechanism of antibody-mediated graft damage, additional biological processes result in EC proliferation, pro-inflammatory cytokine production, and apoptosis. Post-transplant DSA development depends on multiple factors, including donor-recipient HLA mismatches (epitope levels), recipient HLA-class II typing, and immunoregulatory mechanisms. Careful analysis of mismatched epitopes can predict, with some degree of accuracy, the profile of antibodies that will develop post-transplant. The latter is particularly meaningful for subsequent donor searches.
3. The pre-transplant deletion of anti-HLA antibodies, or DS, considerably expands the pool of donors for highly sensitized TCs. This therapeutic approach (or immunomodulation) often includes combinations of different protocols, including the use of PP, IVIG, Rituximab and Bortezomib; however, DS is not a panacea for patients with high PRAs, and not all recipients are susceptible to this treatment. In addition, the rebound effect is a frequent consequence of this type of immunomodulation. Furthermore, all of the aforementioned DS protocols are not free from adverse effects. Although the majority of cases show considerable decreases in DSA antibody levels, they are not completely eliminated (the rate of antibody production is 1000 molecule/PC cell/second). These remaining DSAs represent a risk factor for humoral graft rejection in long-term follow up.
4. The development of DSAs is a major obstacle to long-term graft survival. Because of this, individual immunosuppression/DS is one of the most hopeful future directions for progress in kidney transplantation. This therapeutic approach must incorporate the analysis of the genes that are involved in cytokine (IL-12, TNFα, IFNγ) and chemokine production, the frequency of T regs and NKT cell production, as well as detailed analysis of the alloantibody profiles.

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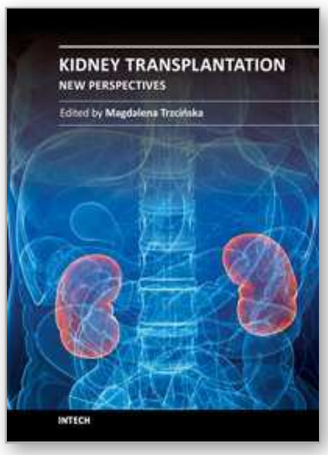

Kidney Transplantation - New Perspectives

Edited by Dr Magdalena Trzcinska

ISBN 978-953-307-684-3
Hard cover, 334 pages
Publisher InTech
Published online 23, August, 2011
Published in print edition August, 2011

Although many years have passed since the first successful kidney transplantation, the method, although no longer considered a medical experiment, is still perceived as controversial and, as such, it triggers many emotions and thatâ€™s why conscious educational efforts are still needed for kidney transplantation, for many people being the only chance for an active lifestyle and improved quality of life, to win common social acceptance and stop triggering negative connotations. Apart from transplantation controversies piling up over years transplantologists also have to face many other medical difficulties. The chapters selected for this book are of high level of content, and the fact that their authors come from many different countries, and sometimes even cultures, has facilitated a comprehensive and interesting approach to the problem of kidney transplantation. The authors cover a wide spectrum of transplant-related topics.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Andrew Lobashevsky (2011). Characteristics, Detection, and Clinical Relevance of Alloantibodies in Kidney Transplantation, Kidney Transplantation - New Perspectives, Dr Magdalena Trzcinska (Ed.), ISBN: 978-953-307-684-3, InTech, Available from: http://www.intechopen.com/books/kidney-transplantation-new-perspectives/characteristics-detection-and-clinical-relevance-of-alloantibodies-in-kidney-transplantation

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