Review Article

A narrative review on progress and development of anti-CD36 antibody detection

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Objective: This article aimed to describe different approaches for the detection of anti-CD36 antibodies.

Background: Antibodies against type I cluster of differentiation 36 (CD36) have been implicated in several immune thrombocytopenic disorders, including foetal and neonatal alloimmune thrombocytopenia (FNAIT), post-transfusion purpura (PTP), and platelet transfusion refractoriness (PTR). Furthermore, transfusion-related acute lung injury (TRALI) associated with anti-CD36 antibodies was also reported. It has been suggested that type I CD36-deficient individuals (lacking CD36 both on platelets and monocytes), not type II (lacking CD36 only on platelets) individuals are at risk of producing anti-CD36 isoantibodies through blood transfusion and pregnancy. CD36 deficiency is very rare in Caucasians, but it is common in Asian and African populations. Until today, several cases of PTR and FNAIT caused by anti-CD36 antibodies have been documented. Therefore, the detection of anti-CD36 antibodies should be considered for Asian and African patients suffering from immune thrombocytopenia.

Methods: We described different methods, such as the platelet suspension immunofluorescence test (PSIFT), mixed passive hemagglutination (MPHA), monoclonal antibody-specific immobilization of platelet antigens (MAIPA), the commercial solid-phase assay (PakPlus), and Luminex bead-based platelet antibody detection assay (PAKLx), to detect anti-CD36 antibodies and illustrate their advantages and disadvantages.

Conclusions: Although most approaches for the detection of platelet antibodies have been used to test CD36 antibodies, but these methods have some drawbacks. Currently, a combination of these methods is necessary to ensure the detection of anti-CD36 antibodies.

Keywords: CD36; CD36 isoantibodies; immune thrombocytopenia

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Introduction

Immune-mediated thrombocytopenia occurs due to alloantibodies against platelet antigens, such as the ABO blood group antigens, HLA class I, and human platelet antigens (HPA). In recent years, more than 30 HPA have been identified (https://www.versiti.org/medical-professionals/precision-medicine-expertise/platelet-antigen-database/hpa-gene-database). Among them, alloantibodies against the HPA-1a formed by point mutation (Leu33Pro) on platelet glycoprotein (GP) IIIa (known as β3 integrin) are responsible for most cases of alloimmune thrombocytopenia in Caucasians (1). However, foetal and neonatal alloimmune thrombocytopenia (FNAIT) caused by anti-HPA-1a antibodies has not been well recognized in other populations. Interestingly, accumulating evidence indicates that immune-mediated thrombocytopenia caused

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by anti-CD36 antibodies is frequently found in Asian and African populations (2-5). CD36 isoantibodies (originally described as anti-Nak[a]) was firstly reported in a Japanese patient who developed platelet-transfusion refractoriness (PTR) (6). According to the expression of CD36 on platelets and monocytes, two types of CD36 deficiency have been identified. Through blood transfusions or during pregnancy, type I deficient, but not type II, individuals may be at risk of developing anti-CD36 isoantibodies, leading to serious immune-mediated thrombocytopenia, such as FNAIT, PTR, and post-transfusion purpura (PTP) (4,7-10).

In recent years, the role of anti-CD36 antibodies in the pathophysiology of immune-mediated thrombocytopenia has been attracting much attention in Asia and across the world. In this review article, all currently available methods for the detection of anti-CD36 antibodies will be discussed. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/aob-21-48).

Methods for anti-CD36 antibody testing

Table 1 shows the list of different methods applicable for the analysis of anti-CD36 antibodies in PTR and FNAIT cases (3,4,6,8,9,11-22). The advantages and disadvantages of these different assays are illustrated in *Table 2*.

Binding assays with intact platelets

In the 1970s, von dem Borne *et al.* developed a simple platelet suspension immunofluorescence test (PSIFT) to detect platelet antibodies using paraformaldehyde-fixed platelets by fluorescence microscopy (23). Although PSIFT is sensitive, this method is difficult to standardize and does not provide an objective quantification, and therefore, analysis by flow cytometry is preferable (*Figure 1A*) (6). In Japan, a mixed passive hemagglutination assay (MPHA) using sheep red cells (MPHA) or magnetic beads (M-MPHA) coated with anti-human IgG as an indicator was established to detect platelet antibodies (*Figure 1B*) (24,25). By this approach, all antibodies reacting with antigens expressed on the platelet surface are detected. Consequently, identifying platelet-specific antibodies (anti-HPA) in a serum sample containing other platelet reactive antibodies (such as anti-HLA) is difficult. To avoid this problem, Nordhagen *et al.* denatured HLA antigenic determinants to produce HLAnull platelets by treatment with chloroquine (26).

This approach, however, does not only cause reduction of HLA class I reactivity, but also diminished the binding of platelet specific antibodies (27). Nevertheless, due to simple practicality, flow cytometry and MPHA methods are widely used by many laboratories to identify platelet antibodies, including anti-CD36 antibodies (*Table 2*). In *Table 1*, 5 of 13 cases of PTR and 3 of 11 cases of FNAIT caused by anti-CD36 antibodies are tested by flow cytometry (3,6,15,18,21). MPHA was only used to test for anti-CD36 antibodies in one PTR case and two FNAIT cases reported in Japan (8,9,19). However, the use of control cells that do not express the antigen (CD36 negative) is mandatory to draw a final statement about the presence of anti-CD36 isoantibodies. Therefore, fresh platelets from CD36-deficient individuals are required to evaluate anti-CD36 antibodies, which are not easily available to many laboratories.

Binding assays with immobilized platelet glycoproteins

To avoid the interference of anti-HLA antibodies and to define the specificities of anti-HPA antibodies in a serum sample, a glycoprotein-specific immunoassay using monoclonal antibodies (mAbs) as capture antibodies was developed. The first generation of such assay was based on the use of platelet lysates. Platelet glycoproteins in platelet lysate were captured by mAbs, and antibodies from the serum sample bound to the immobilized glycoprotein were subsequently detected with radiolabelled secondary antibodies (28,29). Based on the disadvantages of this assay (radioactivity, high background, and low sensitivity), a second generation of the glycoprotein-specific immunoassay, known as MAIPA, was developed. In contrast to the first-generation assay, whole platelets were used. Platelets were first incubated with the serum sample and mAbs and then lysed. A triple molecular complex consisting of mAb-antigen-human antibodies was captured by immobilized anti-mouse IgG. Finally, bound human antibodies were detected by the use of enzyme-labeled secondary antibodies (*Figure 2A*) (30). This approach is currently considered the gold standard for the characterization of platelet antibodies (30,31). In addition, a modified antigen capture ELISA (MACE) was established to prevent non-specific reactions. In this method, human antibodies bound platelets were lysed and then added into the microtiter wells coated directly with mAbs against platelet glycoproteins (*Figure 2B*) (25). However, high sensitivity and specificity of antibody detection could be achieved by both approaches.

Twelve of the reported 24 PTR and FNAIT cases caused

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Table 1 Detection of anti-CD36 antibodies associated with 13 cases of PTR and 11 cases of FNAIT by different assays

Subjects	Age (years)/ sex	Population	Immune-mediated thrombocytopenia	MAIPA results (Pos or Neg) (clone name of mAbs)	PakPlus, PSIFT, MPHA, MACE, PAKLx, PABA, ACA	References
Patient #1	36/F	Japanese	PTR	n.t	PSIFT	Ikeda *et al.*, 1989 (6)
Patient #2	19/M	Japanese	PTR	n.t	MPHA	Fujino *et al.*, 2001 (9)
Patient #3	36/M	?	PTR	Neg (FA6-152; 1A7 and 131.4)	PakPlus	Flesch *et al.*, 2008 (11)
Patient #4	5/F	Lebanese	PTR	Weak Pos (FA6-152)	PakPlus, MACE	Saw *et al.*, 2010 (12)
Patient #5	70/M	Chinese	PTR	Neg (FA6-152)	PakPlus, MACE	Saw *et al.*, 2010 (12)
Patient #6	7/M	Chinese	PTR	n.t	PakPlus	Yin *et al.*, 2011 (13)
Patient #7	22/M	Chinese	PTR	Pos (FA6-152)	PakPlus, PSIFT	Xu *et al.*, 2013 (3)
Patient #8	35/F	Chinese	PTR	Pos (FA6-152)	PakPlus,	Xia *et al.*,2014 (14)
Patient #9	26/F	Chinese	PTR	Pos (FA6-152)	PSIFT	Wu *et al.*, 2014 (15)
Patient #10	21/F	Chinese	PTR	Pos (FA6-152)	PSIFT	Wu *et al.*, 2014 (15)
Patient #11	63/F	Chinese	PTR	Pos (FA6-152)	PSIFT	Wu *et al.*, 2014 (15)
Patient #12	21/M	Chaldean	PTR	n.t	PABA	Khatri *et al.*, 2019 (16)
Patient #13	66/F	African-American	PTR	n.t	PakPlus, PABA	Schmidt *et al.*, 2020 (17)
Patient #14	?/F	Thai	FNAIT	n.t	MPHA	Kankirawatana *et al.*, 2001 (8)
Patient #15	37/F	Nigerian	FNAIT	n.t	PakPlus, MACE	Curtis *et al.*, 2002 (4)
Patient #16	32/F	Italian	FNAIT	n.t	PakPlus, MACE	Curtis *et al.*, 2002 (4)
Patient #17	28/F	African-American	FNAIT	n.t	PakPlus, MACE	Curtis *et al.*, 2002 (4)
Patient #18	21/F	African-American	FNAIT	n.t	PakPlus, MACE	Curtis *et al.*, 2002 (4)
Patient #19	36/F	Japanese	FNAIT	n.t	PSIFT	Okajima *et al.*, 2006 (18)
Patient #20	?/F	Japanese	FNAIT	n.t	MPHA, PakPlus	Taketani *et al.*, 2008 (19)
Patient #21	30/F	Chinese	FNAIT	Neg (FA6-152)	PakPlus, PSIFT, ACA	Xu *et al.*, 2013 (3)
Patient #22	35/F	Chinese	FNAIT	Neg (FA6-152)	PakPlus, ACA	Xu *et al.*, 2018 (20)
Patient #23	26/F	Taiwanese	FNAIT	Neg (FA6-152)	PSIFT, ACA	Lin *et al.*, 2018 (21)
Patient #24	41/F	African	FNAIT	Neg (FA6-152; 10.5 and TR9)	PAKLx	Bertrand *et al.*, 2019 (22)

?, unknown; n.t, not tested; F, female; M, male; Pos, positive; Neg, negative. The ACA was also used to detect the anti-CD36 antibodies in patients #21–23. PTR, platelet transfusion refractoriness; FNAIT, foetal and neonatal alloimmune thrombocytopenia; PakPlus, the commercial solid-phase assay; MAIPA, monoclonal antibody-specific immobilization of platelet antigens; PSIFT, platelet suspension immunofluorescence test; MPHA, mixed passive hemagglutination assay; MACE, modified antigen capture ELISA; PAKLx, Luminex bead-based platelet antibody detection assay; PABA, platelet antibody bead array; ACA, monoclonal antibody-independent antigen capture assay.

by anti-CD36 antibodies were evaluated by MAIPA using reference mAbs FA6-152 against CD36 as the capture antibody (3,11,12,14,15,20-22). MACE was used in six cases (*Table 1*) (5,12). Although both assays are frequently used, false-negative results often occur due to competitive inhibition between capture mouse mAbs and human anti-CD36 antibodies (32). In this cohort, MAIPA identified anti-CD36 antibodies in sera in only 6/12 cases (50.00%) (*Table 1*). In patient #5, negative results were found both in MAIPA and MACE using mAbs FA6-152 and MBC131.4

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Table 2 The advantage and disadvantage of different assays for the detecting of anti-CD36 antibodies

Assay	Principle	Advantage	Disadvantage
PSIFT	Binding assays using intact platelets	Simple practicality, fast	Low specificity and sensitivity, requires a FACS instrument
MPHA		Simple practicality, low cost	Low specificity and sensitivity, anti-HLA antibodies interfere the detection of HPA antibodies
MAIPA	Binding assays with immobilized platelet glycoproteins	High specificity, high sensitivity	Time-consuming, complicated procedure, false-negative results often occur
MACE		High specificity	High cost, false-negative results often occur
PakPlus		High specificity, rapidity, convenient	High cost, not all platelet antibodies could be tested
HP-IPA	Binding assays with CD36 transfected cell lines	High sensitivity	High cost, complicated procedure, transfected cell lines are required
ACA		High sensitivity	High cost, complicated procedure, transfected cell lines are required
PAKLx	Simultaneous binding assays using fluorescent bead-coated antigens	High sensitivity, high throughput, rapidity, simplicity	High cost, requires a Luminex instrument and not all platelet antibodies could be tested

PakPlus, the commercial solid-phase assay; MAIPA, monoclonal antibody-specific immobilization of platelet antigens; PSIFT, platelet suspension immunofluorescence test; MPHA, mixed passive hemagglutination assay; MACE, modified antigen capture ELISA; PAKLx, Luminex bead-based platelet antibody detection assay; ACA, monoclonal antibody-independent antigen capture assay; HP-IPA, HP cell-based mAb-independent immobilization of platelet antigens assay.

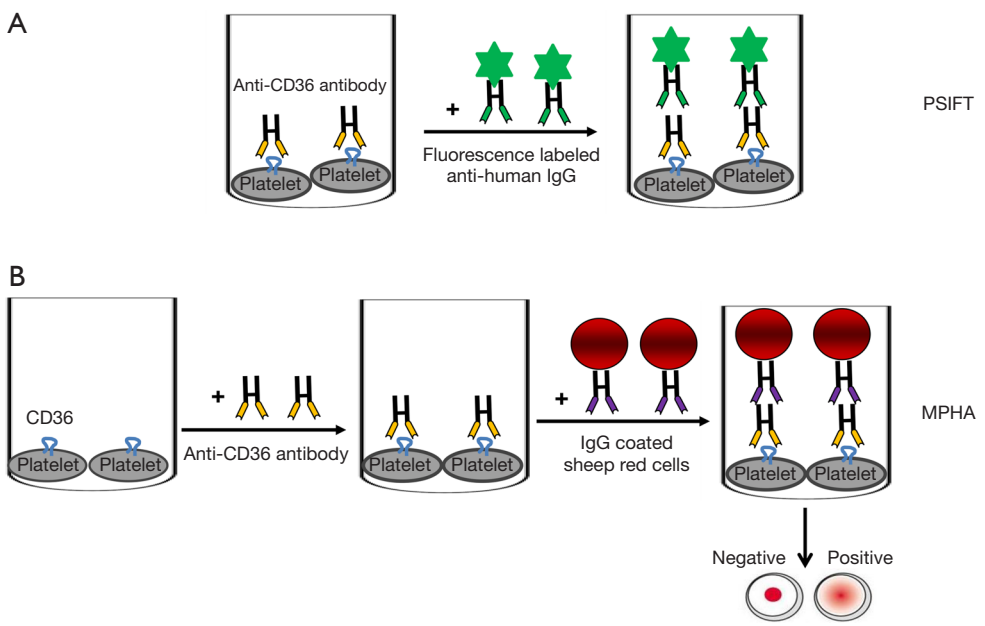

Figure 1 The principle of PSIFT and MPHA for testing of anti-CD36 antibodies using intact platelets. (A) PSIFT: the isolated platelets are incubated firstly with patient's serum, and then fluorescence labeled anti-human IgG is added. The fluorescence intensity is analyzed by a flow cytometer. (B) MPHA: the patient's serum is added onto microtiter wells pre-coated with platelets, and then indicator cells, IgG coated sheep red cells are added. The presence of anti-CD36 antibody can be decided by agglutination patterns. In positive result, the sheep red cells bound to the platelets and spread on the microtiter wells. However, in negative result the indicator cells move to the middle of the microtiter wells due to missing of anti-CD36 antibody. PSIFT, platelet suspension immunofluorescence test; MPHA, mixed passive hemagglutination.

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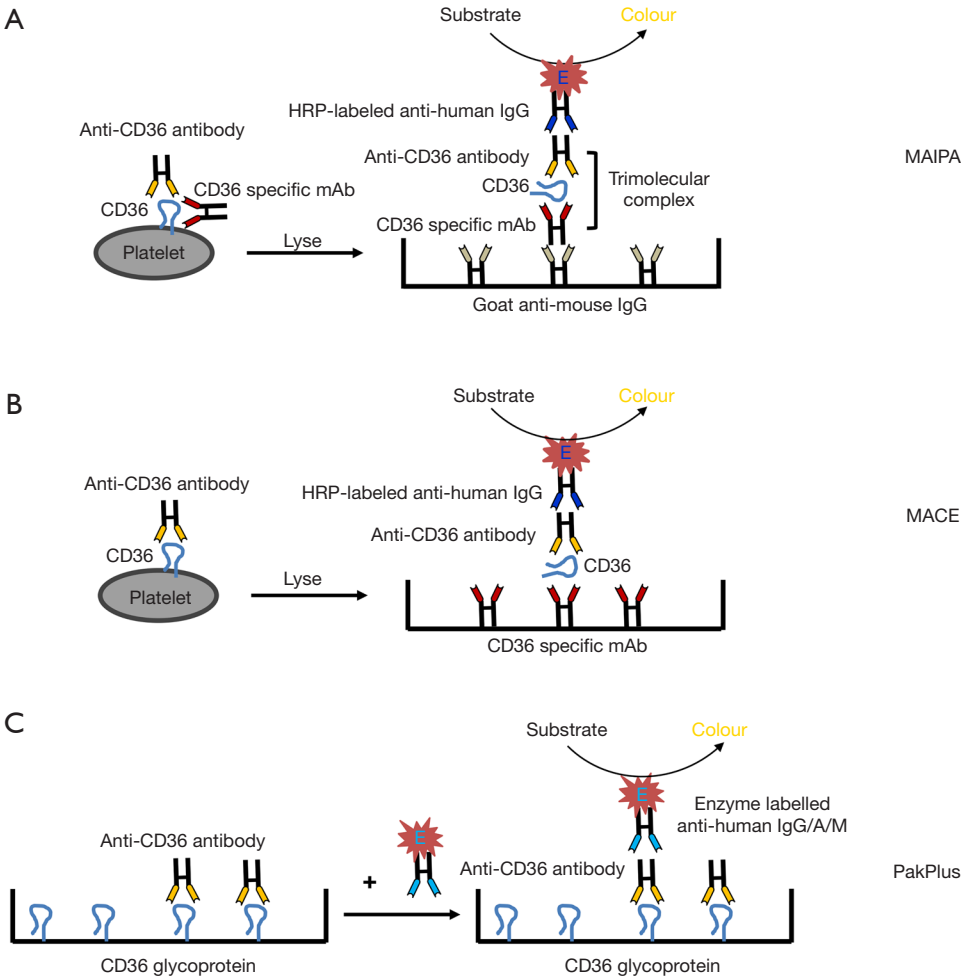

Figure 2 The principle of MAIPA, MACE and PakPlus for testing of anti-CD36 antibodies with immobilized platelet glycoproteins. (A) MAIPA: CD36 positive platelets are incubated with human serum and subsequently CD36 specific monoclonal antibody. After solubilization, a triple molecular complex consisting of anti-CD36 antibody-CD36-CD36 specific mAb is captured by immobilized Goat anti-mouse IgG coated on microtiter wells. Finally, bound human antibodies are detected by the use of HRP-labeled anti-human IgG. (B) MACE: CD36 positive platelets are incubated with human serum and then lysed. The complex consisting of CD36-anti-CD36 antibody is captured by immobilized CD36 specific mAb coated on microtiter wells. Same procedures with MAIPA, bound human antibodies are detected by the use of HRP-labeled anti-human IgG. (C) PakPlus: The patient's serum is added to microtiter wells coated with platelet and HLA glycoproteins allowing antibody to bind. Then bound platelet antibodies are detected by the use of alkaline phosphatase-labeled anti-human IgG/A/M. MAIPA, monoclonal antibody-specific immobilization of platelet antigens; MACE, modified antigen capture ELISA.

as capture antibodies, respectively (12). This observation indicates that the selection of mAbs against CD36 recognizing different epitopes that are distinct from human antibodies is important to minimize false negative result. Although this assay is time-consuming, this methodological approach has several advantages, allowing the quantification of antibodies, direct comparison with other platelet antibodies, and does not need CD36 negative platelets. More importantly, this assay allows cross-match analysis between maternal serum and paternal platelets representing antigen-antibody reaction in FNAIT (*Table 2*).

To simplify the detection of anti-CD36 antibodies, a commercialized ELISA (GTI PakPlus) was developed. This assay is based on the use of immobilized purified platelet glycoprotein CD36 and seems to be specific for identifying anti-CD36 antibodies (*Figure 2C*). As shown in *Table 1*,

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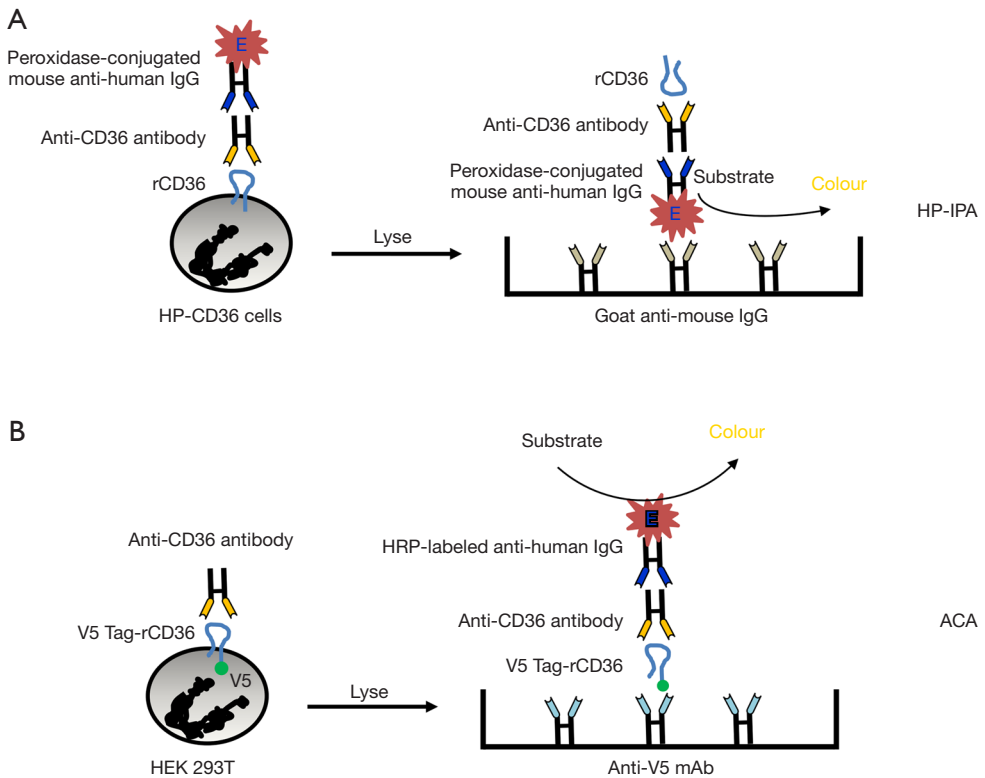

Figure 3 The principle of HP-IPA and ACA for testing of anti-CD36 antibodies with CD36 transfected cell lines. (A) HP-IPA: HP-CD36 cells expressing CD36 antigen in K562 cells (rCD36) firstly react with human serum and then incubate with peroxidase-conjugated mouse anti-human IgG. After solubilization, the lysates in the supernatant are added onto the microtiter wells pre-coated with goat anti-mouse IgG. (B) ACA: the HEK293 cells expressing CD36 antigen harbouring a V5-peptide (V5 Tag-rCD36) incubate with human serum and then lysed. The complex consisting of V5 Tag-rCD36-anti-CD36 antibody is captured by immobilized anti-V5 mAb coated on microtiter wells. Finally, bound human antibodies are detected by the use of HRP-labeled anti-human IgG. HP-IPA, HP cell-based mAb-independent immobilization of platelet antigens assay; ACA, antigen capture assay.

seven cases of FNAIT and seven cases of PTR caused by anti-CD36 could be identified by PakPlus (3,5,11-14,17,19,20). Although this assay is rapid and convenient, the GTI PakPlus Kit may fail to detect or may incorrectly identify clinically significant anti-HPA antibodies (*Table 2*) (33).

Binding assays with CD36 transfected cell lines

To overcome the shortage of low-frequency HPA typed or deficient platelets, a panel of different cell lines stably expressing platelet antigens on the cell surface have been established as an alternative source of phenotype platelets to detect platelet-specific alloantibodies in human serum (34-36). For the detection of anti-CD36 antibodies by flow cytometry, a stably transfected K562 cell line expressing CD36 antigen was introduced to detect anti-CD36 antibodies (37). Compared to other cell lines, K562 cells fail to express the HLA class I antigen; consequently, the presence of anti-HLA antibodies cannot influence this assay. To broaden the use of this K562 cell line expression CD36 (HP-CD36), a monoclonal antibody-independent immobilization of platelet antigens (HP-IPA) assay was developed (38). In this assay, HP-CD36 cells were first reacted with test serum and were then incubated with peroxidase-conjugated mouse anti-human IgG. After solubilization, the lysates in the supernatant were applied onto the microtiter wells pre-coated with goat anti-mouse IgG (*Figure 3A*).

In our laboratory, another monoclonal antibody-independent antigen capture assay (ACA) was established (21). In this approach, recombinant CD36 harbouring a V5-peptide (GKPIPNPLLGLDST) was expressed on the

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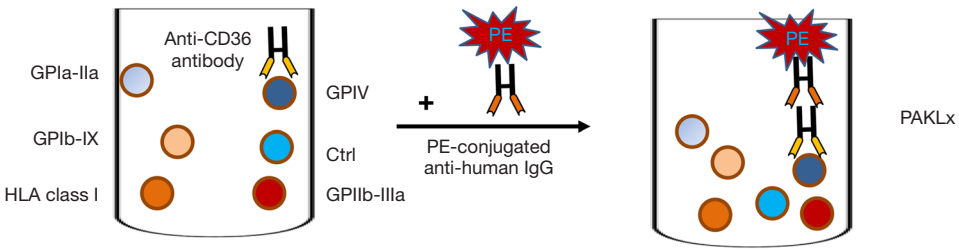

Figure 4 The principle of PAKLx for testing of anti-CD36 antibodies using fluorescent bead-coated antigens. The immobilized polystyrene beads by HPA and HLA glycoproteins are incubated with human serum and then PE-conjugated anti-human IgG is added. Finally, bound human antibodies are analyzed on a Luminex instrument. PAKLx, Luminex bead-based platelet antibody detection assay; HPA, human platelet antigens; PE, phycoerythrin.

surface of mammalian HEK293 cells. After incubating these cells with human sera, the bound anti-CD36 antibodies were detected in the cell lysates after immobilization of the CD36 antigen on a microtiter wells pre-coated with anti-V5 antibodies (*Figure 3B*). This method overcomes the abovementioned problem of false-negative reactions caused by competitive inhibition (*Table 2*). Notably, in patient #23, a negative result was obtained when MAIPA was performed with platelets using mAb FA6-152, but a positive result was obtained by ACA (21). Similar results were obtained with other serum samples (patients #21 and #22; *Table 1*).

Simultaneous binding assays using fluorescent bead-coated antigens

Recently, different approaches have been developed for high-throughput screening of platelet antibodies based on different fluorescence-labeled beads coated with platelet antigen, such as the simultaneous analysis of specific platelet antibodies (SASPA), immunocomplex capture fluorescence analysis (ICFA), and platelet antibody bead array (PABA) (39-41). In comparison to previous assays, all these methods allow the simultaneous analysis of different platelet antibody specificities. For example, by PABA, four serum samples containing anti-CD36 antibodies were correctly identified (41). As shown in *Table 1*, anti-CD36 antibodies in serum sample #12 could be detected by this method as well (16).

Meanwhile, a commercial Luminex bead-based platelet antibody detection method, PAKLx kit, is available. These fluorescence-labeled beads as targets are immobilized with platelet lysate-derived glycoproteins to capture and identify antibodies against HPA, HLA Class I or CD36 (*Figure 4*). Compared to the classical MAIPA, the PAKLx assay has several advantages (rapidity, simplicity, and platelets and mAbs are not needed) (*Table 2*). Interestingly, anti-CD36 antibodies could be identified in serum sample #24 (*Table 1*) by PAKLx, but not by MAIPA (22). However, the stability and heterogeneity of isolated antigens have to be taken into consideration. Accordingly, labile antigens, such as HPA-3 and HPA-15, cannot be reliably detected by this assay (42,43).

Real-time antibody binding assay

All antibody binding assays described above include several washing steps and only allow end-point readout. Therefore, low-avidity antibodies may be overlooked. To overcome this problem, a real-time antigen-antibody binding analysis by surface plasmon resonance technology (SPR) has been developed (44-46). By using a purified HPA-1a antigen, Bakchoul *et al.* demonstrated the existence of low-avidity anti-HPA-1a alloantibodies, which were undetectable by MAIPA (45). This observation was confirmed by another study (46). Similar to PakLx, the isolation of native purified antigens is a difficult hurdle for this approach.

Conclusions

Several methods have been developed to detect anti-CD36 antibodies. However, for routine testing, every assay still has some limitations. Currently, a combination of these methods is necessary to ensure the detection of anti-CD36 antibodies. Nevertheless, further improvement of MAIPA and MACE should be in the foreground. This approach currently allows cross-match analysis between maternal antibody and foetal antigen that reflects antigen-antibody reaction occurring in FNAIT. In addition, only this approach permits the identification of new platelet antigens residing

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on CD36.

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