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PRODUCT INSERT

IVD

FLOWPRA® SPECIFIC AND SINGLE ANTIGEN ANTIBODY DETECTION TESTS

For In Vitro Diagnostic Use

Table 1. Product Description

Cat. No.	Description	Product Components
FL1HD*	**FlowPRA® Single Antigen HLA Class I Antibody Detection Test** (10 tests) A panel composed of 32 microbeads coated with purified HLA Class I single or fractionated antigens divided into 4 groups to further identify HLA Class I IgG antibody specificities in high PRA sera by flow cytometry. There is also one control bead, not coated with antigen, in each group.	1. 4 vials (Groups 1, 2, 3, 4) FlowPRA® Single Antigen Class I beads (Cat.# FL1HDBD1, FL1HDBD2, FL1HDBD3, FL1HDB4) 60 µl each vial, 5 µl per test 2. 10X wash buffer (Cat.# FL-BF) 26 ml 3. 100X FITC conjugated F(ab')$_2$ anti-human IgG (Cat.# FL-AB) 60 µl
FL1HD01* FL1HD02* FL1HD03* FL1HD04* FL1HD05* FL1HD06* FL1HD07* FL1HD08* FL1HD09* FL1HD10*	**FlowPRA® Single Antigen HLA Class I Antibody Detection Test Supplement - 1, 2, 3, 4, 5, 6, 7, 8, 9, 10** (10 tests) Each group contains nine different microbeads—eight beads coated with purified single antigens and one control bead that is not coated with antigen.	1. 1 vial FlowPRA® Single Antigen Class I beads (60 µl each vial; 5 µl per test) 2. 10X wash buffer (Cat.# FL-BFSUP) 7 ml 3. 100X FITC conjugated F(ab')$_2$ anti-human IgG (Cat.# FL-ABSUP) 20 µl
FL2HD*	**FlowPRA® Single Antigen HLA Class II Antibody Detection Test** (10 tests) A panel composed of 32 microbeads coated with purified HLA Class II single or fractionated antigens divided into 4 groups to further identify HLA Class II IgG antibody specificities in high PRA sera by flow cytometry. There is also one control bead, not coated with antigen, in each group.	1. 4 vials (Groups 1, 2, 3, 4) FlowPRA® Single Antigen Class II beads (Cat.# FL2HDBD01, FL2HDBD02, FL2HDBD03, FL2HDB04) 60 µl each vial, 5 µl per test 2. 10X wash buffer (Cat.# FL-BF) 26 ml 3. 100X FITC conjugated F(ab')$_2$ anti-human IgG (Cat.# FL-AB) 60 µl
FL2HD01* FL2HD02* FL2HD03* FL2HD04* FL2HD05*	**FlowPRA® Single Antigen HLA Class II Antibody Detection Test Supplement - 1, 2, 3, 4, 5** (10 tests) Each group contains nine different microbeads - eight beads coated with purified single antigens and one control bead that is not coated with antigen.	1. 1 vial FlowPRA® Single Antigen Class II beads (60 µl each vial; 5 µl per test) 2. 10X wash buffer (Cat.# FL-BFSUP) 7 ml 3. 100X FITC conjugated F(ab')$_2$ anti-human IgG (Cat.# FL-ABSUP) 20 µl
FL1SP*	**FlowPRA® Specific HLA Class I Antibody Detection Test** (10 tests) A panel composed of 32 microbeads coated with purified HLA Class I antigens divided into 4 groups for identifying HLA Class I IgG antibody specificities by flow cytometry. There is also one control bead, not coated with antigen, in each group.	1. 4 vials (Groups 1, 2, 3, 4) FlowPRA® I Specific Class I beads (Cat.# FL1SPBD1, FL1SPBD2, FL1SPBD3, FL1SPBD4), 60 µl each vial, 5 µl per test 2. 10X wash buffer (Cat.# FL-BF), 26ml 3. 100X FITC conjugated F(ab')$_2$ anti-human IgG (Cat.# FL-AB), 60 µl
FL2SP*	**FlowPRA® Specific HLA Class II Antibody Detection Test** (10 tests) A panel composed of 32 microbeads coated with purified HLA Class II antigens divided into 4 groups for identifying HLA Class II IgG antibody specificities by flow cytometry. There is also one control bead, not coated with antigen, in each group.	1. 4 vials (Groups 1, 2, 3, 4) FlowPRA® Specific Class II beads (Cat.# FL2SPBD1, FL2SPBD2, FL2SPBD3, FL2SPBD4), 60 µl each vial, 5 µl per test 2. 10X wash buffer (Cat.# FL-BF), 26ml 3. 100X FITC conjugated F(ab')$_2$ anti-human IgG (Cat.# FL-AB), 60 µl
FL1-PC	**Class I Positive Control Serum** (10 tests)	240 µl
FL2-PC	**Class II Positive Control Serum** (10 tests)	240 µl
FL-NC	**Negative Control Serum** (10 tests)	240 µl
FL-RP	**FlowPRA® Reagent Pack**	1. 10X wash buffer (Cat.# FL-BF), 26 ml 2. 100X FITC conjugated F(ab')$_2$ anti-human IgG (Cat.# FL-AB), 60 µl

INTENDED USE

The FlowPRA® Specific Tests (Cat.# FL1SP and FL2SP) are intended for use in flow cytometric detection of HLA antibodies and their specificities. They provide an extension to the FlowPRA® Screening Tests (Cat.# FL1-30, FL2-30, FL12-60). The FlowPRA® Single Antigen tests are designed to further discriminate specificities in high PRA sera (Figure 6).

Both the Specific and Screening tests use microbeads coated with purified HLA antigens for flow cytometric detection of HLA antibodies in human sera. FlowPRA® Screening Tests can be used as a first test to detect HLA antibodies and percent PRA in human sera. FlowPRA® Specific Tests can then be used to determine antibody specificities in the serum.

SUMMARY AND EXPLANATION

FlowPRA® Specific Antibody Detection Tests consist of panels of microbeads coated with purified Class I or Class II antigens.

- The FlowPRA® Specific Class I (Cat. # FL1SP) or Class II (Cat. # FL2SP) HLA Antibody Detection Tests each contain a panel of 32 Class I or Class II beads. Each panel is divided into four groups (eight beads in each group). Each group also contains a negative control bead, not coated with antigen.
- FlowPRA® Single Antigen contains a panel of Class I or Class II beads with single antigens on each bead. Control beads are included in this test.

PRINCIPLE(S)

FlowPRA® tests provide pre-optimized reagents for rapid flow cytometric detection of HLA antibodies and their specificities in human serum. FlowPRA® Specific or Single Antigen beads consist of a mixture of different colored beads with different fluorescent properties. These beads can be excited at 488 nm, generating a maximum emission of approximately 580 nm, similar to phycoerythrin (PE), which can be detected by the FL2 channel. Since different beads generate different FL2 channel shifts, different colored beads in a group can be separated by a flow cytometer on the FL2 channel.

The testing procedure is the same as for the FlowPRA® Screening Test. Each group of beads is incubated separately with the test serum and then stained with a FITC conjugated anti-human IgG antibody. Beads reacting positively show an FL1 channel shift on the FL1 vs. FL2 dot plots when compared to the negative control serum and the control beads (see Figures 4 and 5).

HLA specificities can be determined by referring to the FlowPRA® Specific or Single Antigen Beads Work Sheet.

REAGENTS

A. Identification

See Table 1: Product Description.

B. Warnings and Cautions

1. Refer to the Material Safety Data Sheet for detailed information.
2. **Warning:** The FlowPRA® test reagents contain 0.1% sodium azide (NaN_3) as a preservative. Under acidic conditions, sodium azide yields hydrazoic acid, an extremely toxic compound. Dilute reagents containing sodium azide in running water before discarding to avoid deposits in plumbing where explosive conditions may develop.
3. **Biohazard Warning:** Test and control sera should be treated as potentially infectious. The serum controls supplied for this product were tested per FDA requirements and found negative. However, no known test method can offer complete assurance that human blood products are not infectious.

C. Preparing Reagents for Use

If buffer salts have precipitated out of solution during shipment or storage, redissolve by gently warming before preparing working dilution.

D. Storage Instructions

1. Upon receipt it is recommended that the package be kept intact and stored frozen within the temperature range of -80° to -65° C until use. This will keep the product stable for the duration of the shelf life of the product (see expiration date on package).
2. After first use and/or upon thawing of the product, store reagents at 2° to 5° C.

   Important: Once thawed, do not refreeze the FlowPRA® beads or the FITC conjugated $F(ab')_2$ anti-human IgG.
3. Thawed beads may be stored at 2° to 5° C for three months or until the expiration date, whichever comes first. Wash Buffer can be stored at 2° to 8° C for 3 months or until the expiration date, whichever comes first. The FITC conjugated F(ab')2 anti-human IgG can be stored at 2° to 5° C for 12 months.

4. The FITC conjugated $F(ab')_2$ anti-human IgG is sensitive to light and must be stored in the dark.
5. The positive and negative control sera may be stored at 2° to 8° C if used within 5 days. However, the sera may become unstable after repeated thawing and refreezing. Therefore, freeze aliquots, or re-freeze the original reagent vial (1X only) and store at -80° to -20° C if the reagents cannot be used within 5 days.

E. Instability Indications

None

INSTRUMENT REQUIREMENTS

A. Required Instrument
Flow cytometer

B. Daily Adjustment and Quality Control
1. Adjust and calibrate the flow cytometer daily according to the manufacturer's recommended start-up procedure.
2. Run a control test using 5 µl FlowPRA® Specific® beads in 0.5 ml PBS on your flow cytometer to set up the FSC, SSC Voltage and AmpGain in order to locate the bead population (Figure 1) and to set up the FL2 Voltage and AmpGain in order to separate different colored beads on the FL2 channel (Figure 3, A and B).
Note: Because the beads are smaller than regular lymphocytes, higher FSC Voltage and AmpGain may be required to visualize the beads.

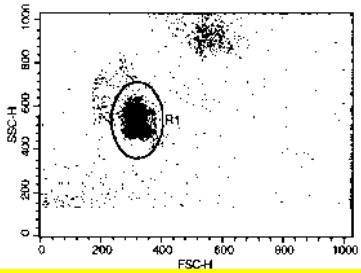

Figure 1. An example of FSC vs. SSC dot plot of FlowPRA® Specific Beads

3. Run positive and negative serum controls daily before the sample analysis to set up FL1 Voltage and AmpGain to obtain maximum separation between positive and negative serum controls (see Figures 4 and 5). Each population of beads may show slight variations on the FL1 channel shift when reacting with the negative serum control. Therefore, it is recommended that each group of beads be tested with the negative control serum for each batch of test serum.
4. Adjust the fluorescent compensation using the FlowPRA® beads that have reacted with positive and negative control sera.
   a) Run a group of the beads that have reacted with the negative control serum and obtain the FL2 vs. FL1 dot plot.
   b) Adjust (FL1-%FL2) so that eight populations of beads are aligned along the FL1-axis (Figure 3, A and B). Examples of improper compensation are shown in Figure 3, C and D.
   c) Run the same group of beads reacting with the positive control serum and obtain the FL2 vs. FL1 dot plot.
   d) Adjust (FL2-%FL1) so that each population of the beads is aligned along the FL2 axis with the same population of beads that reacted with the negative control serum (Figure 3).

SPECIMEN COLLECTION AND PREPARATION

A. Test serum may be fresh or thawed. However, aggregates should be removed from the test serum by centrifugation or filtration prior to testing. Any aggregates or contamination of the serum may generate invalid results.

B. Test serum should not be heat inactivated, because it may give a high background in the test.

PROCEDURE

A. Materials Provided

See Table 1: Product Description

B. Materials Required, but Not Provided

1. Fixing solution: PBS with 0.5% formaldehyde (add 1.35 ml of 37% formaldehyde to 100 ml PBS).
2. Positive control sera (Cat.# FL1-PC and FL2-PC) and negative control serum (Cat.# FL-NC) (order separately from One Lambda).

C. Directions for Use

1. Gently vortex FlowPRA® beads prior to use.
2. Incubate 5 µl of each FlowPRA® bead group with 20 µl of test serum in separate 1.5 ml Eppendorf tubes or in each well of a 96-well plate for 30 minutes at 20 - 25° C with gentle shaking.
3. Dilute 10X wash buffer (Cat.# FL-BF) in distilled water to make a 1X solution.
4. Add 1 ml of 1X wash buffer to each bead/serum solution tube or 150 µl of 1X wash buffer to each well of a 96-well plate and vortex. Centrifuge at 9000 g for 2 minutes or at 1500 g for 10 minutes. Aspirate and discard the supernatant.
5. Repeat Step 4 if tubes are used for the test. If a 96-well plate is used, wash twice with 200 µl wash buffer.
6. Dilute 1 µl per test of 100X FITC conjugated anti-human IgG (Cat.# FL-AB) with 99 µl of 1X wash buffer to make a 1X solution.
7. Add 100 µl of 1X FITC conjugated anti-human IgG to each tube or each well. Incubate for 30 minutes in the dark at 20 - 25°C with gentle shaking.
8. Repeat Step 4 twice if tubes are used for the test. If a 96-well plate is used, wash—first with 100 µl wash buffer and then twice with 200 µl wash buffer.
9. Add 0.5 ml 1X fixing solution to each tube or 200 µl fixing solution to each well of the 96-well plate. The sample is ready for flow analysis, or it can be stored at 2 - 5°C for up to 24 hours before analysis.

RESULTS

Data Acquisition and Analysis

A. Measure green and yellow fluorescence for 5,000 - 10,000 events for each sample.

B. Gate the major population of FlowPRA® Specific beads on the FSC vs. SSC dot plot (R1, Figure 1), and obtain an FL1 vs. FL2 dot plot (see Figures 4 and 5).

C. Use the positive and negative control sera to set the cut-off line on the FL1 vs. FL2 dot plot for each group of beads (see Figures 4 and 5). The negative control serum does not show any HLA antibody activity. The positive and negative cut-off line should be set at the right end of all bead populations on the FL1 vs. FL2 dot plot for the negative control serum. The gate should be set at the same cut-off line on the FL1 vs. FL2 dot plot for the positive control. All the beads that reacted to the positive control serum should move to the positive region.

Because each bead has a slightly different background for the FL1 shift when reacting with the negative control serum, gates around each bead population that have reacted with the negative control are recommended as a reference for the positive/negative control cut-off. Due to the limited number of gates that can be used for certain analysis software, only a few gates can be used to mark the highest and the lowest FL1 shifts on each group of beads that has reacted with the negative control serum. Additionally, the cut-off marker should be set up together with these gates. Alternatively, a transparent copy of the FL1 vs. FL2 dot plot of the negative serum control can be made and used as an overlay on top of other tests for analysis.

D. Use the same positive/negative cut-off line and gate to set two regions on the FL1 vs. FL2 dot plot for each test serum.

E. Optional analysis – HLA Fusion™ software.

LIMITATIONS OF THE PROCEDURE

A. The range of detectable specificities is limited to the HLA antigens of the cell lines used to create the test panel (see product data sheet for HLA antigen panel composition).

B. Contaminant or aggregate containing sera may generate high background. Remove aggregates in the test serum before testing.

C. Serum dilution may cause weak reactivity and is not recommended. Diluted sera may have different positive/negative cut-offs than undiluted sera.

D. The FlowPRA® test may be used with any flow cytometer. However, invalid results could be caused by improper adjustment of the flow cytometer settings. The following problems may be encountered:

1. An incomplete shift of the beads may be caused by improper gating on the FSC vs. SSC dot plot. Although the beads contain multiple populations on the FSC vs. SSC dot plot, only the major population of beads should be gated to avoid an incomplete FL1 shift.

2. Improper adjustment of the fluorescent compensation may cause misalignment of the different-colored bead groups along the FL2-axis on the FL1 vs. FL2 dot plot when running the negative serum (see Figure 3, C and D). Overcompensation will cause the beads to move toward the FL2-axis and contribute to false negative results. Under compensation will cause the beads to move away from the FL2-axis. This may cause false positive results. Fluorescent compensation adjustment is required prior to data acquisition (see *Daily Adjustment and Quality Control,* above).

E. Since different negative sera may generate slightly different FL1 shifts with the same beads, the negative control serum (Cat.# FL-NC) is recommended. Avoid using negative serum with a very low FL1 shift.

F. This product detects IgG, not IgM antibodies.

G. Determination of percent PRA is considered a first screen diagnostic test, but not the sole basis for clinical decisions affecting the patient's treatment. A final crossmatch test is routinely required prior to transplant.

EXPECTED VALUES

A. On the FL1 vs. FL2 dot plots, the populations located to the right of the cut-off line or gate are considered positive reactions while the ones to the left are considered negative reactions. Any populations located at the middle of the cut-off line or gate are considered undetermined reactions (see Figures 2, 4 and 5).

B. Positive reactions for a testing serum can be divided into different levels of reactivity, such as strong, intermediate, and weak reactions. A score system can be applied to represent these levels of reactions (Figure 2).

Score	Assignment	Bead Shift (%)	Example
1	Negative	0 - 10	
2	Negative or weak positive	11 - 20	
4	Weak positive	21 - 50	
6	Positive	51 - 100(L)	
8	Strong positive	100(M) - 100(H)	
		Negative control serum	
		Positive control serum	

Table Legend

= Gate

= Bead population

100(L) = 100% shifted with low FL1 mean channel shift
100(M) = 100% shifted with medium FL1 mean channel shift
100(H) = 100% shifted with high FL1 mean channel shift

Figure 2. Examples of Bead Population Shifts and Their Score Assignments

C. Each serum may have different levels of antibody concentration; therefore, the background and strong or weak positive reactions may have different fluorescent shift ranges. Lower concentration of the antibody level may give lower fluorescent shift of the background and positive reactions; higher concentration of the antibody level may give higher fluorescent shift of the background and positive reactions. The cut-off line should be adjusted slightly according to the serum background level.

D. The negative control beads should stay in the negative region for a valid test. When the control beads move into the positive region in a test:

   1. The beads may not have been adequately washed; therefore, the test should be repeated.

   2. On rare occasions, the test sera may react strongly with the control beads. In such cases, the data may not be valid. The flow histogram should be further evaluated by the laboratory director. Adsorb Out™ (OLI Cat.# ADSORB) may be used to eliminate or reduce non-specific binding.

E. For calculation of % PRA (FlowPRA® Specific), divide the number of positive reactions by the total number of valid reactions.

F. To determine specificity of HLA antibody, enter the reaction score into the work sheet and analyze the reaction pattern.

SPECIFIC PERFORMANCE CHARACTERISTICS

A. Since the FlowPRA® test is a more sensitive assay than the lymphocytotoxicity test and it measures different parameters, i.e., IgG HLA-specific antibody only, and direct binding versus complement activation and cytotoxicity, matching results between the two assays are not expected for certain sera.

B. Single Antigen beads are slightly more sensitive than the Specific Antigen beads, because the single antigen beads are coated with a higher concentration of one particular antigen than the Specific Antigen beads.

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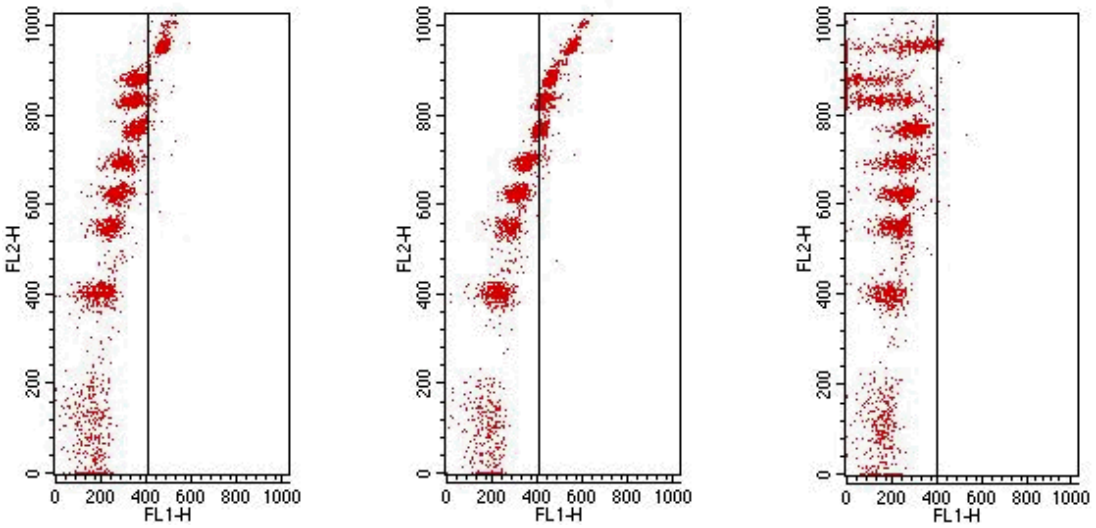
FIGURES

***Note**: The antigen panel examples shown in the following figures do not reflect actual typings of the current lot of beads. For current antigen panel information, please refer to the product work sheet.)*



A: Normal compensation **B: Under-compensation (FL1-%FL2)** **C: Over-compensation (FL1-%FL2)**

Figure 3. FL1 vs. FL2 dot plots of FlowPRA® Single Antigen beads (FL1HD, Group 1)

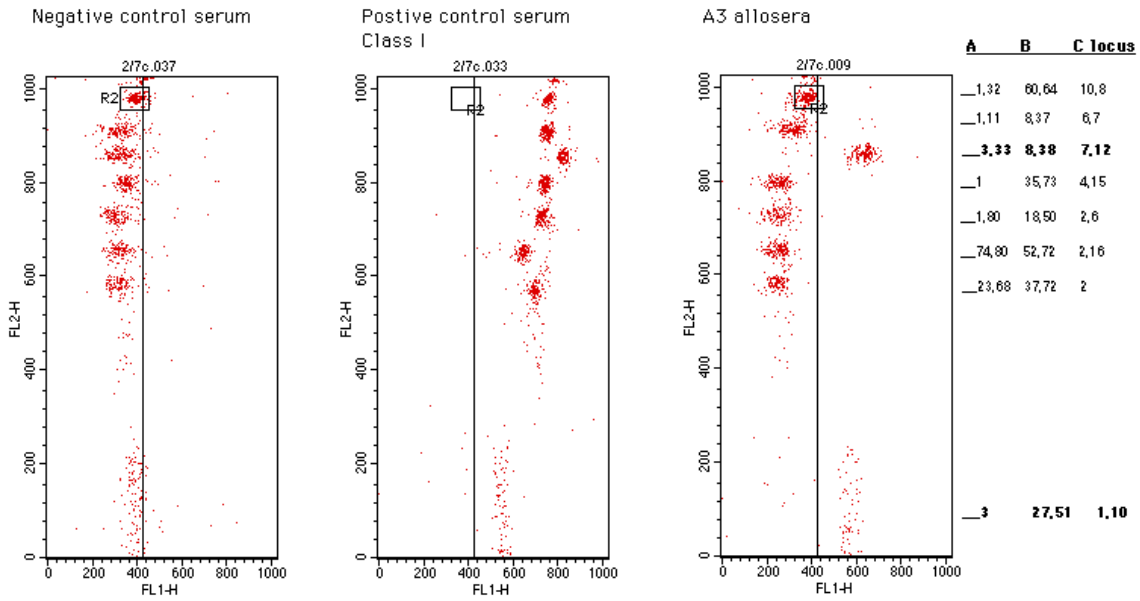


Figure 4. Example of FL1 vs. FL2 dot plots of FlowPRA® Specific bead (FL1SP) Group 1 reactions with negative control serum (FL-NC), Class I positive control serum (FL1-PC), and an alloserum with A3 specificities

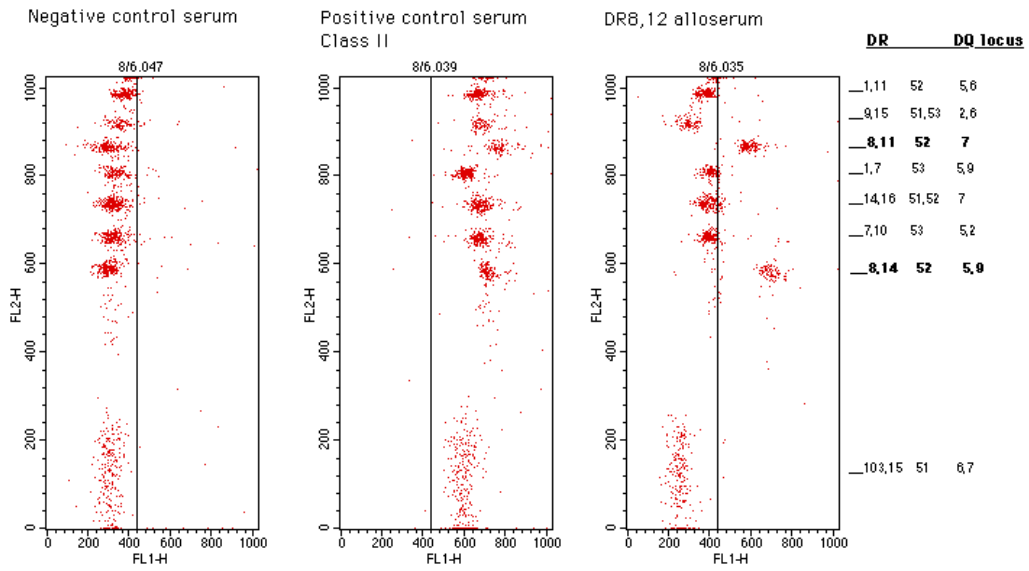


Figure 5. Example of FL1 vs. FL2 dot plots of FlowPRA® Class II Specific beads (FL2SP) Group 3 reactions with negative control serum (FL-NC), Class II positive control serum (FL2-PC) and a DR8, DR12 specific alloserum

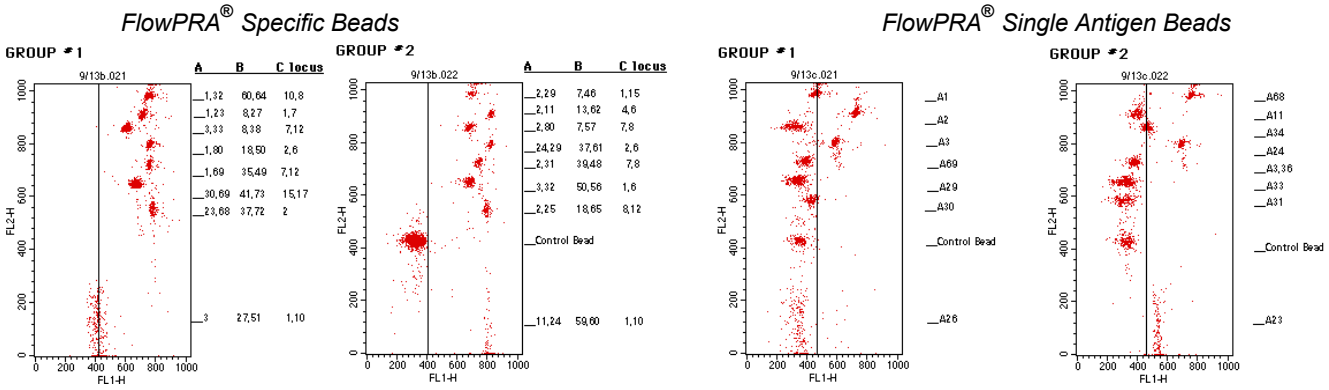


Figure 6. Example of high PRA serum reacting with FlowPRA® Specific vs. FlowPRA® Single Antigen Beads

TRADEMARKS AND PATENTS USED IN THIS DOCUMENT

FlowPRA® is a registered trademark of One Lambda, Inc.
Adsorb Out™ and HLA Fusion™ are trademarks of One Lambda, Inc.
U.S. Patents 5,948,627, 6,150,122 and 6,514,714

EC REP REPRÉSENTANT EUROPÉEN AUTORISE

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REVISION HISTORY

Revision	Date	Revision Description
9	2010/03	PCR#262: FlowPRA Wash Buffer store up to 3 months or until the expiration date at 2°C-8°C after opening the bottle for first usage.
10	2011/11	Add footnote along with 0197 (0197 Applies to Annex II List B products only). Add Additional CE mark for non Annex II list B products.
11	2013/08	Add HLA Fusion software as an option. Insert Table 2 (example of scoring). Major update.

CE 0197*

CE

*0197 Applies to Annex II List B products only