Serologic Specificity of Human Anti-IgA and its Significance in Transfusion

By G. N. Vyas, L. Holmdahl, H. A. Perkins and H. H. Fudenberg

Human antibodies to human gamma globulins are generally detected by agglutination of red cells coated with IgG, most often in the form of incomplete anti-Rh antiserum; normal and myeloma IgG proteins coated by bisdiazotized benzidine and chromic chloride have also been used. These passive hemagglutination methods are applied to genetic typing of human immunoglobulins.

Human anti-IgA antibodies are detected by passive hemagglutination using IgA paraproteins. This paper presents for the first time a detailed serologic system for the detection and characterization of anti-IgA antibodies in human sera. A dichotomy of two types of serologic specificities was observed: a) the class specific (reacting with all IgA coats) detected only in the sera of persons lacking IgA and, b) limited specificity (reacting with one or two of the IgA coats) detected in sera of persons with normal levels of IgA. Immunochemical studies suggest that most of these antibodies are of the IgG class. Preliminary evidence indicated the clinical significance of anti-IgA antibodies because of their association with anaphylactoid and urticarial transfusion reactions. Further evidence supporting this association is presented here. The frequency of anti-IgA antibodies in other clinical conditions related to blood transfusion is also presented.

Materials and Methods

Protein Coats

The panel of proteins used for passive hemagglutination assay is shown in Table 1. Sera from patients with myeloma were used for preparation of IgA paraproteins. An 18 per cent sodium sulfate precipitate from the serum was subjected to starch block electrophoresis, followed by chromatographic purification of the paraprotein using Sephadex G-200 gel.
Table 1.—Panel of Protein Coats Used for Detection and Testing the Specificity of Anti-IgA

<table>
<thead>
<tr>
<th>Designation of Proteins</th>
<th>Source</th>
<th>Immunological Typing of H chains</th>
<th>Typing of L chains</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA (1)</td>
<td>Br myeloma</td>
<td>γA1</td>
<td>λ</td>
</tr>
<tr>
<td>IgA (2)</td>
<td>Lo</td>
<td>γA2</td>
<td>λ</td>
</tr>
<tr>
<td>IgA (3)</td>
<td>Wο</td>
<td>γA1</td>
<td>λ</td>
</tr>
<tr>
<td>IgA (4)</td>
<td>Jo</td>
<td>γA1</td>
<td>λ</td>
</tr>
<tr>
<td>IgA (5)</td>
<td>Ch</td>
<td>γA1</td>
<td>λ</td>
</tr>
<tr>
<td>IgA (6)</td>
<td>He</td>
<td>γA2</td>
<td>λ</td>
</tr>
<tr>
<td>IgA (7)</td>
<td>Cr</td>
<td>γA1</td>
<td>λ</td>
</tr>
<tr>
<td>IgA (8)</td>
<td>Ha</td>
<td>γA1</td>
<td>λ</td>
</tr>
<tr>
<td>IgA (pool)</td>
<td>Pooled normal 120 sera</td>
<td>—</td>
<td>λ and κ</td>
</tr>
<tr>
<td>IgA (CNV)</td>
<td>Normal individual serum</td>
<td>—</td>
<td>λ and κ</td>
</tr>
<tr>
<td>IgG</td>
<td>Commercial Cohn Fraction II</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IgM</td>
<td>Pool of 4 purified macroglobulins</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BJK</td>
<td>Dor. Bence Jones</td>
<td>—</td>
<td>λ</td>
</tr>
<tr>
<td>BJL</td>
<td>Gil. Bence Jones</td>
<td>—</td>
<td>λ</td>
</tr>
<tr>
<td>L. ch.</td>
<td>Pooled L chains from IgC</td>
<td>—</td>
<td>λ and κ; Inv(1)</td>
</tr>
</tbody>
</table>

filtration. Normal IgA proteins from an individual serum and a pool of 120 normal sera were prepared by Tomasi's method. Normal IgG was derived from commercial gamma globulin (Cohn Fr. II, Pentex) by DEAE cellulose chromatography with 0.01 M phosphate buffer, pH 8.0. The IgM was a pool of equal amounts of four purified macroglobulins. Kappa and lambda Bence Jones proteins were previously prepared in our laboratory. Pooled light chains were prepared by reduction, alkylation, acid-dissociation, and gel filtration of normal IgG. Purity of each of the proteins dissolved in saline (10 mg./ml.) was established by immunoelectrophoretic criteria. Each IgA paraprotein and serum IgA had sedimentation coefficient of 7.5 S, except IgA which was 9.3 S when tested in Spinco Model E analytical ultracentrifuge. The IgA paraproteins were tested for their γA1 and γA2 subclasses by formate-8 M urea starch gel electrophoresis and criteria recently described by Grey et al.

Red Cells

Blood from a group O Rh-positive volunteer was collected in EDTA and stored for no longer than 10 days. An aliquot of cells was washed four times with 30 volumes of saline before being used in the coating procedure.

Rabbit Antisera

Anti-whole human serum and monospecific antisera against IgG, IgA, IgM, K and λ for use in immunoelectrophoresis were previously prepared in our laboratory. These antisera were rendered suitable for hemagglutination assay by absorption with eight times washed packed human group O cells.

Anti-Rh

An unusual anti-Rh (Avga) antiserum containing IgG and IgA class of antibodies was derived from an immunized mother. After removing IgG eluted by DEAE cellulose with 0.02 M phosphate buffer, pH 8.0, IgA-rich anti-D was eluted with 0.3 M phosphate buffer, pH 8.0. The second eluate was concentrated to half the volume of starting antiserum and used as IgA anti-Rh. Nine volumes of IgA anti-Rh were incubated with one volume of washed, packed cells at 37 C. for an hour; coated cells were washed three times and coating of the antibody ascertained by testing with anti-IgA rabbit antiserum diluted 1:20 with saline. Anti-Rh serum Ripley, known to contain several of the Gm. and Inv. factors of IgG, was used at 1:20 dilution for coating 10 per cent cell suspension by incubating the mixture at 37 C. for an hour.
Table 2.—Incidence of Human Anti-IgA Antibodies in Various Clinical Conditions

<table>
<thead>
<tr>
<th>Series</th>
<th>No. Tested</th>
<th>Anti-IgA Antibodies</th>
<th>Anti-IgA Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Class-specific</td>
<td>Positive Limited</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td></td>
<td>specificity</td>
</tr>
<tr>
<td>Normal adults</td>
<td>255</td>
<td>251</td>
<td>0</td>
</tr>
<tr>
<td>Antiglobulin positive for Ripley</td>
<td>216</td>
<td>214</td>
<td>0</td>
</tr>
<tr>
<td>Absence of IgA and ataxia telangiectas</td>
<td>34</td>
<td>19</td>
<td>15 *</td>
</tr>
<tr>
<td>Kidney transplants</td>
<td>18</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Open-heart surgery</td>
<td>55</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>Anaphylactoid transfusion reactions</td>
<td>29</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>with rash and hives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>15 *</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

* With total absence of IgA, 3 cases of reaction to transfusion are included in 15 of the series with absence of IgA. Six of these sera agglutinated IgA anti-Rh (Avga) coated cells. † Failed to agglutinate IgA anti-Rh (Avga) coated cells.

**Protein Coating**

For coating red cells with the proteins listed in Table 1, appropriate respective concentrations of proteins and chromic chloride were determined by checkerboard method of preparing various coats and titration of each of the coats with monospecific antisera rendered suitable for hemagglutination. Individual proteins were then coated on to the red cells using the optimal concentration of protein between 0.5-2.0 mg/ml., and the 0.0375 M CrCl₃·6 H₂O solution diluted ten- to thirty-fold. The methods and criteria for satisfactory coating have been described previously.

**Test Sera**

Human sera derived from plain clotted blood of individuals from the series mentioned in Table 2 were tested for anti-IgA antibodies. A panel of 160 normal sera devoid of antiglobulin activity was composed of 96 Caucasians, 40 Negroes and 24 Orientals (Chinese and Japanese); this was used in agglutination inhibition system to define any possible polymorphism of serum IgA.

**Ripley Test**

Serum samples from 1,854 normal blood donors were tested at 1:10 and 1:20 dilution with Ripley anti-Rh coated cells. The ones showing presence of antiglobulin activity in both dilutions were further tested for Cm. and mv. specificity. After removing the sera with anti-Cm. or anti-mv. antibodies, the remaining 216 sera were tested for anti-IgA activity.

**Screening for Anti-IgA**

One drop of 1:4 dilution of the test serum was mixed with a drop of 2 per cent cell suspension of each of the 15 coats (listed in Table 1) on glass tiles and kept in a moist chamber at room temperature for 10 minutes. Direct agglutination of one or more of the IgA coats without agglutination of the IgG, pooled L chains, IgM, K and λ coats was taken as evidence of the presence of possible anti-IgA.

**Titration of Anti-IgA**

The human sera agglutinating one or more of the IgA coats in the preliminary screening were titrated against the same coats using V-shaped microtiter plates and phosphate-buffered saline containing Tween 80 (1:20,000), bovine serum albumin (BSA, 0.5 per cent) and polyvinyl pyrrolidone (PVP, 0.0025 per cent), hereinafter called TAP. The original method of Wegmann and Smithies was adapted for this purpose as previously described. A dis-
crete single button of agglutinated cells in the highest twofold dilution of the serum was taken as the endpoint of the titration, disregarding the usual one or two intermediate reactions before observing a smooth run-down pattern of unagglutinated cells.

*Agglutination Inhibition for Specificity of Anti-IgA*

A dilution eightfold lower than the endpoint of titration was used as an agglutinator for ascertaining the specificity of anti-IgA antibodies by agglutination inhibition test. Human serum with selective absence of IgA, hereinafter called algA, and each of the proteins from the panel at 1 mg./ml. was serially double-diluted with 0.025 ml. TAP. The first row of wells received no agglutinator and served as protein control; the subsequent seven dilutions received 0.025 ml. each of the agglutinator. Ten minutes later, 0.025 ml. of 0.1 per cent coated cell suspension was added to every well. TAP with agglutinator and coated cells served as the agglutinator control, and TAP with only the coated cells served as the cell control.

*Mercaptoethanol Sensitivity*

A 1:4 dilution of serum containing anti-IgA antibodies was treated with 0.2 M mercaptoethanol in 0.55 M Tris, pH 8.2, for three hours at room temperature, followed by alkylation with equal volume of 0.4 M iodoacetamide at 4 C. for an hour and dialysis against saline for 24 hours. The serum thus treated was concurrently titrated with untreated serum for anti-IgA activity against the reactive coat.

*Chromatographic Separation of Anti-IgA Activity*

To determine whether the anti-IgA antibodies belonged to IgG or IgM class of immunoglobulins, purified IgG and IgM were prepared from the sera whenever sufficient amounts were available. The euglobulin precipitated with distilled water was washed three times with 50 volumes of distilled water, dissolved in 0.15 M Tris buffer, pH 7.5, and chromatographed by Sephadex G-200 gel filtration. The first peak of IgM was pooled and concentrated to the original volume of the serum. The IgG was separated by DEAE-cellulose chromatography of the pseudoglobulin and eluted with 0.005 M phosphate buffer, pH 8.0, and the eluate reduced to the original volume of the serum. The whole serum and the IgG and IgM fractions were tested concurrently against the IgA coat. Representative purified IgG and IgM antibody proteins had sedimentation coefficients of 7 S and 19 S, respectively, when tested in Spinco Model E analytical ultracentrifuge.

**RESULTS**

*Anti-IgA Antibodies*

The proteins shown in Table 1 were found useful in detection of anti-IgA antibodies when optimally coated on inert indicator red cells by means of chromic chloride. Antibodies with titers less than 1:4 were eliminated by the screening procedure; and those with titers less than 1:8 were disregarded because of difficulty in establishing their specificity. Sera agglutinating coats other than IgA were excluded from further studies. In determining the specificity of anti-IgA antibodies, the algA serum served as an indispensable control. In the agglutination inhibition of anti-IgA, the first row of wells of the microtiter plates containing each of the proteins (Table 1) and the algA serum (1:4 dilution) did not show direct agglutination of the coat. The anti-IgA antibodies were considered specific only when their reactions with the respective IgA coats were inhibited by 0.25 mg./ml. or lower concentrations of homologous proteins (i.e., one or more of the IgA proteins). They were not considered specific when inhibited by the algA serum or any one of the heterologous proteins (i.e., IgG, IgM, L chains and Bence Jones proteins).
Incidence of Anti-IgA

The incidence of specific anti-IgA antibodies in various clinical conditions involving blood transfusion is outlined in Table 2. Whenever the test serum agglutinated all of the IgA coats, and its reactions were inhibited by each one of the IgA proteins, the antibody was considered class-specific. Four of such class-specific antibodies were also inhibited by each serum from the panel of 160 sera. The majority of the class-specific anti-IgA antibodies had titers higher than 1:1024, with the exception of two agammaglobulinemic sera which had titers of 1:32 and 1:256. The anti-IgA antibodies of limited specificity had titers less than 1:256, and were found in individuals with normal levels of IgA (determined by Mancini's radial diffusion technique). The reactions of these antibodies were inhibited by autologous or antigenically related IgA paraproteins. Six of such sera were available in quantities to permit agglutination inhibition with the panel of 160 sera; no inhibition was observed.

IgA anti-Rh (Avga) coat was agglutinated by six sera with class-specific anti-IgA, but 27 sera with anti-IgA of limited specificity did not agglutinate this coat (Table 2). The 216 samples with antiglobulin activity detected by Ripley test showed only one per cent incidence of anti-IgA antibodies. Class-specific human and rabbit anti-IgA did not agglutinate Ripley coat, which may, therefore, be of little value in the detection of human anti-IgA.

The incidence of 16 per cent anti-IgA in sera from 55 patients who received multiple transfusions due to open-heart surgery is not significantly higher than that in a small series of kidney transplants. In contrast with other groups just mentioned, almost all of the patients with anaphylactoid and urticarial transfusion reactions had anti-IgA antibodies (25/29; 86 per cent). The antibodies from eight of these patients reacted with two coats, whereas the remaining had anti-IgA reacting only with one of the panel coats.

Distribution of Anti-IgA of Limited Specificity

In order to understand the relative significance of the antigens represented by the proteins in the panel, the number of anti-IgA antibodies observed in this study was tabulated with the respective coats they agglutinated (Table 3). The coats in the extended panel detected anti-IgA antibodies, in three patients with transfusion reactions, which were not detected by the original panel (Table 1). The observation that 19 out of 38 anti-IgA of limited specificity reacted with IgA(6) indicated a predominance of this specificity in transfusion and transplantation.

Immunochemical Characterization of Anti-IgA

It will be observed from the results shown in Table 4 that a majority of anti-IgA of both specificities belong to the IgG class and are resistant to treatment with mercaptoethanol. All of the 25 sera from patients with transfusion reactions had anti-IgA antibodies resistant to treatment with mercaptoethanol. Case #7023, with anti-IgA of IgM class, was a normal blood donor. In all probability, class-specific anti-IgA of IgM class in Jor. had low titer (1:32) and was
Table 3.—A Total of 38 Cases of Anti-IgA Antibodies of Limited Specificity Reacting with Respective Protein Coats from Panel

<table>
<thead>
<tr>
<th>Coats Agglutinated</th>
<th>Number of Anti-IgA Antibodies Reacting</th>
<th>Transfusion</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Ripley</td>
<td>Kidney</td>
</tr>
<tr>
<td>IgA (1)</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IgA (2)</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IgA (3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IgA (4)</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>IgA (5)</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IgA (6)</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>IgA (7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IgA (8)</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>IgA (9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA (10)</td>
<td></td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>IgA (11)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IgA (12)</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IgA (13)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IgA (14)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: IgA (9, 10, 11, 12, 13, 14) were used only for testing antibodies in samples of the transfusion reaction series which failed to react with the panel of 8 myeloma proteins.

apparently lost or inactivated when isolation was attempted by chromatographic procedures.

**DISCUSSION**

Human anti-IgA antibodies, too weak for immunoprecipitation in agar gel, can be detected by a passive hemagglutination assay using proteins coupled to red cells with chromic chloride or tannic acid. Serologic specificity can be established simply and objectively by specific inhibition of agglutination with homologous IgA proteins.

Two types of serologic specificities are defined. The class-specific anti-IgA reacts with all IgA coats, and anti-IgA of limited specificity reacts only with a few of the IgA coats. Both types of antibodies are associated with anaphylactoid and urticarial transfusion reactions. The class-specific antibodies are produced by alIgA individuals who presumably recognize human IgA as a foreign antigen. The frequency of alIgA individuals has been estimated to be one out of 500–700 normal persons, who may be regarded as a high risk of immunization if exposed to IgA. Of the 15 alIgA who had anti-IgA antibodies, clinical information could be ascertained in 10 cases, all of whom had a definite history of parenteral exposure to IgA in blood or its components. Three of these patients who had anti-IgA antibodies with titers in the range of 1:2048–1:6400 suffered severe anaphylactoid reactions to small amounts of blood components containing IgA. Attempts to alleviate problems of repeated respiratory infections in some alIgA patients by parenteral plasma administration in large volumes produced equivocal results. Such attempts need to be carefully reviewed in view of the susceptibility of these patients to produce class-specific anti-IgA antibodies. From the results in Table 2, it is evident that a relatively high proportion of patients produce anti-IgA following multiple transfusions.
Table 4.—Immunochemical Data on Anti-IgA Antibodies. IgA without Numerical Designation Indicate Class Specificity

<table>
<thead>
<tr>
<th>Case</th>
<th>Specificity</th>
<th>Mercaptoethanol</th>
<th>Chromatographic Fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IgM</td>
</tr>
<tr>
<td>7023</td>
<td>IgA (2)</td>
<td>Sensitive</td>
<td>+</td>
</tr>
<tr>
<td>Ser.</td>
<td>IgA</td>
<td>Resistant</td>
<td>0</td>
</tr>
<tr>
<td>Sev.</td>
<td>IgA</td>
<td>Resistant</td>
<td>0</td>
</tr>
<tr>
<td>T.L.</td>
<td>IgA (6)</td>
<td>Partially sensitive*</td>
<td>+</td>
</tr>
<tr>
<td>O.M.</td>
<td>IgA (8)</td>
<td>Resistant</td>
<td>±</td>
</tr>
<tr>
<td>C.D.</td>
<td>IgA</td>
<td>Resistant</td>
<td>0</td>
</tr>
<tr>
<td>W.F.</td>
<td>IgA (8)</td>
<td>Resistant</td>
<td>0</td>
</tr>
<tr>
<td>Jor.</td>
<td>IgA</td>
<td>Sensitive</td>
<td>0</td>
</tr>
</tbody>
</table>

* Partially sensitive; IgM isolated was ME sensitive, but IgG was not. The results with the whole serum were inconclusive.

The antibodies with limited specificity have titers lower than 1:256, and are associated with relatively less severe anaphylactoid and urticarial reactions to transfusion of blood and/or its components containing IgA. In an experimental transfusion, strong evidence was obtained incriminating anti-IgA of limited specificity as a causative agent of anaphylactoid reaction to transfusion of plasma.6 The fall in complement level observed after transfusion of incompatible plasma in this patient with anti-IgA of the IgG class is consistent with the findings of other investigators, who have also observed complement binding by anti-IgA of IgG class, and have suggested that the transfusion reactions are complement-mediated.7,20 In every case of anaphylactoid and urticarial transfusion reactions attributed to the presence of anti-IgA in the pretransfusion serum of the recipient, the antibodies were resistant to treatment with mercaptoethanol; this is generally true of the IgG class of antibodies, but not of IgM.21

Patients with anti-IgA can safely be transfused with well-washed red cells.6 Gamma globulins completely free of IgA can be prepared and used for patients with primary immunologic deficiencies when they have problems caused by anti-IgA antibodies. It is quite conceivable that patients having reactions caused by anti-IgA of limited specificity may be safely treated with blood and its derivatives from IgA-compatible donors, when we have acquired adequate knowledge of the allotypes of IgA. Efforts to define such allotypes with the panel of 160 sera and anti-IgA antibodies, four class-specific, and six with limited specificity, were unsuccessful. However, the first allotype of IgA appears to be defined by an anti-IgA antibody of limited specificity from a recent case of anaphylactoid transfusion reaction and will be reported elsewhere.

SUMMARY

Anti-IgA antibodies detected by a passive hemagglutination assay are either specific for the IgA class or they are of limited specificity. Persons lacking IgA can produce class-specific anti-IgA as a result of parenteral exposure to incompatible IgA globulin in blood and its components. In contrast, persons with normal levels of IgA may produce anti-IgA of limited specificity. Either type of anti-IgA antibodies was present in 86 per cent of anaphylactoid and urticarial transfusion reactions. A majority of these antibodies are of the IgG class.
SUMMARIO IN INTERLINGUA

Anticorpore anti IgA detegite per un passive essayo de hemagglutination es (1) specific pro le classe IgA o (2) de specificitate restringite. Subjectos con carentia de IgA pote producer anti-IgA a specificitate de classe post exposition parenteral a incompatibile globulina IgA in sanguine e su componentes. Per contrasto, subjectos con nivei normal de IgA pote producer anti-IgA de specificitate restringite. Ambe iste typos de anticorpore anti IgA esseva presente in 86 pro cento de anaphylactoide e urticarial reactiones transfusional. Le majoritate de iste anticorpores es del classe IgG.

ACKNOWLEDGMENTS

The authors are deeply indebted to Professor P. L. Mollison of M.R.C. Experimental Hematology Research Unit, St. Mary’s Hospital Medical School, London, for the generous gift of IgA anti-Rh serum (Avga). We are grateful to Drs. Rudy Ballieux and Ben Zegers of Utrecht, Netherlands for providing us with some purified IgA myeloma proteins.

ADDENDUM

Specific anti-γA2 subclass antiserum has been recently prepared by immunizing pig-tail monkeys (Macaca nemestrina) with IgA(6) paraprotein and absorption of the immune serum with IgA(1) and IgA(8) paraproteins. Hemagglutination assay was set up with this anti-γA2 antiserum and IgA(2) indicator coat. Out of 19 sera with anti-IgA(6) antibodies (Table 3), 11 samples were available in quantities sufficient for further testing in triplicate for γA2 levels by agglutination inhibition assay. The inhibitory titers of these 11 sera were comparable with that of a pool of 120 normal blood donor sera without anti-IgA activity. The levels of γA2 subclass in normal pooled sera has been less than 10 per cent of the total serum IgA. Thus, the possibility of absence of or gross reduction of γA2 levels in the 11 sera reacting with IgA(6) coat was ruled out.

REFERENCES

HUMAN ANTIBODIES


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