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(54) Title: TELLURIUM-CONTAINING COMPOUNDS FOR FACILITATING TRANSPLANTATION

(57) Abstract: A method of reducing a level of an anli-HLA antibody in a subject in need of organ transplantation may comprise administering to the subject a therapeutically effective amount of a tellurium-containing compound. The tellurium-containing compound may have at least one tellurium dioxo moiety and may have a general formula selected from the group consisting of tellurium dioxide (TeO_2), a complex of TeO_2, and compounds having general formulas such that AS101 is one specific example of one of the general formulas. Also disclosed are methods of using such tellurium-containing compounds in preparing medicaments for use in reducing a level of an anti-HLA antibody in a subject in need of organ transplantation. Pharmaceutical compositions comprising tellurium-containing compounds for organ transplantation are also disclosed.

TELLURIUM-CONTAINING COMPOUNDS FOR FACILITATING TRANSPLANTATION

FIELD AND BACKGROUND OF THE INVENTION

The present invention generally relates to methods for facilitating organ transplantation and, more particularly, to such methods and compositions for decreasing a level of an anti-HLA antibody in subjects in need of transplantation.

The presence of a high titer of anti-HLA antibodies (Ab's) is a barrier to a successful renal transplant. Highly sensitized patients remain on the transplant waiting list for long periods of time, denied many transplant opportunities due to their high titers of anti-HLA antibodies.

Significant efforts have been dedicated to identification of agents or methods that can induce a decrease in the anti-HLA Ab's titer and thus facilitate a successful organ transplant. In vitro incubation of patient sera with desensitizing agents has been shown to reliably reflect the probability that a patient would benefit from de-sensitization protocols.

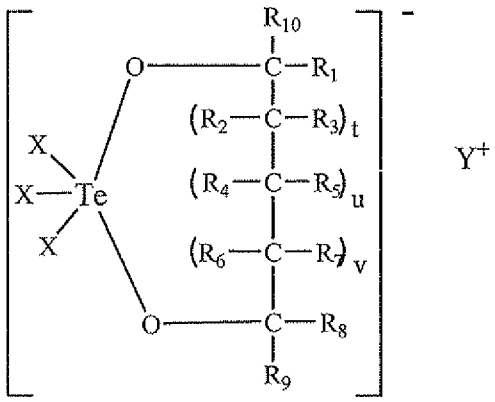
The common protocol for de-sensitization of patients is a combination of IVIg, plasma-pheresis and Rituximab in selected cases. This desensitization protocol is extremely expensive, tedious and is not always effective.

The nontoxic immunomodulator, ammonium trichloro (dioxoethylene-*o, o'*) tellurate (AS101), is a low-molecular-weight (312 Da) synthetic organo-tellurium compound (Albeck et al. 1989). AS101 possesses immunomodulating properties (Rosenblatt-Bin et al. 1998; Sredni et al. 1987; 1988; 1994; 1995a), and has shown beneficial effects in several preclinical and clinical studies.

There is an ongoing need for agents or methods that can induce a decrease in the anti-HLA Ab's titer and thus facilitate a successful organ transplant.

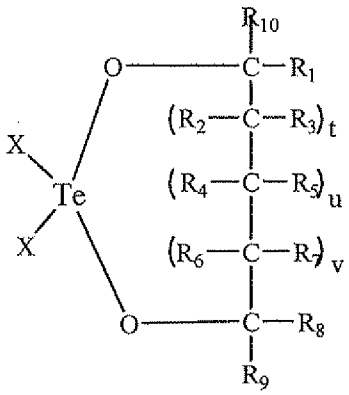
SUMMARY OF THE INVENTION

One aspect of the present invention is directed to a method of reducing a level of an anti-HLA antibody in a subject, the method comprising administering to the subject a therapeutically effective amount of a tellurium-containing compound. In some embodiments of this method, the tellurium-containing compound has a general formula selected from the group consisting of a compound having general Formula I:



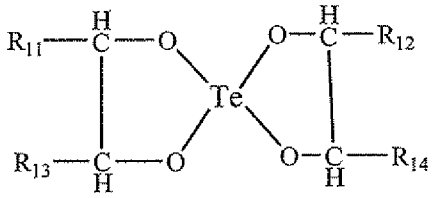
Formula I

a compound having general Formula II:



Formula II

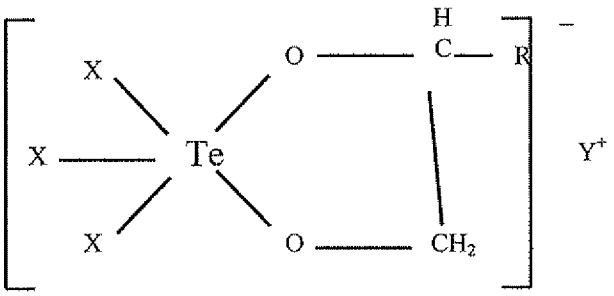
a compound having general Formula III:



Formula III

and a compound having general Formula IV:

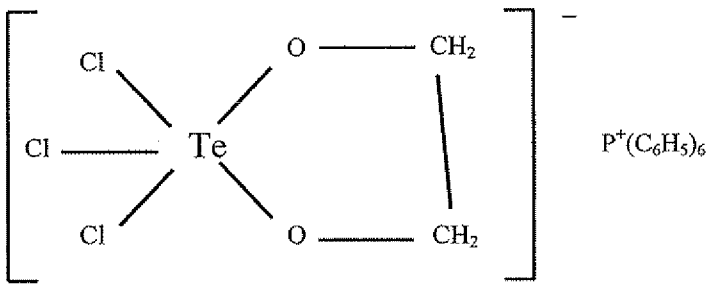
A further aspect of the present invention is a method of reducing a level of an anti-HLA antibody in a subject, the method comprising administering to the subject a therapeutically effective amount of a tellurium-containing compound, wherein. said tellurium-containing compound has a general formula selected from the group consisting of tellurium dioxide (TeO_2), a complex of TeO_2, a compound having general Formula V:



Formula V

wherein X is a halogen atom, Y is ammonium or phosphonium, and R is a hydrogen or alkyl,

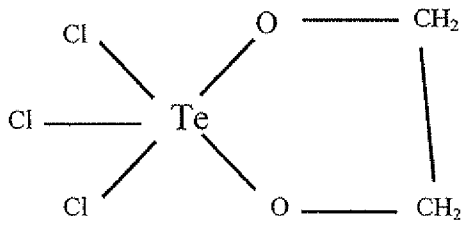
a compound having Formula VI:



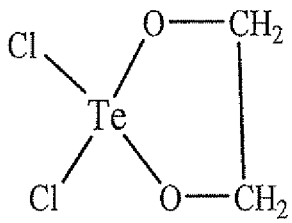
Formula VI

a compound having Formula VII:

Formula VII



and a compound having a Formula VIII



A still further aspect of the present invention is directed to a method of using a tellurium-containing compound to prepare a medicament to facilitate organ transplantation in a subject in need of an organ transplantation, comprising administering to the subject a therapeutically effective amount of a tellurium-containing compound, the compound having a general formula selected from the group consisting of a compound having general Formula V:

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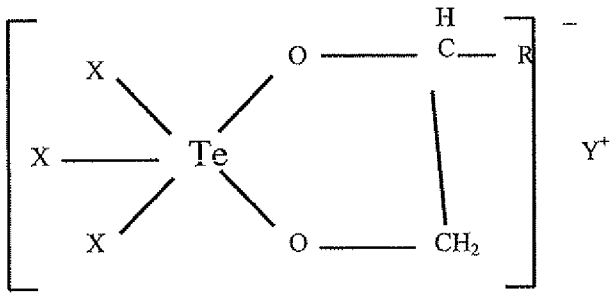
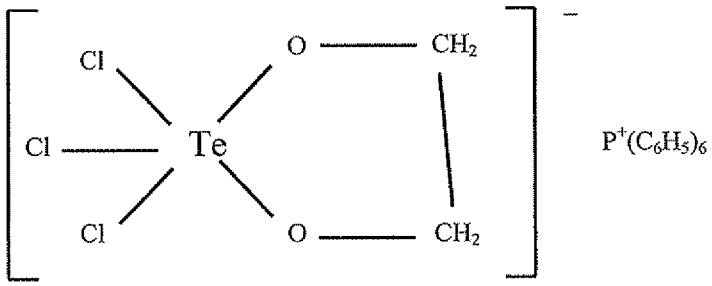


Formula V

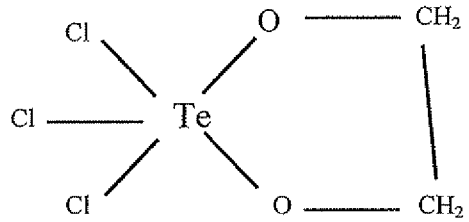
wherein X is a halogen atom, Y is ammonium or phosphonium, and R is a hydrogen or alkyl, a compound having Formula VI:



Formula VI

a compound having Formula VII:

Formula VII



and a compound having a Formula VIII

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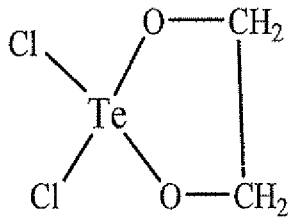


A still further aspect of the present invention is a method of transplanting an organ in a subject in need thereof, the method comprising determining a level of an anti-HLA antibody in the subject, to thereby identify a subject having an elevated level of said antibody; administering to said subject having said elevated level of said antibody a tellurium-containing compound; re-determining said level of said anti-HLA antibody in the subject, to thereby identify a subject having a reduced level of said antibody; and transplanting said organ in the subject.

These and other features, aspects and advantages of the present invention will become better understood with reference to the following drawings, descriptions and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Various embodiments are herein described, by way of example only, with reference to the accompanying drawings, wherein:

FIG. 1 is a graph comparing measured MFI representing titer of anti HLA antibodies in serum incubated in vitro in the presence of IVIg, AS101 and the control compound, PBS with values shown as titer percentage relative to the control;

FIG. 2 is a graph of antibodies detected in sera using varying concentrations and hours of incubation of AS101;

FIG. 3 is a graph depicting the overall effect of AS101 incubation on the anti HLA Ab titer with values shown as titer percentage relative to the control

FIG. 4 is a graph depicting the effect of AS101 incubation on the anti HLA Ab titer of the nine sera that showed a response;

FIG. 5 is a graph showing the effect of AS101 incubation on the Ab titer relative to the control calculated as an average of all 17 sera similar to FIG. 3 except that the data is separated into discrete antibody reactive groups;

FIG. 6 is a graph showing the effect of AS101 incubation on the Ab titer relative to the control but calculated only on the 9 sera that showed a response with the data separated into discrete antibody reactive groups;

FIG. 7 is a graph showing the optimal results as of 2009 of AS101 incubation in a concentration of 4 micrograms/mL among the 9 "responding" samples with the data separated into discrete antibody reactive groups;

FIG. 8 is a graph of 2010 data showing AS101 incubation decreasing the titer of anti-Class I MFI;

FIG. 9 is a graph of 2010 data showing AS101 incubation decreasing the titer of anti-Class II MFI; and

FIG. 10 is a graph showing AS101 effect on Ab titer of patients after IVIg+PP measured as a MFI percentage of control.

DETAILED DESCRIPTION OF THE INVENTION

The following detailed description is of the best currently contemplated modes of carrying out the invention. The description is not to be taken in a limiting sense, but is made merely for the purpose of illustrating the general principles of the invention, since the scope of the invention is best defined by the appended claims.

The present invention generally provides methods and compositions for facilitating tissue transplantation, particularly organ transplantation. These methods may decrease a level of an anti-HLA antibody in subjects in need for transplantation. The present inventors have surprisingly uncovered that a tellurium-containing compound, AS101, reduces the titer of anti-HLA Ab's. These experimental results demonstrate the effect of tellurium-containing compounds in desensitizing subjects that are candidates for organ transplantation and hence in facilitating transplantation.

In contrast to the prior art de-sensitization protocols that may involve combinations of IVIg, plasma-pheresis and Rituximab, which may be extremely expensive, tedious and not always effective, the method of the present invention may involve utilizing a tellurium-containing compound to decrease the level of an anti HLA antibody in a manner that may be less expensive, less tedious and/or more effective. As a result, highly sensitized patients may be on waiting lists for organ

transplant opportunities for shorter periods of time due to their reduced titers of anti-HLA antibodies.

The present invention may be described as a method of reducing a level of an anti-HLA antibody in a subject, the method comprising administering to the subject a therapeutically effective amount of a tellurium-containing compound. The subject may be a subject in need of organ transplantation, for example kidney transplantation. .The method may include administering to the subject a therapeutically effective amount of an agent for reducing a level of an anti-HLA antibody, for example to facilitate and/or promote the transplantation. The agent may be a tellurium-containing compound.. The tellurium-containing compound may comprise at least one tellurium dioxo moiety. As used herein, the phrase "tellurium-containing compound" encompasses any compound that includes one or more tellurium atoms.

Herein throughout, the phrases "tellurium dioxo moiety" and "tellurium dioxide moiety" are used interchangeably, and describe an -O-Te-O- , in which the tellurium center can be further substituted, or a O=Te=O.

The tellurium-containing compound may be an inorganic compound or an organic compound.

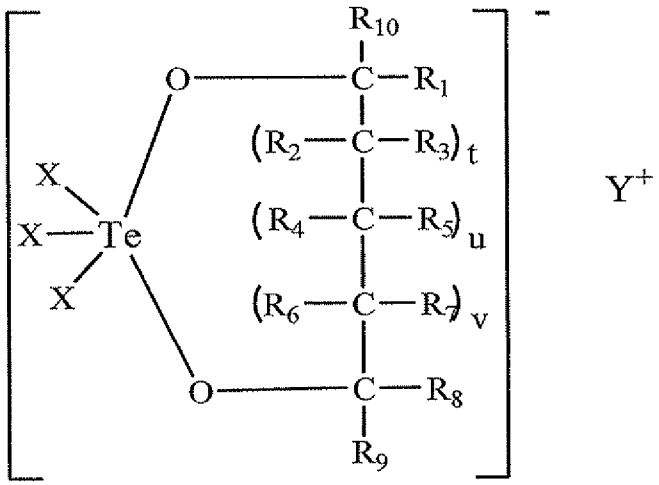
Inorganic tellurium-containing compounds include, for example, tellurium dioxide (TeO_2) *per se*.

Organic tellurium-containing compounds may be in the form of an organic complex such as, for example, a TeO_2 complex with citric acid or ethylene glycol, which may form TeO_2 as an end product in aqueous solutions. A representative example of the latter is the complex $TeO_2 \cdot HOCH_2CH_2OH \cdot NH_4Cl$. .

Otherwise, the tellurium-containing compounds described herein include one or more tellurium atoms and one or more organic moieties that are attached thereto, for example, ammonium salts, or any other salts, of halogenated tellurium-containing compounds having a bidentate cyclic moiety attached to the tellurium atom.

The word “exemplary” is used herein to mean “serving as an example, instance or illustration”.

Exemplary compounds in this category can be collectively represented by the general Formula I:



Formula I

In the general Formula I above, each of t, u and v is independently 0 or 1, such that the compound may include a five-membered ring, a six-membered ring, or a seven-membered ring. Preferably, each of t, u and v is 0, such that the compound includes a five-membered ring.

X is a halogen atom, as described hereinabove, and is preferably chloro.

Y can be ammonium, phosphonium, potassium, sodium and lithium, and is preferably ammonium.

In some preferred embodiments, R_1, R_8, R_9, and R_{10} are all hydrogen.

Each of R_1-R_{10} is independently selected from the group consisting of hydrogen, hydroxyalkyl, hydroxy, thiohydroxy, alkyl, alkenyl, alkynyl, alkoxy, thioalkoxy, halogen, haloalkyl, carboxy, carbonyl, alkylcarbonylalkyl, alkoxy, carboxyalkyl, acyl, amido, cyano, N-monoalkylamidoalkyl, N,N-dialkylamidoalkyl, cyanoalkyl, alkoxyalkyl, carbamyl, cycloalkyl, heteroalicyclic, sulfonyl, sulfinyl, sulfate, amine, aryl, heteroaryl, phosphate, phosphonate and sulfoneamido.

As used herein, the term "alkyl" refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms. More preferably, the alkyl is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, unless otherwise indicated, the alkyl is a lower alkyl having 1 to 5 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group can be as described herein for R_1.

As used herein, the term "hydroxyalkyl" refers to an alkyl, as this term is defined herein, substituted by a hydroxy group, as defined herein, and includes, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxy-n-butyl.

As used herein, the term "halogen", which is also referred to herein interchangeably as "a halogen atom" or "halo", includes chloro (Cl), bromo (Br), iodo (I) and fluoro (F).

The term "haloalkyl" refers to an alkyl, as this term is defined herein, substituted by a halogen, as defined herein, and includes, for example, chloromethyl, 2-iodoethyl, 4-bromo-n-butyl, iodoethyl, 4-bromo-n-pentyl and the like.

The term "alkanoyloxy" refers to a carbonyl group, as define herein and includes, for example, acetyl, propionyl, butanoyl and the like.

The term "carboxyalkyl" refers to an alkyl, as this term is defined herein, substituted by a carboxy group, as defined herein, and includes, for example, carboxymethyl, carboxyethyl, ethylenecarboxy and the like.

The term "alkylcarbonylalkyl" refers to an alkyl, as this term is defined herein, substituted by a carbonyl group, as defined herein, and includes, for example, methanoylmethyl, ethanoylethyl and the like.

The term "amidoalkyl" refers to an alkyl, as this term is defined herein, substituted by an amide group, as defined herein, and includes, for example, $-CH_2CONH_2$; $-CH_2CH_2CONH_2$; $-CH_2CH_2CH_2CONH_2$ and the like.

The term "cyanoalkyl" refers to an alkyl, as this term is defined herein, substituted by an cyano group, as defined herein, and includes, for example, $-CH_2CN$; $-CH_2CH_2CN$; $-CH_2CH_2CH_2CN$ and the like.

The term "N-monoalkylamidoalkyl" refers to an alkyl, as this term is defined herein, substituted by an amide group, as defined herein, in which one of R' and R" is an alkyl, and includes, for example, $-CH_2CH_2CONHCH_3$, and $-CH_-2CONHCH_2CH_3$.

The term N,N-dialkylamidoalkyl refers to an alkyl, as this term is defined herein, substituted by an amide group, as defined herein, in which both R' and R" are alkyl, and includes, for example, $-CH_2CON(CH_3)_2$; $CH_2CH_2CON(CH_2\text{-}CH_3)_2$ and the like.

A "cycloalkyl" group refers to an all-carbon monocyclic or fused ring (i.e., rings which share an adjacent pair of carbon atoms) group wherein one of more of the rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene,

cyclohexane, cyclohexadiene, cycloheptane, cycloheptatriene, and adamantane. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group can be as described herein for R1.

An "alkenyl" group refers to an alkyl group which consists of at least two carbon atoms and at least one carbon-carbon double bond.

An "alkynyl" group refers to an alkyl group which consists of at least two carbon atoms and at least one carbon-carbon triple bond.

An "aryl" group refers to an all-carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted. When substituted, the substituent group can be as described herein for R1.

A "heteroaryl" group refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms, such as, for example, nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Examples, without limitation, of heteroaryl groups include pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, isoquinoline and purine. The heteroaryl group may be substituted or unsubstituted. When substituted, the substituent group can be as described herein for R1.

A "heteroalicyclic" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms such as nitrogen, oxygen and sulfur. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. The heteroalicyclic may be substituted or unsubstituted. When substituted, the substituent group can be as described herein for R1.

A "hydroxy" group refers to an -OH group.

An "alkoxy" group refers to both an -O-alkyl and an -O-cycloalkyl group, as defined herein.

An "aryloxy" group refers to both an -O-aryl and an -O-heteroaryl group, as defined herein.

A "thiohydroxy" group refers to a -SH group.

A "thioalkoxy" group refers to both an -S-alkyl group, and an -S-cycloalkyl group, as defined herein.

A "thioaryloxy" group refers to both an -S-aryl and an -S-heteroaryl group, as defined herein.

A "carbonyl" group refers to a -C(=O)-R' group, where R' is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) or heteroalicyclic (bonded through a ring carbon) as defined herein.

A "thiocarbonyl" group refers to a -C(=S)-R' group, where R' is as defined herein.

A "carboxy" group refers to a -C(=O)-O-R' or a –O-C(=O)-R' group, where R' is as defined herein.

A "sulfinyl" group refers to an -S(=O)-R' group, where R' is as defined herein.

A "sulfonyl" group refers to an $-S(=O)_2-R'$ group, where R' is as defined herein.

A "sulfate" group refers to a $–O-S(=O)_2-OR'$ group, where R' is as defined herein.

A "sulfoneamido" group refers to a $-S(=O)_2-NR'R''$ group or a $R'S(=O)_2-NR''$, with R' is as defined herein and R'' is as defined for R'.

A "carbamyl" or "carbamate" group refers to an -OC(=O)-NR'R'' group or a R''OC(=O)-NR'- group, where R' and R'' are as defined herein.

A "thiocarbamyl" or "thiocarbamate" group refers to an -OC(=S)-NR'R'' group or an R''OC(=S)NR'- group, where R' and R'' are as defined herein.

An "amino" group refers to an –NR'R'' group where R' and R'' are as defined herein.

An "amido" group refers to a -C(=O)-NR'R'' group or a R'C(=O)-NR'' group, where R' and R'' are as defined herein.

A "nitro" group refers to an $-NO_2$ group.

A "cyano" group refers to a -C≡N group.

The term "phosphonyl" describes a -O-P(=O)(OR')(OR") group, with R' and R" as defined hereinabove.

The term "phosphinyl" describes a -PR'R" group, with R' and R" as defined hereinabove.

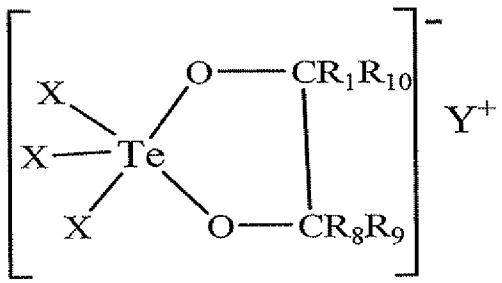
As cited hereinabove, the compounds in this category are salts of organic tellurium-containing compounds. The salts can be, for example, ammonium salts, phsophonium salts and alkaline salts such as potassium salts, sodium salts, lithium salts and the like.

Hence, Y in Formula I above can be a phosphonium group, as defined herein, an ammonium group, as defined herein, potassium (K^+), sodium (Na^+) or lithium (Li^+).

As used herein, the term "phosphonium" describes a $-P^+R'R''R'''$ group, with R' and R'' as defined herein and R''' is as defined for R'. The term "phosphonium", as used herein, further refers to a $-P^+R_6$ group, wherein each of the six R substituents is independently as defined herein for R, R'' and R'''.

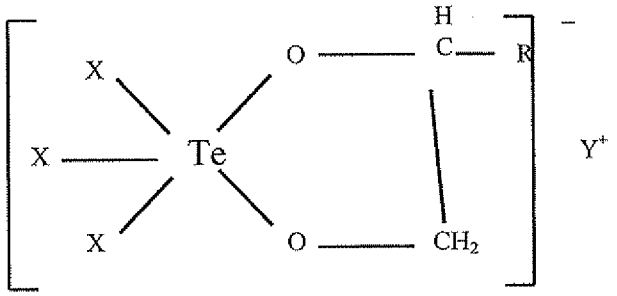
The term "ammonium" describes a $-N^+R'R''R'''$ group, with R', R'' and R''' as defined herein.

Preferred compounds in this category include compounds having the general Formula I described above, in which Y is ammonium or phosphonium, t, u and v are each 0, and each of R_1, R_8, R_9 and R_{10} is independently hydrogen or alkyl. These compounds can be represented by the following structure:



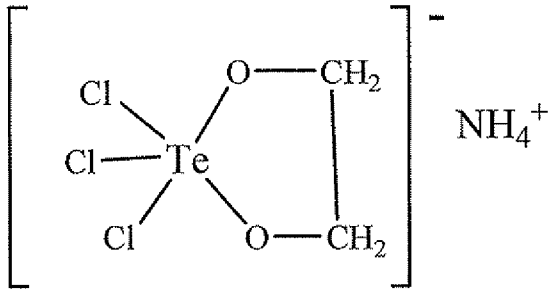
wherein each of R_1, R_8, R_9 and R_{10} is independently hydrogen or alkyl, whereas a preferred alkyl is methyl, and X is halogen, preferably chloro.

A more specific characterization of the above preferred compound may be described as:



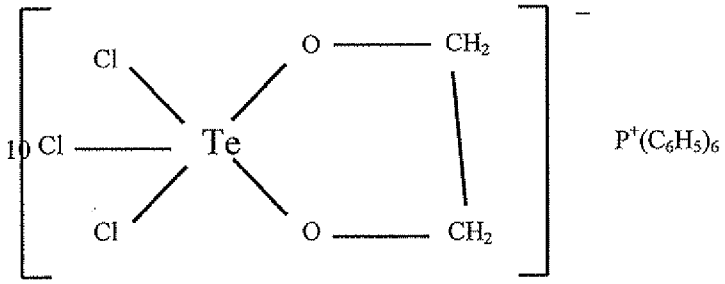
wherein X is a halogen atom, Y is ammonium or phophonium, and R is a hydrogen or alkyl. It is referred to at times herein as general Formula V.

The presently most preferred compound for use in the context of the present embodiments has the following structure:



This compound is ammonium trichloro(dioxyethylene-O,O')tellurate, which is also referred to herein and in the art as AS101.

An additional exemplary compound in this category is:

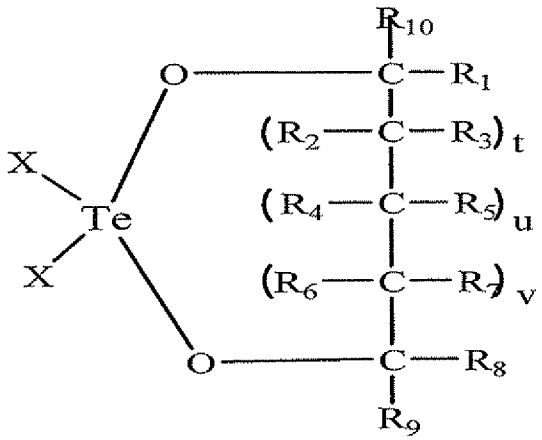


It is referred to at times herein as Formula VI.

Additional representative examples of organic tellurium-containing compounds that are suitable for use in the context of the present invention include halogenated tellurium having a bidentate cyclic moiety to the tellurium atom. The bidentate cyclic moiety is a preferably dioxo ligand having two oxygen atoms attached tot the tellurium atom.

Exemplary compounds in this category can be represented by the general Formula II:

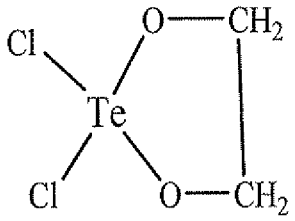
15



Formula II

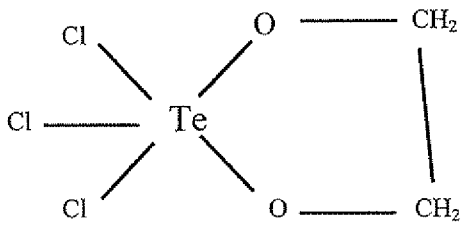
wherein t, u, v, X and R_1-R_{10} are as defined hereinabove.

Preferred compounds are those in which t, u, and v are each 0, and X is chloro, such as, but not limited to, the compound having the following structure:



The above compound is also known in the art and referred to herein as AS103 and is referred to at times herein as Formula VIII. Another preferred formula similar to formula VIII is Formula VII.

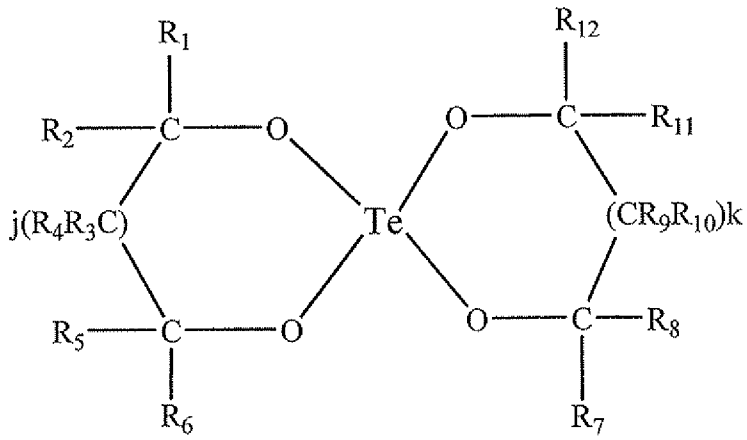
Formula VII



The organic tellurium-containing compounds having Formulae I and II can be readily prepared by reacting tetrahalotelluride such as $TeCl_4$ with a dihydroxy compound, as is described in detail in U.S. Patents Nos. 4,752,614, 4,761,490, 4,764,461 and 4,929,739, which are incorporated by reference as if fully set forth herein.

Additional representative examples of organic tellurium-containing compounds that are suitable for use in the context of the present embodiments include compounds in which two bidentatic cyclic moieties are attached to the tellurium atom. Preferably, each of the cyclic moieties is a dioxo moiety.

Exemplary compounds in this category are collectively represented by the general Formula III:

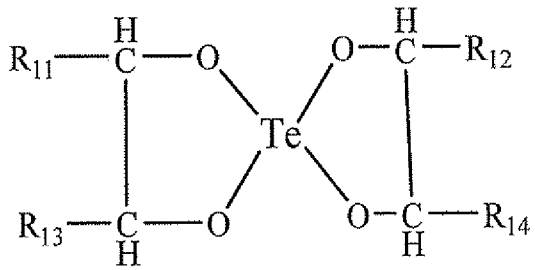


Formula III

In the general Formula III above, each of j and k is independently an integer from 0 to 4, such that the compound may include a five-membered ring, a six-membered ring, a seven-membered ring, an eight-membered ring and/or a nine-membered ring. Preferably, each of j and k is an integer from 0 to 2, such that the compound includes a five-membered ring, a six-membered ring and/or a seven-membered ring. More preferably, each of j and k is 0.

R_1-R_{12} are as defined hereinabove for R_1-R_{10}.

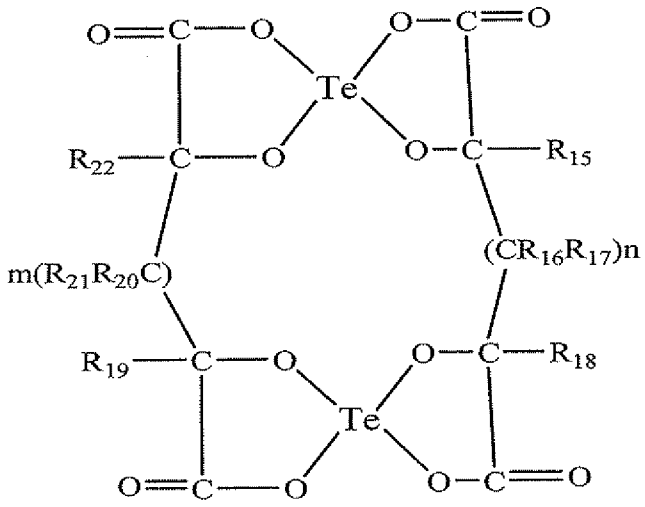
Preferred compounds in this category are those in which j and k are each 0, and R_3, R_4, R_9 and R_{10} are each hydrogen, having the following structure:



wherein each of R_{11}-R_{14} is independently selected from the group consisting of hydrogen, hydroxyalkyl, hydroxy, thiohydroxy, alkyl, alkenyl, alkynyl, alkoxy, thioalkoxy, halogen, haloalkyl, carboxy, carbonyl, alkylcarbonylalkyl, alkoxy, carboxyalkyl, acyl, amido, cyano, N-monoalkylamidoalkyl, N,N-dialkylamidoalkyl, cyanoalkyl, alkoxyalkyl, carbamyl, cycloalkyl, heteroalicyclic, sulfonyl, sulfinyl, sulfate, amine, aryl, heteroaryl, phosphate, phosphonate and sulfoneamido, as these terms are defined herein.

The most preferred compound in this category is a compound in which each of R_{11}-R_{14} is hydrogen. This compound is also known in the art and referred to herein as AS102.

Additional representative examples of organic tellurium-containing compounds that are suitable for use in the context of the present embodiments include the recently disclosed ditellurium compounds having general Formula IV:



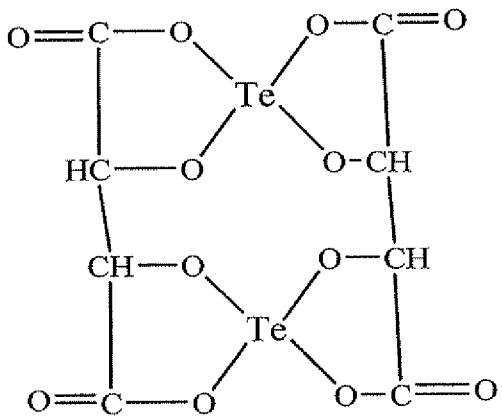
Formula IV

wherein each of R_{15}-R_{22} is independently selected from the group consisting of hydrogen, hydroxyalkyl, hydroxy, thiohydroxy, alkyl, alkenyl, alkynyl, alkoxy, thioalkoxy, halogen, haloalkyl, carboxy, carbonyl, alkylcarbonylalkyl, alkoxy, carboxyalkyl, acyl, amido, cyano, N-monoalkylamidoalkyl, N,N-dialkylamidoalkyl, cyanoalkyl, alkoxyalkyl, carbamyl, cycloalkyl, heteroalicyclic, sulfonyl, sulfinyl, sulfate, amine, aryl, heteroaryl, phosphate, phosphonate and sulfoneamido, as these terms are defined herein; and

m and n are each an integer from 0 to 3.

Exemplary compounds in this category are those in which m and n are each 0.

The presently most preferred compound in this family is a compound in which R_{15}, R_{18}, R_{19} and R_{22} are all hydrogen, referred to hereinafter as SAS, and which has the following structure:



Compounds having the general Formula IV can be readily prepared by reacting substantially equimolar amounts of a tellurium tetralkoxide and a polycarboxylic acvid. These materials are combined in the presence of a water free organic solvent such as dried ethanol, dimethyl sulfoxide, i-propanol and the like. Generally, the reaction may take place at ambient conditions but if desired higher or lower temperatures and higher or lower pressures may be utilized.

According to a most preferred embodiment of the present invention, the tellurium-containing compound is either AS101 or SAS.

The compounds described above can be administered or otherwise utilized in the various aspects of the present invention, either as is or as a pharmaceutically acceptable salt thereof.

The phrase "pharmaceutically acceptable salt" refers to a charged species of the parent compound and its counter ion, which is typically used to modify the solubility characteristics of the parent compound and/or to reduce any significant irritation to an organism by the parent compound, while not abrogating the biological activity and properties of the administered compound.

In addition, a pharmaceutically acceptable carrier may be added to the tellurium-containing compound when administering the tellurium-containing compound to a

subject or in any of the methods or compositions of the present invention that utilize tellurium-containing compounds. As such, the present invention may be described as a pharmaceutical composition identified for use in reducing a level of an anti-HLA antibody in a subject comprising at least one tellurium-containing compound and a pharmaceutically acceptable carrier. The tellurium-containing compound utilized may be any of the tellurium-containing compounds identified herein as suitable for reducing the titer of anti-HLA antibodies or those identified as suitable for facilitating transplantation in a subject in need thereof.

For example, the tellurium-containing compound may be selected from the group consisting of tellurium dioxide (TeO2), a complex of TeO2, a compound having the general formula I, a compound having general formula II a compound having the general formula III, a compound having the general formula IV. In some cases, the tellurium-containing compound may be selected from the group consisting of tellurium dioxide (TeO2), a complex of TeO2, a compound having the general formula V, a compound having the formula VI, a compound having the formula VII and a compound having the formula VIII. The formula I through VIII are those mentioned herein in this patent application..

AS101 is (ammonium trichloro(dioxyethylene-O,O')tellurate)

PBS is (phosphate buffered saline)

SAS is ($[TeO_4(COCH)_2]_2$)

As seen in FIG. 11, the present invention may also be characterized as a method 100 of transplanting an organ in a subject in need of such a transplant. Method 100 may include a step 110 of determining a level of an anti-HLA antibody in the subject, to thereby identify a subject having an elevated level of said antibody. In addition, method 100 may also have a step 120 of administering to said subject having said elevated level of said antibody a tellurium-containing compound.

The step 120 of administering to the subject may be accomplished in ways well-known in the medical art.

The tellurium-containing compound referred to in step 120 may be any of the tellurium-containing compounds mentioned in this patent application as appropriate for use in reducing the level of an anti-HLA antibody in a subject. For example, the tellurium-containing compound may be selected from the group consisting of tellurium dioxide (TeO2), a complex of TeO2, a compound having the general formula I, a

compound having general formula II a compound having the general formula III, a compound having the general formula IV. In some cases, the tellurium-containing compound may be selected from the group consisting of tellurium dioxide (TeO2), a complex of TeO2, a compound having the general formula V, a compound having the formula VI, a compound having the formula VII and a compound having the formula VIII. The formula I through VIII are those mentioned herein in this patent application..

Method 100 may also include a step 130 of re-determining said level of said anti-HLA antibody in the subject, to thereby identify a subject having a reduced level of said antibody. Method 100 may further of comprise step 140 of transplanting said organ in the subject.

Suitable routes of administration of the tellurium-containing compound for any of the methods of the present invention may be those known in the medical arts and may, for example, include the inhalation, oral, buccal, rectal, transmucosal, transdermal, intradermal, transnasal, intestinal and/or parenteral routes; the intramuscular, subcutaneous and/or intramedullary injection routes; the intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, and/or intraocular injection routes; and/or the route of direct injection into a tissue region of a subject.

As used herein, the term "therapeutically effective amount" or “pharmaceutically effective amount” denotes that dose of an active ingredient or a composition comprising the active ingredient that will provide the therapeutic effect for which the active ingredient is indicated. More specifically, a therapeutically effective amount means an amount of active ingredients effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

Determination of a therapeutically effective amount is well within the capability of those skilled in the art.

For any preparation used in the methods of the invention, the therapeutically effective amount or dose can be estimated initially from in vitro assays. For example, a dose can be formulated in animal models and such information can be used to more accurately determine useful doses in humans.

The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. [See e.g., Fingl, et al., (1975) "The Pharmacological Basis of Therapeutics", Ch. 1 p.1].

When administering systemically, a therapeutically effective amount of the tellurium-containing compounds described herein may range, for example, from about 0.01 mg/m^2/day to about 20 mg/m^2/day and thus can be for example, 0.01 mg/m^2/day, 0.02 mg/m^2/day, 0.03 mg/m^2/day, 0.04 mg/m^2/day, 0.05 mg/m^2/day, 0.1 mg/m^2/day, 0.5 mg/m^2/day, 1 mg/m^2/day, 2 mg/m^2/day, 3 mg/m^2/day, 4 mg/m^2/day, 5 mg/m^2/day, and up to 10 mg/m^2/day. Preferably, for systemic administration, a therapeutically effective amount of a compound of formula I, II, III or IV ranges from about 0.01 mg/m^2/day to about 10 mg/m^2/day. Higher therapeutically effective amounts, such as, for example, up to 20 mg/m^2/day can also be employed.

In one embodiment, when administered intraperitoneally, the therapeutically effective amount is 0.01 mg/m^2/day and higher and thus can be, for example,0.01 mg/m^2/day, 0.05 mg/m^2/day, 0.1 mg/m^2/day, 0.2 mg/m^2/day, 0.5 mg/m^2/day, 0.6 mg/m^2/day, 0.7 mg/m^2/day, 0.8 mg/m^2/day, 0.9 mg/m^2/day, 1 mg/m^2/day, 2 mg/m^2/day, 3 mg/m^2/day, 4 mg/m^2/day, 5 mg/m^2/day, and up to 20.0 mg/m^2/day. When administered orally in humans, a daily dose typically ranges between 0.1 mg and 200 mg, more preferably between 1 mg and 100 mg, depending on the age and weight of the subject. The total daily dose may be administered as a single dosage, or may be divided into a number of separate doses.

In any of the methods and uses described herein, the tellurium-containing compounds can be utilized in combination with an additional active agent, preferably being advantageous for treating the indicated condition. For example, any of the methods described herein can further comprise, in addition to administering the tellurium-containing compounds described above, co-administration of an additional active agent. The co-administration can be effected prior to, concomitant with or subsequent to the administration of the tellurium-containing compound. The additional active agent may be used for providing an additive beneficial effect in terms of the condition being treated, conditions associated with the condition being treated or other parameters such as psychological effects and prophylactic effects.

Various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below find experimental support in the following examples.

EXAMPLES

Reference is now made to the following examples, which together with the above descriptions illustrate some embodiments of the invention in a non limiting fashion.

EXAMPLE 1

AS101 in comparison to IVIg

10 sera of highly sensitized patients awaiting a renal transplant (PRA Class I & Class II > 80%) were incubated in vitro in the presence of either IVIg or AS101. Incubation with PBS served as control. Measured MFI (mean fluorescence intensity units) represents titer of anti HLA antibodies in the serum, for both HLA Class I & II. Ab's were detected using the Luminex xMAP platform (Tepnel Lifecodes - Screen).

The results are presented in Figure 1. AS101 caused an average decrease of 16% in the titer of anti-HLA Class I Ab's compared to the control, where 5 of the 10 sera showed beneficial response. IVIg incubation resulted in an average decrease of 13% in the titer of anti-HLA Class I Ab's compared to the control, where 4 of the 10 sera showed advantageous response. Sera incubation in the presence of IVIg and AS101 led to an average decrease of 5% and 15%, respectively, in titer of anti-HLA Class II Ab's. IVIg effect was visible in 4/10 sera while AS101 effect was identified in 6/10 samples.

EXAMPLE 2

AS101 incubation with patient sera

Four experiments were carried out. 24 patients' sera from highly sensitized patients were incubated with different concentrations of AS101 for various incubation periods, as follows:

i. 14 sera, 3.5 hours of incubation, with concentration of 2 μg/mL.

ii. 6 sera, incubation periods of 0.5, 3, 15 hours, with concentration of 2 μg/mL.

iii. 2 sera, 15 hours of incubation, with concentrations of 0, 1, 2 and 4 μg/mL.

iv. 2 sera, 0.5 hours of incubation, with concentrations of 0, 2 and 4 μg/mL.

The results are presented in Figure 2. Ab's were detected using the Luminex xMAP platform (Tepnel Lifecodes - Screen) or using GTI QuickScreen ELISA kits for Class I and Class II.

AS101 in-vitro incubation showed a beneficial reduction in the titer of anti-HLA antibodies. The extent of the antibody titer decrease ranges from 0-30% for Class I and Class II. Class I data is represented as black diamonds and Class II data is represented as gray squares.

EXAMPLE 3

A series of in vitro experiments were carried out between April 2009 and June 2009.

Patient samples: this preliminary stage of the research utilized 17 sera of patients awaiting their second renal transplant. All patients are designated as 'highly sensitized', presenting a PRA level above 30% either in anti-HLA-class-I antibodies or anti-HLA-class-II antibodies or both.

Method: Sera were incubated for three hours in the presence of various AS101 concentrations. Incubation in the presence of PBS was used at the control. Each serum was tested for its anti-HLA antibody titer as measured by the Luminex x-MAP platform using *LifeScreen Deluxe kits*.

The Luminex machine is currently considered as the 'gold standard' in clinical laboratories worldwide for sensitive and accurate measurement and characterization of the anti-HLA Ab profile. *Lifescreen Deluxe* contains a set of beads coated with a pool of class I glycoprotein along with a set of CREG (cross reactive groups) enriched beads. A different set of beads coated with class II glycoprotein along with a set of CREG enriched beads are also included. The titer of anti-HLA Ab's in a serum is presented as the MFI (mean fluorescence intensity) measured from every reactive bead.

Result: 9 out of 17 sera showed a 10-15% decrease in the Ab titer following incubation, relative to the control which was incubated in the presence of PBS.

FIG. 3 describes the overall effect of AS101 incubation on the anti-HLA Ab titer. Values are shown as titer percentage relative to the control. For example, sera incubated in the presence of 1 microgram/mL AS101 showed an averae 10% higher Ab titer than the control sample. AS101 concentrations of 4, 6 and 9 microgram/mL

brought about an average lower titer of Ab's.

FIG. 4 is a graph describing the overall effect of AS101 incubation only on the nine sera that showed a response: FIG. 4 depicts the average relative titer only in the 9 sera that responded. It is evident that after the removal of the non-responsive sample from the calculation, the average Ab titer decrease in the concentrations of 4 and 6 micrograms/mL is more than 10%.

The Lifecodes deluxe kit enables one to evaluate the individual response of different probes according to their antibody reactive group. This allows one to differentiate between specific antibodies responses against specific potential kidney donors. This will eventually be used to detect Donor Specific Antibodies (DSA). It was interesting to find that AS101 effect on antibodies of different CREG's (cross reactive groups) was not uniform. FIG. 5 shows the same data as the first graph separated into the discrete antibody reactive groups. "Probe I" and "Probe II" mean that they describe probes that identify antibodies against Class I or Class II respectively. It is evident that different CREG-designated antibodies respond differently to AS101 incubation. FIG. 5 describes the effect of AS101 incubation on the Ab titer, relative to the control, calculated as an average of all 17 sera.

FIG. 6 describes only the 9 sera who responded, showing the effect of AS101 on each separate bead, presenting a distinct antibody CREG. In FIG. 6, it is noticeable that the consequence of AS101 incubation on antibodies detected by "Probe I – 03" was less pronounced than the antibodies detected by "Probe I – 01" or by "Probe I – 02".

FIG. 7 is a graph that presents the "'optimal' result that we have achieved thus far. The average effect of AS101 incubation, in the concentration of 4 micrograms/mL, among the nine "responding" samples. The average decrease in Ab titer is 11%, range 7-14%.

Conclusion: Incubation of selected sera collected from highly sensitized patients in the presence of AS101 brings about an average 11% decrease in the titer of anti-HLA antibodies

The following summarizes the results obtained as of June 2009 at the end of this Example 3:

In vitro sera incubation in the presence of AS101 caused a 10-15% decrease in the titer of anti-HLA Ab's in comparison to the untreated control. The most favorable

in vitro conditions in which AS101's effect on anti-HLA Ab's is optimally manifested are:

1. AS101 concentrations of 4 micrograms/mL
2. Incubation duration of 3-24 hours
3. Incubation conditions of 25°C (room temperature), constant soft stir of the samples

EXAMPLE 4

On June 7, 2010 twenty-six sera were collected from 23 patients of the following clinical settings at the tissue typing laboratory of the Rabin Medical Center:

1. Two patients awaiting a heart transplant
2. Four patients awaiting a lung transplant
3. Six patients awaiting their first renal transplant
4. Nine kidney recipients awaiting a renal re-transplant
5. Two patients who were treated by IVIg+PP, awaiting a renal re-transplant.

Materials and Methods: Sera were incubated for three hours in the presence of AS101 (4 micrograms/mL). Incubation in the presenced of PBS was used as the control. Each serum was tested for its anti-HLA antibody titer as measured by the Luminex x-MAP platform using LifeScreen Deluxe kits.

Results:

1. AntiHLA Class I antibodies
    a. AS101's effect was detected in 12 of 22 (54%) samples who presented antibodies against HLA Class I
    b. The median decrease in Ab titer among the responding samples was 15%
    c. The median of the strongest reacting probe's MFI was among responding and non-responding samples was 4916 and 9413, respectively ($p<0.05$).
    d. Only 1 in 6 patients awaiting a re-transplant did not present an effect in regard to anti Class I antibodies. In contrast, 4 of 5 patients awaiting their first renal transplant did not present an effect in regard to anti Class I antibodies.

2. Anti HLA Class II antibodies
    a. AS101's effect was detected in 14 of 19 (74) samples who presented antibodies against HLA Class II
    b. The median decrease in Ab titer among the responding samples was 12%
    c. The median of the strongest reacting probe's MFI among responding and non-responding samples was 4615 and 12657, respectively.
    d. Only 1 of 9 awaiting a re-transplant did not present an effect in regard to anti Class I antibodies. Concurrently, only 1 of 4 patients awaiting their first renal transplant did not present an effect in regard to anti Class I antibodies.

3. Patients post IVIg+PP, awaiting their renal re-transplant
    a. Two sera received from patients after IVIg+PP treatment showed an average decrease of 8% and 20% in their MFI values.

The results of this experiment appear in the graphs shown in FIG. 8, FIG. 9 and FIG. 10

Conclusions from Example 4:

1. This current experiment clearly ratified and confirmed previous observations of the effect of AS101 incubation on the anti-HLA Ab titer of patient sera.
2. Sera incubation in the presence of AS101 leads to a 12-15% decrease in the anti-HLA antibody titer
3. Sera with a moderate level of antibody titer present a higher level of responsiveness to the AS101 effect.
4. It is possible that patients with different sensitizing-event background may present dissimilar outcome upon de-sensitization treatment.
5. Ratified and confirmed a previous observation by which a patient who has been treated in vivo with IVIg+PP could benefit from AS101 treatment for de-sensitization.

These results demonstrate that *in vitro* sera incubation in the presence of AS101 causes a decrease in the titer of anti-HLA Ab's. These results indicate the beneficial effect of AS101, as an exemplary tellurium-containing compound, as a potential agent for desensitization of high-PRA patients, and thus for facilitating and/or promoting organ transplantation in such patients.

Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

As used herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a condition, substantially ameliorating clinical or aesthetical symptoms of a condition or substantially preventing the appearance of clinical or aesthetical symptoms of a condition.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent

application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

WHAT IS CLAIMED IS:

1. A method of reducing a level of an anti-HLA antibody in a subject, the method comprising administering to the subject a therapeutically effective amount of a tellurium-containing compound.

2. The method of claim 1, wherein said subject is in need for organ transplantation.

3. The method of claim 1, further comprising administering to the subject a therapeutically effective amount of an agent for reducing a level of an anti-HLA antibody.

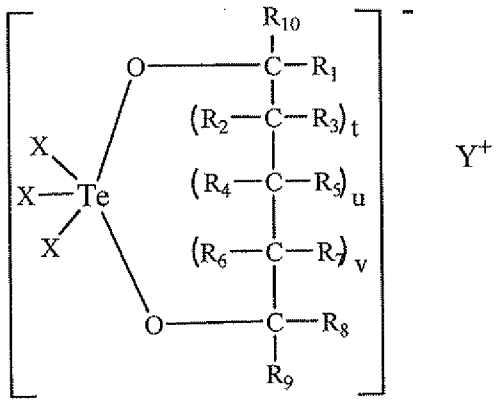
4. The method of claim 2, wherein said subject is in need for kidney transplantation.

5. The method of claim 2, being for facilitating and/or promoting said transplantation.

6. The method of claim 1, wherein said tellurium-containing compound comprises at least one tellurium dioxo moiety.

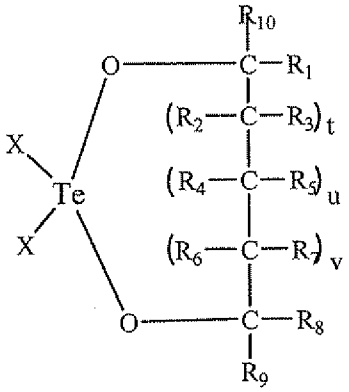
7. The method of claim 6, wherein said tellurium-containing compound has a general formula selected from the group consisting of:

a compound having general Formula I:



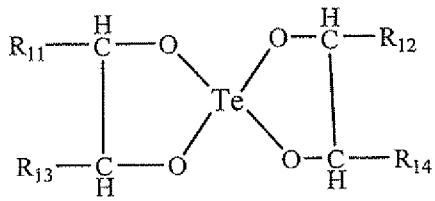
Formula I

a compound having general Formula II:



Formula II

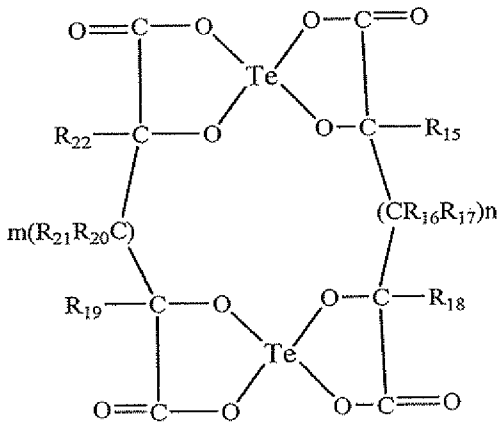
a compound having general Formula III:



Formula III

and

a compound having general Formula IV:



Formula IV

wherein:

each of t, u and v is independently 0 or 1;

each of m and n is independently 0, 1, 2 or 3;

Y is selected from the group consisting of ammonium, phsophonium, potassium, sodium and lithium;

X is a halogen atom; and

each of R_1-R_{22} is independently selected from the group consisting of hydrogen, hydroxyalkyl, hydroxy, thiohydroxy, alkyl, alkenyl, alkynyl, alkoxy, thioalkoxy, halogen, haloalkyl, carboxy, carbonyl, alkylcarbonylalkyl, carboxyalkyl, acyl, amido, cyano, N-monoalkylamidoalkyl, N,N-dialkylamidoalkyl, cyanoalkyl, alkoxyalkyl, carbamyl, cycloalkyl, heteroalicyclic, sulfonyl, sulfinyl, sulfate, amine, aryl, heteroaryl, phosphate, phosphonate and sulfoneamido.

8. The method of claim 7, wherein said tellurium-containing compound has said general Formula I.

9. The method of claim 8, wherein t, u and v are each 0.

10. The method of claim 9, wherein each of R_1, R_8, R_9 and R_{10} is hydrogen.

11. The method of claim 10, wherein X is chloro.

12. The method of claim 11, wherein Y is ammonium.

13. The method of any of claims 1 and 2, wherein said tellurium-containing compound is AS101.

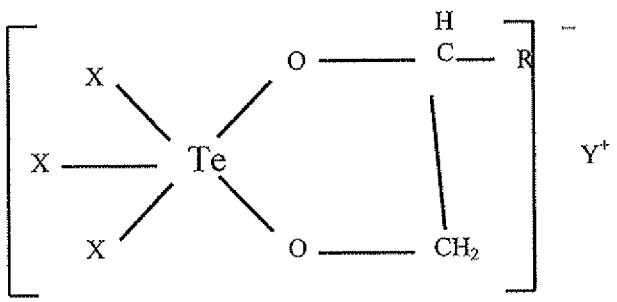
14. The method of claim 7, wherein said compound has said general Formula IV.

15. The method of claim 14, wherein each of m and n is 0.

16. The method of claim 15, wherein each of R_{15}, R_{18}, R_{19} and R_{22} is hydrogen.

17. The method of any of claims 1 and 2, wherein said tellurium-containing compound is SAS.

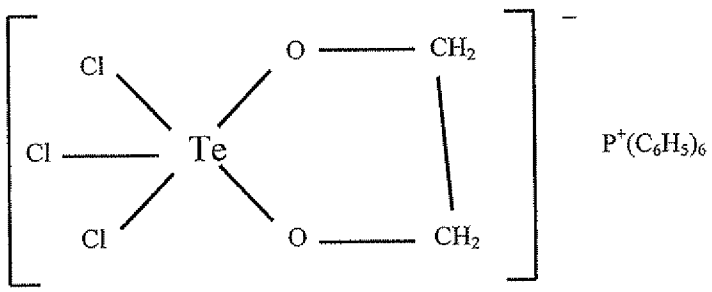
18. A method of reducing a level of an anti-HLA antibody in a subject, the method comprising administering to the subject a therapeutically effective amount of a tellurium-containing compound, wherein. said tellurium-containing compound has a general formula selected from the group consisting of tellurium dioxide (TeO_2), a complex of TeO_2, a compound having general Formula V:



Formula V

wherein X is a halogen atom, Y is ammonium or phosphonium, and R is a hydrogen or alkyl,

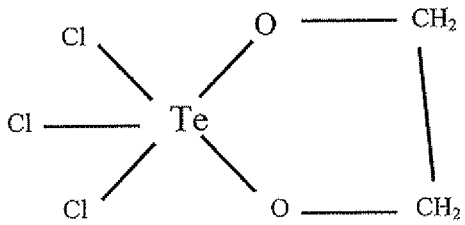
a compound having Formula VI:



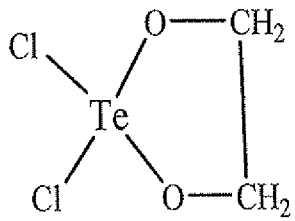
Formula VI

a compound having Formula VII:

Formula VII



and a compound having a Formula VIII



19. The method of claim 18, wherein R is methyl.

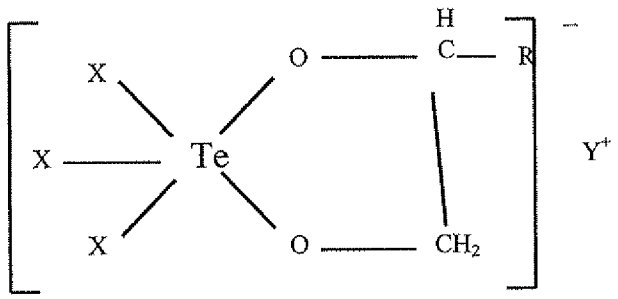
20. The method of claim 18, wherein X is chloro.

21. The method of claim 18, wherein Y is ammonium.

22. The method of claim 18, wherein said complex of TeO_2 is $TeO_2HOCH_2CH_2OHNH_4Cl$.

23. A method of using a tellurium-containing compound to prepare a medicament to facilitate organ transplantation in a subject in need of an organ transplantation, comprising administering to the subject a therapeutically effective amount of a tellurium-containing compound, the compound having a general formula selected from the group consisting of:

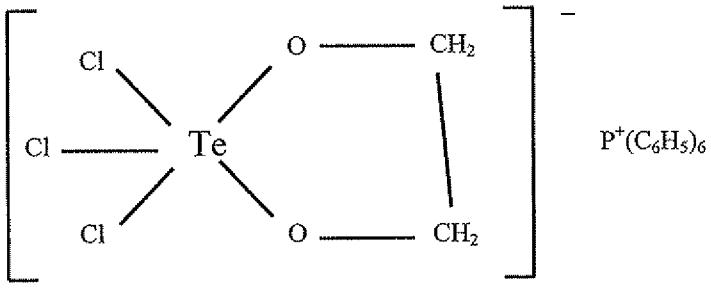
a compound having general Formula V:



Formula V

wherein X is a halogen atom, Y is ammonium or phosphonium, and R is a hydrogen or alkyl,

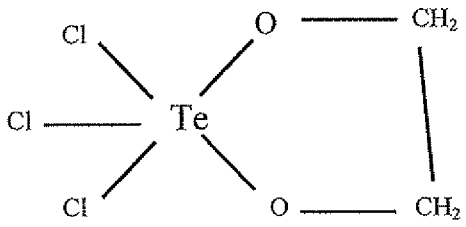
a compound having Formula VI:



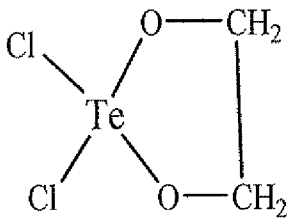
Formula VI

a compound having Formula VII:

Formula VII



and a compound having a Formula VIII



24. A method of transplanting an organ in a subject in need thereof, the method comprising:

determining a level of an anti-HLA antibody in the subject, to thereby identify a subject having an elevated level of said antibody;

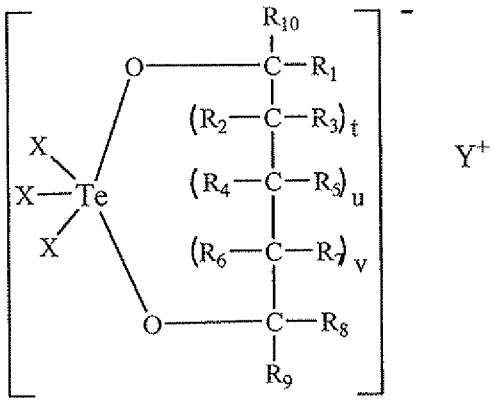
administering to said subject having said elevated level of said antibody a tellurium-containing compound;

re-determining said level of said anti-HLA antibody in the subject, to thereby identify a subject having a reduced level of said antibody; and

transplanting said organ in the subject.

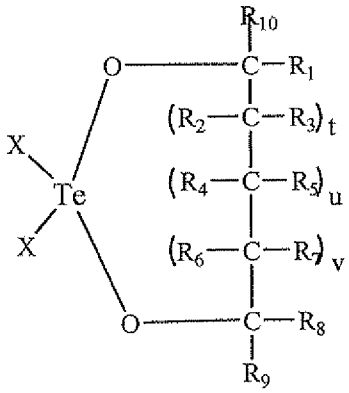
25. The method of claim 24, wherein said tellurium-containing compound has a general formula selected from the group consisting of:

a compound having general Formula I:



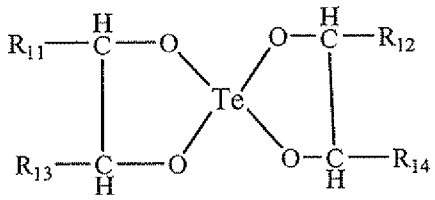
Formula I

a compound having general Formula II:



Formula II

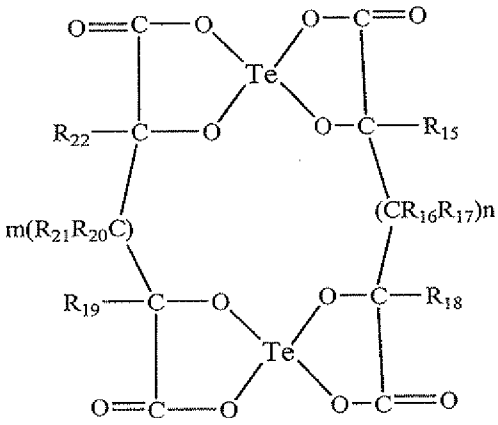
a compound having general Formula III:



Formula III

and

a compound having general Formula IV:



Formula IV

wherein:

each of t, u and v is independently 0 or 1;

each of m and n is independently 0, 1, 2 or 3;

Y is selected from the group consisting of ammonium, phsophonium, potassium, sodium and lithium;

X is a halogen atom; and

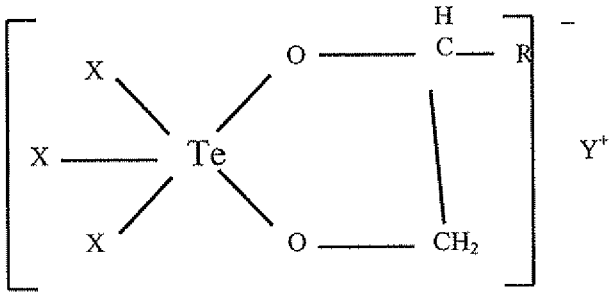
each of R_1-R_{22} is independently selected from the group consisting of hydrogen, hydroxyalkyl, hydroxy, thiohydroxy, alkyl, alkenyl, alkynyl, alkoxy, thioalkoxy, halogen, haloalkyl, carboxy, carbonyl, alkylcarbonylalkyl, carboxyalkyl, acyl, amido, cyano, N-monoalkylamidoalkyl, N,N-dialkylamidoalkyl, cyanoalkyl, alkoxyalkyl, carbamyl, cycloalkyl, heteroalicyclic, sulfonyl, sulfinyl, sulfate, amine, aryl, heteroaryl, phosphate, phosphonate and sulfoneamido.

26. The method of claim 24, wherein said tellurium-containing compound is selected from the group consisting of a compound having said general Formula I and a compound having said general Formula II.

27. The method of claim 24, wherein said tellurium-containing compound has said general Formula III.

28. The method of claim 24, wherein said tellurium-containing compound has a general formula selected from the group consisting of:

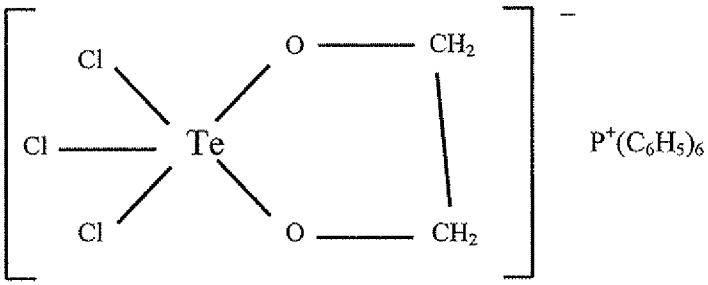
a compound having general Formula V



Formula I

wherein X is a halogen atom, Y is ammonium or phosphonium, and R is a hydrogen or alkyl,

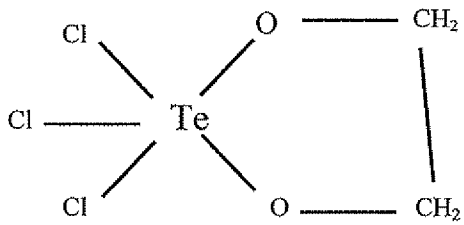
a compound having the Formula VI:



Formula VI

a compound having general Formula VII:

Formula VII



and a compound having a Formula VIII

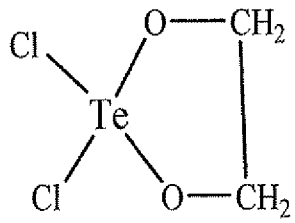


FIG. 1

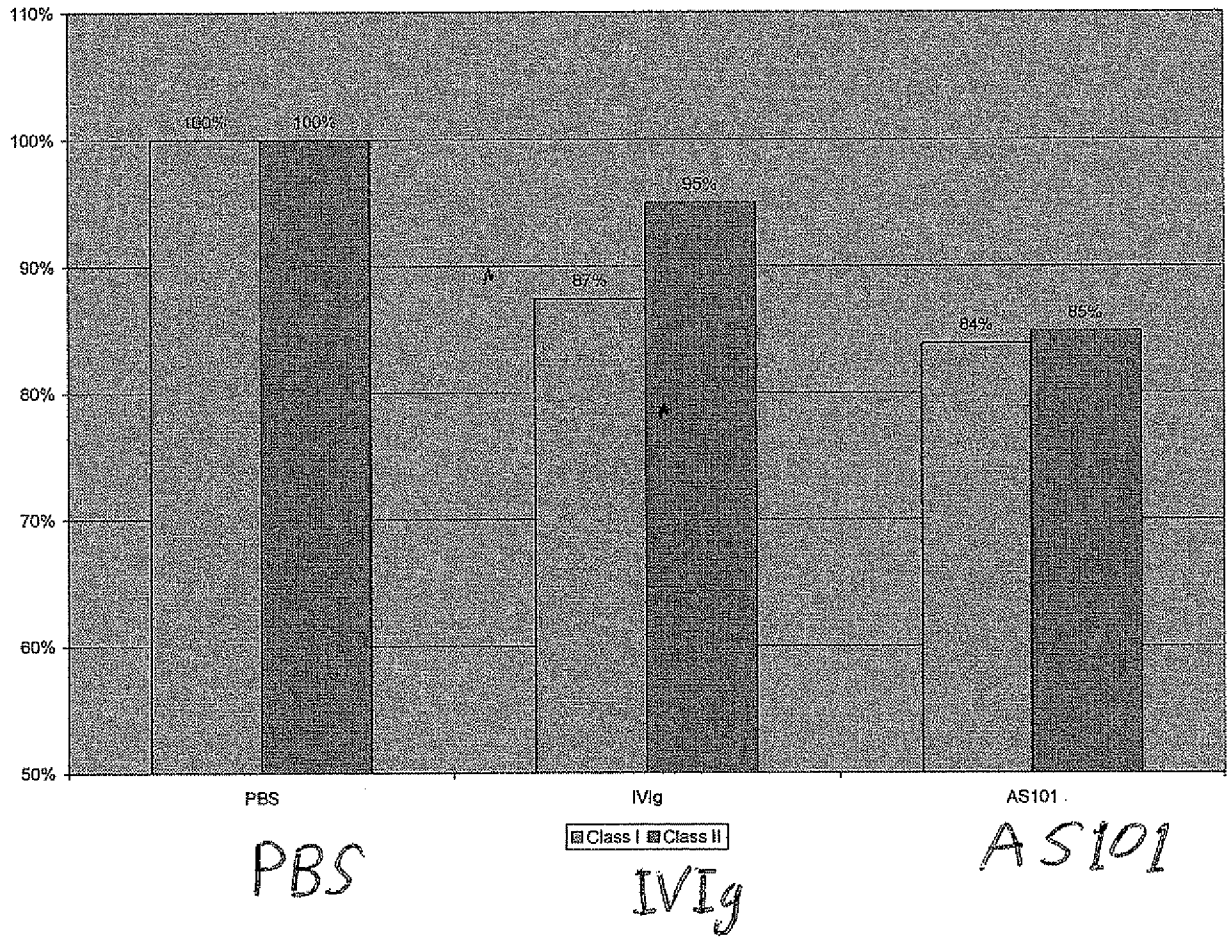
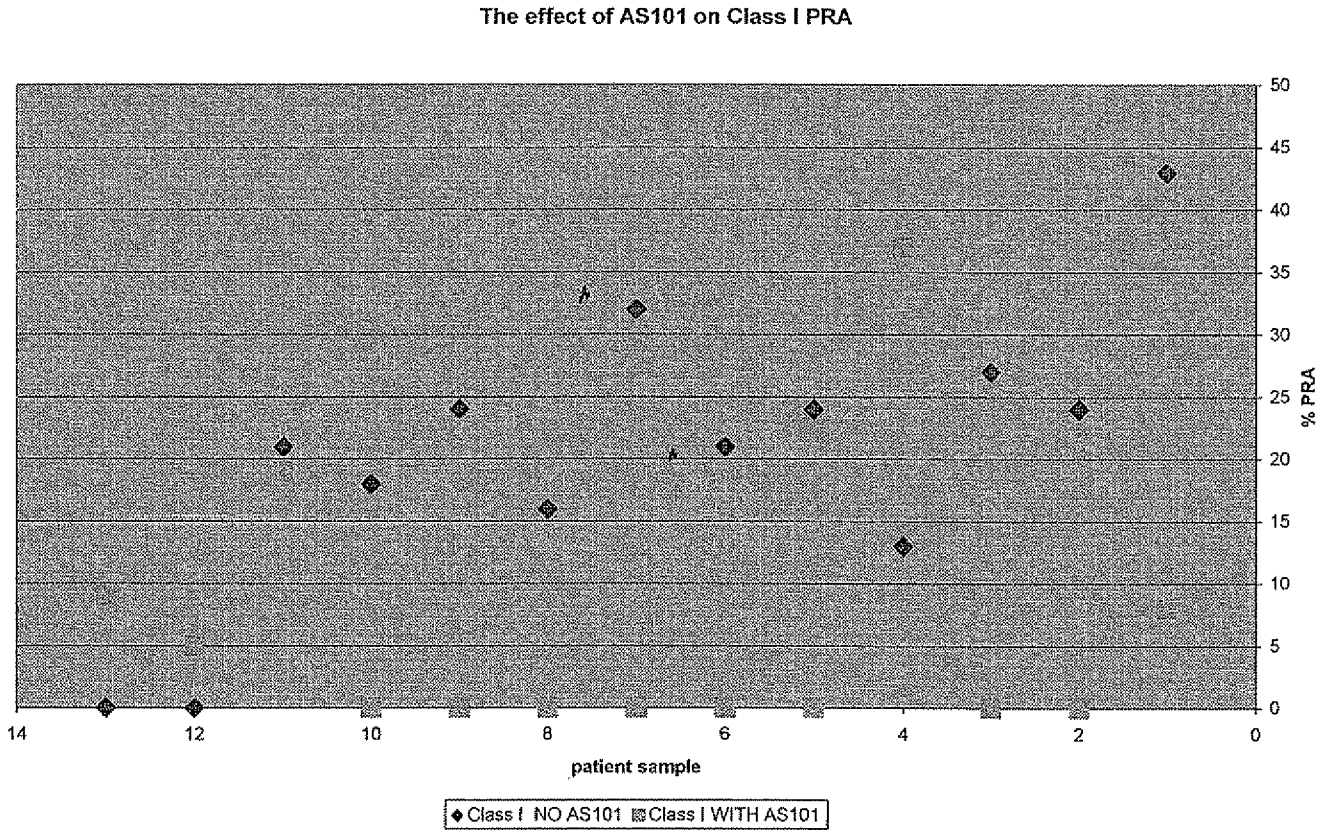

110%
100%
90%
80%
70%
60%
50%
100%
100%
87%
95%
84%
85%
PBS
IVIg
AS101
Class I
Class II
PBS
IVIg
AS101

FIG. 2


The effect of AS101 on Class I PRA
50
45
40
35
30
25
20
15
10
5
0
% PRA
14
12
10
8
6
4
2
0
patient sample
Class I NO AS101
Class I WITH AS101

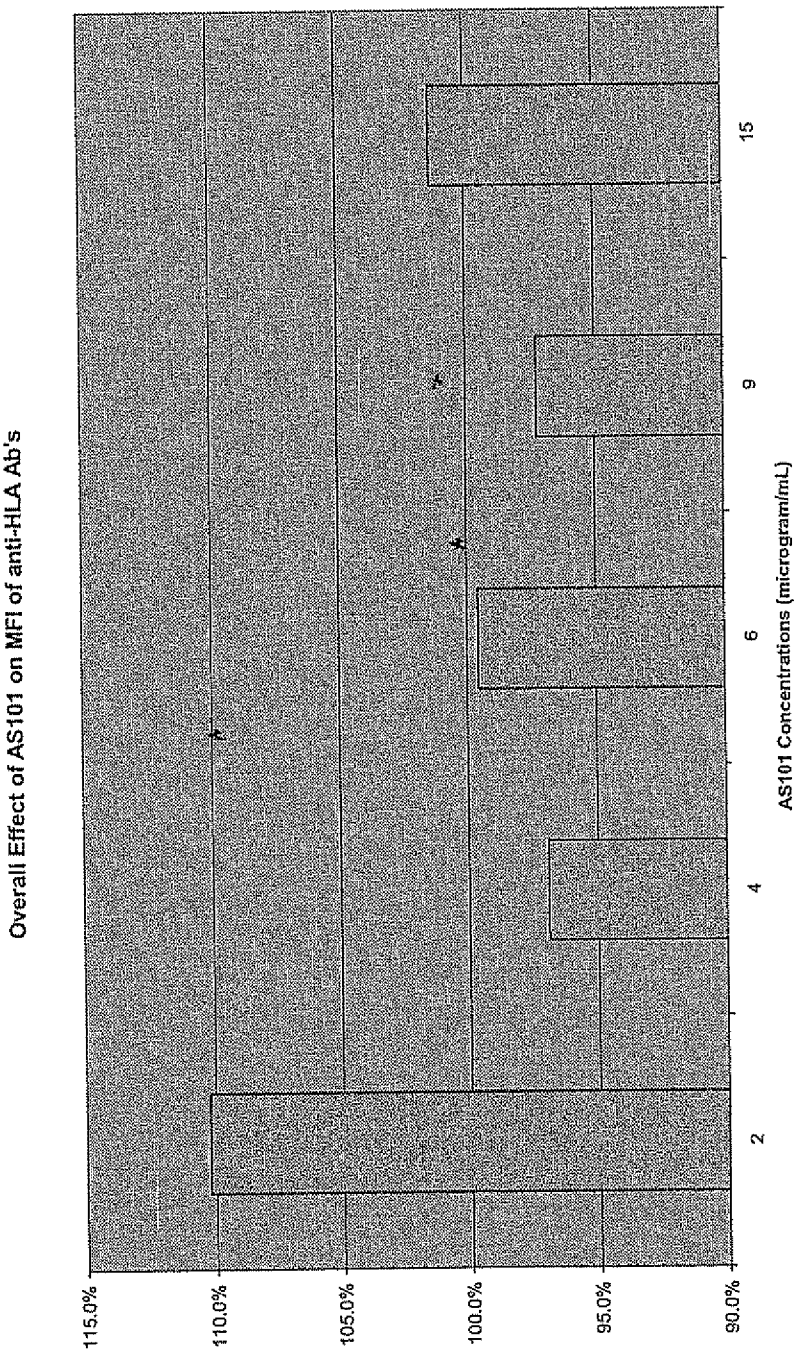

Overall Effect of AS101 on MFI of anti-HLA Ab's
115.0%
110.0%
105.0%
100.0%
95.0%
90.0%
2
4
6
9
15
AS101 Concentrations (microgram/mL)

FIG. 3

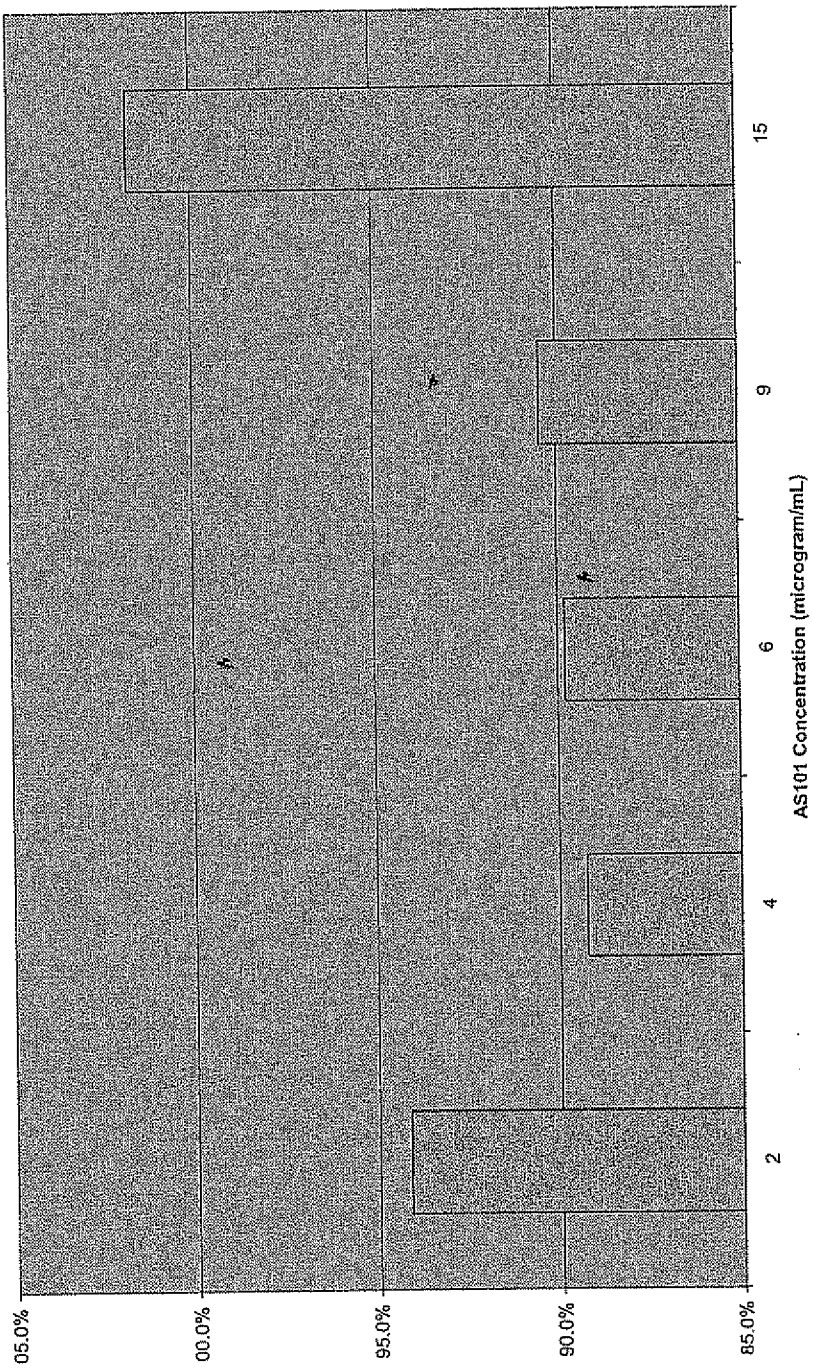

05.0%
00.0%
95.0%
90.0%
85.0%
2
4
6
9
15
AS101 Concentration (microgram/mL)

FIG. 4

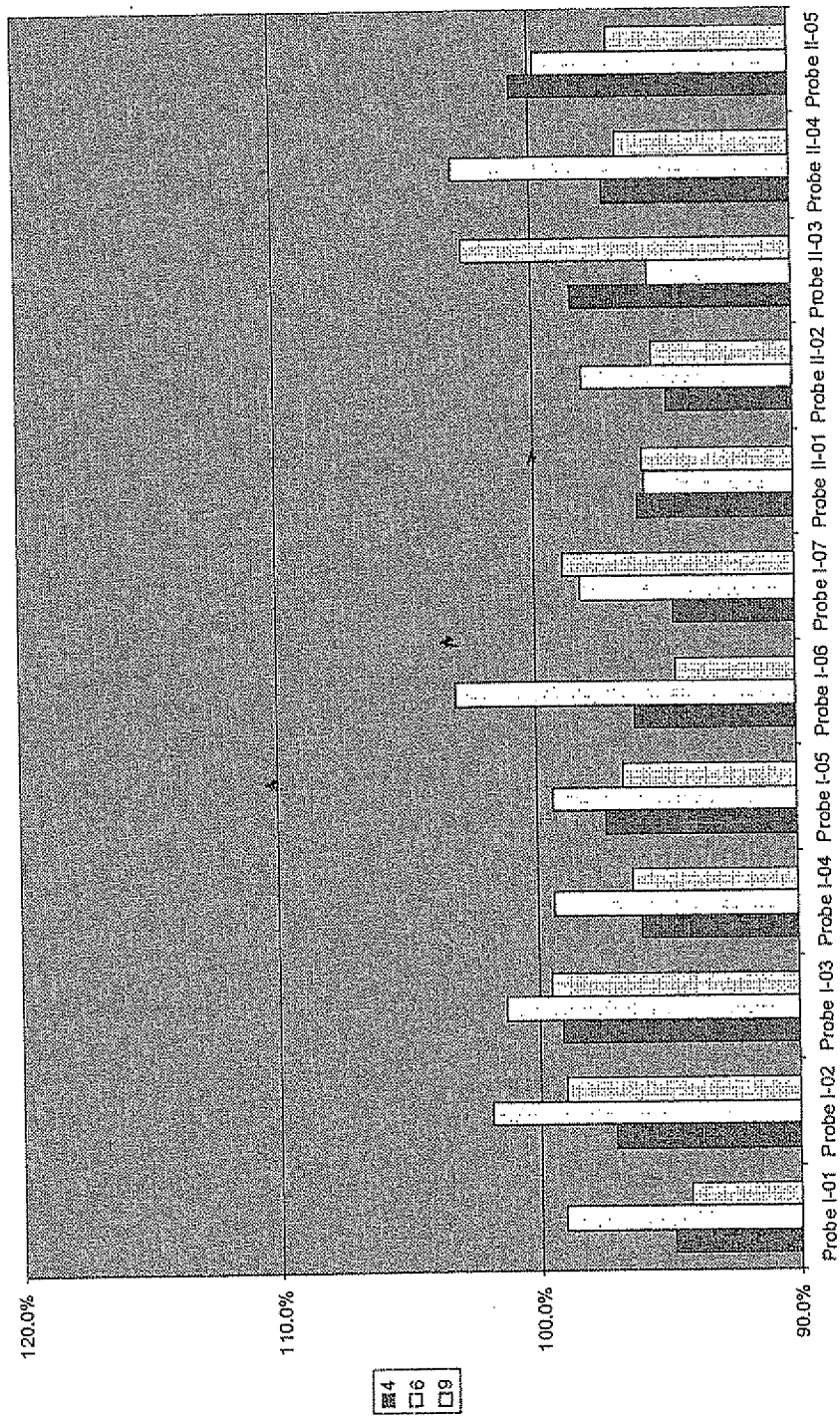

120.0%
110.0%
100.0%
90.0%
Probe I-01
Probe I-02
Probe I-03
Probe I-04
Probe I-05
Probe I-06
Probe I-07
Probe II-01
Probe II-02
Probe II-03
Probe II-04
Probe II-05
4
6
9

FIG. 5

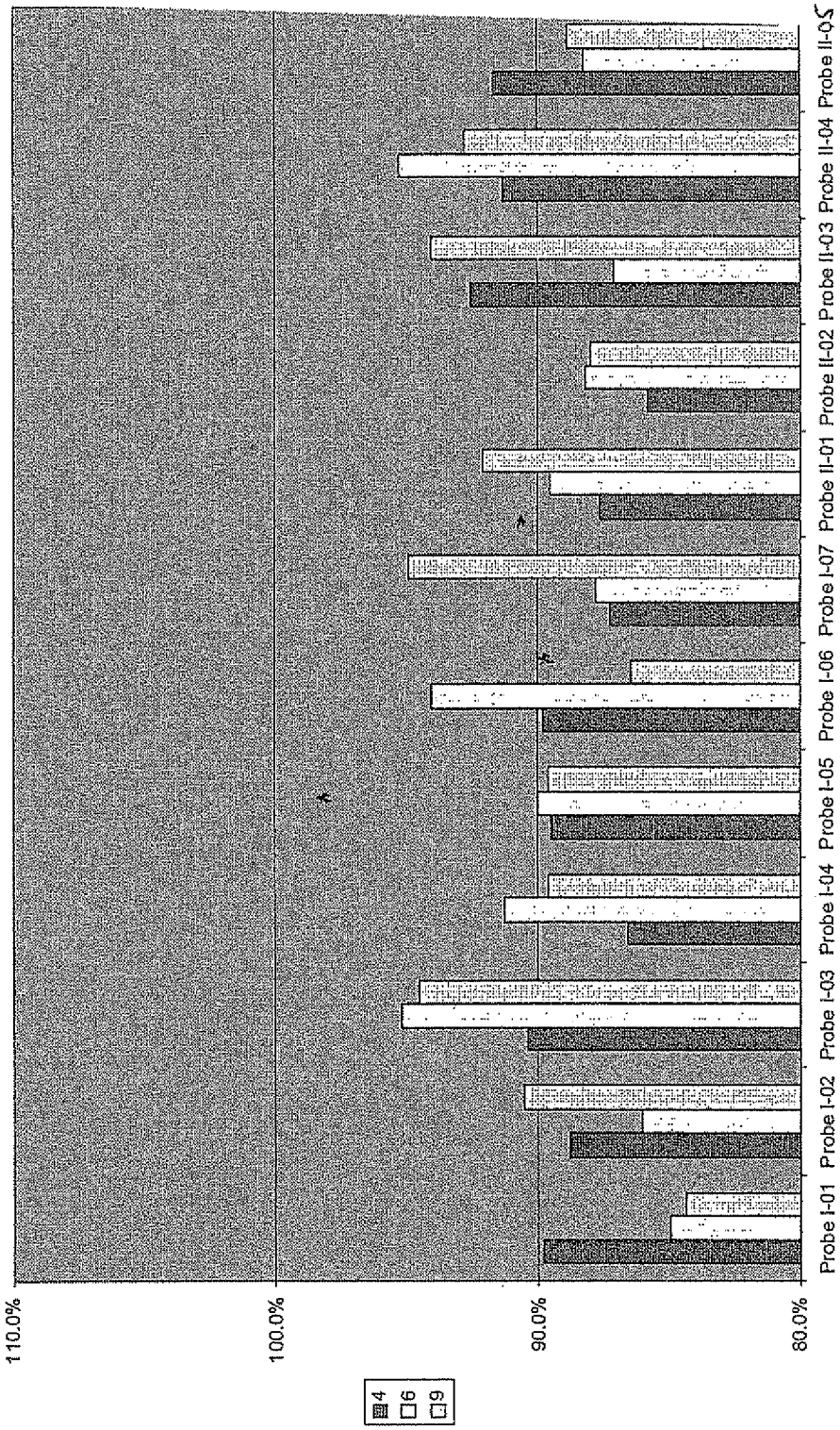

110.0%
100.0%
90.0%
80.0%
4
6
9
Probe I-01
Probe I-02
Probe I-03
Probe I-04
Probe I-05
Probe I-06
Probe I-07
Probe II-01
Probe II-02
Probe II-03
Probe II-04
Probe II-05

FIG. 6

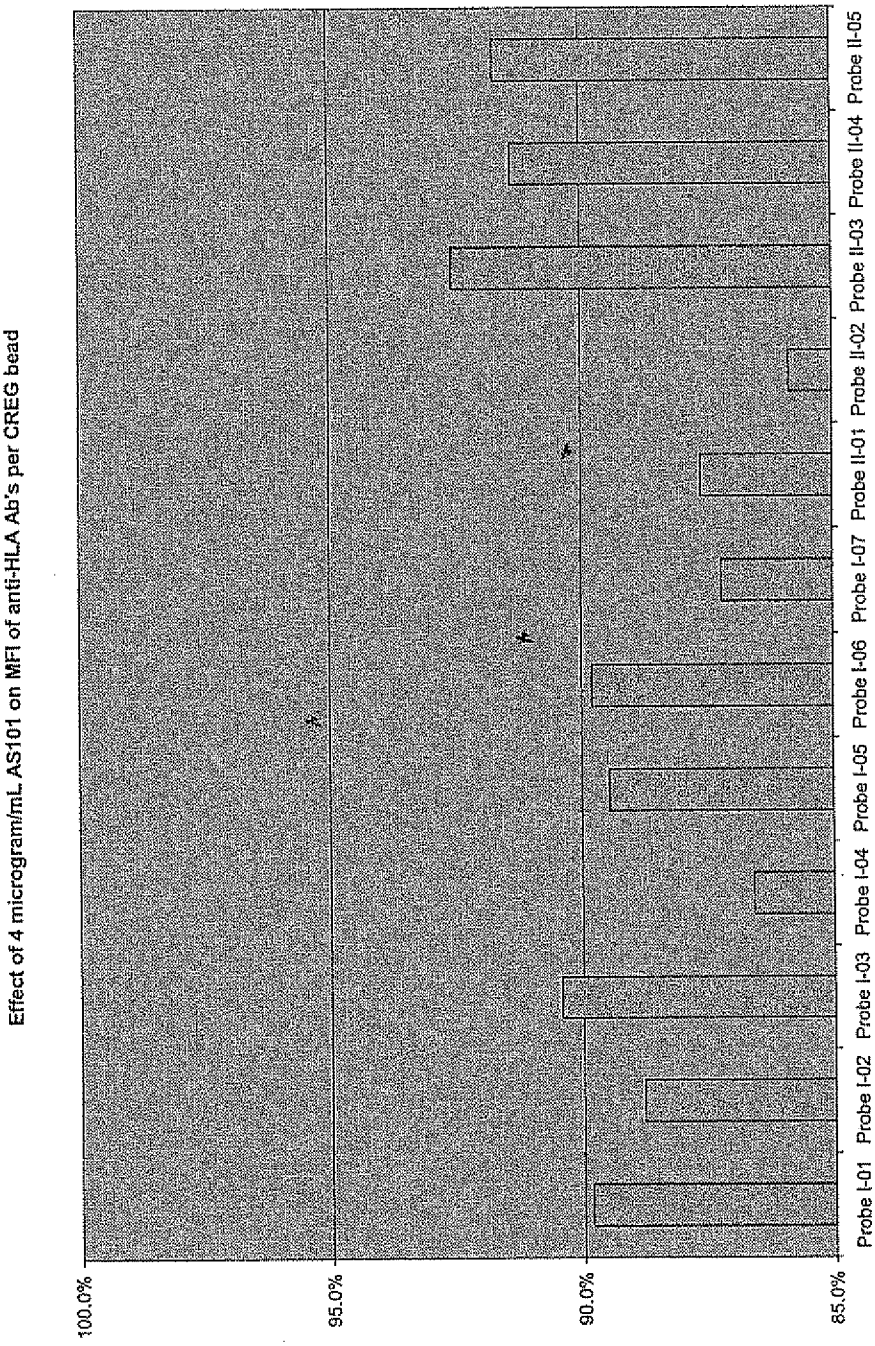

Effect of 4 microgram/mL AS101 on MFI of anti-HLA Ab's per CREG bead
100.0%
95.0%
90.0%
85.0%
Probe I-01
Probe I-02
Probe I-03
Probe I-04
Probe I-05
Probe I-06
Probe I-07
Probe II-01
Probe II-02
Probe II-03
Probe II-04
Probe II-05
CREG bead

FIG. 7

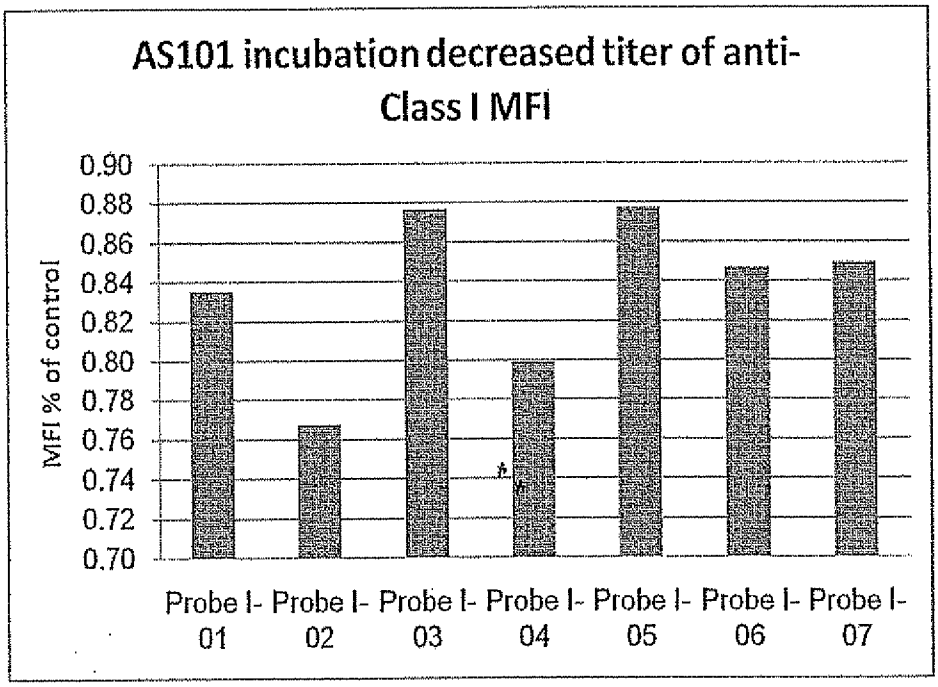

AS101 incubation decreased titer of anti-Class I MFI
MFI % of control
0.90
0.88
0.86
0.84
0.82
0.80
0.78
0.76
0.74
0.72
0.70
Probe I-01
Probe I-02
Probe I-03
Probe I-04
Probe I-05
Probe I-06
Probe I-07

FIG. 8

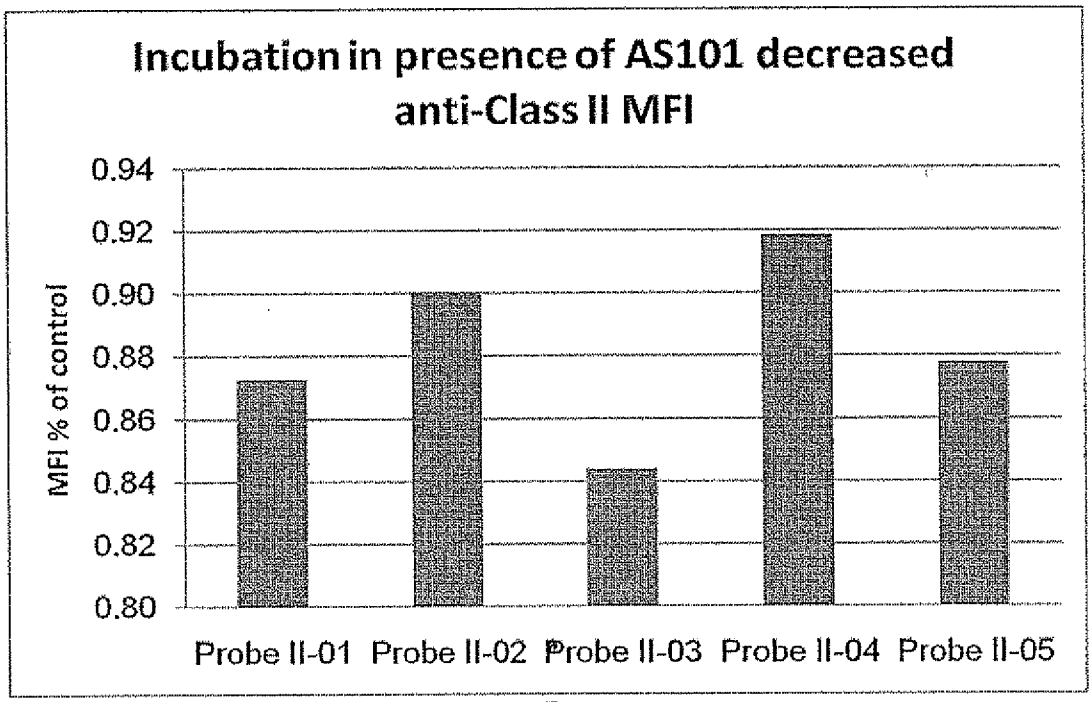

Incubation in presence of AS101 decreased anti-Class II MFI
MFI % of control
0.94
0.92
0.90
0.88
0.86
0.84
0.82
0.80
Probe II-01
Probe II-02
Probe II-03
Probe II-04
Probe II-05

FIG. 9

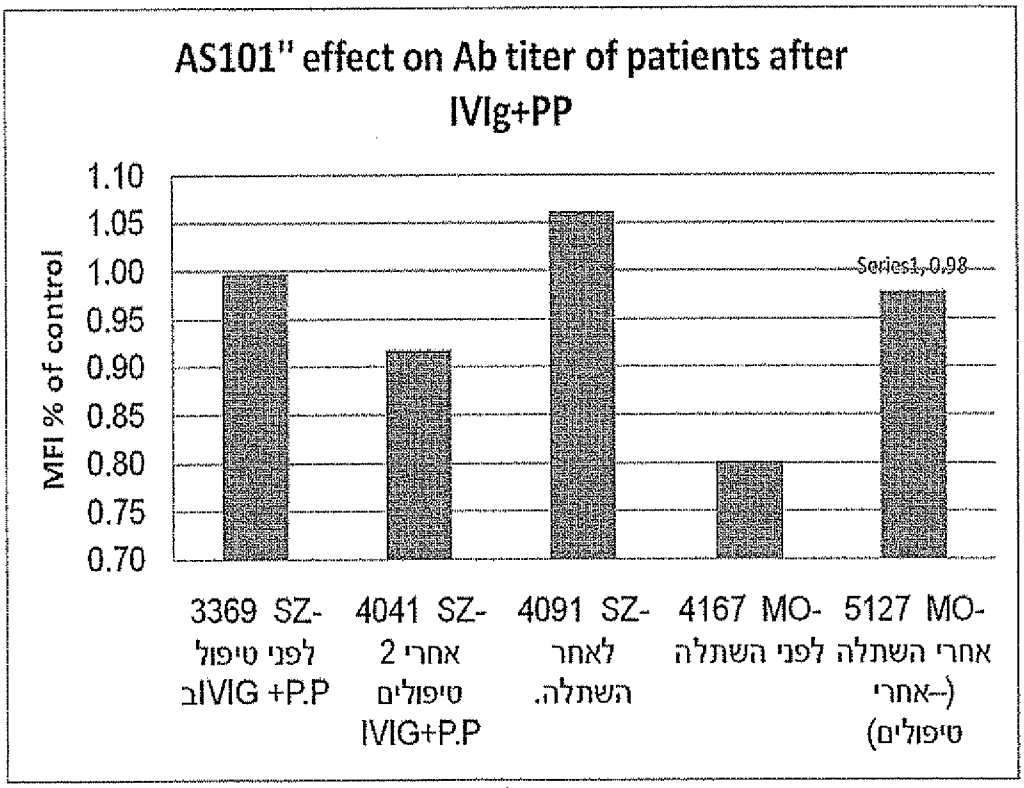

AS101" effect on Ab titer of patients after IVIg+PP
MFI % of control
1.10
1.05
1.00
0.95
0.90
0.85
0.80
0.75
0.70
Series1, 0.98
3369 SZ- לפני טיפול ב IVIG +P.P
4041 SZ- אחרי 2 טיפולים IVIG+P.P
4091 SZ- לאחר השתלה.
4167 MO- אחרי השתלה לפני השתלה
5127 MO- (--אחרי טיפולים)

FIG. 10

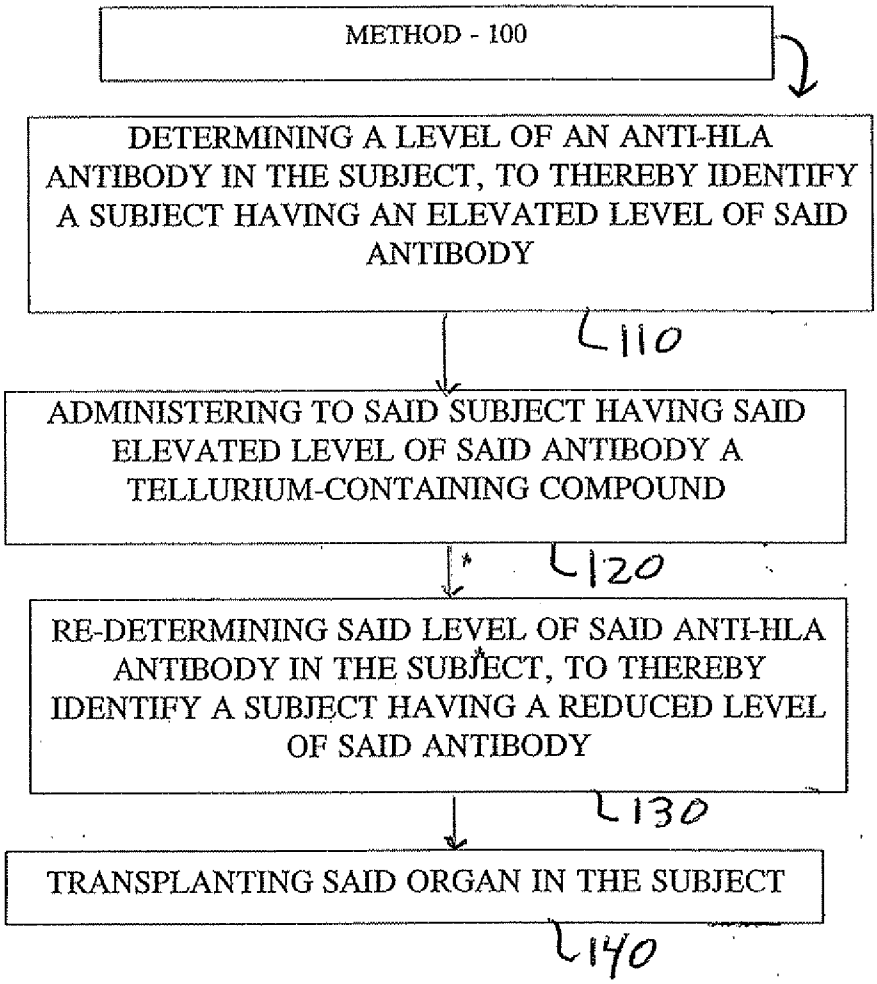

METHOD - 100
DETERMINING A LEVEL OF AN ANTI-HLA ANTIBODY IN THE SUBJECT, TO THEREBY IDENTIFY A SUBJECT HAVING AN ELEVATED LEVEL OF SAID ANTIBODY
110
ADMINISTERING TO SAID SUBJECT HAVING SAID ELEVATED LEVEL OF SAID ANTIBODY A TELLURIUM-CONTAINING COMPOUND
120
RE-DETERMINING SAID LEVEL OF SAID ANTI-HLA ANTIBODY IN THE SUBJECT, TO THEREBY IDENTIFY A SUBJECT HAVING A REDUCED LEVEL OF SAID ANTIBODY
130
TRANSPLANTING SAID ORGAN IN THE SUBJECT
140

FIG. 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 10/52702

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 59/16 (2010.01)
USPC - 424/650
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 424/650

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB, USPT, EPAB, JPAB)
anti-HLA, antibody, antibodies, tellurium, organ transplantation, transplant, kidney, tellurium dioxo moiety, dioxo moiety, AS101, SAS, ammonium or phosphonium, administering, administer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2007/0298124 A1 (ALBECK et.al.) 27 December 2007 (27.12.2007) abstract; figure 2; para [0023]-[0025], [0028]-[0034], [0036], [0066]-[0067], [0077]-[0081], [00139], [0159], [0163],	23 --- 1-22, 24-28
Y	SMITH et.al. Endothelial Cell Activation by Sera Containing HLA Antibodies is Mediated by Interleukin 1; 15 November 1998 (15.11.1998); Volume 66(9), pp 1229-1237; abstract; page 10, para 1-2; page 11, para 1	1-22, 24-28
Y	US 2005/0147692 A1 (ROTH et.al.) 7 July 2005 (07.07.2005) para [0013], [0017], [0029], [0032]-[0034], [0043], [0047], [0152], [0170], [0293]	2, 4-5, 13, 17

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 November 2010 (04.11.2010)	17 NOV 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774