Antibodies that bind specifically to human RON protein

Patent

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The invention provides antibodies or fragments thereof, including human antibodies, specific for Macrophage-Stimulating Protein Receptor (MSP-R or RON), which inhibit RON activation. Also provided are methods to inhibit RON, particularly the use of RON antibodies to treat diseases such as cancer.

SUMMARY OF THE INVENTION

Accordingly, the invention provides for anti-RON antibodies, with substantially higher specific binding than known anti-RON antibodies previously available. The antibodies may be isolated and/or purified. The inventive antibodies are useful for binding to RON, whether encoded by the wild type RON alleles that are typically found in the human population, or variant RON proteins, e.g., those with minor variations or mutations, but that retain RON activity. In one embodiment, the inventive antibody or antibodies are specific for RON, and have a K_{d} (i.e., equilibrium constant for dissociation of an antigen with an antibody) of about 1 \times 10^{-9} \text{M}^{-1} or less. In other embodiments, the inventive purified antibody exhibits a K_{d} that is about 1 \times 10^{-10} \text{M}^{-1} or about 1 \times 10^{-11} \text{M}^{-1} or less. In still other embodiments, the inventive antibody, or functional fragment thereof is fully human in nature.

The invention provides, for example, an antibody that specifically binds to a RON protein that comprises a complementarity determining region (CDR) derived from one or more antibody variable domains selected from the group consisting of RON6 VH, RON6 VL, RON8 VH, RON8 VL, and combinations thereof, wherein the RON6 VH CDRs are SEQ ID NO:17, SEQ ID NO:19 and SEQ ID NO:21; the RON6 VL CDRs are SEQ ID NO:23, SEQ ID NO:25 and SEQ ID NO:27; the RON8 VH CDRs are SEQ ID NO:29, SEQ ID NO:31 and SEQ ID NO:33; and the RON8 VL CDRs are SEQ ID NO:35, SEQ ID NO:37 and SEQ ID NO:39. Each included variable domain may contribute three CDRs. The antibody may be, e.g., a monoclonal antibody, single chain, Fab, Fv, diabody or triabody.

In some embodiments the antibody may comprise CDRs derived from at least two antibody variable domains selected from the group consisting of RON6 VH, RON6 VL, RON8 VH, RON8 VL, and combinations thereof. More preferably, the inventive antibody comprises CDRs derived from at least three antibody variable domains selected from the group consisting of RON6 VH, RON6 VL, RON8 VH, RON8 VL, and combinations thereof. In some embodiments, the antibody is RON6 or RON8.

The invention further provides for an isolated nucleic acid encoding the antibody, as well as a recombinant vector comprising the nucleic acid operably linked to one or more control sequences that allow for expression of the nucleic acid in a host cell of choice. Host cells comprising the recombinant vector are also provided.

The invention further provides a method of producing a RON antibody of the present invention comprising culturing a host cell under conditions permitting expression of the antibody, and optionally purifying the produced antibody.

The invention still further provides a pharmaceutical composition comprising the inventive antibody, and a pharmaceutically acceptable carrier. The pharmaceutical compositions may further comprise one or more other therapeutically effective agents.

Kits comprising the RON antibodies of the present invention, alone or in combination with other agents, e.g., chemotherapeutic agents, are contemplated herein.

Methods of using the inventive antibody are also provided, including, e.g., a method of treating cancer, inhibiting angiogenesis, tumor growth, migration, proliferation or invasion of tumor cells that express RON, comprising administering to a mammal an effective amount of the inventive antibody or fragment thereof to inhibit activation of RON. The tumor cells are, for example, tumor cells originating in the colon, pancreas, prostate, stomach, lung, liver, ovary, kidney, breast and...
brain, or of epithelial or neuroendocrine origin.

The inventive methods further include administering other agents, e.g., a small organic molecule, with the antibody, wherein the other agent may include, but is not limited to, a chemotherapeutic agent, anti-angiogenesis agent or inhibits activation of RON. Optionally, the antibody may be conjugated to the other agent, e.g., to a small organic molecule.

The inventive antibody can be administered with at least one other anticancer treatment, e.g., an anti-angiogenesis agent, FGFR-3 antagonist, a chemotherapeutic agent, radiation, an anti-neoplastic agent, small molecule, or other antibody. For example, the inventive antibody may be administered with at least one additional antibody that inhibits tumors, e.g., an anti-EGFR antibody, such as Erbitux.RTM. (Imclone Systems, Inc. NY, N.Y.).

The inventive antibody can target or bind to a wild type RON or a variant RON.

The inventive methods of the present invention further include a method of detecting RON in a sample comprising, contacting said sample with the inventive antibody to obtain specific binding, and detecting such binding.

Also provided is a method of preventing or treating inflammation in a mammal in need thereof, comprising administering to the mammal an effective amount of an antibody of the present invention.

Also provided is a method of preventing or treating disease, e.g., liver, biliary tract, bile ducts and gall bladder disease in a mammal in need thereof, comprising administering to the mammal an effective amount of an antibody of the present invention.

Also provided is a method of inhibiting phosphorylation of RON, MAPK and/or Akt in a mammal in need thereof, comprising administering to the mammal an effective amount of an antibody of the present invention.

With regard to the foregoing methods, in some embodiments the inventive antibody or fragment thereof may be administered to a mammal in a dose of about 1 to about 10 mg/Kg. In other embodiments, the antibody or fragment thereof may be administered at a dose of about 3 to about 8 mg/Kg.

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Assignee: ImClone LLC (New York, NY)
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