ANTI-Ly6E ANTIBODIES AND METHODS OF USE

FIELD OF THE INVENTION

[0001] The present invention relates to anti-Ly6E antibodies and immunoconjugates and methods of using the same.

BACKGROUND

[0002] Lymphocyte antigen 6 complex, locus E (Ly6E), also known as retinoic acid induced gene E (RIG-E) and stem cell antigen 2 (SCA-2). It is a GPI linked, 131 amino acid length, ~8.4kDa protein of unknown function with no known binding partners. It was initially identified as a transcript expressed in immature thymocyte, thymic medullary epithelial cells in mice. *RIG-E, a human homolog of the murine Ly-6 family, is induced by retinoic acid during the differentiation of acute promyelocytic leukemia cell.* Mao M., Yu M., Tong J.-H., Ye J., Zhu J., Huang Q.-H., Fu G., Yu L., Zhao S.-Y., Waxman S., Lanotte M., Wang Z.-Y., Tan J.-Z., Chan S.-J., Chen Z. Proc. Natl. Acad. Sci. U.S.A. 93:5910-5914 (1996).

[0003] There is a need in the art for agents that target Ly6E for the diagnosis and treatment of Ly6E-associated conditions, such as cancer. The invention fulfills that need and provides other benefits.

SUMMARY ~~OF THE INVENTION~~

[0004] The ~~invention~~ disclosure provides anti-Ly6E antibodies, immunoconjugates and methods of using the same.

[0005] In some ~~embodiments~~aspects, an isolated antibody that binds to Ly6E is provided, wherein the antibody comprises (a) HVR-H3 comprising the amino acid sequence of SEQ ID NO:34, (b) HVR-L3 comprising the amino acid sequence of SEQ ID NO:31, and (c) HVR-H2 comprising the amino acid sequence of SEQ ID NO:33. In some embodiments, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:32, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:33, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:34. In some embodiments, the antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:29; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO:30; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO:31. In some embodiments, the antibody comprises (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:28; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:27; or (c) a VH sequence as in (a) and a VL sequence as in (b). In some embodiments, the antibody comprises a VH sequence of SEQ ID NO:28. In some embodiments, the antibody comprises a VL sequence of SEQ ID NO:27.

[0006] In some ~~embodiments~~aspects, an isolated antibody ~~that binds Ly6E~~ is provided, wherein the antibody comprises a VH sequence of SEQ ID NO:28 and a VL sequence of SEQ ID NO:27.

[0007] In some embodiments, the antibody that binds Ly6E is a monoclonal antibody. In some embodiments, the antibody is a mouse, rabbit, human, humanized, or chimeric antibody. In some embodiments, the antibody is an IgG. In other embodiments, the IgG is an IgG1, IgG2a or IgG2b, or IgG3, or IgG4.

[0008] In some ~~embodiments~~aspects, an isolated nucleic acid encoding any of the antibodies described herein is provided. In some ~~embodiments~~aspects, a host cell comprising the isolated nucleic acid is provided. In some ~~embodiments~~aspects, a method of producing an antibody described herein is provided, comprising culturing the host cell described herein, so that the antibody is produced.

[0009] In some ~~embodiments~~aspects, an immuneoconjugate comprising an antibody described herein and a cytotoxic agent is provided. In some ~~embodiments~~aspects, a pharmaceutical ~~composition~~ formulation comprising the immunoconjugate described herein and a pharmaceutically acceptable carrier is provided.

[0010] In some embodiments, an antibody described herein is conjugated to a label. In some embodiments, the label is a positron emitter. In some such embodiments, the positron emitter is ^{89}Zr.

[0011] In some ~~embodiments~~aspects, methods of detecting human Ly6E in a biological sample are provided. ~~In some embodiments~~, the method ~~comprises~~ comprising contacting the biological sample with an anti-Ly6E antibody described herein under conditions permissive for binding of the anti-Ly6E antibody to a naturally occurring human Ly6E, ~~In some embodiments, the method comprises~~ and detecting whether a complex is formed between the anti-Ly6E antibody and a naturally occurring human Ly6E in the biological sample. In some embodiments, the biological sample is a breast cancer sample, a pancreatic cancer sample, a colon cancer sample, a colorectal cancer sample, melanoma cancer sample, ovarian cancer sample, a non-small cell lung cancer sample, an esophageal cancer sample, a head and neck cancer sample, a kidney cancer sample, a soft tissue cancer sample, an endometrial cancer sample, or a gastric cancer sample.

[0012] In some ~~embodiments~~aspects, methods of detecting a Ly6E-positive cancer are provided, ~~In some embodiments,~~ the method ~~comprises~~ comprising (i) administering a labeled anti-Ly6E antibody to a subject having or suspected of having a Ly6E-positive cancer, wherein the labeled anti-Ly6E antibody comprises an anti-Ly6E antibody described herein, and (ii) detecting the labeled anti-Ly6E antibody in the subject, ~~In some embodiments,~~ wherein detection of the labeled anti-Ly6E antibody indicates a Ly6E-positive cancer in the subject. In some embodiments, the labeled anti-Ly6E antibody comprises an anti-Ly6E antibody described herein conjugated to a positron emitter. In some such embodiments, the positron emitter is ^{89}Zr.

[0013] In some ~~embodiments~~aspects, a method of identifying a cancer patient as having a Ly6E-positive cancer is provided, ~~In some embodiments, the method comprises~~comprising contacting a cancer sample from the patient with an anti-Ly6E antibody described herein under conditions permissive for binding of the anti-Ly6E antibody to a naturally occurring human Ly6E, and ~~In some embodiments, the method comprises~~ detecting whether a complex is formed between the anti-Ly6E antibody and a naturally occurring human Ly6E in the cancer sample. In some embodiments, the cancer patient is identified as having a Ly6E-positive cancer if a

complex is between the anti-Ly6E antibody described herein and a naturally occurring human Ly6E in the cancer biopsy sample is detected.

[0014] In some ~~embodiments~~aspects, methods of selecting a cancer patient for treatment with an immunoconjugate comprising an anti-Ly6E antibody are provided~~.~~, comprising~~In some embodiments, the method comprises~~ contacting a cancer sample from the patient with an anti-Ly6E antibody described herein under conditions permissive for binding of the anti-Ly6E antibody to a naturally occurring human Ly6E~~. In some embodiments, the method comprises~~, and detecting whether a complex is formed between the anti-Ly6E antibody and a naturally occurring human Ly6E in the cancer sample. In some embodiments, the cancer patient is selected if a complex is between the anti-Ly6E antibody and a naturally occurring human Ly6E in the cancer biopsy sample is detected. In some such embodiments, the cancer patient is selected for treatment with an immunoconjugate comprising an anti-Ly6E antibody comprising (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:10, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:11, (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:12, (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:7; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:8; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:9. In some embodiments, the cancer patient is selected for treatment with an immunoconjugate comprising an anti-Ly6E antibody comprising a VH sequence of SEQ ID NO:5 and a VL sequence of SEQ ID NO:3. In some embodiments, the immunoconjugate comprises an anti-Ly6E antibody conjugated to a cytotoxic agent. In some embodiments, the cancer sample is a breast cancer sample, a pancreatic cancer sample, a colon cancer sample, a colorectal cancer sample, melanoma cancer sample, ovarian cancer sample, a non-small cell lung cancer sample, an esophageal cancer sample, a head and neck cancer sample, a kidney cancer sample, a soft tissue cancer sample, an endometrial cancer sample, or a gastric cancer sample. In some embodiments, the breast cancer sample is from a Her2 positive breast cancer, a Her2 negative breast cancer, a Her2 negative/hormone receptor positive (Her2-/ER+/PR+) breast cancer, or a triple negative (Her2-/ER-/PR-) breast cancer. In some embodiments, the gastric cancer sample is from a Her2 positive gastric cancer or a Her2 negative gastric cancer.

BRIEF DESCRIPTION OF THE FIGURES

[0015] Figure 1 shows a sequence alignment comparing the sequences of Ly6E orthologs from human (SEQ ID NO: 1), Cynomolgus monkey (SEQ ID NO: 2), Rhesus (SEQ ID NO: 35), mouse (SEQ ID NO: 36), and rat species (SEQ ID NO: 37). The percent identity at the amino acid level between these sequences in the extracellular domain (ECD) is shown to be ~96% between human and cynomolgus monkey Ly6E and ~52% between human and rat Ly6E.