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

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

[0005] In some aspects, an isolated antibody that binds to Ly6E is provided, wherein 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, (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:34, (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:29, (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:30, and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:31. 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 aspects, an isolated antibody that binds to 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 aspects, an isolated nucleic acid encoding any of the antibodies described herein is provided. In some aspects, a host cell comprising the isolated nucleic acid is provided. In some 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 aspects, an immunoconjugate comprising an antibody described herein and a cytotoxic agent is provided. In some aspects, a pharmaceutical 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 aspects, methods of detecting human Ly6E in a biological sample are provided, the method 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, 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, methods of detecting a Ly6E-positive cancer are provided, the method 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, 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 aspects, a method of identifying a cancer patient as having a Ly6E-positive cancer is provided, 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 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

WHAT IS CLAIMED IS:

1. An isolated antibody that binds to Ly6E, wherein 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, (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:34, (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:29, (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:30, and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:31.

2. The antibody of claim 1, comprising (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).

3. The antibody of claim 1 or claim 2, comprising a VH sequence of SEQ ID NO:28.

4. The antibody of any one of claims 1 to 3, comprising a VL sequence of SEQ ID NO:27.

5. An isolated antibody that binds to Ly6E comprising a VH sequence of SEQ ID NO:28 and a VL sequence of SEQ ID NO:27.

6. The antibody of any one of claims 1 to 5, which is a monoclonal antibody.

7. The antibody of claim 6, which is a mouse, rabbit, human, humanized, or chimeric antibody.

8. The antibody of any one of claims 1 to 7, which is an IgG selected from IgG1, IgG2a, IgG2b, IgG3, and IgG4.

9. Isolated nucleic acid encoding the antibody of any one of claims 1 to 8.

10. A host cell comprising the nucleic acid of claim 9.

11. A method of producing an antibody comprising culturing the host cell of claim 10 so that the antibody is produced.

12. An immunoconjugate comprising the antibody of any one of claims 1 to 8 and a cytotoxic agent.

13. A pharmaceutical formulation comprising the immunoconjugate of claim 12 and a pharmaceutically acceptable carrier.

14. The antibody of any one of claims 1 to 8 conjugated to a label.

15. The antibody of claim 14, wherein the label is a positron emitter.

16. The antibody of claim 15, wherein the positron emitter is ^{89}Zr.

17. A method of detecting human Ly6E in a biological sample comprising contacting the biological sample with the anti-Ly6E antibody of any one of claims 1 to 8 and 14 to 16 under conditions permissive for binding of the anti-Ly6E antibody to a naturally occurring human Ly6E, and detecting whether a complex is formed between the anti-Ly6E antibody and a naturally occurring human Ly6E in the biological sample.

18. The method of claim 17, wherein the anti-Ly6E antibody is an antibody of claim 5.

19. The method of claim 17 or claim 18, wherein 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.

20. A method of identifying a cancer patient as having a Ly6E-positive cancer, comprising contacting a cancer sample from the patient with the anti-Ly6E antibody of any one of claims 1 to 8 and 14 to 16 under conditions permissive for binding of the anti-Ly6E antibody to a naturally occurring human Ly6E, and detecting whether a complex is formed between the anti-Ly6E antibody and a naturally occurring human Ly6E in the cancer sample.

21. The method of claim 20, wherein the cancer patient is identified as having a Ly6E-positive cancer if a complex is between the anti-Ly6E antibody and a naturally occurring human Ly6E in the cancer biopsy sample is detected.

22. A method of selecting a cancer patient for treatment with an immunoconjugate comprising an anti-Ly6E antibody, comprising contacting a cancer sample from the patient with the anti-Ly6E antibody of any one of claims 1 to 8 and 14 to 16 under conditions permissive for binding of the anti-Ly6E antibody to a naturally occurring human Ly6E, and detecting whether a complex is formed between the anti-Ly6E antibody and a naturally occurring human Ly6E in the cancer sample.

23. The method of claim 22, wherein 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.

24. The method of claim 22 or claim 23, wherein the immunoconjugate comprises 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.

25. The method of claim 24, wherein the anti-Ly6E antibody comprises a VH sequence of SEQ ID NO:5 and a VL sequence of SEQ ID NO:3.

26. The method of any one of claims 22 to 25, wherein the immunoconjugate comprises an anti-Ly6E antibody conjugated to a cytotoxic agent.

27. The method of any one of claims 20 to 26, wherein 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.

28. The method of claim 19 or claim 27, wherein 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.

29. The method of claim 19 or claim 27, wherein the gastric cancer sample is from a Her2 positive gastric cancer or a Her2 negative gastric cancer.