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(54) Title: ANTI-MICA/B ANTIBODIES THAT BLOCK MICA/B SHEDDING AND METHODS OF USE

(57) Abstract: Provided herein are antibodies that specifically bind to MICA/B having heavy chain, light chain, variable heavy chain domains (VH), variable light chain domains (VL), and complementarity determining regions (CDRs) disclosed herein, as well as methods and uses thereof.

FIG. 1A

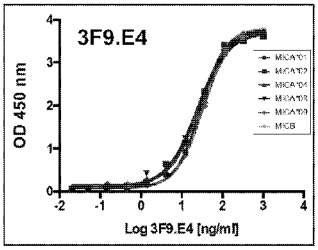
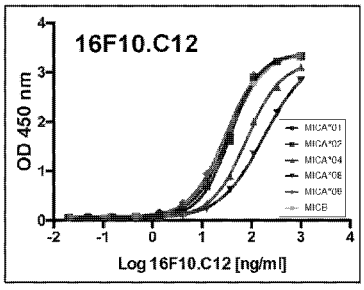


FIG. 1B



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ANTI-MICA/B ANTIBODIES THAT BLOCK MICA/B SHEDDING AND METHODS OF USE

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/712,608 filed July 31, 2018, which is incorporated by reference herein in its entirety.

SUMMARY

[0002] Disclosed herein, are monoclonal antibodies that specifically bind to MICA/B and thereby modulating an immune response against disease cells.

[0003] Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a light chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24. In some embodiments, the monoclonal antibodies or an antigen-binding fragments thereof further comprises a heavy chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26.

[0004] Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a light chain variable domain (VL) comprising an amino acid sequence at least 90% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a light chain variable domain (VL) comprising an amino acid sequence at least 95% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a light chain variable domain (VL) comprising an amino acid sequence at least 99% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a light chain variable domain (VL) comprising an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some instances, the monoclonal

antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 90% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 95% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 99% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 7 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 8. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 15 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 16. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 19 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises heavy chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26. In some instances, the monoclonal antibody or antigen-binding fragment thereof specifically binds to a MICA protein, a MICB protein, or both MICA and MICB protein. In some instances, the monoclonal antibody or antigen-binding fragment thereof binds to an alpha-3 domain of a MICA protein, a MICB protein, or both MICA and MICB protein. In some instances, the MICA protein is membrane-bound MICA protein, soluble MICA protein, or both. In some instances, the MICB protein is membrane-bound MICB protein, soluble MICB protein, or both. In some instances, the monoclonal antibody or antigen-binding fragment thereof is selected from a whole immunoglobulin, an scFv, a Fab, a $F(ab')_2$, or a disulfide linked Fv. In some

instances, the monoclonal antibody or antigen-binding fragment thereof is an IgG or IgM. In some instances, the monoclonal antibody or antigen-binding fragment thereof is humanized or chimeric.

[0005] Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 90% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 95% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 99% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a heavy chain variable domain (VH) comprising an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 90% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 95% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 99% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80%

identical to SEQ ID NO: 8 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 7. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 16 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 15. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 20 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 19. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24. In some instances, the monoclonal antibody or antigen-binding fragment thereof specifically binds to a MICA protein, a MICB protein, or both MICA and MICB protein. In some instances, the monoclonal antibody or antigen-binding fragment thereof binds to an alpha-3 domain of a MICA protein, a MICB protein, or both MICA and MICB protein. In some instances, the MICA protein is membrane-bound MICA protein, soluble MICA protein, or both. In some instances, the MICB protein is membrane-bound MICB protein, soluble MICB protein, or both. In some instances, the monoclonal antibody or antigen-binding fragment thereof is selected from a whole immunoglobulin, an scFv, a Fab, a $F(ab')_2$, or a disulfide linked Fv. In some instances, the monoclonal antibody or antigen-binding fragment thereof is an IgG or IgM. In some instances, the monoclonal antibody or antigen-binding fragment thereof is humanized or chimeric.

[0006] Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a light chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a light chain complementarity determining region (CDR) having an amino acid sequence at least 90% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and

NYGNYLFDY. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a light chain complementarity determining region (CDR) having an amino acid sequence at least 95% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a light chain complementarity determining region (CDR) having an amino acid sequence at least 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a light chain complementarity determining region (CDR) having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 90% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 95% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain complementarity determining region (CDR) having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain complementarity determining region 1 (CDR1) having an amino acid

sequence at least 80% identical to one of SEQ ID NO: 1, SEQ ID NO: 9, or SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NOS: SEQ ID NO: 2, or SEQ ID NO: 10, a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 3, or SEQ ID NO: 11, a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 4, or SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 5, SEQ ID NO: 13, or SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 6, or SEQ ID NO: 14. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 1, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 9, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 10, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 11. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 5, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having

an amino acid sequence at least 80% identical to SEQ ID NO: 13, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 14. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO:16, or SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, or SEQ ID NO: 15; and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, or SEQ ID NO: 16. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, or SEQ ID NO: 16; and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, or SEQ ID NO: 15. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 7 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 8. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 15 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 16. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 19 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain comprising an amino acid sequence at least 80% identical to an

amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises heavy chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26. In some instances, the monoclonal antibody or antigen-binding fragment thereof specifically binds to a MICA protein, a MICB protein, or both MICA and MICB protein. In some instances, the monoclonal antibody or antigen-binding fragment thereof binds to an alpha-3 domain of a MICA protein, a MICB protein, or both MICA and MICB protein. In some instances, the MICA protein is membrane-bound MICA protein, soluble MICA protein, or both. In some instances, the MICB protein is membrane-bound MICB protein, soluble MICB protein, or both. In some instances, the monoclonal antibody or antigen-binding fragment thereof is selected from a whole immunoglobulin, an scFv, a Fab, a $F(ab')_2$, or a disulfide linked Fv. In some instances, the monoclonal antibody or antigen-binding fragment thereof is an IgG or IgM. In some instances, the monoclonal antibody or antigen-binding fragment thereof is humanized or chimeric.

[0007] Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 90% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 95% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 99% identical to at least one of the amino acid

sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof, comprising a heavy chain complementarity determining region (CDR) having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY. In some instances, the monoclonal antibody or antigen-binding fragment comprises a light chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17. In some instances, the monoclonal antibody or antigen-binding fragment comprises a light chain complementarity determining region (CDR) having an amino acid sequence at least 90% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17. In some instances, the monoclonal antibody or antigen-binding fragment comprises a light chain complementarity determining region (CDR) having an amino acid sequence at least 95% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17. In some instances, the monoclonal antibody or antigen-binding fragment comprises a light chain complementarity determining region (CDR) having an amino acid sequence at least 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17. In some instances, the monoclonal antibody or antigen-binding fragment comprises a light chain complementarity determining region (CDR) having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 4, or SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 5, SEQ ID NO: 13, or SEQ ID NO: 18, a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 6, or SEQ ID NO: 14, a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 1, SEQ ID NO: 9, or SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 2, or SEQ ID NO: 10, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ

ID NO: 3, or SEQ ID NO: 11. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 5, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 13, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 14. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 1, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 9, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 10, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 11. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH)

comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO:16, or SEQ ID NO:20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO:19. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO:16, or SEQ ID NO:20; and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO:19. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, or SEQ ID NO: 15; and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, or SEQ ID NO: 16. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 16; and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 15. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 20; and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 19. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24. In some instances, the monoclonal antibody or antigen-binding fragment thereof specifically binds to a MICA protein, a MICB protein, or both MICA and MICB protein. In some instances, the monoclonal antibody or antigen-binding fragment thereof binds to an alpha-3 domain of a MICA

protein, a MICB protein, or both MICA and MICB protein. In some instances, the MICA protein is membrane-bound MICA protein, soluble MICA protein, or both. In some instances, the MICB protein is membrane-bound MICB protein, soluble MICB protein, or both. In some instances, the monoclonal antibody or antigen-binding fragment thereof is selected from a whole immunoglobulin, an scFv, a Fab, a $F(ab')_2$, or a disulfide linked Fv. In some instances, the monoclonal antibody or antigen-binding fragment thereof is an IgG or IgM. In some instances, the monoclonal antibody or antigen-binding fragment thereof is humanized or chimeric.

[0008] Disclosed herein, in certain embodiments, are pharmaceutical compositions comprising: a monoclonal antibody or an antigen-binding fragment thereof according to any one of the disclosures herein; and a pharmaceutically acceptable carrier or excipient.

[0009] Disclosed herein, in certain embodiments, are methods of treating cancer in an individual in need thereof, comprising administering to the individual an effective amount of a monoclonal antibody or an antigen-binding fragment thereof comprising a light chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY. Disclosed herein, in certain embodiments, are methods of treating cancer in an individual in need thereof, comprising administering to the individual an effective amount of a monoclonal antibody or an antigen-binding fragment thereof comprising a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises (a) a light chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17; and (b) a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises (a) a light chain complementarity determining region (CDR) having an amino acid sequence at least 90% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17; and (b) a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 90% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-

14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises (a) a light chain complementarity determining region (CDR) having an amino acid sequence at least 95% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17; and (b) a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 95% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises (a) a light chain complementarity determining region (CDR) having an amino acid sequence at least 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17; and (b) a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises (a) a light chain complementarity determining region (CDR) having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17; and (b) a heavy chain complementarity determining region (CDR) having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 1, SEQ ID NO: 9, or SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NOS: SEQ ID NO: 2, or SEQ ID NO: 10, a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 3, or SEQ ID NO: 11, a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 4, or SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 5, SEQ ID NO: 13, or SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 6, or SEQ ID NO: 14. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 1, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain

complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 9, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 10, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 11. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 17 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 1, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 5, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 13, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 14. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO:16, or SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or

SEQ ID NO: 19; and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 7 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 8. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 15 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 16. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 19 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26. In some instances, the monoclonal antibody or antigen-binding fragment thereof specifically binds to a MICA protein, a MICB protein, or both MICA and MICB protein. In some instances, the monoclonal antibody or antigen-binding fragment thereof binds to an alpha-3 domain of a MICA protein, a MICB protein, or both MICA and MICB protein. In some instances, the MICA protein is membrane-bound MICA protein, soluble MICA protein, or both. In some instances, the MICB protein is membrane-bound MICB protein, soluble MICB protein, or both. In some instances, the monoclonal antibody or antigen-binding fragment thereof is selected from a whole immunoglobulin, an scFv, a Fab, a $F(ab')_2$, or a disulfide linked Fv. In some instances, the monoclonal antibody or antigen-binding fragment thereof is an IgG or IgM. In some instances, the monoclonal antibody or antigen-binding fragment thereof is humanized or chimeric. In some instances, the monoclonal antibody or antigen-binding fragment thereof reduces level of soluble MICA protein, soluble MICB protein, or both. In some instances, the monoclonal antibody or antigen-binding fragment thereof reduces shedding of soluble MICA protein, soluble MICB protein, or both. In some instances, the monoclonal antibody or antigen-binding fragment thereof inhibits shedding of soluble MICA protein, soluble MICB protein, or both. In some instances, the cancer is hepatocellular carcinoma.

[0010] Disclosed herein, in certain embodiments, are methods of treating hepatocellular carcinoma in an individual in need thereof, comprising administering to the individual an effective amount of a monoclonal antibody or an antigen-binding fragment thereof comprising a light chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY. Disclosed herein, in certain embodiments, are methods of treating hepatocellular carcinoma in an individual in need thereof, comprising administering to the individual an effective amount of a monoclonal antibody or an antigen-binding fragment thereof comprising a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises (a) a light chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17; and (b) a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises (a) a light chain complementarity determining region (CDR) having an amino acid sequence at least 90% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17; and (b) a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 90% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises (a) a light chain complementarity determining region (CDR) having an amino acid sequence at least 95% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17; and (b) a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 95% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises (a) a light chain complementarity determining region (CDR) having an amino acid sequence at least 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17; and (b) a heavy chain complementarity determining region (CDR) having an amino acid sequence at least

99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises (a) a light chain complementarity determining region (CDR) having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17; and (b) a heavy chain complementarity determining region (CDR) having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 1, SEQ ID NO: 9, or SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NOS: SEQ ID NO: 2, or SEQ ID NO: 10, a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 3, or SEQ ID NO: 11, a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 4, or SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 5, SEQ ID NO: 13, or SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 6, or SEQ ID NO: 14. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 1, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 9, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 10, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 11. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 17 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 1, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3. In some instances, the monoclonal antibody or antigen-binding

fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 5, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 13, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 14. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO:16, or SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19; and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 7 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 8. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 15 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 16. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain

variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 19 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26. In some instances, the monoclonal antibody or antigen-binding fragment thereof specifically binds to a MICA protein, a MICB protein, or both MICA and MICB protein. In some instances, the monoclonal antibody or antigen-binding fragment thereof binds to an alpha-3 domain of a MICA protein, a MICB protein, or both MICA and MICB protein. In some instances, the MICA protein is membrane-bound MICA protein, soluble MICA protein, or both. In some instances, the MICB protein is membrane-bound MICB protein, soluble MICB protein, or both. In some instances, the monoclonal antibody or antigen-binding fragment thereof is selected from a whole immunoglobulin, an scFv, a Fab, a $F(ab')_2$, or a disulfide linked Fv. In some instances, the monoclonal antibody or antigen-binding fragment thereof is an IgG or IgM. In some instances, the monoclonal antibody or fragment thereof is humanized or chimeric. In some instances, the monoclonal antibody or antigen binding fragment thereof reduces level of soluble MICA protein, soluble MICB protein, or both. In some instances, the monoclonal antibody or antigen binding fragment thereof reduces shedding of soluble MICA protein, soluble MICB protein, or both. In some instances, the monoclonal antibody or antigen binding fragment thereof inhibits shedding of soluble MICA protein, soluble MICB protein, or both.

[0011] Disclosed herein, in certain embodiments, are methods of reducing level of soluble MICA protein, soluble MICB protein, or both in an individual in need thereof, comprising administering to the individual an effective amount of a monoclonal antibody or an antigen-binding fragment thereof comprising a light chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY. Disclosed herein, in certain embodiments, are methods of reducing level of soluble MICA protein, soluble MICB protein, or both in an individual in need thereof, comprising administering to the individual an effective amount of a monoclonal antibody or an antigen-binding fragment thereof comprising a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of

the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises (a) a light chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17; and (b) a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises (a) a light chain complementarity determining region (CDR) having an amino acid sequence at least 90% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17; and (b) a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 90% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises (a) a light chain complementarity determining region (CDR) having an amino acid sequence at least 95% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17; and (b) a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 95% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises (a) a light chain complementarity determining region (CDR) having an amino acid sequence at least 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17; and (b) a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises (a) a light chain complementarity determining region (CDR) having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17; and (b) a heavy chain complementarity determining region (CDR) having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 1, SEQ ID NO: 9, or SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NOS: SEQ ID NO: 2, or SEQ ID NO: 10, a light chain complementarity

determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 3, or SEQ ID NO: 11, a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 4, or SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 5, SEQ ID NO: 13, or SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 6, or SEQ ID NO: 14. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 1, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 9, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 10, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 11. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 5, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 13, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 14. In some instances, the monoclonal antibody or antigen-binding

fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, SEQ ID NO: 19. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO:16, or SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19; and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 7 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 8. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 15 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 16. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 19 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 20. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a light chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24. In some instances, the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26. In some instances, the monoclonal antibody or antigen-binding fragment thereof specifically binds to a MICA protein, a MICB protein, or both MICA and MICB protein. In some instances, the monoclonal antibody or antigen-binding fragment thereof binds to an alpha-3 domain of a MICA protein, a MICB protein, or both MICA and MICB

protein. In some instances, the MICA protein is membrane-bound MICA protein, soluble MICA protein, or both. In some instances, the MICB protein is membrane-bound MICB protein, soluble MICB protein, or both. In some instances, the monoclonal antibody or antigen-binding fragment thereof is selected from a whole immunoglobulin, an scFv, a Fab, a $F(ab')_2$, or a disulfide linked Fv. In some instances, the monoclonal antibody or antigen-binding fragment thereof is an IgG or IgM. In some instances, the monoclonal antibody or fragment thereof is humanized or chimeric. In some instances, the monoclonal antibody or antigen-binding fragment thereof reduces or inhibits shedding of soluble MICA protein, soluble MICB protein, or both, thereby reducing level of soluble MICA protein, soluble MICB protein, or both in the individual. In some instances, the individual has a cancer characterized by elevated levels of soluble MICA protein, soluble MICB protein, or both. In some instances, the cancer is hepatocellular carcinoma.

[0012] Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof according to any one of disclosures herein for use in treating cancer in an individual in need thereof. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof according to any one of disclosures herein for use in preparation of a medicament for treating cancer in an individual in need thereof. In some instances, the cancer is hepatocellular carcinoma.

[0013] Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof that competitively bind to MICA/B with an antibody comprising a light chain variable domain (VL) having an amino acid sequence at least about 80% identical to an amino acid sequence set forth as SEQ ID NO: 27. Disclosed herein, in certain embodiments, are monoclonal antibodies or an antigen-binding fragments thereof that competitively bind to MICA/B with an antibody comprising a heavy chain variable domain (VH) having an amino acid sequence at least about 80% identical to an amino acid sequence set forth as SEQ ID NO: 28.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] An understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0015] FIG. 1A-FIG. 1B exemplify binding of antibodies 3F9.E4 (**FIG. 1A**) and 16F10.C12 (**FIG. 1B**) to MICA/B alleles by ELISA.

[0016] FIG. 2 exemplifies antibody 3F9.E4 binds to the cell surface MICA, evaluated by staining of TRAMP C2 cells transfected with MICA*08 in comparison to parental TC2 cells.

[0017] FIG. 3 exemplifies antibodies 3F9.E4 and 16F10.C12 inhibit MICA shedding from PLC/PRF/5 cells.

[0018] FIG. 4A-FIG. 4B exemplifies antibodies 3F9.E4 (**FIG. 4A**) and 16F10.C12 (**FIG. 4B**) enhance NK-92 cells mediated cytotoxicity of PLC/PRF/5 cells.

[0019] FIG. 5 exemplifies antitumor activity of antibody 3F9 against B16/MICA transfectants relative to isotype control (IC).

[0020] FIG. 6A-FIG. 6C exemplify higher percentage of NKG2D positive NK cells (**FIG. 6A**), CD8+ T cells (**FIG. 6B**) and gamma delta T cells (**FIG. 6C**) are observed in tumor infiltrates (TILs) in 3F9 antibody treated tumors compared to isotype control.

[0021] FIG. 7A-FIG. 7B exemplify treatment with 3F9 antibody in B16/MICA in MICA transgenic animals reduces levels of soluble MICA (**FIG. 7A**) and surface MICA in tumors (**FIG. 7B**).

[0022] FIG. 8A-FIG. 8C exemplify competition binding assay to illustrate that all antibodies bind to a "structural" epitope and antibody 3F9.E4 competitively binds antibody PDI-1 (**FIG. 8B**) and antibody 16F10 binds a slightly different epitope than PDI-1 and 3F9, but in close proximity (**FIG. 8C**).

DETAILED DESCRIPTION

[0023] Disclosed herein, in some embodiments, are monoclonal antibodies that bind specifically to MICA/B. In some embodiments, MICA/B antibodies herein bind to MICA/B proteins or fragments thereof and modulate immune response in an individual, thereby treating cancer (e.g. hepatocellular carcinoma).

[0024] Major histocompatibility complex class I-related chain A and B (MICA/B) are two stress-inducible ligands for natural killer cell (NK) receptor NKG2D and play an important role in mediating the cytotoxicity of NK and T cells. Soluble MICA/B shed by diseased cells (e.g. cancer cells) desensitizes NK and T cells through binding of NKG2D receptor, thereby suppressing the immune response. Accordingly, modulation of MICA/B is useful in modulating an immune response in an individual, for example, in an individual suffering from cancer. Antibodies binding to MICA/B and modulating its activity are desirable for the development of novel therapeutics for treatment of cancer.

Certain terminology

[0025] As used herein "MICA/B" refers to MICA protein, MICB protein or both MICA and MICB proteins, including their variants, isoforms, and species homologs of human MICA/B.

[0026] As used herein "antibody" refers to a glycoprotein which exhibits binding specificity to a specific antigen. An antibody often comprises a variable domain and a constant domain in each of a heavy chain and a light chain. Accordingly, most antibodies have a heavy chain variable domain (VH) and a light chain variable domain (VL) that together form the portion of the antibody that

binds to the antigen. Within each variable domain are three complementarity determining regions (CDR) which form loops in the heavy chain variable domain (VH) and light chain variable domain (VL) that contact the surface of the antigen. Antibodies herein also include "antigen binding portion" or fragments of the antibody that are capable of binding to the antigen.

[0027] As used herein "chimeric" antibodies are antibodies having a portion of the heavy and/or light chain identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (see *e.g.,* Morrison *et al.*, Proc. Natl. Acad. Sci. USA 81:6851-6855 (1984)). "Humanized antibodies" herein refers chimeric antibodies having human sequences substituted in the antibody sequence.

[0028] The terms "recipient", "individual", "subject", "host", and "patient", are used interchangeably herein and in some cases, refer to any mammalian subject for whom diagnosis, treatment, or therapy is desired, particularly humans. "Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and laboratory, zoo, sports, or pet animals, such as dogs, horses, cats, cows, sheep, goats, pigs, mice, rats, rabbits, guinea pigs, monkeys etc. In some embodiments, the mammal is human.

[0029] As used herein, the terms "treatment," "treating," and the like, in some cases, refer to administering an agent, or carrying out a procedure, for the purposes of obtaining an effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of effecting a partial or complete cure for a disease and/or symptoms of the disease. "Treatment," as used herein, may include treatment of a disease or disorder (e.g. cancer) in a mammal, particularly in a human, and includes: (a) preventing the disease or a symptom of a disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it (e.g., including diseases that may be associated with or caused by a primary disease; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., causing regression of the disease. Treating may refer to any indicia of success in the treatment or amelioration or prevention of a cancer, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the disease condition more tolerable to the patient; slowing in the rate of degeneration or decline; or making the final point of degeneration less debilitating. The treatment or amelioration of symptoms is based on one or more objective or subjective parameters; including the results of an examination by a physician. Accordingly, the term "treating" includes the administration of the compounds or

agents of the present invention to prevent or delay, to alleviate, or to arrest or inhibit development of the symptoms or conditions associated with diseases (e.g. cancer). The term "therapeutic effect" refers to the reduction, elimination, or prevention of the disease, symptoms of the disease, or side effects of the disease in the subject.

[0030] A "therapeutically effective amount" in some cases means the amount that, when administered to a subject for treating a disease, is sufficient to effect treatment for that disease.

[0031] As used herein, singular forms “a”, “and,” and “the” include plural referents unless the context clearly indicates otherwise. Thus, for example, reference to “an antibody” includes a plurality of antibodies and reference to “an antibody” in some embodiments includes multiple antibodies, and so forth.

[0032] As used herein, all numerical values or numerical ranges include whole integers within or encompassing such ranges and fractions of the values or the integers within or encompassing ranges unless the context clearly indicates otherwise. Thus, for example, reference to a range of 90-100%, includes 91%, 92%, 93%, 94%, 95%, 95%, 97%, etc., as well as 91.1%, 91.2%, 91.3%, 91.4%, 91.5%, etc., 92.1%, 92.2%, 92.3%, 92.4%, 92.5%, etc., and so forth. In another example, reference to a range of 1-5,000 fold includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, fold, etc., as well as 1.1, 1.2, 1.3, 1.4, 1.5, fold, etc., 2.1, 2.2, 2.3, 2.4, 2.5, fold, etc., and so forth.

[0033] “About” a number, as used herein, refers to range including the number and ranging from 10% below that number to 10% above that number. “About” a range refers to 10% below the lower limit of the range, spanning to 10% above the upper limit of the range.

[0034] Percent (%) identity” refers to the extent to which two sequences (nucleotide or amino acid) have the same residue at the same positions in an alignment. For example, “an amino acid sequence is X% identical to SEQ ID NO: Y” refers to % identity of the amino acid sequence to SEQ ID NO:Y and is elaborated as X% of residues in the amino acid sequence are identical to the residues of sequence disclosed in SEQ ID NO: Y. Generally, computer programs are employed for such calculations. Exemplary programs that compare and align pairs of sequences, include ALIGN (Myers and Miller, 1988), FASTA (Pearson and Lipman, 1988; Pearson, 1990) and gapped BLAST (Altschul et al., 1997), BLASTP, BLASTN, or GCG (Devereux et al., 1984).

MICA/B

[0035] Disclosed herein, in some embodiments, are monoclonal antibodies that bind specifically to MICA/B. Further disclosed herein, in some embodiments, are monoclonal antibodies that competitively bind to MICA/B.

[0036] Major Histocompatibility Complex (MHC) class I Chain-related gene A and gene B protein (MICA/B) are glycosylated, polymorphic and membrane-anchored non-classical MHC class I proteins. MICA/B are related to MHC class I and have similar domain structure comprising three extra-cellular Ig-like domains (alpha-1, alpha-2 and alpha-3), a transmembrane domain and a C-terminal cytoplasmic tail. However, MICA/B do not associate with β2-microglobulin, lack a CD8 binding site and do not present any antigens. MICA/B are ligands to C-type lectin-like activating receptor Natural Killer Group 2D (NKG2D) on immune effector cells, including NK, NKT and both αβ and γδ $CD8^+$ T cells. The interaction of MICA/B and NKG2D plays a role in tumor surveillance, and immune response.

[0037] MICA/B proteins are expressed normally at low levels in normal cells, but are induced to higher levels in stressed or transformed cells (e.g. cancer cells). The interaction of NKG2D-bearing immune effector cells with stressed or diseased cells expressing MICA/B ligands on the cell surface creates a cellular immune response against the stressed/diseased cell that culminates in the death of the MICA/B expressing cells. In cancer cells, the truncated MICA/B proteins (proteins that lack the transmembrane domain and cytoplasmic tail but retain the three extracellular domain comprising alpha- 1, -2 and -3 domains) are frequently shed into the blood by the action of proteases and results in the down-modulation (receptor internalization) of its intended receptor, NKG2D, on effector immune cells. In some instances, MICA/B glycoproteins are produced intracellularly that are not routinely destined to become cell surface membrane-bound, but instead are incorporated within exosomes and released outside the cell where interaction with NKG2D receptors on immune cells occurs. These truncated or soluble MICA/B ligands shed from the surface of cancer cells function like decoy molecules and lead to down-modulation of the NKG2D receptor on immune effector cells such as NK, NKT and various $CD8^+$ T cells. In some instances, the formation of soluble MICA/B leads to the unusual situation where the effectors of the innate defense system, whose natural role is to seek and destroy transformed cells, are shut down by the immunosuppressive actions of these decoy ligand molecules, thereby enabling the cancer cells to hide from the immune system and to grow unchecked.

Hepatocellular Carcinoma (HCC)

[0038] In some embodiments, anti-MICA/B antibodies disclosed herein bind to MICA/B proteins or fragments thereof and modulate immune response in an individual, thereby treating cancer (e.g. hepatocellular carcinoma).

[0039] Hepatocellular carcinoma (HCC) is a primary malignancy of the liver and occurs predominantly in individuals with underlying chronic liver disease and cirrhosis. Tumors progress

with local expansion, intrahepatic spread, and distant metastases. Hepatitis B and Hepatitis C predisposes individuals to the development of chronic liver disease and subsequent development of HCC. Obesity, diabetes, and alcohol abuse are some other causes that predispose individuals to the subsequent development of HCC.

Anti-MICA/B Antibodies

[0040] Provided herein are antibodies that specifically bind to MICA/B proteins. In some embodiments, anti-MICA/B antibodies comprise at least one heavy chain and anti-MICA/B antibodies comprise at least one light chain. In some embodiments, anti-MICA/B antibodies comprise at least one heavy chain comprising a heavy chain variable domain (VH) and at least one light chain comprising a light chain variable domain (VL). Each VH and VL comprises three complementarity determining regions (CDR). The amino acid sequences of the VH and VL and the CDRs determine the antigen binding specificity and antigen binding strength of the antibody. The amino acid sequences of the Heavy and Light chains, VH and VL and the CDRs are summarized in Table 1.

Table 1: Anti-MICA/B Monoclonal Antibody Sequences

	SEQUENCE	SEQ ID NO:
3F9.E4 Light Chain CDR1	RSSKSLLHSNGNTYLY	1
3F9.E4 Light Chain CDR2	RMSNLAS	2
3F9.E4 Light Chain CDR3	MQHLEYPFT	3
3F9.E4 Heavy Chain CDR1	GFTFSNYAMS	4
3F9.E4 Heavy Chain CDR2	YISPGGDYIYYADTVKG	5
3F9.E4 Heavy Chain CDR3	DRRHYGSYAMDY	6
3F9.E4 Light Chain Variable domain	DIVMTQAAPSVPVTPGESVSISCRSSKSLLHSNGNTYLYWFLQRPGQSPQLLIYRMSNLASGVPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPFTFGSGTKLEIK	7
3F9.E4 Heavy Chain Variable domain	EVQLQESGEGLVKPGGSLKLSCAASGFTFSNYAMSWVRQTPEKRLEWVAYISPGGDYIYYADTVKGRFTISRDNARNTLYLQMSSLKSEDTAMYYCTTDRRHYGSYAMDYWGQGISVTVSS	8
16F10.C12 Light Chain CDR1	TASSSVSSNYLH	**9**
16F10.C12 Light Chain CDR2	TTSNLAS	**10**
16F10.C12 Light Chain CDR3	HQFHRSPFT	**11**

Table 1: Anti-MICA/B Monoclonal Antibody Sequences		
16F10.C12 Heavy Chain CDR1	GFSLTAFGVN	**12**
16F10.C12 Heavy Chain CDR2	MIWGDGNTDYNSTLRS	**13**
16F10.C12 Heavy Chain CDR3	ETYYGNYAGLGY	**14**
16F10.C12 Light Chain Variable domain	QIVLTQSPAIMSASIGERVTMTCTASSSVSSNYLHWYQQKPRSSPKL WIYTTSNLASGVPTRFSGSGSGTSYSLTISSMEAEDAATYYCHQFHRS PFTFGSGTKLEIK	**15**
16F10.C12 Heavy Chain Variable domain	EVQLQESGPGLVAPSQSLSITCTVSGFSLTAFGVNWVRQPPGKGLEW LGMIWGDGNTDYNSTLRSRLSISKDNSKSQVFLKLNSLQTDDTARYF CARETYYGNYAGLGYWGQGTLVTVSA	**16**
3F9H1L3L Light Chain CDR1	RSSKSLLHSNLNTYLY	**17**
3F9H1L3L Light Chain CDR2	RMSNLAS	**2**
3F9H1L3L Light Chain CDR3	MQHLEYPFT	**3**
3F9H1L3L Heavy Chain CDR1	GFTFSNYAMS	**4**
3F9H1L3L Heavy Chain CDR2	YISPGGDYIYYADSVKG	**18**
3F9H1L3L Heavy Chain CDR3	DRRHYGSYAMDY	**6**
3F9H1L3L Light Chain Variable domain	DIVMTQSPLSLPVTPGEPASISCRSSKSLLHSNLNTYLYWFLQKPGQS PQILIYRMSNLASGVPDRFSGSGSGTAFTLKISRVEAEDVGVYYCMQ HLEYPFTFGPGTKLEIKR	**19**
3F9H1L3L Heavy Chain Variable domain	QVQLVESGGGLVKPGGSLRLSCAASGFTFSNYAMSWIRQAPGKGLE WVSYISPGGDYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCTT	**20**
3F9H1L3L Light Chain	DIVMTQSPLSLPVTPGEPASISCRSSKSLLHSNLNTYLYWFLQKPGQS PQILIYRMSNLASGVPDRFSGSGSGTAFTLKISRVEAEDVGVYYCMQ HLEYPFTFGPGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC*	**21**
3F9H1L3L Heavy Chain	QVQLVESGGGLVKPGGSLRLSCAASGFTFSNYAMSWIRQAPGKGLE WVSYISPGGDYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCTTDRRHYGSYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN	**22**

Table 1: Anti-MICA/B Monoclonal Antibody Sequences		
	WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG**	
PDI-1 humanized LC5 Light Chain	METDTLLLWVLLLWVPGSTGDIQMTQSPSTLSASVGDRVTITCSASQ GISNYLNWYQQKPGKAPKLLIQYTSLLHSGVPSRFSGSGSGTEYTLTI SSLQPDDFATYFCQQYSKFPRTFGGGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*	**23**
PDI-1 humanized LC4 Light Chain	METDTLLLWVLLLWVPGSTGDIQMTQSPSSLSASVGDRVTITCSASQ GISNYLNWYQQKPGKAPKLLIQYTSLLHSGVPSRFSGSGSGTDYTLTI SSLQPEDFATYFCQQYSKFPRTFGGGTKVEIKRTVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*	**24**
PDI-1 humanized HC4 Heavy Chain	MDPKGSLSWRILLFLSLAFELSYGQIQLVQSGSELKKPGASVKVSCK AFGYTFTNYGMNWVKQAPGQGLKWMGWINTYTGEPTYAQGFTGR FVFSLETSVSTAYLQISSLKAEDTAVYFCARNYGNYLFDYWGQGTL VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPG*	**25**
PDI-1 humanized HC6 Heavy Chain	MDPKGSLSWRILLFLSLAFELSYGQIQLVQSGAEVKKPGASVKVSCK AFGYTFTNYGMNWVKQAPGQGLKWMGWINTYTGEPTYADDFKGR VTFTLETSISTAYMELSRLRSDDTAVYFCARNYGNYLFDYWGQGTL VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPG*	**26**
PDI-1 Light Chain Variable domain	DIQMTQTTSSLSASLGDRVTISCSASQGISNYLNWYQQKPDGTLKLLI QYTSLLHSGVPSRFSGSGSGTEYSLTISNLEPEDIATYFCQQYSKFPRT FGGGTKLEIKR	**27**
PDI-1 Heavy Chain Variable domain	QIQLVQSGPELKKSGETVKISCKAFGYTFTNYGMNWVKQAPGKGLK WMGWINTYTGEPTYADDFKGRFAFSLETSASTAYLQINHLKNEDTA TYFCARNYGNYLFDYWGQGTTLTVSS	**28**

[0041] In some embodiments, the antibodies specifically bind to a MICA protein. In some embodiments, the antibodies specifically bind to a MICB protein. In some embodiments, the antibodies specifically bind to both MICA and MICB protein. In some embodiments, the antibodies bind to an alpha-3 domain of a MICA protein. In some embodiments, the antibodies bind to an

alpha-3 domain of a MICB protein. In some embodiments, the antibodies bind to an alpha-3 domain of both MICA and MICB protein. In some embodiments, the antibodies bind to a MICA protein that is membrane-bound MICA protein. In some embodiments, the antibodies bind to a MICA protein that is soluble MICA protein. In some embodiments, the antibodies bind to a MICA protein that is both membrane-bound MICA protein and soluble MICA protein. In some embodiments, the antibodies bind to a MICB protein that is membrane-bound MICB protein. In some embodiments, the antibodies bind to a MICB protein that is soluble MICB protein. In some embodiments, the antibodies bind to a MICB protein that is both membrane-bound MICB protein and soluble MICB protein.

[0042] In some embodiments, antibodies that specifically bind to MICA/B are monoclonal antibodies. In some embodiments, the antibody is an antigen binding fragment. In some embodiments, the antibody is selected from a whole immunoglobulin, an scFv, a Fab, a F(ab')2, or a disulfide linked Fv. In some embodiments, the antibody is an IgG or an IgM. In some embodiments, the antibody is humanized. In some embodiments, the antibody is chimeric.

MICA/B Antibody Heavy and Light Chain

[0043] Disclosed herein are antibodies that specifically bind to MICA/B having a light chain. In some embodiments, antibodies binding to MICA/B comprise a light chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24. In some embodiments the light chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24. In some embodiments, the light chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24.

[0044] Further disclosed herein are antibodies that specifically bind to MICA/B having a heavy chain. In some embodiments, antibodies binding to MICA/B comprise a heavy chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26. In some embodiments the heavy chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26. In some embodiments, the heavy chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26.

[0045] Also disclosed herein are antibodies binding to MICA/B comprising a light chain and a heavy chain. In some embodiments, antibodies binding to MICA/B comprise a light chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24 and a heavy chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26. In some embodiments the light chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24 and the heavy chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26. In some embodiments, the light chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24 and the heavy chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26.

[0046] In some embodiments, antibodies binding to MICA/B comprise a light chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 21 and a heavy chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 22. In some embodiments the light chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 21 and the heavy chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 22. In some embodiments, the light chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 21 and the heavy chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 22.

[0047] In some embodiments, antibodies binding to MICA/B comprise a light chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 23 and a heavy chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 25. In some embodiments the light chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 23 and the heavy chain has an amino acid sequence at least about 75%, 80%, 81%,

82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 25. In some embodiments, the light chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 23 and the heavy chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 25.

[0048] In some embodiments, antibodies binding to MICA/B comprise a light chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 23 and a heavy chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 26. In some embodiments the light chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 23 and the heavy chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 26. In some embodiments, the light chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 23 and the heavy chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 26.

[0049] In some embodiments, antibodies binding to MICA/B comprise a light chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 24 and a heavy chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 25. In some embodiments the light chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 24 and the heavy chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 25. In some embodiments, the light chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 24 and the heavy chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 25.

[0050] In some embodiments, antibodies binding to MICA/B comprise a light chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 24 and a heavy chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 26. In some embodiments the light chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%,

92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 24 and the heavy chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 26. In some embodiments, the light chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 24 and the heavy chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 26.

MICA/B Antibody Variable Domain

[0051] Disclosed herein are antibodies that specifically bind to MICA/B having a light chain comprising a light chain variable domain (VL). In some embodiments, antibodies binding to MICA/B comprise a light chain variable domain (VL) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. In some embodiments the VL has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. In some embodiments, the VL has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19.

[0052] Further disclosed herein are antibodies that specifically bind to MICA/B having a heavy chain comprising a heavy chain variable domain (VH). In some embodiments, antibodies binding to MICA/B comprise a heavy chain variable domain (VH) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some embodiments the VH has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some embodiments, the VH has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20.

[0053] Also disclosed herein are antibodies binding to MICA/B comprising a light chain variable domain (VL) and a heavy chain variable domain (VH). In some embodiments, antibodies binding to MICA/B comprise a light chain variable domain (VL) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19 and a heavy chain variable domain (VH) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some embodiments the VL has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%,

or 99% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19 and the VH has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some embodiments, the VL has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19 and the VH has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20.

[0054] In some embodiments, antibodies binding to MICA/B comprise a light chain variable domain (VL) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 7 and a heavy chain variable domain (VH) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 8. In some embodiments the VL has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 7 and the VH has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 8. In some embodiments, the VL has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 7 and the VH has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 8.

[0055] In some embodiments, antibodies binding to MICA/B comprise a light chain variable domain (VL) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 15 and a heavy chain variable domain (VH) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 16. In some embodiments the VL has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 15 and the VH has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 16. In some embodiments, the VL has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 15 and the VH has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 16.

[0056] In some embodiments, antibodies binding to MICA/B comprise a light chain variable domain (VL) having an amino acid sequence at least about 70% identical to an amino acid

sequence set forth as SEQ ID NO: 19 and a heavy chain variable domain (VH) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 20. In some embodiments the VL has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 19 and the VH has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 20. In some embodiments, the VL has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 19 and the VH has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 20.

MICA/B Antibody Complementarity Determining Regions

[0057] Disclosed herein are antibodies that specifically bind to MICA/B having a light chain comprising a light chain complementarity determining region (CDR). In some embodiments, antibodies binding to MICA/B comprise a light chain CDR sequence having an amino acid sequence at least about 70% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17. In some embodiments, antibodies binding to MICA/B comprise a light chain CDR sequence having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17. In some embodiments, antibodies binding to MICA/B comprise a light chain CDR sequence having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17.

[0058] Further disclosed herein are antibodies that specifically bind to MICA/B having a heavy chain comprising a heavy chain complementarity determining region (CDR). In some embodiments, antibodies binding to MICA/B comprise a heavy chain CDR sequence having an amino acid sequence at least about 70% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some embodiments, antibodies binding to MICA/B comprise a heavy chain CDR sequence having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some embodiments, antibodies binding to MICA/B comprise a heavy chain CDR sequence having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18.

[0059] Also disclosed herein are antibodies binding to MICA/B comprising a light chain complementarity determining region (CDR) and a heavy chain complementarity determining region (CDR). In some embodiments, antibodies binding to MICA/B comprise a light chain CDR sequence having an amino acid sequence at least about 70% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17 and a heavy chain CDR sequence having an amino acid sequence at least about 70% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some embodiments, antibodies binding to MICA/B comprise a light chain CDR sequence having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17 and a heavy chain CDR sequence having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some embodiments, antibodies binding to MICA/B comprise a light chain CDR sequence having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17 and a heavy chain CDR sequence having an amino acid sequence at least about 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18.

[0060] In some embodiments, antibodies binding to MICA/B comprise a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least about 70% identical to one of SEQ ID NO: 1, SEQ ID NO: 9, or SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least about 70% identical to one of SEQ ID NOS: SEQ ID NO: 2, or SEQ ID NO: 10, a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least about 70% identical to one of SEQ ID NO: 3, or SEQ ID NO: 11, a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least about 70% identical to one of SEQ ID NO: 4, or SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least about 70% identical to one of SEQ ID NO: 5, SEQ ID NO: 13, or SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least about 70% identical to one of SEQ ID NO: 6, or SEQ ID NO: 14. In some embodiments, antibodies binding to MICA/B comprise a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to one of SEQ ID NO: 1, SEQ ID NO: 9, or SEQ ID NO: 17, a light chain complementarity

determining region 2 (CDR2) having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to one of SEQ ID NOS: SEQ ID NO: 2, or SEQ ID NO: 10, a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to one of SEQ ID NO: 3, or SEQ ID NO: 11, a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to one of SEQ ID NO: 4, or SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to one of SEQ ID NO: 5, SEQ ID NO: 13, or SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to one of SEQ ID NO: 6, or SEQ ID NO: 14. In some embodiments, antibodies binding to MICA/B comprise a light chain complementarity determining region 1 (CDR1) having an amino acid sequence 100% identical to one of SEQ ID NO: 1, SEQ ID NO: 9, or SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence 100% identical to one of SEQ ID NOS: SEQ ID NO: 2, or SEQ ID NO: 10, a light chain complementarity determining region 3 (CDR3) having an amino acid sequence 100% identical to one of SEQ ID NO: 3, or SEQ ID NO: 11, a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence 100% identical to one of SEQ ID NO: 4, or SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence 100% identical to one of SEQ ID NO: 5, SEQ ID NO: 13, or SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence 100% identical to one of SEQ ID NO: 6, or SEQ ID NO: 14.

[0061] In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 1, a light chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 2, and a light chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 3. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain a light chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical

to an amino acid sequence set forth as SEQ ID NO: 1, a light chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 2, and a light chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 3. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 1, a light chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 2, and a light chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 3.

[0062] In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 9, a light chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 10, and a light chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 11. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain a light chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 9, a light chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 10, and a light chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 11. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 9, a light chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 10, and a light chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 11.

[0063] In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 17, a light chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 2, and a light chain CDR3 having an

amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 3. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain a light chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 17, a light chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 2, and a light chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 3. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 17, a light chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 2, and a light chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 3.

[0064] In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 5, a heavy chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 5, a heavy chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 5, a heavy chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 6.

[0065] In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 12, a heavy chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 13, a heavy chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 14. In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 12, a heavy chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 13, a heavy chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 14. In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 12, a heavy chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 13, a heavy chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 14.

[0066] In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 18, a heavy chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 18, a heavy chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having

an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 18, a heavy chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 6.

[0067] In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 1, a light chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 2, a light chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 3, a heavy chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 5, and a heavy chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 1, a light chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 2, a light chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 3, a heavy chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 5, and a heavy chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 1, a light chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 2, a light chain CDR3 having an amino acid sequence 100% identical to an

amino acid sequence set forth as SEQ ID NO: 3, a heavy chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 5, and a heavy chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 6.

[0068] In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 9, a light chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 10, a light chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 11, a heavy chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 12, a heavy chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 13, and a heavy chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 14. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 9, a light chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 10, a light chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 11, a heavy chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 12, a heavy chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 13, and a heavy chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 14. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 9, a light chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set

forth as SEQ ID NO: 10, a light chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 11, a heavy chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 12, a heavy chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 13, and a heavy chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 14.

[0069] In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 17, a light chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 2, a light chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 3, a heavy chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 18, and a heavy chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 17, a light chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 2, a light chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 3, a heavy chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 18, and a heavy chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 17, a

light chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 2, a light chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 3, a heavy chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 18, and a heavy chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 6.

[0070] In some embodiments, antibodies binding to MICA/B do not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY.

Competitive binding

[0071] Disclosed herein, in some embodiments, are antibodies that competitively bind to MICA/B with an antibody comprising a light chain variable domain (VL) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 27. In some embodiments the VL has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 27. In some embodiments, the VL has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 27.

[0072] Disclosed herein, in some embodiments, are antibodies that competitively bind to MICA/B with an antibody comprising a heavy chain variable domain (VH) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 28. In some embodiments the VH has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 28. In some embodiments, the VH has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 28.

[0073] Disclosed herein, in some embodiments, are antibodies that competitively bind to MICA/B with an antibody comprising a light chain variable domain (VL) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 27 and a heavy chain variable domain (VH) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 28. In some embodiments the VL has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 27 and the VH has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an

amino acid sequence set forth as SEQ ID NO: 28. In some embodiments, the VL has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 27 and the VH has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 28.

Methods of Treatment and Use

[0074] Provided herein are methods of treating cancer (e.g. hepatocellular carcinoma) in an individual in need thereof comprising administration of an anti-MICA/B antibody disclosed herein.

[0075] Further provided herein are methods of reducing level of soluble MICA/B proteins in an individual in need thereof comprising administration of an anti-MICA/B antibody disclosed herein.

[0076] Also provided herein are methods of alleviating or inhibiting the immunosuppressive environment by preventing or blocking the interaction between soluble MICA/B and NKG2D receptors in an individual in need thereof comprising administration of an anti-MICA/B antibody disclosed herein.

[0077] In some embodiments, antibodies binding to MICA/B comprise a light chain CDR sequence having an amino acid sequence at least about 70% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17. In some embodiments, antibodies binding to MICA/B comprise a light chain CDR sequence having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17. In some embodiments, antibodies binding to MICA/B comprise a light chain CDR sequence having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17.

[0078] In some embodiments, antibodies binding to MICA/B comprise a heavy chain CDR sequence having an amino acid sequence at least about 70% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some embodiments, antibodies binding to MICA/B comprise a heavy chain CDR sequence having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some embodiments, antibodies binding to MICA/B comprise a heavy chain CDR sequence having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18.

[0079] In some embodiments, antibodies binding to MICA/B comprise a light chain CDR sequence having an amino acid sequence at least about 70% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17 and a heavy chain CDR sequence having an

amino acid sequence at least about 70% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some embodiments, antibodies binding to MICA/B comprise a light chain CDR sequence having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17 and a heavy chain CDR sequence having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18. In some embodiments, antibodies binding to MICA/B comprise a light chain CDR sequence having an amino acid sequence 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17 and a heavy chain CDR sequence having an amino acid sequence at least about 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18.

[0080] In some embodiments, antibodies binding to MICA/B comprise a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least about 70% identical to one of SEQ ID NO: 1, SEQ ID NO: 9, or SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least about 70% identical to one of SEQ ID NOS: SEQ ID NO: 2, or SEQ ID NO: 10, a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least about 70% identical to one of SEQ ID NO: 3, or SEQ ID NO: 11, a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least about 70% identical to one of SEQ ID NO: 4, or SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least about 70% identical to one of SEQ ID NO: 5, SEQ ID NO: 13, or SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least about 70% identical to one of SEQ ID NO: 6, or SEQ ID NO: 14. In some embodiments, antibodies binding to MICA/B comprise a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to one of SEQ ID NO: 1, SEQ ID NO: 9, or SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to one of SEQ ID NOS: SEQ ID NO: 2, or SEQ ID NO: 10, a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,

97%, 98%, or 99% identical to one of SEQ ID NO: 3, or SEQ ID NO: 11, a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to one of SEQ ID NO: 4, or SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to one of SEQ ID NO: 5, SEQ ID NO: 13, or SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to one of SEQ ID NO: 6, or SEQ ID NO: 14. In some embodiments, antibodies binding to MICA/B comprise a light chain complementarity determining region 1 (CDR1) having an amino acid sequence 100% identical to one of SEQ ID NO: 1, SEQ ID NO: 9, or SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence 100% identical to one of SEQ ID NOS: SEQ ID NO: 2, or SEQ ID NO: 10, a light chain complementarity determining region 3 (CDR3) having an amino acid sequence 100% identical to one of SEQ ID NO: 3, or SEQ ID NO: 11, a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence 100% identical to one of SEQ ID NO: 4, or SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence 100% identical to one of SEQ ID NO: 5, SEQ ID NO: 13, or SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence 100% identical to one of SEQ ID NO: 6, or SEQ ID NO: 14.

[0081] In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 1, a light chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 2, and a light chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 3. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain a light chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 1, a light chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 2, and a light chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,

98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 3. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 1, a light chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 2, and a light chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 3.

[0082] In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 9, a light chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 10, and a light chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 11. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain a light chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 9, a light chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 10, and a light chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 11. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 9, a light chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 10, and a light chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 11.

[0083] In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 17, a light chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 2, and a light chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 3. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain a light chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 17, a light chain CDR2 having an amino acid

sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 2, and a light chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 3. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 17, a light chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 2, and a light chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 3.

[0084] In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 5, a heavy chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 5, a heavy chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 5, a heavy chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 6.

[0085] In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 12, a heavy chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 13, a heavy chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID

NO: 14. In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 12, a heavy chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 13, a heavy chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 14. In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 12, a heavy chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 13, a heavy chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 14.

[0086] In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 18, a heavy chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 18, a heavy chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a heavy chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 18, a heavy chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 6.

[0087] In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 1, a light chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 2, a light chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 3, a heavy chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 5, and a heavy chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 1, a light chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 2, a light chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 3, a heavy chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 5, and a heavy chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 1, a light chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 2, a light chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 3, a heavy chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ

ID NO: 5, and a heavy chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 6.

[0088] In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 9, a light chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 10, a light chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 11, a heavy chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 12, a heavy chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 13, and a heavy chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 14. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 9, a light chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 10, a light chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 11, a heavy chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 12, a heavy chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 13, and a heavy chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 14. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 9, a light chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 10, a light chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 11, a heavy chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 12, a heavy chain

CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 13, and a heavy chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 14.

[0089] In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 17, a light chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 2, a light chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 3, a heavy chain CDR1 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 18, and a heavy chain CDR3 having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 17, a light chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 2, a light chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 3, a heavy chain CDR1 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 18, and a heavy chain CDR3 having an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 6. In some embodiments, antibodies binding to MICA/B comprise at least one of a light chain CDR1 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 17, a light chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 2, a light chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 3, a heavy chain CDR1 having an amino acid

sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 4, a heavy chain CDR2 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 18, and a heavy chain CDR3 having an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 6.

[0090] In some embodiments, antibodies binding to MICA/B do not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY.

[0091] In some embodiments, antibodies binding to MICA/B comprise a light chain variable domain (VL) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. In some embodiments the VL has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19. In some embodiments, the VL has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19.

[0092] In some embodiments, antibodies binding to MICA/B comprise a heavy chain variable domain (VH) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some embodiments the VH has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some embodiments, the VH has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20.

[0093] In some embodiments, antibodies binding to MICA/B comprise a light chain variable domain (VL) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19 and a heavy chain variable domain (VH) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some embodiments the VL has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19 and the VH has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20. In some embodiments, the VL has an

amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19 and the VH has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20.

[0094] In some embodiments, antibodies binding to MICA/B comprise a light chain variable domain (VL) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 7 and a heavy chain variable domain (VH) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 8. In some embodiments the VL has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 7 and the VH has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 8. In some embodiments, the VL has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 7 and the VH has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 8.

[0095] In some embodiments, antibodies binding to MICA/B comprise a light chain variable domain (VL) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 15 and a heavy chain variable domain (VH) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 16. In some embodiments the VL has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 15 and the VH has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 16. In some embodiments, the VL has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 15 and the VH has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 16.

[0096] In some embodiments, antibodies binding to MICA/B comprise a light chain variable domain (VL) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 19 and a heavy chain variable domain (VH) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 20. In some embodiments the VL has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 19 and the VH has an amino acid

sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 20. In some embodiments, the VL has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 19 and the VH has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 20.

[0097]

[0098] In some embodiments, antibodies binding to MICA/B comprise a light chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24. In some embodiments the light chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24. In some embodiments, the light chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24.

[0099] In some embodiments, antibodies binding to MICA/B comprise a heavy chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26. In some embodiments the heavy chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26. In some embodiments, the heavy chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26.

[00100] Also disclosed herein are antibodies binding to MICA/B comprising a light chain and a heavy chain. In some embodiments, antibodies binding to MICA/B comprise a light chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24 and a heavy chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26. In some embodiments the light chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24 and the heavy chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26. In some embodiments, the light chain has an amino acid

sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24 and the heavy chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26.

[00101] In some embodiments, antibodies binding to MICA/B comprise a light chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 21 and a heavy chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 22. In some embodiments the light chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 21 and the heavy chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 22. In some embodiments, the light chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 21 and the heavy chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 22.

[00102] In some embodiments, antibodies binding to MICA/B comprise a light chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 23 and a heavy chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 25. In some embodiments the light chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 23 and the heavy chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 25. In some embodiments, the light chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 23 and the heavy chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 25.

[00103] In some embodiments, antibodies binding to MICA/B comprise a light chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 23 and a heavy chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 26. In some embodiments the light chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 23 and the heavy chain has an amino acid sequence at least about 75%, 80%, 81%,

82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 26. In some embodiments, the light chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 23 and the heavy chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 26.

[00104] In some embodiments, antibodies binding to MICA/B comprise a light chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 24 and a heavy chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 25. In some embodiments the light chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 24 and the heavy chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 25. In some embodiments, the light chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 24 and the heavy chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 25.

[00105] In some embodiments, antibodies binding to MICA/B comprise a light chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 24 and a heavy chain having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 26. In some embodiments the light chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 24 and the heavy chain has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 26. In some embodiments, the light chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 24 and the heavy chain has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 26.

[00106] In some embodiments, antibodies competitively bind to MICA/B with an antibody comprising a light chain variable domain (VL) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 27. In some embodiments the VL has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid

sequence set forth as SEQ ID NO: 27. In some embodiments, the VL has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 27.

[00107] In some embodiments, antibodies competitively bind to MICA/B with an antibody comprising a heavy chain variable domain (VH) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 28. In some embodiments the VH has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 28. In some embodiments, the VH has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 28.

[00108] In some embodiments, antibodies competitively bind to MICA/B with an antibody comprising a light chain variable domain (VL) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 27 and a heavy chain variable domain (VH) having an amino acid sequence at least about 70% identical to an amino acid sequence set forth as SEQ ID NO: 28. In some embodiments the VL has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 27 and the VH has an amino acid sequence at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to an amino acid sequence set forth as SEQ ID NO: 28. In some embodiments, the VL has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 27 and the VH has an amino acid sequence 100% identical to an amino acid sequence set forth as SEQ ID NO: 28.

[00109] In some embodiments, the antibodies specifically bind to a MICA protein. In some embodiments, the antibodies specifically bind to a MICB protein. In some embodiments, the antibodies specifically bind to both MICA and MICB protein. In some embodiments, the antibodies bind to an alpha-3 domain of a MICA protein. In some embodiments, the antibodies bind to an alpha-3 domain of a MICB protein. In some embodiments, the antibodies bind to an alpha-3 domain of both MICA and MICB protein. In some embodiments, the antibodies bind to a MICA protein that is membrane-bound MICA protein. In some embodiments, the antibodies bind to a MICA protein that is soluble MICA protein. In some embodiments, the antibodies bind to a MICA protein that is both membrane-bound MICA protein and soluble MICA protein. In some embodiments, the antibodies bind to a MICB protein that is membrane-bound MICB protein. In some embodiments, the antibodies bind to a MICB protein that is soluble MICB protein. In some embodiments, the antibodies bind to a MICB protein that is both membrane-bound MICB protein and soluble MICB protein.

[00110] In some embodiments, antibodies that specifically bind to MICA/B are monoclonal antibodies. In some embodiments, the antibody is an antigen binding fragment. In some embodiments, the antibody is selected from a whole immunoglobulin, an scFv, a Fab, a F(ab')2, or a disulfide linked Fv. In some embodiments, the antibody is an IgG or an IgM. In some embodiments, the antibody is humanized. In some embodiments, the antibody is chimeric.

[00111] In some embodiments, the antibodies disclosed herein reduce level of soluble MICA protein. In some embodiments, the antibodies disclosed herein reduce level of soluble MICB protein. In some embodiments, the antibodies disclosed herein reduce level of both soluble MICA protein and soluble MICB protein. In some embodiments, the antibodies disclosed herein reduce shedding of soluble MICA protein. In some embodiments, the antibodies disclosed herein reduce shedding of soluble MICB protein. In some embodiments, the antibodies disclosed herein reduce shedding of both soluble MICA protein and soluble MICB protein. In some embodiments, the antibodies disclosed herein inhibit shedding of soluble MICA protein. In some embodiments, the antibodies disclosed herein inhibit shedding of soluble MICB protein. In some embodiments, the antibodies disclosed herein inhibit shedding of both soluble MICA protein and soluble MICB protein.

[00112] Any suitable route of administration is contemplated for use with the methods disclosed herein. In some embodiments, the antibody is administered by intravenous administration. In some embodiments, the antibody is administered by subcutaneous administration. In some embodiments, the antibody is administered locally. In some embodiments, the antibody is administered systemically (e.g., intravenously, intramuscularly, subcutaneously, intradermally, orally, intranasally, sublingually). In some embodiments, the antibody is formulated as a salve, lotion or emulsion. In some embodiments, the antibody is formulated as a solution. In some embodiments, the antibody is formulated for topical, oral, buccal, or nasal administration.

[00113] In some embodiments, the individual is monitored prior to administration of the antibody. Symptoms are identified and their severity is assessed. An antibody as described herein is administered alone or in combination with additional treatments, singly or multiply over time as discussed herein or known to one of skill in the art. In some embodiments, the individual is monitored such that the efficacy of the treatment regimen is determined. In some embodiments, a treatment regimen is modified in response to preliminary treatment outcomes, such that treatment dose or frequency or dose and frequency is altered so as to attain a desired level of subject response in light of symptom alleviation, side effect reduction, or a combination of symptom alleviation and side effect reduction.

[00114] Therapeutically effective amounts or dosages are contemplated to include dosages of about 0.01 mg/kg to about 20 mg/kg, about for example, about 0.01 mg/kg, about 0.02 mg/kg, about 0.03 mg/kg, about 0.04 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.09 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1.0 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg, about 1.5 mg/kg, about 1.6 mg/kg, about 1.7 mg/kg, about 1.8 mg/kg, about 1.9 mg/kg, about 2 mg/kg, about 2.1 mg/kg, about 2.2 mg/kg, about 2.3 mg/kg, about 2.4 mg/kg, about 2.5 mg/kg, about 2.6 mg/kg, about 2.7 mg/kg, about 2.8 mg/kg, about 2.9 mg/kg, about 3 mg/kg, about 3.1 mg/kg, about 3.2 mg/kg, about 3.3 mg/kg, about 3.4 mg/kg, about 3.5 mg/kg, about 3.6 mg/kg, about 3.7 mg/kg, about 3.8 mg/kg, about 3.9 mg/kg, about 4 mg/kg, about 4.1 mg/kg, about 4.2 mg/kg, about 4.3 mg/kg, about 4.4 mg/kg, about 4.5 mg/kg, about 4.6 mg/kg, about 4.7 mg/kg, about 4.8 mg/kg, about 4.9 mg/kg, about 5 mg/kg, about 5.1 mg/kg, about 5.2 mg/kg, about 5.3 mg/kg, about 5.4 mg/kg, about 5.5 mg/kg, about 5.6 mg/kg, about 5.7 mg/kg, about 5.8 mg/kg, about 5.9 mg/kg, about 6 mg/kg, about 6.1 mg/kg, about 6.2 mg/kg, about 6.3 mg/kg, about 6.4 mg/kg, about 6.5 mg/kg, about 6.6 mg/kg, about 6.7 mg/kg, about 6.8 mg/kg, about 6.9 mg/kg, about 7 mg/kg, about 7.1 mg/kg, about 7.2 mg/kg, about 7.3 mg/kg, about 7.4 mg/kg, about 7.5 mg/kg, about 7.6 mg/kg, about 7.7 mg/kg, about 7.8 mg/kg, about 7.9 mg/kg, about 8 mg/kg, about 8.1 mg/kg, about 8.2 mg/kg, about 8.3 mg/kg, about 8.4 mg/kg, about 8.5 mg/kg, about 8.6 mg/kg, about 8.7 mg/kg, about 8.8 mg/kg, about 8.9 mg/kg, about 9 mg/kg, about 9.1 mg/kg, about 9.2 mg/kg, about 9.3 mg/kg, about 9.4 mg/kg, about 9.5 mg/kg, about 9.6 mg/kg, about 9.7 mg/kg, about 9.8 mg/kg, about 9.9 mg/kg, about 10 mg/kg, about 10.1 mg/kg, about 10.2 mg/kg, about 10.3 mg/kg, about 10.4 mg/kg, about 10.5 mg/kg, about 10.6 mg/kg, about 10.7 mg/kg, about 10.8 mg/kg, about 10.9 mg/kg, about 11 mg/kg, about 11.1 mg/kg, about 11.2 mg/kg, about 11.3 mg/kg, about 11.4 mg/kg, about 11.5 mg/kg, about 11.6 mg/kg, about 11.7 mg/kg, about 11.8 mg/kg, about 11.9 mg/kg, about 12 mg/kg, about 12.1 mg/kg, about 12.2 mg/kg, about 12.3 mg/kg, about 12.4 mg/kg, about 12.5 mg/kg, about 12.6 mg/kg, about 12.7 mg/kg, about 12.8 mg/kg, about 12.9 mg/kg, about 13 mg/kg, about 13.1 mg/kg, about 13.2 mg/kg, about 13.3 mg/kg, about 13.4 mg/kg, about 13.5 mg/kg, about 13.6 mg/kg, about 13.7 mg/kg, about 13.8 mg/kg, about 13.9 mg/kg, about 14 mg/kg, about 14.1 mg/kg, about 14.2 mg/kg, about 14.3 mg/kg, about 14.4 mg/kg, about 14.5 mg/kg, about 14.6 mg/kg, about 14.7 mg/kg, about 14.8 mg/kg, about 14.9 mg/kg, about 15 mg/kg, about 15.1 mg/kg, about 15.2 mg/kg, about 15.3 mg/kg, about 15.4 mg/kg, about 15.5 mg/kg, about 15.6 mg/kg, about 15.7 mg/kg, about 15.8 mg/kg, about 15.9 mg/kg, about 16 mg/kg, about 16.1 mg/kg, about 16.2 mg/kg, about 16.3 mg/kg, about 16.4 mg/kg, about 16.5 mg/kg, about 16.6 mg/kg, about 16.7

mg/kg, about 16.8 mg/kg, about 16.9 mg/kg, about 17 mg/kg, about 17.1 mg/kg, about 17.2 mg/kg, about 17.3 mg/kg, about 17.4 mg/kg, about 17.5 mg/kg, about 17.6 mg/kg, about 17.7 mg/kg, about 17.8 mg/kg, about 17.9 mg/kg, about 18 mg/kg, about 18.1 mg/kg, about 18.2 mg/kg, about 18.3 mg/kg, about 18.4 mg/kg, about 18.5 mg/kg, about 18.6 mg/kg, about 18.7 mg/kg, about 18.8 mg/kg, about 18.9 mg/kg, about 19 mg/kg, about 19.1 mg/kg, about 19.2 mg/kg, about 19.3 mg/kg, about 19.4 mg/kg, about 19.5 mg/kg, about 19.6 mg/kg, about 19.7 mg/kg, about 19.8 mg/kg, about 19.9 mg/kg, about or 20 mg/kg. Therapeutically effective amounts or dosages, in some cases, are contemplated to include dosages of about 0.1 mg/kg to about 2.0 mg/kg.

[00115] Methods of treatment herein comprise one or more administrations of anti-MICA/B antibodies in doses disclosed herein. In some embodiments, methods comprise one administration of anti-MICA/B antibodies. In some embodiments, methods comprise two administrations of anti-MICA/B antibodies. In some embodiments, methods comprise three administrations of anti-MICA/B antibodies. In some embodiments, methods comprise four administrations of anti-MICA/B antibodies. In some embodiments, methods comprise five administrations of anti-MICA/B antibodies. In some embodiments, methods comprise six administrations of anti-MICA/B antibodies. In some embodiments, one or more administrations of anti-MICA/B antibodies are administered daily. In some embodiments, one or more administrations of anti-MICA/B antibodies are administered weekly. In some embodiments, one or more administrations of anti-MICA/B antibodies are administered biweekly. In some embodiments, one or more administrations of anti-MICA/B antibodies are administered monthly. In some embodiments, one or more administrations of anti-MICA/B antibodies are administered every three months. In some embodiments, one or more administrations of anti-MICA/B antibodies are administered every six months. In some embodiments, one or more administrations of anti-MICA/B antibodies are administered yearly.

[00116] In some embodiments, the methods of treatment disclosed herein, is a monotherapy. In some embodiments, the methods of treatment disclosed herein, is a combination therapy. In some embodiments, combination therapy comprises administrations of anti-MICA/B antibodies in combination with another therapeutic agent. In some embodiments, the therapeutic agent comprises a chemotherapeutic agent. In some embodiments, the chemotherapeutic agent include, but is not limited to, cytotoxic agents, anti-metabolite agents (e.g., folate antagonists, purine analogs, pyrimidine analogs, etc.), topoisomerase inhibitors (e.g., camptothecin derivatives, anthracenedione, anthracyclines, epipodophyllotoxins, quinoline alkaloids, etc.), anti-microtubule agents (e.g., taxanes, vinca alkaloids), protein synthesis inhibitors (e.g., cephalotaxine, camptothecin derivatives, quinoline alkaloids), alkylating agents (e.g., alkyl sulfonates, ethylenimines, nitrogen mustards, nitrosoureas, platinum derivatives, triazenes, etc.), alkaloids, terpenoids, kinase inhibitors and immune

checkpoint inhibitors. In some embodiments, the anti-MICA/B antibodies disclosed herein are administered in combination with a therapeutic agent that induces an immune response. In some embodiments, the anti-MICA/B antibodies disclosed herein are administered in combination with a therapeutic agent that inhibits downregulation of an immune response. In some embodiments, inducing an immune response comprises activation or upregulating activity of NK cells. In some embodiments, inducing an immune response comprises activation or upregulating activity of T cells. In some embodiments, the immune check point inhibitor target comprises PD-1. In some embodiments, the immune check point inhibitor target comprises PD-L1. In some embodiments, the immune checkpoint inhibitor comprises Pembrolizumab, Nivolumab, Cemiplimab, AMP-224, AMP-514, PDR001, Atezolizumab, Avelumab, Durvalumab, BMS-936559, and CK-301.

Pharmaceutical Compositions

[00117] Also disclosed herein are pharmaceutical compositions comprising anti-MICA/B antibodies disclosed herein and a pharmaceutically acceptable carrier or excipient.

[00118] In some embodiments, excipients for use with the compositions disclosed herein include maleic acid, tartaric acid, lactic acid, citric acid, acetic acid, sodium bicarbonate, sodium phosphate, histidine, glycine, sodium chloride, potassium chloride, calcium chloride, zinc chloride, water, dextrose, N-methylpyrrolidone, dimethyl sulfoxide, N,N-dimethylacetamide, ethanol, propylene glycol, polyethylene glycol, diethylene glycol monoethyl ether, and surfactant polyoxyethylene-sorbitan monooleate.

[00119] In some embodiments, the compositions further comprise an additional therapeutic agent. In some embodiments, the therapeutic agent is a chemotherapeutic agent. The chemotherapeutic agents can include, among others, cytotoxic agents, anti-metabolite agents (e.g., folate antagonists, purine analogs, pyrimidine analogs, etc.), topoisomerase inhibitors (e.g., camptothecin derivatives, anthracenedione, anthracyclines, epipodophyllotoxins, quinoline alkaloids, etc.), anti-microtubule agents (e.g., taxanes, vinca alkaloids), protein synthesis inhibitors (e.g., cephalotaxine, camptothecin derivatives, quinoline alkaloids), alkylating agents (e.g., alkyl sulfonates, ethylenimines, nitrogen mustards, nitrosoureas, platinum derivatives, triazenes, etc.), alkaloids, terpenoids, and kinase inhibitors.

[00120] In some embodiments, the antibody and the therapeutic agent are in the same formulation. In some embodiments, the antibody and the therapeutic agent are in different formulation. In some embodiments, antibody described herein is used prior to the administration of the other therapeutic agent. In some embodiments, antibody described herein is used concurrently

with the administration of the other therapeutic agent. In some embodiments, antibody described herein is used subsequent to the administration of the other therapeutic agent.

[00121] Pharmaceutical formulations, in some embodiments, are made to be compatible with a particular local, regional or systemic administration or delivery route. Thus, pharmaceutical formulations include carriers, diluents, or excipients suitable for administration by particular routes. Specific non-limiting examples of routes of administration for compositions herein are parenteral, e.g., intravenous, intra-arterial, intradermal, intramuscular, subcutaneous, intra-pleural, transdermal (topical), transmucosal, intra-cranial, intra-spinal, intra-ocular, rectal, oral (alimentary), mucosal administration, and any other formulation suitable for the treatment method or administration protocol.

[00122] In some embodiments, solutions or suspensions used for parenteral application include: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfate; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. In some embodiments, pH is adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

[00123] Pharmaceutical formulations for injection include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.), or phosphate buffered saline (PBS). In some embodiments, the carrier is a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), or suitable mixtures thereof. Fluidity is maintained, in some embodiments, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion, and by the use of surfactants. Antibacterial and antifungal agents include, for example, parabens, chlorobutanol, phenol, ascorbic acid, and thimerosal. Isotonic agents, for example, sugars; polyalcohols such as mannitol or sorbitol; or sodium chloride, in some embodiments, are included in the composition. In some cases, also included is an agent which delays absorption, in some embodiments, for example, aluminum monostearate or gelatin prolongs absorption of injectable compositions.

[00124] In some embodiments, sterile injectable formulations are prepared by incorporating the active composition in the required amount in an appropriate solvent with one or a combination of above ingredients. Generally, dispersions are prepared by incorporating the active composition

into a sterile vehicle containing a basic dispersion medium and any other ingredient. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation include, for example, vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously prepared solution thereof.

[00125] For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. In some embodiments, transmucosal administration is accomplished through the use of nasal sprays, inhalation devices (e.g., aspirators) or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, creams or patches.

[00126] In some embodiments, the pharmaceutical formulations are prepared with carriers that protect against rapid elimination from the body, such as a controlled release formulation or a time delay material such as glyceryl monostearate or glyceryl stearate. The formulations, in some embodiments, are also delivered using articles of manufacture such as implants and microencapsulated delivery systems to achieve local, regional or systemic delivery or controlled or sustained release.

EXAMPLES

[00127] The following examples are given for the purpose of illustrating various embodiments of the invention and are not meant to limit the present invention in any fashion. The present examples, along with the methods described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Changes therein and other uses which are encompassed within the spirit of the invention as defined by the scope of the claims will occur to those skilled in the art.

Example 1. Antibody Binding Kinetics Measurement

[00128] Affinity kinetics was determined on a ForteBio Octet Red96 analyzer. Briefly, anti-MICA/B mAb (30μg/ml) was captured on Dip and Read™ Anti-mouse IgG Fc Capture (AMC) Biosensors (ForteBio) at room temperature in an assay buffer of PBS + 0.1% BSA + 0.02% Tween-20 (pH 7.2). Sensors were washed in assay buffer and then incubated with purified 6xHis-MICA*08 or 6xHis-MICA*04 proteins (100nM), in 2-fold dilution series for 5 minutes in assay buffer to determine association kinetics of the antibody with the protein antigen. Sensors were then incubated in assay buffer for 10 minutes to determine dissociation kinetics. The resulting kinetics

parameters were calculated with ForteBio analysis suite 8.0 using a 1:1 model. Results for these assays are shown in Table 2.

Table 2. Kinetic measurements of anti-MICA/B antibodies to MICA antigen by BioLayer Interferometry.

Antibody	KD (M)	kon(1/Ms)	kdis(1/s)
3F9.E4	1.18E-09	3.83E+05	4.21E-04
16F10.C12	6.45E-09	9.33E+04	5.48E-04

Example 2. Antibody Binding to MICA/B alleles

[00129] Recombinant MICA*01, MICA*02, MICA*04, MICA*08, MICA*09, and MICB proteins were diluted to 1μg/ml in 50mM sodium carbonate buffer, pH 9.6, and coated onto high binding 96-well microplates (Corning #9018), 100ng in 100ul per well. The following morning, coated ELISA plates were washed three times with TBS-Tween-20, pH 7.4 and then blocked in SuperBlock T20 Blocking Buffer (Pierce #37536). After blocking, ELISA plates were washed once with TBS-T and incubated with serially diluted anti-MICA antibody (0-1μg/ml) for approximately two hours at room temperature. Following the incubation, ELISA plates were washed three times with TBS-T and then incubated with Goat anti-Mouse IgG (H+L)-HRP conjugate (ThermoFisher Scientific #626520) for 45 minutes at room temperature with shaking (~400rpm). After the incubation, ELISA plates were washed three times with TBS-T and incubated with Super Sensitive Liquid Substrate TMB (Sigma #T4444), 100ul per well, until color development was sufficient. The reaction was stopped with 1N sulfuric acid, 100ul per well. Optical density (OD) values were measured at 450nm using a microplate reader. The results of this assay are shown in **FIG. 1A-FIG. 1B**.

Example 3. Antibody Binding to cell surface MICA

[00130] Mouse prostate adenocarcinoma TRAMP-C2 cells (TC2) (ATCC, Manassas, VA) were used to generate a stable cell line expressing MICA*08 allele (TC2-MICA-08). Binding of anti-MICA antibody to TC2-MICA-08 was analyzed by flow cytometry. Briefly, cells were first stained with LIVE/DEAD Near IR Stain (Thermo) for 30min at 4°C, and then washed once by centrifugation with FACS Buffer (1mM EDTA, 25mM HEPES, 2% FBS in 1X PBS). About 2-3x10^5 TC2-MICA-08 cells were incubated with 100μl of FACS Buffer containing 500ng anti-MICA antibody at 4°C for 30min, followed by incubation with 100μl 2μg/ml PE conjugated goat-anti-mouse IgG (Biolegend, San Diego, CA) secondary Ab at 4°C for 30min. Cells were then washed once and cell pellet resuspended with FACS Buffer for FACS analysis gated on live cells. Significantly higher PE fluorescence signal was observed with TC2-MICA-08 cells compared to parental TC2 cells indicated binding of anti-MICA mAb to surface expressed MICA. Result for this assay is shown in **FIG. 2**.

Example 4. Antibody inhibits MICA shedding from PLC/PRF/5 cells

[00131] $4x10^4$ PLC/PRF/5 cells (Hepatocellular Carcinoma) (ATCC, Manassas, VA) were plated in 96-well plate and incubated at 37°C overnight. Cells were then treated with 100µl Complete Media (MEM + 10% FBS, Thermo, Grand Island, NY) containing anti-MICA antibody that binds to MICA α3 domain and negative control antibodies, respectively, and incubated at 37°C for another day. Cell supernatants containing shed MICA were used to determine the level of soluble MICA by ELISA. Briefly, 96-well plate was coated with 100µl 2µg/ml anti-human MICA/B (clone BAMO1, MBL, Japan) overnight at 4°C. Plate was blocked and then incubated with cell supernatants and MICA standards for 2 hours. After incubation, plates were washed and followed by 1 hour incubation with 1µg/ml proprietary anti-human MICA/MICB mAb, clone 10E9 conjugated with biotin. Next, 100µl HRP conjugated streptavidin (HRP-SA) (R&D Systems, Minneapolis, MN) was added to wells and incubated for 30min. Samples were developed with TMB for 4min, stopped with 1N sulfuric acid and detected with absorbance at 450nm. Soluble MICA level was interpolated from standard curve. Result for this assay is shown in **FIG. 3**.

Example 5. Antibody enhances NK-92 cells mediated cytotoxicity to PLC/PRF/5 cells

[00132] PLC/PRF/5 (Target) cells were suspended in RPMI-1640 with 10% FBS, and plated into 96-well flat bottom plates (Costar) at 6000 cells/well. Cells were then incubated with anti-MICA antibody (10µg/ml) that binds to MICA α3 domain for 24 hours before being labeled with calcein AM (1µM) for 3 hours at 37°C, 5% CO_2. Wells were washed, and NK-92 cells (Effector) suspended in RPMI-1640 with 10% FBS were then added to wells at various Effector-to-Target (E:T) ratios as indicated and co-cultured with target cells for 4 hours. At the end of the cultures, the supernatant was removed, replaced with PBS, and the calcein AM signal was measured using a VICTOR Multilabel plate reader (Perkin Elmer). An isotype matched nonreactive immunoglobulin (R&D) antibody was used as a control. Results for this assay are shown in **FIG. 4A-FIG.4B**.

Example 6. Efficacy of 3F9.E4 in tumor therapy *in vivo* (survival) and NKG2S expression by tumor-infiltrating lymphocytes in tumor-bearing mice

[00133] MICA transgenic mice (MICAgen) were inoculated with 10^4 B16F10-MICA*01 cells (B16 transfectant) and, upon day 11, when tumors reached the desired threshold size, mice were treated with 3F9.E4 or isotype control (arrows indicate days of injection) (Log-rank test). Results are shown in **FIG. 5**.

[00134] Mice were sacrificed when reaching a high tumor load and tumor-infiltrating lymphocytes analyzed for NKG2D expression (SFI) by NK cells, CD8 αβ T cells, and γδ T cells. NKG2D expression strength (SFI) of NKG2D-expressing cells are shown in **FIG. 6A-FIG. 6C**. Each symbol represents analyses of an individual mouse. (One-way ANOVA + Tukey's multiple comparisons test).

Example 7. MICA expression by B16 transfectant tumors *ex vivo* and detection of soluble MICA in sera of tumor-bearing mice

[00135] MICA transgenic mice (MICAgen) were inoculated with 10^4 B16F10-MICA*01 cells (B16 transfectant) and, upon day 11, when tumors reached the desired threshold size, mice were treated with 3F9.E4 or BAMO3 or isotype control. Mice were sacrificed when reaching a high tumor load and isolated single tumor cells analyzed for MICA expression with mAb AMO1 staining (One-way ANOVA + Tukey's multiple comparisons test). AMO1 binds to the a1a2-domain of MICA (≠ BAMO3 and 3F9). Each symbol represents analysis of an individual mouse. Results are shown in **FIG. 7B**. Sera was also analyzed for sMICA using AMO1/BAMO1 sandwich ELISA. Each symbol represents an individual mouse (Unpaired t-test). Results are shown in **FIG. 7A**.

Example 8. Epitope binning

[00136] MICA *04-His protein (30 μg/ml) was immobilized onto Ni-NTA (FortrBio, # 18-5101) biosensor tips for a biolayer interferometry instrument (Octet Red, ForteBio) for 300 s. The baseline signal was measured again for 60 s before biosensor tips were immersed into wells containing 1mM or 0.5mM of primary antibody for 300 s. Following this process, biosensors were immersed into wells containing 100 nM or 50 nM of a second mAb for 300 s. Percent binding of a second mAbs in the presence of the first mAb was determined by comparing the maximal signal of the second mAb after the first mAb was added to the maximum signal of the second mAb alone. mAbs were considered noncompeting if maximum binding of the second mAb was ≥66% of its uncompeted binding. A level between 33% and 66% of its uncompeted binding was considered intermediate competition, and ≤33% was considered competing. Results for this assay are shown in **FIG. 8A-FIG.8C**.

[00137] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those

skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments described herein may be employed. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A monoclonal antibody or an antigen-binding fragment thereof, comprising a light chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24.

2. The monoclonal antibody of claim 1, further comprising a heavy chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26.

3. A monoclonal antibody or an antigen-binding fragment thereof, comprising a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19.

4. The monoclonal antibody of claim 3, wherein the light chain variable domain (VL) comprises an amino acid sequence at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19.

5. The monoclonal antibody of claim 3, further comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20.

6. The monoclonal antibody of claim 3, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 7 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 8.

7. The monoclonal antibody of claim 3, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 15 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 16.

8. The monoclonal antibody of claim 3, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 19 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 20.

9. The monoclonal antibody of claim 3, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain comprising an amino acid sequence at least 80%

identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24.

10. The monoclonal antibody of claim 3, wherein the monoclonal antibody or antigen-binding fragment thereof comprises heavy chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26.

11. The monoclonal antibody of claim 3, wherein the monoclonal antibody or antigen-binding fragment thereof specifically binds to a MICA protein, a MICB protein, or both MICA and MICB protein.

12. The monoclonal antibody of claim 3, wherein the monoclonal antibody or antigen-binding fragment thereof binds to an alpha-3 domain of a MICA protein, a MICB protein, or both MICA and MICB protein.

13. The monoclonal antibody of claim 11, wherein the MICA protein is membrane-bound MICA protein, soluble MICA protein, or both.

14. The monoclonal antibody of claim 11, wherein the MICB protein is membrane-bound MICB protein, soluble MICB protein, or both.

15. The monoclonal antibody of claim 3wherein the monoclonal antibody or antigen-binding fragment thereof is selected from a whole immunoglobulin, an scFv, a Fab, a $F(ab')_2$, or a disulfide linked Fv.

16. The monoclonal antibody of claim 3, wherein the monoclonal antibody or antigen-binding fragment thereof is an IgG or IgM.

17. The monoclonal antibody of claim 3, wherein the monoclonal antibody or antigen-binding fragment thereof is humanized or chimeric.

18. A monoclonal antibody or an antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20.

19. The monoclonal antibody of claim 18, wherein the heavy chain variable domain (VH) comprises an amino acid sequence at least 90%, at least 95%, at least 99%, or 100% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20.

20. The monoclonal antibody of claim 18, further comprising a light chain variable domain (VL) comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 99%, or

100% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19.

21. The monoclonal antibody of claim 18, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 8 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 7.

22. The monoclonal antibody of claim 18, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 16 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 15.

23. The monoclonal antibody of claim 18, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 20 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 19.

24. The monoclonal antibody of claim 18, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26.

25. The monoclonal antibody of claim 18, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24.

26. The monoclonal antibody of claim 18, wherein the monoclonal antibody or antigen-binding fragment thereof specifically binds to a MICA protein, a MICB protein, or both MICA and MICB protein.

27. The monoclonal antibody of claim 18, wherein the monoclonal antibody or antigen-binding fragment thereof binds to an alpha-3 domain of a MICA protein, a MICB protein, or both MICA and MICB protein.

28. The monoclonal antibody of claim 26, wherein the MICA protein is membrane-bound MICA protein, soluble MICA protein, or both.

29. The monoclonal antibody of claim 26, wherein the MICB protein is membrane-bound MICB protein, soluble MICB protein, or both.

30. The monoclonal antibody of claim 18, wherein the monoclonal antibody or antigen-binding fragment thereof is selected from a whole immunoglobulin, an scFv, a Fab, a $F(ab')_2$, or a disulfide linked Fv.

31. The monoclonal antibody of claim 18, wherein the monoclonal antibody or antigen-binding fragment thereof is an IgG or IgM.

32. The monoclonal antibody of claim 18, wherein the monoclonal antibody or antigen-binding fragment thereof is humanized or chimeric.

33. A monoclonal antibody or an antigen-binding fragment thereof, comprising a light chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY.

34. The monoclonal antibody of claim 33, wherein the light chain complementarity determining region (CDR) has an amino acid sequence at least 90%, at least 95%, at least 99%, or 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY.

35. The monoclonal antibody of claim 33, further comprising a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 80%, at least 90%, at least 95%, at least 99%, or 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18.

36. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 1, SEQ ID NO: 9, or SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NOS: SEQ ID NO: 2, or SEQ ID NO: 10, a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 3, or SEQ ID NO: 11, a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 4, or SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino

acid sequence at least 80% identical to one of SEQ ID NO: 5, SEQ ID NO: 13, or SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 6, or SEQ ID NO: 14.

37. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 1, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3.

38. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 9, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 10, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 11.

39. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3.

40. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 5, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6.

41. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 13, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 14.

42. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6.

43. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19.

44. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO:16, or SEQ ID NO: 20.

45. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19; and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20.

46. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 7 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 8.

47. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 15 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 16.

48. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 19 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 20.

49. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24.

50. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof comprises heavy chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26.

51. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof specifically binds to a MICA protein, a MICB protein, or both MICA and MICB protein.

52. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof binds to an alpha-3 domain of a MICA protein, a MICB protein, or both MICA and MICB protein.

53. The monoclonal antibody of claim 51, wherein the MICA protein is membrane-bound MICA protein, soluble MICA protein, or both.

54. The monoclonal antibody of claim 51, wherein the MICB protein is membrane-bound MICB protein, soluble MICB protein, or both.

55. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof is selected from a whole immunoglobulin, an scFv, a Fab, a $F(ab')_2$, or a disulfide linked Fv.

56. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof is an IgG or IgM.

57. The monoclonal antibody of claim 33, wherein the monoclonal antibody or antigen-binding fragment thereof is humanized or chimeric.

58. A monoclonal antibody or an antigen-binding fragment thereof, comprising a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY.

59. The monoclonal antibody of claim 58, wherein the heavy chain complementarity determining region (CDR) has an amino acid sequence at least 90%, at least 95%, at least 99%, or 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY.

60. The monoclonal antibody of claim 58, further comprising a light chain complementarity determining region (CDR) having an amino acid sequence at least 80%, at least 90%, at least 95%, at least 99%, or 100% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17.

61. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 4, or SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 5, SEQ ID NO: 13, or SEQ ID NO: 18, a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 6, or SEQ ID NO: 14, a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 1, SEQ ID NO: 9, or SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 2, or SEQ ID NO: 10, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 3, or SEQ ID NO: 11.

62. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 5, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6.

63. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80%

identical to SEQ ID NO: 13, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 14.

64. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6.

65. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 1, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3.

66. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 9, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 10, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 11.

67. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3.

68. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO:16, or SEQ ID NO:20.

69. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid

sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO:19.

70. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO:16, or SEQ ID NO:20; and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO:19.

71. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8 and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7.

72. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 16; and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 15.

73. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 20; and a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 19.

74. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26.

75. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24.

76. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof specifically binds to a MICA protein, a MICB protein, or both MICA and MICB protein.

77. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof binds to an alpha-3 domain of a MICA protein, a MICB protein, or both MICA and MICB protein.

78. The monoclonal antibody of claim 76, wherein the MICA protein is membrane-bound MICA protein, soluble MICA protein, or both.

79. The monoclonal antibody of claim 76, wherein the MICB protein is membrane-bound MICB protein, soluble MICB protein, or both.

80. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof is selected from a whole immunoglobulin, an scFv, a Fab, a $F(ab')_2$, or a disulfide linked Fv.

81. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof is an IgG or IgM.

82. The monoclonal antibody of claim 58, wherein the monoclonal antibody or antigen-binding fragment thereof is humanized or chimeric.

83. A pharmaceutical composition comprising: a monoclonal antibody or an antigen-binding fragment thereof according to any one of claims 1 to 82; and a pharmaceutically acceptable carrier or excipient.

84. A method of treating cancer in an individual in need thereof, comprising administering to the individual an effective amount of a monoclonal antibody or an antigen-binding fragment thereof comprising a light chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY.

85. The method of claim 84, wherein the monoclonal antibody or an antigen-binding fragment thereof further comprises a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18, wherein the monoclonal antibody does not have at least

one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY.

86. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 1, SEQ ID NO: 9, or SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NOS: SEQ ID NO: 2, or SEQ ID NO: 10, a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 3, or SEQ ID NO: 11, a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 4, or SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 5, SEQ ID NO: 13, or SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 6, or SEQ ID NO: 14.

87. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 1, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3.

88. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 9, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 10, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 11.

89. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 17 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 1, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3.

90. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 5, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6.

91. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 13, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 14.

92. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6.

93. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19.

94. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO:16, or SEQ ID NO: 20.

95. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19; and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20.

96. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 7 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 8.

97. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 15 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 16.

98. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 19 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 20.

99. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24.

100. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26.

101. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof specifically binds to a MICA protein, a MICB protein, or both MICA and MICB protein.

102. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof binds to an alpha-3 domain of a MICA protein, a MICB protein, or both MICA and MICB protein.

103. The method of claim 101, wherein the MICA protein is membrane-bound MICA protein, soluble MICA protein, or both.

104. The method of claim 101, wherein the MICB protein is membrane-bound MICB protein, soluble MICB protein, or both.

105. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof is selected from a whole immunoglobulin, an scFv, a Fab, a $F(ab')_2$, or a disulfide linked Fv.

106. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof is an IgG or IgM.

107. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof is humanized or chimeric.

108. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof reduces level of soluble MICA protein, soluble MICB protein, or both.

109. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof reduces shedding of soluble MICA protein, soluble MICB protein, or both.

110. The method of claim 84, wherein the monoclonal antibody or antigen-binding fragment thereof inhibits shedding of soluble MICA protein, soluble MICB protein, or both.

111. The method of claim 84, wherein the cancer is hepatocellular carcinoma.

112. A method of reducing level of soluble MICA protein, soluble MICB protein, or both in an individual in need thereof, comprising administering to the individual an effective amount of a monoclonal antibody or an antigen-binding fragment thereof comprising a light chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 1-3, 9-11, and 17, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY.

113. The method of claim 112, wherein the monoclonal antibody or an antigen-binding fragment thereof further comprises a heavy chain complementarity determining region (CDR) having an amino acid sequence at least 80% identical to at least one of the amino acid sequences set forth as SEQ ID NOS: 4-6, 12-14, and 18, wherein the monoclonal antibody does not have at least one CDR selected from the list comprising: SASQGISNYLN, TSLLHSG, QQYSKFPRT, GYTFTNYGMN, INTYTGEPTYADDFKG, and NYGNYLFDY.

114. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 1, SEQ ID NO: 9, or SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NOS: SEQ ID NO: 2, or SEQ ID NO: 10, a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 3, or SEQ ID NO: 11, a heavy chain complementarity determining

region 1 (CDR1) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 4, or SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 5, SEQ ID NO: 13, or SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to one of SEQ ID NO: 6, or SEQ ID NO: 14.

115. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 1, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3.

116. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 9, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 10, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 11.

117. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a light chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 17, a light chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 2, and a light chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 3.

118. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 5, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6.

119. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 12, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80%

identical to SEQ ID NO: 13, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 14.

120. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof comprises at least one of a heavy chain complementarity determining region 1 (CDR1) having an amino acid sequence at least 80% identical to SEQ ID NO: 4, a heavy chain complementarity determining region 2 (CDR2) having an amino acid sequence at least 80% identical to SEQ ID NO: 18, and a heavy chain complementarity determining region 3 (CDR3) having an amino acid sequence at least 80% identical to SEQ ID NO: 6.

121. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, SEQ ID NO: 19.

122. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO:16, or SEQ ID NO: 20.

123. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 7, SEQ ID NO: 15, or SEQ ID NO: 19; and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 8, SEQ ID NO: 16, or SEQ ID NO: 20.

124. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 7 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 8.

125. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 15 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 16.

126. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain variable domain (VL) comprising an amino acid sequence

at least 80% identical to SEQ ID NO: 19 and a heavy chain variable domain (VH) comprising an amino acid sequence at least 80% identical to SEQ ID NO: 20.

127. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a light chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 21, SEQ ID NO: 23, or SEQ ID NO: 24.

128. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino acid sequence at least 80% identical to an amino acid sequence set forth as SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 26.

129. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof specifically binds to a MICA protein, a MICB protein, or both MICA and MICB protein.

130. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof binds to an alpha-3 domain of a MICA protein, a MICB protein, or both MICA and MICB protein.

131. The method of claim 129, wherein the MICA protein is membrane-bound MICA protein, soluble MICA protein, or both.

132. The method of claim 129, wherein the MICB protein is membrane-bound MICB protein, soluble MICB protein, or both.

133. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof is selected from a whole immunoglobulin, an scFv, a Fab, a $F(ab')_2$, or a disulfide linked Fv.

134. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof is an IgG or IgM.

135. The method of claim 112, wherein the monoclonal antibody or fragment thereof is humanized or chimeric.

136. The method of claim 112, wherein the monoclonal antibody or antigen-binding fragment thereof reduces or inhibits shedding of soluble MICA protein, soluble MICB protein, or both, thereby reducing level of soluble MICA protein, soluble MICB protein, or both in the individual.

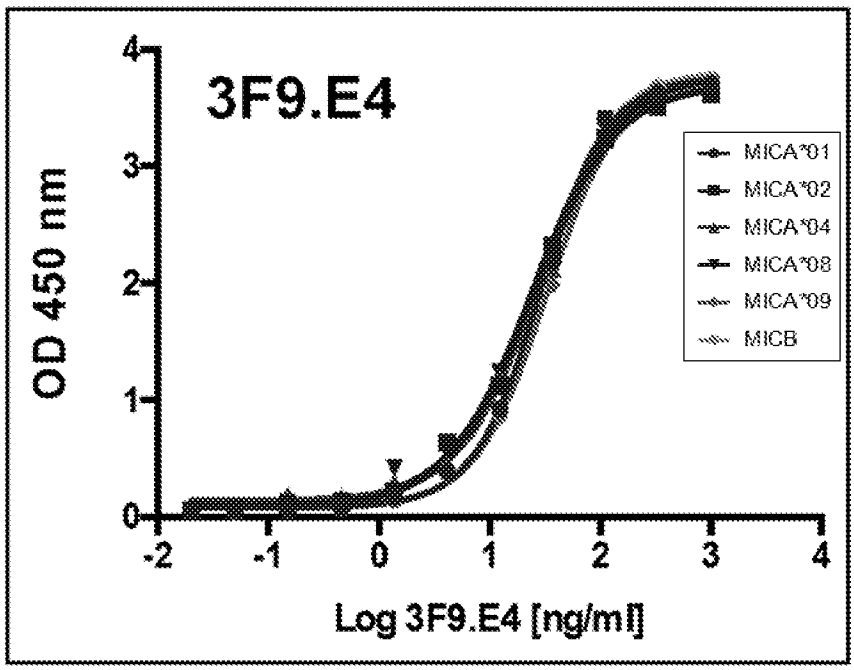
137. The method of claim 112, wherein the individual has a cancer characterized by elevated levels of soluble MICA protein, soluble MICB protein, or both.

138. The method of claim 137, wherein the cancer is hepatocellular carcinoma.

139. A monoclonal antibody or an antigen-binding fragment thereof that competitively bind to MICA/B with an antibody comprising a light chain variable domain (VL) having an amino acid sequence at least about 80% identical to an amino acid sequence set forth as SEQ ID NO: 27.

140. A monoclonal antibody or an antigen-binding fragment thereof that competitively bind to MICA/B with an antibody comprising a heavy chain variable domain (VH) having an amino acid sequence at least about 80% identical to an amino acid sequence set forth as SEQ ID NO: 28.

FIG. 1A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Log 3F9.E4 [ng/ml]
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MICA*02
MICA*04
MICA*08
MICA*09
MICB

FIG. 1B

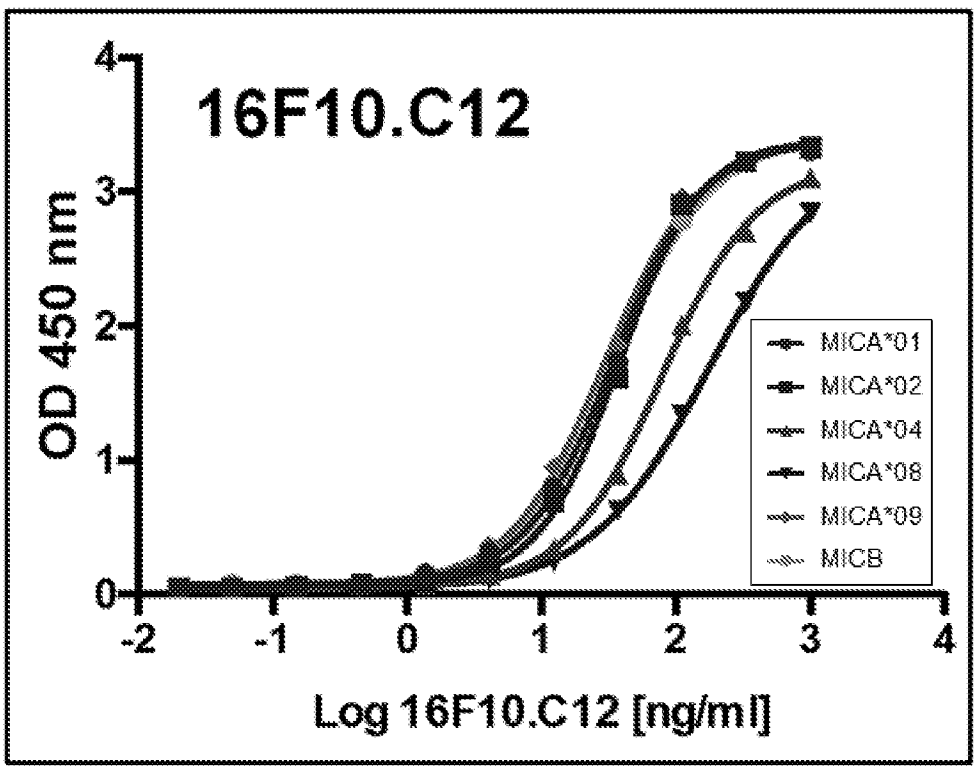

16F10.C12
OD 450 nm
Log 16F10.C12 [ng/ml]
MICA*01
MICA*02
MICA*04
MICA*08
MICA*09
MICB

FIG. 2

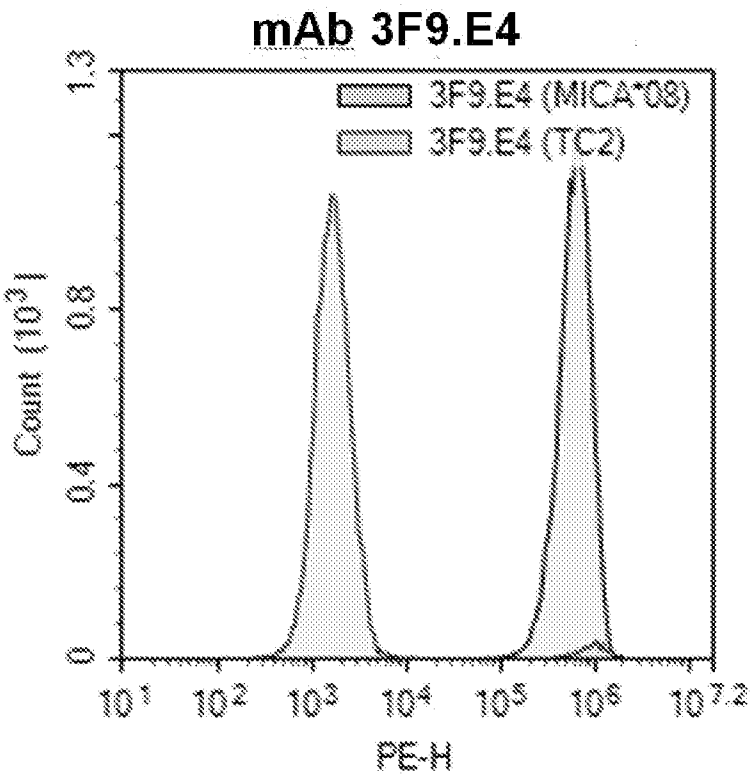

mAb 3F9.E4
3F9.E4 (MICA*08)
3F9.E4 (TC2)
Count (10^3)
1.3
0.8
0.4
0
10^1
10^2
10^3
10^4
10^5
10^6
$10^{7.2}$
PE-H

FIG. 3

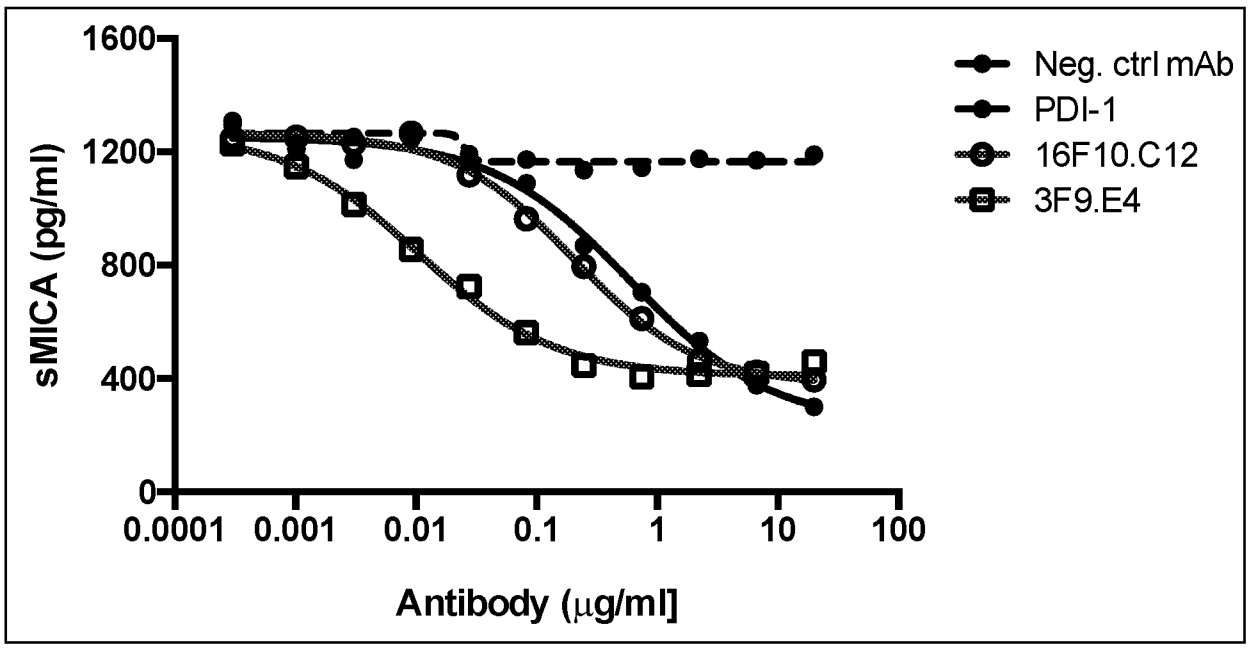

1600
1200
800
400
0
sMICA (pg/ml)
0.0001
0.001
0.01
0.1
1
10
100
Antibody (μg/ml]
Neg. ctrl mAb
PDI-1
16F10.C12
3F9.E4

FIG. 4A

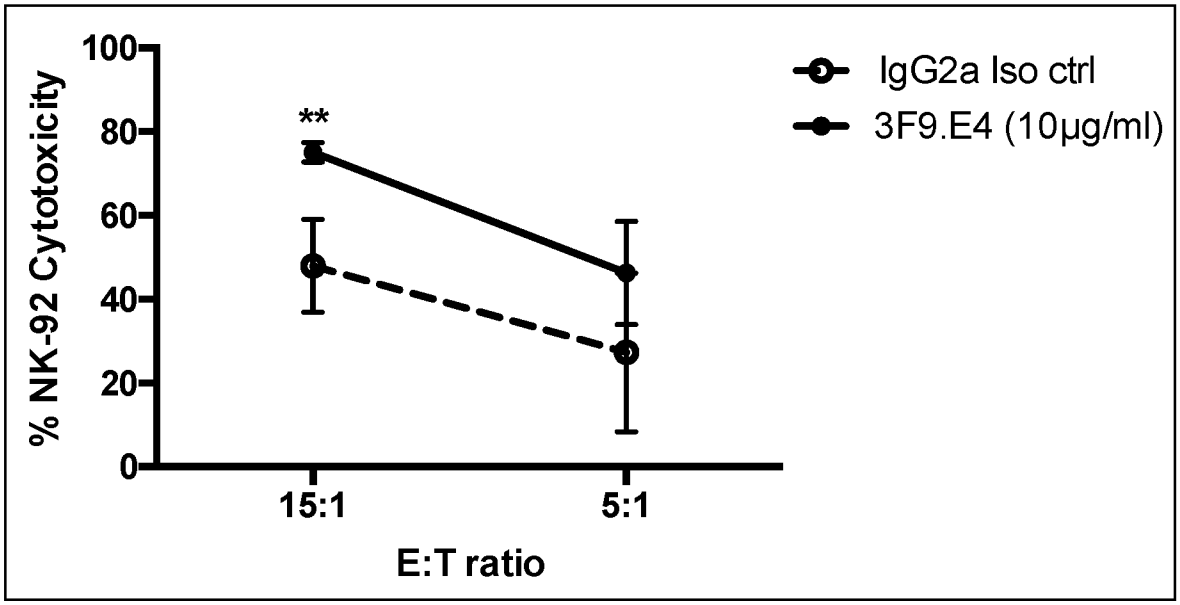

100
80
60
40
20
0
% NK-92 Cytotoxicity
**
15:1
5:1
E:T ratio
IgG2a Iso ctrl
3F9.E4 (10µg/ml)

FIG. 4B

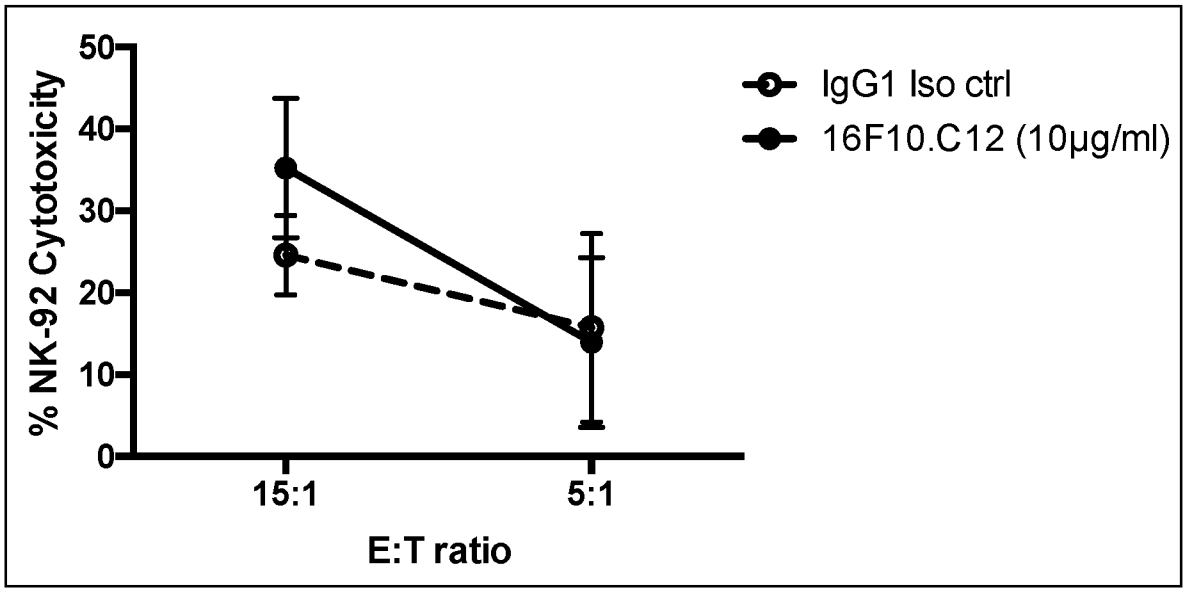

50
40
30
20
10
0
% NK-92 Cytotoxicity
15:1
5:1
E:T ratio
IgG1 Iso ctrl
16F10.C12 (10µg/ml)

FIG. 5

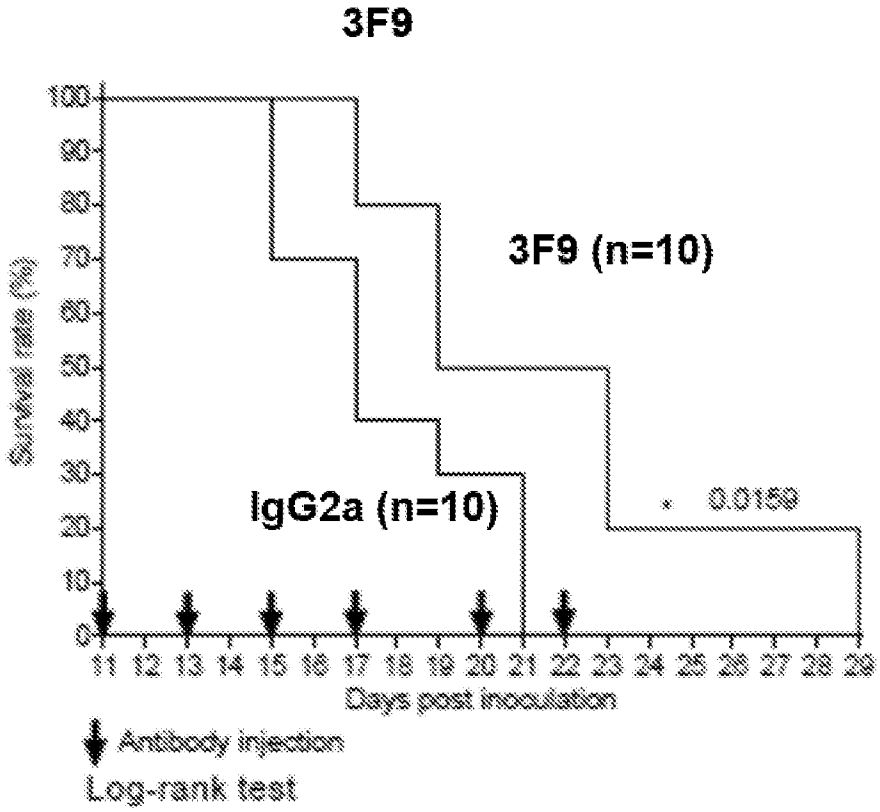

3F9
Survival rate (%)
100
90
80
70
60
50
40
30
20
10
0
3F9 (n=10)
IgG2a (n=10)
* 0.0159
11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
Days post inoculation
Antibody injection
Log-rank test

FIG. 6A

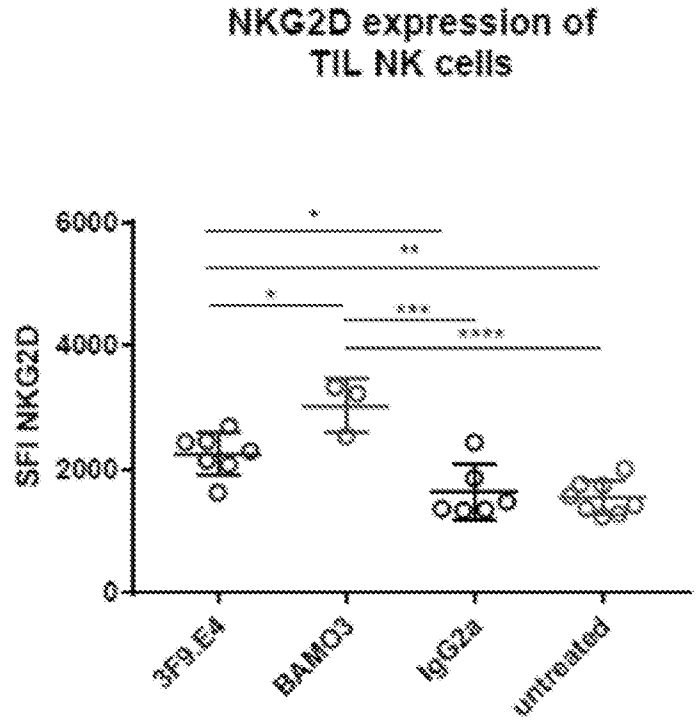

NKG2D expression of
TIL NK cells
SFI NKG2D
6000
4000
2000
0
*
**
*
***
****
3F9.E4
BAM03
IgG2a
untreated

FIG. 6B

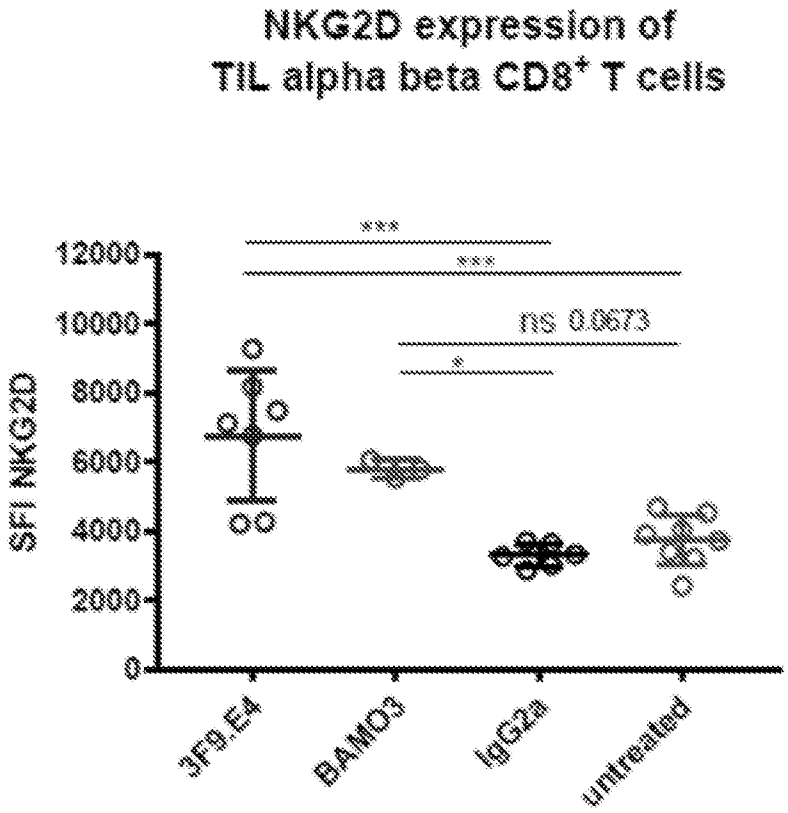

NKG2D expression of
TIL alpha beta CD8+ T cells
SFI NKG2D
12000
10000
8000
6000
4000
2000
0
***
***
ns 0.0673
*
3F9.E4
BAMO3
IgG2a
untreated

FIG. 6C

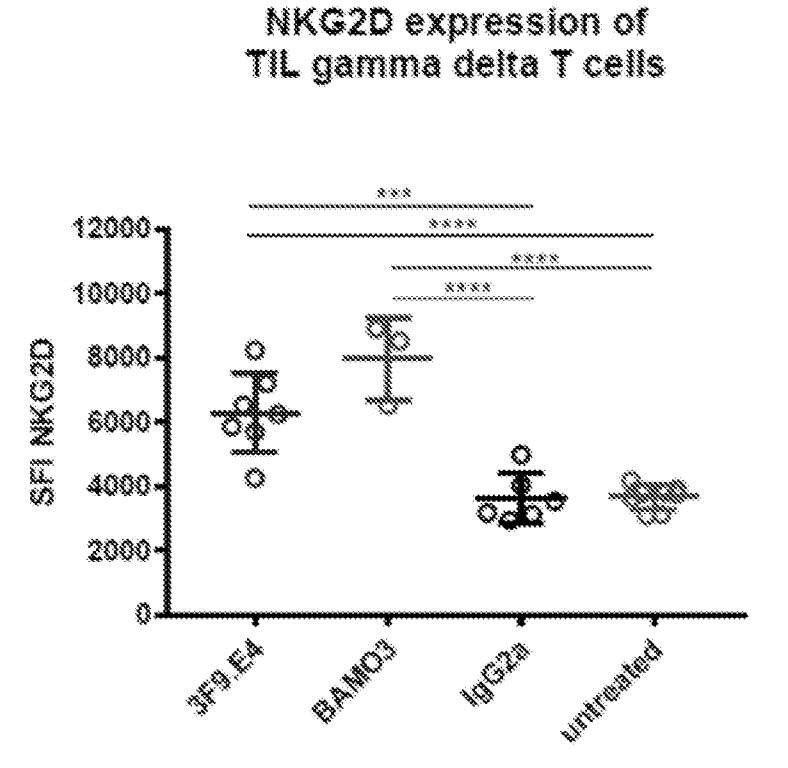

NKG2D expression of
TIL gamma delta T cells
SFI NKG2D
12000
10000
8000
6000
4000
2000
0
***
****
****
****
3F9.E4
BAMO3
IgG2a
untreated

FIG. 7A

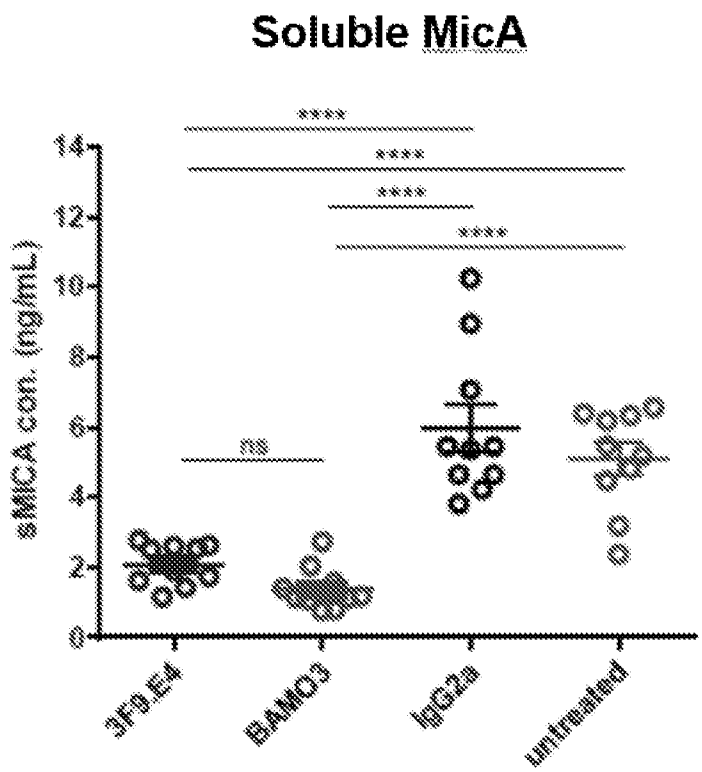
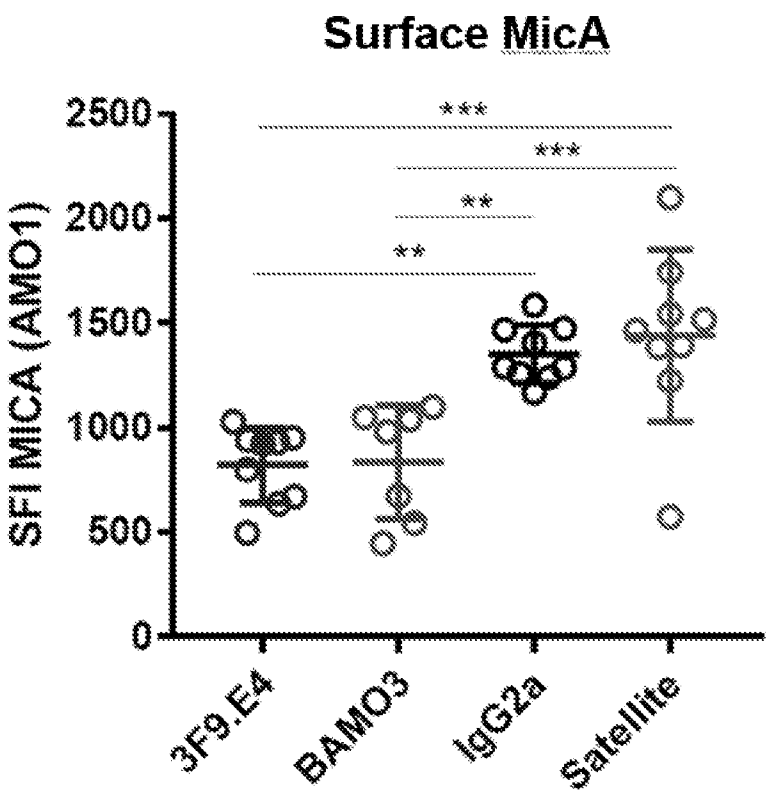

Soluble MicA
sMICA con. (ng/mL)
0
2
4
6
8
10
12
14
****
****
****
****
ns
3F9.E4
BAMO3
IgG2a
Untreated

FIG. 7B


Surface MicA
SFI MICA (AMO1)
0
500
1000
1500
2000
2500
***
***
**
**
3F9.E4
BAMO3
IgG2a
Satellite

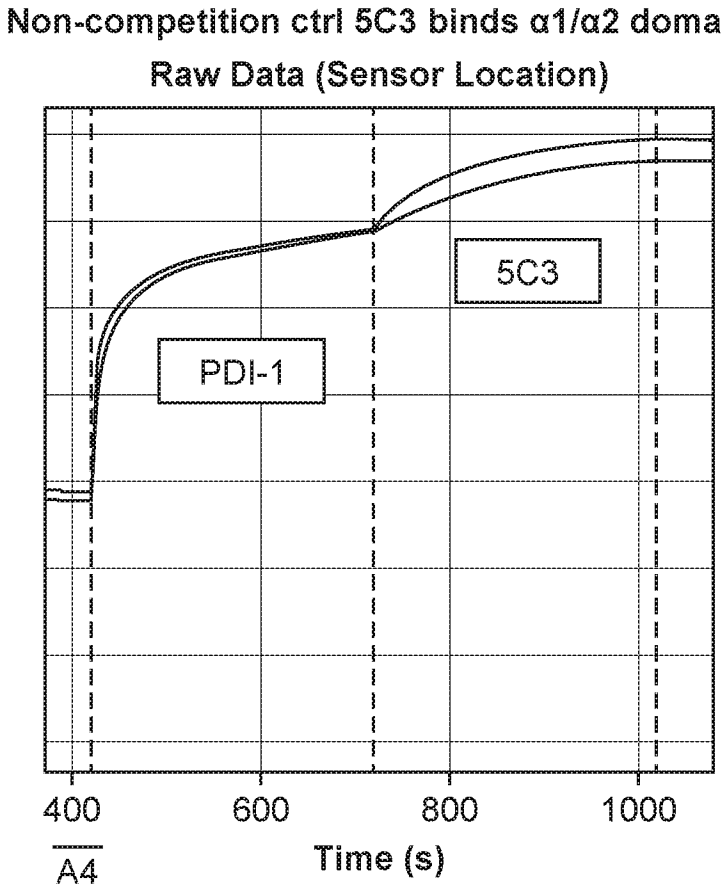

Non-competition ctrl 5C3 binds α1/α2 domain
Raw Data (Sensor Location)
5C3
PDI-1
400
600
800
1000
A4
Time (s)

FIG. 8A

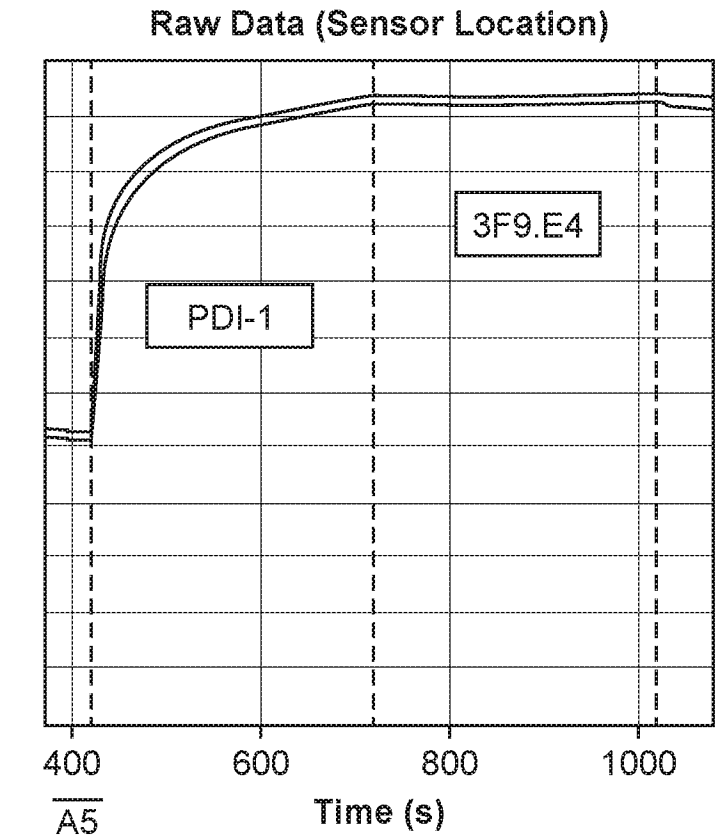

Raw Data (Sensor Location)
3F9.E4
PDI-1
400
600
800
1000
A5
Time (s)

FIG. 8B

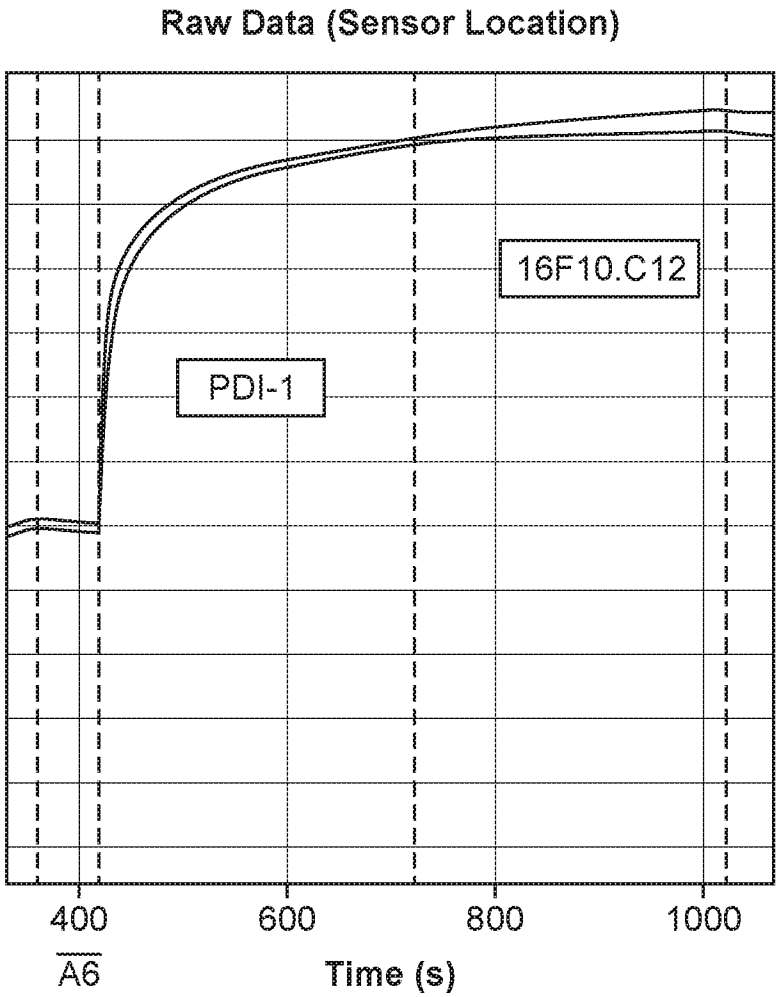

Raw Data (Sensor Location)
16F10.C12
PDI-1
400
600
800
1000
A6
Time (s)

FIG. 8C

SEQUENCE LISTING

<110> PDI THERAPEUTICS, INC.

<120> ANTI-MICA/B ANTIBODIES THAT BLOCK MICA/B SHEDDING AND METHODS OF
USE

<130> 53620-702.601

<140> PCT/US2019/044234
<141> 2019-07-30

<150> 62/712,608
<151> 2018-07-31

<160> 34

<170> PatentIn version 3.5

<210> 1
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 1
Arg Ser Ser Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Tyr
1 5 10 15

<210> 2
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
peptide

<400> 2
Arg Met Ser Asn Leu Ala Ser

1 5

<210> 3
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 3
Met Gln His Leu Glu Tyr Pro Phe Thr
1 5

<210> 4
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 4
Gly Phe Thr Phe Ser Asn Tyr Ala Met Ser
1 5 10

<210> 5
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 5
Tyr Ile Ser Pro Gly Gly Asp Tyr Ile Tyr Tyr Ala Asp Thr Val Lys
1 5 10 15

Gly

<210> 6
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 6
Asp Arg Arg His Tyr Gly Ser Tyr Ala Met Asp Tyr
1 5 10

<210> 7
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 7
Asp Ile Val Met Thr Gln Ala Ala Pro Ser Val Pro Val Thr Pro Gly
1 5 10 15

Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile

65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His
85 90 95

Leu Glu Tyr Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 8
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 8
Glu Val Gln Leu Gln Glu Ser Gly Glu Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Tyr Ile Ser Pro Gly Gly Asp Tyr Ile Tyr Tyr Ala Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Arg Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Thr Thr Asp Arg Arg His Tyr Gly Ser Tyr Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Ile Ser Val Thr Val Ser Ser
115 120

<210> 9
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 9
Thr Ala Ser Ser Ser Val Ser Ser Asn Tyr Leu His
1 5 10

<210> 10
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 10
Thr Thr Ser Asn Leu Ala Ser
1 5

<210> 11
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 11
His Gln Phe His Arg Ser Pro Phe Thr
1 5

<210> 12
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 12
Gly Phe Ser Leu Thr Ala Phe Gly Val Asn
1 5 10

<210> 13
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 13
Met Ile Trp Gly Asp Gly Asn Thr Asp Tyr Asn Ser Thr Leu Arg Ser
1 5 10 15

<210> 14
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 14
Glu Thr Tyr Tyr Gly Asn Tyr Ala Gly Leu Gly Tyr
1 5 10

<210> 15
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 15
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Ile Gly
1 5 10 15

Glu Arg Val Thr Met Thr Cys Thr Ala Ser Ser Ser Val Ser Ser Asn
20 25 30

Tyr Leu His Trp Tyr Gln Gln Lys Pro Arg Ser Ser Pro Lys Leu Trp
35 40 45

Ile Tyr Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Thr Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Ser Met Glu
65 70 75 80

Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Phe His Arg Ser Pro
85 90 95

Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 16
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 16
Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ala Phe
20 25 30

Gly Val Asn Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Met Ile Trp Gly Asp Gly Asn Thr Asp Tyr Asn Ser Thr Leu Arg
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65 70 75 80

Lys Leu Asn Ser Leu Gln Thr Asp Asp Thr Ala Arg Tyr Phe Cys Ala
85 90 95

Arg Glu Thr Tyr Tyr Gly Asn Tyr Ala Gly Leu Gly Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ala
115 120

<210> 17
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 17
Arg Ser Ser Lys Ser Leu Leu His Ser Asn Leu Asn Thr Tyr Leu Tyr
1 5 10 15

<210> 18
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 18
Tyr Ile Ser Pro Gly Gly Asp Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 19
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 19
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser
20 25 30

Asn Leu Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Ile Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His
85 90 95

Leu Glu Tyr Pro Phe Thr Phe Gly Pro Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg

<210> 20
<211> 98
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 20
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Pro Gly Gly Asp Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Thr

<210> 21
<211> 219
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 21
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser
20 25 30

Asn Leu Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Ile Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His

85 90 95

Leu Glu Tyr Pro Phe Thr Phe Gly Pro Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 22
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 22

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Pro Gly Gly Asp Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Thr Asp Arg Arg His Tyr Gly Ser Tyr Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val

180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225 230 235 240

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
245 250 255

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
260 265 270

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
290 295 300

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
305 310 315 320

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
325 330 335

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly
450

<210> 23
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 23
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser
20 25 30

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Gly

35 40 45

Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
50 55 60

Lys Leu Leu Ile Gln Tyr Thr Ser Leu Leu His Ser Gly Val Pro Ser
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Tyr Thr Leu Thr Ile Ser
85 90 95

Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Phe Cys Gln Gln Tyr Ser
100 105 110

Lys Phe Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
115 120 125

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
130 135 140

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
145 150 155 160

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
165 170 175

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
180 185 190

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
195 200 205

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
210 215 220

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230

<210> 24
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 24
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
20 25 30

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Gln Gly
35 40 45

Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
50 55 60

Lys Leu Leu Ile Gln Tyr Thr Ser Leu Leu His Ser Gly Val Pro Ser
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser
85 90 95

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Tyr Ser
100 105 110

Lys Phe Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg

115 120 125

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
130 135 140

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
145 150 155 160

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
165 170 175

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
180 185 190

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
195 200 205

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
210 215 220

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230

<210> 25
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 25
Met Asp Pro Lys Gly Ser Leu Ser Trp Arg Ile Leu Leu Phe Leu Ser
1 5 10 15

Leu Ala Phe Glu Leu Ser Tyr Gly Gln Ile Gln Leu Val Gln Ser Gly
20 25 30

Ser Glu Leu Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala
35 40 45

Phe Gly Tyr Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala
50 55 60

Pro Gly Gln Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr Gly
65 70 75 80

Glu Pro Thr Tyr Ala Gln Gly Phe Thr Gly Arg Phe Val Phe Ser Leu
85 90 95

Glu Thr Ser Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala
100 105 110

Glu Asp Thr Ala Val Tyr Phe Cys Ala Arg Asn Tyr Gly Asn Tyr Leu
115 120 125

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
130 135 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
145 150 155 160

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
165 170 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
180 185 190

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser

195 200 205

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
210 215 220

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
225 230 235 240

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly
465 470

<210> 26
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 26
Met Asp Pro Lys Gly Ser Leu Ser Trp Arg Ile Leu Leu Phe Leu Ser
1 5 10 15

Leu Ala Phe Glu Leu Ser Tyr Gly Gln Ile Gln Leu Val Gln Ser Gly
20 25 30

Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala

35 40 45

Phe Gly Tyr Thr Phe Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala
50 55 60

Pro Gly Gln Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr Thr Gly
65 70 75 80

Glu Pro Thr Tyr Ala Asp Asp Phe Lys Gly Arg Val Thr Phe Thr Leu
85 90 95

Glu Thr Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser
100 105 110

Asp Asp Thr Ala Val Tyr Phe Cys Ala Arg Asn Tyr Gly Asn Tyr Leu
115 120 125

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
130 135 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
145 150 155 160

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
165 170 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
180 185 190

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
195 200 205

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
210 215 220

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
225 230 235 240

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
245 250 255

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
260 265 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
290 295 300

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305 310 315 320

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
325 330 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
340 345 350

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
355 360 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
370 375 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385 390 395 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
405 410 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
420 425 430

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
435 440 445

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
450 455 460

Ser Leu Ser Leu Ser Pro Gly
465 470

<210> 27
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 27
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Ser Ala Ser Gln Gly Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Leu Lys Leu Leu Ile
35 40 45

Gln Tyr Thr Ser Leu Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Tyr Ser Leu Thr Ile Ser Asn Leu Glu Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Tyr Ser Lys Phe Pro Arg
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 28
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<220>
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<400> 28
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Ser Gly Glu
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Thr Val Lys Ile Ser Cys Lys Ala Phe Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Asn His Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys

85 90 95

Ala Arg Asn Tyr Gly Asn Tyr Leu Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
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<210> 29
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1 5 10

<210> 30
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<220>
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<400> 30
Thr Ser Leu Leu His Ser Gly
1 5

<210> 31
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<223> Description of Artificial Sequence: Synthetic
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<210> 32
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1 5 10

<210> 33
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<400> 33
Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Lys Gly
1 5 10 15

<210> 34
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Asn Tyr Gly Asn Tyr Leu Phe Asp Tyr
1 5