new drug target (Enninga et al., 2016; Kawashima et al. BJU Int 2014; 113: 320–332; Kageshita et al., Int J Cancer. 2002 Jun 20;99(6):809-16, and references therein). Galectin-9 has been described to play an important role in in a number of cellular processes such as adhesion, cancer cell aggregation, apoptosis, and chemotaxis. Recent studies have shown a role for Galectin-9 in immune modulation in support of the tumor, e.g., through negative regulation of Th1 type responses, Th2 polarization and polarization of macrophages to the M2 phenotype. This work also includes studies that have shown that Galectin-9 participates in direct inactivation of T cells through interactions with the T-cell immunoglobulin and mucin protein 3 (TIM-3) receptor (Dardalhon et al., *J Immunol.,* 2010, 185, 1383-1392; Sanchez-Fueyo et al., *Nat Immunol.,* 2003, 4, 1093-1101). Galectin-9 has also been found to play a role in polarizing T cell differentiation into tumor suppressive phenotypes), as well as promoting tolerogenic macrophage programming and adaptive immune suppression (Daley et al., *Nat Med.,* 2017, 23, 556-567). In mouse models of pancreatic ductal adenocarcinoma (PDA), blockade of the checkpoint interaction between Galectin-9 and the receptor Dectin-1 found on innate immune cells in the tumor microenvironment (TME) has been shown to increase anti-tumor immune responses in the TME and to slow tumor progression (Daley et al., *Nat Med., 2017, 23, 556-567*). Galectin-9 also has been found to bind to CD206, a surface marker of M2 type macrophages, resulting in a reduced secretion of CVL22 (MDC), a macrophage derived chemokine which has been associated with longer survival and lower recurrence risk in lung cancer (Enninga et al, J Pathol. 2018 Aug;245(4):468-477).

Accordingly, modulating the activity of Galectin-9 and/or one or more of its receptors may provide a novel cancer therapy approach, alone or in combination with existing therapies. Described herein are novel human antibodies which bind to human Galectin-9 and their therapeutic use in the treatment of cancer.

SUMMARY

The present disclosure is based, at least in part, on the development of anti-Galectin-9 antibodies that potently suppress signaling triggered by Galectin-9. Such antibodies are capable of suppressing Galectin-9 signaling and/or eliminating Galectin-9 positive pathologic cells, thereby benefiting treatment of diseases associated with Galectin-9.

Accordingly, one example of the present disclosure provides an isolated anti-Galectin-9 antibody, which binds to an epitope in a carbohydrate recognition domain (CRD) of a Galectin-9 polypeptide, for example, a human Galectin-9 polypeptide. In some examples, the anti-

Galactin-9 antibody described herein may bind to both a human Galactin-9 polypeptide and a non-human Galactin-9 polypeptide (e.g., a mouse Galactin-9, a rat Galactin-9, or a primate Galactin-9). In some examples, the anti-Galactin-9 antibody binds exclusively to one of the Galectin-9 CRDs. In some examples, the anti-Galactin-9 antibody binds to both of the Galectin-9 CRDs, e.g., with similar or different affinities. In some examples, the anti-Galectin-9 antibody disclosed herein binds an epitope within the CRD1 region. In some examples, the anti-Galectin-9 antibody disclosed herein binds an epitope within the CRD1 region, which CRD1 region may have the amino acid sequence of SEQ ID NO: 3. In some examples, the anti-Galectin-9 antibody disclosed herein binds an epitope within the CRD1 region having the amino acid sequence of SEQ ID NO: 3. In some examples, the anti-Galectin-9 antibody binds to the same epitope as a reference antibody selected from the group consisting of G9.1-1, G9.1-2, G9.1-3, G9.1-4, G9.1-5, G9.1-6, G9.1-7, G9.1-8, G9.1-8m1, G9.1-8m2, G9.1-8m3, G9.1-8m4, G9.1-8m5, G9.1-8m6, G9.1-8m7, G9.1-8m8, G9.1-8m9, G9.1-8m10, G9.1-8m11, G9.1-8m12, G9.1-8m13, G9.1-8m14, G9.1-9, G9.1-10, and G9.1-11 antibodies, and/or competes against the reference antibody from binding to the CRD1 region. In some examples, the anti-Galectin-9 antibody binds to the same epitope as antibody G9.1-8 or antibody G9.1-8m13 and/or competes against antibody G9.1-8 or antibody G9.1-8m13 from binding to the CRD1 region.

In some examples, the anti-Galectin-9 antibody disclosed herein is an antibody selected from the group consisting of G9.1-1, G9.1-2, G9.1-3, G9.1-4, G9.1-5, G9.1-6, G9.1-7, G9.1-8, G9.1-8m1, G9.1-8m2, G9.1-8m3, G9.1-8m4, G9.1-8m5, G9.1-8m6, G9.1-8m7, G9.1-8m8, G9.1-8m9, G9.1-8m10, G9.1-8m11, G9.1-8m12, G9.1-8m13, G9.1-8m14, G9.1-9, G9.1-10, and G9.1-11 antibodies. In some examples, the anti-Galectin-9 antibody is G9.1-8 antibody. In some examples, the antibody is G9.1-8m13 antibody. In some examples, the anti-Galectin-9 antibody may comprise the same heavy chain complementarity determining regions (CDRs) and the same light chain CDRs as the reference antibody, e.g., any of the reference antibodies provided herein. In one specific example, the anti-Galectin-9 antibody comprises the same heavy chain variable region and the same light chain variable region as the reference antibody, e.g., any of the reference antibodies provided above and elsewhere herein.

In some examples, the anti-Galectin-9 antibody has a V_L sequence comprising SEQ ID NO: 21 or consisting essentially of SEQ ID NO: 21 or consisting of SEQ ID NO: 21. In some examples, the anti-Galectin-9 antibody has a V_H sequence comprising SEQ ID NO: 86 or consisting essentially of SEQ ID NO: 86 or consisting of SEQ ID NO: 86. In some examples, the anti-Galectin-9antibody has a V_L sequence comprising SEQ ID NO: 21 and a

V_H sequence comprising SEQ ID NO: 86. In some examples, the anti-Galectin-9antibody has a V_L sequence consisting essentially of SEQ ID NO: 21 and a V_H sequence consisting essentially of SEQ ID NO: 86. In some examples, the anti-Galectin-9antibody has a V_L sequence consisting of SEQ ID NO: 21 and a V_H sequence consisting of SEQ ID NO: 86.

In some examples, the anti-Galectin antibody has a V_H sequence comprising SEQ ID NO: 22 or consisting essentially of SEQ ID NO: 22 or consisting of SEQ ID NO: 22. In some examples, the anti-Galectin-9 antibody has a V_L sequence comprising SEQ ID NO: 21 and a V_H sequence comprising SEQ ID NO: 22. In some examples, the anti-Galectin-9antibody has a V_L sequence consisting essentially of SEQ ID NO: 21 and a V_H sequence consisting essentially of SEQ ID NO: 22. In some examples, the anti-Galectin-9antibody has a V_L sequence consisting of SEQ ID NO: 21 and a V_H sequence consisting of SEQ ID NO: 22.

In some examples, the anti-Galectin-9 antibody has a V_L sequence comprising one or more of the sequences set forth in SEQ ID NOs: 328, 329, and 337. In some examples, the anti-Galectin-9 antibody has a V_H sequence comprising one or more of the sequences set forth in SEQ ID NOs: 361, 364, 374, 366, and 383. In some examples, the anti-Galectin-9 antibody has a V_L sequence comprising one or more of the sequences set forth in SEQ ID NOs: 328, 329, and 337, and a V_H sequence comprising one or more of the sequences set forth in SEQ ID NOs: 361, 364, and 374. In some examples, the anti-Galectin-9 antibody has a V_L sequence comprising one or more of the sequences set forth in SEQ ID NOs: 328, 329, and 337, and a V_H sequence comprising one or more of the sequences set forth in SEQ ID NOs: 361, 366, and 383.

In some examples, the anti-Galectin-9 antibody disclosed herein binds an epitope within the Galectin-9 CRD2 region. In some examples, the anti-Galectin-9 antibody disclosed herein binds an epitope within the Galectin-9 CRD2 region, which CRD2 region may have the amino acid sequence of SEQ ID NO: 4. In some examples, the anti-Galectin-9 antibody disclosed herein binds an epitope within the CRD2 region having the amino acid sequence of SEQ ID NO: 4. In some examples, the anti-Galectin-9 antibody binds an epitope within the Galectin-9 CRD2 region that comprises a tryptophan residue corresponding with residue W309 of SEQ ID NO: 1. In some examples, the anti-Galectin-9 antibody binds an epitope within the Galectin-9 CRD2 region that does not comprise one or more residues corresponding with R253, R271, Y330, R334, R341 and Y236 of SEQ ID NO: 1. In some examples, the anti-Galectin-9 antibody may bind an epitope within the Galectin-9 CRD2 region that comprises a tryptophan residue corresponding with residue W309 of SEQ ID NO: 1 and additionally does not comprise one or more residues corresponding to R253, R271, Y330, R334, R341 and Y236 of SEQ ID NO: 1. In some examples, the anti-Galectin-9 antibody

binds to the same epitope as a reference antibody selected from the group consisting of G9.2-1, G9.2-2, G9.2-3, G9.2-4, G9.2-5, G9.2-6, G9.2-7, G9.2-8, G9.2-9, G9.2-10, G9.2-11, G9.2-12, G9.2-13, G9.2-14, G9.2-15, G9.2-16, G9.2-17, G9.2-17mut6, G9.2-18, G9.2-19, G9.2-20, G9.2-21, G9.2-22, G9.2-23, G9.2-24, G9.2-25, G9.2-26, and G9.2-low affinity binder antibodies, and/or competes against the reference antibody from binding to the CRD2 region. In some examples, the anti-Galectin-9 antibody binds to the same epitope as antibody G9.2-17 or antibody G9.2-17mut6 and/or competes against antibody G9.2-17 or antibody G92-17mut6 from binding to the CRD2 region. In some examples, the anti-Galectin-9 antibody is an antibody selected from the group consisting of G9.2-1, G9.2-2, G9.2-3, G9.2-4, G9.2-5, G9.2-6, G9.2-7, G9.2-8, G9.2-9, G9.2-10, G9.2-11, G9.2-12, G9.2-13, G9.2-14, G9.2-15, G9.2-16, G9.2-17, G9.2-17mut6, G9.2-18, G9.2-19, G9.2-20, G9.2-21, G9.2-22, G9.2-23, G9.2-24, G9.2-25, and G9.2-26 antibodies. In some examples, the anti-Galectin-9 antibody is G9.2-17 antibody or G9.2-17mut6 antibody. In some examples, the anti-Galectin-9 antibody has a V_L sequence comprising SEQ ID NO: 54 or consisting essentially of SEQ ID NO: 54 or consisting of SEQ ID NO: 54. In some examples, the anti-Galectin-9 antibody has a V_H sequence comprising SEQ ID NO: 55 or consisting essentially of SEQ ID NO: 55 or consisting of SEQ ID NO: 55. In some examples, the anti-Galectin-9antibody has a V_L sequence comprising SEQ ID NO: 54 and a V_H sequence comprising SEQ ID NO: 55. In some examples, the anti-Galectin-9antibody has a V_L sequence consisting essentially of SEQ ID NO: 54 and a V_H sequence consisting essentially of SEQ ID NO: 55. In some examples, the anti-Galectin-9antibody has a V_L sequence consisting of SEQ ID NO: 54 and a V_H sequence consisting of SEQ ID NO: 55. In some examples, the antibody has a V_H sequence comprising SEQ ID NO: 56. In some examples, the antibody has a V_H sequence consisting essentially of SEQ ID NO: 56 or consisting of SEQ ID NO: 56. In some examples, the isolated antibody has a V_L sequence comprising SEQ ID NO: 54 and a V_H sequence comprising SEQ ID NO: 56. In some examples, the isolated antibody has a V_L sequence consisting essentially of SEQ ID NO: 54 and a V_H sequence consisting essentially of SEQ ID NO: 56. In some examples, the isolated antibody has a V_L sequence consisting of SEQ ID NO: 54 and a V_H sequence consisting of SEQ ID NO: 56.

In some examples, the anti-Galectin-9 antibody has a V_L sequence comprising one or more of the sequences set forth in SEQ ID NOs: 328, 329, and 352. In some examples, the anti-Galectin-9 antibody has a V_H sequence comprising one or more of the sequences set forth in SEQ ID NOs: 361, 388, 406, and 407. In some examples, the anti-Galectin-9 antibody has a V_L sequence comprising one or more of the sequences set forth in SEQ ID NOs: 328, 329, and

352, and a V_H sequence comprising one or more of the sequences set forth in SEQ ID NOs: 361, 388, and 406. In some examples, the anti-Galectin-9 antibody has a V_L sequence comprising one or more of the sequences set forth in SEQ ID NOs: 328, 329, and 352, and a V_H sequence comprising one or more of the sequences set forth in SEQ ID NOs: 361, 388, and 407.

In some examples, the anti-Galectin-9 antibody may comprise the same heavy chain complementarity determining regions (CDRs) and the same light chain CDRs as the reference antibody, e.g., any of the reference antibodies provided herein. In one specific example, the anti-Galectin-9 antibody comprises the same heavy chain variable region and the same light chain variable region as a reference antibody, e.g., any of the reference antibodies provided herein. In some examples, the anti-Galectin-9 antibody comprises a heavy chain complementarity determining region 1 (CDR1), a heavy chain complementary determining region 2 (CDR2), and a heavy chain complementary determining region 3 (CDR3), which collectively are at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) identical to the heavy chain CDRs of a reference antibody, e.g., any of the reference antibodies provided herein. In some examples, the anti-Galectin-9 antibody comprises a light chain CDR1, a light chain CDR2, and a light chain CDR3, which collectively are at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) identical to the light chain CDRs of a reference antibody, e.g., any of the reference antibodies provided herein.

In some examples, the anti-Galectin-9 antibody comprises both a heavy chain complementarity determining region 1 (CDR1), a heavy chain complementary determining region 2 (CDR2), and a heavy chain complementary determining region 3 (CDR3), which collectively are at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) identical to the heavy chain CDRs of a reference antibody, e.g., any of the reference antibodies provided herein and a light chain CDR1, a light chain CDR2, and a light chain CDR3, which collectively are at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%) identical to the light chain CDRs of a reference antibody, e.g., any of the reference antibodies provided herein. In some examples, the anti-Galectin-9 antibody may comprise the same heavy chain CDRs and the same light chain CDRs as the reference antibodies noted above. In one specific example, the anti-Galectin-9 antibody may comprise the same heavy chain variable region and the same light chain variable region as of a reference antibody, e.g., any of the reference antibodies provided herein. In some examples, the exemplary isolated anti-Galectin 9 antibodies which bind to CRD1 include G9.1-1, G9.1-2, G9.1-3, G9.1-4, G9.1-5, G9.1-6, G9.1-7, G9.1-8, G9.1-9, G9.1-10, G9.1-11, G9.1-8m1, G9.1-8m2, G9.1-8m3, G9.1-8m4, G9.1-8m5, G9.1-8m6,G9.1-8m7, G9.1-8m8, G9.1-8m9, G9.1-8m10, G9.1-8m11, G9.1-

8m12, G9.1-8m13, and G9.1-8m14. In some examples, the exemplary isolated anti-Galectin 9 antibodies which bind to CRD2 include G9.2-1, G9.2-2, G9.2-3, G9.2-4, G9.2-5, G9.2-6, G9.2-7, G9.2-8, G9.2-9, G9.2-10, G9.2-11, G9.2-12, G9.2-13, G9.2-14, G9.2-15, G9.2-16, G9.2-17, G9.2-17mut6 , G9.2-18, G9.2-19, G9.2-20, G9.2-21, G9.2-22, G9.2-23, G9.2-24, G9.2-25, G9.2-26, and G9.2-low affinity binder.

In some examples, the isolated anti-Galectin 9 antibodies, or antigen binding portion thereof, comprise heavy and light chain variable regions, wherein the light chain variable region comprises an amino acid sequence selected from SEQ ID NO: 29, 13, 34, 36, 38, 40, 42, 44, 46, 48, 34, 54, 58, 61, 63, 65, 73, 67, 69, and 71. In some examples, the light chain variable regions consists of an amino acid sequence selected from SEQ ID NO: 29, 13, 34, 36, 38, 40, 42, 44, 46, 48, 34, 54, 58, 61, 63, 65, 73, 67, 69, and 71. In some examples, the isolated anti-Galectin 9 antibodies, or antigen binding portions thereof, comprise heavy and light chain variable regions, wherein the heavy chain variable region comprises an amino acid sequence selected from SEQ ID NO: 30, 31, 32, 33, 35, 37, 39, 41, 43, 45, 47, 49, 50, 51, 52, 53, 55, 56, 57, 59, 60, 62, 64, 66, 68, 70, 72 and 73. In some examples, the heavy chain variable regions consists of an amino acid sequence selected from SEQ ID NO: 30, 31, 32, 33, 35, 37, 39, 41, 43, 45, 47, 49, 50, 51, 52, 53, 55, 56, 57, 59, 60, 62, 64, 66, 68, 70, 72 and 73.

In some examples, the isolated anti-Galectin 9 antibodies, or antigen binding portion thereof, comprise heavy and light chain variable regions, wherein the light chain variable region comprises an amino acid sequence selected from SEQ ID NO: 29, 13, 34, 36, 38, 40, 42, 44, 46, 48, 34, 54, 58, 61, 63, 65, 73, 67, 69, and 71, and the heavy chain variable region comprises an amino acid sequence selected from SEQ ID NO: 30, 31, 32, 33, 35, 37, 39, 41, 43, 45, 47, 49, 50, 51, 52, 53, 55, 56, 57, 59, 60, 62, 64, 66, 68, 70, 72 and 73. In some examples, the isolated anti-Galectin 9 antibodies, or antigen binding portion thereof, comprise heavy and light chain variable regions, wherein the light chain variable region consists of an amino acid sequence selected from SEQ ID NO: 29, 13, 34, 36, 38, 40, 42, 44, 46, 48, 34, 54, 58, 61, 63, 65, 73, 67, 69, and 71, and the heavy chain variable region consists of an amino acid sequence selected from SEQ ID NO: 30, 31, 32, 33, 35, 37, 39, 41, 43, 45, 47, 49, 50, 51, 52, 53, 55, 56, 57, 59, 60, 62, 64, 66, 68, 70, 72 and 73.

In some examples, the isolated anti-Galectin 9 antibodies, or antigen binding portions thereof, comprise heavy and light chain variable regions, wherein the light chain variable region comprises an amino acid sequence selected from SEQ ID NO: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, and 27. In some examples, the light chain variable regions consist of an amino acid sequence selected from SEQ ID NO: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, and 27. In

some examples, the isolated anti-Galectin 9 antibodies, or antigen binding portions thereof, comprise heavy and light chain variable regions, wherein the heavy chain variable region comprises an amino acid sequence selected from SEQ ID NO: 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, and 87. In some examples, the heavy chain variable regions consist of an amino acid sequence selected from SEQ ID NO: 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, and 87. Accordingly, in some examples, provided herein are isolated anti-Galectin 9 antibodies, or antigen binding portions thereof, comprising heavy and light chain variable regions, wherein the light chain variable region comprises an amino acid sequence selected from SEQ ID NO: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, and 27 and the heavy chain variable region comprises an amino acid sequence selected from SEQ ID NO: 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, and 87. In some examples, the light chain variable regions consists of an amino acid sequence selected from SEQ ID NO: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, and 27, and the heavy chain variable regions consists of an amino acid sequence selected from SEQ ID NO: 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, and 87.

In some examples, any of the anti-Galectin-9 antibody disclosed herein may comprise a heavy chain variable domain (V_H) that is at least 85% identical to the V_H of a reference antibody disclosed herein. Alternatively or in addition, the anti-Galectin-9 antibody may comprise a light chain variable domain (V_L) that is at least 85% identical to the V_L of the reference antibody.

In some examples, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region comprising SEQ ID NO: 54. In some examples, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VH region comprising SEQ ID NO: 55. In some examples, the anti-Galectin-9 antibody comprises a VL region consisting of SEQ ID NO: 54. In some examples, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VH region consisting of SEQ ID NO: 55. In some examples, the anti-Galectin-9 antibody comprises a VL and VH region comprising SEQ ID NO: 54 and 55, respectively. In some specific examples, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL and VH region consisting of SEQ ID NO: 54 and 55, respectively. In some examples, the anti-Galectin-9 antibody is clone 9.2-17. In some examples, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VH region comprising SEQ ID NO: 56. In some examples, the anti-Galectin-9 antibody comprises a VL and VH region comprising SEQ ID NO: 54 and 56, respectively. In some

specific examples, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL and VH region consisting of SEQ ID NO: 54 and 56, respectively. In some examples, the anti-Galectin-9 antibody is clone 9.2-17 mut6.

In some examples, the anti-Galectin-9 antibody comprises a VL region comprising SEQ ID NO: 21. In some examples, the anti-Galectin-9 antibody comprises a VL region consisting of SEQ ID NO: 21. In some examples, the anti-Galectin-9 antibody comprises a V_H region comprising SEQ ID NO: 86. In some examples, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VH region consisting of SEQ ID NO: 86. In some examples, the anti-Galectin-9 antibody comprises a VL and VH region comprising SEQ ID NO: 21 and 86, respectively. In some examples, the anti-Galectin-9 antibody comprises a VL and VH region consisting of SEQ ID NO: 21 and 86, respectively, In some examples, the anti-Galectin-9 antibody is clone G9.1-8m13. In some examples, the anti-Galectin-9 antibody comprises a V_H region comprising SEQ ID NO: 22. In some examples, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VH region consisting of SEQ ID NO: 22. In some examples, the anti-Galectin-9 antibody comprises a VL and VH region comprising SEQ ID NO: 21 and 22, respectively. In some examples, the anti-Galectin-9 antibody comprises a VL and VH region consisting of SEQ ID NO: 21 and 22, respectively. In some examples, the anti-Galectin-9 antibody is clone G9.1-8.

In some examples, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region which has the same amino acid sequence as the VL region of antibody 9.1-8m13 (SEQ ID NO: 21). In some examples, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VH region which has the same amino acid sequence as the VH region of antibody 9.1-8m13 (SEQ ID NO: 86). In some examples, the anti-Galectin-9 antibody comprises VL and VH regions which have the same amino acid sequences as the VL and VH regions of antibody 9.1-8m13 (SEQ ID NO: 21 and 86, respectively).

In some examples, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region which has the same amino acid sequence as the VL region of antibody 9.2-17 (SEQ ID NO: 54). In some examples, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VH region which has the same amino acid sequence as the VH region of antibody 9.2-17 (SEQ ID NO: 55). In some examples, the anti-Galectin-9 antibody comprises VL and VH regions which have the same amino acid sequences as the VL and VH regions of 9.2-17 (SEQ ID NO: 54 and 55, respectively).

In some examples, the anti-Galectin-9 antibody comprises a VL region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VL region set forth in SEQ ID NO: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, and 27. In some examples, the anti-Galectin-9 antibody comprises a VH region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VH region set forth in SEQ ID NOs: 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, and 87. In some examples, the anti-Galectin-9 antibody comprises a VL region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VL region set forth in SEQ ID NOs: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, and 27 and a VH region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VH region set forth in SEQ ID NOs: 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, and 87.

In some examples, the anti-Galectin-9 antibody comprises a VL region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VL region set forth in SEQ ID NOs: 13, 29, 34, 36, 38, 40, 42, 44, 46, 48, 29, 34, 54, 58, 61, 63, 65, 73, 67, 69, and 71. In some examples, the anti-Galectin-9 antibody comprises a VH region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VH region set forth in SEQ ID NOs: 30, 31, 32, 33, 35, 37, 39, 41, 43, 45, 47, 49, 50, 51, 52, 53, 55, 56, 57, 59, 60, 62, 64, 66, 68, 70, 72 and 73. In some examples, the anti-Galectin-9 antibody comprises a VL region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VL region set forth in SEQ ID NOs: 13, 29, 34, 36, 38, 40, 42, 44, 46, 48, 29, 34, 54, 58, 61, 63, 65, 73, 67, 69, and 71 and a VH region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VH region set forth in SEQ ID NOs: 30, 31, 32, 33, 35, 37, 39, 41, 43, 45, 47, 49, 50, 51, 52, 53, 55, 56, 57, 59, 60, 62, 64, 66, 68, 70, 72 and 73.

In some examples, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VL region set forth in SEQ ID NO: 21.

In some examples, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VH region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VH region set forth in SEQ ID NO: 86. In some examples, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL

and VH region that have at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VL and VH regions set forth in SEQ ID NO: 21 and 86, respectively.

In some specific examples, the anti-Galectin-9 antibody or antigen binding fragment thereof comprises a VL that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VL region set forth in SEQ ID NO: 54. In some specific examples, the anti-Galectin-9 antibody or antigen binding fragment thereof comprises a VH region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VH region set forth in SEQ ID NO: 55. In some specific examples, the anti-Galectin-9 antibody or antigen binding fragment thereof comprises a VL and/or VH region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VL and/or VH region set forth in SEQ ID NO: 54 and 55, respectively. In some specific examples, the anti-Galectin-9 antibody comprises a VL region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VL region of G9.1-8m13. In some specific examples, the anti-Galectin-9 antibody comprises a VH region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VH region of G9.1-8m13. In some specific examples, the anti-Galectin-9 antibody comprises VL and VH regions that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to VL and VH regions of G9.1-8m13. In some specific examples, the anti-Galectin-9 antibody comprises a VL region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VL region of G9.2-17. In some specific examples, the anti-Galectin-9 antibody comprises a VH region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VH region of G9.2-17. In some specific examples, the anti-Galectin-9 antibody comprises VL and VH regions that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to VL and VH regions of G9.2-17.

Accordingly, in some examples, anti-Galectin-9 antibodies or antigen binding portions thereof comprise (a) VL CDR1 amino acid sequence set forth in SEQ ID NO: 328; (b) VL CDR2 amino acid sequence set forth in SEQ ID NO: 329; (c) VL CDR3 amino acid sequence selected from SEQ ID NO: 341-360; (d) VH CDR1 amino acid sequence set forth in SEQ ID NO: 361, 427, 428, 431, 435, 436, 437; (d) VH CDR2s amino acid sequence selected from SEQ ID NO: 362, 363, 387-389 and 446-466;(e) VH CDR3 amino acid sequence selected

from SEQ ID NO: 390-417. Accordingly, in some examples, anti-Galectin-9 antibodies or antigen binding portions thereof comprise (a) VL CDR1 amino acid sequence set forth in SEQ ID NO: 328; (b) VL CDR2 amino acid sequence set forth in SEQ ID NO: 329; (c) VL CDR3 amino acid sequence selected from SEQ ID NO: 330-340; (d) VH CDR1 amino acid sequence set forth in SEQ ID NO: 361, 424-434; (e) VH CDR2 amino acid sequence selected from SEQ ID NO: 362-366 and 438-445; (f) VH CDR3 amino acid sequence selected from SEQ ID NO: 367-386.

In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR1 comprises SEQ ID NO: 328. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR2 comprises $X_1X_2X_3X_4X_5SX_6X_7X_8$SYADSVKG (SEQ ID NO: 467), in which X_1 = Y or S, X_2 = I or S, X_3 = Y or S, X_4 = P or S, X_5 = Y or S, X_6 = G or S, X_7 = Y or S, and X_8 = T or S. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR3 comprises $X_1SX_2X_3X_4X_5X_6X_7X_8X_9X_{10}KX_{11}X_{12}X_{13}$GMDY (SEQ ID NO: 468), in which X_1 = Y or S, X_2 = T, S, or absent, X_3 = Y, S, or absent, X_4 = S or absent, X_5 = W, S, or absent, X_6 = S or absent, X_7 = G, S, or absent, X_8 = G, T, S, or absent, X_9 = I, Y, S, or absent, X_{10} = G, S, or Y, X_{11} = W or S, X_{12} = V or S, and X_{13} = W or S. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR1 consists of SEQ ID NO: 328. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR2 consists of $X_1X_2X_3X_4X_5SX_6X_7X_8$SYADSVKG (SEQ ID NO: 467), in which X_1 = Y or S, X_2 = I or S, X_3 = Y or S, X_4 = P or S, X_5 = Y or S, X_6 = G or S, X_7 = Y or S, and X_8 = T or S. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR3 consists of $X_1SX_2X_3X_4X_5X_6X_7X_8X_9X_{10}KX_{11}X_{12}X_{13}$GMDY (SEQ ID NO: 468), in which X_1 = Y or S, X_2 = T, S, or absent, X_3 = Y, S, or absent, X_4 = S or absent, X_5 = W, S, or absent, X_6 = S or absent, X_7 = G, S, or absent, X_8 = G, T, S, or absent, X_9 = I, Y, S, or absent, X_{10} = G, S, or Y, X_{11} = W or S, X_{12} = V or S, and X_{13} = W or S.

In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR1 comprises SEQ ID NO: 328. In some examples, the anti-Galectin-9 antibody or binding portion thereof

comprises heavy and light chain variable regions, wherein the light chain variable region CDR2 comprises SEQ ID NO: 329. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR3 comprises SEQ ID NO: 337. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR1 consists of SEQ ID NO: 328. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR2 consists of SEQ ID NO: 329. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR3 consists of SEQ ID NO: 337. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR1, CDR2, and CDR3 regions comprise SEQ ID NO: 328, 329, and 337, respectively. In some examples, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, respectively. In some examples, the antibody comprises the same VL CDRs as G9.1-8m13. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1 comprises SEQ ID NO: 361. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR2 comprises SEQ ID NO: 366. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR3 region comprises SEQ ID NO: 383. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1 consists of SEQ ID NO: 361. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR2 consists of SEQ ID NO: 366. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR3 region consists of SEQ ID NO: 383. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 regions comprise SEQ ID NO: 361, 366, and 383, respectively. In some examples, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 361, 366, and 383, respectively. In some examples, the anti-Galectin-9 antibody comprises the same VH CDRs

as G9.1-8m13. In one specific example, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein: the light chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 328, 329, and 337, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 366, and 383, respectively. In some examples, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, respectively, and SEQ ID NO: 361, 366, and 383, respectively. In one specific example, the anti-Galectin-9 antibody comprises the same VL and VH CDRs as G9.1-8m13.

In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR1 comprises SEQ ID NO: 328. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR2 comprises SEQ ID NO: 329. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR3 comprises SEQ ID NO: 352. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR1 consists of SEQ ID NO: 328. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR2 consists of SEQ ID NO: 329. In some examples, the anti-Galectin-9 antibody or binding portion thereof consists of heavy and light chain variable regions, wherein the light chain variable region CDR3 comprises SEQ ID NO: 352. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR1, CDR2, and CDR3 regions comprise SEQ ID NO: 328, 329, and 352, respectively. In some examples, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 352, respectively. In some examples, the anti-Galectin-9 antibody comprises the same VL CDRs as G9.2-17. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 regions comprise SEQ ID NO: 361, 388, and 406, respectively. In some examples, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 361, 388, and 406, respectively. In some examples, the antibody comprises the same VH CDRs as G9.2-17. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR1, CDR2, and CDR3 regions comprise SEQ ID NO:

328, 329, and 352, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 388, and 406, respectively. In some examples, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 352, respectively, and SEQ ID NO: 361, 388, and 406, respectively. In one specific example, the anti-Galectin-9 antibody comprises the same VL and VH CDRs as G9.2-17.

Accordingly, in some examples, anti-Galectin-9 antibodies or antigen binding portions thereof comprise (a) VL CDR1 amino acid sequence that has at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VL CDR1 amino acid sequence set forth in SEQ ID NO: 328; (b) VL CDR2 amino acid sequence that has at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VL CDR2 amino acid sequence set forth in SEQ ID NO: 329; (c) VL CDR3 amino acid sequence that has at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VL CDR3 amino acid sequence selected from SEQ ID NO: 330-340; (d) VH CDR1 amino acid sequence that has at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VH CDR1 amino acid sequence set forth in SEQ ID NO: SEQ ID NO: 361, 427, 428, 431, 435, 436, 437; (e) VH CDR2 amino acid sequence that has at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VH CDR2 amino acid sequence selected from SEQ ID NO: 362-366 and 438-445; (f) VH CDR3 amino acid sequence that has at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VH CDR3 amino acid sequence selected from SEQ ID NO: 367-386. Accordingly, in some examples, anti-*G*alectin-9 antibodies or antigen binding portions thereof comprise (a) VL CDR1 amino acid sequence that has at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VL CDR1 amino acid sequence set forth in SEQ ID NO: 328; (b) VL CDR2 amino acid sequence that has at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VL CDR2 amino acid sequence set forth in SEQ ID NO: 329; (c) VL CDR3 amino acid sequence that has at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VL CDR3 amino acid sequence selected from SEQ ID NO: 341-360; (d) VH CDR1 amino acid sequence that has at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VH CDR1 amino acid sequence set forth in SEQ ID NO: 361, 424-434; (d) VH CDR2 amino acid sequence that has at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VH CDR2 amino acid sequence selected from SEQ ID NO: 362, 363, 387-389 and 446-466;(e) VH CDR3

amino acid sequence that has at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to a VH CDR3 amino acid sequence selected from SEQ ID NO: 390-417.

In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR1, CDR2, and CDR3 amino acid sequences have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the light chain variable region CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NO: 328, 329, and 337, respectively. In some examples, the antibody VL CDR1, CDR2, and CDR3 amino acid sequences have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VL CDR1, CDR2, and CDR3 amino acid sequences of G9.1-8m13. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 amino acid sequences have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the heavy chain variable region CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NO: 361, 366, and 383, respectively. In some examples, the antibody VH CDR1, CDR2, and CDR3 amino acid sequences have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VH CDR1, CDR2, and CDR3 amino acid sequences of G9.1-8m13. In one specific example, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein: the light chain variable region CDR1, CDR2, and CDR3 amino acid sequences have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the light chain variable region CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NO: 328, 329, and 337, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 amino acid sequences have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the heavy chain variable region CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NO: 361, 366, and 383, respectively. In one specific example, the antibody VL CDR1, CDR2, and CDR3 and VH CDR1, CDR2, and CDR3 amino acid sequences have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VL CDR1, CDR2, and CDR3 and VH CDR1, CDR2, and CDR3 amino acid sequences as G9.1-8m13. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR1, CDR2, and CDR3 amino acid sequences have at least

80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the light chain variable region CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NO: 328, 329, and 352, respectively. In some examples, the antibody VL CDR1, CDR2, and CDR3 amino acid sequences have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VL CDR1, CDR2, and CDR3 amino acid sequences ofG9.2-17. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 amino acid sequences have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the heavy chain variable region CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NO: 361, 388, and 406, respectively. In some examples, the antibody VH CDR1, CDR2, and CDR3 amino acid sequences have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VH CDR1, CDR2, and CDR3 amino acid sequences of G9.2-17. In some examples, the anti-Galectin-9 antibody or binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR1, CDR2, and CDR3 amino acid sequences have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the light chain variable region CDR1, CDR2, and CDR3 amino acid sequences set forth in comprise SEQ ID NO: 328, 329, and 352, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 amino acid sequences have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the heavy chain variable region CDR1, CDR2, and CDR3 amino acid sequences set forth in SEQ ID NO: 361, 388, and 406, respectively. In one specific example, the antibody VL CDR1, CDR2, and CDR3 and VH CDR1, CDR2, and CDR3 amino acid sequences have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the VL CDR1, CDR2, and CDR3 and VH CDR1, CDR2, and CDR3 amino acid sequences of G9.2-17.

In some examples of any of the anti-Galectin antibodies provided herein, the heavy chain constant region of the anti-Galectin-9 antibody is from a human IgG (a gamma heavy chain) of any IgG subfamily as described herein, e.g., IgG1 or IgG4.

In some examples, the amino acid sequences of exemplary anti-Galectin antibody light chains correspond to sequences set forth in SEQ ID NO: 88-98 and SEQ ID NO: 99-115. In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 108. In some examples, light chains of anti-Galectin-9 antibodies comprise an amino acid sequence that has at least 80% (e.g., 85%,

90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the light chain sequence set forth in SEQ ID NO: 95 (or their variable regions). In some examples, light chains of anti-Galectin-9 antibodies comprise an amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the light chain sequence set forth in SEQ ID NO: 108 (or their variable regions). In some examples, the amino acid sequences of exemplary anti-Galectin antibody heavy chains correspond to sequences set forth in SEQ ID NO: 116-140; 169-193; 222-246; 275-299 (anti-Galectin-9 antibodies binding to CRD1) and SEQ ID NO: 141-168; 194-220; 247-274; 300-327 (anti-Galectin-9 antibodies binding to CRD2). In some examples, the heavy chain constant region of the anti-Galectin-9 antibody is from a human IgG1. In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 136. In some examples, the IgG1 is a mutant with minimal Fc receptor engagement. In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 189. In some examples, the heavy chain constant region of the anti-Galectin-9 antibody is from a human IgG4. In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 242. In some examples, the IgG4 is IgG4 exchange mutant. In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 295.

In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 157. In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 210. In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 263. In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 316.

In some examples, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the heavy chain sequence set forth in SEQ ID NO: 136 (or its variable region). In some examples, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the heavy chain sequence set forth in SEQ ID NO: 189 (or its variable region). In some examples, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%,

97%, 98%, 99% and any increment therein) sequence identity to the heavy chain sequence set forth in SEQ ID NO: 242 (or its variable region). In some examples, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the heavy chain sequence set forth in SEQ ID NO: 295 (or its variable region). In some examples, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the heavy chain sequence set forth in SEQ ID NO: 157 (or its variable region). In some examples, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the heavy chain sequence set forth in SEQ ID NO: 210 (or its variable region). In some examples, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the heavy chain sequence set forth in SEQ ID NO: 263 (or its variable region). In some examples, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to the heavy chain sequence set forth in SEQ ID NO: 316 (or its variable region). In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 95 and a heavy chain sequence of SEQ ID NO: 136. In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 95 and a heavy chain sequence of SEQ ID NO: 189. In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 95 and a heavy chain sequence of SEQ ID NO: 242.

In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 95 and a heavy chain sequence of SEQ ID NO: 295. In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 108 and a heavy chain sequence of SEQ ID NO: 157.

In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 108 and a heavy chain sequence of SEQ ID NO: 210.

In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 108 and a heavy chain sequence of SEQ ID NO: 263.

In some examples, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 108 and a heavy chain sequence of SEQ ID NO: 316.

In one example, the anti-Galectin-9 antibody comprises a light chain amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 95 and a heavy chain amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 136. In one example, the anti-Galectin-9 antibody comprises a light chain amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 95 and a heavy chain amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 189. In one example, the anti-Galectin-9 antibody comprises a light chain amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 95 and a heavy chain amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 242. In one example, the anti-Galectin-9 antibody comprises a light chain amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 95 and a heavy chain amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 295.

In one example, the anti-Galectin-9 antibody comprises a light chain amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 108 and a heavy chain amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to f SEQ ID NO: 157 . In one example, the anti-Galectin-9 antibody comprises a light chain amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 108 and a heavy chain amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 210 . In one example, the anti-Galectin-9 antibody comprises a light chain amino acid sequence that has at least 80% (e.g.,

85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 108 and a heavy chain amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 263. In one example, the anti-Galectin-9 antibody comprises a light chain amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 108 and a heavy chain amino acid sequence that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 316.

Any of the anti-Galectin-9 antibodies provided herein may comprise a heavy chain variable region framework of VH 3-48; and/or a light chain variable region framework of Vκ 1-39. In some examples, any of the VH and/or VL frameworks described herein are germline VH and/or VL genes. In some examples, the anti-Galectin-9 antibodies described herein is a full-length antibody (*e.g.*, an IgG molecule) or an antigen-binding fragment thereof. In some examples, the antibody is a Fab or a single-chain antibody. In any instances, the antibody can be a human antibody or a humanized antibody.

In another example, the present disclosure provides an isolated nucleic acid or set of nucleic acids which encode or collectively encode any of the anti-Galectin-9 antibodies disclosed herein. In some instances, the heavy chain and light chain of the antibody are encoded by two separate nucleic acid molecules (a set of nucleic acids). In other instances, the heavy chain and light chain of the antibody are encoded by one nucleic acid molecule, which may be in multicistronic format, or under the control of distinct promoters. In some examples, the nucleic acid or set of nucleic acids are located on one or two vectors. In some examples, the one or two vectors can be one or two expression vectors. Further, the present disclosure provides a host cell comprising any of the isolated nucleic acid or set of nucleic acids coding for the anti-Galectin-9 antibodies described herein.

Also provided herein is a method for producing the anti-Galectin-9 antibody, comprising culturing the host cell described herein under suitable conditions allowing for expressing of the antibody, and harvesting the antibody thus produced from the cell culture (*e.g.*, from the culture medium).

Further, the present disclosure provides a pharmaceutical composition, comprising any of the anti-Galectin-9 antibodies or a nucleic acid(s) encoding such, and a pharmaceutically acceptable carrier.

In yet another example, the present disclosure features a method of inhibiting Galectin-9-mediated cell signaling in a subject, the method comprising administering to a subject in need thereof an effective amount of an anti-Galectin-9 antibody or a pharmaceutical composition comprising an anti-Galectin-9 antibody. In some examples, the anti-Galectin-9 antibody is any of the anti-Galectin-9 antibodies disclosed herein or a pharmaceutical composition comprising such. In some examples, the subject in need thereof is a human patient having, suspected of having, or at risk for having, an autoimmune disease, a solid cancer, a microbial disease, a hematological malignancy, or an allergic disorder. Exemplary autoimmune diseases include, but are not limited to, a rheumatoid condition (*e.g.*, rheumatoid arthritis), an autoimmune respiratory disease, an autoimmune metabolic and/or endocrine disorder (*e.g.*, type I diabetes), or a fibrotic condition. Exemplary solid tumors include, but are not limited to, pancreatic ductal adenocarcinoma (PDA), colorectal cancer (CRC), melanoma, cholangiocarcinoma, breast cancer, small cell and non small cell lung cancer, upper and lower gastrointestinal malignancies, gastric cancer, squamous cell head and neck cancer, genitourinary cancer, hepatocellular carcinoma, ovarian cancer, sarcomas, mesothelioma, glioblastoma, esophageal cancer, bladder cancer, urothelial cancer, renal cancer, cervical and endometrial cancer. Exemplary hematological malignancies include, but are not limited to, acute lymphoblastic leukemia, chronic lymphocytic leukemia, lymphomas, multiple myeloma, and acute myelogenous leukemia, chronic myelogenous leukemia, myelodysplastic syndromes, or myeloproliferative neoplasms and other myeloproliferative and myelodysplastic disorders. In some examples, the effective amount of the pharmaceutical composition is sufficient to block interaction between Galectin-9 and Dectin-1. In some examples, the effective amount of the pharmaceutical composition is sufficient to block interaction between Galectin-9 and CD206. Alternatively, or in addition, but not limited to, the effective amount of the pharmaceutical composition is sufficient to block interaction between Galactin-9 and Tim-3.

Further, the present disclosure provides a method for modifying, eliminating and/or reducing pathologic cells expressing Galectin-9 (*e.g.*, via antibody-dependent cell cytotoxicity or ADCC), the method comprising administering to a subject having pathologic cells expressing Galectin-9 an effective amount of an anti-Galectin-9 antibody, such as any of the anti-Galectin-9 antibodies described herein, or a pharmaceutical composition thereof. In some examples, the subject is a human patient having cancer cells expressing Galectin-9 and/or pathologic immune cells expressing Galectin-9. In some examples, the effective amount of the pharmaceutical composition is sufficient to initiate antibody-dependent cell cytotoxicity (ADCC) and/or block against pathologic cells expressing Galectin-9.

Any of the treatment methods described herein may further comprise administering to the subject an inhibitor of a checkpoint molecule, an activator of a co-stimulatory receptor, or an inhibitor of an innate immune cell target. Examples of checkpoint molecules include, but are not limited to, PD-1, PD-L1, PD-L2, CTLA-4, LAG3, TIM-3 and A2aR. Examples of co-stimulatory receptors include, but are not limited to, OX40, GITR, CD137, CD40, CD27, and ICOS. Examples of innate immune cell targets include, but are not limited to, KIR, NKG2A, CD96, TLR, and IDO.

The present disclosure also provides pharmaceutical compositions for use in treating a disease associated with Galectin-9 (*e.g.*, those described herein), wherein the pharmaceutical composition comprises an anti-Galectin-9 antibody, such as any of the anti-Galectin-9 antibodies described herein, or a nucleic acid(s) encoding such antibody, and a pharmaceutically acceptable carrier. Also, the present disclosure provides uses of the anti-Galectin-9 antibodies or the encoding nucleic acids for manufacturing a medicament for use in treating the target diseases as described herein.

In one aspect, the present disclosure relates to an isolated nucleic acid or a set of nucleic acid molecules comprising nucleic acid sequence(s) encoding a heavy chain comprising a heavy chain variable region (VH) and a light chain comprising a light chain variable region (VL) of an anti-Galectin-9 antibody, wherein the VH comprises a heavy chain complementarity determining region 1 (CDR1) set forth as SEQ ID NO: 361, a heavy chain complementary determining region 2 (CDR2) set forth as SEQ ID NO: 388, and a heavy chain complementary determining region 3 (CDR3) set forth as SEQ ID NO: 406 ; and the VL comprises a light chain complementarity determining region 1 (CDR1) set forth as SEQ ID NO: 328, a light chain complementary determining region 2 (CDR2) set forth as SEQ ID NO: 329, and a light chain complementary determining region 3 (CDR3) set forth as SEQ ID NO: 352.

In another aspect, the presence disclosure relates to a vector or a set of vectors comprising the nucleic acid molecule or the set of nucleic acid molecules as disclosed herein.

In another aspect, the presence disclosure relates to a method for producing an antibody that binds human Galectin-9, comprising: culturing the host cell of claim 15 under suitable conditions for expression of the antibody; and harvesting the antibody thus produced from the cell culture.

The details of one or more embodiments of the invention are set forth in the description below. Other features or advantages of the present invention will be apparent from the following drawing and detailed description of several embodiments, and also from the appended claims.

BRIEF DESCRIPTION OF DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure, which can be better understood by reference to the drawing in combination with the detailed description of specific embodiments presented herein.

Figs. 1A-1B include charts showing a binding characterization of Fabs for Galectin-9 CRD2 using phage ELISAs. Fig. 1A: binding to human and mouse Galectin-9 shown by phage ELISA. Fig. 1B: affinity of Fabs clones to Galectin-9 CRD2 determined by competition phage ELISA.

Figs. 2A-2B include charts showing a binding characterization of Fabs for Galectin-9 CRD1 using phage ELISA. Fig. 2A: binding of Fab clones to human and mouse Galectin-9 CRD1 shown by phage ELISA. Fig. 2B: affinity of Fabs clones to Galectin-9 CRD1 determined by competition phage ELISA.

Figs. 3A-3B include charts showing epitope binning of G.9-2 Fab clones (binding to CRD2) using competition phage ELISA. Fig. 3A: mouse Galectin-9 CRD2-coated wells pre-

What Is Claimed Is:

1. An isolated nucleic acid or a set of nucleic acid molecules comprising nucleic acid sequence(s) encoding a heavy chain comprising a heavy chain variable region (VH) and a light chain comprising a light chain variable region (VL) of an anti-Galectin-9 antibody, wherein

the VH comprises a heavy chain complementarity determining region 1 (CDR1) set forth as SEQ ID NO: 361, a heavy chain complementary determining region 2 (CDR2) set forth as SEQ ID NO: 388, and a heavy chain complementary determining region 3 (CDR3) set forth as SEQ ID NO: 406 ; and

the VL comprises a light chain complementarity determining region 1 (CDR1) set forth as SEQ ID NO: 328, a light chain complementary determining region 2 (CDR2) set forth as SEQ ID NO: 329, and a light chain complementary determining region 3 (CDR3) set forth as SEQ ID NO: 352.

2. The isolated nucleic acid molecule or the set of nucleic acid molecules of claim 1, wherein the nucleic acid sequences encode a VH set forth as SEQ ID NO: 55 and a VL set forth as SEQ ID NO: 54.

3. The isolated nucleic acid molecule or the set of nucleic acid molecules of claim 1, wherein the antibody is a full-length antibody or an antigen-binding fragment thereof.

4. The isolated nucleic acid molecule or the set of nucleic acid molecules of claim 1, wherein antibody is a single chain antibody.

5. The isolated nucleic acid molecule or the set of nucleic acid molecules of claim 1, wherein the antibody is a human antibody or a humanized antibody.

6. The isolated nucleic acid molecule or the set of nucleic acid molecules of claim 1, wherein the antibody is an IgG molecule.

7. The isolated nucleic acid molecule or the set of nucleic acid molecules of claim 6, wherein the IgG molecule is an IgG1 or IgG4 molecule.

8. The isolated nucleic acid molecule or the set of nucleic acid molecules of claim 7, wherein the IgG4 molecule has a S228P mutation.

9. The isolated nucleic acid molecule or the set of nucleic acid molecules of claim 1, wherein the heavy chain further comprises a heavy chain constant region set forth as SEQ ID NO: 422, and wherein the light chain further comprises a light chain constant region set forth as SEQ ID NO: 418.

10. The isolated nucleic acid molecule or the set of nucleic acid molecules of claim 1, wherein the nucleic acid sequences encode the heavy chain set forth as SEQ ID NO: 316 and the light chain set forth in SEQ ID NO: 108.

11. A vector or a set of vectors comprising the nucleic acid molecule or the set of nucleic acid molecules of claim 1.

12. The vector or the set of vectors of claim 11, wherein the vector(s) is an expression vector(s).

13. The vector or the set of vectors of claim 12, wherein the nucleic acid molecule or the set of nucleic acid molecules comprise nucleic acid sequence encoding a VH set forth as SEQ ID NO: 55 and a VL set forth as SEQ ID NO: 54.

14. The vector or the set of vectors of claim 13, wherein the nucleic acid molecule or the set of nucleic acid molecules comprise nucleic acid sequences encoding a heavy chain set forth as SEQ ID NO: 316 and a light chain set forth as SEQ ID NO: 108.

15. A host cell comprising a vector or a set of vectors set forth in any one of claims 11-14.

16. The host cell of claim 15, wherein the host cell is selected from the group consisting of an E. coli cell, a simian COS cell, a Chinese hamster ovary (CHO) cell, and a myeloma cell.

17. A method for producing an antibody that binds human Galectin-9, comprising: culturing the host cell of claim 15 under suitable conditions for expression of the antibody; and harvesting the antibody thus produced from the cell culture.