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(54) **Titre : ANTICORPS ANTI-GALECTINE-9 ET LEURS UTILISATIONS**
(54) **Title: ANTI-GALECTIN-9 ANTIBODIES AND USES THEREOF**

(57) **Abrégé/Abstract:**
Disclosed herein are anti-Galectin-9 antibodies and methods of using such for inhibiting a signaling pathway mediated by Galectin-9 or eliminating pathologic cells expressing Galectin-9. Such anti-Galectin-9 antibodies may also be used to diagnose and/or to treat diseases associated with Galectin-9, such as autoimmune diseases and solid tumors.

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(54) Title: ANTI-GALECTIN-9 ANTIBODIES AND USES THEREOF

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ANTI-GALECTIN-9 ANTIBODIES AND USES THEREOF

BACKGROUND OF INVENTION

Immune checkpoint blockade has demonstrated unprecedented success in the past few years as cancer treatment. Often antibodies are used to block immune inhibitory pathways, such as the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death 1 (PD-1) pathways. While therapies targeting those two pathways have shown success in treating several cancer types, anti-CTLA-4 and anti-PD-1 therapies have a response rate of 10 to 60% of treated patients, depending on cancer type, and have not yet shown the ability to exceed a response rate of 60%, even when used in combination (Kyvistborg et al., Enhancing responses to cancer immunotherapy; Science. 2018 Feb 2;359(6375):516-517). Additionally, a large number of cancer types are refractory to these therapies. As part of efforts to improve existing immunotherapies in the clinic, the field has started to focus on the role of abnormalities in interferon signaling and upregulation of alternative checkpoints as potential causes for the limitation of current therapies. One such potential alternate checkpoint is T-cell immunoglobulin mucin-3 (Tim-3) /Galectin-9 (e.g., reviewed in Yang and Hung; The role of T-cell immunoglobulin mucin-3 and its ligand galectin-9 in antitumor immunity and cancer immunotherapy; Cancer biology and cancer treatment; Oct 2017, Vol.60 No.10: 1058–1064, and references therein).

Galectin-9 is a tandem-repeat lectin consisting of two carbohydrate recognition domains (CRDs) and was discovered and described for the first time in 1997 in patients suffering from Hodgkin's lymphoma (HL) (Tureci et al., J. Biol. Chem. 1997, 272, 6416–6422). Three isoforms exist, and can be located within the cell or extracellularly. Elevated Galectin-9 levels have been in observed a wide range of cancers, including melanoma, Hodgkin's lymphoma, hepatocellular, pancreatic, gastric, colon and clear cell renal cell cancers (Wdowiak et al. Int. J. Mol. Sci. 2018, 19, 210). In renal cancer, patients with high Galectin-9 expression showed more advanced progression of the disease with larger tumor size and necrosis (Kawashima et al.; BJU Int. 2014;113:320–332). In melanoma - a cancer considered as one of the most lethal cancers due to its aggressive metastasis and resistance to therapy - Galectin-9 was expressed in 57% of tumors and was significantly increased in the plasma of patients with advanced melanoma compared to healthy controls (Enninga et al., Melanoma Res. 2016 Oct; 26(5): 429–441). A number of studies have shown utility for Gal-9 as a prognostic marker, and more recently as a potential

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 OF INVENTION

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 aspect 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 embodiments, the anti-

Galectin-9 antibody described herein may bind to both a human Galectin-9 polypeptide and a non-human Galectin-9 polypeptide (e.g., a mouse Galectin-9, a rat Galectin-9, or a primate Galectin-9). In some embodiments, the anti-Galectin-9 antibody binds exclusively to one of the Galectin-9 CRDs. In some embodiments, the anti-Galectin-9 antibody binds to both of the Galectin-9 CRDs, e.g., with similar or different affinities. In some embodiments, the anti-Galectin-9 antibody disclosed herein binds an epitope within the CRD1 region. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the anti-Galectin-9 antibody is G9.1-8 antibody. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the anti-Galectin-9 antibody disclosed herein binds an epitope within the Galectin-9 CRD2 region. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the anti-Galectin-9 antibody is G9.2-17 antibody or G9.2-17mut6 antibody. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the antibody has a V_H sequence comprising SEQ ID NO: 56. In some embodiments, the antibody has a V_H sequence consisting essentially of SEQ ID NO: 56 or consisting of SEQ ID NO: 56. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region comprising SEQ ID NO: 54. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VH region comprising SEQ ID NO: 55. In some embodiments, the anti-Galectin-9 antibody comprises a VL region consisting of SEQ ID NO: 54. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VH region consisting of SEQ ID NO: 55. In some embodiments, the anti-Galectin-9 antibody comprises a VL and VH region comprising SEQ ID NO: 54 and 55, respectively. In some specific embodiments, 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 embodiments, the anti-Galectin-9 antibody is clone 9.2-17. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VH region comprising SEQ ID NO: 56. In some embodiments, the anti-Galectin-9 antibody comprises a VL and VH region comprising SEQ ID NO: 54 and 56, respectively. In some

specific embodiments, 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 embodiments, the anti-Galectin-9 antibody is clone 9.2-17 mut6.

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

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

as G9.1-8m13. In one specific embodiment, 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 embodiments, 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 embodiment, the anti-Galectin-9 antibody comprises the same VL and VH CDRs as G9.1-8m13.

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

Accordingly, in some embodiments, 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 embodiments, 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 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiment, 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 embodiment, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiment, 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 embodiments 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 embodiments, 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 embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 108. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the heavy chain constant region of the anti-Galectin-9 antibody is from a human IgG1. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 136. In some embodiments, the IgG1 is a mutant with minimal Fc receptor engagement. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 189. In some embodiments, the heavy chain constant region of the anti-Galectin-9 antibody is from a human IgG4. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 242. In some embodiments, the IgG4 is IgG4 exchange mutant. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 295.

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

In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiment, 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 embodiment, 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 embodiment, 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 embodiment, 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 embodiment, 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 embodiment, 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 embodiment, 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 embodiment, 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 embodiments, any of the VH and/or VL frameworks described herein are germline VH and/or VL genes. In some embodiments, 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 aspect, 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 embodiments, 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 aspect, 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 embodiments, the anti-Galectin-9 antibody is any of the anti-Galectin-9 antibodies disclosed herein or a pharmaceutical composition comprising such. In some embodiments, 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 embodiments, 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 Galectin-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 embodiments, the subject is a human patient having cancer cells expressing Galectin-9 and/or pathologic immune cells expressing Galectin-9. In some embodiments, 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.

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-

incubated with purified G9.2-1 or G9.2-3 Fabs prior to addition of phage-displayed Galectin-9 CRD2 binding Fab clones. Fig. 3B: human Galectin-9 CRD2-coated wells pre-incubated with purified G9.2-15 or G9.2-17 Fabs prior to addition of phage-displayed Galectin-9 CRD2 binding Fab clones.

Fig. 4 includes diagrams showing the affinity of purified G9.2 Fabs to Galectin-9 CRD2, characterized using a bead-based binding assay. The curves show the best fit of the one-to-one binding model. Top left: G9.2-1 Fab. Top right: G9.2-3 Fab. Bottom left: G9.2-15 Fab. Bottom right: G9.2-17 Fab. Apparent Kd values are shown in the table.

Fig. 5 includes diagrams showing the affinity of purified G9.1 Fabs to Galectin-9 CRD1, characterized using a bead-based binding assay. Experiments were performed in the same manner as in Fig. 4. Top left: G9.1-6 Fab. Top right: G9.1-5 Fab. Bottom left: G9.1-8 Fab. Bottom right: G9.1-11 Fab. Apparent Kd values are shown in the table.

Fig. 6 includes diagrams showing a surface plasmon resonance analysis of Fab G9.2-15 and Fab G9.2.17 binding to CRD2 of human (top) and mouse (bottom) Galectin-9. The binding and dissociation phases of the experiments are marked in the top panels. Left: G9.2-15 Fab. Right: G9.2-17 Fab.

Fig. 7 includes diagrams showing an SPR analysis of G9.2-17 human IgG4 binding to CRD2 of human (top) and mouse (bottom) Galectin-9. The gray lines show the sensorgrams for the non-binding negative control, G9.2-iso human IgG4.

Fig. 8 includes diagrams showing the staining of cell line samples with Fabs for Galectin-9 CRD2. Histograms for flow cytometry data are shown. Top left: G9.2-1 Fab. Top right: G9.2-3 Fab. Bottom left: G9.2-15 Fab. Bottom right: G9.2-17 Fab.

Fig. 9 is a chart showing the inhibitory effects of G9.2-17 and G9.1-8 on Galectin-9 mediated activation of Dectin-1 signaling.

Figs. 10A-10B include diagrams showing epitope mapping of G.9-2.17 on human Galectin-9 CRD2 by systematic mutagenesis. Fig. 10A: A diagram showing the binding activity of G9.2-17 to Galectin-9 CRD2 mutants as determined by phage ELISA. The reduction in ELISA signal indicates a site on the Galectin-9 CRD2 that is critical to G9.2-17 binding. Fig. 10B: a diagram depicting the location of W309 as mapped on the crystal structure of human Galectin-9 CRD2 (PDB ID 3NV2), which is opposite to the binding site of the sugar ligand as mapped on the crystal structure (W309 corresponds with W277 in UniProt ID 000182-2; PDB ID 3NV2).

Fig. 11 contains charts showing size-exclusion chromatography analyses of Fab G9.2-17 (top), Fab G9.2-17mut6 (middle) and Fab G9.2-Iso (bottom). Purified Fab samples were run on TOSOH TSK Bioassist G2WXL™ Column in PBS and detected using absorbance at 280 nm.

Fig. 12 contains charts showing surface plasmon resonance analyses of Fab G9.2-17 (top) and Fab G9.2.17mut6 (bottom) binding to the CRD2 of human (left) and mouse (right) Galectin-9. Human or mouse Galectin-9 CRD2 was immobilized on an Avicap™ chip preloaded with neutravidin on a Pall ForteBio Pioneer™ instrument. Fab samples were then flowed using the OneStep method. The binding and dissociation phases of the experiments are marked in the top panels.

Fig. 13 is a graph showing a binding characterization of G9.2 Fab clone for wild-type Galectin-9 CRD2 or the W3039K mutant using phage ELISA. Binding of Fab clones to human Galectin-9 CRD2 assayed using phage ELISA. Either biotinylated wild type human Galectin-9 CRD2, the W309K Galectin-9 CRD2 mutant, or Galectin-9 CRD2 pre-incubated with G9.2-17 IgG was immobilized to neutravidin-coated wells and incubated with individual phage-displayed Fab clones.

Fig. 14 is a Kaplan–Meier plot showing that blocking Galectin-9 results in significant extension of survival in animal models of pancreatic cancer (KPC mice).

Fig. 15 is a photograph of mouse tumors showing that blocking galectin-9 and anti-PD1 generates a superior response.

Fig. 16 is a bar graph showing the tumor mass of mice treated with G9.2-17 mIgG1. Mice (n=10/group) with orthotopically implanted KPC tumors were treated with commercial isotype (200μg) or commercial αGal9 (200μg) mAb or G9.2-Iso mIgG1 (200μg) or G9.2-17 mIgG1 at two doses (200μg or 400μg) once weekly for three weeks. Tumors were removed and weighed, and subsequently processed and stained for flow cytometry.

Figs. 17 depicts a bar graph showing tumor weight of mice treated with G9.2-17 mIgG2a alone or in combination with αPD1 mAb. Mice (n=10/group) with orthotopically implanted KPC tumors were treated with commercial αPD-1 (200μg) mAb or G9.2-17 mIg2a (200μg), or a combination of G9.2-17 and αPD-1, or matched isotype once weekly for three weeks. Tumors were removed and weighed and subsequently processed and stained for flow cytometry. Each point represents one mouse; $*p<0.05$; $**p<0.01$; $***p<0.001$; $****p<0.0001$; by unpaired Student's *t*-test.

Figs. 18A-18C depict graphs showing binding of purified G9.1-8m1-5 mIgG1 to human Galectin-9 CRD1 as characterized using a bead-based binding assay.

Figs. 19A-19G depict graphs showing binding of purified G9.1-8m6-11 Fabs to human Galectin-9 CRD1 as characterized using a bead-based binding assay.

Figs. 20A-20C depict graphs showing the affinity of purified G9.1-8m8, 9, and 11 mIgG2a antibodies to human Galectin-9 CRD1 as characterized using a bead-based binding assay.

Figs. 21A-21D depict graphs showing binding of purified G9.1-8m11-14 Fabs to human Galectin-9 CRD1 as characterized using a bead-based binding assay.

Figs. 22A-22D depict graphs showing binding of purified G9.1-8m12-14 mIgG2a antibodies to human Galectin-9 CRD1 as characterized using a bead-based binding assay.

Figs. 23A and 23B depict graphs showing the results of an apoptosis assay demonstrating that Gal-9 antibodies inhibit Galectin-9 induced apoptosis of Jurkat cells. Jurkat cells were treated with or without Galectin-9 (280 nM), G9.2-17 IgG (1 μM), and/or G9.1-8m13 IgG (1 μM) for 6 hours (Fig. 23A).Cells were then stained with annexin-V and PI followed by flow cytometry analysis. AnnexinV positive cells represent cells in both early and late stage apoptosis. Bars represent average of three replicates, represented as individual data points. Statistical analysis performed by unpaired Student's *t*-test. (*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001).

Fig. 24 depicts a graph showing the readout of assays demonstrating anti-Galectin-9 antibodies disclosed herein disrupt the interaction between Galectin-9 and CD206. Fig. 24A depicts a graph showing an ELISA measuring the interaction between immobilized human Galectin-9 and soluble CD206 in the absence and presence of the addition of G9.1-8m13, or G9.2-17 antibody. Isotype antibody wells serves as control. Galectin-9 coated wells were incubated with CD206 with or without G9.1-8m13, G9.2-17, a combination of both antibodies, or an isotype. (Experiments performed in triplicate; *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; by unpaired Student's t-test). These results indicate that both G9.1-8m13 and G9.2-17 antibodies inhibit the interaction between Galectin-9 and CD206 and their effects are additive.

Fig. 25 depicts a line graph showing binding of purified G9.1-8m12-14 mIgG2a antibodies to human Galectin-9 CRD2 as compared to G9.18 (WT) as characterized using a bead-based binding assay.

Figs. 26A and ***26B*** depict bar graphs showing TNF-alpha (Fig. 26A) and IFNgamma (Fig. 26B) expression in CD3+ T cells in pancreatic adenocarcinoma primary tumor sample patient-derived organotypic tumor spheroids (PDOTs) treated with 9.2-17 IgG4 (100 nM) as compared to isotype control (100 nM).

Figs. 27A - 27C depict bar graphs showing CD44 (Fig. 27A), TNF-alpha (Fig. 27B) and IFNgamma (Fig. 27C) expression in CD3+ T cells in pancreatic adenocarcinoma primary tumor sample patient-derived organotypic tumor spheroids (PDOTS) treated with 9.2-17 IgG1 (100 nM) or 9.2-17 IgG4 (100 nM) as compared to IgG1 or IgG4 isotype control (100 nM).

Figs. 28A – 28F depict bar graphs showing immune profile expression in a Gall Bladder Cancer tumor sample (PDOTS) treated with 9.2-17 IgG4 (100 nM) as compared to IgG4 isotype control (100 nM); CD44 in CD3+ T cells (Fig. 28A), TNF-alpha in CD3+ T cells (Fig. 28B), CD44 in CD4+ T cells (Fig. 28C), TNF-alpha in CD4+ T cells (Fig. 28D), CD44 in CD8+ T cells (Fig. 28E), TNF-alpha in CD8+ T cells (Fig. 28F).

Figs. 29A - 29C depict bar graphs showing CD44 (Fig. 29A), TNF-alpha (Fig. 29B) and IFNgamma (Fig. 29C) expression in CD3+ T cells in a sample of liver metastasis from a colorectal cancer patient (PDOTs) treated with 9.2-17 IgG1 (100 nM) or 9.2-17 IgG4 (100 nM) as compared to IgG1 (100 nM) or untreated control (Utx).

Fig. 30 depicts a line graph showing the effect of 9.2-17 in a B16F10 subcutaneous syngeneic model. Tumors were engrafted subcutaneously and treated with G9.2-17 IgG1 mouse mAb. Animals were dosed on day 0 and day 4 intravenously (i.v.) unless otherwise specified in the legend.

Fig. 31 depicts a line graph showing the effect of 9.2-17 in a B16F10 subcutaneous syngeneic model. Tumors were engrafted subcutaneously and treated with G9.2-17 IgG2a mouse mAb. Animals were dosed on day 0 and once every 4 days thereafter until the end of the experiment. mAbs were administered i.v. unless otherwise specified in the legend.

Fig. 32 depicts a graph showing a cell based binding assay CRL-2134 cell lines were incubated with a biotinylated Fab, and bound Fab was detected using neutravidin conjugated with DyLight 650. Samples were then analyzed using flow cytometry. Strong signals were observed for the Galectin-9 antibody 9.2-17, but not for the isotype controls. The K_D (nM) values for the Gal-9 antibodies in the two formats were as follows: G9.2-17 hIgG1: 0.41±0.07; G9.2-17 mIgG1: 2.91±0.66.

Fig. 33A and ***33B*** depict graphs showing a thermal stability determination of anti-Galectin-9 antibodies. The first derivative of the fluorescence emission plotted as a function of temperature (−dF/dT). The melting temperature is represented as the temperature at which a peak is observed. Thermal transition was determined using change in binding of fluorophor SYPRO Orange (ThermoFisher) using a real-time PCR instrument with a heating rate of 1°C per minute, essentially following a method as described in Vedadi et al., Chemical screening

methods to identify ligands that promote protein stability, protein crystallization, and structure determination; Proc Natl Acad Sci U S A. 2006 Oct 24;103(43):15835-40.

DETAILED DESCRIPTION OF INVENTION

Provided herein are antibodies capable of binding to Galectin-9 (*e.g.*, human, mouse, or both). In some embodiments, the anti-Galectin-9 antibodies bind to one or more epitopes in the CRD1 and/or CRD2 domains. Such anti-Galectin-9 antibodies are capable of suppressing the signaling mediated by Galectin-9 (*e.g.*, the signaling pathway mediated by Galectin-9/Dectin-1 or Galectin-9/Tim-3) or eliminating pathologic cells expressing Galectin-9 via, *e.g.*, ADCC. Accordingly, the anti-Galectin-9 antibodies described herein can be used for inhibiting any of the Galectin-9 signaling and/or eliminating Galectin-9 positive pathologic cells, thereby benefiting treatment of diseases associated with Galectin-9, for example, autoimmune diseases, solid tumors, allergic disorders, or hematological disorders such as hematological malignancies.

Galectin-9, a tandem-repeat lectin, is a beta-galactoside-binding protein, which has been shown to have a role in modulating cell-cell and cell-matrix interactions. It is found to be strongly overexpressed in Hodgkin's disease tissue and in other pathologic states. It may also be found circulating in the tumor microenvironment (TME).

Galectin-9 is found to interact with Dectin-1, an innate immune receptor which is highly expressed on macrophages in PDA, as well as on cancer cells (Daley D, et al. Dectin 1 activation on macrophages by galectin 9 promotes pancreatic carcinoma and peritumoral immune tolerance; *Nat Med.* 2017;23(5):556-6). Regardless of the source of Galectin-9, disruption of its interaction with Dectin-1 has been shown to lead to the reprogramming of $CD4^+$ and $CD8^+$ cells into indispensable mediators of anti-tumor immunity. Thus, Galectin-9 serves as a valuable therapeutic target for blocking the signaling mediated by Dectin-1. Accordingly, in some embodiments, the anti-Galectin-9 antibodies describe herein disrupt the interaction between Galectin-9 and Dectin-1.

Galectin-9 is also found to interact with TIM-3, a type I cell surface glycoprotein expressed on the surface of leukemic stem cells in all varieties of acute myeloid leukemia (except for M3 (acute promyelocytic leukemia)), but not expressed in normal human hematopoietic stem cells (HSCs). TIM-3 signaling resulting from Galectin-9 ligation has been found to have a pleiotropic effect on immune cells, inducing apoptosis in Th1 cells (Zhu et al., *Nat Immunol.*, 2005, 6:1245-1252) and stimulating the secretion of tumor necrosis factor-α (TNF-α), leading to the maturation of monocytes into dendritic cells, resulting in inflammation by innate immunity (Kuchroo et al., *Nat Rev Immunol.*, 2008, 8:577-580). Further Galectin-

9/TIM-3 signaling has been found to co-activate NF-κB and β-catenin signaling, two pathways that promote LSC self-renewal (Kikushige et al., *Cell Stem Cell,* 2015, 17(3):341-352). An anti-Galectin-9 antibody that interferes with Galectin-9/TIM-3 binding could have a therapeutic effect, especially with respect to leukemia and other hematological malignancies. Accordingly, in some embodiments, the anti-Galectin-9 antibodies described herein disrupt the interaction between Galectin-9 and TIM-3.

Galectin-9 is also found to interact with CD206, a mannose receptor highly expressed on M2 polarized macrophages, thereby promoting tumor survival (Enninga et al., CD206-positive myeloid cells bind galectin-9 and promote a tumor-supportive microenvironment. J Pathol. 2018 Aug;245(4):468-477). Tumor-associated macrophages expressing CD206 are mediators of tumor immunosuppression, angiogenesis, metastasis, and relapse (see, e.g., Scodeller et al., Precision Targeting of Tumor Macrophages with a CD206 Binding Peptide. M1 and M2 had been described as the functional states of macrophages; Sci Rep. 2017 Nov 7;7(1):14655, and references therein). Specifically, M1 (also termed classically activated macrophages) are trigged by Th1-related cytokines and bacterial products, express high levels of IL-12, and are tumoricidal. By contrast, M2 (so-called alternatively activated macrophages) are activated by Th2-related factors, express high level of anti-inflammatory cytokines, such as IL-10, and facilitate tumor progression (Biswas and Mantovani; Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm; Nat Immunol. 2010 Oct; 11(10):889-96). The pro-tumoral effects of M2 include the promotion of angiogenesis, advancement of invasion and metastasis, and the protection of the tumor cells from chemotherapy-induced apoptosis (Hu et al., Functional significance of macrophages in pancreatic cancer biology;Tumour Biol. 2015 Dec; 36(12): 9119–9126, and references therein). Tumor-associated macrophages are thought be of M2-like phenotype and have a protumor role. Galectin-9 has been shown to mediate myeloid cell differentiation toward an M2 phenotype (Enninga et al., Galectin-9 modulates immunity by promoting Th2/M2 differentiation and impacts survival in patients with metastatic melanoma; Melanoma Res. 2016 Oct;26(5):429-41). It is possible that Galectin-9 binding CD206 may result in reprogramming TAMs towards the M2 phenotype, similar to what has been previously shown for Dectin. Without wishing to be bound by theory, blocking the interaction of Galectin-9 with CD206 may provide one mechamism by which an anti-Galectin antibody, e.g., es described herein in Table 1 and Table 2, such as antibody 9.1-8m13 and/or antibody 9.2-17, can be therapeutically beneficial. Accordingly, in some embodiments, the anti-Galectin-9 antibodies described herein disrupt the interaction between Galectin-9 and CD206.

Galectin-9 has also been shown to interact with protein disulfide isomerase (PDI) and 4-1BB (Bi S, et al. Galectin-9 binding to cell surface protein disulfide isomerase regulates the redox environment to enhance T-cell migration and HIV entry; Proc Natl Acad Sci U S A. 2011;108(26):10650-5; Madireddi et al. Galectin-9 controls the therapeutic activity of 4-1BB-targeting antibodies. J Exp Med. 2014;211(7):1433-48).

Anti-Galectin-9 antibodies can serve as therapeutic agents for treating diseases associated with Galectin-9 (*e.g.*, those in which a Galectin-9 signaling plays a role). Without being bound by theory, an anti-Galectin-9 antibody may block a signaling pathway mediated by Galectin-9. For example, the antibody may interfere with the interaction between Galectin-9 and its binding partner (*e.g.*, Dectin-1, TIM-3 or CD206), thereby blocking the signaling triggered by the Galectin-9/Ligand interaction. Alternatively, or in addition, an anti-Galectin-9 antibody may also exert its therapeutic effect by inducing blockade and/or cytotoxicity, for example, ADCC, CDC, or ADCP against pathologic cells that express Galectin-9. A pathologic cell refers to a cell that contributes to the initiation and/or development of a disease, either directly or indirectly.

Accordingly, described herein are anti-Galectin-9 antibodies and therapeutic uses thereof for treating diseases associated with Galectin-9.

Antibodies Binding to Galectin-9

The present disclosure provides antibodies that bind Galectin-9, for example, human and/or mouse Galectin-9.

In some instances, the anti-Galectin antibody described herein binds to an epitope in a carbohydrate recognition domain (CRD) of Galectin-9, *e.g.*, CRD1 or CRD2. . In some instances, the anti-Galectin antibody may bind to CRD1 and CRD2. Galectin-9 is a protein well known in the art. For example, NCBI GenBank Accession Nos. BAB83625.1 and NP_034838.2 provide information for human and mouse Galectin-1, respectively. Provided herein are exemplary human and mouse Galectin-9 polypeptides; Human galectin-9 (isoform 1; aka "long;") is provided as SEQ ID NO: 1; human CRD1 and CRD2 are provided herein as SEQ ID NO: 3 and SEQ ID NO: 4, respectively; mouse galectin-9 (isoform 1; aka "long;") is provided as SEQ ID NO: 2; human and mouse CRD1 and CRD2 are provided herein as SEQ ID NO: 5 and SEQ ID NO: 6, respectively.

The CRD1 domain of human Galectin-9 (SEQ ID NO: 3) encompasses residues 1-148 of SEQ ID NO:1, and the CRD2 domain (SEQ ID NO: 4) spans residues 218-355 of SEQ ID NO: 1. Similarly, the CRD1 domain of murine Galectin-9 (SEQ ID NO: 5) spans residues 1-147 of

SEQ ID NO:2, and the CRD2 domain (SEQ ID NO: 6) spans residues 226-353 of SEQ ID NO: 2.

Galectin-9 polypeptides from other species are known in the art and can be obtained from publicly available gene database, for example, GenBank, using either the human sequence or the mouse sequence as a query. The CRD1 and CRD2 domains of a Galectin-9 polypeptide can be identified by aligning the sequence of that Galectin-9 polypeptide with that of the human or mouse Galectin-9 as described herein.

The antibodies described herein bind Galectin-9 or a fragment thereof (*e.g.*, CRD1 or CRD2). As used herein, the term "anti-Galectin-9 antibody" refers to any antibody capable of binding to a Galectin-9 polypeptide, which can be of a suitable source, for example, human or a non-human mammal (*e.g.*, mouse, rat, rabbit, primate such as monkey, etc.). In some embodiments, the anti-Galectin-9 antibody can be used therapeutically to suppress the bioactivity of Galectin-9. In some embodiments, the anti-Galectin-9 antibody may be used in research or may be used in diagnostic/prognostic methods, *e.g.,* for the detection of cells expressing Galectin-9 in an assessment of treatment eligibility and/or efficacy. Alternatively, or in addition, an anti-Galectin-9 antibody may block the interaction between Galectin-9 and its ligand (*e.g.,* Dectin-1, TIM-3), thereby suppressing the signaling pathway triggered by, for example, the Galectin-9/Dectin-1 or Galectin-9/TIM-3 interaction. An anti-Galectin-9 antibody may also elicit the death of cells expressing Galectin-9, for example, through an antibody-dependent cellular cytotoxicity (ADCC) mechanism.

An antibody (interchangeably used in plural form) is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term "antibody", *e.g.*, anti-Galectin-9 antibody, encompasses not only intact (*e.g.,* full-length) polyclonal or monoclonal antibodies, but also antigen-binding fragments thereof (such as Fab, Fab', F(ab')2, Fv), single chain (scFv), mutants thereof, fusion proteins comprising an antibody portion, humanized antibodies, chimeric antibodies, diabodies, nanobodies, linear antibodies, single chain antibodies, multispecific antibodies (*e.g.,* bispecific antibodies) and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site of the required specificity, including glycosylation variants of antibodies, amino acid sequence variants of antibodies, and covalently modified antibodies. An antibody, e.g., anti-Galectin-9 antibody, includes an antibody of any class, such as IgD, IgE, IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class. Depending on the antibody amino acid sequence of

the constant domain of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), *e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The heavy-chain constant domains that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

A typical antibody molecule comprises a heavy chain variable region (V_H) and a light chain variable region (V_L), which are usually involved in antigen binding. The V_H and V_L regions can be further subdivided into regions of hypervariability, also known as "complementarity determining regions" ("CDR"), interspersed with regions that are more conserved, which are known as "framework regions" ("FR"). Each V_H and V_L is typically composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The extent of the framework region and CDRs can be precisely identified using methodology known in the art, for example, by the Kabat definition, the Chothia definition, the AbM definition, and/or the contact definition, all of which are well known in the art. See, *e.g.*, Kabat, E.A., *et al.* (1991) *Sequences of Proteins of Immunological Interest, Fifth Edition*, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, Chothia et al., (1989) Nature 342:877; Chothia, C. et al. (1987) J. Mol. Biol. 196:901-917, Al-lazikani et al (1997) J. Molec. Biol. 273:927-948; and Almagro, J. Mol. Recognit. 17:132-143 (2004).

The anti-Galectin-9 antibody described herein may be a full-length antibody, which contains two heavy chains and two light chains, each including a variable domain and a constant domain. Alternatively, the anti-Galectin-9 antibody can be an antigen-binding fragment of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding fragment" of a full length antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and C_H1 domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment including two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and C_H1 domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward *et al.*, (1989) *Nature* 341:544-546), which consists of a V_H domain; and (vi) an isolated complementarity determining region (CDR) that retains functionality. Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a

synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules known as single chain Fv (scFv). See *e.g.*, Bird *et al.* (1988) *Science* 242:423-426; and Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883.

The anti-Galectin-9 antibody as described herein, e.g., in Table 1 and/or Table 2, can bind and inhibit (e.g., reduce or eliminate) the activity of Galectin-9. In some embodiments, the anti-Galectin-9 antibody as described herein can bind and inhibit the activity of Galectin-9 by at least 30% (*e.g.*, 31%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). The apparent inhibition constant (Ki^{app} or $K_{i,app}$), which provides a measure of inhibitor potency, is related to the concentration of inhibitor required to reduce enzyme activity and is not dependent on enzyme concentrations. The inhibitory activity of an anti-Galectin-9 antibody described herein can be determined by routine methods known in the art.

The $K_{i,}^{app}$ value of an antibody may be determined by measuring the inhibitory effect of different concentrations of the antibody on the extent of the reaction (*e.g.*, enzyme activity); fitting the change in pseudo-first order rate constant (v) as a function of inhibitor concentration to the modified Morrison equation (Equation 1) yields an estimate of the apparent Ki value. For a competitive inhibitor, the Ki^{app} can be obtained from the y-intercept extracted from a linear regression analysis of a plot of $K_{i,}^{app}$ versus substrate concentration.

$$v = A \cdot \frac{([E]-[I]-K_i^{app}) + \sqrt{([E]-[I]-K_i^{app})^2 + 4[E]\cdot K_i^{app}}}{2} \qquad \text{(Equation 1)}$$

Where A is equivalent to v_o/E, the initial velocity (v_o) of the enzymatic reaction in the absence of inhibitor (I) divided by the total enzyme concentration (E). In some embodiments, the anti-Galectin-9 antibody described herein may have a Ki^{app} value of 1000, 900, 800, 700, 600, 500, 400, 300, 200, 100, 50, 40, 30, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5 pM or less for the target antigen or antigen epitope. In some embodiments, the anti-Galectin-9 antibody may have a lower Ki^{app} for a first target (*e.g.*, the CRD2 of Galectin-9) relative to a second target (*e.g.*, CRD1 of Galectin-9). Differences in Ki^{app} (*e.g.*, for specificity or other comparisons) can be at least 1.5, 2, 3, 4, 5, 10, 15, 20, 37.5, 50, 70, 80, 91, 100, 500, 1000, 10,000 or 10^5 fold. In some examples, the anti-Galectin-9 antibody inhibits a first antigen (*e.g.*, a first protein in a first conformation or mimic thereof) greater relative to a second antigen (*e.g.*,

the same first protein in a second conformation or mimic thereof; or a second protein). In some embodiments, any of the anti-Galectin-9 antibodies may be further affinity matured to reduce the Ki^{app} of the antibody to the target antigen or antigenic epitope thereof.

In some embodiments, the anti-Galectin-9 antibody suppresses the Dectin-1 signaling, e.g., in tumor infiltrating immune cells, such as macrophages. In some embodiments, the anti-Galectin-9 antibody suppresses the Dectin-1 signaling triggered by Galectin-9 by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). Such inhibitory activity can be determined by conventional methods or the assays described herein, for example, Example 2. Alternatively or in addition, the anti-Galectin-9 antibody may suppress the T cell immunoglobulin mucin-3 (TIM-3) signaling initiated by Galectin-9. In some embodiments, the anti-Galectin-9 antibody suppresses the T cell immunoglobulin mucin-3 (TIM-3) signaling, e.g., in tumor infiltrating immune cells, e.g., in some embodiments by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). Such inhibitory activity can be determined by conventional methods or the assays described herein, for example, Example 2.

In some embodiments, the anti-Galectin-9 antibody suppresses the CD206 signaling, e.g., in tumor infiltrating immune cells. In some embodiments, the anti-Galectin-9 antibody suppresses the CD206 signaling triggered by Galectin-9 by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). Such inhibitory activity can be determined by conventional methods or the assays described herein, for example, Example 13. In some embodiments, the anti-Galectin-9 antibody blocks or prevents binding of Galectin-9 to CD206 by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). Such inhibitory activity can be determined by conventional methods or the assays described herein, for example, Example 13.

In some embodiments, any of the anti-Galectin-9 antibodies described herein induce cell cytotoxicity, such as ADCC, in target cells expressing Galectin-9, e.g., wherein the target cells are cancer cells or immune suppressive immune cells. In some embodiments, the anti-Galectin-9 antibody induces apoptosis in immune cells, such as T cells, or cancer cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). Such inhibitory activity can be determined by conventional methods or the assays described herein, for example, Example 14. In some embodiments, any of the anti-Galectin-9 antibodies described herein induce cell cytotoxicity such as complement-dependent cytotoxicity (CDC) against target cells expressing Galectin-9.

Antibody-dependent cell-mediated phagocytosis (ADCP) is an important mechanism of action for antibodies that mediate part or all of their action though phagocytosis. In that case, antibodies mediate uptake of specific antigens by antigen presenting cells. ADCP can be mediated by monocytes, macrophages, neutrophils, and dendritic cells, through FcγRIIa, FcγRI, and FcγRIIIa, of which FcγRIIa (CD32a) on macrophages represent the predominant pathway.

In some embodiments, any of the anti-Galectin-9 antibodies described herein induce cell phagocytosis of target cells, e.g., cancer cells or immune suppressive immune cells expressing Galectin-9 (ADCP). In some embodiments, the anti-Galectin-9 antibody increases phagocytosis of target cells, e.g., cancer cells or immune suppressive immune cells, by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein).

In some embodiments, any of the anti-Galectin-9 antibodies described herein induce cell cytotoxicity such as complement-dependent cytotoxicity (CDC) against target cells, e.g., cancer cells or immune suppressive immune cells. In some embodiments, the anti-Galectin-9 antibody increases CDC against target cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein).

In some embodiments, any of the anti-Galectin-9 antibodies described herein induce T cell activation, e.g., in tumor infiltrating T cells, i.e., suppress Galectin-9 mediated inhibition of T cell activation, either directly or indirectly. In some embodiments, the anti-Galectin-9 antibody promotes T cell activation by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). T cell activation can be determined by conventional methods or the assays described herein, for example, Example 6 (e.g., measurement of CD44, OX40, IFNgamma, PD-1). In some embodiments, the anti-Galectin-9 antibody promotes CD4+ cell activation by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). In a non-limiting example, the anti-Galectin antibody induces CD44 expression in CD4+ cells. In some embodiments, the anti-Galectin-9 antibody increases CD44 expression in CD4+ cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). In a non-limiting example, the anti-Galectin antibody induces IFNgamma expression in CD4+ cells. In some embodiments, the anti-Galectin-9 antibody increases IFNgamma expression in CD4+ cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). In a non-limiting example, the anti-Galectin antibody induces TNFalpha expression in CD4+ cells. In some embodiments, the anti-Galectin-9 antibody increases TNFalpha expression in CD4+ cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein).

In some embodiments, the anti-Galectin-9 antibody promotes CD8+ cell activation by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater), including any increment therein). In a non-limiting example, the anti-Galectin antibody induces CD44 expression in CD8+ cells. In some embodiments, the anti-Galectin-9 antibody increases CD44 expression in CD8+ cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). In a non-limiting example, the anti-Galectin antibody induces IFNgamma expression in CD8+ cells. In some embodiments, the anti-Galectin-9 antibody increases IFNgamma expression in CD8+ cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). In a non-limiting example, the anti-Galectin antibody induces TNFalpha expression in CD8+ cells. In some embodiments, the anti-Galectin-9 antibody increases TNFalpha expression in CD8+ cells by at least 30% (*e.g.*, 31%, 35%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein).

The antibodies described herein can be murine, rat, human, or any other origin (including chimeric or humanized antibodies). Such antibodies are non-naturally occurring, *i.e.*, would not be produced in an animal without human act (*e.g.*, immunizing such an animal with a desired antigen or fragment thereof or isolated from antibody libraries).

Any of the antibodies described herein, e.g., anti-Galectin-9 antibody, can be either monoclonal or polyclonal. A "monoclonal antibody" refers to a homogenous antibody population and a "polyclonal antibody" refers to a heterogeneous antibody population. These two terms do not limit the source of an antibody or the manner in which it is made.

In some embodiments, the anti-Galectin-9 antibody is a humanized antibody. In some embodiments, the anti-Galectin-9 antibody is a humanized antibody having one of more of the elements or characteristics described below or elsewhere herein. Humanized antibodies refer to forms of non-human (*e.g.*, murine) antibodies that are specific chimeric immunoglobulins, immunoglobulin chains, or antigen-binding fragments thereof that contain minimal sequence derived from non-human immunoglobulin. In general, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, the humanized antibody may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences, but are included to further refine and optimize antibody performance. In some instances, the humanized antibody

may comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Antibodies may have Fc regions modified as described in WO 99/58572. Other forms of humanized antibodies have one or more CDRs (one, two, three, four, five, or six) which are altered with respect to the original antibody, which are also termed one or more CDRs "derived from" one or more CDRs from the original antibody. Humanized antibodies may also involve affinity maturation.

Methods for constructing humanized antibodies are also well known in the art. See, *e.g.*, Queen *et al.*, Proc. Natl. Acad. Sci. USA, 86:10029-10033 (1989). In one example, variable regions of V_H and V_L of a parent non-human antibody are subjected to three-dimensional molecular modeling analysis following methods known in the art. Next, framework amino acid residues predicted to be important for the formation of the correct CDR structures are identified using the same molecular modeling analysis. In parallel, human V_H and V_L chains having amino acid sequences that are homologous to those of the parent non-human antibody are identified from any antibody gene database using the parent V_H and V_L sequences as search queries. Human V_H and V_L acceptor genes are then selected.

The CDR regions within the selected human acceptor genes can be replaced with the CDR regions from the parent non-human antibody or functional variants thereof. When necessary, residues within the framework regions of the parent chain that are predicted to be important in interacting with the CDR regions can be used to substitute for the corresponding residues in the human acceptor genes.

In some embodiments, the anti-Galectin-9 antibody is a chimeric antibody. In some embodiments, the anti-Galectin-9 antibody is a chimeric antibody which may include a heavy constant region and a light constant region from a human antibody. Chimeric antibodies refer to antibodies having a variable region or part of variable region from a first species and a constant region from a second species. Typically, in these chimeric antibodies, the variable region of both light and heavy chains mimics the variable regions of antibodies derived from one species of mammals (*e.g.*, a non-human mammal such as mouse, rabbit, and rat), while the constant portions are homologous to the sequences in antibodies derived from another mammal such as human. In some embodiments, amino acid modifications can be made in the variable region and/or the constant region.

In some embodiments, the anti-Galectin-9 antibodies described herein specifically bind to the corresponding target antigen or an epitope thereof, e.g., Galectin-9 antigen or epitope. An antibody that "specifically binds" to an antigen or an epitope is a term well understood in the art. A molecule is said to exhibit "specific binding" if it reacts more frequently, more rapidly, with greater duration and/or with greater affinity with a particular target antigen than it does with alternative targets. An antibody "specifically binds" to a target antigen or epitope if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances. For example, an antibody that specifically (or preferentially) binds to an antigen (Galectin-9) or an antigenic epitope therein is an antibody that binds this target antigen with greater affinity, avidity, more readily, and/or with greater duration than it binds to other antigens or other epitopes in the same antigen. It is also understood with this definition that, for example, an antibody that specifically binds to a first target antigen may or may not specifically or preferentially bind to a second target antigen. As such, "specific binding" or "preferential binding" does not necessarily require (although it can include) exclusive binding. In some examples, an antibody that "specifically binds" to a target antigen or an epitope thereof may not bind to other antigens or other epitopes in the same antigen *(i.e.*, only baseline binding activity can be detected in a conventional method). In some embodiments, the anti-Galectin-9 antibodies described herein specifically bind to Galectin-9. In some embodiments, the anti-Galectin-9 antibodies described herein specifically bind to the CRD2 of Galectin-9. In some embodiments, the anti-Galectin-9 antibodies described herein specifically bind to the CRD1 of Galectin-9. Alternatively, or in addition, the anti-Galectin-9 antibody described herein specifically binds human Galectin-9 or a fragment thereof as relative to the mouse counterpart, or *vice versa* (*e.g.*, having a binding affinity at least 10-fold higher to one antigen than the other as determined in the same assay under the same assay conditions).

In some embodiments, the anti-Galectin -9 antibody binds only to CRD1 (and not CRD2), for example, meaningful binding to CRD2 or binding to CRD2 is not detectable by a routine assay method. In some embodiments, the anti-Galectin -9 or a fragment thereof binds only to CRD2 (and not CRD1). In some embodiments, certain antibodies described herein may bind to both CRD1 and CRD2. In some embodiments, certain antibodies or fragments thereof described herein may bind to both CRD1 and CRD2, but with a lower affinity to CRD2. In some embodiments, certain antibodies or fragments thereof described herein may bind to both CRD1 and CRD2, but with a lower affinity to CRD1.

In some embodiments, the effect of a CRD1 binding Gal-9 antibody and a CRD2 binding Gal-9 antibody may be additive. In some embodiments, the effect of a CRD1 binding Gal-9

antibody and a CRD2 binding Gal-9 antibody may be synergistic. In some embodiments, a "cocktail" *i.e.*, a mixture of two or more antibodies may be used in a composition. Such compositions may comprise one or more antibodies that bind to CRD1 described herein and one or more antibodies that bind to CRD2 described herein. In a non-limiting example, an antibody comprising the variable region of clone 9.1-8m13 (e.g., SEQ ID NO: 21 (light chain and SEQ ID NO: 86) can be combined with an antibody comprising the variable region of clone 9.2-17 (SEQ ID NO: 54 (light chain and SEQ ID NO: 55) in a composition. Antibodies may be mixed in equimolar amounts or in other ratios, as determined optimal for performance.

In some embodiments, an antibody might bind to both CRD1 and CRD2. In other instances, the anti-Galectin-9 antibody described herein may cross-react to human and a non-human Galectin-9 (*e.g.*, mouse), *e.g.*, the difference in binding affinity to the human and the non-human Galectin-9 is less than 5-fold, *e.g.*, less than 2-fold, or substantially similar.

In some embodiments, an anti-Galectin-9 antibody as described herein has a suitable binding affinity for the target antigen (*e.g.*, Galectin-9) or antigenic epitopes thereof. As used herein, "binding affinity" refers to the apparent association constant or K_A. The K_A is the reciprocal of the dissociation constant (K_D). The anti-Galectin-9 antibody described herein may have a binding affinity (K_D) of at least 10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10} M, or lower for the target antigen or antigenic epitope. An increased binding affinity corresponds to a decreased K_D. Higher affinity binding of an antibody for a first antigen relative to a second antigen can be indicated by a higher K_A (or a smaller numerical value K_D) for binding the first antigen than the K_A (or numerical value K_D) for binding the second antigen. In such cases, the antibody has specificity for the first antigen (*e.g.*, a first protein in a first conformation or mimic thereof) relative to the second antigen (*e.g.*, the same first protein in a second conformation or mimic thereof; or a second protein). In some embodiments, the anti-Galectin-9 antibodies described herein have a higher binding affinity (a higher K_A or smaller K_D) to the CRD1 of Galectin-9 as compared to the binding affinity to the CRD2 of Galectin-9. In some embodiments, the anti-Galectin-9 antibodies described herein have a higher binding affinity (a higher K_A or smaller K_D) to the CRD2 of Galectin-9 as compared to the binding affinity to the CRD1 of Galectin-9. Differences in binding affinity (*e.g.*, for specificity or other comparisons) can be at least 1.5, 2, 3, 4, 5, 10, 15, 20, 37.5, 50, 70, 80, 91, 100, 500, 1000, 10,000 or 10^5 fold. In some embodiments, any of the anti-Galectin-9 antibodies may be further affinity matured to increase the binding affinity of the antibody to the target antigen or antigenic epitope thereof.

Binding affinity (or binding specificity) can be determined by a variety of methods including equilibrium dialysis, equilibrium binding, gel filtration, ELISA, surface plasmon

resonance, or spectroscopy (*e.g.*, using a fluorescence assay). Exemplary conditions for evaluating binding affinity are in HBS-P buffer (10 mM HEPES pH7.4, 150 mM NaCl, 0.005% (v/v) Surfactant P20).

These techniques can be used to measure the concentration of bound binding protein as a function of target protein concentration. Under certain conditions, the fractional concentration of bound binding protein ([Bound]/[Total]) is generally related to the concentration of total target protein ([Target]) by the following equation:

$$[Bound]/[Total] = [Target]/(Kd+[Target])$$

It is not always necessary to make an exact determination of K_A, though, since sometimes it is sufficient to obtain a quantitative measurement of affinity, *e.g.*, determined using a method such as ELISA or FACS analysis, is proportional to K_A, and thus can be used for comparisons, such as determining whether a higher affinity is, *e.g.*, 2-fold higher, to obtain a qualitative measurement of affinity, or to obtain an inference of affinity, *e.g.*, by activity in a functional assay, *e.g.*, an *in vitro* or *in vivo* assay. In some cases, the *in vitro* binding assay is indicative of *in vivo* activity. In other cases, the *in vitro* binding assay is not necessarily indicative of *in vivo* activity. In some cases tight binding is beneficial, but in other cases tight binding may not be as desirable *in vivo*, and an antibody with lower binding affinity may be more desirable. A number of exemplary anti-Galectin-9 antibodies (specific to CRD1 or CRD2) are provided herein.

Exemplary antibody clones (reference antibodies) of the disclosure binding 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. Exemplary antibody clones (reference antibodies) of the disclosure binding 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.

Variable regions

Exemplary anti-Galectin-9 antibodies described herein binding to CRD1 are antibodies, e.g., monoclonal, recombinant, and/or human antibodies, having the CDR and/or variable region sequences of antibodies 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. Exemplary anti-Galectin-9 antibodies described herein binding to CRD2 are antibodies, e.g., monoclonal, recombinant, and/or human antibodies, having the CDR and/or variable region sequences of antibodies 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. Exemplary sequences and SEQ ID NOs are listed in Table 1 and 2. CDRs determined using the Kabat methodology are shown in boldface. Table 3 presents the CDRs, determined with Kabat methodology, of selected clones. Herein the terms "m" and "mut", e.g., "9.1-8m" and "9.1-8mut" are used interchangeably. For example, the "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" are used interchangeably with "G9.1-8mut1", "G9.1-8mut2", "G9.1-8mut3", "G9.1-8mut4", "G9.1-8mut5", "G9.1-8mut6", "G9.1-8mut7", "G9.1-8mut8", "G9.1-8mut9", "G9.1-8mut10", "G9.1-8mut11", "G9.1-8mut12", "G9.1-8mut13", and "G9.1-8mut14, respectively.

Table 1. Antibodies directed against CRD1

Clone	Sequence	VR	CDR 1	CDR 2	CDR 3	LC/ HC IgG1	IgG1 LALA	IgG4	IgG 4 mut
		SEQ ID NO:							
G9.1-1	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF SGSRSGTDFTLTISSLQPEDFAT YYC**QQSWVGSLIT**FGQGTKV EIKR	7	328	329	330	88	88	88	88
G9.1-1	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTFSSSSIH**WVRQAP GKGLEWVA**SIYSSYGYTYYA DSVKG**RFTISADTSKNTAYLQ MNSLRAEDTAVYYCAR**YYW GWSQNQGFWWYGLDY**WGQ GTLVTVSS	8	431	438	367	116	169	222	275
G9.1-2	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF SGSRSGTDFTLTISSLQPEDFAT YYC**QQWQWGYSLVT**FGQGT KVEIKR	9	328	329	331	89	89	89	89
G9.1-2	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTISSSSIH**WVRQAP GKGLEWVA**SISSYYGSTYYAD SVKG**RFTISADTSKNTAYLQM NSLRAEDTAVYYCAR**SWSSSF WYNWALDY**WGQGTLVTVSS	10	435	439	368	117	170	223	276

G9.1-3	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQSWYSNKPIT**FGQGTKVEIKR	11	328	329	332	90	90	90	90
G9.1-3	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTIYSSSIH**WVRQAPGKGLEWVA**YIYSSSGYTSYADSVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**YSHSSLYYSWIWALDY**WGQGTLVTVSS	12	436	363	369	118	171	224	277
G9.1-4	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQSSSSLIT**FGQGTKVEIKR	13	328	329	333	91	91	91	91
G9.1-4	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTIYYSSIH**WVRQAPGKGLEWVA**SISSSSGSTSYADSVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**SYRPYSSYYWGMDY**WGQGTLVTVSS	14	437	440	370	119	172	225	278
G9.1-5	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQYYGWFYPVT**FGQGTKVEIKR	15	328	329	334	92	92	92	92
G9.1-5	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTIYYSSIH**WVRQAPGKGLEWVA**SISSSYGSTYYADSVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**SVSWYPYYYYYGYGSGLDY**WGQGTLVTVSS	16	437	441	371	120	173	226	279
G9.1-6	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQYHSSLFT**FGQGTKVEIKR	17	328	329	335	93	93	93	93
G9.1-6	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTLSSSSIH**WVRQAPGKGLEWVA**SIYSSYGSTSYADSVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**SSHWYMYWSYWGWYIGMDY**WGQGTLVTVSS	18	427	442	372	121	174	227	280
G9.1-7	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQYPGYRGLIT**FGQGTKVEIKR	19	328	329	336	94	94	94	94
G9.1-7	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTVSSSSIH**WVRQA	20	361	443	373	122	175	228	281

	PGKGLEWVA**SISSYYGYTYYA** **DSVKG**RFTISADTSKNTAYLQ MNSLRAEDTAVYYCAR**SYSY** **GYDYFVKYYTMDY**WGQGTL VTVSS								
G9.1-8	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF SGSRSGTDFTLTISSLQPEDFAT YYC**QQSYYDSNPIT**FGQGTKV EIKR	21	328	329	337	95	95	95	95
G9.1-8	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQA PGKGLEWVA**YIYPYSGYTSY** **ADSVKG**RFTISADTSKNTAYL QMNSLRAEDTAVYYCAR**YST** **YSWGGIGKWVWGMDY**WGQ GTLVTVSS	22	361	364	374	123	176	229	282
G9.1-9	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF SGSRSGTDFTLTISSLQPEDFAT YYC**QQSYFHKIPIT**FGQGTKV EIKR	23	328	329	338	96	96	96	96
G9.1-9	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQA PGKGLEWVA**YIYSSSGYTSYA** **DSVKG**RFTISADTSKNTAYLQ MNSLRAEDTAVYYCAR**YSSY** **HYPYWLFAMDY**WGQGTLVT VSS	24	361	363	384	138	191	244	297
G9.1-10	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF SGSRSGTDFTLTISSLQPEDFAT YYC**QQWYWYYPVT**FGQGTK VEIKR	25	328	329	339	97	97	97	97
G9.1-10	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSYSSIH**WVRQA PGKGLEWVA**SIYSYYGSTYYA** **DSVKG**RFTISADTSKNTAYLQ MNSLRAEDTAVYYCAR**GHYQ** **EGRKSGFSYWSPALDY**WGQ GTLVTVSS	26	429	444	385	139	192	245	298
G9.1-11	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF SGSRSGTDFTLTISSLQPEDFAT YYC**QQTYWGLIT**FGQGTKVE IKR	27	328	329	340	98	98	98	98
G9.1-11	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVYSSSIH**WVRQA PGKGLEWVA**SIYSYYGYTSYA** **DSVKG**RFTISADTSKNTAYLQ MNSLRAEDTAVYYCAR**STEG** **YDRWGYYSSYWSSGLDY**WG QGTLVTVSS	28	428	445	386	140	193	246	299
G9.1-8m1	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF	21	328	329	337	95	95	95	95

	SGSRSGTDFTLTISSLQPEDFAT YYC**QQSYYDSNPIT**FGQGTKV EIKR								
G9.1-8m1	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQA PGKGLEWVA**SSSSSSGYTSYA DSVKG**RFTISADTSKNTAYLQ MNSLRAEDTAVYYCAR**YSTY SWGGIGKWVWGMDY**WGQG TLVTVSS	74	361	365	374	124	177	230	283
G9.1-8m2	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF SGSRSGTDFTLTISSLQPEDFAT YYC**QQSYYDSNPIT**FGQGTKV EIKR	21	328	329	337	95	95	95	95
G9.1-8m2	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQA PGKGLEWVA**YIYPYSSSSSYA DSVKG**RFTISADTSKNTAYLQ MNSLRAEDTAVYYCAR**YSTY SWGGIGKWVWGMDY**WGQG TLVTVSS	75	361	366	374	125	178	231	284
G9.1-8m3	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF SGSRSGTDFTLTISSLQPEDFAT YYC**QQSYYDSNPIT**FGQGTKV EIKR	21	328	329	337	95	95	95	95
G9.1-8m3	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQA PGKGLEWVA**YIYPYSGYTSY ADSVKG**RFTISADTSKNTAYL QMNSLRAEDTAVYYCAR**SSSS SWGGIGKWVWGMDY**WGQG TLVTVSS	76	361	364	375	126	179	232	285
G9.1-8m4	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF SGSRSGTDFTLTISSLQPEDFAT YYC**QQSYYDSNPIT**FGQGTKV EIKR	21	328	329	337	95	95	95	95
G9.1-8m4	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQA PGKGLEWVA**YIYPYSGYTSY ADSVKG**RFTISADTSKNTAYL QMNSLRAEDTAVYYCAR**YST YSSSSSSKWVWGMDY**WGQG TLVTVSS	77	361	364	376	127	180	233	286
G9.1-8m5	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF SGSRSGTDFTLTISSLQPEDFAT YYC**QQSYYDSNPIT**FGQGTKV EIKR	21	328	329	337	95	95	95	95
G9.1-8m5	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQA PGKGLEWVA**YIYPYSGYTSY ADSVKG**RFTISADTSKNTAYL QMNSLRAEDTAVYYCAR**YST**	78	361	364	377	128	181	234	287

	YSWGGIGSSSSSMDYWGQGT LVTVSS								
G9.1-8m6	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF SGSRSGTDFTLTISSLQPEDFAT YYC**QQSYYDSNPIT**FGQGTKV EIKR	21	328	329	337	95	95	95	95
G9.1-8m6	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQA PGKGLEWVA**YIYPYSGYTSY ADSVKG**RFTISADTSKNTAYL QMNSLRAEDTAVYYCAR**YST YSSSSSKWVWGMDY**WGQGT LVTVSS	79	361	364	378	129	182	235	288
G9.1-8m7	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF SGSRSGTDFTLTISSLQPEDFAT YYC**QQSYYDSNPIT**FGQGTKV EIKR	21	328	329	337	95	95	95	95
G9.1-8m7	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQA PGKGLEWVA**YIYPYSGYTSY ADSVKG**RFTISADTSKNTAYL QMNSLRAEDTAVYYCAR**YST YSSSSKWVWGMDY**WGQGTL VTVSS	80	361	364	379	130	183	236	289
G9.1-8m8	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF SGSRSGTDFTLTISSLQPEDFAT YYC**QQSYYDSNPIT**FGQGTKV EIKR	21	328	329	f337	95	95	95	95
G9.1-8m8	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQA PGKGLEWVA**YIYPYSGYTSY ADSVKG**RFTISADTSKNTAYL QMNSLRAEDTAVYYCAR**YST YSSSKWVWGMDY**WGQGTLV TVSS	81	361	364	380	131	184	237	290
G9.1-8m9	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF SGSRSGTDFTLTISSLQPEDFAT YYC**QQSYYDSNPIT**FGQGTKV EIKR	21	328	329	337	95	95	95	95
G9.1-8m9	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQA PGKGLEWVA**YIYPYSGYTSY ADSVKG**RFTISADTSKNTAYL QMNSLRAEDTAVYYCAR**YST YSSKWVWGMDY**WGQGTLVT VSS	82	361	364	383	132	185	238	291
G9.1-8m10	V_L:DIQMTQSPSSLSASVGDRV TITC**RASQSVSSAVA**WYQQKP GKAPKLLIY**SASSLYS**GVPSRF SGSRSGTDFTLTISSLQPEDFAT YYC**QQSYYDSNPIT**FGQGTKV EIKR	21	328	329	337	95	95	95	95

G9.1-8m10	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTVSSSSIH**WVRQAPGKGLEWVA**YIYPYSGYTSY****ADSVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**YSTYSKWVWGMDY**WGQGTLVTVSS	83	361	364	381	133	186	239	292
G9.1-8m11	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQSYYDSNPIT**FGQGTKVEIKR	21	328	329	337	95	95	95	95
G9.1-8m11	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTVSSSSIH**WVRQAPGKGLEWVA**YIYPYSGYTSY****ADSVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**YSTYKWVWGMDY**WGQGTLVTVSS	84	361	364	382	134	187	240	293
G9.1-8m12	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQSYYDSNPIT**FGQGTKVEIKR	21	328	329	337	95	95	95	95
G9.1-8m12	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTVSSSSIH**WVRQAPGKGLEWVA**YIYPYSSSSSYA****DSVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**YSTYSSSKWVWGMDY**WGQGTLVTVSS	85	361	366	380	135	188	241	294
G9.1-8m13	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQSYYDSNPIT**FGQGTKVEIKR	21	328	329	337	95	95	95	95
G9.1-8m13	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTVSSSSIH**WVRQAPGKGLEWVA**YIYPYSSSSSYA****DSVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**YSTYSSKWVWGMDY**WGQGTLVTVSS	86	361	366	383	136	189	242	295
G9.1-8m14	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQSYYDSNPIT**FGQGTKVEIKR	21	328	329	337	95	95	95	95
G9.1-8m14	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTVSSSSIH**WVRQAPGKGLEWVA**YIYPYSSSSSYA****DSVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**YSTYKWVWGMDY**WGQGTLVTVSS	87	361	366	382	137	190	243	296

Table 2. Antibodies directed against CRD2

Clone	Sequence	VR	CDR 1	CDR 2	CDR 3	LC /HC IgG1	IgG1 LALA	IgG4	IgG4 mut
		SEQ ID NO:							
G9.2-1	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQYKSKYPFT**FGQGTKVEIKR	29	328	329	341	99	99	99	99
G9.2-1	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTLYSSSIH**WVRQAPGKGLEWVA**SIYSSSGYTYYAD SVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**TYTWKSS WSYQTGYGLDY**WGQGTLVTVSS	30	424	446	390	141	194	247	300
G9.2-2	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQSSSSLIT**FGQGTKVEIKR	13	328	329	333	91	91	91	91
G9.2-2	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTFSSSSIH**WVRQAPGKGLEWVA**SISPYYGSTYYAD SVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**AVYYYVY NRSWYWWSGGFDY**WGQGTLVTVSS	31	431	447	391	142	195	248	301
G9.2-3	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQSSSSLIT**FGQGTKVEIKR	13	328	329	333	91	91	91	91
G9.2-3	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTFSSSSIH**WVRQAPGKGLEWVA**SISSSSGSTSYADS VKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**PAYSYPYY YFHYGAMDY**WGQGTLVTVSS	32	431	448	392	143	196	249	302
G9.2-4	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYY**C QQSSSSLIT**FGQGTKVEIKR	13	328	329	342	91	91	91	91
G9.2-4	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTFSSSSIH**WVRQAPGKGLEWVA**SIYPSYGYTSYAD SVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**AWYHHE YWGHYSGMDY**WGQGTLVTVSS	33	431	449	393	144	197	250	303
G9.2-5	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQSSWGLIT**FGQGTKVEIKR	34	328	329	343	100	100	100	100

G9.2-5	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTFSSSSIH**WVRQAPGKGLEWVA**SIYSSYGSTYYAD SVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**SGYSHPY YSYYSGMDY**WGQGTLVTVSS	35	431	450	394	145	198	251	304
G9.2-6	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQFWGSKLFT**FGQGTKVEIKR	36	328	329	344	101	101	101	101
G9.2-6	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTFSSSSIH**WVRQAPGKGLEWVA**SIYSYSGYTYYAD SVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**TYMAGY KYYFISGYGFDY**WGQGTLVTVSS	37	431	451	395	146	199	252	305
G9.2-7	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQMYYPGYLIT**FGQGTKVEIKR	38	328	329	345	102	102	102	102
G9.2-7	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTFSYSSIH**WVRQAPGKGLEWVA**SIYPSYGYTYYAD SVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**YWDYGW MYFDPAMDY**WGQGTLVTVSS	39	425	452	396	147	200	253	306
G9.2-8	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQDRWWSALT**FGQGTKVEIKR	40	328	329	346	103	103	103	103
G9.2-8	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTFSYSSIH**WVRQAPGKGLEWVA**SIYSYSGYTSYAD SVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**YMENWE WPYHSAMDY**WGQGTLVTVSS	41	425	453	397	148	201	254	307
G9.2-9	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQSYGSWYPIT**FGQGTKVEIKR	42	328	329	347	104	104	104	104
G9.2-9	V_H:EVQLVESGGGLVQPGGSLRLSCAASG**FTFYSSSIH**WVRQAPGKGLEWVA**SIYSSYGSTYYAD SVKG**RFTISADTSKNTAYLQMNSLRAEDTAVYYCAR**SWWYPY WQYYPGGWHSSGFDY**WGQGTLVTVSS	43	426	454	398	149	202	255	308
G9.2-10	V_L:DIQMTQSPSSLSASVGDRVTITC**RASQSVSSAVA**WYQQKPGKAPKLLIY**SASSLYS**GVPSRFSGSRSGTDFTLTISSLQPEDFATYYC**QQGWYASPIT**FGQGTKVEIKR	44	328	329	348	105	105	105	105

G9.2-10	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTFYSSSIH**WVRQAP GKGLEWVA**YISPSSGYTSYADS VKG**RFTISADTSKNTAYLQMNS LRAEDTAVYYCAR**YTMTYQY YPSGAMDY**WGQGTLVTVSS	45	426	387	399	150	203	256	309
G9.2-11	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQYSSHKYPFT**FGQGTKVEIKR	46	328	329	349	106	106	106	106
G9.2-11	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTIYSSYIH**WVRQAP GKGLEWVA**SIYSSSGYTYYAD SVKG**RFTISADTSKNTAYLQMN SLRAEDTAVYYCAR**SYIYYMW QYNYGMSGYGLDY**WGQGTLV TVSS	47	432	455	400	151	204	257	310
G9.2-12	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQWVYPGSLIT**FGQGTKVEIK R	48	328	329	350	107	107	107	107
G9.2-12	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTLSYSSIH**WVRQAP GKGLEWVA**SISSSYGYTYYAD SVKG**RFTISADTSKNTAYLQMN SLRAEDTAVYYCAR**HSPYYLH SWWWSGLDY**WGQGTLVTVSS	49	433	456	401	152	205	258	311
G9.2-13	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQYKSKYPFT**FGQGTKVEIKR	29	328	329	341	99	99	99	99
G9.2-13	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTLYYSSIH**WVRQAP GKGLEWVA**SISPSYGSTSYADS VKG**RFTISADTSKNTAYLQMNS LRAEDTAVYYCAR**HSWYYPY YYYALDY**WGQGTLVTVSS	50	434	362	402	153	206	259	312
G9.2-14	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQSSSSLIT**FGQGTKVEIKR	13	328	329	333	91	91	91	91
G9.2-14	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQAP GKGLEWVA**SISSSSGYTYYADS VKG**RFTISADTSKNTAYLQMNS LRAEDTAVYYCAR**YWSYPYVY FLAFDY**WGQGTLVTVSS	51	361	457	403	154	207	260	313
G9.2-15	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQSSWGLIT**FGQGTKVEIKR	34	328	329	343	100	100	100	100
G9.2-15	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQAP GKGLEWVA**SIYSSSGYTSYADS**	52	361	458	404	155	208	261	314

	VKGRFTISADTSKNTAYLQMNS LRAEDTAVYYCAR**NVENYPY WAWPWGYYGAIDY**WGQGTL VTVSS								
G9.2-16	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQSSSSLIT**FGQGTKVEIKR	13	328	329	333	91	91	91	91
G9.2-16	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQAP GKGLEWVA**SIYSSSGYTYYAD SVKG**RFTISADTSKNTAYLQMN SLRAEDTAVYYCAR**TYKWSYY TGYGFDY**WGQGTLVTVSS	53	361	459	405	156	209	262	315
G9.2-17	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYY**C QQSSTDPIT**FGQGTKVEIKR	54	328	329	352	108	108	108	108
G9.2-17	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQAP GKGLEWVA**YISSSSGYTYYAD SVKG**RFTISADTSKNTAYLQMN SLRAEDTAVYYCAR**YWSYPSW WPYRGMDY**WGQGTLVTVSS	55	361	388	406	157	210	263	316
G9.2-17mut6	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQSSTDPIT**FGQGTKVEIKR	54	328	329	352	108	108	108	108
G9.2-17mut6 (mutation is underlined)	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSSSIH**WVRQAP GKGLEWVA**YISSSSGYTYYAD SVKG**RFTISADTSKNTAYLQMN SLRAEDTAVYYCAR**YWSYPSW S**PYRGMDY**WGQGTLVTVSS	56	361	388	407	158	211	264	317
G9.2-18	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQSSSSLIT**FGQGTKVEIKR	13	328	329	333	91	91	91	91
G9.2-18	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSYSIH**WVRQAP GKGLEWVA**YIYSSSGYTSYAD SVKG**RFTISADTSKNTAYLQMN SLRAEDTAVYYCAR**VGYYYPY LYLGDGLDY**WGQGTLVTVSS	57	430	363	408	159	212	265	318
G9.2-19	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQSSQYDLIT**FGQGTKVEIKR	58	328	329	354	109	109	109	109
G9.2-19	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSSYSIH**WVRQAP GKGLEWVA**SISSSSGSTSYADS VKG**RFTISADTSKNTAYLQMNS LRAEDTAVYYCAR**NAWHYEPS YWYGNYATYGFDY**WGQGTLV TVSS	59	430	460	409	160	213	266	319

G9.2-20	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQSSTDPIT**FGQGTKVEIKR	54	328	329	352	108	108	108	108
G9.2-20	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSYSSIH**WVRQAP GKGLEWVA**SISSSSSSTYYADS VKG**RFTISADTSKNTAYLQMNS LRAEDTAVYYCAR**GQQYYPD QYWGLDY**WGQGTLVTVSS	60	429	461	410	161	214	267	320
G9.2-21	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQSSSSSLFT**FGQGTKVEIKR	61	328	329	355	110	110	110	110
G9.2-21	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVSYSSIH**WVRQAP GKGLEWVA**SIYSSSGYTYYAD SVKG**RFTISADTSKNTAYLQMN SLRAEDTAVYYCAR**TYYTYFD WWRTAVYYGFDY**WGQGTLV TVSS	62	429	462	411	162	215	268	321
G9.2-22	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQRWYPGDLIT**FGQGTKVEIK R	63	328	329	356	111	111	111	111
G9.2-22	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVYSSSIH**WVRQAP GKGLEWVA**SISSSYGYTSYADS VKG**RFTISADTSKNTAYLQMNS LRAEDTAVYYCAR**DYYNYMSS YWWYSALDY**WGQGTLVTVSS	64	428	463	412	163	216	269	322
G9.2-23	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQSYFPSLVT**FGQGTKVEIKR	65	328	329	357	112	112	112	112
G9.2-23	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVYSSSIH**WVRQAP GKGLEWVA**SIYPYYGYTSYAD SVKG**RFTISADTSKNTAYLQMN SLRAEDTAVYYCAR**KIFWPVS WMWQGYYPALDY**WGQGTLV TVSS	66	428	464	413	164	217	270	323
G9.2-24	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQWSQSPVT**FGQGTKVEIKR	67	328	329	358	113	113	113	113
G9.2-24	V_H:EVQLVESGGGLVQPGGSLR LSCAASG**FTVYSSSIH**WVRQAP GKGLEWVA**SIYSSYGYTSYAD SVKG**RFTISADTSKNTAYLQMN SLRAEDTAVYYCAR**SYSSETHY GWAMDY**WGQGTLVTVSS	68	428	465	414	165	218	271	324
G9.2-25	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK	69	328	329	359	114	114	114	114

	APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQSYVYYPFT**FGQGTKVEIKR								
G9.2-25	V_H:EVQLVESGGGLVQPGGSLR LSCAAS**GFTLSSSSIH**WVRQAP GKGLEWVA**SIYSSYGSTSYADS VKG**RFTISADTSKNTAYLQMNS LRAEDTAVYYCAR**QYYTYFE WYMGWGYALDY**WGQGTLVT VSS	70	427	466	415	166	219	272	325
G9.2-26	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQGGWYYGPIT**FGQGTKVEIK R	71	328	329	360	115	115	115	115
G9.2-26	V_H:EVQLVESGGGLVQPGGSLR LSCAAS**GFTVSSSSIH**WVRQAP GKGLEWVA**YISSYSGSTYYAD SVKG**RFTISADTSKNTAYLQMN SLRAEDTAVYYCAR**SSALYWM DFSYSALDY**WGQGTLVTVSS	72	361	389	416	167	220	273	326
G9.2-low affinity binder	V_L:DIQMTQSPSSLSASVGDRVTI TC**RASQSVSSAVA**WYQQKPGK APKLLIY**SASSLYS**GVPSRFSGS RSGTDFTLTISSLQPEDFATYYC **QQSSTDPIT**FGQGTKVEIKR	54	328	329	352	108	108	108	108
G9.2-low affinity binder	V_H:EVQLVESGGGLVQPGGSLR LSCAAS**GFTVSSSSIH**WVRQAP GKGLEWVA**YISSSSGYTYYAD SVKG**RFTISADTSKNTAYLQMN SLRAEDTAVYYCAR**SSSSSSSSS SSSSDY**WGQGTLVTVSS	73	361	388	417	168	221	274	327

Table 3. Selected Antibody CDR Sequences

Clone		Sequence	SEQ ID NO:
G9.1-8	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSYYDSNPIT	337
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YIYPYSGYTSYADSVKG	364
	V_H CDR3	YSTYSWGGIGKWVWGMDY	374
G9.1-8m1	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSYYDSNPIT	337
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	SSSSSSGYTSYADSVKG	365
	V_H CDR3	YSTYSWGGIGKWVWGMDY	374
G9.1-8m2	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSYYDSNPIT	337
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YIYPYSSSSSYADSVKG	366

	V_H CDR3	YSTYSWGGIGKWVWGMDY	374
G9.1-8m3	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSYYDSNPIT	337
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YIYPYSGYTSYADSVKG	364
	V_H CDR3	SSSSSWGGIGKWVWGMDY	375
G9.1-8m4	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSYYDSNPIT	337
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YIYPYSGYTSYADSVKG	364
	V_H CDR3	YSTYSSSSSSKWVWGMDY	376
G9.1-8m5	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSYYDSNPIT	337
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YIYPYSGYTSYADSVKG	364
	V_H CDR3	YSTYSWGGIGSSSSSMDY	377
G9.1-8m6	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSYYDSNPIT	337
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YIYPYSGYTSYADSVKG	364
	V_H CDR3	YSTYSSSSSKWVWGMDY	378
G9.1-8m7	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSYYDSNPIT	337
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YIYPYSGYTSYADSVKG	364
	V_H CDR3	YSTYSSSSKWVWGMDY	379
G9.1-8m8	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSYYDSNPIT	337
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YIYPYSGYTSYADSVKG	364
	V_H CDR3	YSTYSSSKWVWGMDY	380
G9.1-8m9	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSYYDSNPIT	337
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YIYPYSGYTSYADSVKG	364
	V_H CDR3	YSTYSSKWVWGMDY	383
G9.1-8m10	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSYYDSNPIT	337
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YIYPYSGYTSYADSVKG	364

	V_H CDR3	YSTYSKWVWGMDY	381
G9.1-8m11	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSYYDSNPIT	337
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YIYPYSGYTSYADSVKG	364
	V_H CDR3	YSTYKWVWGMDY	382
G9.1-8m12	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSYYDSNPIT	337
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YIYPYSSSSSYADSVKG	366
	V_H CDR3	YSTYSSSKWVWGMDY	380
G9.1-8m13	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSYYDSNPIT	337
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YIYPYSSSSSYADSVKG	366
	V_H CDR3	YSTYSSKWVWGMDY	383
G9.1-8m14	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSYYDSNPIT	337
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YIYPYSSSSSYADSVKG	366
	V_H CDR3	YSTYKWVWGMDY	382
G9.2-17	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSSTDPIT	352
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YISSSSGYTYYADSVKG	388
	V_H CDR3	YWSYPSWWPYRGMDY	406
G9.2-17m6	V_L CDR1	RASQSVSSAVA	328
	V_L CDR2	SASSLYS	329
	V_L CDR3	QQSSTDPIT	352
	V_H CDR1	FTVSSSSIH	361
	V_H CDR2	YISSSSGYTYYADSVKG	388
	V_H CDR3	YWSYPSWSPYRGMDY	407

Such CRD1 and CRD2 binding anti-Galectin-9 antibodies are isolated and structurally characterized as described herein. The disclosure also contemplates antibodies having at least 80% identity (e.g., at least 85%, at least 90%, at least 95%, or at least 99% identity) to their variable region or CDR sequences. The VL amino acid sequences 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, G9.2-low affinity binder are set forth in SEQ ID NO: 29,

13, 34, 36, 38, 40, 42, 44, 46, 48, 29, 34, 54, 58, 61, 63, 65, 73, 67, 69, and 71. The VH amino acid sequences 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, G9.2-low affinity binder are set forth in 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. Accordingly, provided herein are isolated anti-Galectin-9 antibodies, or antigen binding portion thereof, comprising 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, 29, 34, 54, 58, 61, 63, 65, 73, 67, 69, and 71. In some embodiments, 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, 29, 34, 54, 58, 61, 63, 65, 73, 67, 69, and 71. Also provided are isolated anti-Galectin-9 antibodies, or antigen binding portions thereof, comprising 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 embodiments, 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. Accordingly, provided herein are isolated anti-Galectin-9 antibodies, or antigen binding portion thereof, comprising 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, 29, 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. Accordingly, provided herein are isolated anti-Galectin-9 antibodies, or antigen binding portion thereof, comprising 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, 29, 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 embodiments, the anti-Galectin-9 antibody comprises a VL region having the sequence of SEQ ID NO: 54. In some embodiments, the anti-Galectin-9 antibody comprises a VH region having the sequence of SEQ ID NO: 55. In some embodiments, the anti-Galectin-9 antibody comprises a VH region having the sequence of SEQ ID NO: 56. In some

embodiments, the anti-Galectin-9 antibody comprises a VL region having the sequence of SEQ ID NO: 54 and a VH region having the sequence of SEQ ID NO: 55. In some embodiments, the anti-Galectin-9 antibody comprises a VL region having the sequence of SEQ ID NO: 54 and a VH region having the sequence of SEQ ID NO: 56.

The VL amino acid sequences 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, G9.1-9, 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, G9.1-8m14 are set forth in SEQ ID NO: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, and 27, respectively. The VH amino acid sequences 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, G9.1-9, 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, G9.1-8m14 are set forth in 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, 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. In some embodiments, the light chain variable region consists of an amino acid sequence selected from SEQ ID NO: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, and 27. Also provided are isolated anti-Galectin-9 antibodies, or antigen binding portions thereof, comprising 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 embodiments, 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. Accordingly, 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 embodiments, 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 embodiments, the anti-Galectin-9 antibody comprises a VL region having the sequence of SEQ ID NO: 21. In some embodiments, the anti-Galectin-9 antibody comprises a VH region having the sequence of SEQ ID NO: 22. In some embodiments, the anti-Galectin-9 antibody comprises a VH region having the sequence of SEQ ID NO: 86. In some embodiments, the anti-Galectin-9 antibody comprises a VL region having the sequence of SEQ ID NO: 21 and a VH region having the sequence of SEQ ID NO: 22. In some embodiments, the anti-Galectin-9 antibody comprises a VL region having the sequence of SEQ ID NO: 21 and a VH region having the sequence of SEQ ID NO: 86.

In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises any of SEQ ID NO: 7-87. In some specific embodiments, the anti-Galectin-9 antibody comprises one or more sequences of any sequence(s) selected from SEQ ID NO: 7-87 and any combination(s) thereof.

In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises any of SEQ ID NOs: 7-28 and 74-87. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises one or more sequences of any sequence(s) selected from SEQ ID NO: 7-28 and 74-87 and any combination(s) thereof.

In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises any of SEQ ID NOs: 13, 29-73. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises one or more sequences of any sequence(s) selected from SEQ ID NO: 13, 29-73 and any combination(s) thereof. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises any of SEQ ID NOs: 54, 55, or 54 and 56. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises one or more sequences of any sequence(s) selected from SEQ ID NO: 54, 55, or 54 and 56 and any combination(s) thereof.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region comprising SEQ ID NO: 54. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VH region comprising SEQ ID NO: 55. In some embodiments, the anti-Galectin-9 antibody comprises a VL region consisting of SEQ ID NO: 54. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VH region consisting of SEQ ID NO: 55. In some embodiments, the anti-Galectin-9 antibody comprises a VL and VH region comprising SEQ ID NO: 54 and 55. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL and VH region consisting of SEQ ID NO: 54 and 55.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region comprising SEQ ID NO: 21. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region consisting of SEQ ID NO: 21. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VH region comprising SEQ ID NO: 86. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VH region consisting of SEQ ID NO: 86. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL and VH region comprising SEQ ID NO: 21 and 86. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL and VH region consisting of SEQ ID NO: 21 and 86.

In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL or VH region comprising any of of SEQ ID NOs: 21, 22 and 74-87. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL or VH region consisting of SEQ ID NOs: 21, 22 and 74-87. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL and/or VH region comprising sequence(s) selected from SEQ ID NO: 21, 22 and 74-87 and any combination(s) thereof. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL and/or VH region consisting of sequence(s) selected from SEQ ID NO: 21, 22 and 74-87 and any combination(s) thereof.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 7 and SEQ ID NO: 8. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 9 and SEQ ID NO: 10. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 11 and SEQ ID NO: 12. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 13 and SEQ ID NO: 14. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 15 and SEQ ID NO: 16. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 17 and SEQ ID NO: 18. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 19 and SEQ ID NO: 20. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 21 and SEQ ID NO:

22. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 23 and SEQ ID NO: 24. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 25 and SEQ ID NO: 26. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 27 and SEQ ID NO: 28. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 21 and SEQ ID NO: 74. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 21 and SEQ ID NO: 75. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 21 and SEQ ID NO: 76. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 21 and SEQ ID NO: 77. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 21 and SEQ ID NO: 78. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 21 and SEQ ID NO: 79. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 21 and SEQ ID NO: 80. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 21 and SEQ ID NO: 81. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 21 and SEQ ID NO: 82. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 21 and SEQ ID NO: 83. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 21 and SEQ ID NO: 84. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 108 and SEQ ID NO: 85. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 21 and SEQ ID NO: 86. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 29 and SEQ ID NO: 30. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 13 and SEQ ID NO:

31. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 13 and SEQ ID NO: 32. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 13 and SEQ ID NO: 33. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 34 and SEQ ID NO: 35. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 36 and SEQ ID NO: 37. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 38 and SEQ ID NO: 39. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 40 and SEQ ID NO: 41. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 42 and SEQ ID NO: 43. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 44 and SEQ ID NO: 45. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 46 and SEQ ID NO: 47. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 48 and SEQ ID NO: 49. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 29 and SEQ ID NO: 50. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 13 and SEQ ID NO: 51. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 34 and SEQ ID NO: 52. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 13 and SEQ ID NO: 53. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 54 and SEQ ID NO: 55. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 13 and SEQ ID NO: 57. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 58 and SEQ ID NO: 59. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 54 and SEQ ID NO:

60. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 61 and SEQ ID NO: 62. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 63 and SEQ ID NO: 64. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 65 and SEQ ID NO: 66. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 54 and SEQ ID NO: 56. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 67 and SEQ ID NO: 68. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 69 and SEQ ID NO: 70. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 71 and SEQ ID NO: 72. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region comprising SEQ ID NO: 54 and SEQ ID NO: 73. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 7 and SEQ ID NO: 8. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 9 and SEQ ID NO: 10. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 11 and SEQ ID NO: 12. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 13 and SEQ ID NO: 14. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 15 and SEQ ID NO: 16. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 17 and SEQ ID NO: 18. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 19 and SEQ ID NO: 20. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 21 and SEQ ID NO: 22. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 23 and SEQ ID NO: 24. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding

portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 25 and SEQ ID NO: 26. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 27 and SEQ ID NO: 28. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 21 and SEQ ID NO: 74. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 21 and SEQ ID NO: 75. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 21 and SEQ ID NO: 76. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 21 and SEQ ID NO: 77. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 21 and SEQ ID NO: 78. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 21 and SEQ ID NO: 79. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 21 and SEQ ID NO: 80. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 21 and SEQ ID NO: 81. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 21 and SEQ ID NO: 82. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 21 and SEQ ID NO: 83. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 21 and SEQ ID NO: 84. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 108 and SEQ ID NO: 85. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 21 and SEQ ID NO: 86. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 29 and SEQ ID NO: 30. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 13 and SEQ ID NO: 31. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding

portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 13 and SEQ ID NO: 32. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 13 and SEQ ID NO: 33. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 34 and SEQ ID NO: 35. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 36 and SEQ ID NO: 37. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 38 and SEQ ID NO: 39. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 40 and SEQ ID NO: 41. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 42 and SEQ ID NO: 43. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 44 and SEQ ID NO: 45. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 46 and SEQ ID NO: 47. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 48 and SEQ ID NO: 49. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 29 and SEQ ID NO: 50. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 13 and SEQ ID NO: 51. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 34 and SEQ ID NO: 52. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 13 and SEQ ID NO: 53. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 54 and SEQ ID NO: 55. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 13 and SEQ ID NO: 57. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 58 and SEQ ID NO: 59. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding

portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 54 and SEQ ID NO: 60. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 61 and SEQ ID NO: 62. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 63 and SEQ ID NO: 64. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 65 and SEQ ID NO: 66. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 54 and SEQ ID NO: 56. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 67 and SEQ ID NO: 68. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 69 and SEQ ID NO: 70. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 71 and SEQ ID NO: 72. In some specific embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises a VL region and a VH region consisting of SEQ ID NO: 54 and SEQ ID NO: 73.

In some embodiments, the anti-Galectin-9 antibody comprises sequence having at least 80% (*e.g.*, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any incremental percent therein) sequence identity with any of the anti-Galectin-9 antibodies described in the previous paragraphs. In some embodiments, 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. In some embodiments, 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 embodiments, 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 embodiments, the anti-Galectin-9 antibody comprises a VL 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 or VH region set forth in SEQ ID NOs: 7-288 and 74-87. In some specific embodiments, the anti-Galectin-9 antibody comprises a VL 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 or VH region set forth in SEQ ID NO: 7-288 and 74-87and any combination(s) thereof.

In some embodiments, 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 of an antibody selected from 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 embodiments, 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 of an antibody selected from 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 embodiments, the anti-Galectin-9 antibody comprises a VL 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 VL or VH region of an antibody selected from 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 specific embodiments, the anti-Galectin-9 antibody comprises a VL 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 or VH region set forth in any of SEQ ID NOs: 21, 22 and 74-87. In some specific embodiments, the anti-Galectin-9 antibody comprises a VL 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 or VH region set forth in SEQ ID NO: 21, 22 and 74-87and any combination(s) thereof.

In some specific embodiments, 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 embodiments, 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 embodiments, the anti-Galectin-9 antibody comprises a VL 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 the VL or VH region of G9.1-8m13.

In some embodiments, 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 embodiments, 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 embodiments, 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.

In some embodiments, 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: 13, 29, 34, 36, 38, 40, 42, 44, 46, 48, 29, 34, 54, 58, 61, 63, 65, 73, 67, 69, and 71. In some embodiments, 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 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 embodiments, 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: 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 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 specific embodiments, the anti-Galectin-9 antibody comprises a VL 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 or VH region set forth in SEQ ID NO: 29-75 and 77-85. In some specific embodiments, the anti-Galectin-9 antibody comprises a VL 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 or VH region set forth in SEQ ID NO: 13, 29-73 and any combination(s) thereof. In some specific embodiments, the anti-Galectin-9 antibody comprises a VL 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 or VH region set forth in any of SEQ ID NOs: 54, 55, and 56.

In some embodiments, 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 of an antibody selected from 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 embodiments, 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 of an antibody selected from 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 embodiments, 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 an antibody selected from 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 embodiments, the anti-Galectin-9 antibody comprises a heavy chain CDR having at least 80% (*e.g.*, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any incremental percent therein) sequence identity with a sequence selected from any of SEQ ID NO: 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 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 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, and 87. Alternatively or in addition, the anti-Galectin-9 antibody comprises a light chain CDR having at least 80% (*e.g.*, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any incremental percent therein) sequence identity with a sequence selected from any of SEQ ID NO: 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 34, 36, 38, 40, 42, 44, 46, 48, 54, 58, 61, 63, 65, 67, 69, 71, and 73.

In some specific embodiments, 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 embodiments, 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 embodiments, 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.

In some specific embodiments, 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 embodiments, 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 embodiments, 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.

Complementarity Determining Regions (CDRs)

Anti-Galectin-9 antibodies, e.g., binding to CRD1, can comprise the light and heavy chain CDR1s, CDR2s and CDR3s 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, G9.1-9, 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, or combinations thereof. The amino acid sequence of the VL CDR1s 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, G9.1-9, 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 is set forth in SEQ ID NO: 328. The amino acid sequence of the VL CDR2s 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, G9.1-9, 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 is set forth in SEQ ID NO: 329. The amino acid sequences of the VL CDR3s 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, G9.1-9, 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 are set forth in SEQ ID NO: 330-340. The amino acid sequences of the VH CDR1s 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, G9.1-9, 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 are set forth in SEQ ID NO: 361, 427,

428, 431, 435, 436, 437. The amino acid sequences of the VH CDR2s 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, G9.1-9, 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 are set forth in SEQ ID NO: 362-366, and 438-445. The amino acid sequences of the VH CDR3s 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, G9.1-9, 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 are set forth in SEQ ID NO: 367-386.

In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR1 having the sequence of SEQ ID NO: 328. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR2 having the sequence of SEQ ID NO: 329. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR3 having a sequence selected from any of SEQ ID NOs: 330-340. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR3 having the sequence of SEQ ID NO: 337. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR1 having the sequence of SEQ ID NO: 328, a VL CDR2 having the sequence of SEQ ID NO: 329, and a VL CDR3 having a sequence selected from any of SEQ ID NOs: 330-340. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR1 having the sequence of SEQ ID NO: 328, a VL CDR2 having the sequence of SEQ ID NO: 329, and a VL CDR3 having the sequence of SEQ ID NO: 337. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR1 having a sequence selected from any of SEQ ID NOs: 361, 427, 428, 431, 435, 436, and 437. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR1 having the sequence of SEQ ID NO: 361. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR2 having a sequence selected from any of SEQ ID NOs: 362-366, and 438-445. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR2 having a sequence selected from SEQ ID NO: 364 or 366. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR3 having a sequence selected from any of SEQ ID NOs: 367-386. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR3 having the sequence of SEQ ID NO: 374 or 383. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR1 having a sequence selected from any of SEQ ID NOs: 361, 427, 428, 431, 435, 436, and 437, a VH CDR2 having a sequence selected from any of SEQ ID NOs: 362-366 and 438-445, and a VH CDR3 having a sequence selected from any of SEQ ID NOs: 367-386. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR1 having the sequence of SEQ ID NO: 361, a VH CDR2 having the sequence of SEQ ID NO: 364, and a VH CDR3 having the sequence of SEQ ID NO: 374. In some embodiments, the anti-Galectin-9 antibody comprises a

VH CDR1 having the sequence of SEQ ID NO: 361, a VH CDR2 having the sequence of SEQ ID NO: 366, and a VH CDR3 having the sequence of SEQ ID NO: 383. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR1 having the sequence of SEQ ID NO: 328, a VL CDR2 having the sequence of SEQ ID NO: 329, a VL CDR3 having a sequence selected from any of SEQ ID NOs: 330-340, a VH CDR1 having a sequence selected from any of SEQ ID NOs: 361, 427, 428, 431, 435, 436, and 437, a VH CDR2 having a sequence selected from any of SEQ ID NOs: 362-366 and 438-445, and a VH CDR3 having a sequence selected from any of SEQ ID NOs: 367-386. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR1 having the sequence of SEQ ID NO: 328, a VL CDR2 having the sequence of SEQ ID NO: 329, a VL CDR3 having the sequence of SEQ ID NO: 337, a VH CDR1 having the sequence of SEQ ID NO: 361, a VH CDR2 having the sequence of SEQ ID NO: 364, and a VH CDR3 having the sequence of SEQ ID NO: 374. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR1 having the sequence of SEQ ID NO: 328, a VL CDR2 having the sequence of SEQ ID NO: 329, a VL CDR3 having the sequence of SEQ ID NO: 337, a VH CDR1 having the sequence of SEQ ID NO: 361, a VH CDR2 having the sequence of SEQ ID NO: 366, and a VH CDR3 having the sequence of SEQ ID NO: 383. In any of these embodiments, the anti-Galectin-9 antibody binds to CRD1.

In some embodiments, the anti-Galectin-9 antibodies, e.g., binding to CRD2, comprise the light and heavy chain CDR1s, CDR2s and CDR3s 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, or combinations thereof. The amino acid sequence of the VL CDR1s 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 is set forth in SEQ ID NO: 328. The amino acid sequence of the VL CDR2s 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 is set forth in SEQ ID NO: 329. The amino acid sequences of the VL CDR3s 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 are set forth in SEQ ID NO: 341-360. The amino acid sequences of the VH CDR1 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 are set forth in SEQ ID NO: 361, 424-434. The amino acid sequences of the VH CDR2s 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 are set forth in SEQ ID NO: 362, 363, 387-389 and 446-466. The amino acid sequences of the VH CDR3s 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 are set forth in SEQ ID NO: 390-417.

In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR1 having the sequence of SEQ ID NO: 328. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR2 having the sequence of SEQ ID NO: 329. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR3 having a sequence selected from any of SEQ ID NOs: 341-360. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR3 having the sequence of SEQ ID NO: 352. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR1 having the sequence of SEQ ID NO: 328, a VL CDR2 having the sequence of SEQ ID NO: 329, and a VL CDR3 having a sequence selected from any of SEQ ID NOs: 341-360. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR1 having the sequence of SEQ ID NO: 328, a VL CDR2 having the sequence of SEQ ID NO: 329, and a VL CDR3 having the sequence of SEQ ID NO: 352. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR1 having a sequence selected from any of SEQ ID NOs: 361, and 424-434. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR1 having the sequence of SEQ ID NO: 361. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR2 having a sequence selected from any of SEQ ID NOs: 362, 363, 387-389 and 446-466. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR2 having the sequence of SEQ ID NO: 388. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR3 having a sequence selected from any of SEQ ID NOs: 390-417. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR3 having the sequence of SEQ ID NO: 406 or 407. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR1 having a sequence selected from any of SEQ ID NOs: 361, and 424-434, a VH CDR2 having a sequence selected from any of SEQ ID NOs: 362, 363, 387-389 and 446-466, and a VH CDR3 having a sequence

selected from any of SEQ ID NOs: 390-417. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR1 having the sequence of SEQ ID NO: 361, a VH CDR2 having the sequence of SEQ ID NO: 388, and a VH CDR3 having the sequence of SEQ ID NO: 406. In some embodiments, the anti-Galectin-9 antibody comprises a VH CDR1 having the sequence of SEQ ID NO: 361, a VH CDR2 having the sequence of SEQ ID NO: 388, and a VH CDR3 having the sequence of SEQ ID NO: 407. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR1 having the sequence of SEQ ID NO: 328, a VL CDR2 having the sequence of SEQ ID NO: 329, a VL CDR3 having a sequence selected from any of SEQ ID NOs: 341-360, a VH CDR1 having a sequence selected from any of SEQ ID NOs: 361, and 424-434, a VH CDR2 having a sequence selected from any of SEQ ID NOs: 362, 363, 387-389 and 446-466, and a VH CDR3 having a sequence selected from any of SEQ ID NOs: 390-417. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR1 having the sequence of SEQ ID NO: 328, a VL CDR2 having the sequence of SEQ ID NO: 329, a VL CDR3 having the sequence of SEQ ID NO: 352, a VH CDR1 having the sequence of SEQ ID NO: 361, a VH CDR2 having the sequence of SEQ ID NO: 388, and a VH CDR3 having the sequence of SEQ ID NO: 406. In some embodiments, the anti-Galectin-9 antibody comprises a VL CDR1 having the sequence of SEQ ID NO: 328, a VL CDR2 having the sequence of SEQ ID NO: 329, a VL CDR3 having the sequence of SEQ ID NO: 352, a VH CDR1 having the sequence of SEQ ID NO: 361, a VH CDR2 having the sequence of SEQ ID NO: 388, and a VH CDR3 having the sequence of SEQ ID NO: 407. In any of these embodiments, the anti-Galectin-9 antibody binds to CRD1.

Because Galectin-9 binding specificity is dictated essentially by the CDR1, 2 and 3 regions, the VH CDR1, 2 and 3 sequences and the VL CDR1, 2 and 3 sequences disclosed above, can be mixed and matched to generate new Galectin-9 binding antibodies, as long as each resulting new antibody has a VL CDR1, 2 and 3 and a VH CDR1, 2 and 3. Such antibodies resulting from a new combination of CDRs described herein can be tested using the binding assays described herein. In some embodiments, the CDR1, CDR2 and/or CDR3 sequence from a particular VH or VL sequence is replaced with a structurally similar CDR sequence(s). Novel VH and VL sequences can be created by substituting one or more VH and/or VL CDR sequence(s) with structurally similar sequences from the CDR sequences disclosed herein, according to methods known in the art.

Accordingly, in some embodiments, 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 and 341-360 (d) VH CDR1 amino acid sequence set forth in SEQ ID NO: SEQ ID NO: 361, 427, 428, 431, 435, 436, 437; and SEQ ID NO: 361, 424-434 (e) VH CDR2 amino acid sequence selected from SEQ ID NO: 362-366 and 438-445, 362, 363, and 387-389 and 446-466; (f) VH CDR3 amino acid sequence selected from SEQ ID NO: 367-386 and 390-417.

In some embodiments, anti-Galectin-9 antibodies or antigen binding portions thereof comprise a VL CDR1 amino acid sequence set forth in SEQ ID NO: 328. In some embodiments, anti-Galectin-9 antibodies or antigen binding portions thereof comprise a VL CDR2 amino acid sequence set forth in SEQ ID NO: 329. In some embodiments, anti-Galectin-9 antibodies or antigen binding portions thereof comprise a VL CDR3 amino acid sequence selected from SEQ ID NO: 330-340. In some embodiments, anti-Galectin-9 antibodies or antigen binding portions thereof comprise a VH CDR1 amino acid sequence set forth in SEQ ID NO: 361, 427, 428, 431, 435, 436, 437. In some embodiments, anti-Galectin-9 antibodies or antigen binding portions thereof comprise a VH CDR2 amino acid sequence selected from SEQ ID NO: 362-366, and 438-445. In some embodiments, anti-Galectin-9 antibodies or antigen binding portions thereof comprise a VH CDR3 amino acid sequence selected from SEQ ID NO: 367-386. Accordingly, in some embodiments, 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, 427, 428, 431, 435, 436, 437; (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 embodiments, anti-Galectin-9 antibodies or antigen binding portions thereof comprise a VL CDR1 amino acid sequence set forth in SEQ ID NO: 328. In some embodiments, anti-Galectin-9 antibodies or antigen binding portions thereof comprise a VL CDR2 amino acid sequence set forth in SEQ ID NO: 329. In some embodiments, anti-Galectin-9 antibodies or antigen binding portions thereof comprise a VL CDR3 amino acid sequence selected from SEQ ID NO: 341-360. In some embodiments, anti-Galectin-9 antibodies or antigen binding portions thereof comprise a VH CDR1 amino acid sequence set forth in SEQ ID NO: 361, 424-434. In some embodiments, anti-Galectin-9 antibodies or antigen binding portions thereof comprise a VH CDR2 amino acid sequence selected from SEQ ID NO: 362, 363, 387-389 and 446-466. In some embodiments, anti-Galectin-9 antibodies or antigen binding portions thereof comprise a VH CDR3 amino acid sequence selected from SEQ ID NO: 390-417.

Accordingly, in some embodiments, 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; (e) VH CDR2s amino acid sequence selected from SEQ ID NO: 362, 363, 387-389 and 446-466;(f) VH CDR3 amino acid sequence selected from SEQ ID NO: 390-417.

9.1 Antibody Clones and Related CDRs

Clone 9.1-derived Light Chain Variable Regions

In some embodiments, the anti-Galectin-9 antibody or antigen 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 330, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 328, 329, and 330, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.1-1.

In some embodiments, the anti-Galectin-9 antibody or antigen 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 331, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 328, 329, and 331, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.1-2.

In some embodiments, the anti-Galectin-9 antibody or antigen 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 332, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 328, 329, and 332, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.1-3.

In some embodiments, the anti-Galectin-9 antibody or antigen 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 333, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 328, 329, and 333, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.1-4.

In some embodiments, the anti-Galectin-9 antibody or antigen 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 334, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 328, 329, and 334, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.1-5.

In some embodiments, the anti-Galectin-9 antibody or antigen 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 335, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 328, 329, and 335, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.1-6.

In some embodiments, the anti-Galectin-9 antibody or antigen 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 336, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 328, 329, and 336, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.1-7.

In some embodiments, the anti-Galectin-9 antibody or antigen 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. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 328, 329, and 337, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.1-8.

In some embodiments, the anti-Galectin-9 antibody or antigen 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 338, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 328, 329, and 338, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.1-9.

In some embodiments, the anti-Galectin-9 antibody or antigen 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 339, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO:

328, 329, and 339, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.1-10.

In some embodiments, the anti-Galectin-9 antibody or antigen 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 340, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 328, 329, and 340, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.1-11.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR1 comprises SEQ ID NO: 328. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR2 comprises SEQ ID NO: 329. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the light chain variable region CDR3 comprises SEQ ID NO: 337. In some embodiments, the anti-Galectin-9 antibody or antigen 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 embodiments, the anti-Galectin-9 antibody or antigen 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 embodiments, the anti-Galectin-9 antibody or antigen 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 embodiments, the antibody comprises the same VL CDRs as 9.1-8, 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, or G9.1-8m14. In some embodiments, the antibody comprises the same VL CDRs as G9.1-8m12. In some embodiments, the antibody comprises the same VL CDRs as G9.1-8m13.

In some embodiments, 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: 328. In some embodiments, 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 embodiments, 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 contains G at X_7, Y at X_8, and/or T at X_9 in the heavy chain CDR2 domain. Alternatively, or in addition, the anti-Galectin-9 antibody contains deletions at one or more of X_4 – X_7 in the heavy chain CDR3 domain. In other examples, the anti-Galectin-9 antibody contains S at one or more of X_6 – X_8 in the heavy chain CDR2 domain. Alternatively or in addition, the anti-Galectin-9 antibody contains deletions at one or more of X_5 – X_7 in the heavy chain CDR3 domain. In a further example, the anti-Galectin-9 antibody contains S at one or more of X_6 – X_8 in the heavy chain CDR2 domain. Alternatively or in addition, the anti-Galectin-9 antibody contains deletions at one or more of X_3 – X_9 and/or X_{10} is Y in the heavy chain CDR3 domain.

Clone 9.1-derived Heavy Chain Variable Regions

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 431, 438, and 367, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 431, 438, and 367, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-1.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 435, 439, and 368, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 435, 439, and 368, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-2.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 436, 363, and 369, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 436, 363, and 369, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-3.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 437, 440, and 370, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 437, 440, and 370, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-4.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 437, 441, and 371, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 437, 441, and 371, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-5.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 427, 442, and 372, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 427, 442, and 372, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-6.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 443, and 373, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 443, and 373, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-7.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 364, and 374, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 364, and 374, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-8.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 363, and 384, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO:

361, 363, and 384, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-9.

In some embodiments, 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 comprise SEQ ID NO: 429, 444, and 385, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 429, 444, and 385, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-10. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 428, 445, and 386, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 445, and 386, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-11.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 365, and 374, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 365, and 374, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-8m1.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 366, and 374, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 366, and 374, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-8m2.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 364, and 375, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 364, and 375, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-8m3.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 364, and 376, respectively. In some

embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 361, 364, and 376, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-8m4.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 364, and 377, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 364, and 377, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-8m5.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 364, and 378, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 364, and 378, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-8m6.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 364, and 379, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 364, and 379, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-8m7.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 364, and 380, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 364, and 380, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-8m8.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 364, and 383, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 364, and 383, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-8m9.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 364, and 381, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 364, and 381, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-8m10.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 364, and 382, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 364, and 382, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-8m11.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 366, and 380, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 366, and 380, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-8m12.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1 comprises SEQ ID NO: 361. In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR2 comprises SEQ ID NO: 366. In some embodiments, the anti-Galectin-9 antibody or antigen 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 embodiments, the anti-Galectin-9 antibody or antigen 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 embodiments, the anti-Galectin-9 antibody or antigen 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 embodiments, the anti-Galectin-9 antibody or antigen 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 embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and

CDR3 comprise SEQ ID NO: 361, 366, and 383, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 366, and 383, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-8m13.

In some embodiments, the anti-Galectin-9 antibody or antigen binding portion thereof comprises heavy and light chain variable regions, wherein the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 366, and 382, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 361, 366, and 382, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.1-8m14.

Clone 9.1-9.1 Heavy and Light Chain Variable Regions

In one specific embodiment, the anti-Galectin-9 antibody or antigen 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 330, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 431, 438, and 367, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 consist of SEQ ID NO: 328, 329, and 330 and SEQ ID NO: 431, 438, and 367, respectively. In some embodiments, the antibody comprises the same VL and VH CDRs as G9.1-1.

In one specific embodiment, 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 331, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 435, 439, and 368, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 331 and SEQ ID NO: 435, 439, and 368. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-2. In one specific embodiment, 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 332, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 436, 363, and 369, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 332 and SEQ ID NO: 436, 363, and 369. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-3.

In one specific embodiment, 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 333, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 437, 440, and 370, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 333, and SEQ ID NO: 437, 440, and 370. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-4.

In one specific embodiment, 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 334, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 437, 441, and 371, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 334, and SEQ ID NO: 437, 441, and 371. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-5.

In one specific embodiment, 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 335, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 427, 442, and 372, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 335, and SEQ ID NO: 427, 442, and 372. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-6.

In one specific embodiment, 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 336, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 443, and 373, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 336, and SEQ ID NO: 361, 443, and 373. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-7.

In one specific embodiment, 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, 364, and 374. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions

consist of SEQ ID NO: 328, 329, and 337, and SEQ ID NO: 361, 364, and 374. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-8.

In one specific embodiment, 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 338, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 363, and 384. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 338, and SEQ ID NO: 361, 363, and 384. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-9.

In one specific embodiment, 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 339, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 429, 444, and 385. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 339, and SEQ ID NO: 429, 444, and 385. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-10.

In one specific embodiment, 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 340, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 428, 445, and 386. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 340, and SEQ ID NO: 428, 445, and 386. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-11.

In one specific embodiment, 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, 365, and 374. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, and SEQ ID NO: 361, 365, and 374. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-8m1.

In one specific embodiment, 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 374. In

some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, and SEQ ID NO: 361, 366, and 374. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-8m2.

In one specific embodiment, 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, 364, and 375. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, and SEQ ID NO: 361, 364, and 375. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-8m3.

In one specific embodiment, 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, 364, and 376. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, and SEQ ID NO: 361, 364, and 376. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-8m4.

In one specific embodiment, 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, 364, and 377. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, and SEQ ID NO: 361, 364, and 377. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-8m5.

In one specific embodiment, 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, 364, and 378. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, and SEQ ID NO: 361, 364, and 378. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-8m6.

In one specific embodiment, 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, 364, and 379. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, and SEQ ID NO: 361, 364, and 379. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-8m7.

In one specific embodiment, 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, 364, and 380. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, and SEQ ID NO: 361, 364, and 380. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-8m8.

In one specific embodiment, 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, 364, and 383. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, and SEQ ID NO: 361, 364, and 383. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-8m9.

In one specific embodiment, 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, 364, and 381. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, and SEQ ID NO: 361, 364, and 381. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-8m10.

In one specific embodiment, 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, 364, and 382. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, and SEQ ID NO: 361, 364, and 382. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-8m11.

In one specific embodiment, 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 380. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, and SEQ ID NO: 361, 366, and 380. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-8m12.

In one specific embodiment, 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. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, and SEQ ID NO: 361, 366, and 383.

In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-8m13. In one specific embodiment, 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 382, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 337, and SEQ ID NO: 361, 366, and 382. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.1-8m14.

Sequence Identity

In some embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise light chain CDRs that have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity, individually or collectively, as compared with the corresponding V_L CDRs of an exemplary antibody described herein. Alternatively or in addition, the anti-Galectin-9 antibody (e.g., specific to CRD1 or CRD2) may comprise heavy chain CDRs that have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity, individually or collectively, as compared with the V_H CDRs as an exemplary antibody described herein.

In some embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise light chain CDRs that have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity, individually or collectively, as compared with the corresponding V_L CDRs of an antibody or antigen binding portion thereof

selected from 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 embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise heavy chain CDRs that have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity, individually or collectively, as compared with the corresponding V_H CDRs of an antibody or antigen binding portion thereof selected from 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 embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise light chain CDRs and heavy chain CDRs that have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity, individually or collectively, as compared with the corresponding V_L CDRs and V_H CDRs of an antibody or antigen binding portion thereof selected from 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 embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may 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 VL CDR1 amino acid sequence set forth in SEQ ID NO: 374. In some embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise a 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. In some embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise a 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.

In some embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise a 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 a VH CDR1 amino acid sequence set forth in SEQ ID NO: 361, 427, 428, 431, 435, 436, 437. In some embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise

a 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. In some embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise a 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 embodiments, 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: 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.

In some embodiments, 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 embodiments, 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 embodiments, 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. In some embodiments, 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 embodiment, 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. In one specific embodiment, 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.

9.2 Antibody Clones and Related CDRs

Clone 9.2-derived Light Chain Variable Region

In some embodiments, 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 341, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 341, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-1.

In some embodiments, 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 333, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 333, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-2.

In some embodiments, 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 333, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 333, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-3.

In some embodiments, 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 342, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 342, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-4.

In some embodiments, 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 343, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 343, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-5.

In some embodiments, 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 344, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 344, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-6.

In some embodiments, 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 345, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 345, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-7. In some embodiments, 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 346, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 346. In some embodiments, the antibody comprises the same VL CDRs as G9.2-8.

In some embodiments, 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 347, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 347, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-9.

In some embodiments, 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 348, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 348, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-10.

In some embodiments, 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 349, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 349, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-11.

In some embodiments, 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 350, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 350, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-12.

In some embodiments, 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 341, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 341. In some embodiments, the antibody comprises the same VL CDRs as G9.2-13.

In some embodiments, 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 333, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ

ID NO: 328, 329, and 333, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-14.

In some embodiments, 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 343, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 343, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-15.

In some embodiments, 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 333, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 333. In some embodiments, the antibody comprises the same VL CDRs as G9.2-16.

In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 352, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-17.

In some embodiments, 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 embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 352, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-17mut6.

In some embodiments, 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 333, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 333, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-18.

In some embodiments, 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 354, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 354. In some embodiments, the antibody comprises the same VL CDRs as G9.2-19.

In some embodiments, 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 embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 352, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-20.

In some embodiments, 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 355, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 355, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-21.

In some embodiments, 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 356, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ

ID NO: 328, 329, and 356, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-22.

In some embodiments, 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 357, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 357, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-23.

In some embodiments, 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 358, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 358, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-24.

In some embodiments, 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 359, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 359, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-25.

In some embodiments, 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 360, respectively. In some embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 360, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-26.

In some embodiments, 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 embodiments, the light chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 352, respectively. In some embodiments, the antibody comprises the same VL CDRs as G9.2-low affinity binder.

Clone 9.2-derived Heavy Chain Variable Region

In some embodiments, 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: 424, 446, and 390, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 424, 446, and 390, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-1.

In some embodiments, 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: 431, 447, and 391, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 431, 447, and 391, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-2.

In some embodiments, 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: 431, 448, and 392, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 431, 448, and 392. In some embodiments, the antibody comprises the same VH CDRs as G9.2-3.

In some embodiments, 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: 431, 449, and 393, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 431, 449, and 393, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-4.

In some embodiments, 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: 431, 450, and 394, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 431, 450, and 394, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-5.

In some embodiments, 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: 431, 451, and 395, respectively. In

some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 431, 452, and 395. In some embodiments, the antibody comprises the same VH CDRs as G9.2-6.

In some embodiments, 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: 425, 453, and 396, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 425, 453, and 396, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-7.

In some embodiments, 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: 425, 453, and 397, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 425, 453, and 397, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-8.

In some embodiments, 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: 426, 454, and 398, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 426, 454, and 398, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-9.

In some embodiments, 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: 426, 387, and 399, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 426, 387, and 399, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-10.

In some embodiments, 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: 432, 455, and 400, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 432, 455, and 400, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-11.

In some embodiments, 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: 433, 456, and 401, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 433, 456, and 401, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-12.

In some embodiments, 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: 434, 362, and 402, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 434, 362, and 402, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-13.

In some embodiments, 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, 457, and 403, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 361, 457, and 403, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-14.

In some embodiments, 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, 458, and 404, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 361, 458, and 404, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-15.

In some embodiments, 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, 459, and 405, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 361, 459, and 405, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-16.

In some embodiments, 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 embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ

ID NO: 361, 388, and 406. In some embodiments, the antibody comprises the same VH CDRs as G9.2-17.

In some embodiments, 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 407, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 361, 388, and 407, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-17mut6.

In some embodiments, 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: 430, 363, and 408, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 430, 363, and 408, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-18.

In some embodiments, 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: 430, 460, and 409, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 430, 460, and 409, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-19.

In some embodiments, 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: 429, 461, and 410, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 429, 461, and 410, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-20.

In some embodiments, 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: 429, 462, and 411, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 429, 462, and 411, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-21.

In some embodiments, 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: 428, 463, and 412, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 428, 463, and 412, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-22.

In some embodiments, 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: 428, 464, and 413, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 428, 464, and 413, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-23.

In some embodiments, 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: 428, 465, and 414, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 428, 465, and 414, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-24.

In some embodiments, 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: 427, 466, and 415, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 427, 466, and 415. In some embodiments, the antibody comprises the same VH CDRs as G9.2-25.

In some embodiments, 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, 389, and 416, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 361, 389, and 416, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-26.

In some embodiments, 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 417, respectively. In some embodiments, the heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 361, 388, and 417, respectively. In some embodiments, the antibody comprises the same VH CDRs as G9.2-low affinity binder.

Clone 9.2-derived Heavy and light chain variable regions

In some embodiments, 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 341, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 424, 446, and 390 respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 341, and SEQ ID NO: 424, 446, and 390. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-1.

In some embodiments, 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 333, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 431, 447, and 391, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 333, and SEQ ID NO: 431, 447, and 391. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-2.

In some embodiments, 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 333, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 431, 448, and 392, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 333, and SEQ ID NO: 431, 448, and 392. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-3.

In some embodiments, 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 342, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 431, 449, and 393, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 342, and SEQ ID NO: 431, 449, and 393. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-4.

In some embodiments, 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 343, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 431, 450, and 394, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and

CDR3 regions consist of SEQ ID NO: 328, 329, and 343, and SEQ ID NO: 431, 450, and 394. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-5.

In some embodiments, 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 344, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 431, 451, and 395, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 344, and SEQ ID NO: 431, 451, and 395. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-6.

In some embodiments, 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 345, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 425, 452, and 396, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 345, and SEQ ID NO: 425, 452, and 396. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-7.

In some embodiments, 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 346, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 245, 453, and 397, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 346, and SEQ ID NO: 245, 453, and 397.In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-8.

In some embodiments, 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 347, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 426, 454, and 398, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 347, and SEQ ID NO: 426, 454, and 398. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-9.

In some embodiments, 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 348, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 426, 387, and 399,

respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 348, and SEQ ID NO: 426, 387, and 399. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-10.

In some embodiments, 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 349, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 432, 455, and 400, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 349, and SEQ ID NO: 432, 455, and 400. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-11.

In some embodiments, 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 350, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 433, 456, and 401, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 350, and SEQ ID NO: 433, 456, and 401. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-12.

In some embodiments, 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 341, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 434, 362, and 402, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 341, and SEQ ID NO: 434, 362, and 402. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-13.

In some embodiments, 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 333, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 457, and 403, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 333, and SEQ ID NO: 361, 457, and 403. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-14.

In some embodiments, 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 343, respectively, and the heavy chain

variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 458, and 404, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 343, and SEQ ID NO: 361, 458, and 404. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-15.

In some embodiments, 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 333, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 459, and 405, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 333, and SEQ ID NO: 361, 459, and 405. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-16.

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

In some embodiments, 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 404, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 352, and SEQ ID NO: 361, 388, and 404. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-17mut6.

In some embodiments, 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 333, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 430, 363, and 408, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 333, and SEQ ID NO: 430, 363, and 408. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-18.

In some embodiments, 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 354, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 430, 460, and 409, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 354, and SEQ ID NO: 430, 460, and 409. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-19.

In some embodiments, 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: 429, 461, and 410, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 352, and SEQ ID NO: 429, 461, and 410. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-20.

In some embodiments, 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 355, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 429, 462, and 411, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 355, and SEQ ID NO: 429, 462, and 411. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-21.

In some embodiments, 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 356, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 428, 463, and 412, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 356, and SEQ ID NO: 428, 463, and 412. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-22.

In some embodiments, 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 357, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 428, 464, and 413, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and

CDR3 regions consist of SEQ ID NO: 328, 329, and 357, and SEQ ID NO: 428, 464, and 413. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-23.

In some embodiments, 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 358, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 428, 465, and 414, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 358, and SEQ ID NO: 428, 465, and 414.In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-24.

In some embodiments, 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 359, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 427, 466, and 415, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 359, and SEQ ID NO: 427, 466, and 415. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-25.

In some embodiments, 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 360, respectively, and the heavy chain variable region CDR1, CDR2, and CDR3 comprise SEQ ID NO: 361, 389, and 416, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 360, and SEQ ID NO: 361, 389, and 416. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-26.

In some embodiments, 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 417, respectively. In some embodiments, the light and heavy chain variable region CDR1, CDR2, and CDR3 regions consist of SEQ ID NO: 328, 329, and 352, and SEQ ID NO: 361, 388, and 417. In one specific embodiment, the antibody comprises the same VL and VH CDRs as G9.2-low affinity binder.

Sequence Identity

In some embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise light chain CDRs that have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity, individually or collectively, as compared with the corresponding V_L CDRs of an antibody or antigen binding portion thereof selected from 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 embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise heavy chain CDRs that have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity, individually or collectively, as compared with the corresponding V_H CDRs of an antibody or antigen binding portion thereof selected from 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 embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise light chain CDRs and heavy chain CDRs that have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity, individually or collectively, as compared with the corresponding V_L CDRs and V_H CDRs of an antibody or antigen binding portion thereof selected from 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 embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may 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. In some embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise a 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. In some embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise a 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: 341-360.

In some embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise a 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. In some embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise a 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. In some embodiments, the anti-Galectin-9 antibody (*e.g.*, specific to CRD1 and/or CRD2) may comprise a 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.

Accordingly, in some embodiments, 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 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 embodiments, 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 embodiments, 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 G9.2-17. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiment, 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.

Epitopes and Constant Regions

In some embodiments, the anti-Galectin-9 antibodies described herein bind to the same epitope as any of the exemplary antibodies described herein (e.g., antibody comprising any of SEQ ID NO: 7-87 or the CDRs thereof) or competes against the exemplary antibody from binding to the Galectin-9 antigen. An "epitope" refers to the site on a target antigen that is recognized and bound by an antibody. The site can be entirely composed of amino acid components, entirely composed of chemical modifications of amino acids of the protein (*e.g.*, glycosyl moieties), or composed of combinations thereof. Overlapping epitopes include at least one common amino acid residue. An epitope can be linear, which is typically 6-15 amino acids

in length. Alternatively, the epitope can be conformational. The epitope to which an antibody binds can be determined by routine technology, for example, the epitope mapping method (see, *e.g.*, descriptions below). An antibody that binds the same epitope as an exemplary antibody described herein may bind to exactly the same epitope or a substantially overlapping epitope (*e.g.*, containing less than 3 non-overlapping amino acid residue, less than 2 non-overlapping amino acid residues, or only 1 non-overlapping amino acid residue) as the exemplary antibody. Whether two antibodies compete against each other from binding to the cognate antigen can be determined by a competition assay, which is well known in the art.

In some embodiments, the anti-Galectin-9 antibody may bind to an epitope at least a segment of which is in CRD1 of a galectin-9 protein (e.g., a human galectin-9 or a mouse galectin-9). In some embodiments, the antibody may bind an epitope which is entirely within the CRD1 of the Galectin-9 protein. In some embodiments, the antibody may bind an epitope which is partially within the CRD1 of the Galectin-9 protein. In some embodiments, the epitope to which the anti-Galectin antibody binds is a linear epitope. In some embodiments, the epitope to which the anti-Galectin antibody binds is a conformational epitope.

In some embodiments, the anti-Galectin-9 antibody may bind an epitope at least a segment of which is in CRD2 of a Galectin-9 protein (e.g., a human galectin-9 or a mouse galectin-9). In some embodiments, the anti-Galectin-9 antibody may bind an epitope which is entirely within the CRD2 of the Galectin-9 protein. In some specific embodiments in which the anti-Galectin-9 antibody binds an epitope partially or entirely within CDR2, the antibody binds an epitope comprising at least residue W309. In some specific embodiments, in which the anti-Galectin-9 antibody binds an epitope partially or entirely within CDR2, the epitope to which the anti-Galectin-9 antibody binds does not contain one or more of R253, R271, Y330, R334, R341, and Y236 of SEQ ID NO:1. In some embodiments, the epitope to which the anti-Galectin antibody binds is a linear epitope encompassing residue W309. In some embodiments, the epitope to which the anti-Galectin antibody binds is a conformational epitope comprising W309.

In some examples, the anti-Galectin-9 antibody comprises the same V_H and/or V_L CDRs as an exemplary antibody described herein. Two antibodies having the same V_H and/or V_L CDRs means that their CDRs are identical when determined by the same approach (*e.g.*, the Kabat approach or the Chothia approach as known in the art). Such anti-Galectin-9 antibodies may have the same V_H, the same V_L, or both as compared to an exemplary antibody described herein.

Two heavy chain variable regions (or two light chain variable regions) having the same CDRs means that the CDRs in the two heavy chain variable regions (or light chain variable

regions) as determined by the same numbering scheme are identical. Exemplary numbering schemes for determining antibody CDRs include the "Kabat" numbering scheme (Kabat et al. (1991), 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md.), the "Chothia" numbering scheme (Al-Lazikani et al., (1997) JMB 273,927-948), the "Contact" numbering scheme (MacCallum et al., J. Mol. Biol. 262:732-745 (1996)), the "IMGT" numbering scheme (Lefranc M P et al., Dev Comp Immunol, 2003 January; 27(1):55-77), and the "AHo" numbering scheme (Honegger A and Pluckthun A, J Mol Biol, 2001 Jun. 8; 309(3):657-70). As known to those skilled in the art, the CDR regions of the exemplary anti-pKal and anti-FXII antibodies identified herein are determined by the "Chothia" numbering scheme, which is used as an example.

Also within the scope of the present disclosure are functional variants of any of the exemplary anti-Galectin-9 antibodies as disclosed herein. Such functional variants are substantially similar to the exemplary antibody, both structurally and functionally. A functional variant comprises substantially the same V_H and V_L CDRs as the exemplary antibody. For example, it may comprise only up to 5 (*e.g.*, 4, 3, 2, or 1) amino acid residue variations in the total CDR regions of the antibody and binds the same epitope of Galectin-9 with substantially similar affinity (*e.g.*, having a K_D value in the same order). Alternatively or in addition, the amino acid residue variations are conservative amino acid residue substitutions. As used herein, a "conservative amino acid substitution" refers to an amino acid substitution that does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references which compile such methods, *e.g.* Molecular Cloning: A Laboratory Manual, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or Current Protocols in Molecular Biology, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Conservative substitutions of amino acids include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D.

The "percent identity" of two amino acid sequences is determined using the algorithm of Karlin and Altschul Proc. Natl. Acad. Sci. USA 87:2264-68, 1990, modified as in Karlin and Altschul Proc. Natl. Acad. Sci. USA 90:5873-77, 1993. Such an algorithm is incorporated into the NBLAST and XBLAST programs (version 2.0) of Altschul, et al. J. Mol. Biol. 215:403-10, 1990. BLAST protein searches can be performed with the XBLAST program, score=50, wordlength=3 to obtain amino acid sequences homologous to the protein molecules of interest.

Where gaps exist between two sequences, Gapped BLAST can be utilized as described in Altschul et al., *Nucleic Acids Res.* 25(17):3389-3402, 1997. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. The anti-Galectin-9 antibody may comprise a heavy chain variable region framework derived from a subclass of germline VH fragment. Such germline VH regions are well known in the art. See, e.g., the IMGT database. Examples include the IGHV1 subfamily (*e.g.*, IGHV1-2, IGHV1-3, IGHV1-8, IGHV1-18, IGHV1-24, IGHV1-45, IGHV1-46, IGHV1-58, and IGHV1-69), the IGHV2 subfamily (*e.g.*, IGHV2-5, IGHV2-26, and IGHV2-70), the IGHV3 subfamily (*e.g.*, IGHV3-7, IGHV3-9, IGHV3-11, IGHV3-13, IGHV3-15, IGHV3-20, IGHV3-21, IGHV3-23, IGHV3-30, IGHV3-33, IGHV3-43, IGHV3-48, IGHV3-49, IGHV3-53, IGHV3-64, IGHV3-66, IGHV3-72, and IGHV3-73, IGHV3-74), the IGHV4 subfamily (*e.g.*, IGHV4-4, IGHV4-28, IGHV4-31, IGHV4-34, IGHV4-39, IGHV4-59, IGHV4-61, and IGHV4-B), the IGHV subfamily (*e.g.*, IGHV5-51, or IGHV6-1), and the IGHV7 subfamily (*e.g.*, IGHV7-4-1).

Alternatively or in addition, the anti-Galectin-9 antibody may comprise a light chain variable region that contains a framework derived from a germline Vκ fragment. Examples include an IGKV1 framework (*e.g.*, IGKV1-05, IGKV1-12, IGKV1-27, IGKV1-33, or IGKV1-39), an IGKV2 framework (*e.g.*, IGKV2-28), an IGKV3 framework (*e.g.*, IGKV3-11, IGKV3-15, or IGKV3-20), and an IGKV4 framework (*e.g.*, IGKV4-1). In other instances, the anti-Galectin-9 antibody may comprise a light chain variable region that contains a framework derived from a germline Vλ fragment. Examples include an IGλ1 framework (*e.g.*, IGλV1-36, IGλV1-40, IGλV1-44, IGλV1-47, IGλV1-51), an IGλ2 framework (e.g., IGλV2-8, IGλV2-11, IGλV2-14, IGλV2-18, IGλV2-23,), an IGλ3 framework (e.g., IGλV3-1, IGλV3-9, IGλV3-10, IGλV3-12, IGλV3-16, IGλV3-19, IGλV3-21, IGλV3-25, IGλV3-27,), an IGλ4 framework (e.g., IGλV4-3, IGλV4-60, IGλV4-69,), an IGλ5 framework (e.g., IGλV5-39, IGλV5-45,), an IGλ6 framework (e.g., IGλV6-57,), an IGλ7 framework (e.g., IGλV7-43, IGλV7-46,), an IGλ8 framework (*e.g.*, IGλV8-61), an IGλ9 framework (*e.g.*, IGλV9-49), or an IGλ10 framework (*e.g.*, IGλV10-54).

In some embodiments, the heavy chain of any of the anti-Galectin-9 antibodies as described herein may further comprise a heavy chain constant region (CH) or a portion thereof (*e.g.*, CH1, CH2, CH3, or a combination thereof). The heavy chain constant region can be of any suitable origin, *e.g.*, human, mouse, rat, or rabbit. In one specific example, the heavy chain

constant region is from a human IgG (a gamma heavy chain) of any IgG subfamily as described herein.

In some embodiments, the heavy chain constant region of the antibodies described herein may comprise a single domain (*e.g.*, CH1, CH2, or CH3) or a combination of any of the single domains, of a constant region (*e.g.*, SEQ ID NO: 419-423). In some embodiments, the light chain constant region of the antibodies described herein may comprise a single domain (*e.g.*, CL), of a constant region (*e.g.*, SEQ ID NO: 418). Exemplary light and heavy chain sequences are listed below. The hIgG1 LALA sequence includes two mutations, L234A and L235A, which suppress FcgR binding as well as a P329G mutation to abolish complement C1q binding, thus abolishing all immune effector functions. These mutations are underlined and bolded in the sequences listed below. The hIgG4 Fab Arm Exchange Mutant sequence includes a mutation to suppress Fab Arm Exchange (S228P), underlined and bolded. The light chain sequence for G9.2-17 is identical among all G9.-2-17 constructs. Similarly, the light chain sequence for G9.1-8m13 is identical among all G9.1-8m13 constructs. **Bolded** residues are the VH and VL regions. A IL2 signal sequence (MYRMQLLSCIALSLALVTNS; SEQ ID NO: 469) is located N-terminally of the variable region. It is used in expression vectors, which is cleaved during secretion and thus not in the mature antibody molecule. The mature protein (after secretion) starts with "EVQ" for the heavy chain and "DIM" for the light chain.

Exemplary Heavy and Light Chain sequences

G9.2-17 hIgG1 Heavy Chain (SEQ ID NO: 157)

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYISSSSGYTYYADSVKGRFTI
SADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD
KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*

Light Chain (SEQ ID NO: 108)

DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTD
FTLTISSLQPEDFATYYCQQSSTDPITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY
PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN
RGEC*

G9.2-17 hIgG1 LALA Heavy Chain (SEQ ID NO: 210)

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYISSSSGYTYYADSVKGRFTI
SADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL**G**APIEKTISKAKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD
KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*

Date Reçue/Date Received 2022-07-18

Light Chain (SEQ ID NO: 108)

DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTD
FTLTISSLQPEDFATYYCQQSSTDPITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY
PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN
RGEC*

G9.2-17 hIgG4 Heavy Chain (SEQ ID NO: 263)

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYISSSSGYTYYADSVKGRFTI
SADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLVTVSSASTKGPSVFPLAPCSR
STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD
HKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN
WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP
QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSR
WQEGNVFSCSVMHEALHNHYTQKSLSLSPGK*

Light Chain (SEQ ID NO: 108)

DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTD
FTLTISSLQPEDFATYYCQQSSTDPITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY
PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN
RGEC*

G9.2-17 hIgG4 Fab Arm Exchange mut Heavy Chain (SEQ ID NO: 316)

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYISSSSGYTYYADSVK
GRFTISADTSKNTAYLQMNSLRAEDTAVYYCARYWSYPSWWPYRGMDYWGQGTLVTVSSASTKGPSVFPL
APCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTY
TCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDP
EVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKG
QPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLT
VDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK*

Light Chain (SEQ ID NO: 108)

DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTD
FTLTISSLQPEDFATYYCQQSSTDPITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY
PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN
RGEC*

G9.1-8m13 hIgG1 Heavy Chain (SEQ ID NO: 136)

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYIYPYSSSSSYADSVKGRFTI
SADTSKNTAYLQMNSLRAEDTAVYYCARYSTYSSKWVWGMDYWGQGTLVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH
KPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR
EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*

Light Chain (SEQ ID NO:95)

DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTD
FTLTISSLQPEDFATYYCQQSYYDSNPITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN
FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS
FNRGEC*

Date Reçue/Date Received 2022-07-18

G9.1-8m13 hIgG1 LALA Heavy Chain (SEQ ID NO: 189)

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYIYPYSSSSSYADSVKGRFTI
SADTSKNTAYLQMNSLRAEDTAVYYCARYSTYSSKWVWGMDYWGQGTLVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH
KPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL**G**APIEKTISKAKGQPR
EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*

Light Chain (SEQ ID NO: 95)

DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTD
FTLTISSLQPEDFATYYCQQSYYDSNPITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN
FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS
FNRGEC*

G9.1-8m13 hIgG4 Heavy Chain (SEQ ID NO: 242)

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYIYPYSSSSSYADSVKGRFTI
SADTSKNTAYLQMNSLRAEDTAVYYCARYSTYSSKWVWGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRS
TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDH
KPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW
YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQ
VYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW
QEGNVFSCSVMHEALHNHYTQKSLSLSPGK*

Light Chain (SEQ ID NO: 95)

DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTD
FTLTISSLQPEDFATYYCQQSYYDSNPITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN
FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS
FNRGEC*

G9.1-8m13 hIgG4 Fab Arm Exchange mut Heavy Chain (SEQ ID NO: 295)

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSSSIHWVRQAPGKGLEWVAYIYPYSSSSSYADSVKGRFTI
SADTSKNTAYLQMNSLRAEDTAVYYCARYSTYSSKWVWGMDYWGQGTLVTVSSASTKGPSVFPLAPCSRS
TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDH
KPSNTKVDKRVESKYGPPCP**P**CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW
YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQ
VYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRW
QEGNVFSCSVMHEALHNHYTQKSLSLSPGK*

Light Chain (SEQ ID NO: 95)

DIQMTQSPSSLSASVGDRVTITCRASQSVSSAVAWYQQKPGKAPKLLIYSASSLYSGVPSRFSGSRSGTD
FTLTISSLQPEDFATYYCQQSYYDSNPITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN
FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS
FNRGEC

In some embodiments, the anti-Galectin 9 antibody has a light chain comprising, consisting essentially of, or consisting of SEQ ID NO: 108. In some embodiments, the anti-Galectin 9 antibody has a heavy chain comprising, consisting essentially of, or consisting of any one of the sequences selected from the group consisting of SEQ ID NO: 295, 242, 189, 157,

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210, 263, 316, and 136. In some embodiments, the anti-Galectin 9 antibody has a light chain comprising, consisting essentially of, or consisting of SEQ ID NO: 108 and a heavy chain comprising, consisting essentially of, or consisting of any one of the sequences selected from the group consisting of SEQ ID NO: 295, 242, 189, 157, 210, 263, 316, and 136. In some embodiments, the anti-Galectin 9 antibody has a light chain comprising SEQ ID NO: 108 and a heavy chain comprising any one of the sequences selected from the group consisting of SEQ ID NO: 295, 242, 189, 157, 210, 263, 316, and 136. In some embodiments, the anti-Galectin 9 antibody has a light chain consisting essentially of SEQ ID NO: 108 and a heavy chain consisting essentially of any one of the sequences selected from the group consisting of SEQ ID NO: 295, 242, 189, 157, 210, 263, 316, and 136. In some embodiments, the anti-Galectin 9 antibody has a light chain consisting of SEQ ID NO: 108 and a heavy chain consisting of any one of the sequences selected from the group consisting of SEQ ID NO: 295, 242, 189, 157, 210, 263, 316, and 136.

In some embodiments, the constant region is from human IgG4. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 423. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region comprising SEQ ID NO: 423. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region consisting of SEQ ID NO: 423. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 421. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region comprising SEQ ID NO: 421. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region consisting of SEQ ID NO: 421.

In some embodiments, the constant region of the anti-Galectin-9 antibody comprises a light chain IgG4 constant region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 418. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a light chain IgG4 constant region comprising SEQ ID No: 418. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a light chain IgG4 constant region consisting of SEQ ID NO: 418. In some embodiments, the constant region is from a human IgG1. In some embodiments, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG1 constant region that has at

least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 419. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG1 constant region comprising SEQ ID NO: 419. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region consisting of SEQ ID NO: 419. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a light chain IgG1 constant region comprising SEQ ID NO: 418. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a light chain IgG4 constant region consisting of SEQ ID NO: 418.

In some embodiments, the anti-Galectin-9 antibody comprises a modified constant region. In some embodiments, the anti-Galectin-9 antibody comprise a modified constant region that is immunologically inert, *e.g.*, does not trigger complement mediated lysis, or does not stimulate antibody-dependent cell mediated cytotoxicity (ADCC). ADCC activity can be assessed using methods disclosed in U.S. Pat. No. 5,500,362. In other embodiments, the constant region is modified as described in *Eur. J. Immunol.* (1999) 29:2613-2624; PCT Application No. PCT/GB99/01441; and/or UK Patent Application No. 9809951.8. In some embodiments, the IgG4 constant region is a mutant with reduced heavy chain exchange. In some embodiments, the constant region is from a human IgG4 Fab Arm Exchange mutant S229P. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 422. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region comprising SEQ ID NO: 422. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG4 constant region consisting of SEQ ID NO: 422. In some embodiments, the constant region of the anti-Galectin-9 antibody comprises a light chain IgG4 constant region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 418. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a light chain IgG4 constant region comprising SEQ ID NO: 418. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a light chain IgG4 constant region consisting of SEQ ID NO: 418. In some embodiments, the IgG is a mutant with minimal Fc receptor engagement. In one example, the constant region is from a human IgG1 LALA. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG1 constant region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 420. In one embodiment, the constant region of the anti-Galectin-9 antibody

comprises a heavy chain IgG1 constant region comprising SEQ ID NO: 420. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a heavy chain IgG1 constant region consisting of SEQ ID NO: 420. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a light chain IgG1 constant region that has at least 80% (e.g., 85%, 90%, 95%, 96%, 97%, 98%, 99% and any increment therein) sequence identity to SEQ ID NO: 418. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a light chain IgG1 constant region comprising SEQ ID NO: 418. In one embodiment, the constant region of the anti-Galectin-9 antibody comprises a light chain IgG4 constant region consisting of SEQ ID NO: 418.

In some embodiments, the anti-Galectin -9 antibody has chains corresponding to SEQ ID NO: 88-98 (anti-Galectin-9 antibodies binding to CRD1) and SEQ ID NO: 99-115 (anti-Galectin-9 antibodies binding to CRD2) for the light chains; The amino acid sequences of exemplary heavy chains correspond to SEQ ID NO: 116-140 (hIgG1); 169-193 (hIgG1 LALA); 222-246 (hIgG4); 275-299 (hIgG4 exchange mut) (anti-Galectin-9 antibodies binding to CRD1) and SEQ ID NO: 141-168 (hIgG1); 194-221(hIgG1 LALA); 247-274 (hIgG4); 300-327 (hIgG4 exchange mut) (anti-Galectin-9 antibodies binding to CRD2) for the heavy chains. IgG LALA, IgG4 exchange mut are located in the heavy chains; accordingly the light chains are the same for all IgG1 and IgG4 sequences disclosed herein. In some embodiments, 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.

Clone 9.1-derived Light Chains

In some embodiments, 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 any of the light chains set forth herein (or their variable regions), (e.g., light chain sequences set forth in SEQ ID NO: 88-98. In some embodiments, light chains of anti-Galectin-9 antibodies consist of 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 any of the light chains set forth herein, (e.g., light chain sequences set forth in SEQ ID NO: 88-98. In some embodiments, light chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 88-98. In some embodiments, light chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 88-98.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 88. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 89. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 90. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 91. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 92. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 93. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 94. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 95. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 96. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 97. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 98.

In some embodiments, 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 embodiments, light chains of anti-Galectin-9 antibodies consist of 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. In some embodiments, light chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 95 (or their variable regions). In some embodiments, light chains of anti-Galectin-9 antibodies consist of the amino acid sequence set forth in SEQ ID NO: 95.

Clone 9.1-derived Heavy chains

In some embodiments, the amino acid sequences of exemplary anti-Galectin antibody heavy chains correspond to sequences set forth in SEQ ID NO: 116-140 (hIgG1); 169-193 (hIgG1 LALA); 222-246 (hIgG4); 275-299 (hIgG4 exchange mut) (anti-Galectin-9 antibodies binding to CRD1).In some embodiments, 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 any of the heavy chains set forth herein (or their variable regions), e.g., sequences set forth in SEQ ID NO: 116-140; 169-193; 222-246; 275-299 (anti-Galectin-9 antibodies binding to CRD1). In some embodiments, heavy chains of anti-Galectin-9 antibodies consist of 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 any of the heavy chains set forth herein, e.g., sequences set forth in SEQ ID NO: 116-140; 169-193; 222-246; 275-299 (anti-Galectin-9 antibodies binding to CRD1).

In some embodiments, heavy chains of anti-Galectin-9 antibodies comprise an heavy chain amino acid sequence set forth in SEQ ID NO: 116-140; 169-193; 222-246; 275-299 (anti-Galectin-9 antibodies binding to CRD1). In some embodiments, heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 116-140; 169-193; 222-246; 275-299 (anti-Galectin-9 antibodies binding to CRD1).

In some embodiments, the constant region is IgG1. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 116. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 117. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 118. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 119. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 120. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 121. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 122. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 123. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 124. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 125. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 126. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 127. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 128. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 129. In

some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 130. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 131. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 132. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 133. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 134. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 135. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 136. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 137. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 138. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 139. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 140.

In some embodiments, the constant region is IgG1 LALA. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 169. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 170. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 171. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 172. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 173. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 174. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 175. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 176. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 177. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 178. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a

heavy chain sequence of SEQ ID NO: 179. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 180. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 181. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 182. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 183. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 184. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 185. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 186. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 187. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 188. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 189. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 190. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 191. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 192. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 193.

In some embodiments, the constant region is IgG4. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 222. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 223. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 224. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 225. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 226. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 227. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 228. In some embodiments, the anti-Galectin-9 antibodies

or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 229. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 230. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 231. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 232. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 233. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 234. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 235. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 236. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 237. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 238. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 29. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 240. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 241. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 242. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 243. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 244. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 245. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 246.

In some embodiments, the constant region is IgG4mut. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 275. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 276. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 277. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 278. In some

embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 279. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 280. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 281. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 282. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 283. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 284. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 285. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 286. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 287. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 288. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 289. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 290. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 291. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 292. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 293 In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 294.In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 295. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 296. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 297. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 298. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 299.

In some embodiments, 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 embodiments, heavy chains of anti-Galectin-9 antibodies consist of 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. In some embodiments, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 136 (or its variable region). In some embodiments, heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 136.

In some embodiments, 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 embodiments, heavy chains of anti-Galectin-9 antibodies consist of 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. In some embodiments, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 189 (or its variable region). In some embodiments, heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 189.

In some embodiments, 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 embodiments, heavy chains of anti-Galectin-9 antibodies consist of 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. In some embodiments, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 242 (or its variable region). In some embodiments, heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 242.

In some embodiments, 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 embodiments, heavy chains of anti-Galectin-9 antibodies consist of 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. In some embodiments, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 295. In some embodiments, heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 295.

Clone 9.1 derived heavy and light chains

A VH domain can comprise the amino acid sequence of any VH domain described herein fused to a human IgG, e.g., an IgG1, constant region, such as human IgG1 constant domain amino acid sequence, hIgG LALA, hIgG4, or IgG4mut .

In some embodiments, the amino acid sequences of exemplary anti-Galectin antibody light chains correspond to SEQ ID NO: 88 -98, orthe amino acid sequences of the exemplary anti-Galectin antibody heavy chains correspond to SEQ ID NO: 116-140; 169-193;222-246; 275-299.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 88 and a heavy chain having a sequence selected from of SEQ ID NO: 116, 169, 222, or 275.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 89 and a heavy chain having a sequence selected from of SEQ ID NO: 117, 170, 223, or 276.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 90 and a heavy chain having a sequence selected from of SEQ ID NO: 118, 171, 224, or 277.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 91 and a heavy chain having a sequence selected from of SEQ ID NO: 119, 172, 225, or 278.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 92 and a heavy chain having a sequence selected from of SEQ ID NO: 120, 173, 226, or 279.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 93 and a heavy chain having a sequence selected from of SEQ ID NO: 121, 174, 227, or 280.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 94 and a heavy chain having a sequence selected from of SEQ ID NO: 122, 175, 228, or 281.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 95 and a heavy chain having a sequence selected from of SEQ ID NO: 123, 176, 229, or 282.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 96 and a heavy chain having a sequence selected from of SEQ ID NO: 138, 191, 244, or 297.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 97 and a heavy chain having a sequence selected from of SEQ ID NO: 139, 192, 245, or 298.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 98 and a heavy chain having a sequence selected from of SEQ ID NO: 140, 193, 246, or 299.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 95 and a heavy chain having a sequence selected from of SEQ ID NO: 124, 177, 230, or 283.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 95 and a heavy chain having a sequence selected from of SEQ ID NO: 125, 178, 231, or 284.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 95 and a heavy chain having a sequence selected from of SEQ ID NO: 126, 179, 232, or 285.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 95 and a heavy chain having a sequence selected from of SEQ ID NO: 127,180, 233, or 286,

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 95 and a heavy chain having a sequence selected from of SEQ ID NO: 128, 181, 234, or 287.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 95 and a heavy chain having a sequence selected from of SEQ ID NO: 129, 182, 235, or 288.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 95 and a heavy chain having a sequence selected from of SEQ ID NO: 130, 183, 236, or 289.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 95 and a heavy chain having a sequence selected from of SEQ ID NO: 131, 184, 237, or 290.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 95 and a heavy chain having a sequence selected from of SEQ ID NO: 132, 185, 238, or 291.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 95 and a heavy chain having a sequence selected from of SEQ ID NO: 133, 186, 239, o r292.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 95 and a heavy chain having a sequence selected from of SEQ ID NO: 137, 187, 240, or 293.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 95 and a heavy chain having a sequence selected from of SEQ ID NO: 138, 188, 241, or 294.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 95 and a heavy chain having a sequence selected from of SEQ ID NO: 139, 189, 242, or 295.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 95 and a heavy chain having a sequence selected from of SEQ ID NO: 140, 190, 243, or 296.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 95 and comprise a heavy chain sequence of SEQ ID NO: 136.In some embodiments, 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), and 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 embodiments, light chains of anti-Galectin-9 antibodies consist of 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 and heavy chains of anti-Galectin-9 antibodies consist of 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. In some embodiments, light chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 95 (or their variable regions) heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 136 (or its variable region). In some embodiments, light chains of anti-Galectin-9 antibodies consist of the amino acid sequence set forth in SEQ ID NO: 95 and heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 136.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 95 and comprise a heavy chain sequence of SEQ ID NO: 189. In some embodiments, 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) and 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) and heavy chains of anti-Galectin-9 antibodies consist of 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 . In some embodiments, light chains of anti-Galectin-9 antibodies consist of 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. In some embodiments, light chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 95 (or their variable regions) and heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 189 (or its variable region). In some embodiments, light chains of anti-Galectin-9 antibodies consist of the amino acid sequence set forth in SEQ ID NO: 95 and heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 189.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 95 and comprise a heavy chain sequence of SEQ ID NO: 242. In some embodiments, 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) and 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 embodiments, light chains of anti-Galectin-9 antibodies consist of 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 and heavy chains of anti-Galectin-9 antibodies consist of 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. In some embodiments, light chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 95 (or their variable regions) and heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 242 (or its variable region). In some embodiments, light chains of anti-Galectin-9 antibodies consist of the amino acid sequence set forth in SEQ ID NO: 95 and heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 242.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 95 and comprise a heavy chain sequence of SEQ ID NO: 295.In some embodiments, 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) and 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 embodiments, light chains of anti-Galectin-9 antibodies consist of 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 and heavy chains of anti-Galectin-9 antibodies consist of 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. In some embodiments, light chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 95 (or their variable regions) and heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 295. In some embodiments, light chains of anti-Galectin-9 antibodies consist of the amino acid sequence set forth in SEQ ID NO: 95 and heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 295.

Clone 9.2-derived Light Chains

In some embodiments, 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 any of the light chains set forth herein (or their variable regions), (e.g., light chain sequences set forth in SEQ ID NO: 99-115). In some embodiments, light chains of anti-Galectin-9 antibodies consist of 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 any of the light chains set forth herein, (e.g., light chain sequences set forth in SEQ ID NO: 99-115).

In some embodiments, light chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 99-115. In some embodiments, light chains of anti-Galectin-9 antibodies consist of a sequence set forth in SEQ ID NO: 99-115.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 99. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 100. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 101. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 102. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 103. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 104. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 105. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 106. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 107. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 108. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 109. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 110. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 111. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 112. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 113. In some embodiments, the anti-Galectin-9

antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 114. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 115. In some embodiments, 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 embodiments, light chains of anti-Galectin-9 antibodies consist of 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.

In some embodiments, light chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 108 (or their variable regions). In some embodiments, light chains of anti-Galectin-9 antibodies consist set forth in SEQ ID NO: 108.

Clone 9.2-derived Heavy Chains

In some embodiments, the amino acid sequences of exemplary anti-Galectin antibody heavy chains correspond to sequences set forth in SEQ ID NO: 141-168 (hIgG1); 194-221(hIgG1 LALA); 247-274 (hIgG4); 300-327 (hIgG4 exchange mut) (anti-Galectin-9 antibodies binding to CRD2) for the heavy chains.

In some embodiments, 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 any of the heavy chains set forth herein (or their variable regions), e.g., sequences set forth in SEQ ID NO: 141-168; 194-220; 247-274; 300-327 (anti-Galectin-9 antibodies binding to CRD2). In some embodiments, heavy chains of anti-Galectin-9 antibodies consist of 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 any of the heavy chains set forth herein, e.g., sequences set forth in SEQ ID NO: 141-168; 194-220; 247-274; 300-327 (anti-Galectin-9 antibodies binding to CRD2).

In some embodiments, heavy chains of anti-Galectin-9 antibodies comprise an heavy chain amino acid sequence set forth in SEQ ID NO: 141-168; 194-220; 247-274; 300-327 (anti-Galectin-9 antibodies binding to CRD2). In some embodiments, heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 141-168; 194-220; 247-274; 300-327 (anti-Galectin-9 antibodies binding to CRD2).

In some embodiments, the constant region is IgG1. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 141. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 142. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 143. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 144. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 145. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 146. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 147. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 148. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 149. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 150. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 151. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 152. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 153. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 154. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 155. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 156. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 157. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 158. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 159. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 160. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 161. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 162. In

some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 163. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 164. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 165. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 166. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 167. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 168.

In some embodiments, the constant region is IgG1 LALA. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 194. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 195. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 196. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 197. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 198. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 199. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 200. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 201. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 202. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 203. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 304. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 205. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 206. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 207. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 208. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 209. In

some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 210. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 211. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 212. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 213. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 214. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 215. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 216. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 217. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 218. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 219. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 220. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 221.

In some embodiments, the constant region is IgG4. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 247. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 248. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 249. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 250. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 251. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 252. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 253. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 254. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 255. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 256. In

some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 257. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 258. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 259. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 260. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 261. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 262. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 263. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 264. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 265. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 266. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 267. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 268. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 269. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 270. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 271. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 272. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 273. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 274.

In some embodiments, the constant region is IgG4 mut. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 300. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 301. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 302. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 303. In some

embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 304. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 305. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 306. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 307. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 308. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 309. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 310. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 311. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 312. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 313. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 314. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 315. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 316. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 317. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 318. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 319. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 320. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 321. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 322. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 323. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 324. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID

NO: 325. In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a heavy chain sequence of SEQ ID NO: 326.

In some embodiments, 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 embodiments, heavy chains of anti-Galectin-9 antibodies consist of 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.In some embodiments, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 157 (or its variable region). In some embodiments, heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 157.

In some embodiments, 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 embodiments, heavy chains of anti-Galectin-9 antibodies consist of 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. In some embodiments, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 210 (or its variable region). In some embodiments, heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 210.In some embodiments, 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 embodiments, heavy chains of anti-Galectin-9 antibodies consist of 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.

In some embodiments, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 263 (or its variable region). In some embodiments, heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 263.

In some embodiments, 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 embodiments, heavy chains of anti-Galectin-9 antibodies consist of 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. In some embodiments, heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 316 (or its variable region). In some embodiments, heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 316.

Clone 9.2 Derived Heavy and Light Chains

In some embodiments, the amino acid sequences of exemplary anti-Galectin antibody light chains correspond to SEQ ID NO: 99-108, and the amino acid sequences of the exemplary anti-Galectin antibody heavy chains correspond to SEQ ID NO: 141-168; 194-221;249-274; 300-327.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 99 and a heavy chain having a sequence selected from SEQ ID NO: 141, 194, 247, or 300.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 91 and a heavy chain having a sequence selected from SEQ ID NO: 142, 195, 248, or 301.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 91 and a heavy chain having a sequence selected from SEQ ID NO: 143, 196, 249, or 302.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 91 and a heavy chain having a sequence selected from SEQ ID NO: 144, 197, 250, or 303.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 100 and a heavy chain having a sequence selected from SEQ ID NO: 145, 198, 251, or 304.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 101 and a heavy chain having a sequence selected from SEQ ID NO: 146, 199, 252, or 305.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 102 and a heavy chain having a sequence selected from SEQ ID NO: 147, 200, 253, or 306.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 103 and a heavy chain having a sequence selected from SEQ ID NO: 148, 201, 254, or 307.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 104 and a heavy chain having a sequence selected from SEQ ID NO: 149, 202, 255, or 308.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 105 and a heavy chain having a sequence selected from SEQ ID NO: 150, 203, 256, or 309.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 106 and a heavy chain having a sequence selected from SEQ ID NO: 151, 204, 257, or 310.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 107 and a heavy chain having a sequence selected from SEQ ID NO: 152, 205, 258, or 311.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 99 and a heavy chain having a sequence selected from SEQ ID NO: 153, 206, 259, or 312.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 91 and a heavy chain having a sequence selected from SEQ ID NO: 154, 207, 260, or 313.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 100 and a heavy chain having a sequence selected from SEQ ID NO: 155, 208, 261, or 314.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 91 and a heavy chain having a sequence selected from SEQ ID NO: 156, 209, 262, or 315.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 108 and a heavy chain having a sequence selected from SEQ ID NO: 157, 210, 263, or 316.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 108 and a heavy chain having a sequence selected from SEQ ID NO: 158, 211, 264, or 317.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 91 and a heavy chain having a sequence selected from SEQ ID NO: 159, 212, 265, or 318.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 109 and a heavy chain having a sequence selected from SEQ ID NO: 160, 213, 266, or 319.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 108 and a heavy chain having a sequence selected from SEQ ID NO: 161, 214, 267, or 320.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 110 and a heavy chain having a sequence selected from SEQ ID NO: 162, 215, 268, or 321.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 111 and a heavy chain having a sequence selected from SEQ ID NO: 163, 216, 269, or 322.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 112 and a heavy chain having a sequence selected from SEQ ID NO: 164, 217, 270, or 323.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 113 and a heavy chain having a sequence selected from SEQ ID NO: 165, 218, 271, or 324.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 114 and a heavy chain having a sequence selected from SEQ ID NO: 166, 219, 272, or 325.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 115 and a heavy chain having a sequence selected from SEQ ID NO: 167, 220, 273, or 326.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain having the sequence of SEQ ID NO: 108 and a heavy chain having a sequence selected from SEQ ID NO: 168, 221, 274, or 327.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 108 and comprise a heavy chain sequence of SEQ ID NO: 157. In some embodiments, 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), and 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 embodiments, light chains of anti-Galectin-9 antibodies consist of 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 and heavy chains of anti-Galectin-9 antibodies consist of 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. In some embodiments, light chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 108 (or their variable regions) heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 157 (or its variable region). In some embodiments, light chains of anti-Galectin-9 antibodies consist of the amino acid sequence set forth in SEQ ID NO: 108 and heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 157.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 108 and comprise a heavy chain sequence of SEQ ID NO: 210. In some embodiments, 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) and 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) and heavy chains of anti-Galectin-9 antibodies consist of 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 . In some embodiments, light chains of anti-Galectin-9 antibodies consist of 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. In some embodiments, light chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 108 (or their variable regions) and heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 210 (or its variable region). In some embodiments, light chains of anti-Galectin-9 antibodies consist of the amino

acid sequence set forth in SEQ ID NO: 108 and heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 210.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 108 and comprise a heavy chain sequence of SEQ ID NO: 263. In some embodiments, 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) and 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 embodiments, light chains of anti-Galectin-9 antibodies consist of 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 and heavy chains of anti-Galectin-9 antibodies consist of 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. In some embodiments, light chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 108 (or their variable regions) and heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 263 (or its variable region). In some embodiments, light chains of anti-Galectin-9 antibodies consist of the amino acid sequence set forth in SEQ ID NO: 108 and heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 263.

In some embodiments, the anti-Galectin-9 antibodies or antigen-binding portion thereof comprise a light chain sequence of SEQ ID NO: 108 and comprise a heavy chain sequence of SEQ ID NO: 316.In some embodiments, 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) and 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 embodiments, light chains of anti-Galectin-9 antibodies consist of 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 and heavy chains of anti-Galectin-9 antibodies consist of 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. In some embodiments, light chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 108 (or their variable regions) and heavy chains of anti-Galectin-9 antibodies comprise an amino acid sequence set forth in SEQ ID NO: 316. In some embodiments, light chains of anti-Galectin-9 antibodies consist of the amino acid sequence set forth in SEQ ID NO: 108 and heavy chains of anti-Galectin-9 antibodies consist of an amino acid sequence set forth in SEQ ID NO: 316.

In some embodiments, the anti-Galectin-9 antibody comprises an IgG1 heavy chain having the sequence of SEQ ID NO: 157 and a light chain having the sequence of SEQ ID NO: 108. In some embodiments, the anti-Galectin-9 antibody comprises an IgG1 heavy chain having the sequence of SEQ ID NO: 210 and a light chain having the sequence of SEQ ID NO: 108. In some embodiments, the anti-Galectin-9 antibody comprises an IgG4 heavy chain having the sequence of SEQ ID NO: 263 and a light chain having the sequence of SEQ ID NO: 108. In some embodiments, the anti-Galectin-9 antibody comprises an IgG4 heavy chain having the sequence of SEQ ID NO: 316 and a light chain having the sequence of SEQ ID NO: 108. In some embodiments, the anti-Galectin-9 antibody comprises an IgG1 heavy chain having the sequence of SEQ ID NO: 136 and a light chain having the sequence of SEQ ID NO: 108. In some embodiments, the anti-Galectin-9 antibody comprises an IgG1 heavy chain having the sequence of SEQ ID NO: 189 and a light chain having the sequence of SEQ ID NO: 108. In some embodiments, the anti-Galectin-9 antibody comprises an IgG4 heavy chain having the sequence of SEQ ID NO: 242 and a light chain having the sequence of SEQ ID NO: 108. In some embodiments, the anti-Galectin-9 antibody comprises an IgG4 heavy chain having the sequence of SEQ ID NO: 295 and a light chain having the sequence of SEQ ID NO: 108.

Antibody heavy and light chain constant regions are well known in the art, *e.g.*, those provided in the IMGT database.

Preparation of Anti-Galectin-9 Antibodies

Antibodies capable of binding Galectin-9 as described herein can be made by any method known in the art. See, for example, Harlow and Lane, (1998) Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York.

In some embodiments, antibodies specific to a target antigen (*e.g.*, Galectin-9 or a CRD thereof) are made by conventional hybridoma technology. The full-length target antigen or a fragment thereof, optionally coupled to a carrier protein such as KLH, can be used to immunize

a host animal for generating antibodies binding to that antigen. The route and schedule of immunization of the host animal are generally in keeping with established and conventional techniques for antibody stimulation and production, as further described herein. General techniques for production of mouse, humanized, and human antibodies are known in the art and are described herein. It is contemplated that any mammalian subject including humans or antibody producing cells therefrom can be manipulated to serve as the basis for production of mammalian, including human hybridoma cell lines. Typically, the host animal is inoculated intraperitoneally, intramuscularly, orally, subcutaneously, intraplantar, and/or intradermally with an amount of immunogen, including as described herein.

Hybridomas can be prepared from the lymphocytes and immortalized myeloma cells using the general somatic cell hybridization technique of Kohler, B. and Milstein, C. (1975) *Nature* 256:495-497 or as modified by Buck, D. W., et al., *In Vitro*, 18:377-381 (1982). Available myeloma lines, including, but not limited to, X63-Ag8.653 and those from the Salk Institute, Cell Distribution Center, San Diego, Calif., USA, may be used in the hybridization. Generally, the technique involves fusing myeloma cells and lymphoid cells using a fusogen such as polyethylene glycol, or by electrical means well known to those skilled in the art. After the fusion, the cells are separated from the fusion medium and grown in a selective growth medium, such as hypoxanthine-aminopterin-thymidine (HAT) medium, to eliminate unhybridized parent cells. Any of the media described herein, supplemented with or without serum, can be used for culturing hybridomas that secrete monoclonal antibodies. As another alternative to the cell fusion technique, EBV immortalized B cells may be used to produce the anti-Galectin-9 monoclonal antibodies described herein. The hybridomas are expanded and subcloned, if desired, and supernatants are assayed for anti-immunogen activity by conventional immunoassay procedures (*e.g.*, radioimmunoassay, enzyme immunoassay, or fluorescence immunoassay).

Hybridomas that may be used as source of antibodies encompass all derivatives, progeny cells of the parent hybridomas that produce monoclonal antibodies capable of interfering with the Galectin-9 activity. Hybridomas that produce such antibodies may be grown *in vitro* or *in vivo* using known procedures. The monoclonal antibodies may be isolated from the culture media or body fluids, by conventional immunoglobulin purification procedures such as ammonium sulfate precipitation, gel electrophoresis, dialysis, chromatography, and ultrafiltration, if desired. Undesired activity if present, can be removed, for example, by running the preparation over adsorbents made of the immunogen attached to a solid phase and eluting or releasing the desired antibodies off the immunogen. Immunization of a host animal with a target

antigen or a fragment containing the target amino acid sequence conjugated to a protein that is immunogenic in the species to be immunized, *e.g.*, keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor using a bifunctional or derivatizing agent, for example maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, SOCl, or R1N=C=NR, where R and R1 are different alkyl groups, can yield a population of antibodies (*e.g.*, monoclonal antibodies).

If desired, an antibody (monoclonal or polyclonal) of interest (*e.g.*, produced by a hybridoma) may be sequenced and the polynucleotide sequence may then be cloned into a vector for expression or propagation. The sequence encoding the antibody of interest may be maintained in vector in a host cell and the host cell can then be expanded and frozen for future use. In an alternative, the polynucleotide sequence may be used for genetic manipulation to "humanize" the antibody or to improve the affinity (affinity maturation), or other characteristics of the antibody. For example, the constant region may be engineered to more resemble human constant regions to avoid immune response if the antibody is used in clinical trials and treatments in humans. It may be desirable to genetically manipulate the antibody sequence to obtain greater affinity to the target antigen and greater efficacy in inhibiting the activity of Galectin-9. It will be apparent to one of skill in the art that one or more polynucleotide changes can be made to the antibody and still maintain its binding specificity to the target antigen.

In other embodiments, fully human antibodies are obtained using commercially available mice that have been engineered to express specific human immunoglobulin proteins. Transgenic animals that are designed to produce a more desirable (*e.g.*, fully human antibodies) or more robust immune response may also be used for generation of humanized or human antibodies. Examples of such technology are Xenomouse^{RTM} from Amgen, Inc. (Fremont, Calif.) and HuMAb-Mouse^{RTM} and TC MouseTM from Medarex, Inc. (Princeton, N.J.). In other embodiments, antibodies are made recombinantly by phage display or yeast technology. See, for example, U.S. Pat. Nos. 5,565,332; 5,580,717; 5,733,743; and 6,265,150; and Winter et al., (1994) *Annu. Rev. Immunol.* 12:433-455. In alternate embodiments, phage display technology (McCafferty et al., (1990) *Nature* 348:552-553) is used to produce human antibodies and antibody fragments *in vitro*, from immunoglobulin variable (V) domain gene repertoires from unimmunized donors.

In alternate embodiments, antibodies capable of binding to the target antigens as described herein are isolated from a suitable antibody library. Antibody libraries, which contain a plurality of antibody components, can be used to identify antibodies that bind to a specific

target antigen (*e.g.*, the CRD1 or CRD2 of Galectin-9 in this case) following routine selection processes as known in the art. In the selection process, an antibody library can be probed with the target antigen or a fragment thereof and members of the library that are capable of binding to the target antigen can be isolated, typically by retention on a support. Such screening process may be performed by multiple rounds (e.g., including both positive and negative selections) to enrich the pool of antibodies capable of binding to the target antigen. Individual clones of the enriched pool can then be isolated and further characterized to identify those having desired binding activity and biological activity. Sequences of the heavy chain and light chain variable domains can also be determined via conventional methodology. There are a number of routine methods known in the art to identify and isolate antibodies capable of binding to the target antigens described herein, including phage display, yeast display, ribosomal display, or mammalian display technology.

As an example, phage displays typically use a covalent linkage to bind the protein (*e.g.*, antibody) component to a bacteriophage coat protein. The linkage results from translation of a nucleic acid encoding the antibody component fused to the coat protein. The linkage can include a flexible peptide linker, a protease site, or an amino acid incorporated as a result of suppression of a stop codon. Phage display is described, for example, in U.S. Pat. No. 5,223,409; Smith (1985) *Science* 228:1315-1317; WO 92/18619; WO 91/17271; WO 92/20791; WO 92/15679; WO 93/01288; WO 92/01047; WO 92/09690; WO 90/02809; de Haard et al. (1999) *J. Biol. Chem* 274:18218-30; Hoogenboom et al. (1998) *Immunotechnology* 4:1-20; Hoogenboom et al. (2000) *Immunol Today* 2:371-8 and Hoet et al. (2005) *Nat Biotechnol.* 23(3)344-8. Additional suitable methods are described in Miller et al., *PloS One,* 2012, 7, e43746; Fellouse et al., *J Mol Biol,* 2007, 373, 924-940. Bacteriophage displaying the protein component can be grown and harvested using standard phage preparatory methods, *e.g.* PEG precipitation from growth media. After selection of individual display phages, the nucleic acid encoding the selected protein components can be isolated from cells infected with the selected phages or from the phage themselves, after amplification. Individual colonies or plaques can be selected, and then the nucleic acid may be isolated and sequenced.

Other display formats include cell-based display (see, *e.g.*, WO 03/029456), protein-nucleic acid fusions (see, *e.g.*, U.S. Pat. No. 6,207,446), ribosome display (See, *e.g.*, Mattheakis et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:9022 and Hanes et al. (2000) *Nat Biotechnol.* 18:1287-92; Hanes et al. (2000) *Methods Enzymol.* 328:404-30; and Schaffitzel et al. (1999) *J Immunol Methods.* 231(1-2):119-35), and *E. coli* periplasmic display (*J Immunol Methods.* 2005 Nov 22;PMID: 16337958).

After display library members are isolated for binding to the target antigen, each isolated library member can be also tested for its ability to bind to a non-target molecule to evaluate its binding specificity. Examples of non-target molecules include streptavidin on magnetic beads, blocking agents such as bovine serum albumin, non-fat bovine milk, soy protein, any capturing or target immobilizing monoclonal antibody, or non-transfected cells which do not express the target. A high-throughput ELISA screen can be used to obtain the data, for example. The ELISA screen can also be used to obtain quantitative data for binding of each library member to the target as well as for cross species reactivity to related targets or subunits of the target antigen and also under different condition such as pH 6 or pH 7.5. The non-target and target binding data are compared (*e.g.*, using a computer and software) to identify library members that specifically bind to the target.

After selecting candidate library members that bind to a target, each candidate library member can be further analyzed, *e.g.*, to further characterize its binding properties for the target, *e.g.*, Galectin-9. Each candidate library member can be subjected to one or more secondary screening assays. The assay can be for a binding property, a catalytic property, an inhibitory property, a physiological property (*e.g.*, cytotoxicity, renal clearance, immunogenicity), a structural property (*e.g.*, stability, conformation, oligomerization state) or another functional property. The same assay can be used repeatedly, but with varying conditions, *e.g.*, to determine pH, ionic, or thermal sensitivities.

As appropriate, the assays can use a display library member directly, a recombinant polypeptide produced from the nucleic acid encoding the selected polypeptide, or a synthetic peptide synthesized based on the sequence of the selected polypeptide. In the case of selected Fabs, the Fabs can be evaluated or can be modified and produced as intact IgG proteins. Exemplary assays for binding properties are described below.

Binding proteins can also be evaluated using an ELISA assay. For example, each protein is contacted to a microtitre plate whose bottom surface has been coated with the target, *e.g.*, a limiting amount of the target. The plate is washed with buffer to remove non-specifically bound polypeptides. Then the amount of the binding protein bound to the target on the plate is determined by probing the plate with an antibody that can recognize the binding protein, *e.g.*, a tag or constant portion of the binding protein. The antibody is linked to a detection system (*e.g.*, an enzyme such as alkaline phosphatase or horse radish peroxidase (HRP) which produces a colorimetric product when appropriate substrates are provided).

Alternatively, the ability of a binding protein described herein to bind a target antigen can be analyzed using a homogenous assay, *i.e.*, after all components of the assay are added,

additional fluid manipulations are not required. For example, fluorescence resonance energy transfer (FRET) can be used as a homogenous assay (see, for example, Lakowicz et al., U.S. Patent No. 5,631,169; Stavrianopoulos, et al., U.S. Patent No. 4,868,103). A fluorophore label on the first molecule (*e.g.*, the molecule identified in the fraction) is selected such that its emitted fluorescent energy can be absorbed by a fluorescent label on a second molecule (*e.g.*, the target) if the second molecule is in proximity to the first molecule. The fluorescent label on the second molecule fluoresces when it absorbs to the transferred energy. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, the spatial relationship between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. A binding event that is configured for monitoring by FRET can be conveniently measured through standard fluorometric detection means, *e.g.*, using a fluorimeter. By titrating the amount of the first or second binding molecule, a binding curve can be generated to estimate the equilibrium binding constant.

Surface plasmon resonance (SPR) can be used to analyze the interaction of a binding protein and a target antigen. SPR or Biomolecular Interaction Analysis (BIA) detects biospecific interactions in real time, without labeling any of the interactants. Changes in the mass at the binding surface (indicative of a binding event) of the BIA chip result in alterations of the refractive index of light near the surface (the optical phenomenon of SPR). The changes in the refractivity generate a detectable signal, which are measured as an indication of real-time reactions between biological molecules. Methods for using SPR are described, for example, in U.S. Patent No. 5,641,640; Raether, 1988, Surface Plasmons Springer Verlag; Sjolander and Urbaniczky, 1991, *Anal. Chem.* 63:2338-2345; Szabo et al., 1995, *Curr. Opin. Struct. Biol.* 5:699-705 and on-line resources provide by BIAcore International AB (Uppsala, Sweden).

Information from SPR can be used to provide an accurate and quantitative measure of the equilibrium dissociation constant (K_D), and kinetic parameters, including K_{on} and K_{off}, for the binding of a binding protein to a target. Such data can be used to compare different biomolecules. For example, selected proteins from an expression library can be compared to identify proteins that have high affinity for the target or that have a slow K_{off}. This information can also be used to develop structure-activity relationships (SAR). For example, the kinetic and equilibrium binding parameters of matured versions of a parent protein can be compared to the parameters of the parent protein. Variant amino acids at given positions can be identified that correlate with particular binding parameters, *e.g.*, high affinity and slow K_{off}. This information can be combined with structural modeling (*e.g.*, using homology modeling, energy

minimization, or structure determination by x-ray crystallography or NMR). As a result, an understanding of the physical interaction between the protein and its target can be formulated and used to guide other design processes.

As a further example, cellular assays may be used. Binding proteins can be screened for ability to bind to cells which transiently or stably express and display the target of interest on the cell surface. For example, Galectin-9 binding proteins can be fluorescently labeled and binding to Galectin-9 in the presence or absence of antagonistic antibody can be detected by a change in fluorescence intensity using flow cytometry *e.g.*, a FACS machine.

Antigen-binding fragments of an intact antibody (full-length antibody) can be prepared via routine methods. For example, F(ab')2 fragments can be produced by pepsin digestion of an antibody molecule, and Fab fragments that can be generated by reducing the disulfide bridges of F(ab')2 fragments.

Genetically engineered antibodies, such as humanized antibodies, chimeric antibodies, single-chain antibodies, and bi-specific antibodies, can be produced via, *e.g.*, conventional recombinant technology. In one example, DNA encoding a monoclonal antibodies specific to a target antigen can be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). Once isolated, the DNA may be placed into one or more expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. See, *e.g.*, PCT Publication No. WO 87/04462. The DNA can then be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences, Morrison et al., (1984) *Proc. Nat. Acad. Sci.* 81:6851, or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. In that manner, genetically engineered antibodies, such as "chimeric" or "hybrid" antibodies; can be prepared that have the binding specificity of a target antigen.

Techniques developed for the production of "chimeric antibodies" are well known in the art. See, *e.g.*, Morrison et al. (1984) *Proc. Natl. Acad. Sci. USA* 81, 6851; Neuberger et al. (1984) *Nature* 312, 604; and Takeda et al. (1984) *Nature* 314:452.

Methods for constructing humanized antibodies are also well known in the art. See, *e.g.*, Queen et al., *Proc. Natl. Acad. Sci. USA*, 86:10029-10033 (1989). In one example, variable regions of V_H and V_L of a parent non-human antibody are subjected to three-dimensional

molecular modeling analysis following methods known in the art. Next, framework amino acid residues predicted to be important for the formation of the correct CDR structures are identified using the same molecular modeling analysis. In parallel, human V_H and V_L chains having amino acid sequences that are homologous to those of the parent non-human antibody are identified from any antibody gene database using the parent V_H and V_L sequences as search queries. Human V_H and V_L acceptor genes are then selected.

The CDR regions within the selected human acceptor genes can be replaced with the CDR regions from the parent non-human antibody or functional variants thereof. When necessary, residues within the framework regions of the parent chain that are predicted to be important in interacting with the CDR regions (see above description) can be used to substitute for the corresponding residues in the human acceptor genes.

A single-chain antibody can be prepared via recombinant technology by linking a nucleotide sequence coding for a heavy chain variable region and a nucleotide sequence coding for a light chain variable region. Preferably, a flexible linker is incorporated between the two variable regions. Alternatively, techniques described for the production of single chain antibodies (U.S. Patent Nos. 4,946,778 and 4,704,692) can be adapted to produce a phage or yeast scFv library and scFv clones specific to Galectin-9 can be identified from the library following routine procedures. Positive clones can be subjected to further screening to identify those that inhibit Galectin-9 activity.

Antibodies obtained following a method known in the art and described herein can be characterized using methods well known in the art. For example, one method is to identify the epitope to which the antigen binds, or "epitope mapping." There are many methods known in the art for mapping and characterizing the location of epitopes on proteins, including solving the crystal structure of an antibody-antigen complex, competition assays, gene fragment expression assays, and synthetic peptide-based assays, as described, for example, in Chapter 11 of Harlow and Lane, Using Antibodies, a Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1999. In an additional example, epitope mapping can be used to determine the sequence, to which an antibody binds. The epitope can be a linear epitope, *i.e.*, contained in a single stretch of amino acids, or a conformational epitope formed by a three-dimensional interaction of amino acids that may not necessarily be contained in a single stretch (primary structure linear sequence). Peptides of varying lengths (*e.g.*, at least 4-6 amino acids long) can be isolated or synthesized (*e.g.*, recombinantly) and used for binding assays with an antibody. In another example, the epitope to which the antibody binds can be determined in a systematic screening by using overlapping peptides derived from the target antigen sequence and

determining binding by the antibody. According to the gene fragment expression assays, the open reading frame encoding the target antigen is fragmented either randomly or by specific genetic constructions and the reactivity of the expressed fragments of the antigen with the antibody to be tested is determined. The gene fragments may, for example, be produced by PCR and then transcribed and translated into protein in vitro, in the presence of radioactive amino acids. The binding of the antibody to the radioactively labeled antigen fragments is then determined by immunoprecipitation and gel electrophoresis. Certain epitopes can also be identified by using large libraries of random peptide sequences displayed on the surface of phage particles (phage libraries). Alternatively, a defined library of overlapping peptide fragments can be tested for binding to the test antibody in simple binding assays. In an additional example, mutagenesis of an antigen binding domain, domain swapping experiments and alanine scanning mutagenesis can be performed to identify residues required, sufficient, and/or necessary for epitope binding. For example, domain swapping experiments can be performed using a mutant of a target antigen in which various fragments of the Galectin-9 polypeptide have been replaced (swapped) with sequences from a closely related, but antigenically distinct protein (such as another member of the β-galactoside-binding soluble lectin family). By assessing binding of the antibody to the mutant Galectin-9, the importance of the particular antigen fragment to antibody binding can be assessed.

Alternatively, competition assays can be performed using other antibodies known to bind to the same antigen to determine whether an antibody binds to the same epitope as the other antibodies. Competition assays are well known to those of skill in the art.

In some examples, an anti-Galectin-9 antibody is prepared by recombinant technology as exemplified below.

Nucleic acids encoding the heavy and light chain of an anti-Galectin-9 antibody as described herein can be cloned into one expression vector, each nucleotide sequence being in operable linkage to a suitable promoter. In one example, each of the nucleotide sequences encoding the heavy chain and light chain is in operable linkage to a distinct promoter. Alternatively, the nucleotide sequences encoding the heavy chain and the light chain can be in operable linkage with a single promoter, such that both heavy and light chains are expressed from the same promoter. When necessary, an internal ribosomal entry site (IRES) can be inserted between the heavy chain and light chain encoding sequences.

In some examples, the nucleotide sequences encoding the two chains of the antibody are cloned into two vectors, which can be introduced into the same or different cells. When the two chains are expressed in different cells, each of them can be isolated from the host cells

expressing such and the isolated heavy chains and light chains can be mixed and incubated under suitable conditions allowing for the formation of the antibody.

Generally, a nucleic acid sequence encoding one or all chains of an antibody can be cloned into a suitable expression vector in operable linkage with a suitable promoter using methods known in the art. For example, the nucleotide sequence and vector can be contacted, under suitable conditions, with a restriction enzyme to create complementary ends on each molecule that can pair with each other and be joined together with a ligase. Alternatively, synthetic nucleic acid linkers can be ligated to the termini of a gene. These synthetic linkers contain nucleic acid sequences that correspond to a particular restriction site in the vector. The selection of expression vectors/promoter would depend on the type of host cells for use in producing the antibodies.

A variety of promoters can be used for expression of the antibodies described herein, including, but not limited to, cytomegalovirus (CMV) intermediate early promoter, a viral LTR such as the *Rous sarcoma* virus LTR, HIV-LTR, HTLV-1 LTR, the simian virus 40 (SV40) early promoter, *E. coli* lac UV5 promoter, and the herpes simplex tk virus promoter.

Regulatable promoters can also be used. Such regulatable promoters include those using the lac repressor from *E. coli* as a transcription modulator to regulate transcription from lac operator-bearing mammalian cell promoters [Brown, M. et al., *Cell*, 49:603-612 (1987)], those using the tetracycline repressor (tetR) [Gossen, M., and Bujard, H., *Proc. Natl. Acad. Sci. USA* 89:5547-5551 (1992); Yao, F. et al., *Human Gene Therapy*, 9:1939-1950 (1998); Shockelt, P., et al., *Proc. Natl. Acad. Sci. USA*, 92:6522-6526 (1995)]. Other systems include FK506 dimer, VP16 or p65 using astradiol, RU486, diphenol murislerone, or rapamycin. Inducible systems are available from Invitrogen, Clontech and Ariad.

Regulatable promoters that include a repressor with the operon can be used. In one embodiment, the lac repressor from *E. coli* can function as a transcriptional modulator to regulate transcription from lac operator-bearing mammalian cell promoters (M. Brown et al., *Cell*, 49:603-612 (1987); Gossen and Bujard (1992); M. Gossen et al., *Natl. Acad. Sci. USA*, 89:5547-5551 (1992)) combined the tetracycline repressor (tetR) with the transcription activator (VP 16) to create a tetR-mammalian cell transcription activator fusion protein, tTa (tetR-VP 16), with the tetO-bearing minimal promoter derived from the human cytomegalovirus (hCMV) major immediate-early promoter to create a tetR-tet operator system to control gene expression in mammalian cells. In one embodiment, a tetracycline inducible switch is used. The tetracycline repressor (tetR) alone, rather than the tetR-mammalian cell transcription factor fusion derivatives can function as potent trans-modulator to regulate gene expression in

mammalian cells when the tetracycline operator is properly positioned downstream for the TATA element of the CMVIE promoter (Yao et al., *Human Gene Therapy*, 10(16):1392-1399 (2003)). One particular advantage of this tetracycline inducible switch is that it does not require the use of a tetracycline repressor-mammalian cells transactivator or repressor fusion protein, which in some instances can be toxic to cells (Gossen et al., *Natl. Acad. Sci. USA*, 89:5547-5551 (1992); Shockett et al., *Proc. Natl. Acad. Sci. USA*, 92:6522-6526 (1995)), to achieve its regulatable effects.

Additionally, the vector can contain, for example, some or all of the following: a selectable marker gene, such as the neomycin gene for selection of stable or transient transfectants in mammalian cells; enhancer/promoter sequences from the immediate early gene of human CMV for high levels of transcription; transcription termination and RNA processing signals from SV40 for mRNA stability; SV40 polyoma origins of replication and ColE1 for proper episomal replication; internal ribosome binding sites (IRESes), versatile multiple cloning sites; and T7 and SP6 RNA promoters for *in vitro* transcription of sense and antisense RNA. Suitable vectors and methods for producing vectors containing transgenes are well known and available in the art.

Examples of polyadenylation signals useful to practice the methods described herein include, but are not limited to, human collagen I polyadenylation signal, human collagen II polyadenylation signal, and SV40 polyadenylation signal.

One or more vectors (*e.g.*, expression vectors) comprising nucleic acids encoding any of the antibodies may be introduced into suitable host cells for producing the antibodies. The host cells can be cultured under suitable conditions for expression of the antibody or any polypeptide chain thereof. Such antibodies or polypeptide chains thereof can be recovered by the cultured cells (*e.g.*, from the cells or the culture supernatant) via a conventional method, *e.g.*, affinity purification. If necessary, polypeptide chains of the antibody can be incubated under suitable conditions for a suitable period of time allowing for production of the antibody.

In some embodiments, methods for preparing an antibody described herein involve a recombinant expression vector that encodes both the heavy chain and the light chain of an anti-Galectin-9 antibody, as also described herein. The recombinant expression vector can be introduced into a suitable host cell (*e.g.*, a dhfr- CHO cell) by a conventional method, *e.g.*, calcium phosphate-mediated transfection. Positive transformant host cells can be selected and cultured under suitable conditions allowing for the expression of the two polypeptide chains that form the antibody, which can be recovered from the cells or from the culture medium. When

necessary, the two chains recovered from the host cells can be incubated under suitable conditions allowing for the formation of the antibody.

In one example, two recombinant expression vectors are provided, one encoding the heavy chain of the anti-Galectin-9 antibody and the other encoding the light chain of the anti-Galectin-9 antibody. Both of the two recombinant expression vectors can be introduced into a suitable host cell (*e.g.*, dhfr- CHO cell) by a conventional method, *e.g.*, calcium phosphate-mediated transfection. Alternatively, each of the expression vectors can be introduced into a suitable host cells. Positive transformants can be selected and cultured under suitable conditions allowing for the expression of the polypeptide chains of the antibody. When the two expression vectors are introduced into the same host cells, the antibody produced therein can be recovered from the host cells or from the culture medium. If necessary, the polypeptide chains can be recovered from the host cells or from the culture medium and then incubated under suitable conditions allowing for formation of the antibody. When the two expression vectors are introduced into different host cells, each of them can be recovered from the corresponding host cells or from the corresponding culture media. The two polypeptide chains can then be incubated under suitable conditions for formation of the antibody.

Standard molecular biology techniques are used to prepare the recombinant expression vector, transfect the host cells, select for transformants, culture the host cells and recovery of the antibodies from the culture medium. For example, some antibodies can be isolated by affinity chromatography with a Protein A or Protein G coupled matrix.

Any of the nucleic acids encoding the heavy chain, the light chain, or both of an anti-Galectin-9 antibody as described herein, vectors (*e.g.*, expression vectors) containing such; and host cells comprising the vectors are within the scope of the present disclosure.

Anti-Galectin-9 antibodies thus prepared can be can be characterized using methods known in the art, whereby reduction, amelioration, or neutralization of Galectin-9 biological activity is detected and/or measured. For example, an ELISA-type assay may be suitable for qualitative or quantitative measurement of Galectin-9 inhibition of Dectin-1 or TIM-3 signaling.

The bioactivity of an anti-Galectin-9 antibody can verified by incubating a candidate antibody with Dectin-1 and Galectin-9, and monitoring any one or more of the following characteristics: (a) binding between Dectin-1 and Galectin-9 and inhibition of the signaling transduction mediated by the binding; (b) preventing, ameliorating, or treating any aspect of a solid tumor; (c) blocking or decreasing Dectin-1 activation; (d) inhibiting (reducing) synthesis, production or release of Galectin-9. Alternatively, TIM-3 can be used to verify the bioactivity

of an anti-Galectin-9 antibody using the protocol described above. Alternatively, CD206 can be used to verify the bioactivity of an anti-Galectin-9 antibody using the protocol described above.

Additional assays to determine bioactivity of an anti-Galectin-9 antibody include measurement of CD8+ and CD4+ (conventional) T-cell activation (in an in vitro or in vivo assay, e.g., by measuring inflammatory cytokine levels, e.g., IFNgamma, TNFalpha, CD44, ICOS granzymeB, Perforin, IL2 (upregulation); CD26L and IL-10 (downregulation)); measurement of reprogramming of macrophages (in vitro or in vivo), e.g., from the M2 to the M1 phenotype (e.g., increased MHCII, reduced CD206, increased TNF-alpha and iNOS). Alternatively, levels of ADCC can be assessed, e.g., in an in vitro assay, as described herein.

Methods of Treatment

The present disclosure provides pharmaceutical compositions comprising at least one anti-Galectin-9 antibody described herein or antigen binding fragment thereof and uses of such for inhibiting or reducing a signaling mediated by Galectin-9 or eliminating or reducing Galectin-9 positive cells. Any of the anti-Galectin-9 antibodies described herein can be used in any of the methods described herein. In some embodiments, the anti-Galentin-9 antibody is selected from 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, or combinations thereof. In some embodiments, the anti-Galectin-9 antibody is selected from 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, or combinations thereof. Non-limiting examples of such antibodies include for example antibody 9.2-17 or 9.1-8mut13. Such antibodies can be used for treating diseases associated with Galectin-9. In some aspects, the invention provides methods of treating cancer. In some embodiments, the present disclosure methods for reducing, ameliorating, or eliminating one or more symptom(s) associated with cancer.

In some embodiments, the disclosure provides a method for treating cancer in a subject, the method comprising administering to a subject in need thereof an effective amount of an anti-Galectin-9 antibody described herein or antigen binding fragment thereof. In some embodiments, the disclosure provides a method for treating cancer in a subject, the method comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising an anti-Galectin-9 antibody described herein or antigen binding

fragment thereof. In some embodiments, the anti-Galectin-9 antibody is 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, G9.1-9, 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 antibodies, or combinations thereof. In some embodiments, the anti-Galectin-9 antibody is 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, or combinations thereof. Non-limiting examples of such antibodies include for example antibody 9.2-17 or 9.1-8mut13.

Given that pro-tumor action of Galectin-9 is mediated through interaction with immune cells (i.e., interactions with with lymphoid cells via TIM-3, CD44, and 41BB, and with macrophages via dectin-1 and CD206) and given that Galectin-9 is expressed in a large number of tumors, targeting Galectin-9, e.g., using a Galectin-9 binding antibody to inhibit interaction with its receptors, provides a therapeutic approach that can be applied across a variety of different tumor types.

In some embodiments, the cancer is selected from adrenal cancer, adrenocortical carcinoma, anal cancer, appendix cancer, bile duct cancer, bladder cancer, bone cancer (e.g., Ewing sarcoma tumors, osteosarcoma, malignant fibrous histiocytoma), brain cancer (e.g., astrocytomas, brain stem glioma, craniopharyngioma, ependymoma), bronchial tumors, cholangiocarcinoma, cholangiosarcoma, central nervous system tumors, breast cancer, Castleman disease, cervical cancer, colon cancer, rectal cancer, colorectal cancer, endometrial cancer, esophageal cancer, eye cancer, gallbladder cancer, gastrointestinal cancer, gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, genitourinary cancers, gestational trophoblastic disease, heart cancer, Kaposi sarcoma, kidney cancer, laryngeal cancer, hypopharyngeal cancer, leukemia (e.g., acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia), liver cancer, lung cancer (for example, non-small cell lung cancer, NSCLC, and small cell lung cancer, SCLC), lymphoma (e.g., AIDS-related lymphoma, Burkitt lymphoma, cutaneous T cell lymphoma, Hogkin lymphoma, Non-Hogkin lymphoma, primary central nervous system lymphoma), malignant mesothelioma, multiple myeloma, myelodysplastic syndrome, nasal cavity cancer, paranasal sinus cancer, pancreatic duct adenocarcinoma (PDA) nasopharyngeal cancer, neuroblastoma, oral cavity cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, penile cancer, pituitary tumors, prostate cancer, retinoblastoma, rhabdomyosarcoma, rhabdoid

tumor, salivary gland cancer, sarcoma, skin cancer (e.g., basal cell carcinoma, melanoma), squamous cell head and neck cancer, small intestine cancer, stomach cancer, teratoid tumor, testicular cancer, throat cancer, thymus cancer, thyroid cancer, unusual childhood cancers, upper and lower gastrointestinal malignancies (including, but not limited to, esophageal, gastric, and hepatobiliary cancer), urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and Wilms tumor. In some embodiments, the cancer is selected from hematological malignancies include acute lymphoblastic leukemia, chronic lymphocytic leukemia, lymphomas, multiple myeloma, acute myelogenous leukemia, chronic myelogenous leukemia, myelodysplastic syndromes and the myeloproliferative neoplasms, such as essential thrombocythemia, polycythemia vera, myelofibrosis, and gallbladder cancer (adenocarcinomas or squamous cell carcinoma). In some embodiments, the symptom(s) associated thereof include, but are not limited to, anemia, loss of appetite, irritation of bladder lining, bleeding and bruising (thrombocytopenia), changes in taste or smell, constipation, diarrhea, dry mouth, dysphagia, edema, fatigue, hair loss (alopecia), infection, infertility, lymphedema, mouth sores, nausea, pain, peripheral neuropathy, tooth decay, urinary tract infections, and/or problems with memory and concentration. The method may comprise preparing a pharmaceutical composition with an anti-Galectin-9 antibody described herein, and administering the pharmaceutical composition to a subject in a therapeutically effective amount.

In some embodiments, the disclosure provides a method for treating gall bladder cancer in a subject, the method comprising administering to a subject in need thereof an effective amount of an anti-Galectin-9 antibody described herein, e.g., in Table 1 or Table 2 herein, including but not limited to, 9.1-8m13 and/or 9.2-17, or an antigen binding fragment thereof.

In certain embodiments, administering the pharmaceutical composition, e.g., one or more of the anti-Galectin-9 antibodies described herein, e.g., in Table 1 and/or Table 2,including, but not limited to, 9.2-17 and 9.1-8m13, to the subject reduces cell proliferation, tumor growth, and/or tumor volume in a subject, or reduces the number of metastatic lesions over time. In some embodiments, administering the composition results in complete response, partial response, or stable disease.

Pancreatic ductal adenocarcinoma (PDA) is a devastating disease with few long-term survivors (Yadav et al., *Gastroenterology*, 2013, 144, 1252-1261). Inflammation is paramount in PDA progression as oncogenic mutations alone, in the absence of concomitant inflammation, are insufficient for tumorigenesis (Guerra et al., *Cancer Cell*, 2007, 11, 291-302). Innate and adaptive immunity cooperate to promote tumor progression in PDA. In particular, specific innate immune subsets within the tumor microenvironment (TME) are apt at educating adaptive

immune effector cells towards a tumor-permissive phenotype. Antigen presenting cell (APC) populations, including M2-polarized tumor-associated macrophages (TAMs) and myeloid dendritic cells (DC), induce the generation of immune suppressive Th2 cells in favor of tumor-protective Th1 cells (Ochi et al., *J of Exp Med.*, 2012, 209, 1671-1687; Zhu et al., *Cancer Res.*, 2014, 74, 5057-5069) . Similarly, it has been shown that myeloid derived suppressor cells (MDSC) negate anti-tumor $CD8^+$ cytotoxic T-Lymphocyte (CTL) responses in PDA and promote metastatic progression (Connolly et al., *J Leuk Biol.*, 2010, 87, 713-725; Pylayeva-Gupta et al., *Cancer Cell,* 2012, 21, 836-847; Bayne et al., *Cancer Cell,* 2012, 21, 822-835).

Recently, dectin-1 on macrophages was shown to bind galectin-9 in pancreatic ductal adenocarcinoma (PDA) (Daley et al., 2017). Removal of dectin-1 signaling (in Dectin-/- mice) resulted in a decrease in tumor infiltration of M2 type (suppressive CD206+) macrophages. Additionally, antibody-based Galectin-9 neutralization only enhanced T cell activation in Dectin-1+/+ hosts, indicating that Galectin-9 exerts primary immune-suppressive effects specific to Dectin-1 signaling. Upon interruption of the Dectin-1–Galectin-9 axis, CD4+ and CD8+ T cells – which are dispensable to PDA progression in hosts with an intact signaling axis – became reprogrammed into indispensable mediators of anti-tumor immunity. Without wishing to be bound by theory, blocking Galectin-9-Dectin-1 signaling presents one exemplary mechanism (in addition to TIM-3 and other signaling pathways) that could underlie a strong anti-tumor response a Galectin-9 targeting immunotherapy approach in PDA e.g., by administering an antibody that binds to Galectin-9, such as those described herein.

In some embodiments, the disclosure provides a method for treating pancreatic ductal adenocarcinoma (PDA) in a subject, the method comprising administering to a subject in need thereof an effective amount of an anti-Galectin-9 antibody described herein or antigen binding fragment thereof. In some embodiments, the anti-Galentin-9 antibody is 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, G9.1-9, 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 antibodies , and combinations thereof. In some embodiments, the anti-Galectin-9 antibody is 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 combinations thereof. Non-limiting examples of such antibodies include for example antibody 9.2-17 or 9.1-8mut13. In any of these methods of treatment, the anti-Galectin-9 antibody is antibody 9.2-17 and/or antibody 9.1-8mut13.

In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is any of the antibodies described herein in Table 1 and/or Table 2, and wherein the cancer is pancreatic ductal adenocarcinoma (PDA). In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is antibody 9.1-8m13 and/or 9.2-17, and wherein the cancer is pancreatic ductal adenocarcinoma (PDA). Colorectal cancer (CRC), also known as bowel cancer, colon cancer, or rectal cancer, is any cancer affecting the colon and the rectum. CRC is known to be driven by genetic alterations of tumor cells and is also influenced by tumor-host interactions. Recent reports have demonstrated a direct correlation between the densities of certain T lymphocyte subpopulations and a favorable clinical outcome in CRC, supporting a major role of T-cell-mediated immunity in repressing tumor progression of CRC.

Tim-3, as noted elsewhere herein, is an immune regulatory molecule, which triggers downstream cascade events upon stimulation by galectin-9 (Zhu C, et al. The Tim-3 ligand galectin-9 negatively regulates T helper type 1 immunity; Nature immunology. 2005; 6:1245–1252). Tim-3 has been found to be a critical mediator in CRC progression (Yu et al;, Tim-3 is upregulated in human colorectal carcinoma and associated with tumor progression; Mol Med Rep. 2017 Feb; 15(2): 689–695). In this study, expression of Tim-3 was significantly associated with tumor size ($P=0.007$), tumor-node-metastasis staging ($P<0.0001$) and distant metastasis ($P<0.0001$). Additionally, increased Tim-3 expression is associated with M2 macrophage polarization in colon cancer and promotes tumor growth. Blockade of the Tim-3 pathway inhibited both the polarization of tumor-supporting macrophages and colon cancer growth (Jiang et al., Tim-3 promotes tumor-promoting M2 macrophage polarization by binding to STAT1 and suppressing the STAT1-miR-155 signaling axis; Oncoimmunology, 2016 Aug 3;5(9):e1211219). Given these findings and high expression of Galectin-9 observed in colorectal cancers (Lahm et al., J. Cancer Res. Clin. Oncol.2001;127:375–386), modulating the Galectin-9/TIM-3 axis by inhibiting the interaction between Galectin-9 and TIM-3, e.g., by administrating an antibody that binds to Galectin-9, is a novelapproach to treating such cancers in the clinic which may result in improved outcomes.

In some embodiments, the disclosure provides a method for treating colorectal cancer (CRC) in a subject, the method comprising administering to a subject in need thereof an effective amount of an anti-Galectin-9 antibody described herein or antigen binding fragment thereof. In some embodiments, the anti-Galentin-9 antibody is 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, G9.1-9, 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 antibodies, and combinations thereof. In some embodiments, the anti-Galectin-9 antibody is 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 combinations thereof. Non-limiting examples of such antibodies include for example antibody 9.2-17 or 9.1-8mut13. In any of these methods of treatment, the anti-Galectin-9 antibody is antibody 9.2-17 and/or antibody 9.1-8mut13.

In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is any of the antibodies described herein in Table 1 and/or Table 2, and wherein the cancer is colorectal cancer(CRC). In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is antibody 9.1-8m13 and/or 9.2-17, and wherein the cancer is colorectal cancer (CRC).

Melanoma is the deadliest form of skin cancer and has been increasing in incidence for the past 30 years, especially in young adults. Recent advances have resulted in the development of numerous immune-activating therapies that have greatly improved patient survival.

Accumulation of genetic disorders, most frequently mutations in B-Raf and N-Ras, in the melanocyte are a hallmark of melanoma (Rodríguez-Cerdeira et al., Advances in Immunotherapy for Melanoma: A Comprehensive Review; Mediators Inflamm. 2017; 2017: 3264217, and references therein). However, the interaction between the microenvironment is necessary for these alterations to result in the transformation of a dysplastic melanocyte into a melanoma cell. The microenvironment then also further promotes invasion and metastasis. New therapeutic strategies including CTLA-4, PD-1 and PD-L1/2 blockers, have been developed and have dramatically improved outcomes for melanoma patients (Farkona et al., Cancer immunotherapy: the beginning of the end of cancer? BMC Med. 2016;14:73). However, these therapies depend on the presence of a functional immune system, which is suppressed in patients with advanced cancer, and new methods to reactivate this suppressed systemic immunity are needed to further improve outcomes for melanoma patients.

In patients with metastatic melanoma, high blood levels of galectin-9 are correlated with worse overall survival and a bias towards a Th2 inflammatory state supportive of tumor growth. Additionally, galectin-9 is co-localized with the M2 macrophage population in metastatic

melanoma and soluble forms of galectin-9 in the blood correspond with poor survival (Enninga et al., Melanoma Res. 2016 Oct;26(5):429-41). Association of Galectin-9 with M2 macrophages was found to be due to Galectin-9 ligation to CD206 on M2 macrophages, which resulted in pro-tumor phenotype in the local microenvironment. Accordingly, both Galectin-9/dectin-1 and Galectin-9/CD206 interactions may promote macrophage mediated immune suppressive effects. Without wishing to be bound by theory, these findings indicate that inhibiting Galectin-9/dectin-1 and Galectin-9/CD206 interactions, e.g., by administering an antibody that binds to Galectin-9, may present a rationale for employing anti-Galectin-9 antibodies in a therapeutic approach in melanoma, which will lead to improved overall survival, in patients, including but not limited to those refractory to anti- CTLA-4, PD-1 and PD-L1/2 therapies.

In some embodiments, the disclosure provides a method for treating melanoma in a subject, the method comprising administering to a subject in need thereof an effective amount of an anti-Galectin-9 antibody described herein or antigen binding fragment thereof. In some embodiments, the anti-Galentin-9 antibody is 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, G9.1-9, 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 antibodies, and combinations thereof. In some embodiments, the anti-Galectin-9 antibody is 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 combinations thereof. Non-limiting examples of such antibodies include for example antibody 9.2-17 or 9.1-8mut13. In any of these methods of treatment, the anti-Galectin-9 antibody is antibody 9.2-17 and/or antibody 9.1-8mut13.

In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is any of the antibodies described herein in Table 1 and/or Table 2, and wherein the cancer is melanoma. In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is antibody 9.1-8m13 and/or 9.2-17, and wherein the cancer is melanoma.

Cholangiocarcinoma (CCA) is an epithelial cancer that forms in the bile ducts and is the most common biliary malignancy and the second most common hepatic malignancy after hepatocellular carcinoma and the overall incidence of cholangiocarcinoma has increased progressively worldwide over the past four decades. CCAs are classified into three subtypes

based on their anatomic location, intrahepatic cholangiocarcinoma (iCCA), perihilar CCA (pCCA), and distal CCA (dCCA) (see, e.g., Loeuillard et al., Animal models of cholangiocarcinoma; Biochim Biophys Acta Mol Basis Dis. 2018 Apr 5., and Rizvi et al., Cholangiocarcinoma — evolving concepts and therapeutic strategies; Nat Rev Clin Oncol. 2018 Feb; 15(2): 95–111).

In a restrospective immune profiling study in of 99 surgically resected iHCC, TIM-3-positive staining of centrally located, tumor infiltrative lymphocytes was observed, at levels 3 times greater than PD-1 staining. Overall survival was significantly associated with lower numbers of TIM-3 tumor infiltrating lymphocytes. Accordingly, reducing TIM-3 activity or signaling, e.g., by inhibiting the Gal-9/Tim-3 interaction in an immunotherapeutic approach, e.g., by administering an anti-Galectin-9 antibody such as one or more of the anti-Galectin-9 antibodies described herein, may have a positive impact on overall survival.

In some embodiments, the disclosure provides a method for treating cholangiocarcinoma in a subject, the method comprising administering to a subject in need thereof an effective amount of an anti-Galectin-9 antibody described herein or antigen binding fragment thereof. In some embodiments, the anti-Galentin-9 antibody is 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, G9.1-9, 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 antibodies, and combinations thereof. In some embodiments, the anti-Galectin-9 antibody is 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 combinations thereof. Non-limiting examples of such antibodies include for example antibody 9.2-17 or 9.1-8mut13. In any of these methods of treatment, the anti-Galectin-9 antibody is antibody 9.2-17 and/or antibody 9.1-8mut13.

In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is any of the antibodies described herein in Table 1 and/or Table 2, and wherein the cancer is cholangiocarcinoma. In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is antibody 9.1-8m13 and/or 9.2-17, and wherein the cancer is cholangiocarcinoma.

Renal Cell Carcinoma (RCC) has the highest mortality rate of the genitourinary cancers and the incidence of RCC has risen steadily, while the outcome remains poor. Approximately 273,000 new cases of kidney cancer are diagnosed worldwide each year. About one third of patients with localized disease will suffer recurrence or metastasis. Once metastasis occurs, malignancy metastasize, the 5-year survival for patients is less than 10 %. Clear-cell renal cell carcinoma (ccRCC) is the major histological subtype, which accounts for 80–90 % of all the RCCs. RCC is sensitive to immunotherapy and targeted therapy while highly resistant to both chemotherapy and radiation therapy.

In RCC patients, Gal-9 is expressed at much higher levels in cancerous lesions than the surrounding normal tissue, and patients with high Galectin-9 expression showed more advanced progression of the disease with larger tumor size and necrosis (Kawashima et al.; BJU Int. 2014;113:320–332). Gal-9 in tumor tissue of ccRCC patients was significantly positively associated with tumor size, Fuhrman grade, necrosis, and impaired clinical outcome including poor survival and early recurrence (Fu et al., Galectin-9 predicts postoperative recurrence and survival of patients with clear-cell renal cell carcinoma;Tumour Biol. 2015 Aug;36(8):5791-9). TIM-3 is also associated with poor prognosis in RCC, and knockdown of TIM-3 suppresses the proliferation and invasion capacity of ccRCC cell lines (Yuan et al., Prognostic implication of Tim-3 in clear cell renal cell carcinoma. Neoplasma. 2014;61:35–40). Accordingly, the Gal-9/TIM-3 axis might play an important role in the development of renal cell carcinoma and administration of immunotherapeutic agents which inhibit Gal-9 binding to TIM-3, such as the anti-Galectin-9 antibodies described herein, e.g., in Table 1 and/or Table 2, may result in increased survival and lower reoccurrence in RCC.

In some embodiments, the disclosure provides a method for treating renal cancer in a subject, the method comprising administering to a subject in need thereof an effective amount of an anti-Galectin-9 antibody described herein or antigen binding fragment thereof. In some embodiments, the anti-Galentin-9 antibody is 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, G9.1-9, 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 antibodies, and combinations thereof. In some embodiments, the anti-Galectin-9 antibody is 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 combinations thereof. Non-limiting examples of such antibodies include for example antibody 9.2-17 or antibody 9.1-8mut13. In any of these methods of treatment, the anti-Galectin-9 antibody is antibody 9.2-17 and/or antibody 9.1-8mut13.

In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is any of the antibodies described herein in Table 1 and/or Table 2, and wherein the cancer is renal cell carcinoma (RCC). In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is antibody 9.1-8m13 and/or 9.2-17, and wherein the cancer is renal cell carcinoma (RCC).

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. Hepatocellular carcinoma occurs most often in people with chronic liver diseases, such as cirrhosis caused by hepatitis B or hepatitis C infection. HCC is usually accompanied by cirrhotic liver with extensive lymphocyte infiltration due to chronic viral infection. Many studies have demonstrated that tumor-infiltrating effector CD8+ T cells and T helper 17 (Th17) cells correlate with improved survival after surgical resection of tumors. However, tumor-infiltrating effector T cells fail to control tumor growth and metastasis Pang et al., The immunosuppressive tumor microenvironment in hepatocellular carcinoma; Cancer Immunol Immunother 2009;58:877-886).

The TIM-3/galectin-9 interaction contributes to immune dysfunction in human HCC (Li, et al., Tim-3/galectin-9 signaling pathway mediates T-cell dysfunction and predicts poor prognosis in patients with hepatitis B virus-associated hepatocellular carcinoma; Hepatology. 2012 Oct;56(4):1342-51). High Galectin-9 expression is found on myeloid APCs and high numbers of Tim-3+ T cells are found in HBV-associated HCC, and blocking Tim-3/galectin-9 signaling using TIM-3 antibodies recovers effector T-cell function in T cells isolated from human HCC. Thus, the targeting Tim-3/Galectin-9 axis, e.g., by administering anti-Galectin-9 antibodies, e.g., such as anti-Galectin-9 antibodies shown in Table 1 and Table 2 herein, including, but not limited to, antibody 9.1-8mut13 and/or antibody 9.2-17, constitutes a novel immune therapeutic strategy for treating patients with HBV-associated HCC.

In some embodiments, the disclosure provides a method for treating hepatocellular carcinoma in a subject, the method comprising administering to a subject in need thereof an effective amount of an anti-Galectin-9 antibody described herein or antigen binding fragment

thereof. In some embodiments, the anti-Galentin-9 antibody is 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, G9.1-9, 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 antibodies, and combinations thereof. In some embodiments, the anti-Galectin-9 antibody is 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 combinations thereof. Non-limiting examples of such antibodies include for example antibody 9.2-17 or 9.1-8mut13. In any of these methods of treatment, the anti-Galectin-9 antibody is antibody 9.2-17 and/or antibody 9.1-8mut13.Acute myeloid leukemia (AML) is the most common form of acute leukemia, with an incidence that increases with advanced age. Commonly of unknown etiology, AML can also occur as a result of exposure to genotoxic agents or following a previous hematologic disorder. AML is complex, with genetic, epigenetic, and phenotypic heterogeneity (Lowenberg and Rowe, Introduction to the review series on advances in acute myeloid leukemia (AML); Blood 2016 127:1).

In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is any of the antibodies described herein in Table 1 and/or Table 2, and wherein the cancer is hepatocellular carcinoma (HCC). In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is antibody 9.1-8m13 and/or 9.2-17, and wherein the cancer is hepatocellular carcinoma (HCC).

Recent studies suggest that the TIM-3/Gal-9 axis that TIM-3 and Gal-9 are connected to the establishment of AML. Malignant stem cells achieve dominant clonal selection through acquisition of multiple genetic abnormalities. These genetic abnormalities progressively accumulate in self-renewing hematopoietic stem cells (HSCs), and, as a consequence, these genetically impaired preleukemic HSCs transform into leukemic stem cells (LSCs). As part of this process, preleukemic HSCs outgrow normal HSCs, and finally self-renew at a hematopoietic progenitor cell stage to become myeloid LSCs (Walter et al., Clonal architecture of secondary acute myeloid leukemia; N. Engl. J. Med., 366 (2012), pp. 1090-1098). Kikshige et al., (Kikushige et al., A TIM-3/Gal-9 Autocrine Stimulatory Loop Drives Self-Renewal of Human Myeloid Leukemia Stem Cells and Leukemic Progression (Cell Stem Cell 17; 3(2015), 341-352) observed that serum Galectin-9 levels were significantly elevated in AML patients and

that the Tim3/Gal-9 axis stimulates an autocrine loop which functions to allow clonal dominancy and self-renewal of LSCs. Gal-9-mediated TIM-3 stimulation lead to the induction of LSC self renewal pathways. Of note, since significant upregulation of TIM-3 in HSC and HPC populations, as well as elevation of serum Gal-9, was observed in patients with preleukemic myeloid disorders, acquisition of Galectin-9 secretion likely occurs early during leukemia progression. Accordingly, targeting the Gal-9/TIM-3 axis, e.g., through the administration of an anti-Galectin-9 antibody, such as one or more of the anti-Galectin-9 antibodies described herein, e.g., in Table 1 and/or Table 2, including antibody 9.1-8mut13 and/or antibody 9.2-17, may constitute a novel approach to cancer stem cell therapy common to human myeloid malignancies, and moreover, such therapies may be useful not only to eradicate LSCs in AMLs, but also to prevent progression of preleukemic disorders into overt AML. Such preleukemic disorders include the refractory cytopenia with multilineage displasia (RCMD) stage in myelodysplastic syndromes (MDS) or the chronic phase of myeloproliferative neoplasms (MPN), including chronic myelogenous leukemia.

In some embodiments, the disclosure provides a method for treating a hematological malignancy in a subject, the method comprising administering to a subject in need thereof an effective amount of an anti-Galectin-9 antibody described herein or antigen binding fragment thereof. In some embodiments, the disclosure provides a method for treating acute lymphoblastic leukemia in a subject, the method comprising administering to a subject in need thereof an effective amount of an anti-Galectin-9 antibody described herein or antigen binding fragment thereof. In some embodiments, the disclosure provides a method for treating acute myeloid leukemia in a subject, the method comprising administering to a subject in need thereof an effective amount of an anti-Galectin-9 antibody described herein or antigen binding fragment thereof.

In some embodiments, the disclosure provides a method for preventing progression of preleukemic disorders into acute myeloid leukemia in a subject, the method comprising administering to a subject in need thereof an effective amount of an anti-Galectin-9 antibody described herein or antigen binding fragment thereof. In some embodiments, the preleukemic disorders comprise RCMD stage in MDS or the chronic phase of MPN, including chronic myelogenous leukemia. In some embodiments, the anti-Galentin-9 antibody is 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, G9.1-9, 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

antibodies, and combinations thereof. In some embodiments, the anti-Galectin-9 antibody is 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 combinations thereof. Non-limiting examples of such antibodies include for example antibody 9.2-17 or 9.1-8mut13. In any of these methods of treatment, the anti-Galectin-9 antibody is antibody 9.2-17 and/or antibody 9.1-8mut13.

In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is any of the antibodies described herein in Table 1 and/or Table 2, and wherein the cancer is a hematological malignancy. In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is antibody 9.1-8m13 and/or 9.2-17, and wherein the cancer is hematological malignancy.

In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is any of the antibodies described herein in Table 1 and/or Table 2, and wherein the cancer is AML. In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is antibody 9.1-8m13 and/or 9.2-17, and wherein the cancer is AML.

In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is any of the antibodies described herein in Table 1 and/or Table 2, and wherein the cancer is ALL. In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer, wherein the anti-Galectin-9 antibody is antibody 9.1-8m13 and/or 9.2-17, and wherein the cancer is ALL. In any of the above-described methods, the treatment method further comprises administering to the subject an inhibitor of a checkpoint molecule, an activator of a co-stimulatory receptor, and/or an inhibitor of an innate immune cell target. In some embodiments, the treatment method further comprises administering to the subject an inhibitor of a checkpoint molecule. In some embodiments, the checkpoint molecule is selected from the group consisting of PD-1, PD-L1, PD-L2, CTLA-4, LAG3, TIM-3 and A2aR. In some embodiments, the treatment method further comprises administering to the subject an inhibitor of an activator of a co-stimulatory receptor, and/or an inhibitor of an innate immune cell target. In some embodiments, the co-stimulatory receptor is selected from the group consisting of

OX40, GITR, CD137, CD40, CD27, and ICOS. In some embodiments, the treatment method further comprises administering to the subject an inhibitor of an innate immune cell target. In some embodiments, the innate immune cell target is selected from the group consisting of KIR, NKG2A, CD96, TLR, and IDO. In some embodiments, the anti-Galectin-9 antibody is 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, G9.1-9, 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 antibodies, and combinations thereof. In some embodiments, the anti-Galectin-9 antibody is 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 combinations thereof. Non-limiting examples of such antibodies include for example antibody 9.2-17 or 9.1-8mut13. In any of these methods of treatment, the anti-Galectin-9 antibody is antibody 9.2-17 and/or antibody 9.1-8mut13. In some embodiments, the cancer is selected from pancreatic cancer, e.g., pancreatic ductal adenocarcinoma, cholangiocarcinoma, hepatocellular carcinoma, colorectal cancer, melanoma, renal cell carcinoma, and acute myeloid leukemia.

In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer in combination with a checkpoint inhibitor molecule, e.g., wherein the checkpoint inhibitor molecule is selected from the group consisting of PD-1, PD-L1, PD-L2, CTLA-4, LAG3, TIM-3 and A2aR, wherein the anti-Galectin-9 antibody is any of the antibodies described herein in Table 1 and/or Table 2. In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer in combination with a checkpoint molecule, wherein the checkpoint inhibitor molecule is selected from the group consisting of PD-1, PD-L1, PD-L2, CTLA-4, LAG3, TIM-3 and A2aR, and wherein the anti-Galectin-9 antibody is antibody 9.1-8m13 and/or 9.2-17.

In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer in combination with a co-stimulatory molecule, e.g., wherein the co-stimulatory molecule is selected from the group consisting of OX40, GITR, CD137, CD40, CD27, and ICOS, and wherein the anti-Galectin-9 antibody is any of the antibodies described herein in Table 1 and/or Table 2. In some embodiments, the disclosure provides the use of an anti-Galectin-9 antibody as a medicament for the treatment of cancer in combination with a co-stimulatory, wherein the co-stimulatory molecule is selected from the group consisting of OX40, GITR, CD137, CD40, CD27, and ICOS, wherein the anti-Galectin-9

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LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 169

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS

1. An isolated antibody, which specifically binds human galectin-9, wherein the antibody 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 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 antibody of claim 1, wherein the antibody binds to an epitope in a carbohydrate recognition domain (CRD) of galectin-9.

3. The isolated antibody of claim 2, wherein the CRD is CRD2.

4. The isolated antibody of claim 3, wherein the CRD2 consists of the amino acid sequence of SEQ ID NO: 4.

5. The isolated antibody of any one of claims 1-4, which is a full-lengtntibody or an antigen-binding fragment thereof.

6. The isolated antibody of any one of claims 1-5, which is a single chain antibody.

7. The isolated antibody of any one of claims 1-6, which is a human antibody or a humanized antibody.

8. The isolated antibody of claim 1, wherein the antibody comprises a VH set forth as SEQ ID NO: 55 and a VL set forth as SEQ ID NO: 54.

9. The isolated antibody of claim 8, which is a full-length antibody or an antigen-binding fragment thereof.

10. The isolated antibody of claim 8 or 9, which is a single chain antibody.

11. The isolated antibody of any one of claims 8-10, which is a human antibody or a humanized antibody.

12. The isolated antibody of any one of claims 8-11, which is an IgG molecule.

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13. The isolated antibody of any one of claims 8-12, wherein the antibody is an IgG1 or IgG4 molecule.

14. The isolated antibody of any one of claims 8-13, wherein the antibody is an IgG4 molecule, wherein the IgG4 has a S228P mutation.

15. The isolated antibody of any one of claims 8-14, wherein the antibody comprises a heavy chain constant region set forth as SEQ ID NO: 422, and/or a light chain constant region set forth as SEQ ID NO: 418.

16. The isolated antibody of any one of claims 8-15, wherein the antibody comprises a VH set forth as SEQ ID NO: 55 and a VL set forth as SEQ ID NO: 54, and has a heavy chain constant region set forth as SEQ ID NO: 422 and a light chain constant region set forth as SEQ ID NO: 418.

17. The isolated antibody of claim 16, wherein the antibody comprises a heavy chain set forth as SEQ ID NO: 316 and a light chain set forth as SEQ ID NO:108.

18. A pharmaceutical composition comprising the antibody of any one of claims 1-17 and a pharmaceutically acceptable carrier.

19. Use of the isolated antibody of any one of claims 1-17 or the pharmaceutical composition of claim 18 for inhibiting the activity of galectin-9 in a subject.

20. The use of claim 19 wherein the subject is suspected of having, or is at risk for a solid tumor or a hematological malignancy.

21. The use of claim 20 wherein the solid tumor is selected from the group consisting of glioblastoma, glioma, melanoma, skin squamous cell carcinoma, sarcoma, upper and lower gastrointestinal cancer, carcinoid tumor, neuroendocrine tumor, breast cancer, lung cancer, head and neck cancer, and genitourinary cancer.

22. The use of claim 21, wherein the upper and lower gastrointestinal cancer is selected from the group consisting of esophageal cancer, gastric cancer, pancreatic cancer, colorectal cancer, biliary tract cancer, cholangiocarcinoma, gall bladder cancer, liver cancer, and duodenal cancer.

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23. The use of claim 22, wherein the upper and lower gastrointestinal cancer is pancreatic cancer.

24. The use of claim 22, wherein the upper and lower gastrointestinal cancer is colorectal cancer.

25. The use of claim 21, wherein the solid tumor is melanoma.

26. The use of claim 20, wherein the hematological malignancy is selected from the group consisting of a leukemia, a lymphoma, multiple myeloma, a myelodysplastic syndrome, and a myeloproliferative neoplasm.

27. The use of claim 26, wherein the hematological malignancy is a leukemia.

28. The use of claim 27, wherein the leukemia is myelogenous leukemia.

29. The use of claim 27, wherein the myelogenous leukemia is chronic myelogenous leukemia or acute myelogenous leukemia.

30. The use of claim 29, wherein the myelogenous leukemia is acute myelogenous leukemia.

31. The use of claim 27, wherein the leukemia is lymphoblastic leukemia.

32. The use of claim 31, wherein the lymphoblastic leukemia is acute lymphoblastic leukemia or chronic lymphoblastic leukemia.

33. The use of claim 32, wherein the acute lymphoblastic leukemia is T-cell acute lymphoblastic leukemia or B-cell acute lymphoblastic leukemia.

34. The use of claim 33, wherein the hematological malignancy is T-cell acute lymphoblastic leukemia.

35. The use of claim 26, wherein the hematological malignancy is a lymphoma.

36. The use of claim 35, wherein the lymphoma is AIDS-related lymphoma, Burkitt lymphoma, cutaneous T cell lymphoma, Hodgkin lymphoma, Non-Hodgkin lymphoma, or primary central nervous system lymphoma.

37. The use of claim 36, wherein the lymphoma is Hodgkin's lymphoma.

38. The use of claim 36, wherein the lymphoma is Non-Hodgkin's lymphoma.

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39. The use of claim 38, wherein the non-Hodgkin's lymphoma is diffuse large B cell lymphoma.

40. The use of any one of claims 19-39, wherein the antibody or the pharmaceutical composition is for use in combination with a checkpoint inhibitor.

41. The use of claim 40, wherein the checkpoint inhibitor is an anti-PD-1 antibody.

42. The use of any one of claims 19-41, wherein the antibody or the pharmaceutical composition is for use in combination with a chemotherapeutic agent.

43. The use of claim 42, wherein the chemotherapeutic agent is gemcitabine, paclitaxel or a combination thereof.

44. Use of the isolated antibody of any one of claims 1-17 or the pharmaceutical composition of claim 18 for treating a solid tumor that expresses galectin-9 in a human subject.

45. The use of claim 44, wherein the solid tumor is selected from the group consisting of glioblastoma, glioma, melanoma, skin squamous cell carcinoma, sarcoma, upper and lower gastrointestinal cancer, carcinoid tumor, neuroendocrine tumor, breast cancer, lung cancer, head and neck cancer, and genitourinary cancer.

46. The use of claim 45, wherein the upper and lower gastrointestinal cancer is selected from the group consisting of esophageal cancer, gastric cancer, pancreatic cancer, colorectal cancer, biliary tract cancer, cholangiocarcinoma, gall bladder cancer, liver cancer, and duodenal cancer.

47. The use of claim 46, wherein the upper and lower gastrointestinal cancer is a pancreatic cancer.

48. The use of claim 46, wherein the upper and lower gastrointestinal cancer is a colorectal cancer.

49. The use of claim 45, wherein the solid tumor is melanoma.

50. The use of any one of claims 44-49, wherein the isolated antibody or the pharmaceutical composition is for use in combination with a checkpoint inhibitor.

51. The use of claim 50, wherein the checkpoint inhibitor is an anti-PD-1 antibody.

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52. The use of any one of claims 44-51, wherein the isolated antibody or the pharmaceutical composition is for use in combination with a chemotherapeutic agent.

53. The use of claim 52, wherein the chemotherapeutic agent is gemcitabine, paclitaxel or a combination thereof.

54. Use of the isolated antibody of any one of claims 1-17 or the pharmaceutical composition of claim 18 for treating a hematological malignancy that expresses galectin-9 in a human subject.

55. The use of claim 54, wherein the hematological malignancy is selected from the group consisting of a leukemia, a lymphoma, multiple myeloma, a myelodysplastic syndrome, and a myeloproliferative neoplasm.

56. The use of claim 55, wherein the leukemia is selected from the group consisting of acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphoblastic leukemia and chronic lymphoblastic leukemia.

57. The use of claim 55, wherein the lymphoma is AIDS-related lymphoma, Burkitt lymphoma, cutaneous T cell lymphoma, Hodgkin lymphoma, Non-Hodgkin lymphoma, or primary central nervous system lymphoma.

58. The use of any one of claims 54-57, wherein the isolated antibody or the pharmaceutical composition is for use in combination with a checkpoint inhibitor.

59. The use of claim 58, wherein the checkpoint inhibitor is an anti-PD-1 antibody.

60. The use of any one of claims 54-59, wherein the isolated antibody or the pharmaceutical composition is for use in combination with a chemotherapeutic agent.

61. The use of claim 60, wherein the chemotherapeutic agent is gemcitabine, paclitaxel or a combination thereof.

62. An isolated nucleic acid molecule or a set of nucleic acid molecules, comprising one or more nucleic acid sequence(s) encoding a heavy chain variable region (VH) and a light chain variable region (VL) of an antibody that specifically binds human galectin-9, wherein said antibody comprises: a heavy chain complementarity determining region 1 (CDR1) set

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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 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.

63. The isolated nucleic acid molecule or the set of nucleic acid molecules of claim 62, wherein the antibody that specifically binds human galectin-9 comprises a VH set forth as SEQ ID NO: 55 and a VL set forth as SEQ ID NO: 54.

64. The isolated nucleic acid molecule or the set of nucleic acid molecules of claim 62 or 63, wherein the antibody that specifically binds human galectin-9 is a full-length antibody or an antigen-binding fragment thereof.

65. The isolated nucleic acid molecule or the set of nucleic acid molecules of claim 62, wherein the antibody that specifically binds human galectin-9 is a single chain antibody.

66. The isolated nucleic acid molecule or the set of nucleic acid molecules of any one of claims 62-64, wherein the antibody that specifically binds human galectin-9 is a human antibody or a humanized antibody.

67. The isolated nucleic acid molecule or the set of nucleic acid molecules of any one of claims 62-64 and 66, wherein the antibody that specifically binds human galectin-9 is an IgG molecule.

68. The isolated nucleic acid molecule or the set of nucleic acid molecules of claim 67, wherein the IgG molecule is an IgG1 or IgG4 molecule.

69. The isolated nucleic acid molecule or the set of nucleic acid molecules of claim 68, wherein IgG molecule is an IgG4 molecule, wherein the IgG4 has a S228P mutation.

70. The isolated nucleic acid molecule or the set of nucleic acid molecules of any one of claims 62-64 and 66-69, wherein the antibody that specifically binds human galectin-9 comprises a heavy chain constant region set forth as SEQ ID NO: 422, and a light chain constant region set forth as SEQ ID NO: 418.

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71. The isolated nucleic acid molecule or the set of nucleic acid molecules of any one of claims 62-64 and 66-69, wherein the one or more nucleic acid sequence(s) encode a VH set forth as SEQ ID NO: 55 and a heavy chain (HC) constant region set forth in SEQ ID NO: 422; and a VL set forth as SEQ ID NO: 54 and a light chain (LC) constant region set forth as SEQ ID NO: 418.

72. The isolated nucleic acid molecule or the set of nucleic acid molecules of claim 71, wherein the one or more nucleic acid sequence(s) encode a HC set forth as SEQ ID NO: 316 and a LC set forth in SEQ ID NO: 108.

73. A vector or two vectors, comprising an isolated nucleic acid molecule or a set of nucleic acid molecules according to any one of claims 62-72.

74. A host cell, comprising the vector or the two vectors of claim 73.

75. The host cell of claim 74, wherein the host cell is selected from *Escherichia* coli cells, simian COS cells, and Chinese hamster ovary (CHO) cells.

76. A method of producing an antibody that specifically binds human galectin-9, the method comprising:

(i) culturing the host cell of claim 74 or 75 under conditions allowing for expression of the antibody; and

(ii) harvesting the antibody thus produced from the cell culture.

77. Use of the isolated antibody of any one of claims 1-17 or the pharmaceutical composition of claim 18 for modulating immune response in a solid tumor or a hematological malignancy of a subject.

78. The use of claim 77, wherein the solid tumor is selected from the group consisting of glioblastoma, glioma, melanoma, skin squamous cell carcinoma, sarcoma, upper and lower gastrointestinal cancer, carcinoid tumor, neuroendocrine tumor, breast cancer, lung cancer, head and neck cancer, and genitourinary cancer.

79. The use of claim 78, wherein the upper and lower gastrointestinal cancer is selected from the group consisting of esophageal cancer, gastric cancer, pancreatic cancer, colorectal cancer,

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biliary tract cancer, cholangiocarcinoma, gall bladder cancer, liver cancer, and duodenal cancer.

80. The use of claim 79, wherein the upper and lower gastrointestinal cancer is a pancreatic cancer.

81. The use of claim 79, wherein the upper and lower gastrointestinal cancer is a colorectal cancer.

82. The use of claim 78, wherein the solid tumor is melanoma.

83. The use of claim 77, wherein the hematological malignancy is selected from the group consisting of a leukemia, a lymphoma, multiple myeloma, a myelodysplastic syndrome, and a myeloproliferative neoplasm.

84. The use of claim 83, wherein the leukemia is acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphoblastic leukemia or chronic lymphoblastic leukemia.

85. The use of claim 83, wherein the lymphoma is AIDS-related lymphoma, Burkitt lymphoma, cutaneous T cell lymphoma, Hodgkin lymphoma, Non-Hodgkin lymphoma, or primary central nervous system lymphoma.

86. The use of any one of claims 77-85, wherein the isolated antibody or the pharmaceutical composition is for use in combination with a checkpoint inhibitor.

87. The use of claim 86, wherein the checkpoint inhibitor is an anti-PD-1 antibody.

88. The use of any one of claims 77-87, wherein the isolated antibody or the pharmaceutical composition is for use in combination with a chemotherapeutic agent.

89. The use of claim 88, wherein the chemotherapeutic agent is gemcitabine, paclitaxel or a combination thereof.

90. The use of any one of claims 77-89, wherein modulating the immune response results in T cell activation.

91. The use of 90, wherein the T cell activation comprises CD4+ cell or CD8+ cell activation.

92. The use of claim 90 or 91, wherein the T cell activation comprises CD4+ cell activation.

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93. The use of any one of claims 90-92, wherein the T cell activation comprises CD8+ cell activation.

94. The use of any one of claims 77-93, wherein the use results in an increase in TNFalpha levels compared to a level found prior to administration of the galectin-9 antibody or the pharmaceutical composition.

95. The use of any one of claims 77-94, wherein the use results in an increase in CD44 levels compared to a level found prior to administration of the galectin-9 antibody or the pharmaceutical composition.

96. The use of any one of claims 77-95, wherein the use results in a decrease in IL-10 levels compared to a level found prior to administration of the galectin-9 antibody or the pharmaceutical composition.

97. Use of the isolated antibody of any one of claims 1-17 in manufacture of a medicament for treating a solid tumor or a hematological malignancy that expresses galectin-9 in a human subject.

98. The use of claim 97, wherein the solid tumor is selected from the group consisting of glioblastoma, glioma, melanoma, skin squamous cell carcinoma, sarcoma, upper and lower gastrointestinal cancer, carcinoid tumor, neuroendocrine tumor, breast cancer, lung cancer, head and neck cancer, and genitourinary cancer.

99. The use of claim 98, wherein the upper and lower gastrointestinal cancer is selected from the group consisting of esophageal cancer, gastric cancer, pancreatic cancer, colorectal cancer, biliary tract cancer, cholangiocarcinoma, gall bladder cancer, liver cancer, and duodenal cancer.

100. The use of claim 99, wherein the upper and lower gastrointestinal cancer is a pancreatic cancer.

101. The use of claim 99, wherein the upper and lower gastrointestinal cancer is a colorectal cancer.

102. The use of claim 98, wherein the solid tumor is melanoma.

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103. The use of claim 97, wherein the hematological malignancy is selected from the group consisting of a leukemia, a lymphoma, multiple myeloma, a myelodysplastic syndrome, and a myeloproliferative neoplasm.

104. The use of claim 103, wherein the leukemia is acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphoblastic leukemia or chronic lymphoblastic leukemia.

105 The use of claim 103, wherein the lymphoma is AIDS-related lymphoma, Burkitt lymphoma, cutaneous T cell lymphoma, Hodgkin lymphoma, Non-Hodgkin lymphoma, or primary central nervous system lymphoma.

106. The use of any one of claims 97-105, wherein the medicament is for use in combination with a checkpoint inhibitor.

107. The use of claim 106, wherein the checkpoint inhibitor is an anti-PD-1 antibody.

108. The use of any one of claims 97-107, wherein the medicament is for use in combination with a chemotherapeutic agent.

109. The use of claim 108, wherein the chemotherapeutic agent is gemcitabine, paclitaxel or a combination thereof.

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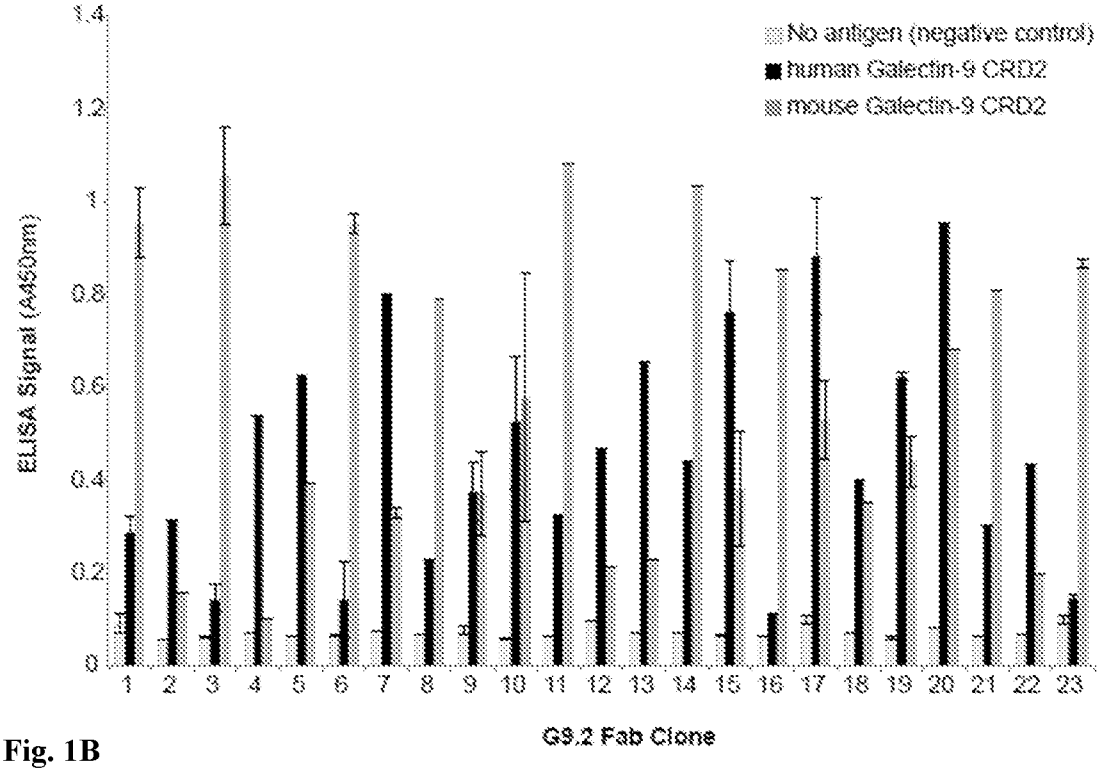
Fig. 1A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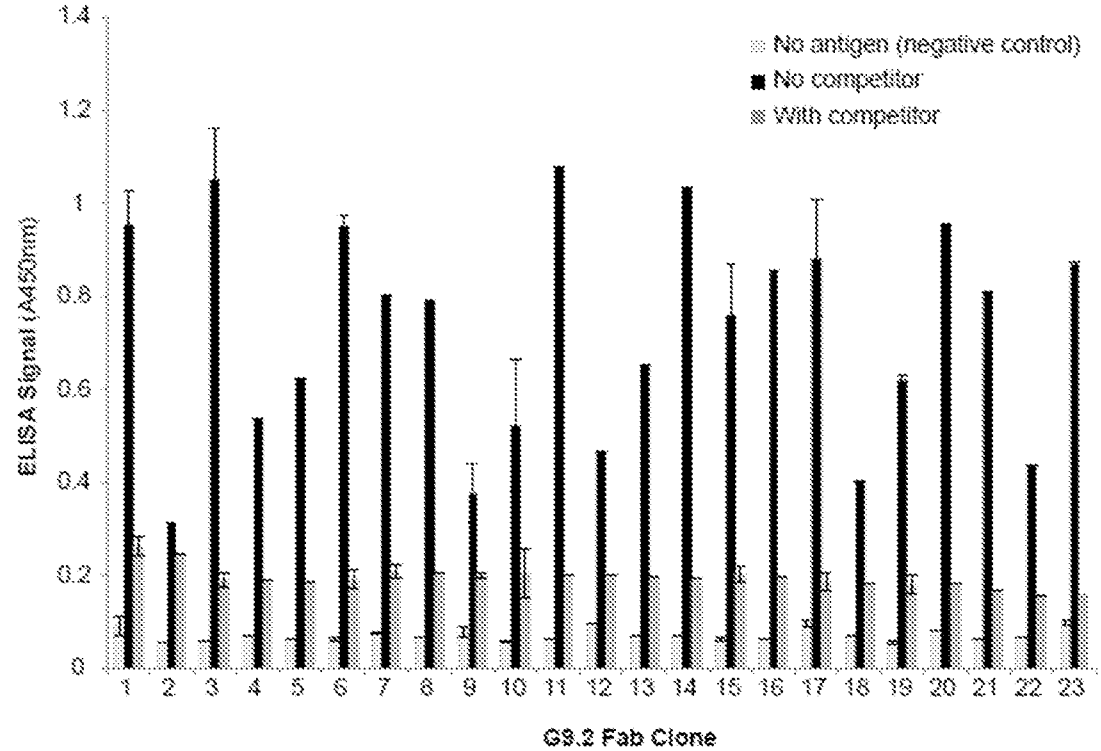
mouse Galectin-9 CRD2
ELISA Signal (A450nm)
G9.2 Fab Clone

Fig. 1B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No competitor
With competitor
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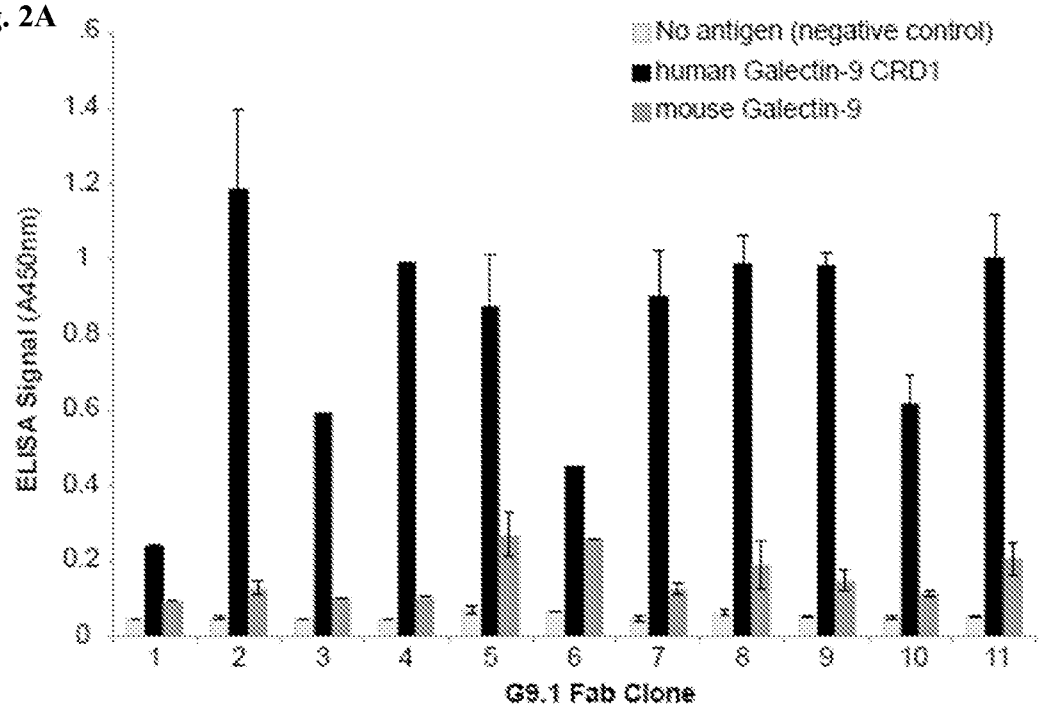
G9.2 Fab Clone

Fig. 2A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mouse Galectin-9
ELISA Signal (A450nm)
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1.2
1
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0.6
0.4
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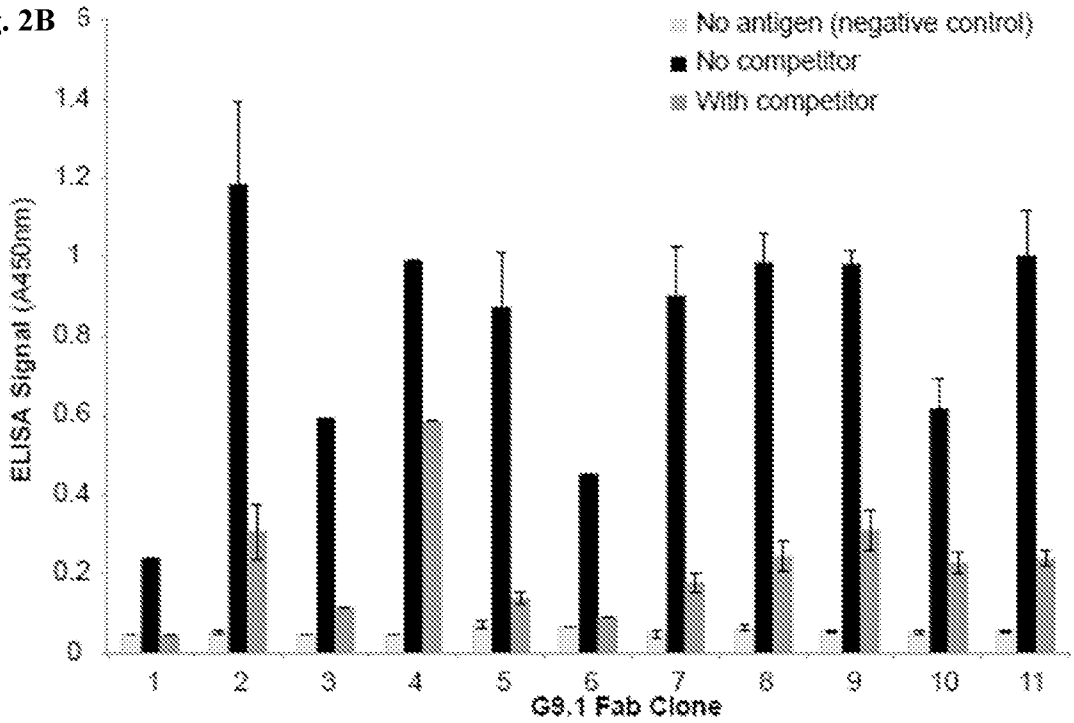
2
3
4
5
6
7
8
9
10
11
G9.1 Fab Clone

Fig. 2B


No antigen (negative control)
No competitor
With competitor
ELISA Signal (A450nm)
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1.4
1.2
1
0.8
0.6
0.4
0.2
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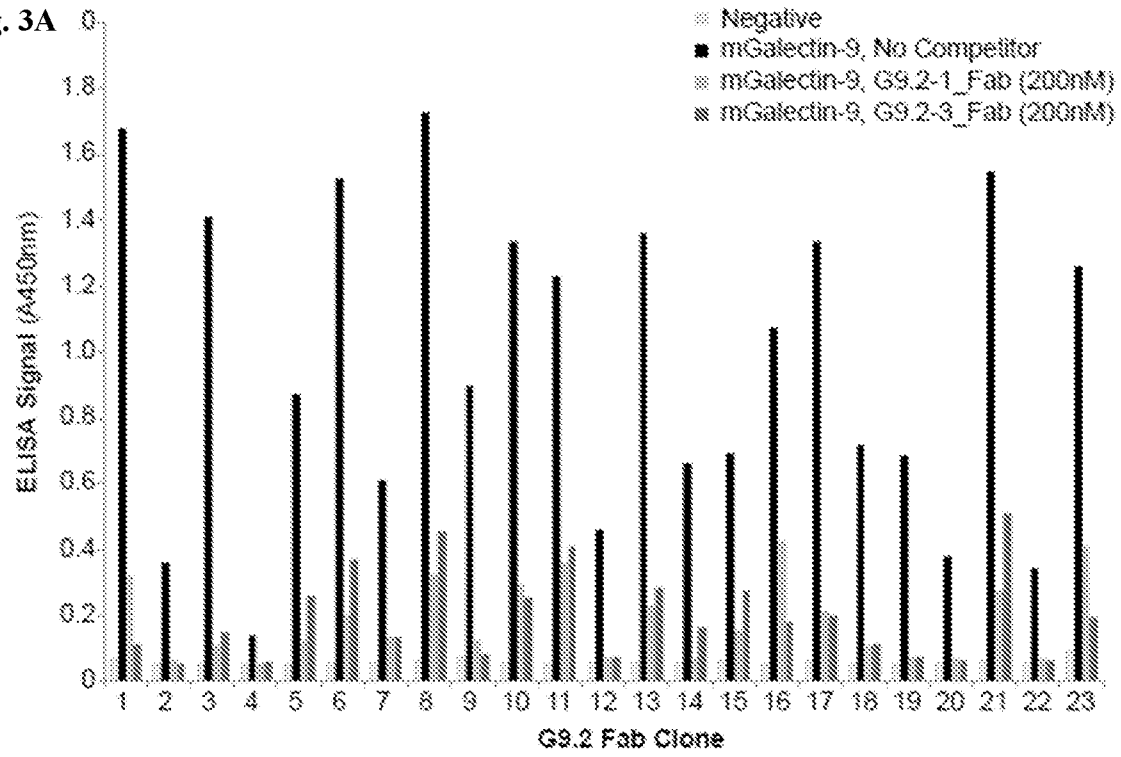
1
2
3
4
5
6
7
8
9
10
11
G9.1 Fab Clone

Fig. 3A


Negative
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mGalectin-9, G9.2-3_Fab (200nM)
ELISA Signal (A450nm)
0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
G9.2 Fab Clone

Fig. 3B

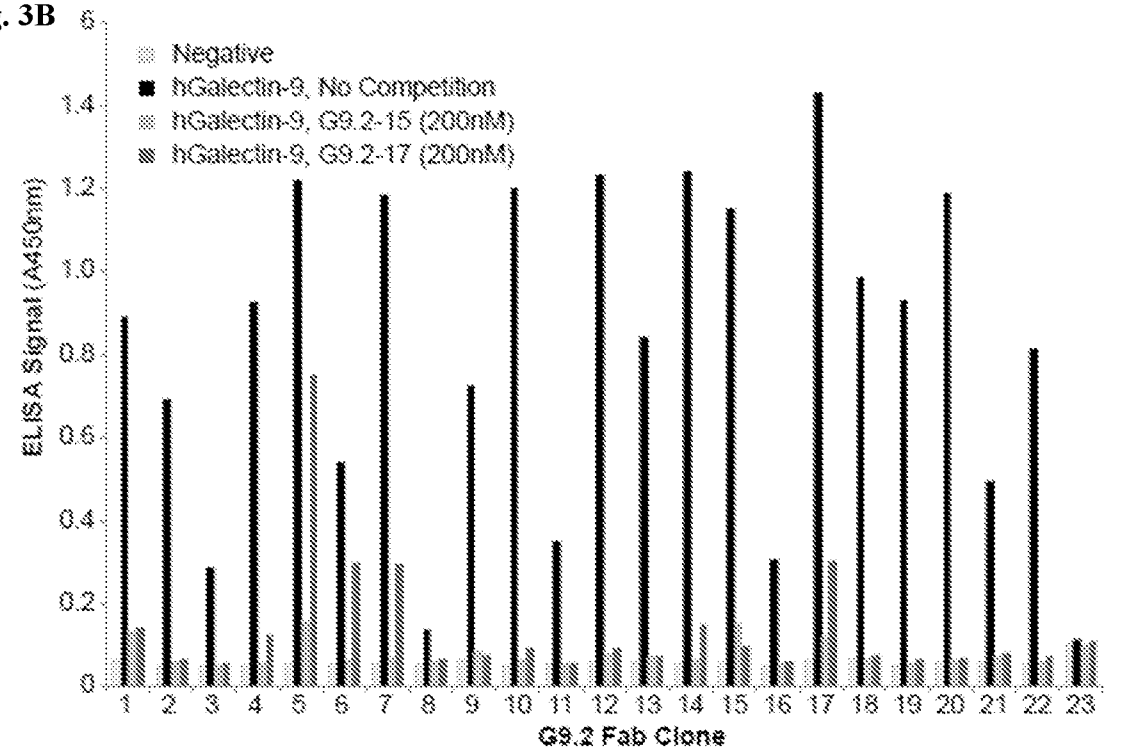
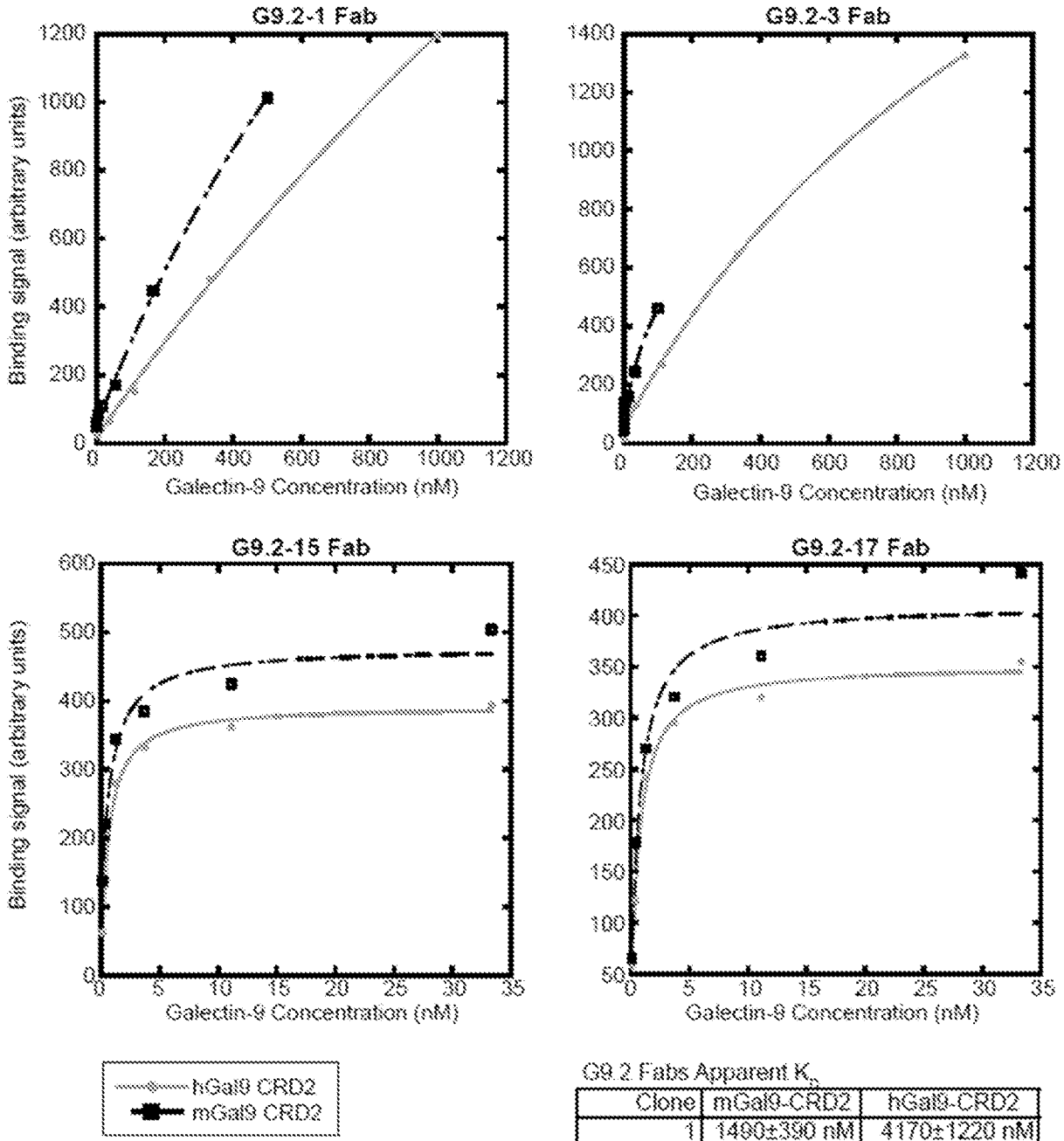

Negative
hGalectin-9, No Competition
hGalectin-9, G9.2-15 (200nM)
hGalectin-9, G9.2-17 (200nM)
ELISA Signal (A450nm)
0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
G9.2 Fab Clone

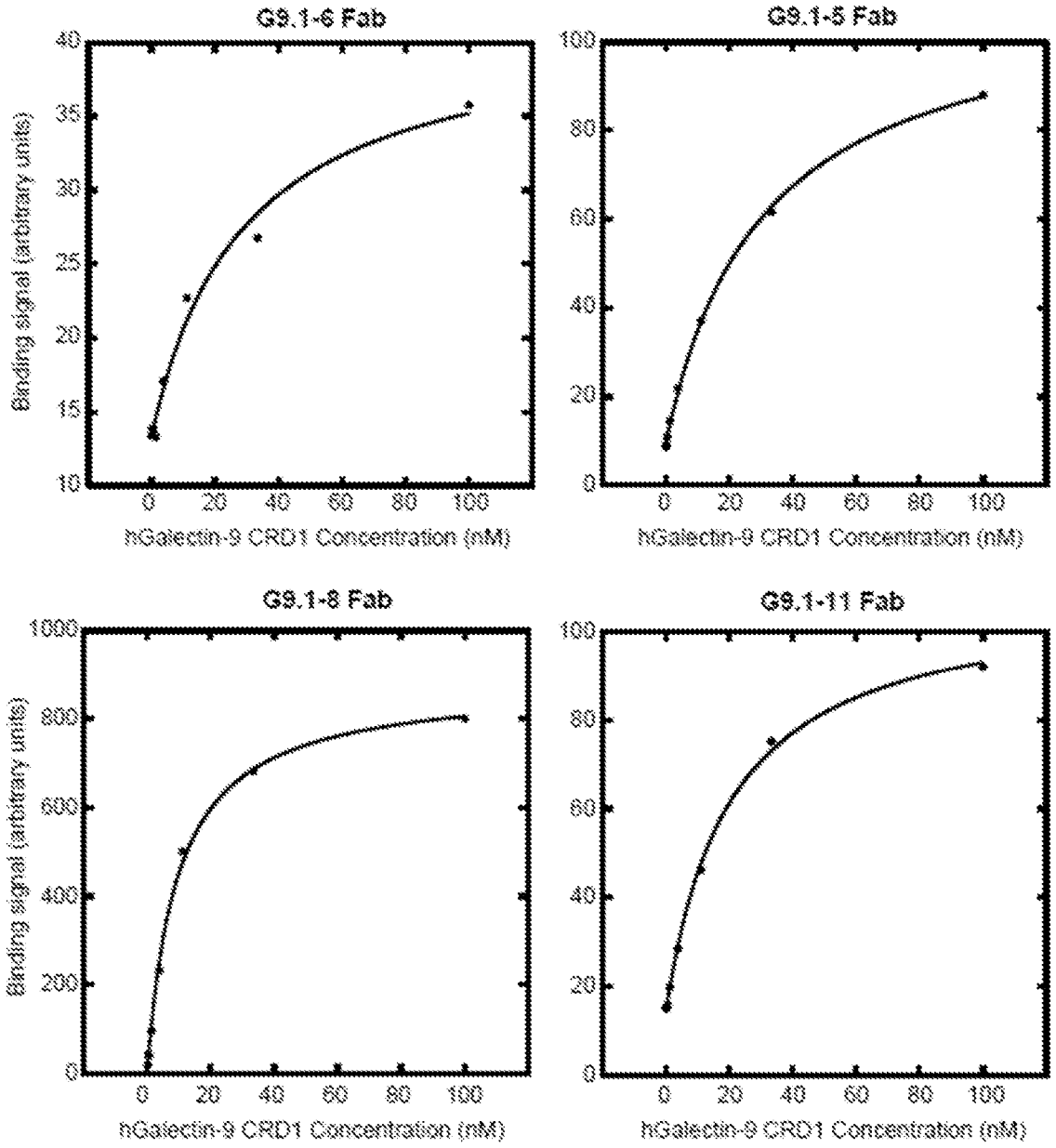
Fig. 4



G9.2 Fabs Apparent K_d

Clone	mGal9-CRD2	hGal9-CRD2
1	1490±390 nM	4170±1220 nM
3	122±89 nM	1380±210nM
15	0.65±0.16 nM	0.71±0.39 nM
17	0.55±0.14 nM	0.76±0.39 nM

Fig. 5



G9.1 Fabs Apparent Kd	
Clone	hGal9-2
5	30.4±2.1 nM
6	29.2±8.5 nM
8	9.8±1.0 nM
11	20.4±1.7 nM

Fig. 6

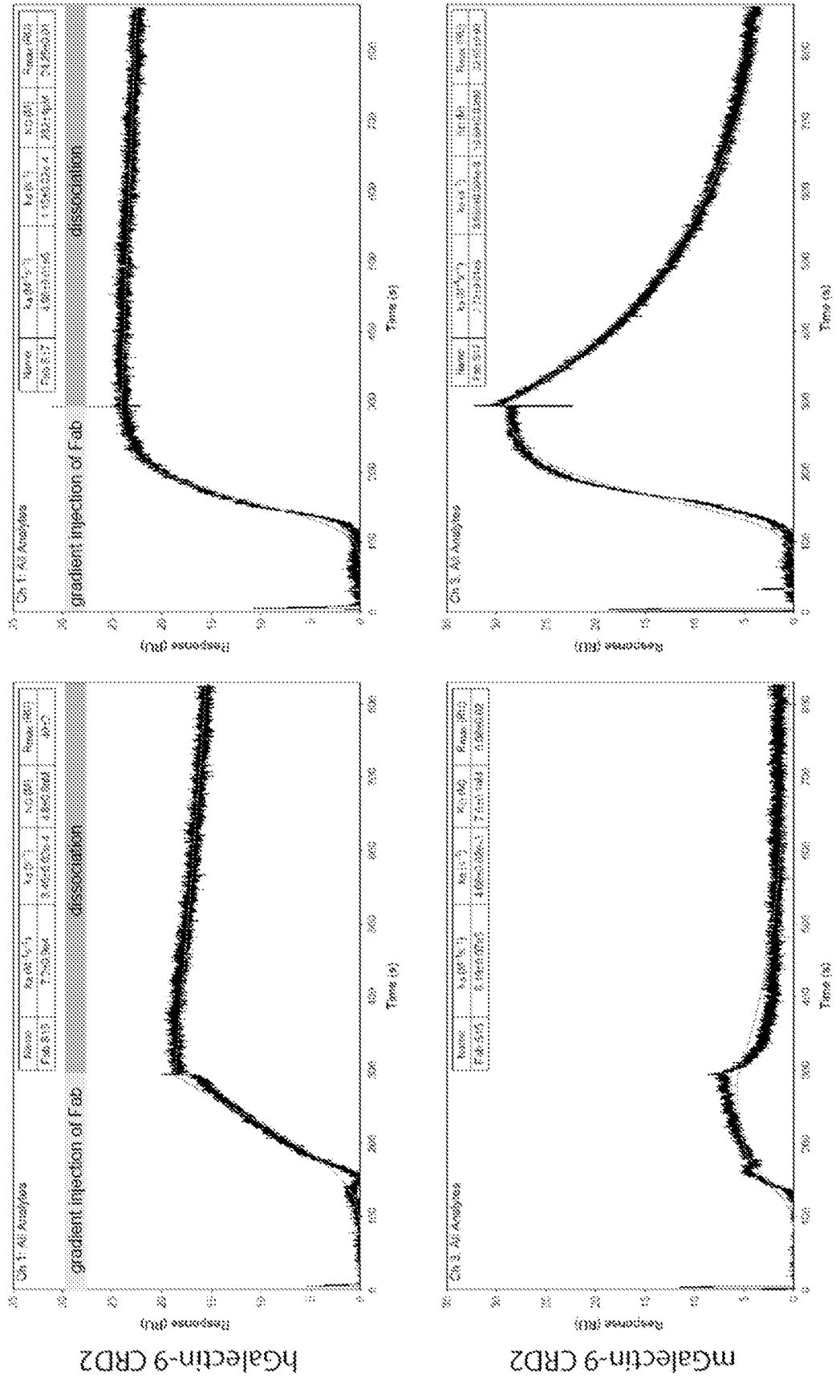

Fab G9.2-15
Fab G9.2-17
hGalectin-9 CRD2
mGalectin-9 CRD2
gradient injection of Fab
dissociation
Response (RU)
Time (s)

Fig. 7

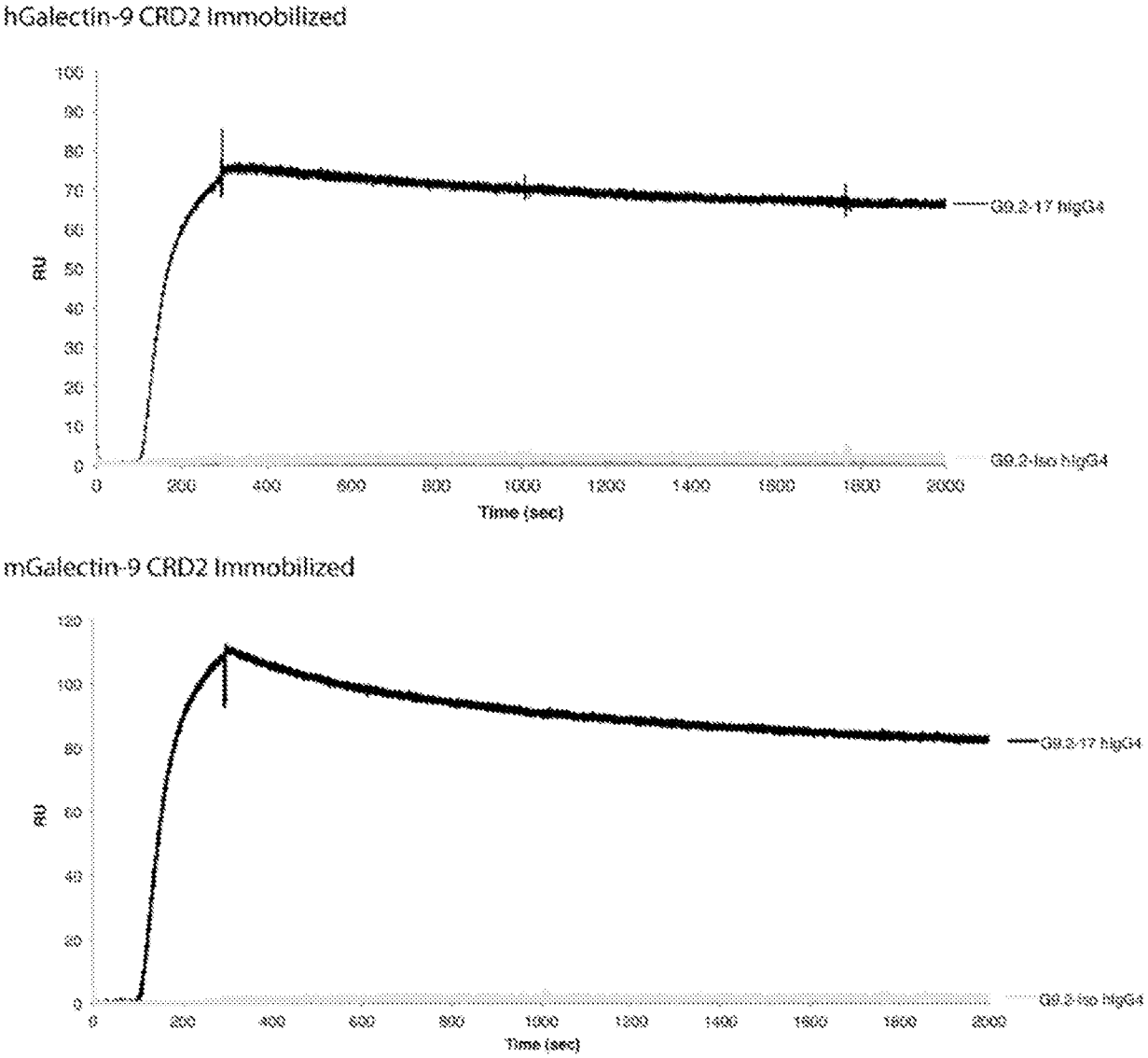

hGalectin-9 CRD2 Immobilized
RU
Time (sec)
G9.2-17 hIgG4
G9.2-iso hIgG4
mGalectin-9 CRD2 Immobilized
RU
Time (sec)
G9.2-17 hIgG4
G9.2-iso hIgG4

Fig. 8

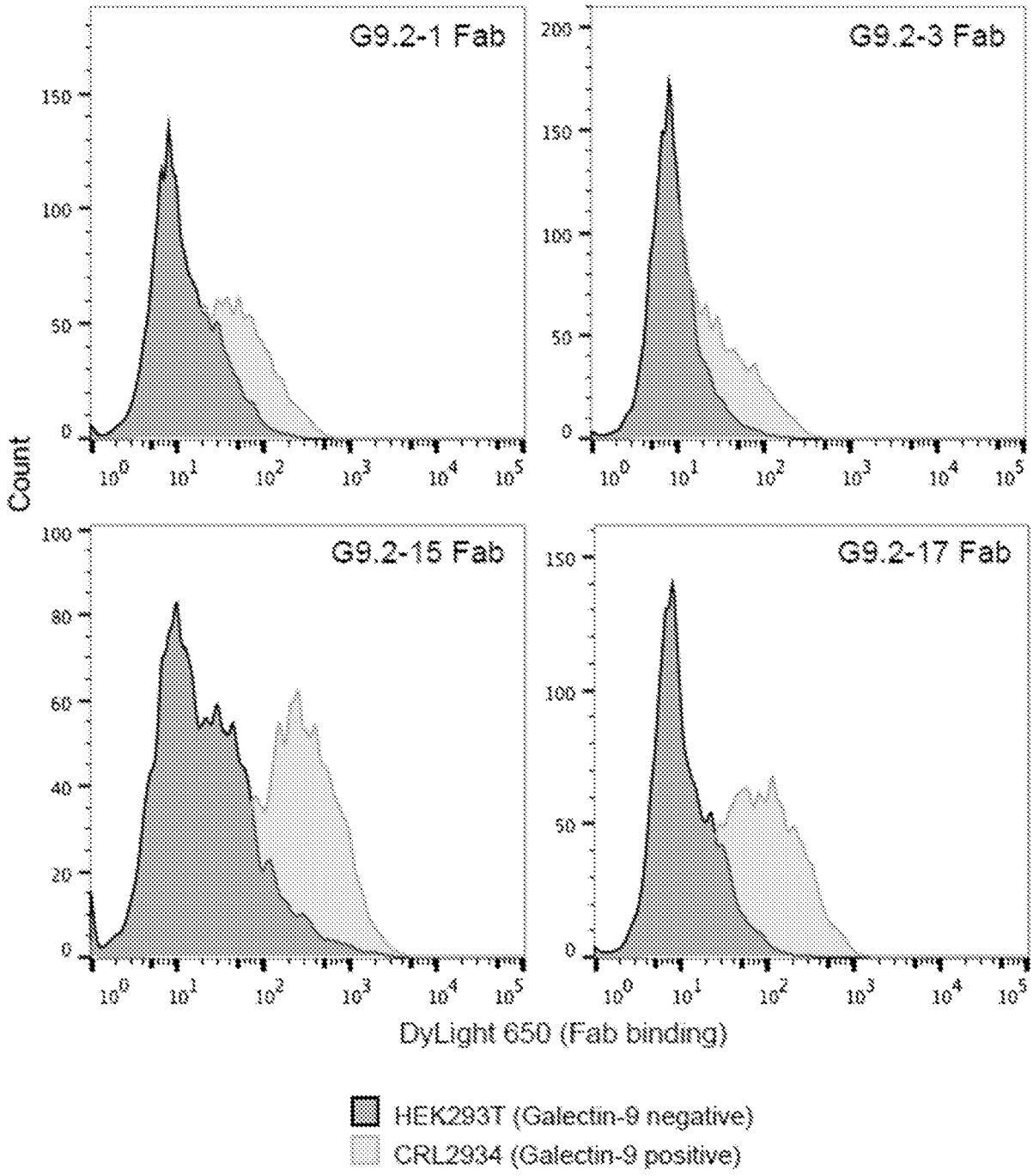

G9.2-1 Fab
G9.2-3 Fab
G9.2-15 Fab
G9.2-17 Fab
Count
DyLight 650 (Fab binding)
HEK293T (Galectin-9 negative)
CRL2934 (Galectin-9 positive)

Fig. 9

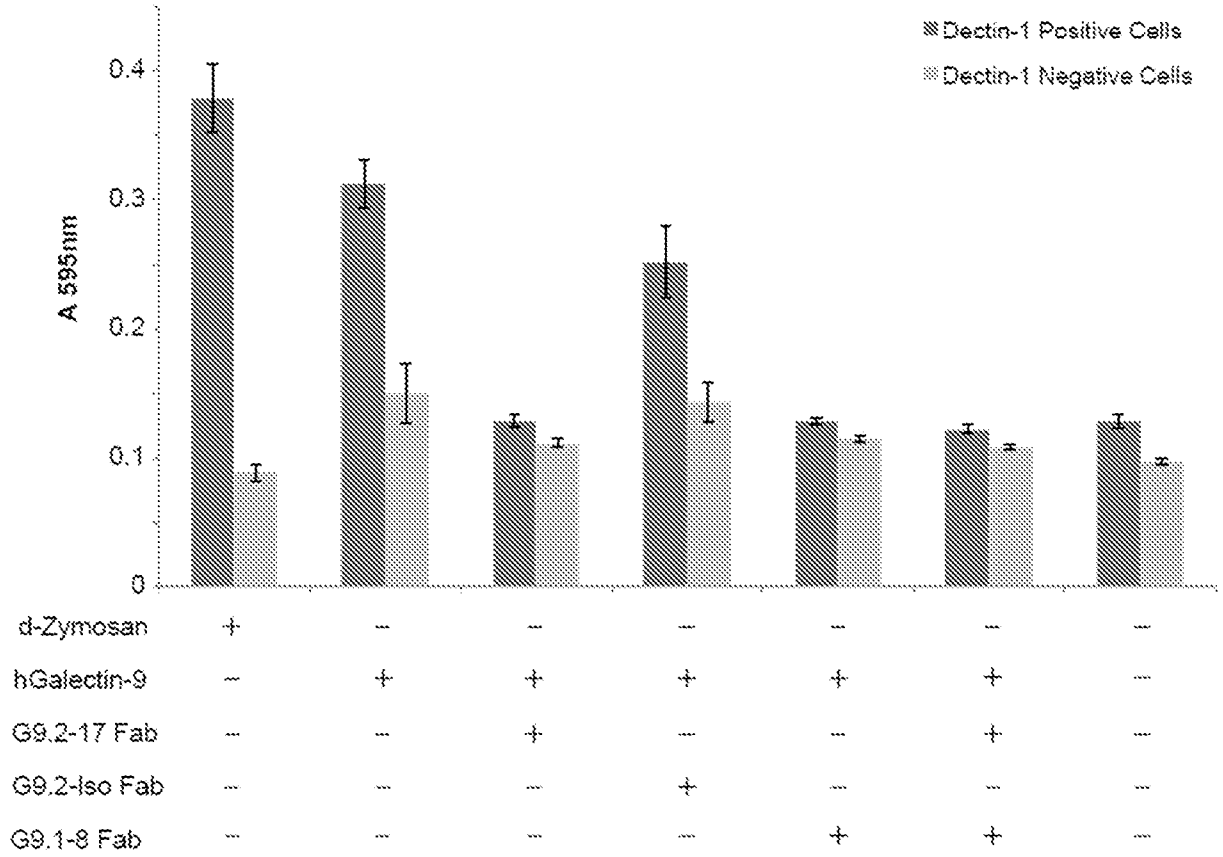

Dectin-1 Positive Cells
Dectin-1 Negative Cells
A 595nm
0.4
0.3
0.2
0.1
0
d-Zymosan + – – – – – –
hGalectin-9 – + + + + + –
G9.2-17 Fab – – + – – + –
G9.2-Iso Fab – – – + – – –
G9.1-8 Fab – – – – + + –

Fig. 10A

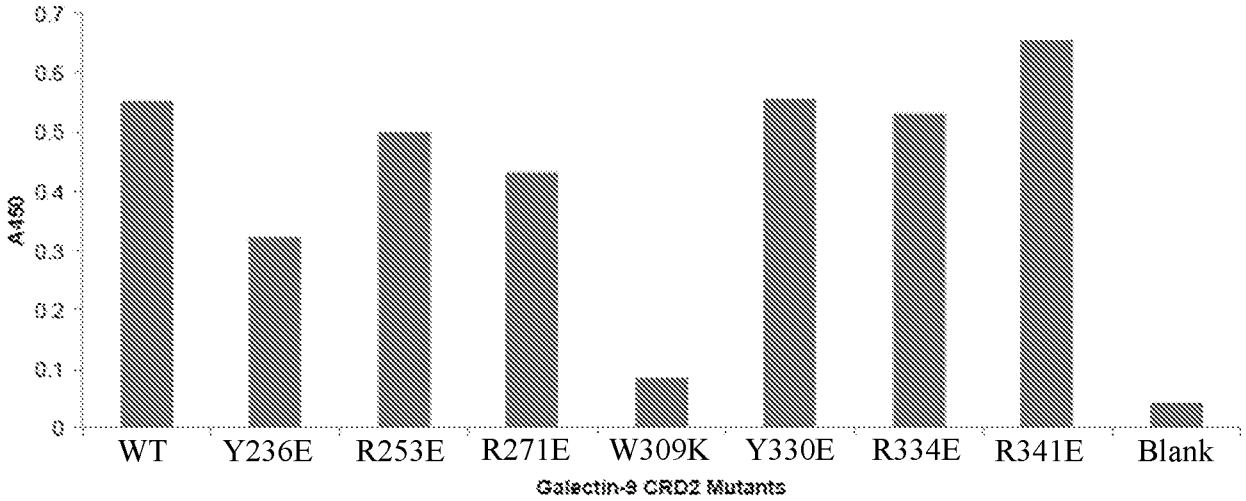


Fig. 10B

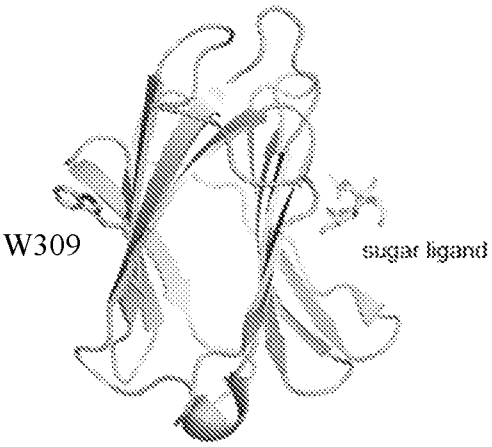


Fig. 11

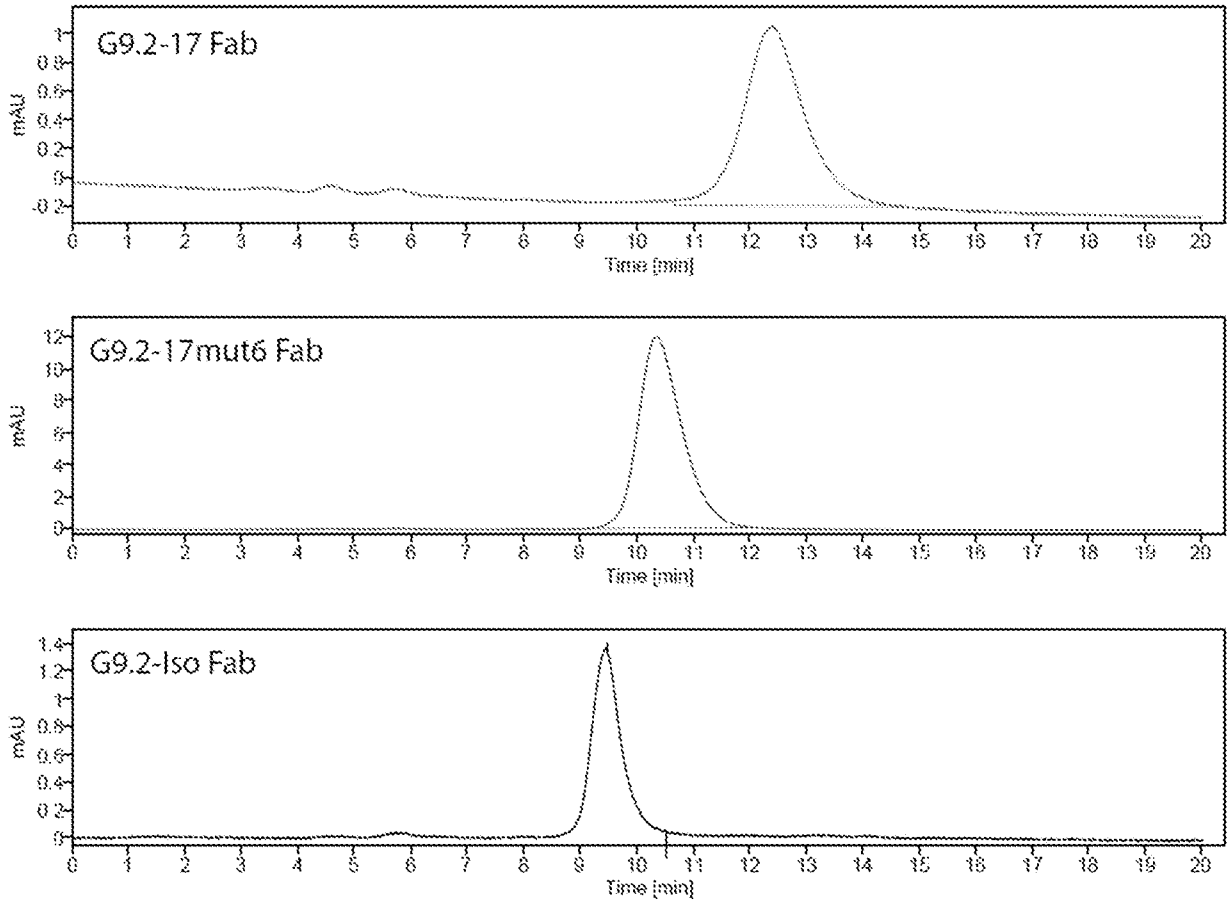

G9.2-17 Fab
mAU
Time [min]
G9.2-17mut6 Fab
mAU
Time [min]
G9.2-Iso Fab
mAU
Time [min]

Fig. 12

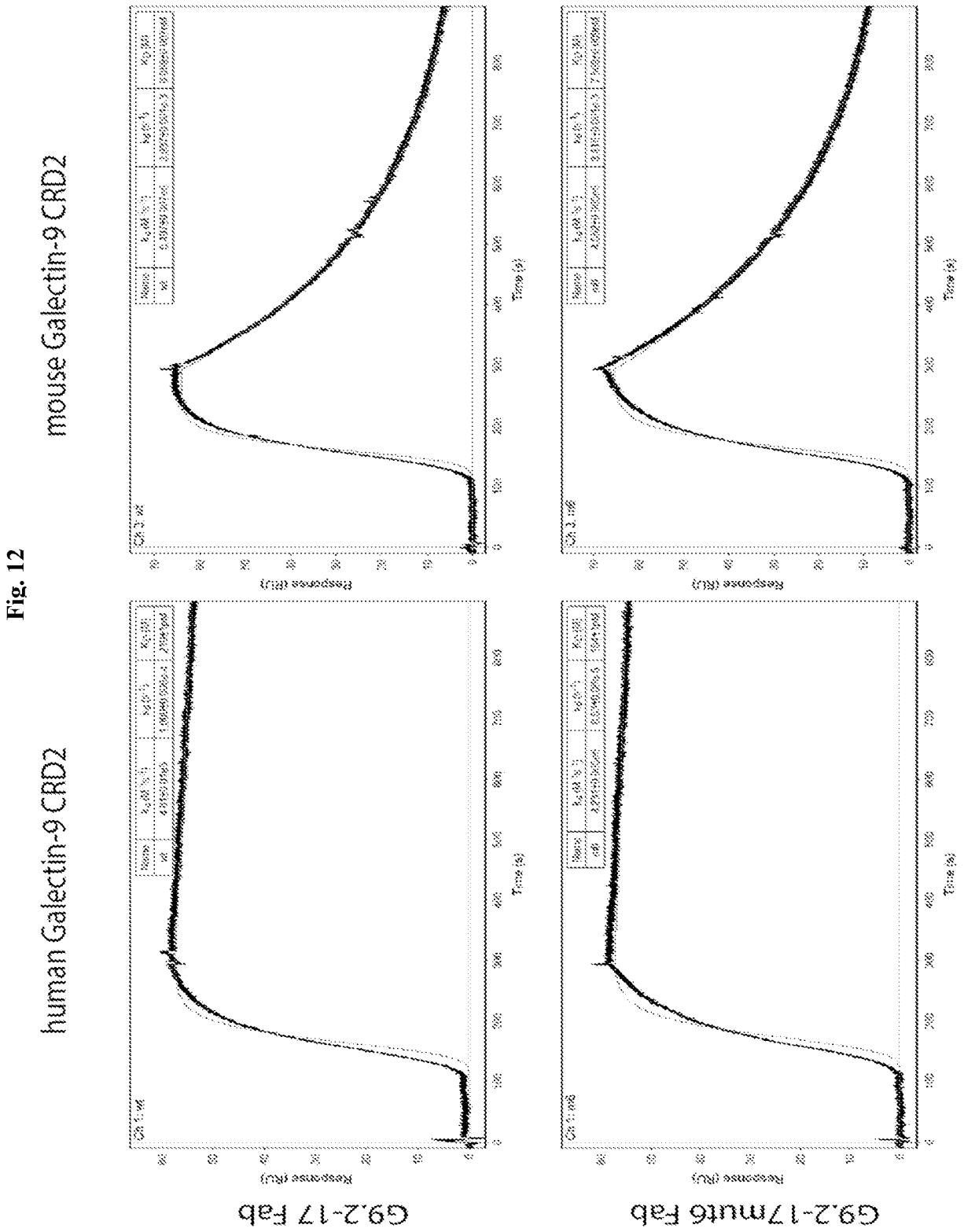

human Galectin-9 CRD2
mouse Galectin-9 CRD2
G9.2-17 Fab
G9.2-17mut6 Fab
Response (RU)
Time (s)

Fig. 13

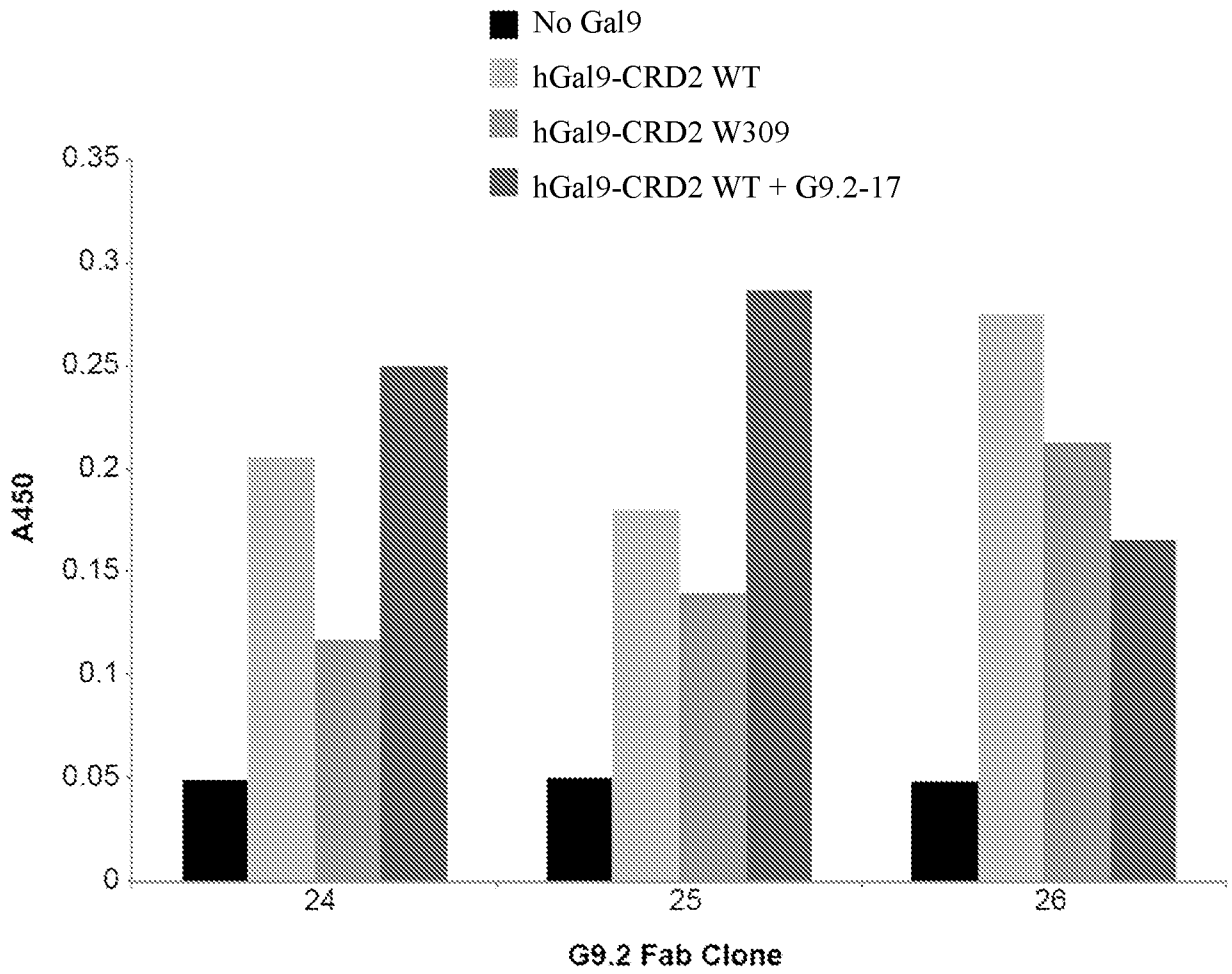

No Gal9
hGal9-CRD2 WT
hGal9-CRD2 W309
hGal9-CRD2 WT + G9.2-17
A450
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
24
25
26
G9.2 Fab Clone

Fig. 14

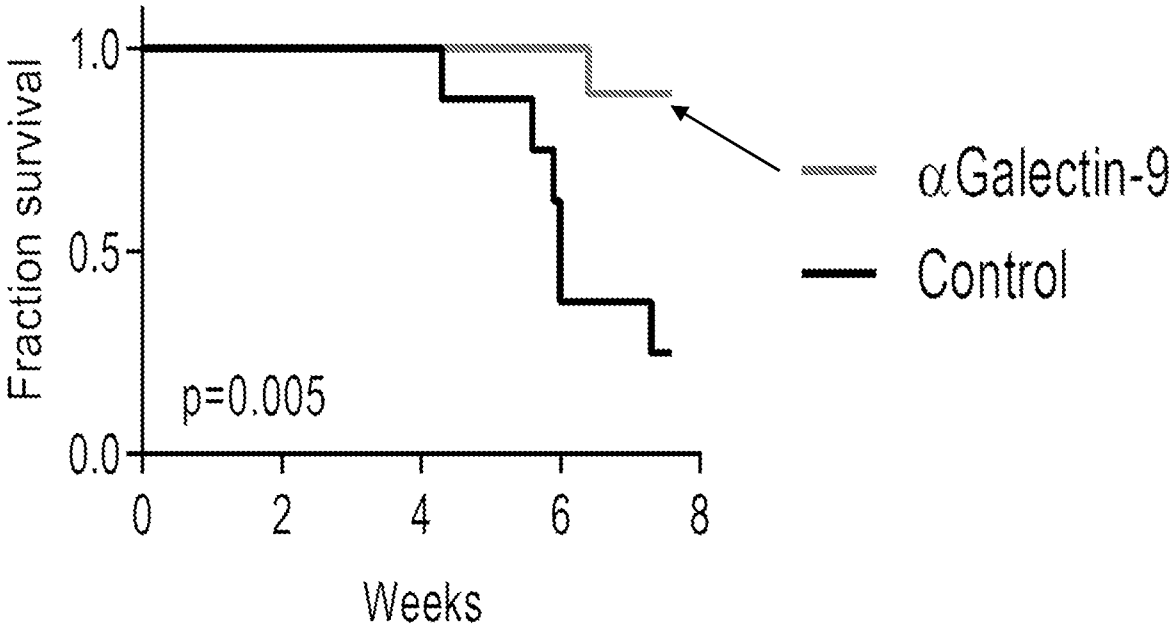

Fraction survival
1.0
0.5
0.0
p=0.005
0
2
4
6
8
Weeks
αGalectin-9
Control

Fig. 15

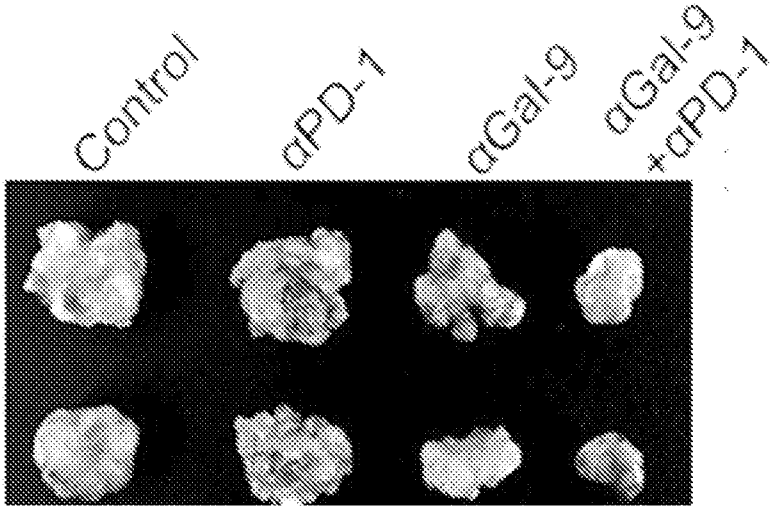

Control
αPD-1
αGal-9
αGal-9
+αPD-1

Fig. 16

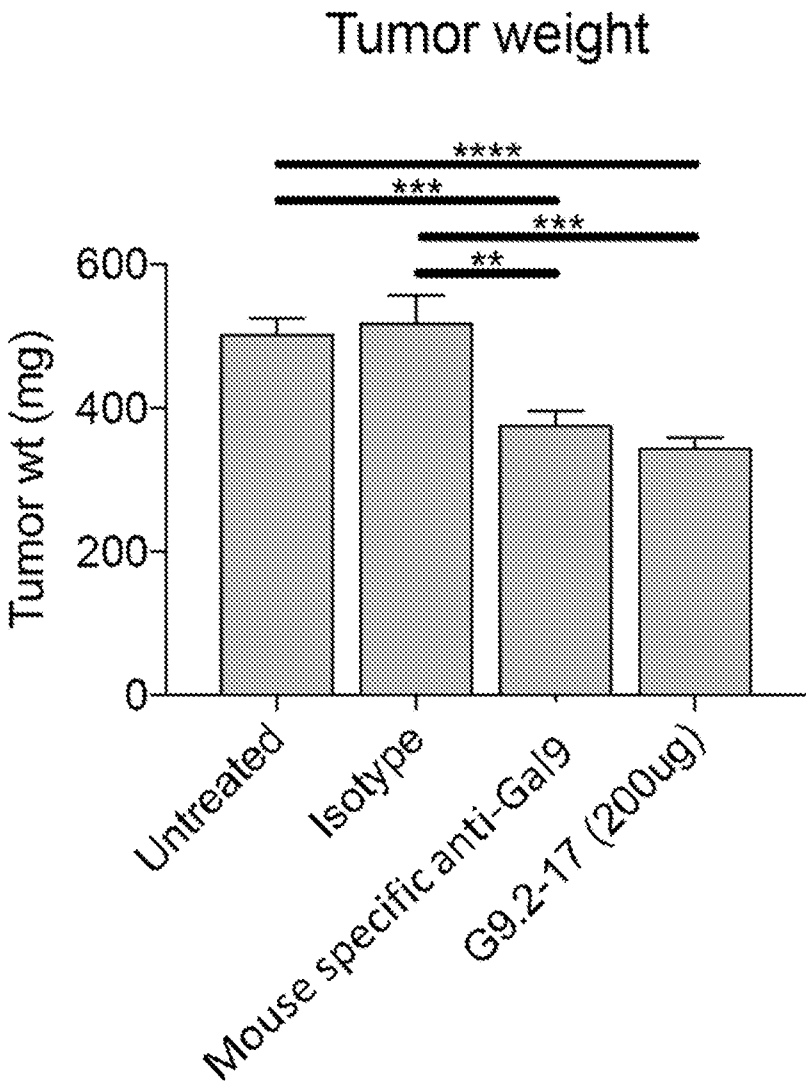

Tumor weight
****
***
***
**
600
400
200
0
Tumor wt (mg)
Untreated
Isotype
Mouse specific anti-Gal9
G9.2-17 (200ug)

Fig. 17

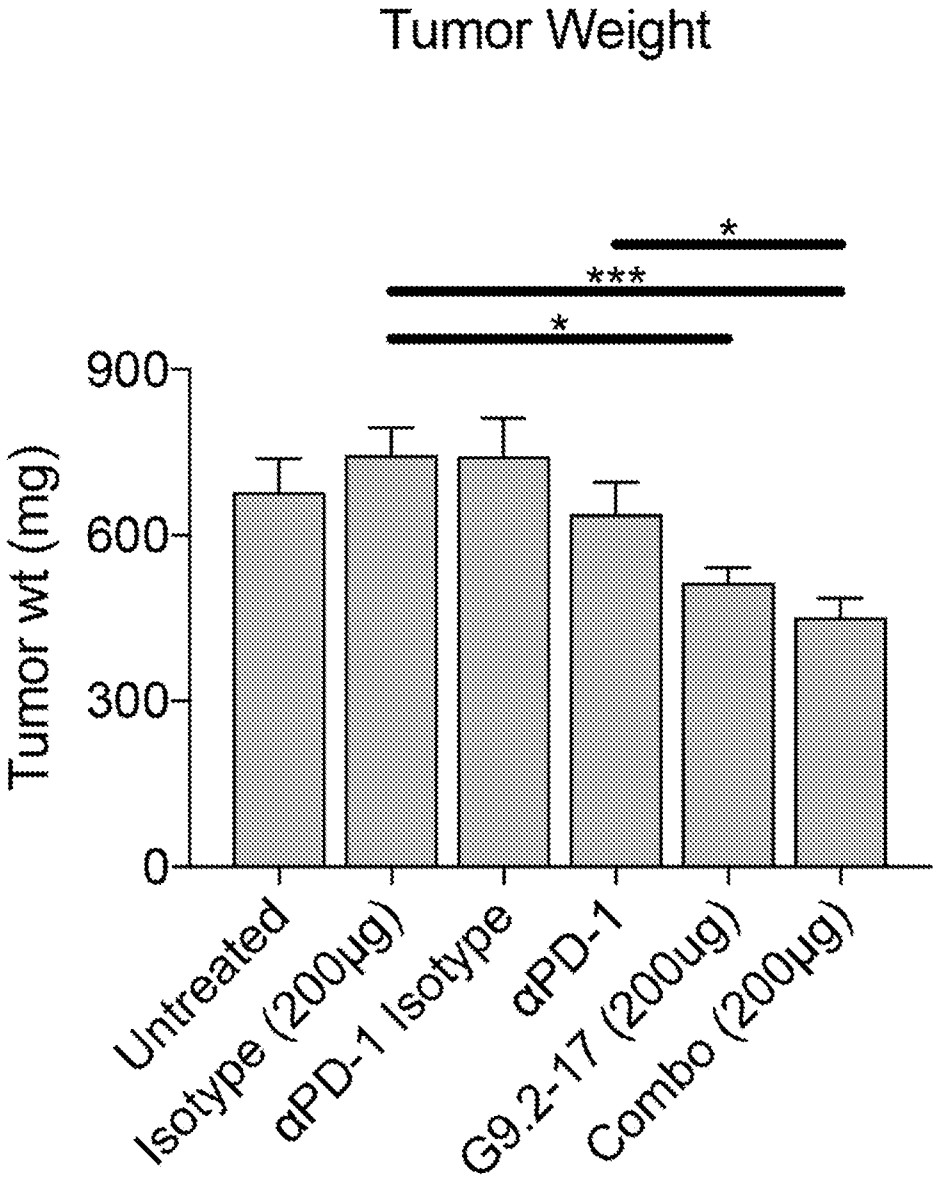

Tumor Weight
*
***
*
900
600
300
0
Tumor wt (mg)
Untreated
Isotype (200µg)
αPD-1 Isotype
αPD-1
G9.2-17 (200ug)
Combo (200µg)

Fig. 18A

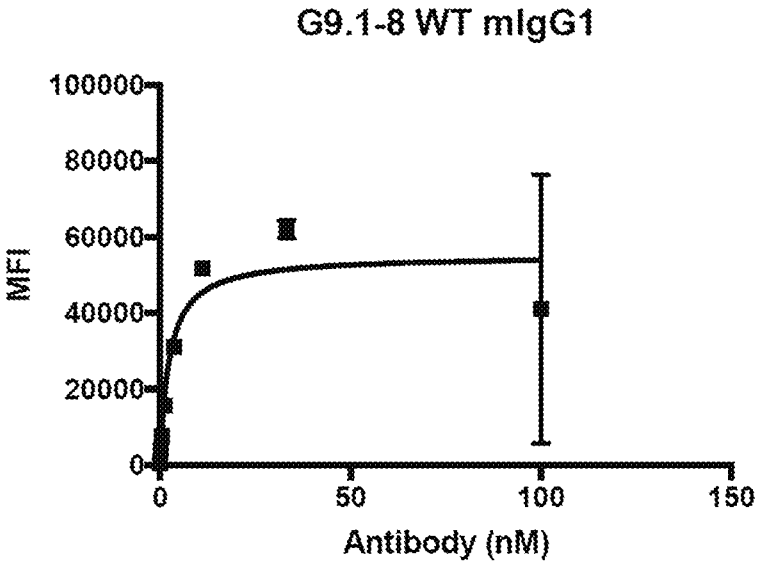


Fig. 18B

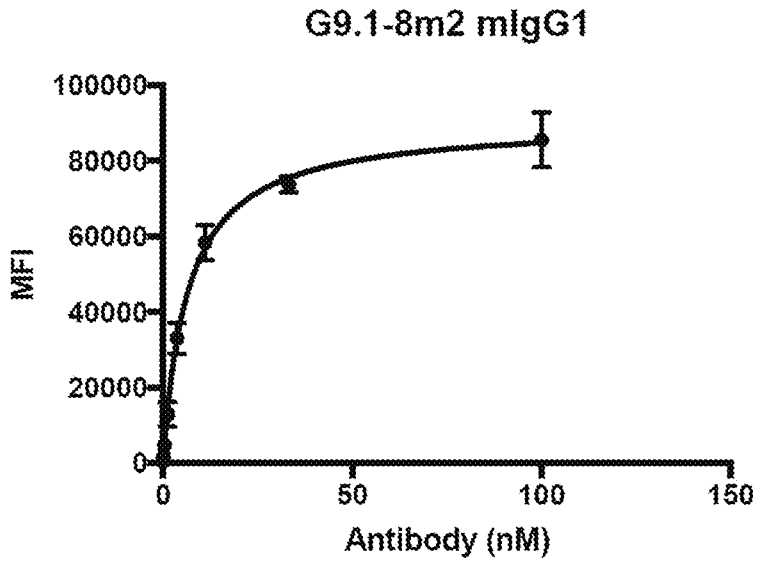


Fig. 18C

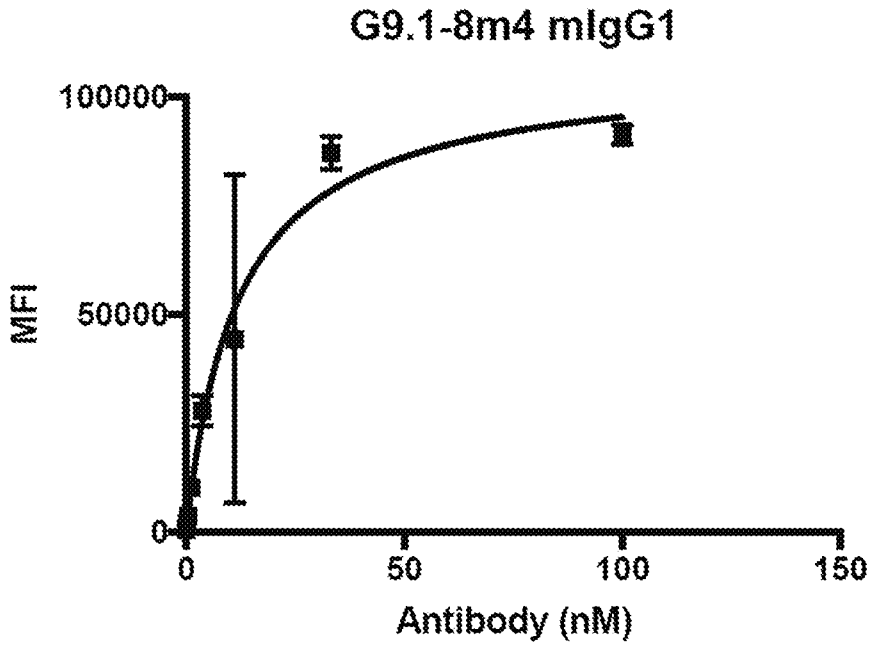


Fig. 19A

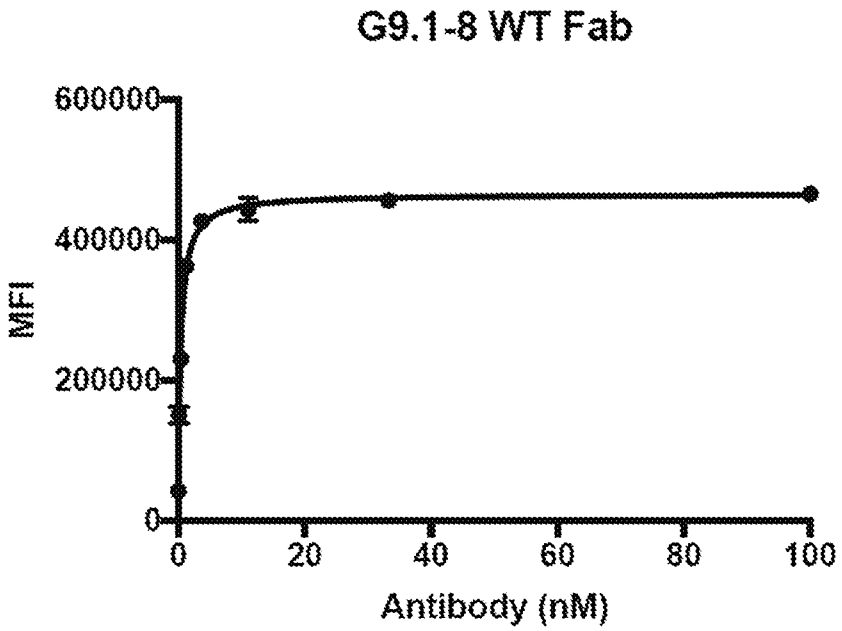


Fig. 19B

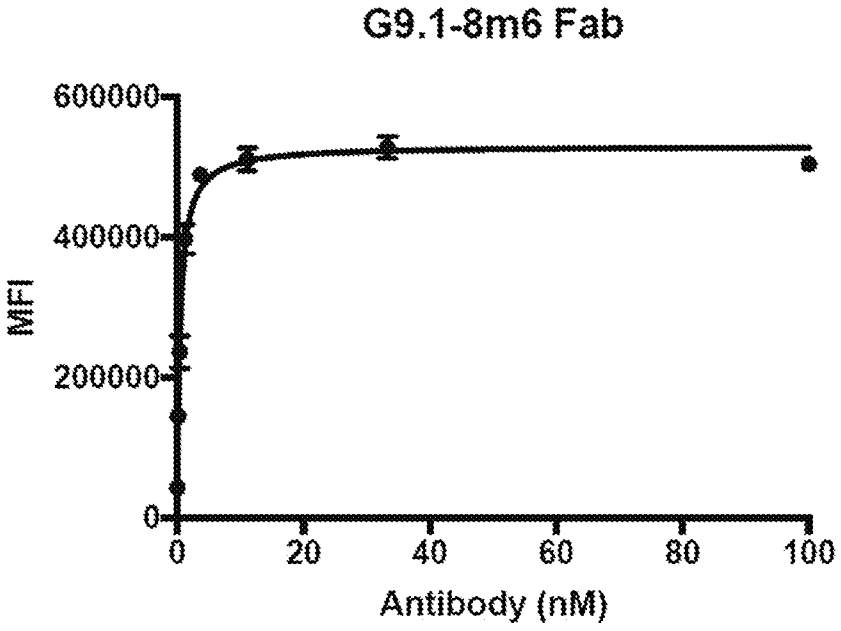


Fig. 19C

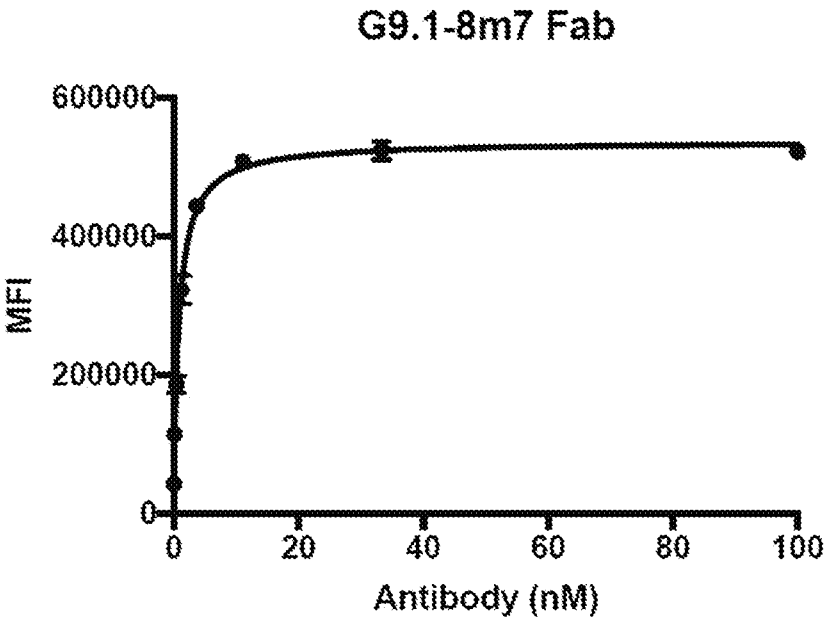


Fig. 19D

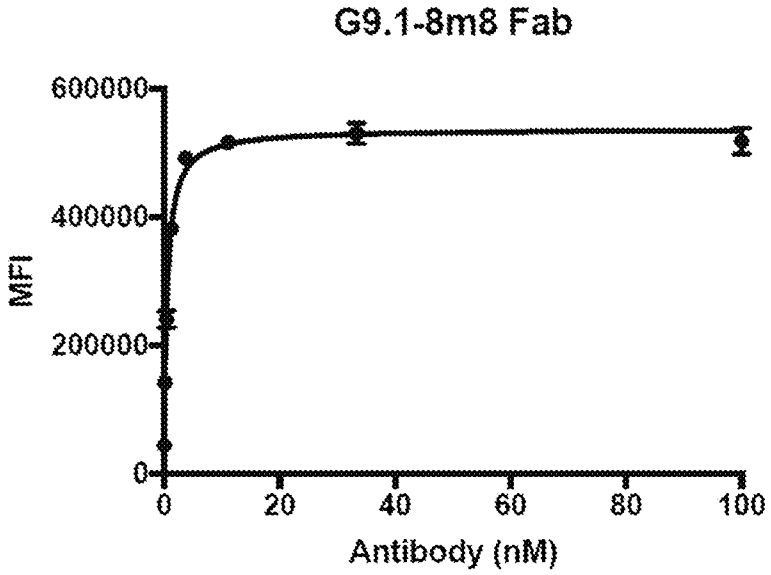


Fig. 19E

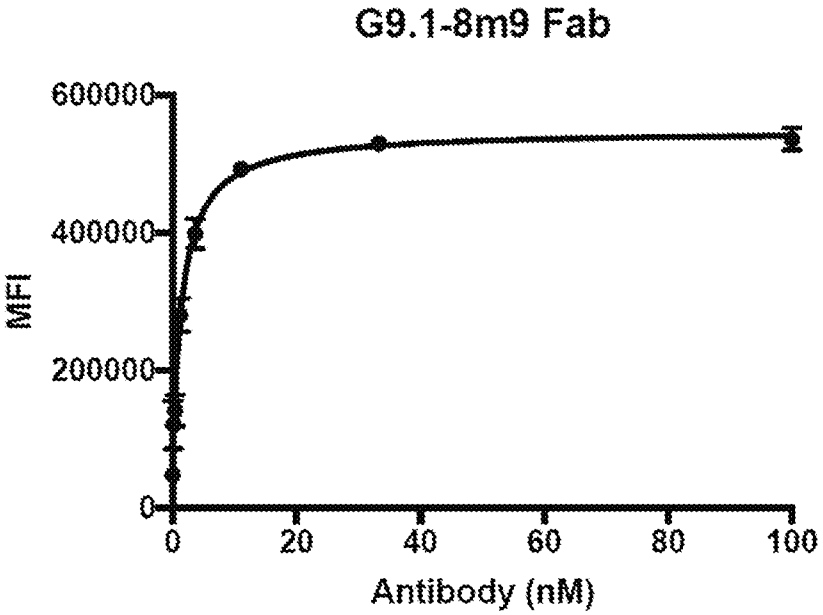


Fig. 19F

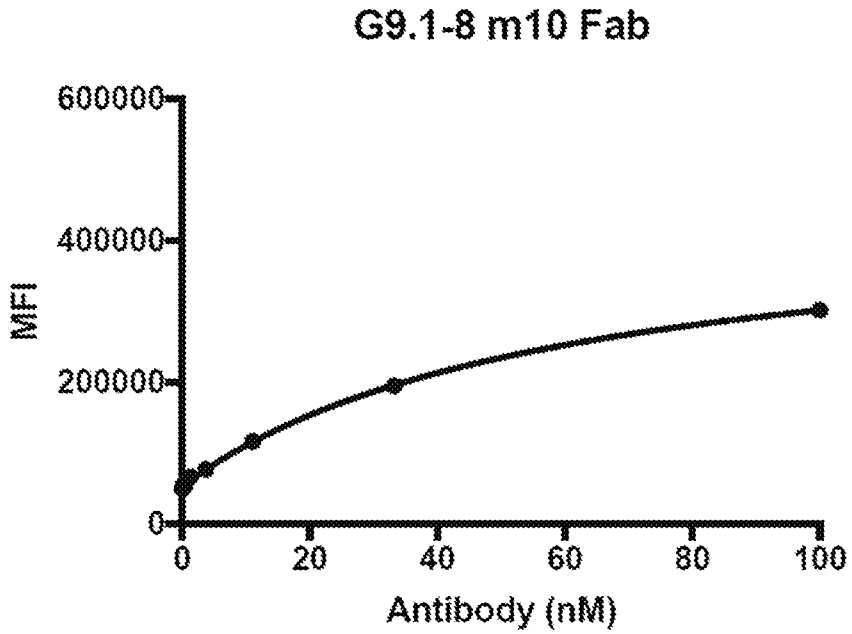


Fig. 19G

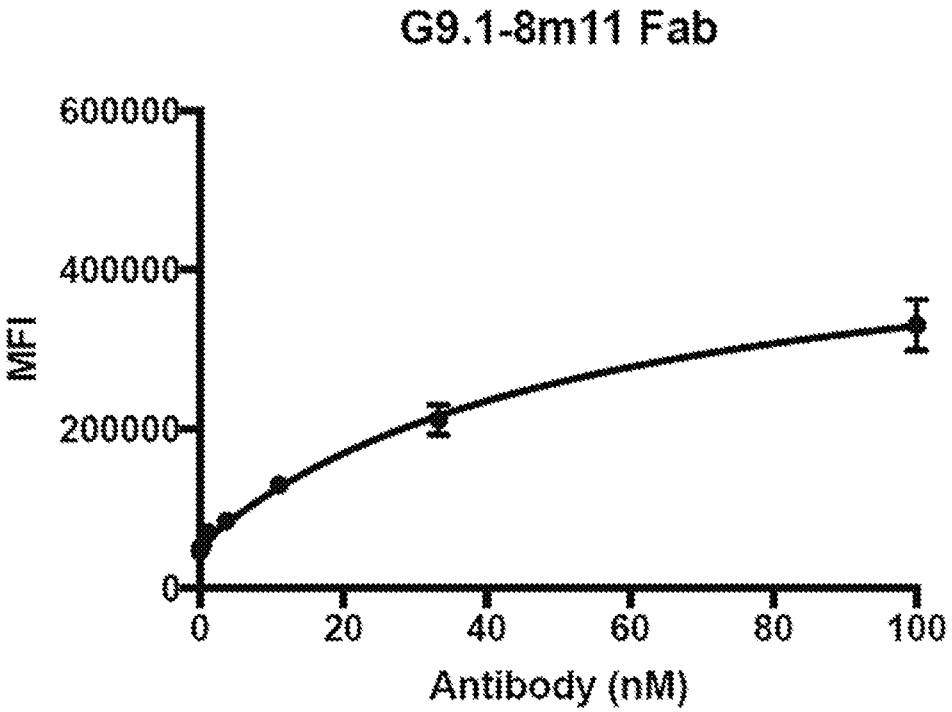

G9.1-8m11 Fab
600000
400000
200000
0
MFI
0
20
40
60
80
100
Antibody (nM)

Fig. 20A

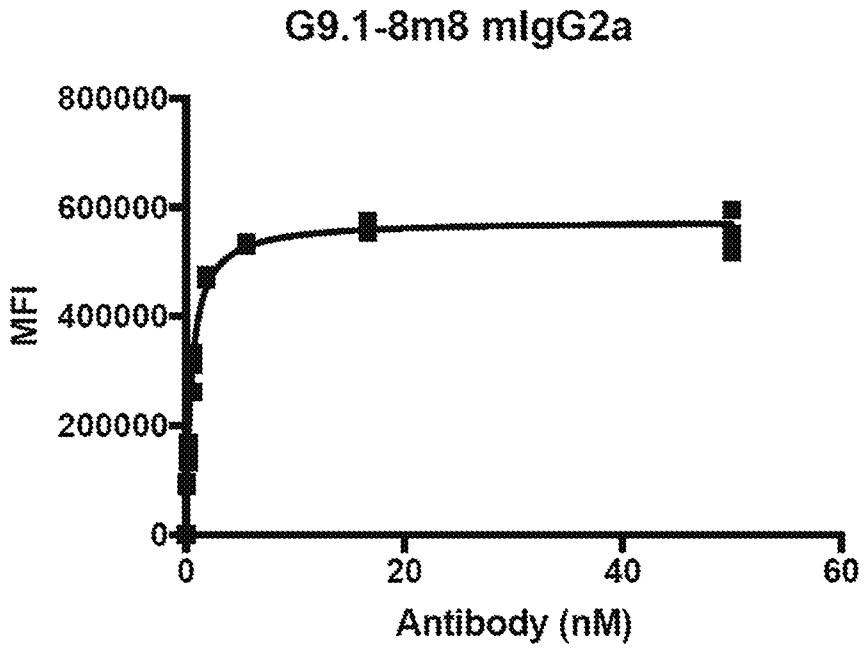


Fig. 20B

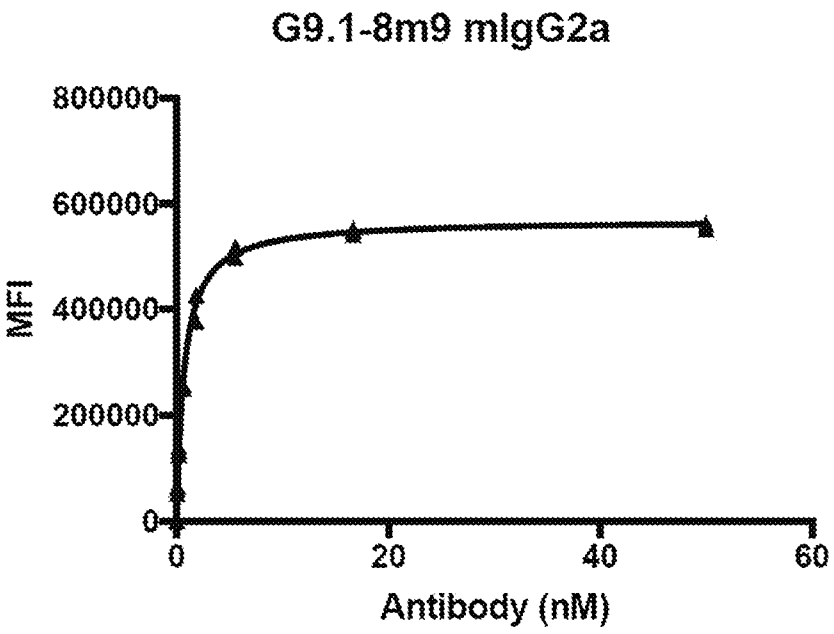


Fig. 20C

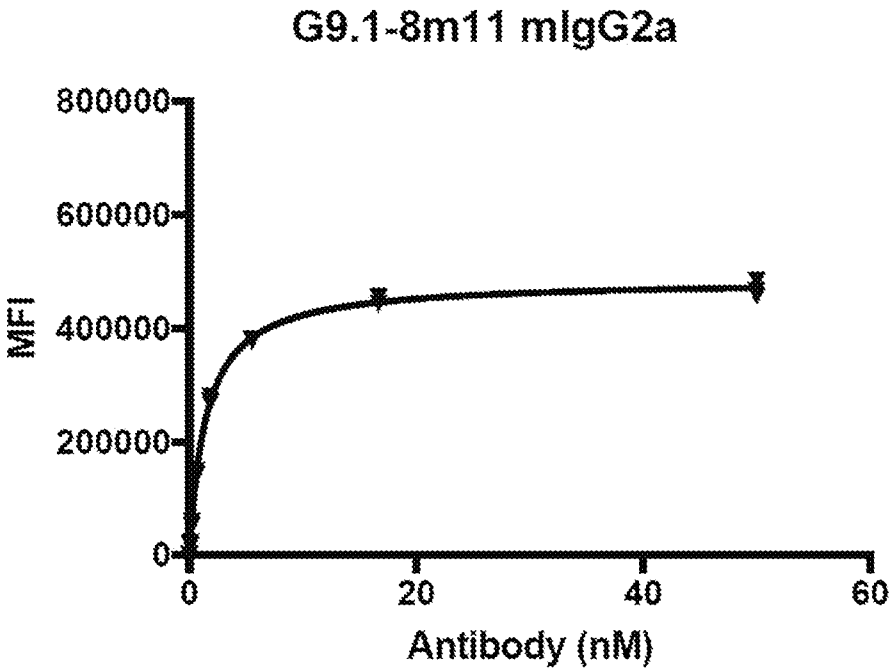

G9.1-8m11 mIgG2a
800000
600000
400000
200000
0
MFI
0
20
40
60
Antibody (nM)

Fig. 21A

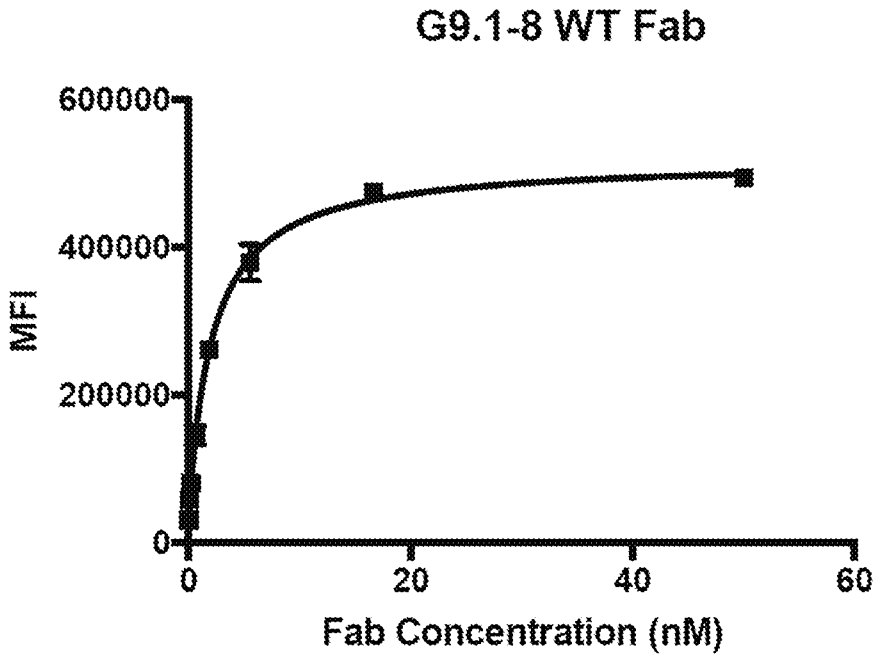


Fig. 21B

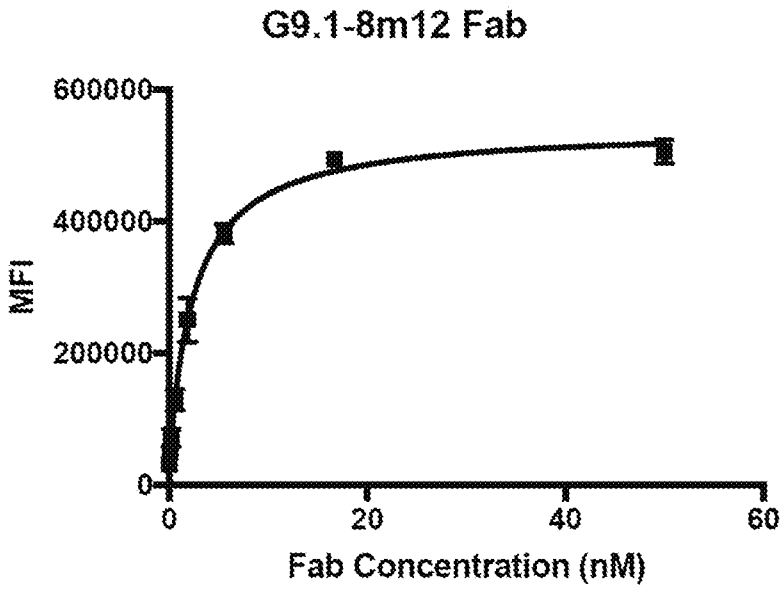


Fig. 21C

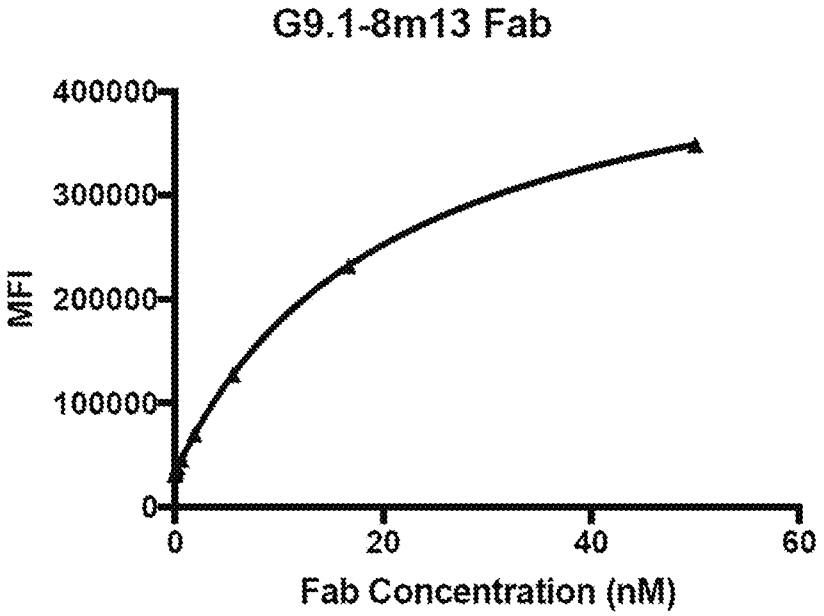


Fig. 21D

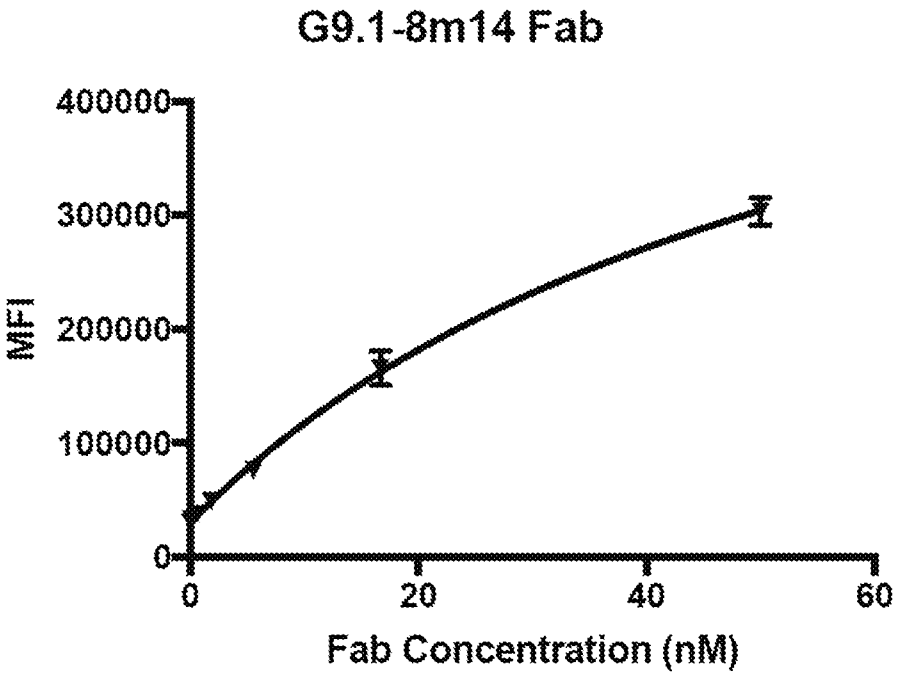


Fig. 22A

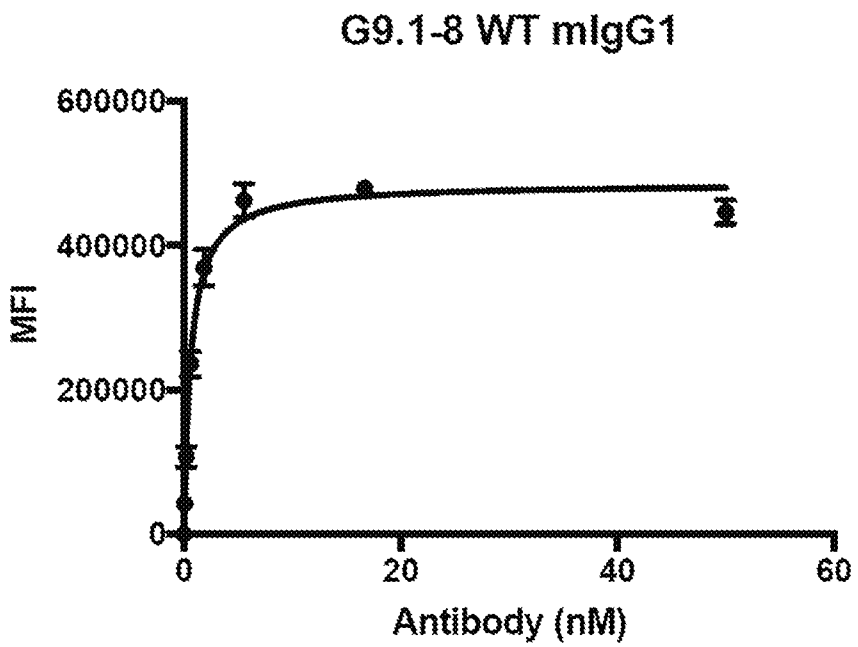


Fig. 22B

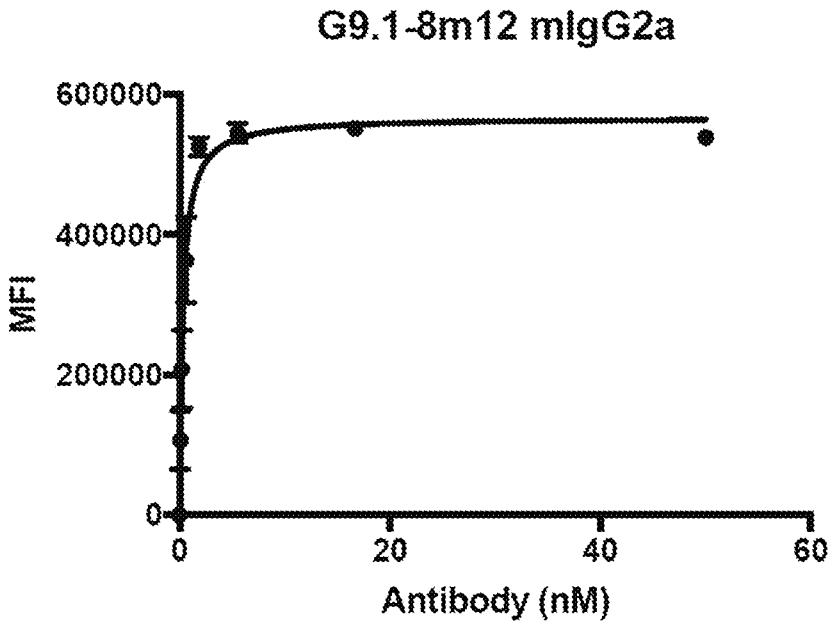


Fig. 22C

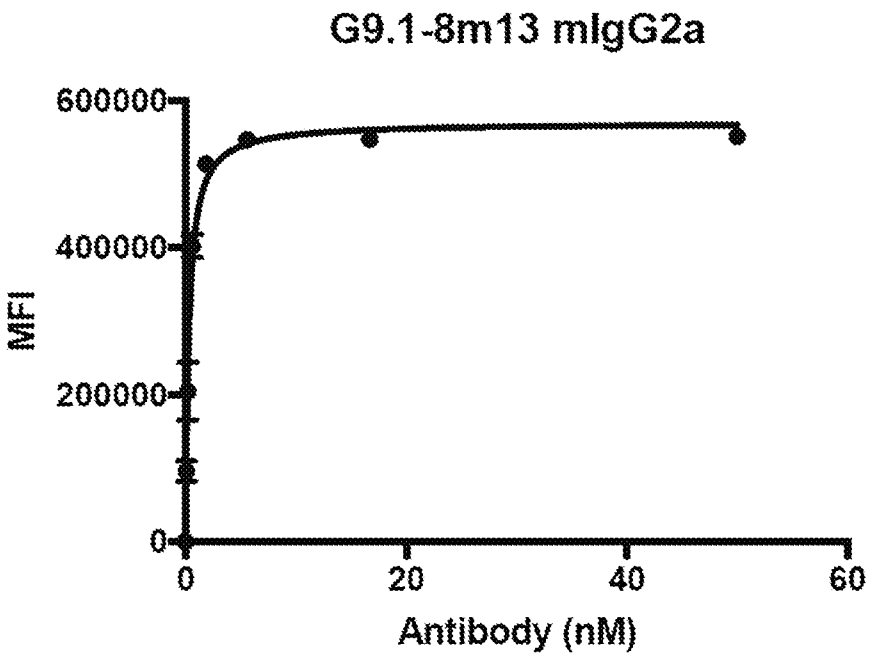


Fig. 22D

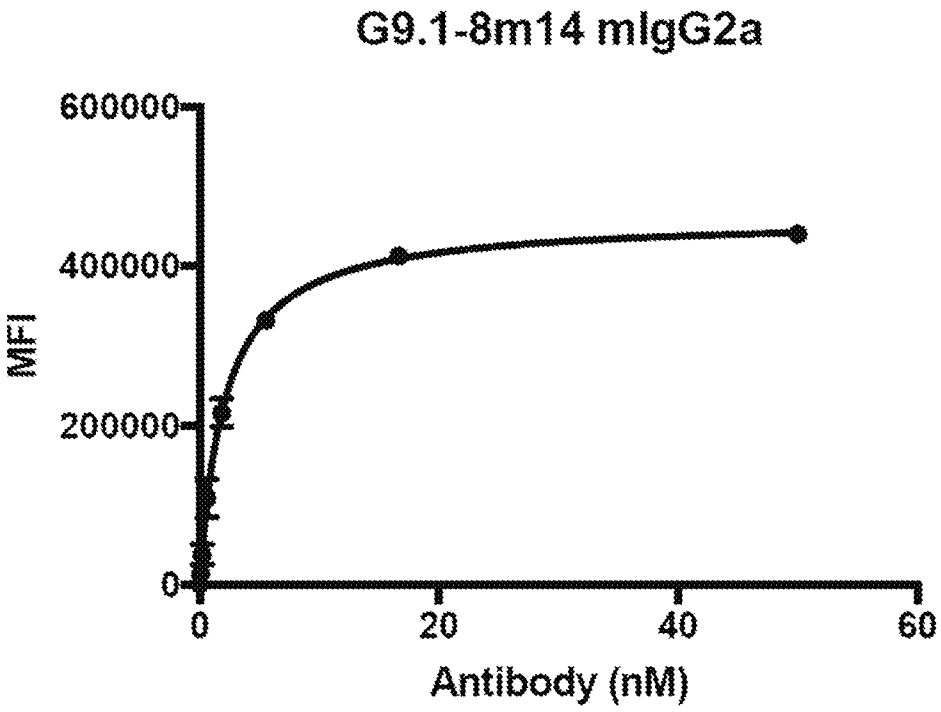


Fig. 23

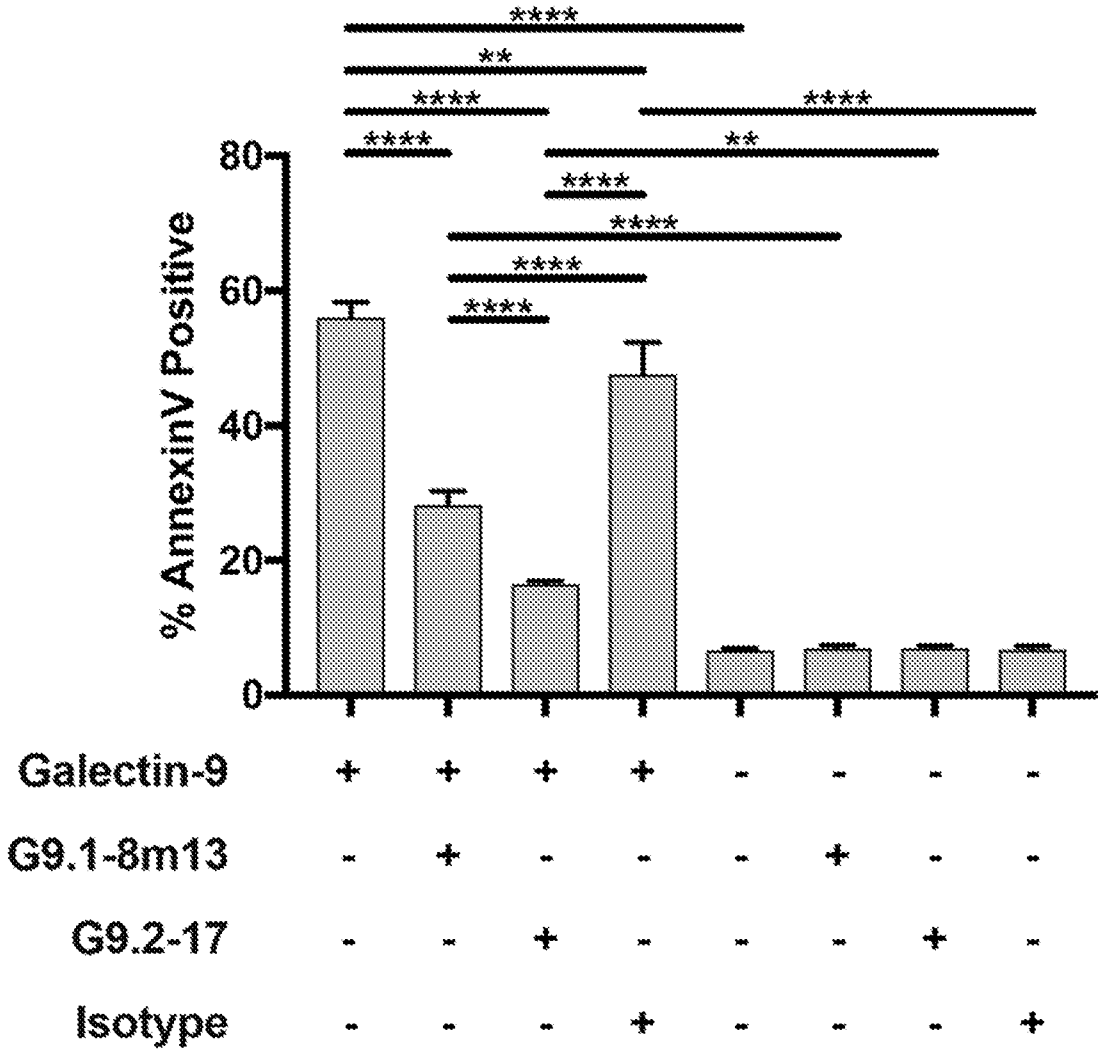

****
**
****
****
****
**
****
****
****
****
80
60
40
20
0
% AnnexinV Positive
Galectin-9 + + + + - - - -
G9.1-8m13 - + - - - + - -
G9.2-17 - - + - - - + -
Isotype - - - + - - - +

Fig. 24

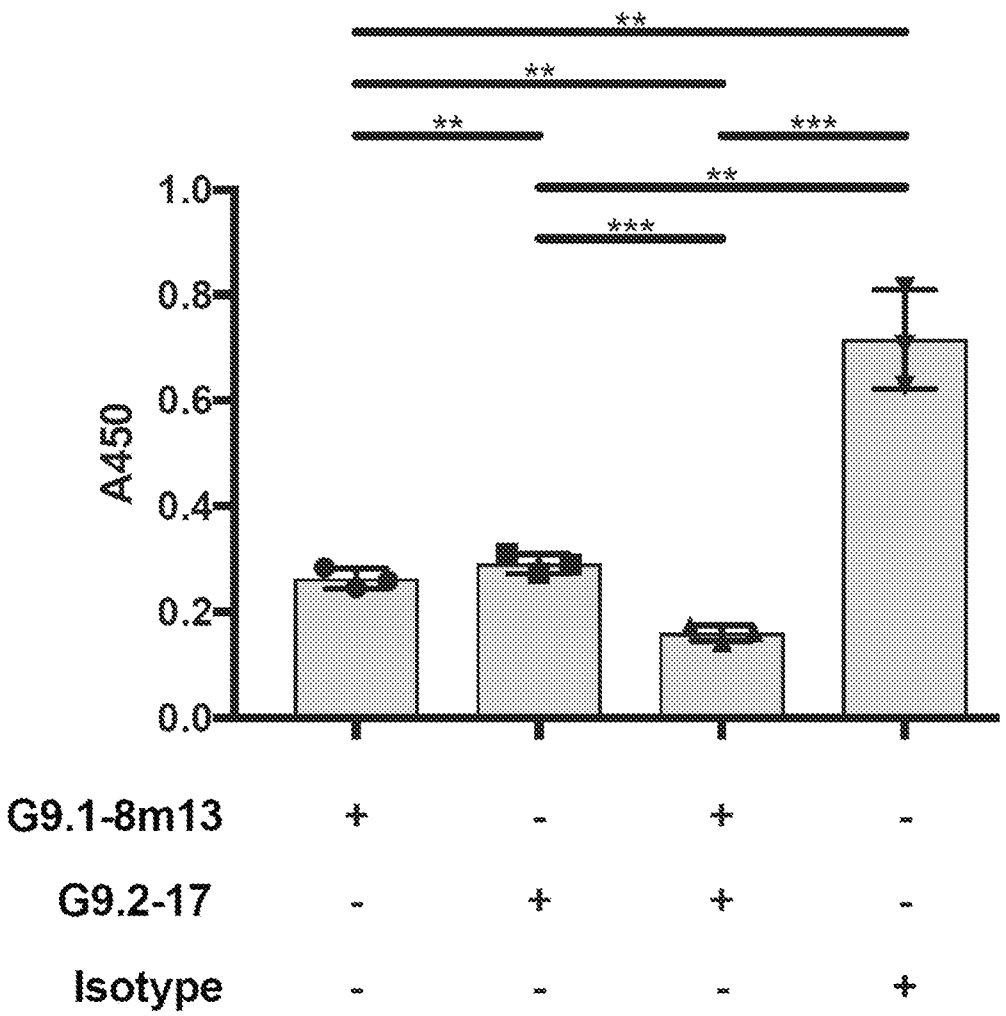


Fig. 25

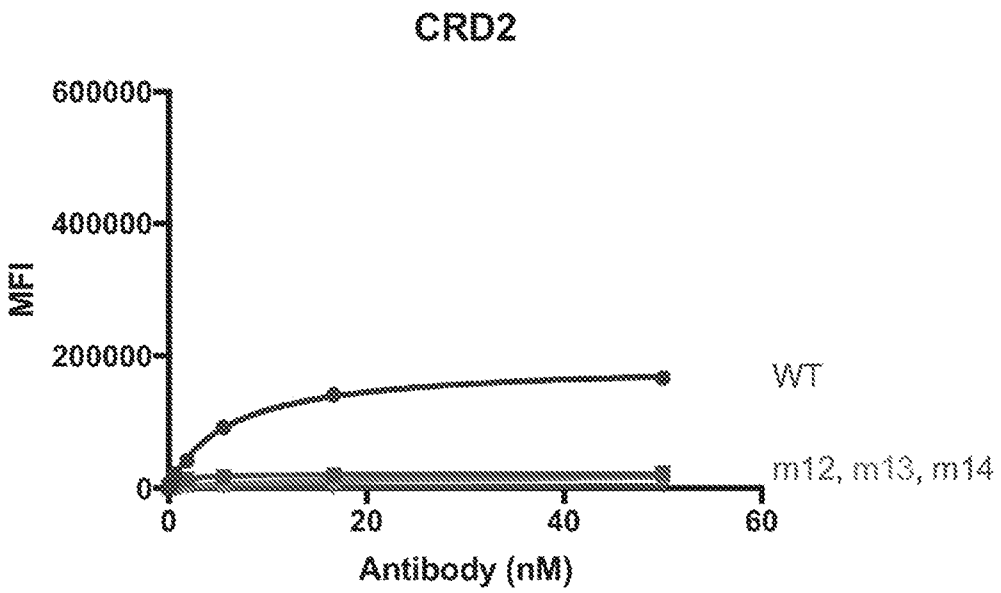

CRD2
600000
400000
200000
0
MFI
WT
m12, m13, m14
0
20
40
60
Antibody (nM)

Fig. 26A

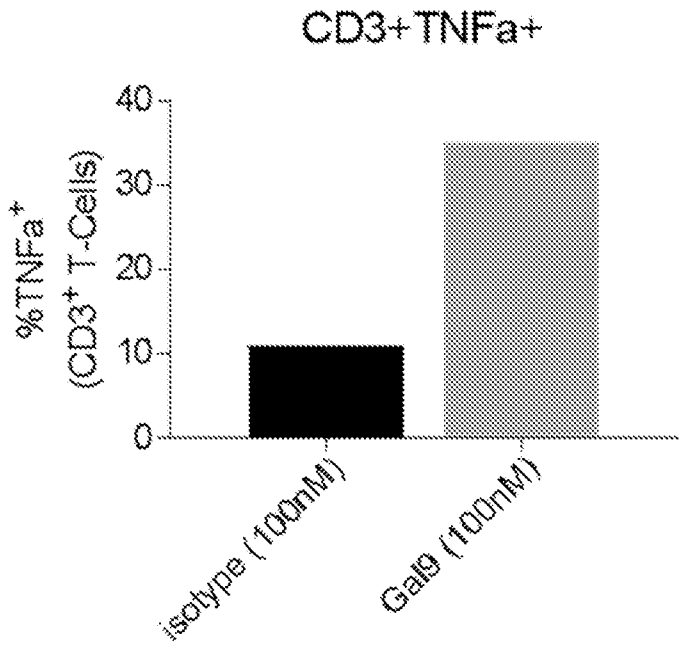


Fig. 26B

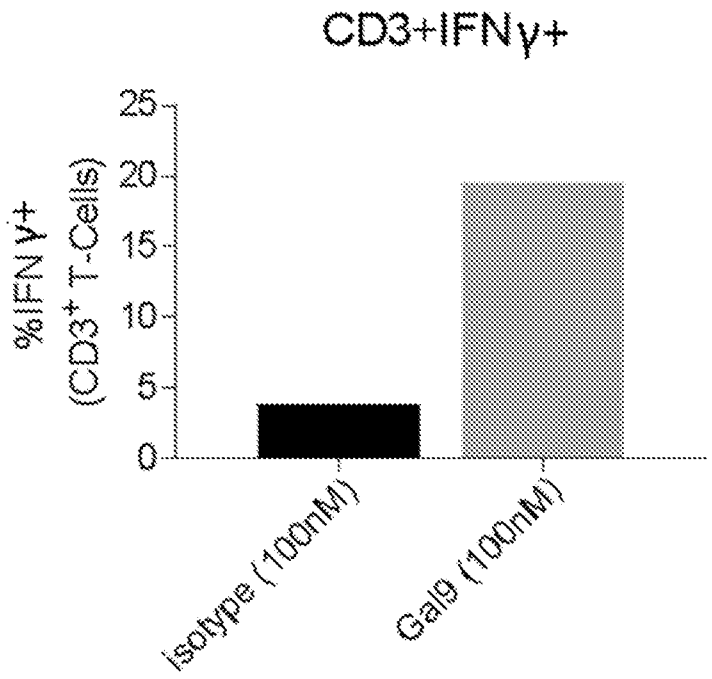


Fig. 27A

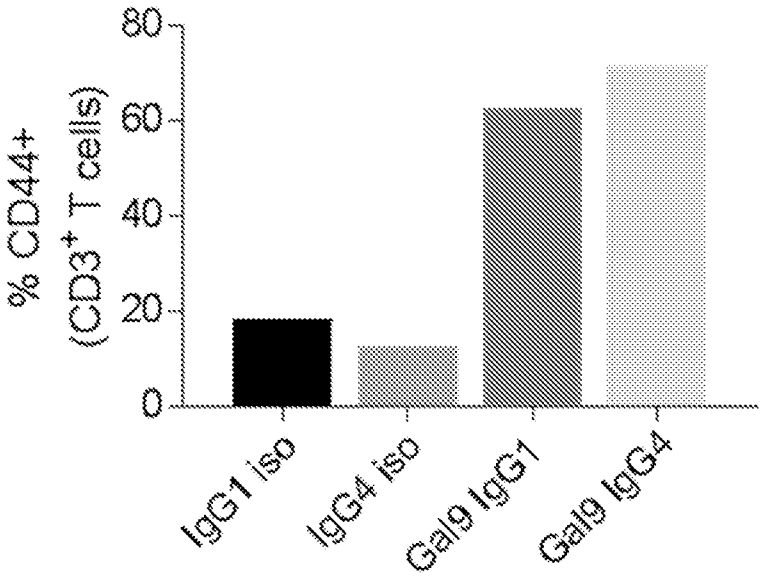


Fig. 27B

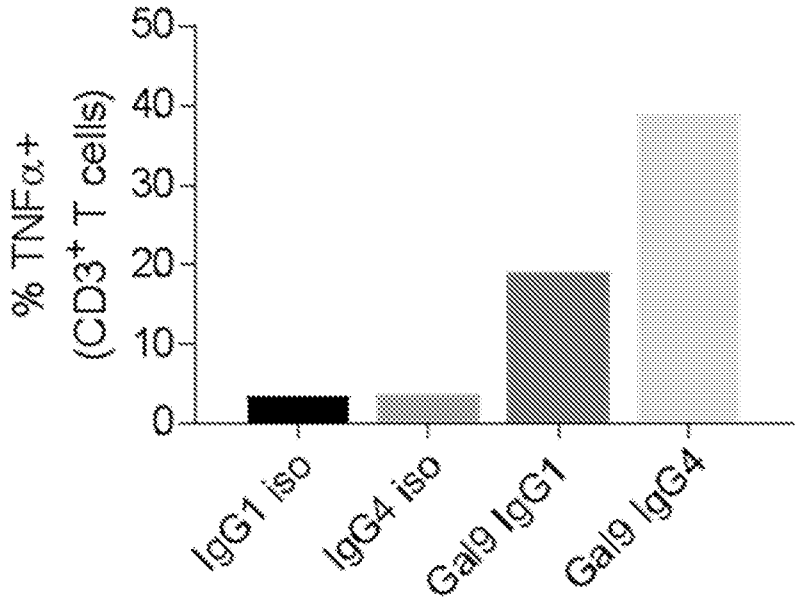


Fig. 27C

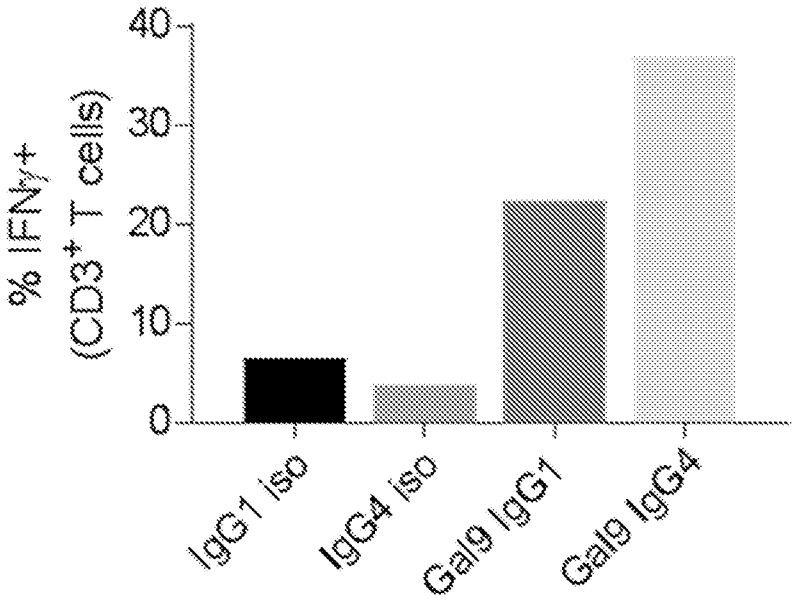

% IFNγ+ (CD3+ T cells)
40
30
20
10
0
IgG1 iso
IgG4 iso
Gal9 IgG1
Gal9 IgG4

Fig. 28A

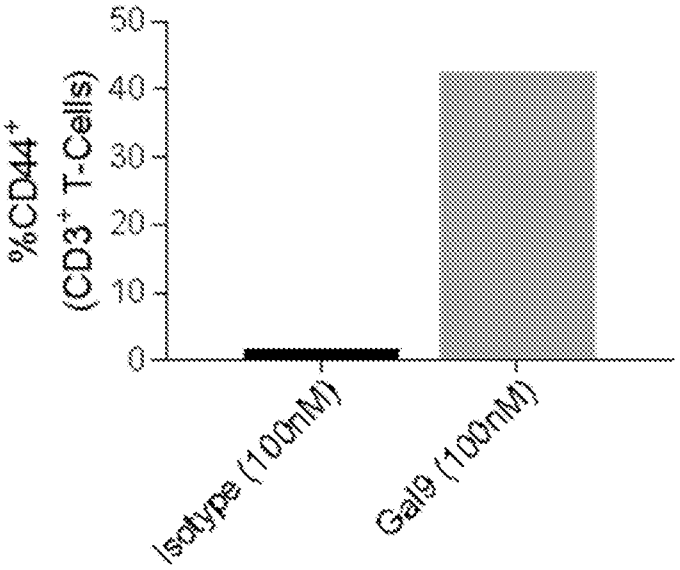


Fig. 28B

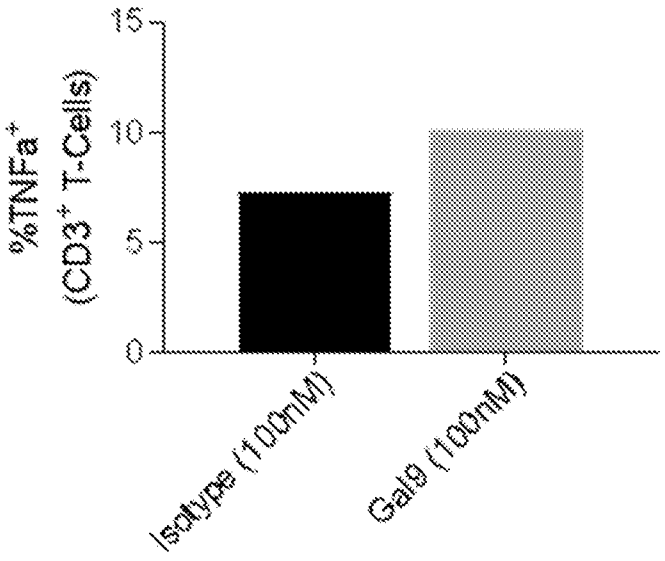


Fig. 28C

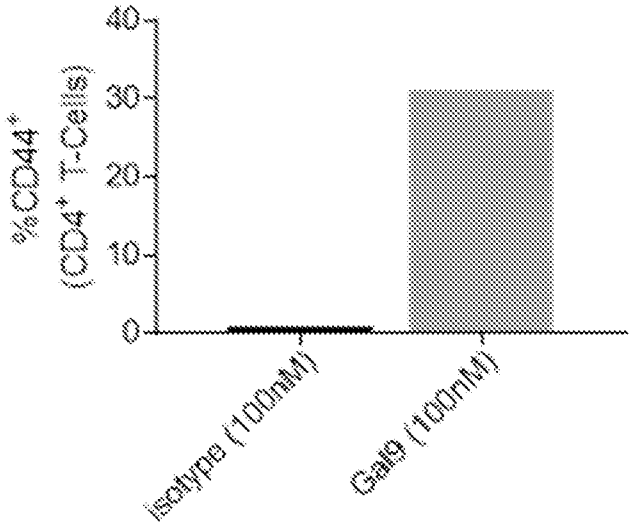


Fig. 28D

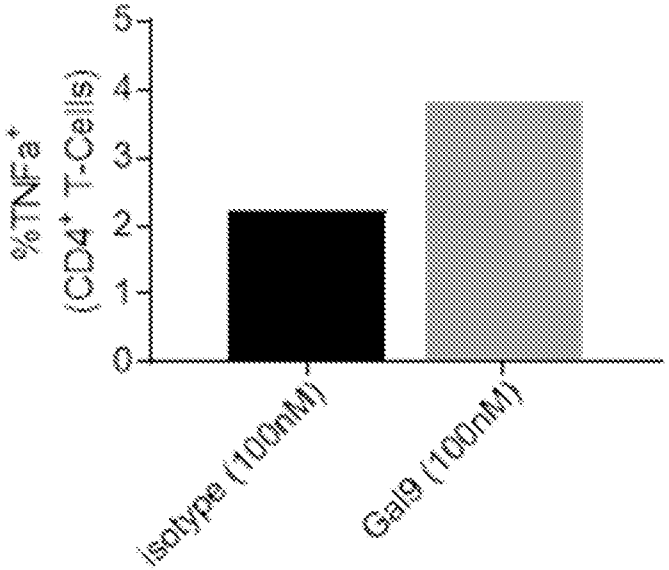


Fig. 28E

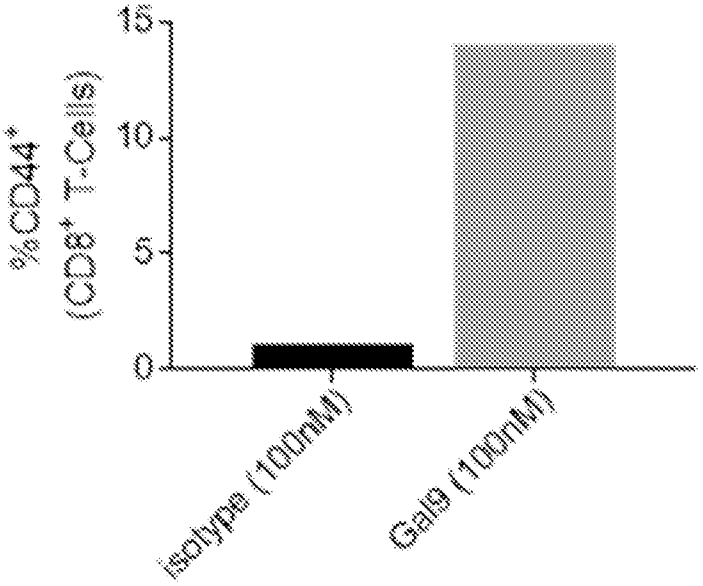


Fig. 28F

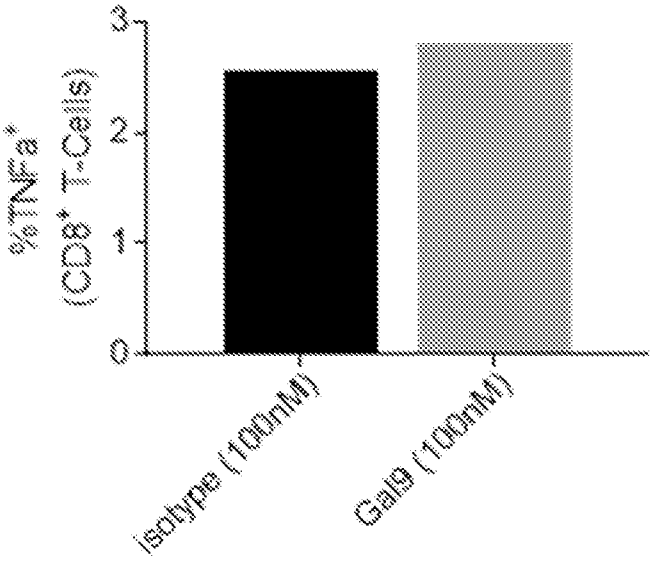


Fig. 29A

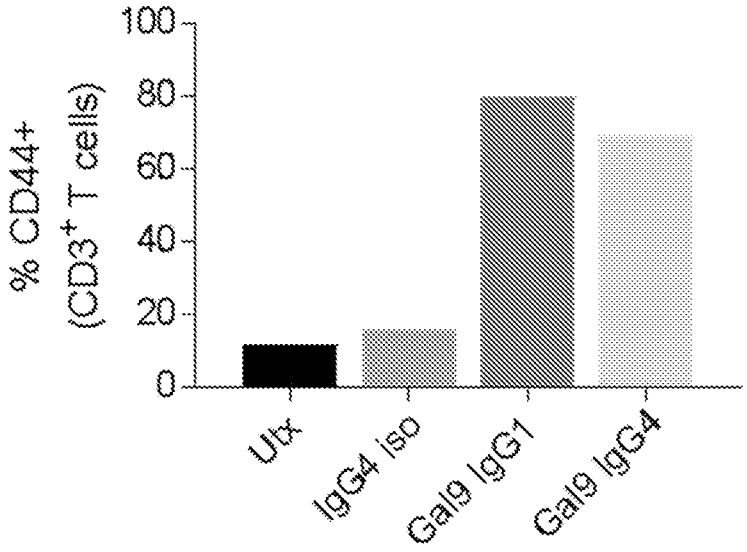


Fig. 29B

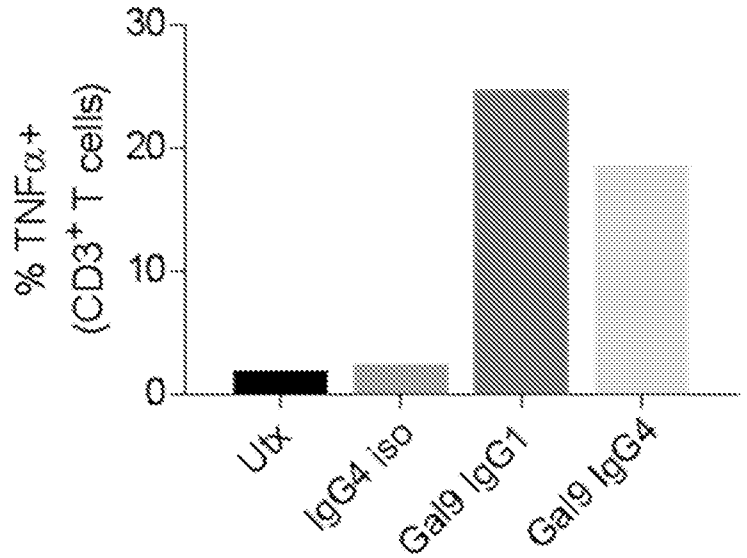


Fig. 29C

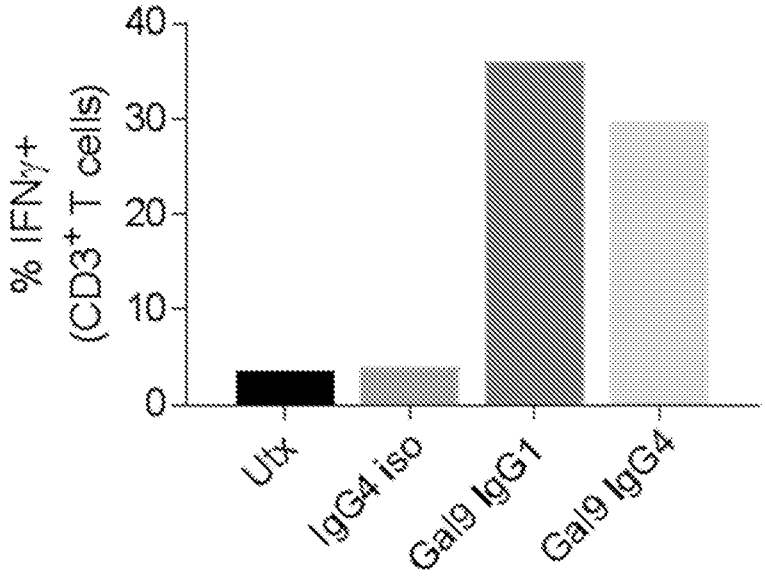


Fig. 30

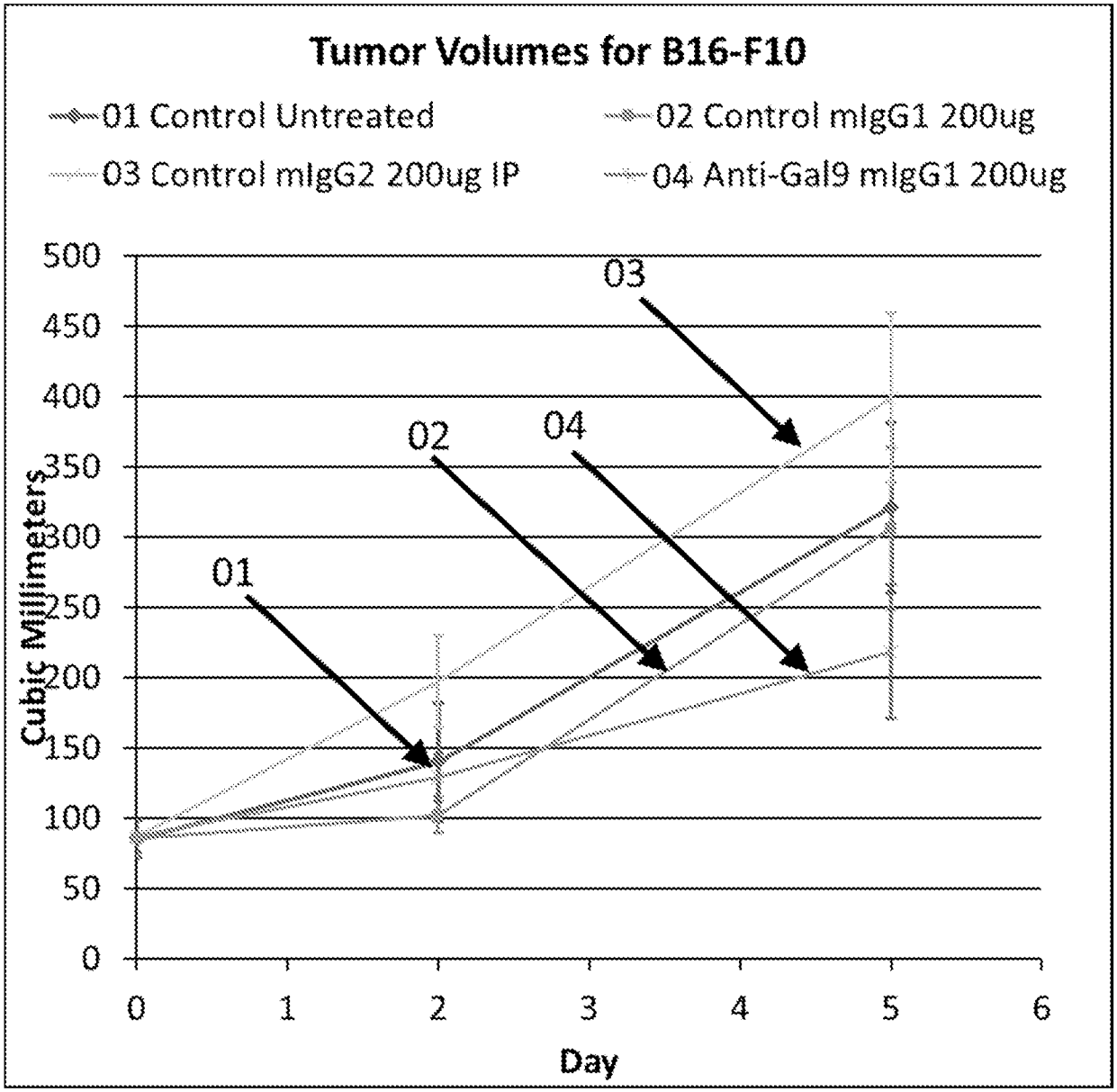

Tumor Volumes for B16-F10
01 Control Untreated
02 Control mIgG1 200ug
03 Control mIgG2 200ug IP
04 Anti-Gal9 mIgG1 200ug
Cubic Millimeters
500
450
400
350
300
250
200
150
100
50
0
0
1
2
3
4
5
6
Day
01
02
03
04

Fig. 31

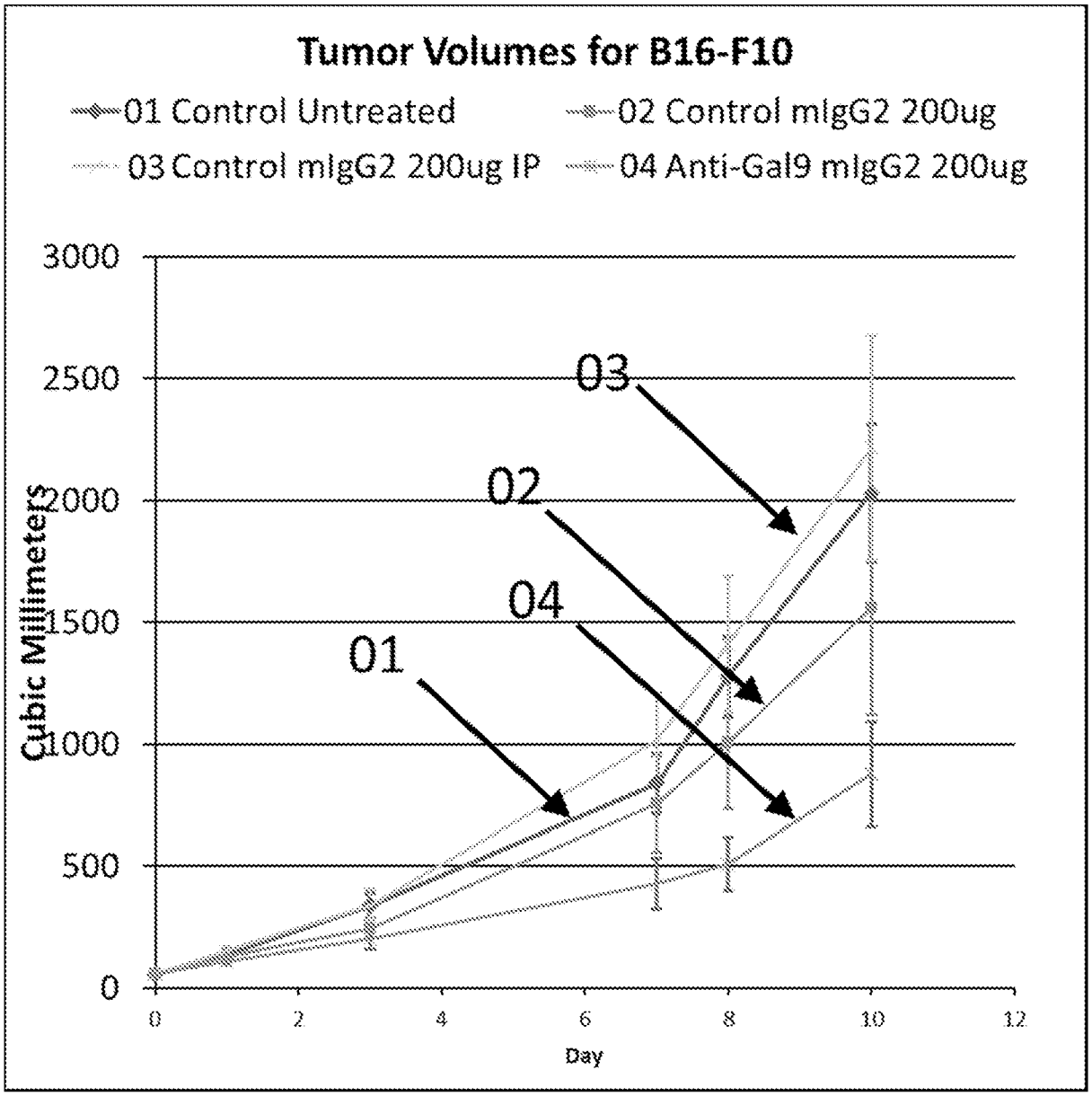

Tumor Volumes for B16-F10
01 Control Untreated
02 Control mIgG2 200ug
03 Control mIgG2 200ug IP
04 Anti-Gal9 mIgG2 200ug
Cubic Millimeters
3000
2500
2000
1500
1000
500
0
0
2
4
6
8
10
12
Day
03
02
04
01

Fig. 32

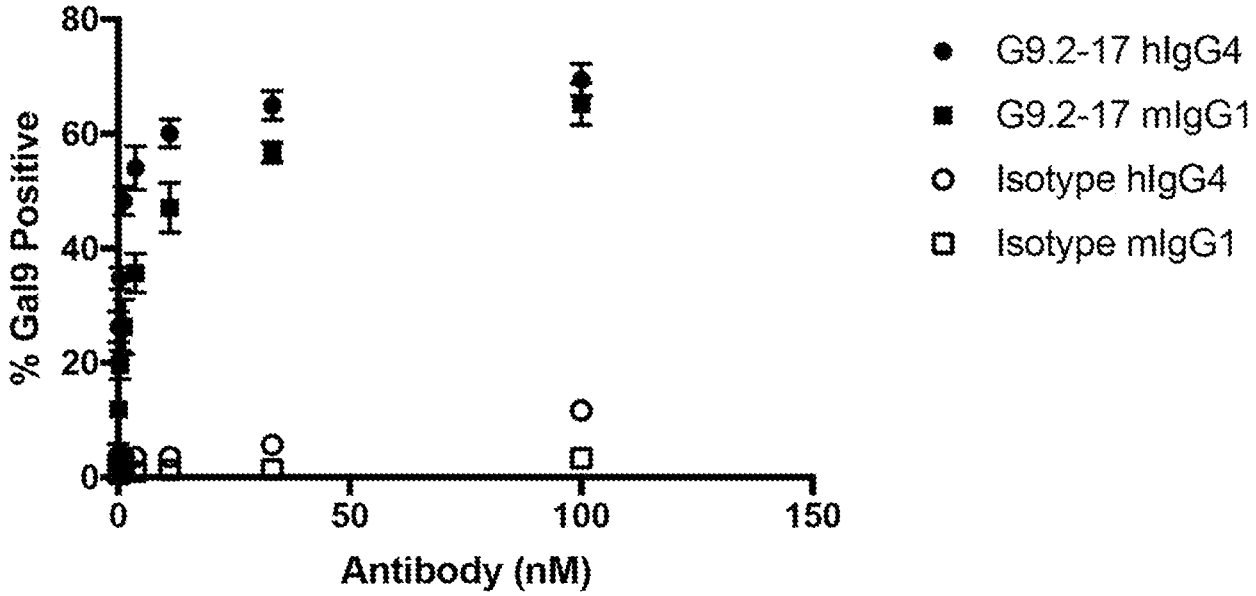

80
60
40
20
0
% Gal9 Positive
0
50
100
150
Antibody (nM)
G9.2-17 hIgG4
G9.2-17 mIgG1
Isotype hIgG4
Isotype mIgG1

Fig. 33A

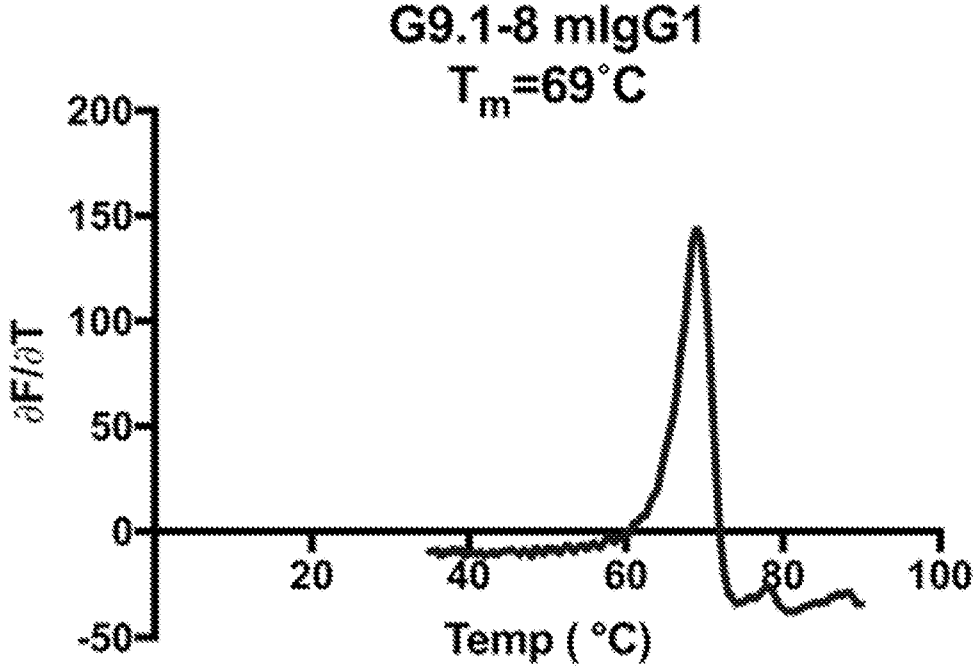


Fig. 33B