ANTIBODIES THAT BIND TO INTEGRIN ALPHA11 AND USES THEREOF

Related Applications

This Patent Cooperation Treaty application claims the benefit of priority of United States Provisional Application No. 63/380,668 filed on October 24, 2022, which is incorporated herein by reference in its entirety.

Background

Interactions between cells and their extracellular microenvironment are primarily mediated by a family of cell surface receptors known as integrins, which are recognized as key molecules involved in myofibroblast differentiation. Integrins are heterodimeric transmembrane receptors composed of α and β subunits that can combine to form 24 different integrin heterodimers. Integrins regulate cytoskeletal dynamics, thereby influencing a number of crucial cellular processes, for example, cell adhesion, migration and differentiation. Integrins also have a key role in the activation of growth factors such as transforming growth factor beta (TGFβ). Integrin alpha chain α11 (ITGA11) interacts with integrin beta chain β1 to form the α11β1 heterodimer. α11β1 preferentially binds to type I collagen and has been shown to be expressed on cultured embryonic fibroblasts, cardiac fibroblasts and in activated liver, lung and renal myofibroblasts. α11β1 has been shown to be upregulated by TGFβ and regulates embryonic mesenchymal cell differentiation on the collagen matrix. α11β1 has also been implicated in inducing tumor growth and the metastatic potential of small-cell lung carcinoma cells. ITGA11 is overexpressed in fibrotic disease tissues, including the lungs of IPF patients and the kidney of patients with chronic allograft nephropathy Accordingly, ITGA11 is a target for therapeutic intervention and there is a need for therapeutic modalities that bind to ITGA11.

Summary

The present disclosure describes antibodies or antigen-binding fragments thereof that bind specifically to integrin α11 (ITGA11). The disclosure also describes methods for treating an ITGA11-associated disorder in a subject, such as a fibrotic disorder, an inflammatory disorder, or a cancer. Also described in the disclosure are related pharmaceutical compositions, polynucleotides, vectors, host cells, methods of production, methods of treatment, diagnostic methods, and kits.

In one aspect, the disclosure describes an antibody or an antigen-binding fragment thereof that binds specifically to integrin α11 (ITGA11), wherein the antibody or antigen-binding fragment thereof includes:

a complementarity-determining region (CDR) heavy chain 1 (CDR-H1) including the amino acid sequence of GFTFSSYA (SEQ ID NO: 1), GFTFSNAW (SEQ ID NO: 9), GFTFSSYS (SEQ ID NO: 14), GYTFTDYY (SEQ ID NO: 28), GFTFSDYW (SEQ ID NO: 36), or GFMFDTHA (SEQ ID NO: 46);

a complementarity-determining region (CDR) heavy chain 2 (CDR-H2) including the amino acid sequence of ISGSGGST (SEQ ID NO: 2), ISSSSSTI (SEQ ID NO: 15), FDPEDGET (SEQ ID NO: 29), or ISGSGGSI (SEQ ID NO: 74);

a complementarity-determining region (CDR) heavy chain 3 (CDR-H3) including the amino acid sequence of AKDLLWAARDAFDI (SEQ ID NO: 37),AKDLDWSGHDAFDI (SEQ ID NO: 3), ARDRGYSYSETSNDAFDI (SEQ ID NO: 10), ARGPDLSDYFDY (SEQ ID NO: 16), AKDPRGSGRDDAFDI (SEQ ID NO: 20), AKDPTTMTTDAFDI (SEQ ID NO: 25), ATLDYRGVVYFDY (SEQ ID NO: 30), AKQTVTSADDYFDY (SEQ ID NO: 43), ARSGETAGTDYFDY (SEQ ID NO: 48);

a complementarity-determining region (CDR) light chain 1 (CDR-L1) including the amino acid sequence of QGINDF (SEQ ID NO: 40),QSISSY (SEQ ID NO: 4), QTIGSY (SEQ ID NO: 21), SGSIASNY (SEQ ID NO: 31), QSVSSSY (SEQ ID NO: 49);

a complementarity-determining region (CDR) light chain 2 (CDR-L2) including the amino acid sequence of AAS (SEQ ID NO: 5), GAS (SEQ ID NO: 22), or EDK (SEQ ID NO: 32); and

a complementarity-determining region (CDR) light chain 3 (CDR-L3) including the amino acid sequence of QQSYSTPLT (SEQ ID NO: 17), QQTYSTPLT (SEQ ID NO: 6), QQSYSTPFT (SEQ ID NO: 11), QSYDSSNHWV (SEQ ID NO: 33), or QQDYNSPYT (SEQ ID NO: 50).

In some examples, the antibody or antigen-binding fragment includes a CDR-H1 including the amino acid sequence of GFTFSSYA (SEQ ID NO: 1).

In some examples, the antibody or antigen-binding fragment includes a CDR-H2 including the amino acid sequence of ISGSGGST (SEQ ID NO: 2).

In some examples, the antibody or antigen-binding fragment includes a CDR-L1 including the amino acid sequence of QSISSY (SEQ ID NO: 4).

In some examples, the antibody or antigen-binding fragment includes a CDR-L2 including the amino acid sequence of AAS (SEQ ID NO: 5).

In some examples, the antibody or antigen-binding fragment includes a CDR-L3 including the amino acid sequence of QQSYSTPFT (SEQ ID NO: 11).

In some examples, the antibody or antigen-binding fragment thereof includes: a CDR-H1 including the amino acid sequence of GFTFSSYA (SEQ ID NO: 1); a CDR-H2 including the amino acid sequence of ISGSGGST (SEQ ID NO: 2); a CDR-H3 including the amino acid sequence of AKDLDWSGHDAFDI (SEQ ID NO: 3); a CDR-L1 including the amino acid sequence of QSISSY (SEQ ID NO: 4); a CDR-L2 including the amino acid sequence of AAS (SEQ ID NO: 5); and a CDR-L3 including the amino acid sequence of QQTYSTPLT (SEQ ID NO: 6). In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 7; and a light chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 8. In some examples, the antibody or antigen-binding fragment thereof includes: a

heavy chain variable domain including the amino acid sequence of SEQ ID NO: 7; and a light chain variable domain including the amino acid sequence of SEQ ID NO: 8.

In some examples, the antibody or antigen-binding fragment thereof includes: a CDR-H1 including the amino acid sequence of GFTFSNAW (SEQ ID NO: 9); a CDR-H2 including the amino acid sequence of ISGSGGST (SEQ ID NO: 2); a CDR-H3 including the amino acid sequence of ARDRGYSYSETSNDAFDI (SEQ ID NO: 10); a CDR-L1 including the amino acid sequence of QSISSY (SEQ ID NO: 4); a CDR-L2 including the amino acid sequence of AAS (SEQ ID NO: 5); and a CDR-L3 including the amino acid sequence of QQSYSTPFT (SEQ ID NO: 11). In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 12; and a light chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 13. In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including the amino acid sequence of SEQ ID NO: 12; and a light chain variable domain including the amino acid sequence of SEQ ID NO: 13.

In some examples, the antibody or antigen-binding fragment thereof includes: a CDR-H1 including the amino acid sequence of GFTFSSYS (SEQ ID NO: 14); a CDR-H2 including the amino acid sequence of ISSSSSTI (SEQ ID NO: 15); a CDR-H3 including the amino acid sequence of ARGPDLSDYFDY (SEQ ID NO: 16); a CDR-L1 including the amino acid sequence of QSISSY (SEQ ID NO: 4); a CDR-L2 including the amino acid sequence of AAS (SEQ ID NO: 5); and a CDR-L3 including the amino acid sequence of QQSYSTPLT (SEQ ID NO: 17). In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 12; and a light chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 13. In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including the amino acid sequence of SEQ ID NO: 12; and a light chain variable domain including the amino acid sequence of SEQ ID NO: 13.

In some examples, the antibody or antigen-binding fragment thereof includes: a CDR-H1 including the amino acid sequence of GFTFSSYA (SEQ ID NO: 1); a CDR-H2 including the amino acid sequence of ISGSGGST (SEQ ID NO: 2); a CDR-H3 including the amino acid sequence of AKDPRGSGRDDAFDI (SEQ ID NO: 20); a CDR-L1 including the amino acid sequence of QTIGSY (SEQ ID NO: 21); a CDR-L2 including the amino acid sequence of GAS (SEQ ID NO: 22); and a CDR-L3 including the amino acid sequence of QQSYSTPFT (SEQ ID NO: 11). In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 23; and a light chain variable domain including an amino acid

sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 24. In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including the amino acid sequence of SEQ ID NO: 23; and a light chain variable domain including the amino acid sequence of SEQ ID NO: 24.

In some examples, the antibody or antigen-binding fragment thereof includes: a CDR-H1 including the amino acid sequence of GFTFSSYA (SEQ ID NO: 1); a CDR-H2 including the amino acid sequence of ISGSGGST (SEQ ID NO: 2); a CDR-H3 including the amino acid sequence of AKDPTTMTTDAFDI (SEQ ID NO: 25); a CDR-L1 including the amino acid sequence of QSISSY (SEQ ID NO: 4); a CDR-L2 including the amino acid sequence of AAS (SEQ ID NO: 5); and a CDR-L3 including the amino acid sequence of QQSYSTPFT (SEQ ID NO: 11). In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 26; and a light chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 27. In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including the amino acid sequence of SEQ ID NO: 26; and a light chain variable domain including the amino acid sequence of SEQ ID NO: 27.

In some examples, the antibody or antigen-binding fragment thereof includes: a CDR-H1 including the amino acid sequence of GYTFTDYY (SEQ ID NO: 28); a CDR-H2 including the amino acid sequence of FDPEDGET (SEQ ID NO: 29); a CDR-H3 including the amino acid sequence of ATLDYRGVVYFDY (SEQ ID NO: 30); a CDR-L1 including the amino acid sequence of SGSIASNY (SEQ ID NO: 31); a CDR-L2 including the amino acid sequence of EDK (SEQ ID NO: 32); and a CDR-L3 including the amino acid sequence of QSYDSSNHWV (SEQ ID NO: 33). In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 34; and a light chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 35. In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including the amino acid sequence of SEQ ID NO: 34; and a light chain variable domain including the amino acid sequence of SEQ ID NO: 35.

In some examples, the antibody or antigen-binding fragment thereof includes: a CDR-H1 including the amino acid sequence of GFTFSDYW (SEQ ID NO: 36); a CDR-H2 including the amino acid sequence of ISGSGGST (SEQ ID NO: 2); a CDR-H3 including the amino acid sequence of AKDLLWAARDAFDI (SEQ ID NO: 37); a CDR-L1 including the amino acid sequence of QSISSY (SEQ ID NO: 4); a CDR-L2 including the amino acid sequence of AAS (SEQ ID NO: 5); and a CDR-L3 including the amino acid sequence of QQSYSTPFT (SEQ ID NO: 11). In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including an amino acid

sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 38; and a light chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 39. In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including the amino acid sequence of SEQ ID NO: 38; and a light chain variable domain including the amino acid sequence of SEQ ID NO: 39.

In some examples, the antibody or antigen-binding fragment thereof includes: a CDR-H1 including the amino acid sequence of GFTFSSYA (SEQ ID NO: 1); a CDR-H2 including the amino acid sequence of ISGSGGST (SEQ ID NO: 2); a CDR-H3 including the amino acid sequence of AKDLLWAARDAFDI (SEQ ID NO: 37); a CDR-L1 including the amino acid sequence of QGINDF (SEQ ID NO: 40); a CDR-L2 including the amino acid sequence of AAS (SEQ ID NO: 5); and a CDR-L3 including the amino acid sequence of QQSYSTPLT (SEQ ID NO: 17). In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 41; and a light chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 42. In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including the amino acid sequence of SEQ ID NO: 41; and a light chain variable domain including the amino acid sequence of SEQ ID NO: 42.

In some examples, the antibody or antigen-binding fragment thereof includes: a CDR-H1 including the amino acid sequence of GFTFSNAW (SEQ ID NO: 9); a CDR-H2 including the amino acid sequence of ISGSGGST (SEQ ID NO: 2); a CDR-H3 including the amino acid sequence of AKQTVTSADDYFDY (SEQ ID NO: 43); a CDR-L1 including the amino acid sequence of QSISSY (SEQ ID NO: 4); a CDR-L2 including the amino acid sequence of AAS (SEQ ID NO: 5); and a CDR-L3 including the amino acid sequence of QQSYSTPFT (SEQ ID NO: 11). In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 44; and a light chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 45. In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including the amino acid sequence of SEQ ID NO: 44; and a light chain variable domain including the amino acid sequence of SEQ ID NO: 45.

In some examples, the antibody or antigen-binding fragment thereof includes: a CDR-H1 including the amino acid sequence of GFMFDTHA (SEQ ID NO: 46); a CDR-H2 including the amino acid sequence of ISGSGGSI (SEQ ID NO: 47); a CDR-H3 including the amino acid sequence of ARSGETAGTDYFDY (SEQ ID NO: 48); a CDR-L1 including the amino acid sequence of QSVSSSY (SEQ ID NO: 49); a CDR-L2 including the amino acid sequence of GAS (SEQ ID NO: 22); and a CDR-L3

including the amino acid sequence of QQDYNSPYT (SEQ ID NO: 50). In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 51; and a light chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, or 99%) sequence identity to the amino acid sequence of SEQ ID NO: 52. In some examples, the antibody or antigen-binding fragment thereof includes: a heavy chain variable domain including the amino acid sequence of SEQ ID NO: 51; and a light chain variable domain including the amino acid sequence of SEQ ID NO: 52.

In some examples, the antibody or antigen-binding fragment thereof includes a heavy chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, 99%, or 100%) sequence identity to the amino acid sequence of any one of SEQ ID NOs: 7, 12, 18, 23, 26, 34, 38, 41, 44, or 51.

In some examples, the antibody or antigen-binding fragment thereof includes a light chain variable domain including an amino acid sequence with at least 90% (e.g., at least 95%, 96%, 97%, 98%, 99%, or 100%) sequence identity to the amino acid sequence of any one of SEQ ID NOs: 8, 13, 19, 24, 35, 39, 42, 45, or 52.

In some examples, the antibody or antigen-binding fragment thereof is selected from the group consisting of a monoclonal antibody or antigen-binding fragment thereof, a polyclonal antibody or antigen-binding fragment thereof, a human antibody or antigen-binding fragment thereof, a humanized antibody or antigen-binding fragment thereof, a primatized antibody or antigen-binding fragment thereof, a bispecific antibody or antigen-binding fragment thereof, a multi-specific antibody or antigen-binding fragment thereof, a dual-variable immunoglobulin domain, a monovalent antibody or antigen-binding fragment thereof, a chimeric antibody or antigen-binding fragment thereof, a single-chain Fv molecule (scFv), a diabody, a triabody, a nanobody, an antibody-like protein scaffold, a domain antibody, a Fv fragment, a Fab fragment, a F(ab')2 molecule, and a tandem scFv (taFv).

In some examples, the antibody or antigen-binding fragment thereof is a human, humanized, or chimeric antibody or antigen-binding fragment thereof.

In some examples, the antibody or antigen-binding fragment thereof binds specifically to a heterodimer of ITGA11 and integrin β1 (ITGA11B1).

In another aspect, the disclosure describes a polynucleotide encoding any antibody or antigen-binding fragment thereof described herein.

In another aspect, the disclosure describes a vector including a polynucleotide described herein (e.g., a polynucleotide encoding any antibody or antigen-binding fragment thereof described herein). In some examples, the vector is an expression vector (e.g., eukaryotic expression vector or a viral vector, such as a viral vector selected from the group consisting of adenovirus (Ad), retrovirus, poxvirus, adeno-associated virus, baculovirus, herpes simplex virus, and a vaccinia virus).

In another aspect, the disclosure describes a host cell including a vector described herein. In some examples, the host cell expresses an antibody or antigen-binding fragment thereof described herein.

In another aspect, the disclosure describes a pharmaceutical composition including an antibody or antigen-binding fragment thereof described herein, a polynucleotide described herein, a vector described herein, or a host cell described herein, and a pharmaceutically acceptable carrier or excipient.

In another aspect, the disclosure describes a kit including an agent selected from an antibody or antigen-binding fragment thereof described herein, a polynucleotide described herein, a vector described herein, or a host cell described herein, or a pharmaceutical composition described herein.

In another example, the disclosure describes a method of treating a subject having or at risk of developing a disorder, the method including administering to the subject an antibody or antigen-binding fragment thereof described herein, a polynucleotide described herein, a vector described herein, or a host cell described herein, or a pharmaceutical composition described herein. In another aspect, the disclosure describes use of an antibody or antigen-binding fragment thereof described herein, a polynucleotide described herein, a vector described herein, or a host cell described herein, or a pharmaceutical composition described herein in the manufacture of a medicament for treating a subject having or at risk of developing a disorder.

In some examples, the disorder is a fibrotic disorder. In some examples, the fibrotic disorder is selected from hepatic fibrosis (e.g., fibrosis associated with cirrhosis (e.g., alcohol-induced cirrhosis, viral-induced cirrhosis, post-hepatitis C cirrhosis, and primary biliary cirrhosis), schistosomiasis, cholangitis (e.g., sclerosing cholangitis), and autoimmune-induced hepatitis), kidney fibrosis (e.g., tubulointerstitial fibrosis, scleroderma, diabetic nephritis, and glomerular nephritis), dermal fibrosis (e.g., scleroderma, hypertrophic and keloid scarring, nephrogenic fibrosing dermatopathy, and burns), myelofibrosis, neurofibromatosis, fibroma, intestinal fibrosis, and fibrotic adhesions resulting from surgical procedures), heart fibrosis (e.g., fibrosis associated with myocardial infarction), vascular fibrosis (e.g., fibrosis associated with postangioplasty arterial restenosis and atherosclerosis), ocular fibrosis (e.g., fibrosis associated with post-cataract surgery, proliferative vitreoretinopathy, and retro-orbital fibrosis), bone marrow fibrosis (e.g., idiopathic myelofibrosis and drug-induced myelofibrosis), pulmonary fibrosis (e.g., pulmonary interstitial fibrosis), glomerulonephritis, heart failure (ischemic and non-ischemic), scleroderma, excessive scar tissue post-surgery or device insertion, trauma or burns, progressive kidney disease, valvular heart disease, hypertensive heart disease, articular and periarticular fibrosis, myelofibrosis, ocular/vitreous fibrosis, intestinal fibrosis and stricture, peritoneal and retro-peritoneal fibrosis, pancreatic fibrosis, nephrogenic systemic fibrosis, primary sclerosing cholangitis, and the elaboration of pathological matrix also has a role in fibroproliferative tumor progression and metastasis.

In some examples, the disorder is an inflammatory disorder. In some examples, the inflammatory disorder is selected from asthma (e.g., allergic asthma, exercise-induced asthma, aspirin sensitive/exacerbated asthma, atopic asthma, severe asthma, mild asthma, moderate to severe asthma, corticosteroid naïve asthma, chronic asthma, corticosteroid resistant asthma, corticosteroid refractory asthma, newly diagnosed and untreated asthma, asthma due to smoking, asthma uncontrolled on corticosteroids, and the like), airway inflammation, airway hyperreactivity, airway hyperresponsiveness, rhinosinusitis, rhinosinusitis with polyps, nasal polyposis, arthritis (e.g., osteoarthritis, rheumatoid arthritis,

collagen-induced arthritis, arthritic joints as a result of injury, etc.), eosinophilic inflammation, mast cell-mediated inflammatory diseases, sepsis, septic shock, seronegative enthesopathy and arthropathy (SEA) syndrome, osteoporosis, eosinophilic esophagitis, scleroderma, dermatitis, atopic dermatitis, allergic rhinitis, bullous pemphigoid, urticaria (e.g., chronic urticaria), cartilage inflammation, polymyalgia rheumatic, polyarteritis nodossa, Wegener's granulomatosis, Behcet's disease, myolitis, polymyolitis, dermatomyolitis, dermatomyositis, vasculitis, arteritis, diabetic nephropathy, interstitial cystitis, graft versus host disease (GVHD), gastrointestinal inflammatory conditions (e.g., inflammatory bowel disease (IBD), ulcerative colitis (UC), Crohn's disease (CD), colitis (e.g., colitis caused by environmental insults (e.g., caused by or associated with a therapeutic regimen, such as chemotherapy, radiation therapy, and the like), infectious colitis, ischemic colitis, collagenous or lymphocytic colitis, necrotizing enterocolitis, colitis in conditions such as chronic granulomatous disease or celiac disease, food allergies, gastritis, infectious gastritis or enterocolitis (e.g., Helicobacter pylori-infected chronic active gastritis), and other forms of gastrointestinal inflammation caused by an infectious agent), and inflammatory pulmonary conditions (e.g., chronic obstructive pulmonary disease (COPD), eosinophilic pulmonary inflammation, infection-induced pulmonary conditions (including those associated with viral (e.g., influenza, parainfluenza, rotavirus, human metapneumovirus, and respiratory syncytial virus), bacterial, fungal (e.g., Aspergillus), parasitic, or prion infection, allergen-induced pulmonary conditions, pollutant-induced pulmonary conditions (e.g., asbestosis, silicosis, or berylliosis), gastric aspiration-induced pulmonary conditions, immune dysregulation, inflammatory conditions with genetic predisposition such as cystic fibrosis, physical trauma-induced pulmonary conditions (e.g., ventilator injury), emphysema, bronchitis, sarcoidosis, histiocytosis, lymphangiomyomatosis, acute lung injury, acute respiratory distress syndrome, chronic lung disease, bronchopulmonary dysplasia, pneumonia (e.g., community-acquired pneumonia, nosocomial pneumonia, ventilator-associated pneumonia, viral pneumonia, bacterial pneumonia, and severe pneumonia), airway exacerbations, and acute respiratory distress syndrome (ARDS)).

In some examples, the disorder is a cancer. In some examples, the cancer is selected from breast cancer, colorectal cancer, hepatic cancer, kidney cancer, liver cancer, lung cancer, pancreatic cancer, gastrointestinal cancer, melanoma, ovarian cancer, prostate cancer, cervical cancer, bladder cancer, glioblastoma, head and neck cancer, and cholangiocarcinoma.

Definitions

To facilitate the understanding of this disclosure, a number of terms are defined below. Terms defined herein have meanings as commonly understood by a person of ordinary skill in the areas relevant to the disclosure. Terms such as "a", "an," and "the" are not intended to refer to only a singular entity, but include the general class of which a specific example may be used for illustration. The terminology herein is used to describe specific embodiments of the disclosure, but their usage does not limit the disclosure, except as outlined in the claims.

As used herein, the term "about" refers to a value that is no more than 10% above or below the

CLAIMS

1. An antibody or an antigen-binding fragment thereof that binds specifically to integrin α11 (ITGA11), wherein the antibody or antigen-binding fragment thereof comprises:

a complementarity-determining region (CDR) heavy chain 1 (CDR-H1) comprising the amino acid sequence of GFTFSSYA (SEQ ID NO: 1), GFTFSNAW (SEQ ID NO: 9), GFTFSSYS (SEQ ID NO: 14), GYTFTDYY (SEQ ID NO: 28), GFTFSDYW (SEQ ID NO: 36), or GFMFDTHA (SEQ ID NO: 46);

a complementarity-determining region (CDR) heavy chain 2 (CDR-H2) comprising the amino acid sequence of ISGSGGST (SEQ ID NO: 2), ISSSSSTI (SEQ ID NO: 15), FDPEDGET (SEQ ID NO: 29), or ISGSGGSI (SEQ ID NO: 74);

a complementarity-determining region (CDR) heavy chain 3 (CDR-H3) comprising the amino acid sequence of AKDLLWAARDAFDI (SEQ ID NO: 37), AKDLDWSGHDAFDI (SEQ ID NO: 3), ARDRGYSYSETSNDAFDI (SEQ ID NO: 10), ARGPDLSDYFDY (SEQ ID NO: 16), AKDPRGSGRDDAFDI (SEQ ID NO: 20), AKDPTTMTTDAFDI (SEQ ID NO: 25), ATLDYRGVVYFDY (SEQ ID NO: 30), AKQTVTSADDYFDY (SEQ ID NO: 43), ARSGETAGTDYFDY (SEQ ID NO: 48);

a complementarity-determining region (CDR) light chain 1 (CDR-L1) comprising the amino acid sequence of QGINDF (SEQ ID NO: 40), QSISSY (SEQ ID NO: 4), QTIGSY (SEQ ID NO: 21), SGSIASNY (SEQ ID NO: 31), QSVSSSY (SEQ ID NO: 49);

a complementarity-determining region (CDR) light chain 2 (CDR-L2) comprising the amino acid sequence of AAS (SEQ ID NO: 5), GAS (SEQ ID NO: 22), or EDK (SEQ ID NO: 32); and

a complementarity-determining region (CDR) light chain 3 (CDR-L3) comprising the amino acid sequence of QQSYSTPLT (SEQ ID NO: 17), QQTYSTPLT (SEQ ID NO: 6), QQSYSTPFT (SEQ ID NO: 11), QSYDSSNHWV (SEQ ID NO: 33), or QQDYNSPYT (SEQ ID NO: 50).

2. The antibody or antigen-binding fragment thereof of claim 1, comprising:

a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 41; and

a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 42.

3. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

a CDR-H1 comprising the amino acid sequence of GFTFSSYA (SEQ ID NO: 1);

a CDR-H2 comprising the amino acid sequence of ISGSGGST (SEQ ID NO: 2);

a CDR-H3 comprising the amino acid sequence of AKDLLWAARDAFDI (SEQ ID NO: 37);

a CDR-L1 comprising the amino acid sequence of QGINDF (SEQ ID NO: 40);

a CDR-L2 comprising the amino acid sequence of AAS (SEQ ID NO: 5); and

a CDR-L3 comprising the amino acid sequence of QQSYSTPLT (SEQ ID NO: 17).

4. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

a CDR-H1 comprising the amino acid sequence of GFTFSSYA (SEQ ID NO: 1);

a CDR-H2 comprising the amino acid sequence of ISGSGGST (SEQ ID NO: 2);

a CDR-H3 comprising the amino acid sequence of AKDLDWSGHDAFDI (SEQ ID NO: 3);

a CDR-L1 comprising the amino acid sequence of QSISSY (SEQ ID NO: 4);

a CDR-L2 comprising the amino acid sequence of AAS (SEQ ID NO: 5); and

a CDR-L3 comprising the amino acid sequence of QQTYSTPLT (SEQ ID NO: 6).

5. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

a CDR-H1 comprising the amino acid sequence of GFTFSNAW (SEQ ID NO: 9);

a CDR-H2 comprising the amino acid sequence of ISGSGGST (SEQ ID NO: 2);

a CDR-H3 comprising the amino acid sequence of ARDRGYSYSETSNDAFDI (SEQ ID NO: 10);

a CDR-L1 comprising the amino acid sequence of QSISSY (SEQ ID NO: 4);

a CDR-L2 comprising the amino acid sequence of AAS (SEQ ID NO: 5); and

a CDR-L3 comprising the amino acid sequence of QQSYSTPFT (SEQ ID NO: 11).

6. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

a CDR-H1 comprising the amino acid sequence of GFTFSSYS (SEQ ID NO: 14);

a CDR-H2 comprising the amino acid sequence of ISSSSSTI (SEQ ID NO: 15);

a CDR-H3 comprising the amino acid sequence of ARGPDLSDYFDY (SEQ ID NO: 16);

a CDR-L1 comprising the amino acid sequence of QSISSY (SEQ ID NO: 4);

a CDR-L2 comprising the amino acid sequence of AAS (SEQ ID NO: 5); and

a CDR-L3 comprising the amino acid sequence of QQSYSTPLT (SEQ ID NO: 17).

7. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

a CDR-H1 comprising the amino acid sequence of GFTFSSYA (SEQ ID NO: 1);

a CDR-H2 comprising the amino acid sequence of ISGSGGST (SEQ ID NO: 2);

a CDR-H3 comprising the amino acid sequence of AKDPRGSGRDDAFDI (SEQ ID NO: 20);

a CDR-L1 comprising the amino acid sequence of QTIGSY (SEQ ID NO: 21);

a CDR-L2 comprising the amino acid sequence of GAS (SEQ ID NO: 22); and

a CDR-L3 comprising the amino acid sequence of QQSYSTPFT (SEQ ID NO: 11).

8. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

a CDR-H1 comprising the amino acid sequence of GFTFSSYA (SEQ ID NO: 1);

a CDR-H2 comprising the amino acid sequence of ISGSGGST (SEQ ID NO: 2);

a CDR-H3 comprising the amino acid sequence of AKDPTTMTTDAFDI (SEQ ID NO: 25);

a CDR-L1 comprising the amino acid sequence of QSISSY (SEQ ID NO: 4);

a CDR-L2 comprising the amino acid sequence of AAS (SEQ ID NO: 5); and

a CDR-L3 comprising the amino acid sequence of QQSYSTPFT (SEQ ID NO: 11).

9. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

a CDR-H1 comprising the amino acid sequence of GYTFTDYY (SEQ ID NO: 28);

a CDR-H2 comprising the amino acid sequence of FDPEDGET (SEQ ID NO: 29);

a CDR-H3 comprising the amino acid sequence of ATLDYRGVVYFDY (SEQ ID NO: 30);

a CDR-L1 comprising the amino acid sequence of SGSIASNY (SEQ ID NO: 31);

a CDR-L2 comprising the amino acid sequence of EDK (SEQ ID NO: 32); and

a CDR-L3 comprising the amino acid sequence of QSYDSSNHWV (SEQ ID NO: 33).

10. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

a CDR-H1 comprising the amino acid sequence of GFTFSDYW (SEQ ID NO: 36);

a CDR-H2 comprising the amino acid sequence of ISGSGGST (SEQ ID NO: 2);

a CDR-H3 comprising the amino acid sequence of AKDLLWAARDAFDI (SEQ ID NO: 37);

a CDR-L1 comprising the amino acid sequence of QSISSY (SEQ ID NO: 4);

a CDR-L2 comprising the amino acid sequence of AAS (SEQ ID NO: 5); and

a CDR-L3 comprising the amino acid sequence of QQSYSTPFT (SEQ ID NO: 11).

11. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

a CDR-H1 comprising the amino acid sequence of GFTFSNAW (SEQ ID NO: 9);

a CDR-H2 comprising the amino acid sequence of ISGSGGST (SEQ ID NO: 2);

a CDR-H3 comprising the amino acid sequence of AKQTVTSADDYFDY (SEQ ID NO: 43);

a CDR-L1 comprising the amino acid sequence of QSISSY (SEQ ID NO: 4);

a CDR-L2 comprising the amino acid sequence of AAS (SEQ ID NO: 5); and

a CDR-L3 comprising the amino acid sequence of QQSYSTPFT (SEQ ID NO: 11).

12. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises:

a CDR-H1 comprising the amino acid sequence of GFMFDTHA (SEQ ID NO: 46);

a CDR-H2 comprising the amino acid sequence of ISGSGGSI (SEQ ID NO: 47);

a CDR-H3 comprising the amino acid sequence of ARSGETAGTDYFDY (SEQ ID NO: 48);

a CDR-L1 comprising the amino acid sequence of QSVSSSY (SEQ ID NO: 49);

a CDR-L2 comprising the amino acid sequence of GAS (SEQ ID NO: 22); and

a CDR-L3 comprising the amino acid sequence of QQDYNSPYT (SEQ ID NO: 50).

13. The antibody or antigen-binding fragment thereof of claim 1, comprising:

(a) (i) a heavy chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 41; and/or

(ii) a light chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 42;

(b) (i) a heavy chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 7; and/or

(ii) a light chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 8;

(c) (i) a heavy chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 12; and/or

(ii) a light chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 13;

(d) (i) a heavy chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 18; and/or

(ii) a light chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 19;

(e) (i) a heavy chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 23; and/or

(ii) a light chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 24;

(f) (i) a heavy chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 26; and/or

(ii) a light chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 27;

(g) (i) a heavy chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 34; and/or

(ii) a light chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 35;

(h) (i) a heavy chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 38; and/or

(ii) a light chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 39;

(i) (i) a heavy chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 44; and/or

(ii) a light chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 45; or

(j) (i) a heavy chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 51; and/or

(ii) a light chain variable domain comprising an amino acid sequence with at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 52.

14. A polynucleotide encoding the antibody or antigen-binding fragment thereof of any one of claims 1-13.

15. A vector comprising the polynucleotide of claim 14.

16. A host cell comprising the vector of claim 15.

17. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-13, the polynucleotide of claim 14, the vector of claim 15, or the host cell of claim 16, and a pharmaceutically acceptable carrier or excipient.

18. A kit comprising an agent selected from the antibody or antigen-binding fragment thereof of any one of claims 1-13, the polynucleotide of claim 14, the vector of claim 15, the host cell of claim 16, or the pharmaceutical composition of claim 17.

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19. Use of the antibody or antigen-binding fragment thereof of any one of claims 1-13, the polynucleotide of claim 14, the vector of claim 15, the host cell of claim 16, or the pharmaceutical composition of claim 17 in the manufacture of a medicament for treating a subject having or at risk of developing a disorder.

20. The use of claim 19, wherein the disorder is:

(a) a fibrotic disorder;

(b) an inflammatory disorder; or

(c) a cancer.

21. The use of claim 20, wherein:

(a) the fibrotic disorder is selected from hepatic fibrosis, kidney fibrosis, dermal fibrosis, heart fibrosis, vascular fibrosis, ocular fibrosis, bone marrow fibrosis, pulmonary fibrosis, glomerulonephritis, heart failure, scleroderma, excessive scar tissue post-surgery or device insertion, trauma or burns, progressive kidney disease, valvular heart disease, hypertensive heart disease, articular and periarticular fibrosis, myelofibrosis, ocular/vitreous fibrosis, intestinal fibrosis and stricture, peritoneal and retro-peritoneal fibrosis, pancreatic fibrosis, nephrogenic systemic fibrosis, and primary sclerosing cholangitis;

(b) the inflammatory disorder is selected from asthma, airway inflammation, airway hyperreactivity, airway hyperresponsiveness, rhinosinusitis, rhinosinusitis with polyps, nasal polyposis, arthritis, eosinophilic inflammation, mast cell-mediated inflammatory diseases, sepsis, septic shock, seronegative enthesopathy and arthropathy (SEA) syndrome, osteoporosis, eosinophilic esophagitis, scleroderma, dermatitis, atopic dermatitis, allergic rhinitis, bullous pemphigoid, urticaria, cartilage inflammation, polymyalgia rheumatic, polyarteritis nodossa, Wegener's granulomatosis, Behcet's disease, myolitis, polymyolitis, dermatomyolitis, dermatomyositis, vasculitis, arteritis, diabetic nephropathy, interstitial cystitis, graft versus host disease (GVHD), gastrointestinal inflammatory conditions, and an inflammatory pulmonary condition; or

(c) the cancer is selected from breast cancer, colorectal cancer, hepatic cancer, kidney cancer, liver cancer, lung cancer, pancreatic cancer, gastrointestinal cancer, melanoma, ovarian cancer, prostate cancer, cervical cancer, bladder cancer, glioblastoma, head and neck cancer, and cholangiocarcinoma.