expression on tumor cells (Czarniecki et al., J. Immunol., 140: 4217, 1988), and inhibition of the proliferation of antigen-activated B lymphocytes in response to B-cell growth factor (Petit-Koskas et al., Eur. J. Immunol., 18: 111, 1988). See also US Patent 7,527,791.

[0004] Antibodies to TGFβ have been described in US Patent Nos. 7,527,791; 7,927,593; 7,494,651; 7,369,111; 7,151,169; 6,492,497; 6,419,928; 6,090,383; 5,783,185; 5,772,998; 5,571,714; and 7,723,486.

SUMMARY

[0005] The present disclosure provides methods and compositions for the treatment of disease or disorders associated with TGFβ expression. The disclosure provides antibodies that bind TGFβ1, TGFβ2 and TGFβ3. It is provided that the antibdoes described herein can have differential affinity for any or all of the TGFβ isoforms. Further, it was discovered herein that the disclosed TGFβ-specific antibodies unexpectedly modulate immune cells in tumors (e.g., infiltrate into tumors) and are contemplated for treatment of tumors associated with TGFβ expression, as well as other conditions or disorders associated with TGFβ expression.

[0006] In one example, the disclosure provides an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3 comprising: (a) a heavy chain complementary determining repeat (CDR)1 amino acid sequence set forth in Table 1 or SEQ ID NOs: 13, 19 and 25, or a variant thereof in which one or two amino acids have been changed; (b) a heavy chain CDR2 amino acid sequence set forth in Table 1 or SEQ ID NOs: 14, 20 and 26 that is from the same heavy chain variable region as (a), or a variant thereof in which one or two amino acids have been changed; and (c) a heavy chain CDR3 amino acid sequence set forth in Table 1 or SEQ ID NOs: 15, 21 and 27 that is from the same heavy chain variable region as (a), or a variant thereof in which one or two amino acids have been changed.

[0007] In a related example, the disclosure provides an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3 comprising: (a) a heavy chain CDR1 amino acid sequence set forth in Table 1 or SEQ ID NOs: 13, 19 and 25, or a variant thereof having at least 70% identity thereto; (b) a heavy chain CDR2 amino acid sequence set forth in Table 1 or SEQ ID NOs: 14, 20 and 26 that is from the same heavy chain variable region as (a), or a variant thereof having at least 70% identity thereto; and (c) a heavy chain CDR3 amino acid

sequence set forth in Table 1 or SEQ ID NOs: 15, 21 and 27 that is from the same heavy chain variable region as (a), or a variant thereof having at least 70% identity thereto.

[0008] In a further example, the disclosure contemplates an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3 comprising: (a) a heavy chain CDR1 amino acid sequence set forth in Table 1 or SEQ ID NOs: 13, 19 and 25, or a variant thereof having at least 70% identity thereto; (b) an independently selected heavy chain CDR2 amino acid sequence set forth in Table 1 or SEQ ID NOs: 14, 20 and 26, or a variant thereof having at least 70% identity thereto; and (c) an independently selected heavy chain CDR3 amino acid sequence set forth in Table 1 or SEQ ID NOs: 15, 21 and 27, or a variant thereof having at least 70% identity thereto.

[0009] In certain examples, at least two of the heavy chain CDR1, CDR2 or CDR3 amino acid sequences are set forth in Table 1 or SEQ ID NOs: 13-15, 19-21 and 25-27. In a related example, three of the heavy chain CDR1, CDR2 and CDR3 amino acid sequences are set forth in Table 1 or SEQ ID NOs: 13-15, 19-21 and 25-27.

[0010] In some examples, it is contemplated that the antibody comprises an amino acid sequence at least 85% identical to a heavy chain variable region amino acid sequence set forth in Table 1 or SEQ ID NOs: 2, 6 and 10. In a related example, the antibody comprises an amino acid sequence at least 95% identical to a heavy chain variable region amino acid sequence set forth in Table 1 or SEQ ID NOs: 2, 6 and 10.

[0011] In still other examples, the antibody comprises a polypeptide sequence having an amino acid sequence at least 70% identical over all three HCDRs in a heavy chain variable region, the amino acid sequences of HCDR1, HCDR2 and HCDR3 set forth in SEQ ID NOs: 13-15, 19-21 and 25-27.

[0012] In certain examples, one or more heavy chain framework amino acids have been replaced with corresponding amino acid(s) from another human antibody amino acid sequence.

[0013] It is contemplated that an antibody described herein further comprises any one of the light chain CDR amino acid sequences set forth in Table 1 or SEQ ID NOs: 16-18, 22-24 and 28-30. In some examples, an antibody cpomprises at least two of the light chain CDR amino acid sequences set forth in Table 1 or SEQ ID NOs: 16-18, 22-24 and 28-30. In other examples, an antibody comprises at least three of the light chain CDR amino acid sequences set forth in Table 1 or SEQ ID NOs: 16-18, 22-24 and 28-30.

[0014] In another example, an antibody described herein comprises (a) a light chain CDR1 amino acid sequence set forth in Table 1 or SEQ ID NOs: 16, 22 and 28, or a variant thereof in which one or two amino acids have been changed; (b) a light chain CDR2 amino acid sequence set forth in Table 1 or SEQ ID NOs: 17, 23 and 29 that is from the same light chain variable region as (a), or a variant thereof in which one or two amino acids have been changed; and (c) a light chain CDR3 amino acid sequence set forth in Table 1 or SEQ ID NOs: 18, 24 and 30 that is from the same light chain variable region as (a), or a variant thereof in which one or two amino acids have been changed.

[0015] In anternative examples, an antibody contemplated herein comprises: (a) a light chain CDR1 amino acid sequence set forth in Table 1 or SEQ ID NOs: 16, 22 and 28, or a variant thereof in which one or two amino acids have been changed; (b) an independently selected light chain CDR2 amino acid sequence set forth in Table 1 or SEQ ID NOs: 17, 23 and 29, or a variant thereof in which one or two amino acids have been changed; and (c) an independently selected light chain CDR3 amino acid sequence set forth in Table 1 or SEQ ID NOs: 18, 24 and 30, or a variant thereof in which one or two amino acids have been changed.

[0016] In certain examples, at least two of the light chain CDR1, CDR2 or CDR3 amino acid sequences are set forth in Table 1 or SEQ ID NOs: 16-18, 22-24 and 28-30.

[0017] It is further contemplated that an antibody described herein comprises a polypeptide sequence having an amino acid sequence at least 70% identical over all three LCDRs of a light chain variable region, the amino acid sequences of LCDR1, LCDR2 and LCDR3 set forth in SEQ ID NOs: 16-18, 22-24 and 28-30.

[0018] In one example, an antibody contemplated herein comprises an amino acid sequence at least 70% identical to a light chain variable region amino acid sequence set forth in Table 1 or SEQ ID NOs: 4, 8 and 12. In a related example, the antibody comprises an amino acid sequence at least 85% identical to a light chain variable region amino acid sequence set forth in Table 1 or SEQ ID NOs: 4, 8 and 12. In a further example, the antibody comprises an amino acid sequence at least 95% identical to a light chain variable region amino acid sequence set forth in Table 1 or SEQ ID NOs: 4, 8 and 12. In still another example, the antibody comprises a light chain variable region amino acid sequence set forth in Table 1 or SEQ ID NOs: 4, 8 and 12.

[0019] In a further example, an antibody described herein comprises (i) an amino acid sequence at least 70% identical over all three LCDRs, of a light chain variable region, the

amino acid sequences of LCDR1, LCDR2 and LCDR3 set forth in SEQ ID NOs: 16-18, 22-24 and 28-30 and (ii) an amino acid sequence at least 70% identical over all three HCDRs of a heavy chain variable region, the amino acid sequences of HCDR1, HCDR2 and HCDR3 set forth in SEQ ID NOs: 13-15, 19-21 and 25-27.

[0020] In another example, the disclosure provides an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3 comprising a light chain variable region and/or a heavy chain variable region, wherein (a) the light chain variable region comprises at least a CDR1 selected from SEQ ID NOs: 16, 22 and 28 or sequences at least 80% identical thereto, a CDR2 selected from SEQ ID NOs: 17, 23 and 29 or sequences at least 80% identical thereto, and/or a CDR3 selected from SEQ ID NOs: 18, 24 and 30 or sequences at least 80% identical thereto; and/or wherein (b) the heavy chain variable region comprises at least a CDR1 selected from SEQ ID NOs: 13, 19 and 25 or sequences at least 80% identical thereto, a CDR2 selected from SEQ ID NOs: 14, 20 and 26 or sequences at least 80% identical thereto, and/or a CDR3 selected from SEQ ID NOs: 15, 21 and 27 or sequences at least 80% identical thereto. In one example, the light chain variable region comprises at least a CDR1 selected from SEQ ID NO: 16 or sequences at least 90% identical thereto, a CDR2 selected from SEQ ID NO: 17 or sequences at least 90% identical thereto, and a CDR3 selected from SEQ ID NO: 18 or sequences at least 90% identical thereto; and/or the heavy chain variable region comprises at least a CDR1 selected from SEQ ID NO: 13 or sequences at least 90% identical thereto, a CDR2 selected from SEQ ID NO: 14 or sequences at least 90% identical thereto, and a CDR3 selected from SEQ ID NO: 15 or sequences at least 90% identical thereto.

[0021] In a related example, the light chain variable region comprises at least a CDR1 selected from SEQ ID NO: 22 or sequences at least 90% identical thereto, a CDR2 selected from SEQ ID NO: 23 or sequences at least 90% identical thereto, and a CDR3 selected from SEQ ID NO: 24 or sequences at least 90% identical thereto; and/or the heavy chain variable region comprises at least a CDR1 selected from SEQ ID NO: 19 or sequences at least 90% identical thereto, a CDR2 selected from SEQ ID NO: 20 or sequences at least 90% identical thereto, and a CDR3 selected from SEQ ID NO: 21 or sequences at least 90% identical thereto.

[0021a] In one aspect, the present disclosure refers to use of an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3, wherein the antibody comprises:

(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 19;
(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 20;
(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 21;
(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 22;
(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 23; and
(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 24;

in the preparation of a medicament for the treatment of colorectal cancer, hepatocellular carcinoma, breast cancer, prostate cancer, pancreatic cancer, renal cancer, lung cancer, fibrotic cancer, idiopathic pulmonary fibrosis (IPF) or fibroproliferative diseases,

wherein the medicament is capable of administration with one or more second agents.

[0021b] In one aspect, the present disclosure refers to use of an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3, wherein the antibody comprises:

(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 19;
(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 20;
(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 21;
(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 22;
(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 23; and
(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 24;

in the preparation of a medicament for the treatment of colorectal cancer, hepatocellular carcinoma, breast cancer, prostate cancer, pancreatic cancer, renal cancer, lung cancer, fibrotic cancer, idiopathic pulmonary fibrosis (IPF) or fibroproliferative diseases,

wherein the antibody comprises an amino acid sequence at least 90% identical to a heavy chain variable region amino acid sequence set out in SEQ ID NO: 6 and an amino acid sequence at least 90% identical to a light chain variable region amino acid sequence set out in SEQ ID NO: 8.

[0021c] In one aspect, the present disclosure refers to use of an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3, wherein the antibody comprises:

(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 19;
(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 20;
(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 21;
(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 22;
(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 23; and
(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 24;

in the preparation of a medicament for the treatment of colorectal cancer, hepatocellular carcinoma, breast cancer, prostate cancer, pancreatic cancer, renal cancer, lung cancer, fibrotic cancer, idiopathic pulmonary fibrosis (IPF) or fibroproliferative diseases,

wherein the antibody is capable of being administered at a dose of about 1 mg/kg, about 3 mg/kg or about 10 mg/kg.

[0021d] In one aspect, the present disclosure refers to use of an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3, wherein the antibody comprises:

(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 19;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 20;

(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 21;

(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 22;

(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 23; and

(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 24;

in the preparation of a medicament for the treatment of colorectal cancer, hepatocellular carcinoma, breast cancer, prostate cancer, pancreatic cancer, renal cancer, lung cancer, fibrotic cancer, idiopathic pulmonary fibrosis (IPF) or fibroproliferative diseases,

wherein the antibody is capable of being administered at a dose of approximately 100 mg/day or 150 mg/day.

[0021e] In one aspect, the present disclosure refers to use of an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3, wherein the antibody comprises:

(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 19;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 20;

(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 21;

(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 22;

(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 23; and

(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 24;

in the preparation of a medicament for the treatment of colorectal cancer, hepatocellular carcinoma, breast cancer, prostate cancer, pancreatic cancer, renal cancer, lung cancer, fibrotic cancer, idiopathic pulmonary fibrosis (IPF) or fibroproliferative diseases,

wherein the antibody is capable of being administered weekly, every 2 weeks, every 3 weeks, or monthly.

[0021f] In one aspect, the present disclosure refers to use of an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3, wherein the antibody comprises:

(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 19;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 20;

(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 21;

(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 22;

(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 23; and

(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 24;

in the preparation of a medicament for the treatment of colorectal cancer, hepatocellular carcinoma, breast cancer, prostate cancer, pancreatic cancer, renal cancer, lung cancer, fibrotic cancer, idiopathic pulmonary fibrosis (IPF) or fibroproliferative diseases,

wherein the antibody is capable of being administered intravenously or subcutaneously.

[0022] In certain examples, the light chain variable region comprises at least a CDR1 selected from SEQ ID NO: 28 or sequences at least 90% identical thereto, a CDR2 selected from SEQ ID NO: 29 or sequences at least 90% identical thereto, and a CDR3 selected from

SEQ ID NO: 30 or sequences at least 90% identical thereto; and/or the heavy chain variable region comprises at least a CDR1 selected from SEQ ID NO: 25 or sequences at least 90% identical thereto, a CDR2 selected from SEQ ID NO: 26 or sequences at least 90% identical thereto, and a CDR3 selected from SEQ ID NO: 27 or sequences at least 90% identical thereto.

[0022a] In one aspect, the present disclosure refers to an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3 comprising:

A. (a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 25, or a variant thereof in which one or two amino acids have been changed;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 26, or a variant thereof in which one or two amino acids have been changed;

(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 27, or a variant thereof in which one or two amino acids have been changed;

(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 28, or a variant thereof in which one or two amino acids have been changed;

(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 29, or a variant thereof in which one or two amino acids have been changed; and

(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 30, or a variant thereof in which one or two amino acids have been changed; or

B. (a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 25, or a variant thereof in which one or two amino acids have been changed;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 26, or a variant thereof in which one or two amino acids have been changed;

(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 27, or a variant thereof in which one or two amino acids have been changed;

(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 16, or a variant thereof in which one or two amino acids have been changed;

(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 17, or a variant thereof in which one or two amino acids have been changed; and

(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 18, or a variant thereof in which one or two amino acids have been changed.

[0023] It is contemplated that the percent identity of any one of the above antibody sequences can be at least 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96% , 97%, 98%, 99% or more identical to a heavy or light chain variable region or any of HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 or LCDR3 disclosed herein.

[0024] In some examples, an antibody of the disclosure further comprises a heavy chain constant region, wherein the heavy chain constant region is a modified or unmodified IgG, IgM, IgA, IgD, IgE, a fragment thereof, or combinations thereof.

[0025] In certain examples, an antibody is provided in which one or more light chain framework amino acids have been replaced with corresponding amino acid(s) from another human antibody amino acid sequence.

[0026] In one example, the antibody of the disclosure is selected from the group consisting of XPA.42.089, XPA.42.068 and XPA.42.681. Heavy and light chain amino acid sequences of XPA.42.089 are set out in SEQ ID NOs: 6 and 8, respectively. Heavy and light chain amino acid sequences of XPA.42.068 are set out in SEQ ID NOs: 2 and 4, respectively, and heavy and light chain amino acid sequences of XPA.42.681 are set out in SEQ ID NOs: 10 and 12, respectively.

[0027] In one example, an antibody described herein further comprises a human light chain constant region attached to said light chain variable region. In some examples, the light chain constant region is a modified or unmodified lambda light chain constant region, a kappa light chain constant region, a fragment thereof, or combinations thereof.

[0028] In a preferred example, the disclosure provides an antibody specific for TGFβ1, TGFβ2 and TGFβ3 with an affinity Kd of 10^{-6} M or less. In some examples, an anti-TGFβ antibody described herein binds at least one isoform of TGFβ with an affinity of 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M or less, or optionally binds two TGFβ isoforms, or all of TGFβ1, 2, or 3 with an affinity of 10^{-6} M. 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, or 10^{-12} M

or less for one or more of the isoforms. In other examples, an antibody described herein binds to TGFβ1 and TGFβ2 with at least 2-50 fold, 10-100 fold, 2-fold, 5-fold, 10-fold, 25-fold, 50-fold or 100-fold, or 20-50%, 50-100%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% higher affinity (e.g., preferentially binds to TGFβ1 and TGFβ2) compared to binding to TGFβ3. Alternatively, an antibody described herein, binds each of TGFβ isoforms TGFβ1, TGFβ2 and TGFβ3 with an affinity within 3-fold, 5-fold or 10-fold of each other. In certain examples, the antibody binds to TGFβ1 and TGFβ2 with greater affinity than TGFβ3. In certain examples, the affinity is measured by surface plasmon resonance or KINEXA assay.

[0029] In some examples, the antibody neutralizes activity of TGFβ1 and TGFβ2 to a greater extent than TGFβ3. In some examples, antibody neutralization of TGFβ1 and TGFβ2 is at least 2-50 fold, 10-100 fold, 2-fold, 5-fold, 10-fold, 25-fold, 50-fold or 100-fold, or 20-50%, 50-100%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% more potent that neutralization of TGFβ3. Exemplary neutralization assays contemplated herein include, but are not limited to, an interleukin-11 release assay and an HT-2 cell proliferation assay. In addtion, a TGFβ activity assay can be carried out to determine if an antibody disclosed herein inhibits one TGFβ isoform preferentially, including a pSMAD phosphorylation assay or an rhLAP binding assay. In a further example, the antibody has a lower IC50 (i.e., better binding, greater potency) for TGFβ1 and TGFβ2 compared to TGFβ3.

[0030] In another example, the disclosure provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes the heavy chain and/or light chain as described herein. In one aspect, the present disclosure refers to an isolated nucleic acid molecule comprising a nucleotide sequence that encodes the heavy chain or light chain as described herein.

[0031] In a further example, the disclosure provides an expression vector comprising a nucleic acid molecule contemplated herein operably linked to an expression control sequence. In one aspect, the present disclosure refers to an expression vector comprising the nucleic acid molecule as described herein operably linked to an expression control sequence. Also contemplated is a host cell comprising an expression vector or a nucleic acid molecule of the disclosure. In certain examples, the disclosure provides a host cell comprising a nucleic acid molecule encoding a heavy chain and a light chain variable region, wherein the heavy chain and light chain nucleic acids are expressed by different nucleic acids or on the same nucleic acid. In one aspect, the present disclosure refers to a recombinant host cell comprising the vector as described herein or a nucleic acid molecule as described herein, excluding cells within a human.

[0032] In a related example, the disclosure provides a method of using the host cell as described herein to produce an antibody, the method comprising culturing the host cell under

suitable conditions and recovering said antibody. In one aspect, the present disclosure refers to a method of using the host cell as described herein to produce an antibody, comprising culturing the host cell as described herein under suitable conditions and recovering said antibody. Also provided is an antibody produced by the method disclosed herein.

[0033] In one aspect, the present disclosure further refers to a sterile pharmaceutical composition comprising the antibody as disclosed herein and a pharmaceutically acceptable carrier.

[0034] In another example, the disclosure provides a method for treating a disease, condition or disorder associated with TGFβ expression comprising the step of administering to a subject in need thereof a therapeutically effective amount of an antibody or a pharmaceutical composition contemplated herein. In one aspect, the present disclosure refers to use of an antibody as described herein or a pharmaceutical composition as described herein in the preparation of a medicament for treating a disease, condition or disorder associated with TGFβ expression. In certain examples, the disease, condition or disorder is selected from the group consisting of a cancer, an eye (e.g., ocular, optic, ophthalmic or ophthalmological) disease, condition or disorder, a disease condition or disorder associated with fibrosis, e.g., fibroproliferative diseases, conditions or disorders, or disease, conditions or disorders having an associated fibrosis.

[0035] Fibroproliferative diseases, conditions or disorders or diseases having an associated fibrosis include those that affect any organ or tissue in the body, including, but not limited to the skin, lung, kidney, heart, brain and eye. Fibroproliferative diseases, conditions or disorders or diseases having an associated fibrosis include, but are not limited to pulmonary fibrosis, idiopathic pulmonary fibrosis, peribronchiolar fibrosis, interstitial lung disease, chronic obstructive pulmonary disease (COPD), small airway disease (e.g., obstructive bronchiolitis), emphysema, adult or acute respiratory distress syndrome (ARDS), acute lung injury (ALI), pulmonary fibrosis due to infectious or toxic agents, kidney fibrosis, glomerulonephritis (GN) of all etiologies, mesangial proliferative GN, immune GN, crescentic GN, glomerulosclerosis, tubulointerstitial injury, renal interstitial fibrosis, renal fibrosis and all causes of renal interstitial fibrosis, renal fibrosis resulting from complications of drug exposure, including cyclosporin treatment of transplant recipients, HIV-associated nephropathy, transplant necropathy, diabetic kidney disease, diabetic nephropathy, nephrogenic systemic fibrosis, diabetes, idiopathic retroperitoneal fibrosis, scleroderma, liver fibrosis, hepatic diseases associated with excessive scarring and progressive sclerosis, liver cirrhosis due to all etiologies, disorders of the biliary tree, hepatic dysfunction attributable to infections, fibrocystic diseases, cardiovascular diseases, congestive heart failure, dilated cardiomyopathy, myocarditis, vascular stenosis cardiac fibrosis, post-infarction cardiac fibrosis, post myocardial infarction, left ventricular hypertrophy, veno-occlusive disease, restenosis, post-angioplasty restenosis, arteriovenous graft failure, atherosclerosis, hypertension, hypertensive heart disease, cardiac hypertrophy, hypertrophic cardiomyopathy,

fibrosis, epiretinal fibrosis, retinal gliosis, subretinal fibrosis (e.g., associated with age related macular degeneration), fibrosis associated with post-retinal and glaucoma surgery, tractional retinal detachment in association with contraction of the tissue in diabetic retinopathy.

[0037] Exemplary fibroproliferative disease, condition, or disorders of the eye, fibrosis of the eye, ocular fibrosis or ophthalmic fibroses include, but are not limited to, proliferative vitreoretinopathy, vitreoretinopathy of any etiology, fibrosis associated with retinal dysfunction, fibrosis asscoatied with wet or dry macular degeneration, fibrosis associated with ocular surgery such as treatment of glaucoma, retinal reattachment, cataract extraction, or drainage procedures of any kind, scarring in the cornea and conjunctiva, fibrosis in the corneal endothelium, fibrosis associated with alkali burn, post-cataract surgery fibrosis of the lens capsule, excess scarring the tissue around the extraocular muscles in the strabismus surgery, anterior subcapsular cataract and posterior capsule opacification, anterior segment fibrotic diseases of the eye, fibrosis of the corneal stroma (e.g., associated with corneal opacification), fibrosis of the trabecular network (e.g., associated with glaucoma), posterior segment fibrotic diseases of the eye, fibrovascular scarring (e.g., in retinal or choroidal vasculature of the eye), retinal fibrosis, epiretinal fibrosis, retinal gliosis, subretinal fibrosis (e.g., associated with age related macular degeneration), fibrosis associated with post-retinal and glaucoma surgery, tractional retinal detachment in association with contraction of the tissue in diabetic retinopathy.

[0038] In various examples, the fibroproliferative disease, condition, or disorders of the eye is selected from the group consisting of proliferative vitreoretinopathy, fibrosis associated with ocular surgery, post-cataract surgery fibrosis of the lens, fibrosis of the corneal stroma and alkali burn.

[0039] In a related example, the disclosure provides a method for treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of an antibody or a pharmaceutical composition contemplated herein. In certain examples, the cancer is selected from the group consisting of lung cancer, prostate cancer, breast cancer, hepatocellular cancer, esophageal cancer, colorectal cancer, pancreatic cancer, bladder cancer, kidney cancer, ovarian cancer, stomach cancer, fibrotic cancer, glioma and melanoma.

[0040] In some examples, the antibody or composition increases the number of natural killer (NK) cells in a tumor. In various examples, the antibody or composition increases

cytolytic activity of NK cells. For example, in various examples, the antibody or composition described herein increases perforin and granzyme production by NK cells. In one example, the antibody is XPA.42.089 or XPA.42.681.

[0041] In various examples, the antibody or composition described herein decreases the number of regulatory T cells in a tumor and/or inhibits regulatory T cell function. For example, in various examples, the antibody or composition described herein inhibits inhibits the ability of Tregs to down-regulate an immune response or to migrate to a site of an immune response.

[0042] In various examples, the antibody or composition increases the number of cytotoxic T cells in a tumor and/or enhances CTL activity, e.g., boosts, increases or promotes CTL activity. For example, in various examples, the antibody or composition described herein increases perforin and granzyme production by CTL and increases cytolytic activity of the CTL. In one example, the antibody is XPA.42.068, XPA.42.089 or XPA.42.681.

[0043] In another example, the antibody or composition decreases the number of monocyte-derived stem cells (MDSC) in a tumor and/or inhibits MDSC function. For example, in various examples, the antibody or composition described herein inhibits the ability of MDSCs to suppress an immune response, inhibits immune suppressive activity of MDSCs, and/or inhibits the ability of MDSCs to promote expansion and/or function of Tregs. In various examples, the antibody is selected from the group consisting of XPA.42.089, XPA.42.068 and XPA.42.681.

[0044] In various examples, the antibody decreases the number of dendritic cells (DC) in a tumor and/or inhibits the tolerogenic function (e.g., tolerogenic effect) of dendritic cells. For example, in various examples, the antibody or composition described herein decreases the toleragenic effect of CD8+ dendritic cells. In one example, the antibody is XPA.42.089 or XPA.42.681.

[0045] In another example, the disclosure provides a method for treating fibrosis comprising administering to a subject in need thereof a therapeutically effective amount of an antibody or a pharmaceutical composition contemplated herein.

[0046] In various examples, the antibody is administered with a second agent. In one example, the second agent is selected from the group consisting of an extracellular matrix degrading protein, an anti-fibrotic agent, surgical therapy, chemotherapy, a cytotoxic agent,

or radiation therapy. Exemplary second agents are disclosed in greater detail in the Detailed Description.

[0047] In various examples, therapy is administered on a period basis, for example, hourly, daily, weekly, every 2 weeks, every 3 weeks, monthly, or at a longer interval. In a related example, in exemplary treatments, the antibody disclosed herein may be administered at a dose of about 1 mg/day, 5 mg/day, 10 mg/day, 20 mg/day, 50 mg/day, 75 mg/day, 100 mg/day, 150 mg/day, 200 mg/day, 250 mg/day, 500 mg/day or 1000 mg/day. These concentrations may be administered as a single dosage form or as multiple doses.

[0048] Also contemplated is a composition comprising any of the foregoing antibodies or compositions of the disclosure that bind TGFβ, or use thereof in preparation of a medicament, for treatment of any of the disorders described herein associated with TGFβ expression. Syringes, e.g., single use or pre-filled syringes, sterile sealed containers, e.g. vials, bottle, vessel, and/or kits or packages comprising any of the foregoing antibodies or compositions, optionally with suitable instructions for use, are also contemplated.

[0049] It is understood that each feature or example, or combination, described herein is a non-limiting, illustrative example of any of the aspects of the disclosure and, as such, is meant to be combinable with any other feature or embodiment, or combination, described herein. For example, where features are described with language such as “one example”, “some examples”, “certain examples”, “further example”, “specific examples”, and/or “another example” “one embodiment”, “some embodiments”, “certain embodiments”, “further embodiment”, “specific exemplary embodiments”, and/or “another embodiment”, each of these types of examples and embodiments is a non-limiting example of a feature that is intended to be combined with any other feature, or combination of features, described herein without having to list every possible combination. Such features or combinations of features apply to any of the aspects of the disclosure. Where examples of values falling within ranges are disclosed, any of these examples are contemplated as possible endpoints of a range, any and all numeric values between such endpoints are contemplated, and any and all combinations of upper and lower endpoints are envisioned.

BRIEF DESCRIPTION OF THE DRAWINGS

[0050] Figure 1 is a graph showing competition of TGFβ1 binding to rhLAP by TGFβ antibodies.

WHAT IS CLAIMED:

1. Use of an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3, wherein the antibody comprises:

(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 19;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 20;

(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 21;

(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 22;

(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 23; and

(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 24;

in the preparation of a medicament for the treatment of colorectal cancer, hepatocellular carcinoma, breast cancer, prostate cancer, pancreatic cancer, renal cancer, lung cancer, fibrotic cancer, idiopathic pulmonary fibrosis (IPF) or fibroproliferative diseases,

wherein the medicament is capable of administration with one or more second agents.

2. Use of an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3, wherein the antibody comprises:

(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 19;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 20;

(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 21;

(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 22;

(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 23; and

(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 24;

in the preparation of a medicament for the treatment of colorectal cancer, hepatocellular carcinoma, breast cancer, prostate cancer, pancreatic cancer, renal cancer, lung cancer, fibrotic cancer, idiopathic pulmonary fibrosis (IPF) or fibroproliferative diseases,

wherein the antibody comprises an amino acid sequence at least 90% identical to a heavy chain variable region amino acid sequence set out in SEQ ID NO: 6 and an amino acid sequence at least 90% identical to a light chain variable region amino acid sequence set out in SEQ ID NO: 8.

3. Use of an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3, wherein the antibody comprises:

(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 19;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 20;

(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 21;

(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 22;

(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 23; and

(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 24;

in the preparation of a medicament for the treatment of colorectal cancer, hepatocellular carcinoma, breast cancer, prostate cancer, pancreatic cancer, renal cancer, lung cancer, fibrotic cancer, idiopathic pulmonary fibrosis (IPF) or fibroproliferative diseases,

wherein the antibody is capable of being administered at a dose of about 1 mg/kg, about 3 mg/kg or about 10 mg/kg.

4. Use of an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3, wherein the antibody comprises:

(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 19;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 20;

(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 21;

(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 22;

(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 23; and

(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 24;

in the preparation of a medicament for the treatment of colorectal cancer, hepatocellular carcinoma, breast cancer, prostate cancer, pancreatic cancer, renal cancer, lung cancer, fibrotic cancer, idiopathic pulmonary fibrosis (IPF) or fibroproliferative diseases,

wherein the antibody is capable of being administered at a dose of approximately 100 mg/day or 150 mg/day.

5. Use of an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3, wherein the antibody comprises:

(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 19;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 20;

(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 21;

(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 22;

(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 23; and

(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 24;

in the preparation of a medicament for the treatment of colorectal cancer, hepatocellular carcinoma, breast cancer, prostate cancer, pancreatic cancer, renal cancer, lung cancer, fibrotic cancer, idiopathic pulmonary fibrosis (IPF) or fibroproliferative diseases,

wherein the antibody is capable of being administered weekly, every 2 weeks, every 3 weeks, or monthly.

6. Use of an antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3, wherein the antibody comprises:

(a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 19;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 20;

(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 21;

(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 22;

(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 23; and

(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 24;

in the preparation of a medicament for the treatment of colorectal cancer, hepatocellular carcinoma, breast cancer, prostate cancer, pancreatic cancer, renal cancer, lung cancer, fibrotic cancer, idiopathic pulmonary fibrosis (IPF) or fibroproliferative diseases,

wherein the antibody is capable of being administered intravenously or subcutaneously.

7. The use of any one of claims 1 or 3-6, wherein the antibody comprises an amino acid sequence at least 90% identical to a heavy chain variable region amino acid sequence set out in SEQ ID NO: 6 and an amino acid sequence at least 90% identical to a light chain variable region amino acid sequence set out in SEQ ID NO: 8.

8**.** The use of any one of claims 1-7, wherein the antibody comprises a heavy chain variable region amino acid sequence set out in SEQ ID NO: 6 and a light chain variable region amino acid sequence set out in SEQ ID NO: 8.

9. The use of any one of claims 1-8, wherein the antibody further comprises a heavy chain constant region, wherein the heavy chain constant region is a modified or unmodified IgG, IgM, IgA, IgD, IgE, a fragment thereof, or combinations thereof.

10. The use of any one of claims 1-9, wherein the antibody further comprises a light chain constant region wherein the light chain constant region is a modified or

unmodified lambda light chain constant region, a kappa light chain constant region, a fragment thereof, or combinations thereof.

11. The use of any one of claims 1-10 in which one or more light chain framework amino acids of the antibody have been replaced with corresponding amino acid(s) from another human antibody amino acid sequence.

12. The use of any one of claims 1-11, wherein the antibody further comprises a human light chain constant region attached to said light chain variable region.

13. The use of any one of claims 1-12, wherein the antibody binds to TGFβ1 and TGFβ2 with greater affinity than TGFβ3.

14. The use of any one of claims 1-13, wherein the antibody neutralizes activity of TGFβ1 and TGFβ2 to a greater extent than TGFβ3.

15. The use of any one of claims 1-14, wherein the antibody is in a sterile pharmaceutical composition comprising the antibody and a pharmaceutically acceptable carrier.

16. The use of any one of claims 1-15, wherein the antibody or composition increases the number of natural killer (NK) cells in a tumor and/or improves NK cell cytolytic activity.

17. The use of any one of claims 1-15, wherein the antibody or composition decreases the number of regulatory T cells in a tumor and/or inhibits regulatory T cell function.

18. The use of any one of claims 1-15, wherein the antibody or composition increases the number of cytotoxic T cells (CTLs) in a tumor and/or enhances CTL function.

19. The use of any one of claims 1-15, wherein the antibody decreases the number of myeloid-derived suppressor cells (MDSC) in a tumor and/or inhibits MDSC function.

20. The use of any one of claims 1-15, wherein the antibody decreases the number of dendritic cells (DC) in a tumor and/or inhibits the tolerogenic function of dendritic cells.

21. The use of any one of claims 2-6, further comprises one or more second agents.

22. The use of claim 1 or claim 21, wherein the second agent is selected from the group consisting of a chemotherapeutic agent, a cytotoxic agent, and azacitidine.

23. The use of claim 22 wherein the chemotherapeutic agent is selected from the group consisting of 5-fluorouracil, oxaliplatin, irinotecan, and combinations thereof.

24. The use according to any one of claims 1-23, wherein the antibody is in lyophilized form or liquid form.

25. The use according to any one of claims 1, 2, 5 or 6 wherein the antibody is capable of being administered at a dose of about 1 mg/kg, about 3 mg/kg or about 10 mg/kg.

26. The use according to any one of claims 1, 2, 5 or 6, wherein the antibody is capable of being administered at a dose of approximately 100 mg/day or 150 mg/day.

27. The use according to any one of claims 1-4, wherein the antibody is capable of being administered weekly, every 2 weeks, every 3 weeks, or monthly.

28. The use according to any one of claims 1-5, wherein the antibody is capable of being administered intravenously or subcutaneously.

29. The use of any one of claims or 21-23, wherein the one or more second agents is capable of administration either simultaneously or sequentially.

30. The use of any one of the preceding claims wherein the disease is idiopathic pulmonary fibrosis (IPF).

31. The use of any one of the preceding claims wherein the disease is colorectal cancer.

32. The use of any one of the preceding claims wherein the disease is pancreatic cancer.

33. An antibody that binds transforming growth factor beta (TGFβ)1, TGFβ2 and TGFβ3 comprising:

A. (a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 25, or a variant thereof in which one or two amino acids have been changed;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 26, or a variant thereof in which one or two amino acids have been changed;

(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 27, or a variant thereof in which one or two amino acids have been changed;

(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 28, or a variant thereof in which one or two amino acids have been changed;

(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 29, or a variant thereof in which one or two amino acids have been changed; and

(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 30, or a variant thereof in which one or two amino acids have been changed; or

B. (a) a heavy chain CDR1 amino acid sequence set forth in SEQ ID NO: 25, or a variant thereof in which one or two amino acids have been changed;

(b) a heavy chain CDR2 amino acid sequence set forth in SEQ ID NO: 26, or a variant thereof in which one or two amino acids have been changed;

(c) a heavy chain CDR3 amino acid sequence set forth in SEQ ID NO: 27, or a variant thereof in which one or two amino acids have been changed;

(d) a light chain CDR1 amino acid sequence set forth in SEQ ID NO: 16, or a variant thereof in which one or two amino acids have been changed;

(e) a light chain CDR2 amino acid sequence set forth in SEQ ID NO: 17, or a variant thereof in which one or two amino acids have been changed; and

(f) a light chain CDR3 amino acid sequence set forth in SEQ ID NO: 18, or a variant thereof in which one or two amino acids have been changed.

34. The antibody of claim 33, that comprises

A. an amino acid sequence at least 90% identical to a heavy chain variable region amino acid sequence set forth in SEQ ID NO: 10 and an amino acid sequence at least 90% identical to a light chain variable region amino acid sequence set forth in SEQ ID NO: 12; or

B. an amino acid sequence at least 90% identical to a heavy chain variable region amino acid sequence set forth in SEQ ID NO: 10 and an amino acid sequence at least 90% identical to a light chain variable region amino acid sequence set forth in SEQ ID NO: 4.

35. The antibody of any one of claims 33 or 34, further comprising a heavy chain constant region, wherein the heavy chain constant region is a modified or unmodified IgG, IgM, IgA, IgD, IgE, a fragment thereof, or combinations thereof.

36. The antibody of any one of claims 33 to 35, in which one or more light chain framework amino acids have been replaced with corresponding amino acid(s) from another human antibody amino acid sequence.

37. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the heavy chain or light chain of any one of claims 33 to 36.

38. An expression vector comprising the nucleic acid molecule of claim 37 operably linked to an expression control sequence.

39. A recombinant host cell comprising the vector of claim 38 or a nucleic acid molecule of claim 37, excluding cells within a human.

40. A method of using the host cell of claim 39 to produce an antibody, comprising culturing the host cell of claim 39 under suitable conditions and recovering said antibody.

41. A sterile pharmaceutical composition comprising the antibody of any one of claims 33-36 and a pharmaceutically acceptable carrier.

42. Use of an antibody of any one of claims 33-36 or a pharmaceutical composition of claim 41 in the preparation of a medicament for treating a disease, condition or disorder associated with TGFβ expression.