



US010106603B2

(12) **United States Patent**
Cook et al.

(10) **Patent No.:** US 10,106,603 B2
(45) **Date of Patent:** Oct. 23, 2018

(54) **TREATMENT OF FIBROSIS**

(71) Applicants: **Singapore Health Services PTE LTD., Singapore (SG); National University of Singapore, Singapore (SG)**

(72) Inventors: **Stuart Alexander Cook, Singapore (SG); Sebastian Schaefer, Singapore (SG)**

(73) Assignees: **Singapore Health Services PTE LTD, Singapore (SG); National University of Singapore, Singapore (SG)**

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **15/988,463**

(22) Filed: **May 24, 2018**

(65) **Prior Publication Data**

US 2018/0265579 A1 Sep. 20, 2018

Related U.S. Application Data

(62) Division of application No. 15/381,622, filed on Dec. 16, 2016, now Pat. No. 10,035,852.

(30) **Foreign Application Priority Data**

Dec. 16, 2015 (GB) 1522186.4

(51) **Int. Cl.**

A61K 39/395 (2006.01)
C07K 16/24 (2006.01)
A61K 39/00 (2006.01)

(52) **U.S. Cl.**

CPC **C07K 16/244** (2013.01); **A61K 2039/505** (2013.01); **A61K 2039/54** (2013.01); **C07K 2317/20** (2013.01); **C07K 2317/76** (2013.01)

(58) **Field of Classification Search**

CPC A61K 2039/505

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,679,339 A	10/1997	Keith et al.
6,126,933 A	10/2000	Warne et al.
6,540,993 B1	4/2003	Warne et al.
6,846,907 B1	1/2005	Shaughnessy et al.
6,953,777 B2	10/2005	Keith et al.
6,998,123 B1	2/2006	Shaughnessy et al.
7,993,637 B2	8/2011	Baca
8,182,814 B2	5/2012	Baca et al.
8,361,966 B2	1/2013	Azuma et al.
8,518,888 B2	8/2013	Jenkins et al.
8,540,977 B2	9/2013	Baca
9,340,618 B2	5/2016	Edwards et al.
2003/0147849 A1	8/2003	Warne et al.
2004/0126358 A1	7/2004	Warne et al.
2004/0142871 A1	7/2004	Shaughnessy et al.

2009/0191147 A1	7/2009	Keith et al.
2009/0202533 A1	8/2009	Baca et al.
2010/0062058 A1	3/2010	Warne et al.
2010/0093976 A1	4/2010	Azuma et al.
2010/0183544 A1	7/2010	Jenkins et al.
2013/0302277 A1	11/2013	Jenkins et al.
2014/0219919 A1	8/2014	Edwards et al.
2016/0031999 A1	2/2016	Edwards et al.
2017/0174759 A1	6/2017	Cook et al.

FOREIGN PATENT DOCUMENTS

EP	1630232 A2	3/2006
KR	20110047179 A	5/2011
WO	WO 1996/019574 A1	6/1996
WO	WO 1998/36061 A2	8/1998
WO	WO 1999/020755 A2	4/1999
WO	WO 2000/078336 A1	12/2000
WO	WO 2002/020609 A2	3/2002
WO	WO 2005/058956 A1	6/2005
WO	WO 2005/070446 A1	8/2005
WO	WO 2005/098041 A2	10/2005
WO	WO 2009/052588 A1	4/2009
WO	WO 2014/121325 A1	8/2014
WO	WO 2017/103108 A1	6/2017

OTHER PUBLICATIONS

International Search Report and Written Opinion for International Patent Application No. PCT/EP2016/081430, dated Apr. 18, 2017. Chapter II Demand filed Aug. 14, 2017 for International Patent Application No. PCT/EP2016/081430.
International Preliminary Report on Patentability (Chapter II) for International Patent Application No. PCT/EP2016/081430, dated Nov. 6, 2017.

Third Party Submission Under 37 C.F.R. § 1.290 for U.S. Appl. No. 15/381,622, filed Apr. 30, 2018.

Ancey et al., A fusion protein of the gp130 and interleukin-6Ralpha ligand-binding domains acts as a potent interleukin-6 inhibitor. J Biol Chem. May 9, 2003;278(19):16968-72.

Bravo et al., Crystal structure of a cytokine-binding region of gp130. EMBO J. Mar. 16, 1998;17(6):1665-74.

Chen et al., IL-11 receptor alpha in the pathogenesis of IL-13-induced inflammation and remodeling. J Immunol. Feb. 15, 2005;174(4):2305-13.

Du et al., Interleukin-11: review of molecular, cell biology, and clinical use. Blood. Jun. 1, 1997;89(11):3897-908.

Garbers et al., Interleukin-6 and interleukin-11: same same but different. Biol Chem. Sep. 2013;394(9):1145-61. doi: 10.1515/hzs-2013-0166.

(Continued)

Primary Examiner — Prema M Mertz

(74) Attorney, Agent, or Firm — Wolf, Greenfield & Sacks, P.C.

(57) **ABSTRACT**

Aspects of the disclosure relate to the treatment, prevention or alleviation of conditions such as fibrosis in a subject. In some embodiments, the treatment, prevention or alleviation of fibrosis in a subject through the administration of an agent capable of inhibiting the action of Interleukin 11 (IL-11) is disclosed.

10 Claims. 66 Drawing Sheets

(56)

References Cited**OTHER PUBLICATIONS**

- Gu et al., Anti-gp130 transducer monoclonal antibodies specifically inhibiting ciliary neurotrophic factor, interleukin-6, interleukin-11, leukemia inhibitory factor or oncostatin M *J Immunol Methods*. Mar. 28, 1996;190(1):21-7.
- Halwani et al., Airway remodeling in asthma. *Curr Opin Pharmacol*. Jun. 2010;10(3):236-45. doi: 10.1016/j.coph.2010.06.004.
- Ham et al., Critical role of interleukin-11 in isoflurane-mediated protection against ischemic acute kidney injury in mice. *Anesthesiology*. Dec. 2013;119(6): 1389-401. doi: 10.1097/ALN.ObO.000043182a950da.
- Kapina et al., Interleukin-11 drives early lung inflammation during *Mycobacterium tuberculosis* infection in genetically susceptible mice. *PLoS One*. 2011;6(7):e21878. doi: 10.1371/journal.pone.0021878.
- Khan et al., Fibrosis in heart disease: understanding the role of transforming growth factor-beta in cardiomyopathy, valvular disease and arrhythmia. *Immunology*. May 2006;118(1):10-24.
- Kimura et al., Identification of cardiac myocytes as the target of interleukin 11, a cardioprotective cytokine. *Cytokine*. May 2007;38(2):107-15.
- Lee et al., Cysteinyl leukotriene upregulates IL-11 expression in allergic airway disease of mice. *J Allergy Clin Immunol*. Jan. 2007;119(1):141-9.
- Lee et al., Endogenous IL-11 signaling is essential in Th2- and IL-13-induced inflammation and mucus production. *Am J Respir Cell Mol Biol*. Dec. 2008;39(6):739-46. doi: 10.1165/rcmb.2008-0053OC. Epub Jul. 10, 2008.
- Lindahl et al., Microarray profiling reveals suppressed interferon stimulated gene program in fibroblasts from scleroderma-associated interstitial lung disease. *Respir Res*. Aug. 2, 2013;14:80. doi: 10.1186/1465-9921-14-80.
- Lokau et al., Proteolytic Cleavage Governs Interleukin-11 Trans-signaling. *Cell Rep*. Feb. 23, 2016;14(7):1761-1773. doi:10.1016/j.celrep.2016.01.053. Epub Feb. 11, 2016.
- Lokau et al., Signal transduction of Interleukin-11 and Interleukin-6 α-Receptors. *Recep Clin Investigation*. 2016;3. 5 pages.
- Minshall et al., IL-11 expression is increased in severe asthma: association with epithelial cells and eosinophils. *J Allergy Clin Immunol*. Feb. 2000;105(2 Pt 1):232-8.
- Molet et al., IL-11 and IL-17 expression in nasal polyps: relationship to collagen deposition and suppression by intranasal fluticasone propionate. *Laryngoscope*. Oct. 2003;113(10):1803-12.
- Murray et al., Targeting interleukin-13 with tralokinumab attenuates lung fibrosis and epithelial damage in a humanized SCID idiopathic pulmonary fibrosis model. *Am J Respir Cell Mol Biol*. May 2014;50(5):985-94. doi: 10.1165/rcmb.2013-0342OC.
- Obana et al., Therapeutic activation of signal transducer and activator of transcription 3 by interleukin-11 ameliorates cardiac fibrosis after myocardial infarction. *Circulation*. Feb. 9, 2010;121(5):684-91. doi:10.1161/CIRCULATIONAHA.109.893677.
- Obana et al., Therapeutic administration of IL-11 exhibits the postconditioning effects against ischemia-reperfusion injury via STAT3 in the heart. *Am J Physiol Heart Circ Physiol*. Sep. 1, 2012;303(5):H569-77. doi: 10.1152/ajpheart.00060.2012.
- Ray et al., Regulated overexpression of interleukin 11 in the lung. Use to dissociate development-dependent and -independent phenotypes. *J Clin Invest*. Nov. 15, 1997;100(10):2501-11.
- Schafer et al., IL-11 is a crucial determinant of cardiovascular fibrosis. *Nature*. Dec. 7, 2017;552(7683):110-115. doi: 10.1038/nature24676. Epub Nov. 13, 2017.
- Shepelkova et al., Therapeutic Effect of Recombinant Mutated Interleukin 11 in the Mouse Model of Tuberculosis. *J Infect Dis*. Aug. 1, 2016;214(3):496-501. doi: 10.1093/infdis/jiw176.
- Stangou et al., Effect of IL-11 on glomerular expression of TGF-beta and extracellular matrix in nephrotoxic nephritis in Wistar Kyoto rats. *J Nephrol*. Jan.-Feb. 2011;24(1): 106-11.
- Tang et al., Targeted expression of IL-11 in the murine airway causes lymphocytic inflammation, bronchial remodeling, and airways obstruction. *J Clin Invest*. Dec. 15, 1996;98(12):2845-53.
- Tang et al., Transforming growth factor-beta stimulates interleukin-11 transcription via complex activating protein-1-dependent pathways. *J Biol Chem*. Mar. 6, 1998;273(10):5506-13.
- Toda et al., Polarized in vivo expression of IL-11 and IL-17 between acute and chronic skin lesions. *J Allergy Clin Immunol*. Apr. 2003;111(4):875-81.
- Trepicchio et al., The therapeutic utility of Interleukin-11 in the treatment of inflammatory disease. *Expert Opin Investig Drugs*. Sep. 1998;7(9):1501-4.
- Wynn, Cellular and molecular mechanisms of fibrosis. *J Pathol*. Jan. 2008;214(2):199-210.
- Yashiro et al., Transforming growth factor-beta stimulates interleukin-11 production by human periodontal ligament and gingival fibroblasts. *J Clin Periodontol*. Mar. 2006;33(3):165-71.
- Zhu et al., IL-11 Attenuates Liver Ischemia/Reperfusion Injury (IRI) through STAT3 Signaling Pathway in Mice. *PLoS One*. May 6, 2015;10(5):e0126296. doi: 10.1371/journal.pone.0126296.
- U.S. Appl. No. 15/381,622, filed Dec. 16, 2016, Cook et al. PCT/EP2016/081430, Nov. 6, 2017, International Preliminary Report on Patentability.
- PCT/EP2016/081430, Apr. 18, 2017, International Search Report and Written Opinion.
- Metz et al., Characterization of the Interleukin (IL)-6 Inhibitor IL-6-RFP: fused receptor domains act as high affinity cytokine-binding proteins. *J Biol Chem*. Jan. 12, 2007;282(2):1238-48. Epub Nov. 3, 2006.
- Chow et al., Structure of an extracellular gp130 cytokine receptor signaling complex. *Science*. Mar. 16, 2001;291(5511):2150-5.
- Johnstone et al., Emerging roles for IL-11 signaling in cancer development and progression: Focus on breast cancer. *Cytokine Growth Factor Rev*. Oct. 2015;26(5):489-98. doi: 10.1016/j.cytogr.2015.07.015. Epub Jul. 14, 2015.
- Lemoli et al., Interleukin-11 (IL-11) acts as a synergistic factor for the proliferation of human myeloid leukaemic cells. *Br J Haematol*. Oct. 1995;91(2):319-26.
- [No Author Listed] Recombinant Human Anti-human Il111 Antibody. Creative Biolabs. May 8, 2018.
- Putoczki et al., Interleukin-11 is the dominant IL-6 family cytokine during gastrointestinal tumorigenesis and can be targeted therapeutically. *Cancer Cell*. Aug. 12, 2013;24(2):257-71. doi: 10.1016/j.ccr.2013.06.017.
- Sommer et al., Constitutively active mutant gp130 receptor protein from inflammatory hepatocellular adenoma is inhibited by an anti-gp130 antibody that specifically neutralizes interleukin 11 signaling. *J Biol Chem*. Apr. 20, 2012;287(17):13743-51. doi: 10.1074/jbc.M111.349167.

Figure 1A

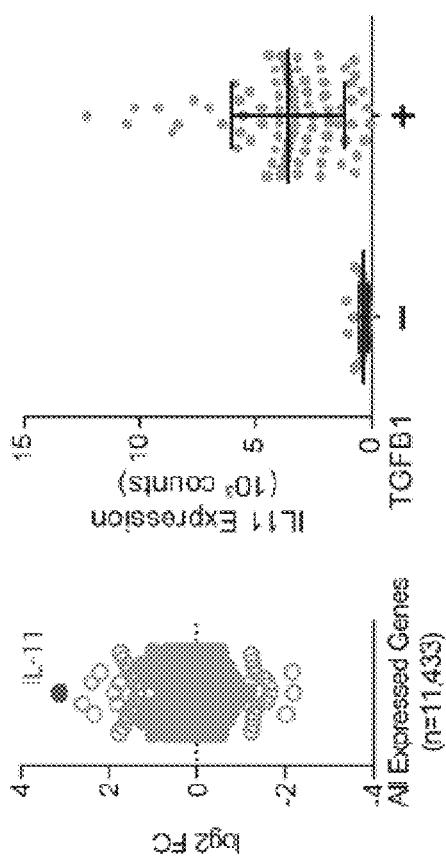


Figure 1B



Figure 1C

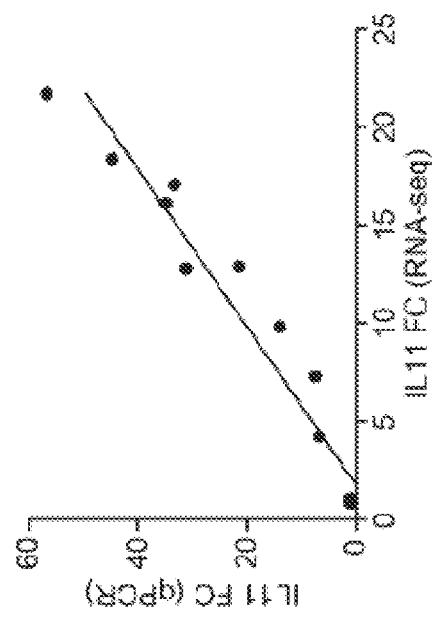


Figure 1D

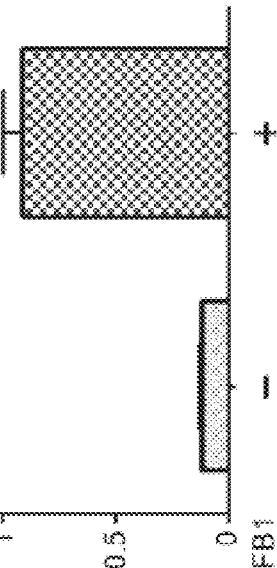


Figure 2B

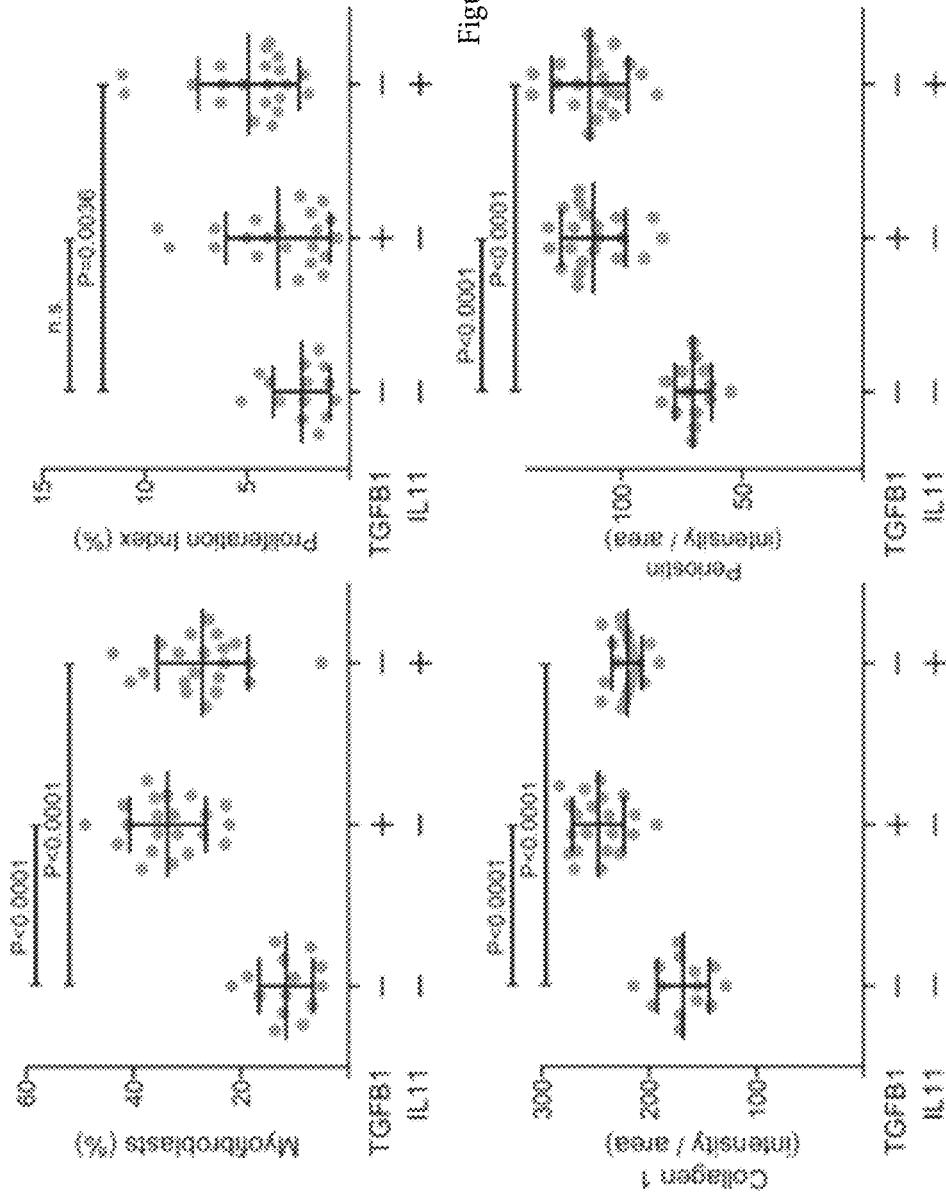


Figure 2A

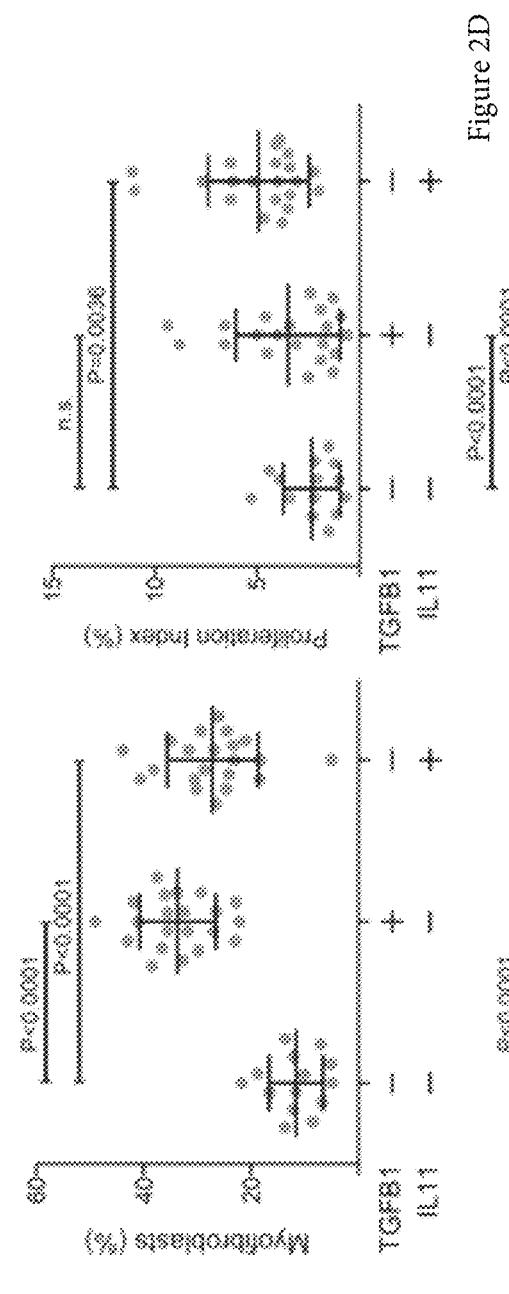
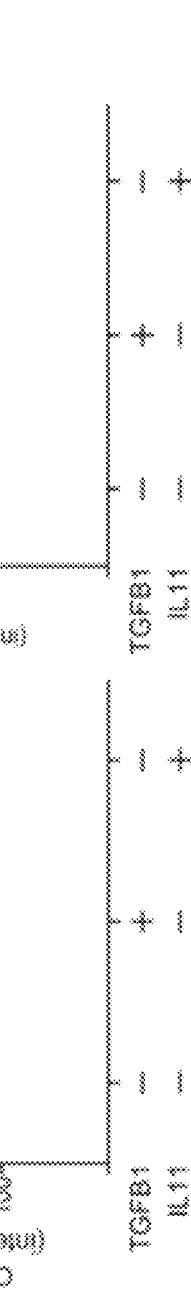
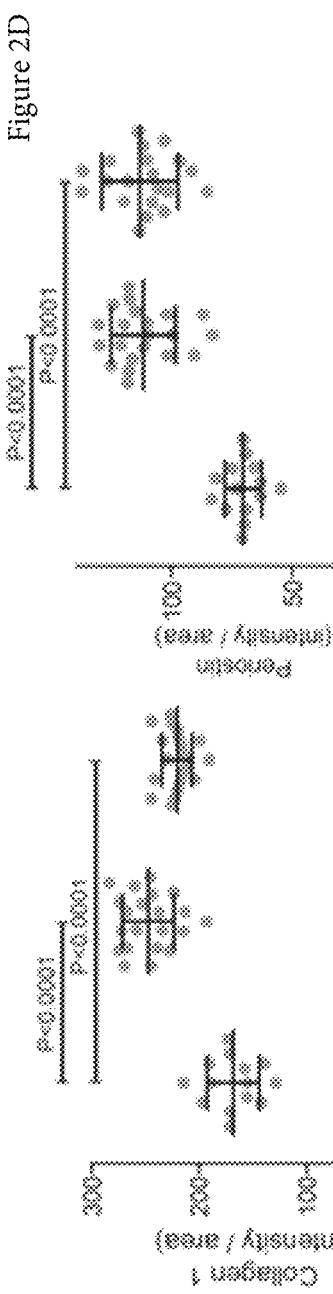


Figure 2C



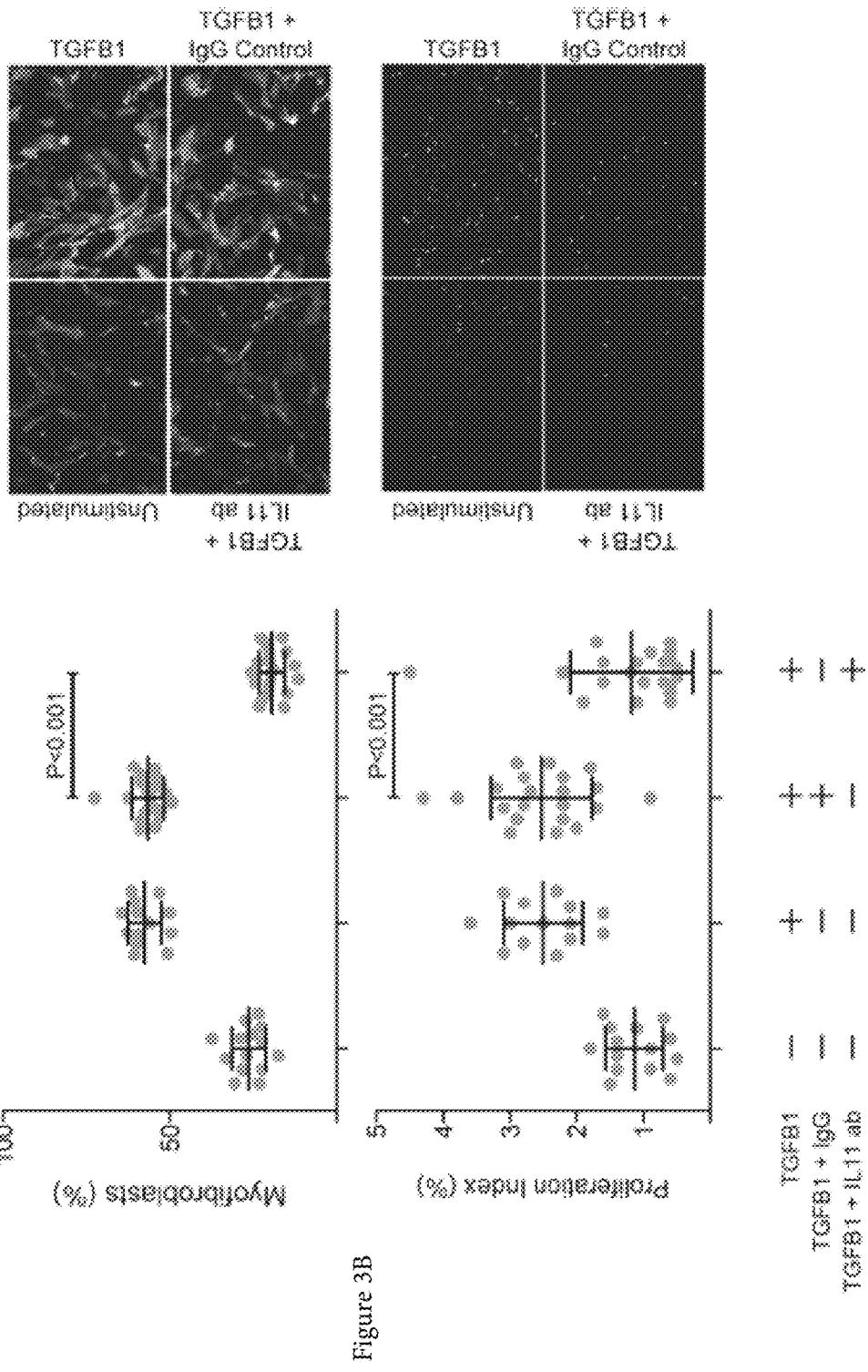


Figure 3A

Figure 3B

Explore Litigation Insights



Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.