



Anlotinib Inhibits PFKFB3-Driven Glycolysis in Myofibroblasts to Reverse Pulmonary Fibrosis

Weimou Chen^{1†}, Jinming Zhang^{1†}, Wenshan Zhong^{1†}, Yuanyuan Liu¹, Ye Lu¹, Zhaojin Zeng¹, Haohua Huang¹, Xuan Wan¹, Xiaojing Meng², Fei Zou², Shaoxi Cai^{1*} and Hangming Dong^{1*}

¹Chronic Airways Diseases Laboratory, Department of Respiratory and Critical Care Medicine, Nanfang Hospital, Southern Medical University, Guangzhou, China, ²Guangdong Provincial Key Laboratory of Tropical Disease Research, Department of Occupational Health and Medicine, School of Public Health, Southern Medical University, Guangzhou, China

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*Correspondence:

Hangming Dong dhm@smu.edu.cn Shaoxi Cai hxkc@smu.edu.cn

[†]These authors have contributed equally to this work

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Chen W, Zhang J, Zhong W, Liu Y, Lu Y, Zeng Z, Huang H, Wan X, Meng X, Zou F, Cai S and Dong H (2021) Anlotinib Inhibits PFKFB3-Driven Glycolysis in Myofibroblasts to Reverse Pulmonary Fibrosis. Front. Pharmacol. 12:744826. doi: 10.3389/fphar.2021.744826 Idiopathic pulmonary fibrosis (IPF) is a fatal disease in which the normal alveolar network is gradually replaced by fibrotic scars. Current evidence suggests that metabolic alterations correlate with myofibroblast activation in IPF. Anlotinib has been proposed to have antifibrotic effects, but the efficacy and mechanisms of anlotinib against lung fibrosis have not been systematically evaluated. The antifibrotic effects of anlotinib were evaluated in bleomycin-induced mouse models and transforming growth factor-beta 1 (TGF-B1)stimulated lung fibroblasts. We measured lactate levels, 2-NBDG glucose uptake and the extracellular acidification rate (ECAR) to assess glycolysis in fibroblasts. RNA-protein coimmunoprecipitation (RIP) and polysome analyses were performed to investigate novel mechanisms of glycolytic reprogramming in pulmonary fibrosis. We found that anlotinib diminished myofibroblast activation and inhibited the augmentation of glycolysis. Moreover, we show that PCBP3 posttranscriptionally increases PFKFB3 expression by promoting its translation during myofibroblast activation, thus promoting glycolysis in myofibroblasts. Regarding mechanism, anlotinib exerts potent antifibrotic effects by downregulating PCBP3, reducing PFKFB3 translation and inhibiting glycolysis in myofibroblasts. Furthermore, we observed that anlotinib had preventative and therapeutic antifibrotic effects on bleomycin-induced pulmonary fibrosis. Therefore, we identify PCBP3 as a protein involved in the regulation of glycolysis reprogramming and lung fibrogenesis and propose it as a therapeutic target for pulmonary fibrosis. Our data suggest that anlotinib has antifibrotic effects on the lungs, and we provide a novel mechanism for this effect. Anlotinib may constitute a novel and potent candidate for the treatment of pulmonary fibrosis.

Keywords: pulmonary fibrosis, anlotinib, glycolysis, PFKFB3, PCBP3

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Abbreviations: IPF, idiopathic pulmonary fibrosis; BLM, bleomycin; RBP, RNA binding protein; α -SMA, α -smooth muscle actin; ECM, extracellular matrix; PFKFB3, 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase-3; F2, 6BP, fructose-2, 6-bisphosphate; PFK1, phosphofructokinase-1; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; TGF- β 1, transforming growth factor-beta 1; TV, tidal volume; Cdyn, dynamic compliance; RI, resistance; HYP, hydroxyproline; IHC, immunohistochemical; H&E, Hematoxylin and eosin; MLF, mouse lung fibroblasts; PPI, protein-protein interaction; MAPK, mitogen-activated protein kinase; ECAR, extracellular acidification rate; siRNA, small interfering RNA; DMSO, dimethylsulfoxide; PBS, phosphate buffered saline; DMEM, Dulbecco's Modified Eagle Medium; FBS, fetal bovine serum; DAPI, 4',6-diamidino-2-phenylindole.

INTRODUCTION

Fibrosis can develop in most organs and cause organ failure. The most common type of lung fibrosis is idiopathic pulmonary fibrosis (IPF), which is highly prevalent and associated with a dramatically increased disease burden worldwide (Wynn and Ramalingam, 2012; Hutchinson et al., 2015). Overall, the development of new therapeutics should be pursued. Currently, only pirfenidone and nintedanib have been approved as therapeutics for IPF (Taniguchi et al., 2010; Sato et al., 2017), and as both drugs have limited efficacy (Spagnolo and Maher, 2017), there is an urgent need to identify new potential therapeutic agents for IPF patients.

Upon chronic microinjury to the alveolar epithelium, fibroblast activation and transdifferentiation into myofibroblasts are among the first responses detectable at the site of damage (Plantier et al., 2018). Myofibroblasts are characterized by de novo expression of a-smooth muscle actin (α -SMA), the formation of stress fibers, and enhanced abilities to proliferate, migrate, and produce extracellular matrix (ECM) (Hinz, 2012; Hinz et al., 2012; Liu et al., 2021). These cells drive a wound-healing response that relies on the deposition of collagen-rich ECM and activates transforming growth factor-beta 1 (TGF-β1) signaling (Kenyon et al., 2003; Sapudom et al., 2015; Nigdelioglu et al., 2016). This transient response must be tightly controlled, otherwise it can become persistent and lead to excessive matrix accumulation and fibrosis. Understanding the molecular bases of fibroblast activation is therefore essential in identifying novel and efficient antifibrotic therapeutic targets to reduce the incidence, morbidity and mortality of people suffering from clinically refractory disorders, including IPF.

Metabolic perturbation is implicated in the pathogenesis of several kinds of tissue fibrosis (DeBerardinis and Thompson, 2012; Chen et al., 2018), including pulmonary fibrosis (Para et al., 2019; Bueno et al., 2020). To cope with the high energy demands of myofibroblasts, including increases in proliferation and matrix production, it is reasonable that activated myofibroblasts exhibit augmented aerobic glycolysis to meet additional bioenergetic and biosynthetic demands, even in oxygen-rich conditions, similar to observations in many cancer cells and other nonmalignant proliferating cells. A major driver of glycolysis is 6phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3), which produces fructose-2,6-bisphosphate (F2,6BP), the most potent allosteric activator of the glycolytic rate-limiting enzyme phosphofructokinase-1 (PFK1) (Van Schaftingen et al., 1982; Cao et al., 2019). Previous studies have shown that augmentation of aerobic glycolysis is an essential step during myofibroblast activation (Para et al., 2019). Ramping down glycolysis is effective in diminishing myofibroblast activation, thus limiting lung fibrosis. However, metabolism-based therapeutics for treating fibrotic disorders are still lacking.

Anlotinib (AL3818) hydrochloride is a novel multitargeted tyrosine kinase inhibitor (TKI) that targets the receptor tyrosine kinases vascular endothelial growth factor receptor (VEGFR) 1 thru 3, epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR) 1 thru 4, platelet-derived growth factor receptor (PDGFR) α and β , and stem cell factor receptor (Sun et al., 2016; Xie et al., 2018). Many studies have reported the therapeutic effects of anlotinib in several diseases, such as nonsmall cell lung cancer (Liang

et al., 2019), endometrial cancers (Taurin et al., 2018) and osteosarcoma (Liang et al., 2019). Interestingly, the targets of anlotinib are similar to those of nintedanib, a drug that has been approved for the treatment of IPF. A recent report suggested that intraperitoneal administration of anlotinib attenuates bleomycin-induced lung fibrosis in mice by suppressing the TGF- β signaling pathway (Ruan et al., 2020). Nevertheless, the mechanism by which anlotinib resolves lung fibrosis and whether anlotinib may be therapeutically used to improve lung function are not well understood.

In the current study, we analyzed the antifibrotic effect of anlotinib on TGF- β 1-induced fibroblast transdifferentiation and bleomycin-induced pulmonary fibrosis. Our data suggest that anlotinib therapy decreases fibrotic markers *in vitro* and *in vivo*. The antifibrotic effect of anlotinib is associated with inhibition of PFKFB3-dependent glycolysis, which is posttranscriptionally regulated by the RNA binding protein PCBP3. These findings provide a theoretical basis for the clinical development and application of anlotinib for the treatment of pulmonary fibrosis.

MATERIALS AND METHODS

Isolation of Primary Mouse Fibroblast Cultures

Normal mouse primary fibroblasts were generated by culturing the lungs of C57BL/6 as previously described (Meng et al., 2014). The cells were cultured in Dulbecco's modified Eagle's medium (DMEM, Gibco, United States) supplemented with 15% fetal bovine serum (FBS, PAN, German). The cells were cultured at 37°C in 5% CO2 and 95% humidity. Unless specifically noted, all experiments were performed with cells at passage 3.

Cell Lines

Human lung fibroblast line IMR90 was purchased from American Type Culture Collection (Manassas, VA). IMR90 were maintained in DMEM supplemented with 10% FBS, 100 units/mL penicillin, and 100 g/ml streptomycin in 5% CO2 and 95% humidity at 37°C.

Western Blotting

Cells or dissected mouse lung tissue samples were lysed in ice-cold RIPA lysis buffer with protease inhibitors. Protein concentrations were determined using a BCA Protein Quantitative Analysis Kit (Fudebio-tech) after which protein samples were separated by 8-12% SDS-PAGE and transferred onto polyvinylidene difluoride membranes (Millipore). The membranes were then incubated at room temperature for 1 h in TBST containing 5% BSA. After blocking, the membranes were incubated with primary antibodies for 24 h at 4°C.The following primary antibodies were used: anti-Fibronectin (Abcam, ab268020); anti-Collagen I (affinity, AF7001); anti-alpha smooth muscle (Abcam, ab5694); anti-PFKFB3 (Abcam, ab181861); anti-Beta actin (proteintech, 66009-1-Ig); anti-Hexokinase 2 (proteintech, 22029-1-AP); anti-PKM2 (Proteintech, 15822-1-AP); anti-LDHA (Proteintech, 19987-1-AP); anti-LDHB (Proteintech, 14824-1-AP); and anti-PCBP3 (Abcam, ab154252). Then, the membranes were washed three times with TBST and incubated with donkey anti-rabbit IgG H&L (Abcam, ab175772) for

1 h at room temperature. The membranes were developed using the ECL method according to the manufacturer's instructions (Millipore) and detected on a GeneGnome XRQ chemiluminescence imaging system (Syngene). ImageJ was used to calculate the relative density of proteins.

Immunofluorescence Staining

The culture medium was washed away with PBS. The cultured cells were fixed with 4% paraformaldehyde for 30 min. Then, the samples were permeabilized with 0.5% Triton X-100 in PBS for 10 min, blocked with 1% BSA in PBS for 1 h at room temperature, and incubated with primary antibodies at 4°C overnight. The primary antibodies included anti- Fibronectin (Abcam, ab268020), anti-alpha smooth muscle (Abcam, ab5694) and anti-PCBP3 (Abcam, ab154252). Then, the cells were washed three times with PBS and incubated with goat anti-rabbit IgG/ Alexa Fluor 555-conjugated secondary antibodies (Biosynthesis, bs-0296GA488 and bs-0295G-AF555) for 1 h at room temperature followed by 10 min of DAPI (4',6-diamidino-2-phenylindole dihydrochloride) staining to visualize cell nuclei visualization as previously described (Chen et al., 2021).

Quantitative RT-PCR (qPCR)

Total RNA was isolated from primary mouse lung fibroblasts using RNA MiniPrep Kits (Zymo Research, R2050). Reverse transcription reactions were performed with a PrimeScriptTM II 1st strand cDNA synthesis Kit (Takara, 6210A/B) according to the manufacturer's recommendations. qPCR analysis was performed using a HiScript RT- SuperMix for qPCR kit (Vazyme, R223-01) with a CFX96 Touch Real-Time PCR Detection System. The mRNA levels of target genes were normalized to the β -actin mRNA level. Primers used for qPCR are listed in (**Table 1**).

Wound-Healing Migration Assay

Cells were seeded in six-well plates and grown until they reach 100% confluence. A "wound" was subsequently created with a sterile 100 μ L pipette tip. The cells were pretreated with anlotinib (1 μ M) for 3 h and then exposed to TGF- β 1 (10 ng/ml) for an additional 24 h. After 24 h, the cells were fixed with 4% paraformaldehyde, and images were obtained using a fluorescence microscope. Wound area can be calculated by manually tracing the cell-free area in captured images using the ImageJ public domain software (NIH, Bethesda, MD).

Cell Proliferation Assay

Cell proliferation was determined by the CCK-8 Kit (Dojindo Laboratories) according to the manufacturer's instructions. Briefly, 10 μ L of CCK-8 solution was added to cultured cells in each well, followed by incubation at 37°C for 1 h. The OD values were measured at 450 nm using a microplate reader. EdU staining was conducted using the BeyoClickTM EdU Cell Proliferation Kit with Alexa Fluor 594 (Beyotime, Cat. No: C00788L). Cells were washed with PBS. Fresh DMEM was added, and then, 10 μ M EdU was added into the medium. The cells were incubated for 2 h at 37°C/5% CO2. After the incubation, the cells were washed with PBS to remove the DMEM and the free EdU probe. The cells were then fixed in 4% paraformaldehyde at room temperature for

30 min before being stained with DAPI for 3 min. After an additional wash in PBS, the cells were observed under Nikon ECLIPSE TS100 (Japan).

Glucose Uptake Assay

Primary mouse lung fibroblasts were pretreated with anlotinib (1 μ M) for 3 h and then exposed to TGF- β 1 (10 ng/ml) for an additional 24 h. Then, the four types of cells were detached and transferred to a 96-well plate in fresh growth medium at a density of 10,000 cells per well for the direct 2-NBDG glucose uptake assay. The cells were rinsed twice with PBS. Glucose uptake was initiated by the addition of 100 μ M 2-NBDG to each well. After 30 min, the medium was removed. The plates were then rinsed with PBS, and the fluorescence was measured at an excitation wavelength of 485 nm and an emission wavelength of 535 nm.

Intracellular and Extracellular Lactate Analysis

To measure lactate production, cells were treated as described for the glucose uptake assay. One hundred thousand cells were then plated into a 12-well plate and incubated in DMEM containing 10% FBS for 10 h. To measure the secretion of lactate, the media were removed, and the cells were incubated in FBS-free DMEM. After incubation for 1 h, the supernatant was collected to measure lactate production (Biovision). The reaction mixture was incubated for 30 min at room temperature in the dark. The lactate levels were measured at 450 nm in a microplate reader and normalized to the protein concentrations. To measure the lactate levels in mouse lung tissue, 10 mg of lung tissues was isolated and homogenized in assay buffer (Biovision). The samples were centrifuged, and the soluble fractions were measured and normalized to the protein concentrations.

Extracellular Acidification Rate

The extracellular acidification rate (ECAR) was measured using the Agilent Seahorse XFp Extracellular Flux Analyzer (Seahorse Bioscience). Experiments were performed according to the manufacturer's instructions. ECAR were measured using Seahorse XF Glycolysis Stress Test Kit (Agilent Technologies). Briefly, cells were transfected or infected as in glucose uptake assay. The transfected cells were harvested and the cell number was counted. After baseline measurements, glucose, the oxidative phosphorylation inhibitor oligomycin, and the glycolytic inhibitor 2-DG were sequentially injected into each well at the indicated time points. Data were analysed by Seahorse XFp Wave software. ECAR is reported in mpH/minute. The cells in each well were digested by trypsin digestion (Gibco, United States), and count cell numbers by cell counting chamber. The results were normalized to normalized to cell number in each well.

RNA Immunoprecipitation (RIP)

Cells were rinsed twice with ice-cold PBS and lysed with an equal pellet volume of RIPA-2 buffer. Protein-A Dynabeads (Invitrogen) were incubated with either mouse IgG or FLAG antibody (Abcam, ab205606). Beads coated in antibody were resuspended in NT2 buffer. Thawed and clarified lysates were added and the bead/antibody/lysate mixture was incubated at

4°C overnight rotating end-over-end. Beads were washed with cold NT2 buffer five times. Proteinase K treatment released RNAs from bound proteins and input and bound RNA was isolated with TRIzol (Invitrogen) and reverse transcribed as described above.

Polysome Analysis

Cells were transfected with empty vector or Flag-PCBP3 and incubated with 100 g/ml cycloheximide for 10 min and lysed with polysome extraction buffer containing 20 mM Tris–HCl, pH 7.5, 100 mM KCl, 5 mM MgCl2 and 0.5% NP-40 as previously described (Kim et al., 2015). Cytoplasmic lysates were fractionated by ultracentrifugation through 10–50% linear sucrose gradients and divided into 12 fractions. The total RNA in each fraction was extracted and analyzed by quantitative RT-PCR analysis.

Overexpression Experiments and RNA Interference

The Plasmid vector encoding PCBP3 and the empty vector were purchased from Hanbio (Shanghai, China). Primary mouse lung fibroblasts were cultured in six well plates (105 cells/well) and added with 2.5 μ g of target plasmid per well. After 12 h, the transfection medium was changed to normal medium. Effects of overexpression on mRNA and protein levels were examined 36 h later. The siRNA targeting mouse PFKFB3 (PFKFB3 siRNA: 5'-CCUCUUGACCCUGAUAAAUTT-3') were synthesized by Genepharma Co. (Shanghai, China). Primary mouse lung fibroblasts were cultured in six well plates (105 cells/well) and transfected using Lipofectamine 3,000 (Invitrogen, CA) with PFKFB3 siRNA or negative control siRNA (NC siRNA) for 48 h following the manufacturer's instructions.

Animal Experiments

All experiments were conducted in accordance with protocols approved by the Southern Medical University Institutional Animal Care and Use Committee. Female mice (C57BL/6), 6-8 weeks of age, were purchased from Southern Medical University. The mice were kept on a 12 h light-dark cycle with free access to food and water. For bleomycin administration, the mice were anesthetized with 2, 2, 2tribromoethanol (Sigma-Aldrich), followed by intratracheal instillation of BLM (5 U/kg, i. t.) in 50 µL phosphate-buffered saline (PBS) or equally volume PBS for 21 days. The mice were administered dimethyl sulfoxide (DMSO) (control group) or anlotinib (1 mg/kg, i. p.) once daily for 21 consecutive days. Further experiments were designed to measure the effects of delayed anlotinib administration. Anlotinib treatment was initiated 1 week after exposure to bleomycin, and the mice were administered with anlotinib (1 or 2 mg/kg/day) for 2 weeks, and the mice were sacrificed at day 21. The lungs were harvested for further analyses.

Pulmonary Function Test

At endpoint, at least 5 mice from each group were anesthetized with 2,2,2-tribromoethanol in saline, tracheotomized below the larynx, and intubated with a tracheal cannula. After the surgery, the mice were placed inside the plethysmographic chamber and the cannula was connected to the machine. Pulmonary function was measured by pulmonary function test system (BUXCO, United States). The system's software automatically records and displays the pulmonary function parameters.

Hydroxyproline Assay

Lung collagen content was measured with a hydroxyproline (HYP) kit (Nanjing Jian Cheng Institute, Nanjing, China). The lung tissues were prepared for hydrolysis, adjusting the PH value to 6.0–6.8. Subsequently, the developing solution was added to the tissues that were incubated at 37° C for 5 min. Absorbance was read at 550 nm using a microplate reader. Data were expressed as micrograms (µg) of HYP per mg of wet lung tissue.

Materials

TGF- β 1 were purchased from R&D Systems, Inc. (Minneapolis, MN, United States). Anlotinib dihydrochloride (AL3818, S8726) were purchased from Selleck (Houston, TX, United States).

Statistical Analysis

The results are expressed as the means \pm standard deviation (SD). Multigroup comparisons were performed using one-way ANOVA. Student's t-test was used for comparisons between two groups. A *p* value of less than 0.05 was considered significant. Replicates consisted of at least three independent experiments. Analyses were performed on SPSS version 25.0 (IBM) for Windows and GraphPad Prism version 6.0 (GraphPad Software, CA).

RESULTS

Anlotinib Represses Myofibroblast Activation and the Profibrogenic Phenotype *in vitro*

Given that TGF- β 1 is the predominant cytokine that stimulates the differentiation of lung fibroblasts into myofibroblasts and induces ECM production (Sapudom et al., 2015; Huang et al., 2020), we examined the effect of anlotinib (the chemical structure is shown in Supplementary Figure S1) on TGF-β1-induced activation of primary mouse lung fibroblasts (MLFs). The CCK-8 assay results showed that anlotinib did not cause significant cytotoxicity at doses of 1 µM (Figure 1A). To mimic the inhibitory effect of anlotinib on the progression of lung fibrosis, primary MLFs were pretreated with anlotinib $(1 \mu M)$ for 3 h and then exposed to TGF- β 1 (10 ng/ml) for an additional 24 h. Our results demonstrated that TGF-B1 induced the expression of fibronectin, collagen I, and a-SMA, but anlotinib reversed the expression of these fibrotic markers (Figures 1B,C). Immunofluorescence analysis of a-SMA and fibronectin showed similar results (Figures 1D,E). We also examined whether anlotinib affected the proliferation and migration of fibroblasts, which have been shown to significantly contribute to many fibrotic pathologies (Jarman et al., 2014; Huang et al., 2020). As shown by the EdU (Figures 1F,G) and CCK-8 results (Figure 1H), anlotinib treatment prevented the TGF-\u00b31-induced proliferation of



FIGURE 1 Anlotinib represses myofibroblast activation and the profibrogenic phenotype *in vitro*. (A) Dose-dependent cytotoxicity of anlotinib in primary mouse lung fibroblast isolated from healthy mice by CCK-8. (B) Western blots analysis of Fibronectin, Collagen I, α -SMA and β -actin in mouse lung fibroblasts treated with anlotinib (1 µM) for 3 h and then exposed to TGF- β 1 (10 ng/ml) for 3 h, followed by TGF- β 1 for an additional 24 h. (C) Quantification for the indicated protein (mean ± SD, n = 3). Immunofluorescence for α -SMA (green) (D) and Fibronectin (green) (E). DAPI-stained nuclei (blue). Scale bar, 25 µm. (F) An EdU assay was used to observe the proliferative cells. Scale bar, 100 µm. (G) The number of EdU-positive cells was recorded (mean ± SD, n = 3). (H) A cck8 assay was used to observe the proliferative cells. (I) Representative images to show scratch-wound assay. Scale bars, 100 µm. Experiments were performed as in B. Images were taken 0, and 24 h after assay (white lines indicate wound edge). (J) Quantitative analysis of migration distance (mean ± SD, n = 3). (K) Western blots analysis of Fibronectin, Collagen I, α -SMA and β -actin in IMR90 cells treated with anlotinib (1 µM) for 3 h and then exposed to TGF- β 1 (10 ng/ml) for an additional 24 h. (L) Quantification for the indicated proteins in IMR90 cells (mean ± SD, n = 3). *p < 0.05, **p < 0.01, ***p < 0.001 VS TGF- β 1-treated group (ANOVA).



FIGURE 2 Anlotinib inhibits PFKFB3-driven glycolysis in lung myofibroblasts. (**A**) Venn diagram to show the overlaps between anlotinib targets and lung fibrosisrelated targets. (**B**) Protein-protein interaction (PPI) network of common targets between anlotinib and IPF. (**C**) The KEGG enrichment analysis of 74 targets of common targets. (**D**)The GO enrichment for each section listed. The mouse lung fibroblasts were pretreated with anlotinib (1 μ M) for 3 h and then exposed to TGF- β 1 (10 ng/ml) for an additional 24 h, and then the cells were lysed and lactate contents in the cellular lysates (**E**) and culture media (**F**) were determined. The data are presented as fold change relative to the levels of the untreated control group (mean ± SD, n = 3). (**G**) Glucose uptake detected with 2-NBDG were determined. The data are presented as fold change relative to the levels of the untreated control group (mean ± SD, n = 3). (**H**) Extracellular acidification rate (ECAR) was assessed. (**I**) Glycolysis and glycolysis capacity were quantified and shown as histograms (mean ± SD, n = 3). (**J**) Western blot analysis of HK2, PKM2, PFKFB3, LDHA and LDHB, β -actin was used as a loading control. (**K**) Quantification of HK2, PKM2, PFKFB3, LDHA and LDHB protein levels relative to β -Actin is shown (mean ± SD, n = 3). **I**, **K**, **p* < 0.05, ***p* < 0.01, ****p* < 0.001 VS TGF- β 1-treated group by ANOVA.



FIGURE 3 | PCBP3 posttranscriptionally increases PFKFB3 expression by promoting its translation during myofibroblast activation.

FIGURE 3 | PCBP3 posttranscriptionally increases PFKFB3 expression by promoting its translation during myofibroblast activation. (A) PFKFB3 degradation in mouse lung fibroblasts when protein synthesis was inhibited by 50 μ M cycloheximide (mean \pm SD, n = 3). (B) Prediction of RNA–protein interaction of PFKFB3 mRNA with PCBP3 protein using the catRAPID algorithm. Red represents interaction strength. (C) Western blot analysis of PFKFB3 and PCBP3 protein levels in mouse lung fibroblasts stimulated with TGF- β 1 for the indicated concentrations. (D) Quantification of PFKFB3 and PCBP3 protein levels relative to β -actin is shown (mean \pm SD, n = 3, **p < 0.01, ***p < 0.001 compared with 0 by one-way ANOVA). (E) Quantification of PFKFB3 and PCBP3 protein levels relative to β -actin is shown (mean \pm SD, n = 3, **p < 0.01, (RIP) in mouse lung fibroblasts. Values were plotted as mean \pm SD from three independent experiments. *p* value was calculated by Student t test. ***p < 0.001. (F) Mouse lung fibroblasts expressing Flag-PCBP3 were fractionated into cytoplasmic extracts through sucrose gradients. The arrow indicates the direction of sedimentation. The distribution of PFKFB3 and β -actin mRNAs was quantified by RT-PCR analysis of RNA isolated from 12 gradient fractions. Statistical analyses were performed using Student t test. ***p < 0.001. (G) Mouse lung fibroblasts were transfected with Flag-PCBP3, and then transfected with PFKFB3-siRNAs or NC-siRNA. The levels of Fibronectin, Collagen I, PFKFB3, α -SMA, PCBP3 and β -actin assessed by western blot. (H) Graphical representation of the relative levels of indicated proteins (mean \pm SD, n = 3, *p < 0.05, **p < 0.001, ***p < 0.001, ***p



0.001 VS TGF-β1-treated group by ANOVA.

primary MLFs. Moreover, anlotinib inhibited the TGF- β 1induced migration of fibroblasts (**Figures 1I,J**). These results were confirmed in the human IMR90 cell line (**Figures 1K, L** and **Supplementary Figures S2A-D**). These data indicate that anlotinib can repress myofibroblast activation and the profibrogenic phenotype *in vitro*.

Anlotinib Inhibits PFKFB3-Driven Glycolysis in Lung Myofibroblasts

To investigate the potential antifibrotic mechanisms of anlotinib, we estimated the most likely macromolecular targets of anlotinib and obtained 100 potential targets through SwissTargetPrediction (Table 2) (Gfeller et al., 2014). A total of 7,360 lung fibrosis-related targets were obtained from the GeneCards database (Table 3) (Safran et al., 2002). To clarify the interaction between potential anlotinib targets and lung fibrosis-related targets, the intersection of the targets was mapped by drawing a Venn diagram and constructing a target network (Figure 2A). Seventy-four common targets were shared between the potential anlotinib targets and lung fibrosis-related targets (Table 4). STRING (version 11.0) was used for proteinprotein interaction (PPI) analysis (Figure 2B) (Szklarczyk et al., 2019). Bioinformatics analysis data identified mitogenactivated protein kinase (MAPK) signaling pathway-related genes as the top hits among the 74 genes (Figure 2C). Given that the MAPK pathway is well recognized as a metabolic regulator and that many of these genes control metabolic processes (Figure 2D) (Ho et al., 2004; Papa et al., 2019; Hu et al., 2020; Wang F. et al., 2020), we first confirmed the presence of glycolytic alterations in lung myofibroblasts. We directly measured the levels of lactate and found that both

intracellular and extracellular lactate levels in lung myofibroblasts treated with TGF-B1 were significantly increased (Figures 2E,F). Consistent with the augmented glycolysis in lung myofibroblasts, these cells also demonstrated increased glucose consumption (Figure 2G). However, anlotinib treatment decreased the production and secretion of lactate and reduced the consumption of glucose (Figures 2E-G). Accordingly, extracellular acidification rate (ECAR) analysis indicated that treatment with TGF-B1 increased glycolysis and glycolytic activity in primary MLFs, both of which were also reduced by anlotinib (Figures 2H,I). To delineate the mechanisms by which anlotinib inhibits the augmented glycolysis observed in lung myofibroblasts, we assessed the expression of key glycolytic enzymes in these cells. We found that PFKFB3 was induced by TGF-B1 in lung fibroblasts and that anlotinib significantly decreased its expression at the protein level (Figures 2J,K). PFKFB3 is not a rate-limiting glycolytic enzyme; instead, PFKFB3 catalyzes the conversion fructose-6-phosphate to fructose-2,6of bisphosphate, which is an allosteric activator of PFK1 and a potent stimulator of glycolysis (Atsumi et al., 2002; De Bock et al., 2013). Taken together, these data suggest that anlotinib can abrogate the PFKFB3-driven increase in glycolysis, participating in myofibroblast activation.

PCBP3 Posttranscriptionally Increases PFKFB3 Expression by Promoting Its Translation During Myofibroblast Activation

Interestingly, the progressive upregulation of PFKFB3 during myofibroblast activation induced by TGF- β 1 that was observed at the protein level was not confirmed at the mRNA level, as measured by RT-PCR (**Supplementary Figures S3A, B**). These



FIGURE 5 | Anlotinib attenuates bleomycin-induced pulmonary fibrosis. (A) Intervention dosing regimen of anlotinib in experimental mouse model of fibrosis. C57BL/6 mice were intraperitonealy injuected with 1 mg/kg of anlotinib or vehicle (n = 5-6 per group) daily after bleomycin instillation. Lungs were harvested at 21 days for the following analyses. Analysis of tidal volume (TV) (B), dynamic compliance (Cdyn) (C), and lung resistance (RI) (D) (mean \pm SD, n = 5). (E) Hydroxyproline (HYP) contents in lung tissues from mice (mean \pm SD, n = 5). Representative images show haematoxylin and eosin (H&E), Masson's trichrome (F), α -SMA and Fibronectin staining (G) of lung sections from the indicated groups of mice. Scale bars, 100 µm. (H) Western blot analysis of Fibronectin, Collagen I and α -SMA, β -actin was used as a loading control. (I) Quantification of Fibronectin, Collagen I and α -SMA protein levels relative to β -actin is shown (mean \pm SD, n = 6). *p < 0.05, **p < 0.01, ***p < 0.001 VS BLM-treated group by one-way ANOVA.



results indicate that TGF- β 1-induced overexpression does not require *de novo* transcription of PFKFB3. To further verify these findings, primary MLFs were incubated with cycloheximide to block new protein synthesis, and immunoblotting was used to measure PFKFB3 levels (**Figure 3A**). The half-life of PFKFB3 was not significantly altered, indicating that TGF- β 1 does not influence PFKFB3 protein stability. Therefore, we postulated that PFKFB3 upregulation is modulated through posttranscriptional mechanisms in this context. To verify this hypothesis, we used the online tool catRAPID to screen for potential proteins that may interact with PFKFB3 mRNA and identified that PCBP3 (**Table 5**) (Agostini et al., 2013; Livi et al.,



FIGURE 7 | Anlotinib accelerates resolution of bleomycin-induced pulmonary fibrosis. (A) Intervention dosing regimen of anlotinib in established pulmonary fibrosis. Bleomycin instillation was used to induce fibrosis and no treatment was given during the first 7 d. Then, mice were intraperitonealy injuected with 1 or 2 mg/kg of anlotinib or vehicle (n = 5-6 per group) daily. Lungs were harvested at 21 days. Tidal volume (TV) (B), dynamic compliance (Cdyn) (C), and lung resistance (RI) (D) of mice were measured (mean \pm SD, n = 5). (E) HYP contents in lung tissues from mice (mean \pm SD, n = 5). Representative images show H&E, Masson's trichrome (F), α -SMA and Fibronectin staining (G) of lung sections from the indicated groups of mice. Scale bars, 100 µm. (H) Western blot analysis of Fibronectin, Collagen I and α -SMA, β -actin was used as a loading control (n = 4). (I) Quantification of Fibronectin, Collagen I and α -SMA protein levels relative to β -actin is shown (mean \pm SD, n = 5). *p < 0.05, **p < 0.01, ***p < 0.001 VS BLM-treated group by one-way ANOVA.

2016), a member of the PCBP family, has a high probability of directly interacting with PFKFB3 mRNA (**Figure 3B**) (Choi et al., 2007; Kang et al., 2012; Leidgens et al., 2013; Wang J. et al., 2020).

We comparatively analyzed the expression of PCBP3 after treatment with different doses of TGF- β 1 by immunoblot analysis and found that PCBP3 protein expression was



TABLE 1 List of prin	st of primer sequences used in this study.						
Gene	Species	Forward primer	Reverse primer				
β-actin	Mus musculus	GGCTGTATTCCCCTCCATCG	CCAGTTGGTAACAATGCCATGT				
PFKFB3	Mus musculus	CCCAGAGCCGGGTACAGAA	GGGGAGTTGGTCAGCTTCG				

increased in primary MLFs after TGF-B1 treatment (Figures 3C,D), which correlated with PFKFB3 overexpression. To better define the connection between PCBP3 function and PFKFB3, we performed RNA-protein coimmunoprecipitation (RIP) studies in primary MLFs transfected with FLAG-tagged PCBP3 (FLAG-PCBP3). An antibody targeting the FLAG protein was used to immunoprecipitate FLAG-PCBP3 and any interacting molecules from the cell lysates. Reverse transcription followed by PCR was then used to identify individual PFKFB3 mRNAs isolated with FLAG-PCBP3. We found that PFKFB3 transcripts were enriched by PCBP3 coimmunoprecipitation compared to control IgG coimmunoprecipitation (Figure 3E), demonstrating that PFKFB3 mRNA is indeed a direct target of PCBP3 in MLFs. To test the possibility that PCBP3 may influence PFKFB3 translation, we performed polysome analysis in cells transfected with FLAG-PCBP3. Cytoplasmic lysates were fractionated through sucrose gradients to separate ribosomal subunits (40S and 60S), monosomes (80S) and progressively larger polysomes. RNA was extracted from each of the 12 fractions, and the levels of PFKFB3 and β -actin mRNA were quantified by quantitative RT-PCR. While PFKFB3 mRNA levels peaked in fraction 7 in control cells, the distribution of PFKFB3 mRNA shifted rightward when PCBP3 was overexpressed, peaking in fraction 9, indicating that PFKFB3 mRNA formed, on average, larger polysomes after PCBP3 overexpression (**Figure 3F**). The distribution of β -actin mRNA was not affected by PCBP3 overexpression. These results indicated that overexpression of

TABLE 2 | Targets of anIotinib obtained through SwissTargetPrediction.

Target	Common name	Uniprot ID	ChEMBL ID	Target class	Probability*	Known actives
	A)//	Dooroo			0.400405704404	(30/20)
Tyrosine-protein kinase receptor UFO	AXL	P30530	CHEMBL4895	Kinase	0.106165761464	72/8 50/0
Tyrosine-protein kinase receptor TYRO3		Q06418	CHEMBL5314	Kinase	0.106165761464	53/3 46/0
kipasa MER	MERIK	Q12866	CHEIVIBL5331	Kinase	0.106165761464	46/3
Recentor protein-tyrosine kinase erbB-2	EBBB2	P04626	CHEMBI 1824	Kinase	0 106165761464	178/5
Tyrosine-protein kinase BBK	PTK6	013882	CHEMBL 4601	Kinase	0.106165761464	22/2
Serine/threonine-protein kinase Aurora-B	AURKB	096GD4	CHEMBL 2185	Kinase	0.106165761464	143/14
Vascular endothelial growth factor receptor 1	FLT1	P17948	CHEMBL1868	Kinase	0.106165761464	79/18
Epidermal growth factor receptor erbB1	EGFR	P00533	CHEMBL203	Kinase	0.106165761464	597/31
Vascular endothelial growth factor receptor 2	KDR	P35968	CHEMBL279	Kinase	0.106165761464	485/95
Tyrosine-protein kinase SRC	SRC	P12931	CHEMBL267	Kinase	0.106165761464	448/42
Hepatocyte growth factor receptor	MET	P08581	CHEMBL3717	Kinase	0.106165761464	314/108
Serine/threonine-protein kinase GAK	GAK	O14976	CHEMBL4355	Kinase	0.106165761464	16/2
Kinesin-1 heavy chain/Tyrosine-protein kinase receptor RET	RET	P07949	CHEMBL2041	Kinase	0.106165761464	72/11
ALK tyrosine kinase receptor	ALK	Q9UM73	CHEMBL4247	Kinase	0.106165761464	207/3
Tyrosine-protein kinase ABL	ABL1	P00519	CHEMBL1862	Kinase	0.106165761464	127/11
Stem cell growth factor receptor	KIT	P10721	CHEMBL1936	Kinase	0.106165761464	106/10
Activin receptor type-1	ACVR1	Q04771	CHEMBL5903	Kinase	0.106165761464	29/1
Vascular endothelial growth factor receptor 3	FLT4	P35916	CHEMBL1955	Kinase	0.106165761464	37/8
Tyrosine-protein kinase receptor FLT3	FLT3	P36888	CHEMBL1974	Kinase	0.106165761464	156/14
Platelet-derived growth factor receptor alpha	PDGFRA	P16234	CHEMBL2007	Kinase	0.106165761464	57/14
Fibroblast growth factor receptor 1	FGFR1	P11362	CHEMBL3650	Kinase	0.106165761464	189/9
TGF-beta receptor type I	TGFBR1	P36897	CHEMBL4439	Kinase	0.106165761464	78/4
Tyrosine-protein kinase LCK	LCK	P06239	CHEMBL258	Kinase	0.106165761464	167/19
Tyrosine-protein kinase BTK	BIK	Q06187	CHEMBL5251	Kinase	0.106165761464	67/5
Tyrosine-protein kinase Lyn	LYN	P07948	CHEMBL3905	Kinase	0.106165761464	76/6
Fibrobiast growth factor receptor 3	FGFR3	P22607	CHEMBL2/42	Kinase	0.106165761464	37/3
beta		P03019		Kinase	0.100105701404	0.4/0
Fibrahlast growth faster recenter 0	YESI FOFDO	P07947	CHEMBL2073	Kinase	0.100105701404	34/3
Fibrobiast growth factor receptor 2	FGFR2	P21802		Kinase	0.100105701404	35/27
Macrophage colony stimulating factor	CSE1B	P07333	CHEMBI 1844	Kinase	0.106165761464	1//4
receptor		10/000	ONEMBEIO	T T T T T T T T T T T T T T T T T T T	0.100100701404	140/1
Tyrosine-protein kinase BLK	BLK	P51451	CHEMBL2250	Kinase	0.106165761464	20/4
Serine/threonine-protein kinase PLK4	PLK4	O00444	CHEMBL3788	Kinase	0.106165761464	14/2
Ephrin receptor	EPHB4	P54760	CHEMBL5147	Kinase	0.106165761464	30/3
Tyrosine-protein kinase FYN	FYN	P06241	CHEMBL1841	Kinase	0.106165761464	36/3
Dual specificity mitogen-activated protein kinase kinase 2	MAP2K2	P36507	CHEMBL2964	Kinase	0.106165761464	11/3
Tyrosine-protein kinase HCK	HCK	P08631	CHEMBL3234	Kinase	0.106165761464	30/4
Serine/threonine-protein kinase 10	STK10	O94804	CHEMBL3981	Kinase	0.106165761464	13/4
Tyrosine-protein kinase ABL2	ABL2	P42684	CHEMBL4014	Kinase	0.106165761464	13/4
Tyrosine-protein kinase TIE-2	TEK	Q02763	CHEMBL4128	Kinase	0.106165761464	24/16
Ephrin type-A receptor 8	EPHA8	P29322	CHEMBL4134	Kinase	0.106165761464	9/3
Serine/threonine-protein kinase 2	SLK	Q9H2G2	CHEMBL4202	Kinase	0.106165761464	17/4
Tyrosine-protein kinase FRK	FRK	P42685	CHEMBL4223	Kinase	0.106165761464	15/3
Epinini type-A receptor 6			CHEIVIBL4526	Kinase	0.100105701404	10/4
Serine/threepine protein kinase		QUKED		Kinase	0.100100701404	2U/4 11/9
Mitogen-activated protein kinase kinase kinase kinase 5	MAP4K5	Q9Y4K4	CHEMBL4852	Kinase	0.106165761464	12/4
Casein kinase Lensilon	CSNK1F	P49674	CHEMBI 4937	Kinase	0 106165761464	12/3
Enhrin type-A recentor 3	FPHA3	P20320	CHEMBI 4954	Kinase	0.106165761464	11/3
Tyrosine-protein kinase recentor Tie-1	TIE1	P35590	CHEMBI 5274	Kinase	0.106165761464	11/4
Mitogen-activated protein kinase kinase kinase 3	MAP4K3	Q8IVH8	CHEMBL5432	Kinase	0.106165761464	14/3

(Continued on following page)

TABLE 2 | (Continued) Targets of anIotinib obtained through SwissTargetPrediction.

Target	Common name	Uniprot ID	ChEMBL ID	Target class	Probability*	Known actives (3D/2D)
Serine/threonine-protein kinase SIK2	SIK2	09H0K1	CHEMBL 5699	Kinase	0 106165761464	12/3
Mitogen-activated protein kinase kinase kinase	MAP4K1	Q92918	CHEMBL5749	Kinase	0.106165761464	14/3
Serine/threonine-protein kinase 33	STK33	Q9BYT3	CHEMBL6005	Kinase	0.106165761464	16/4
Mitogen-activated protein kinase kinase kinase 4	MAP4K4	O95819	CHEMBL6166	Kinase	0.106165761464	17/4
Serine/threonine-protein kinase TAO2	TAOK2	Q9UI 54	CHEMBI 1075195	Kinase	0 106165761464	7/3
Serine/threonine-protein kinase TAO3	TAOK3	Q9H2K8	CHEMBL5701	Kinase	0.106165761464	12/2
Voltage-gated calcium channel alpha2/ delta subunit 1	CACNA2D1	P54289	CHEMBL1919	Calcium channel auxiliary subunit alpha2delta family	0.106165761464	15/0
Voltage-gated calcium channel alpha2/ delta subunit 2	CACNA2D2	Q9NY47	CHEMBL3896	Calcium channel auxiliary subunit	0.106165761464	4/0
Receptor protein-tyrosine kinase erbB-4	ERBB4	Q15303	CHEMBL3009	Kinase	0.106165761464	29/3
Mitogen-activated protein kinase kinase kinase 8	MAP3K8	P41279	CHEMBL4899	Kinase	0.106165761464	32/0
Serine/threonine-protein kinase/ endoribonuclease IRE1	ERN1	O75460	CHEMBL1163101	Enzyme	0.106165761464	18/1
Macrophage-stimulating protein receptor	MST1R	Q04912	CHEMBL2689	Kinase	0.106165761464	8/11
Serine/threonine-protein kinase Aurora-C	AURKC	Q9UQB9	CHEMBL3935	Kinase	0.106165761464	15/2
Fibroblast growth factor receptor 4	FGFR4	P22455	CHEMBL3973	Kinase	0.106165761464	15/2
Ephrin type-A receptor 7	EPHA7	Q15375	CHEMBL4602	Kinase	0.106165761464	7/3
Dual specificity mitogen-activated protein kinase kinase 5	MAP2K5	Q13163	CHEMBL4948	Kinase	0.106165761464	11/4
Serine/threonine-protein kinase RIPK2	RIPK2	O43353	CHEMBL5014	Kinase	0.106165761464	6/4
Discoidin domain-containing receptor 2	DDR2	Q16832	CHEMBL5122	Kinase	0.106165761464	13/3
Activin receptor type-1B	ACVR1B	P36896	CHEMBL5310	Kinase	0.106165761464	6/1
Epithelial discoidin domain-containing receptor 1	DDR1	Q08345	CHEMBL5319	Kinase	0.106165761464	14/4
Mitogen-activated protein kinase kinase kinase 2	MAP4K2	Q12851	CHEMBL5330	Kinase	0.106165761464	15/3
Misshapen-like kinase 1	MINK1	Q8N4C8	CHEMBL5518	Kinase	0.106165761464	14/4
Leukocyte tyrosine kinase receptor	LTK	P29376	CHEMBL5627	Kinase	0.106165761464	10/3
Serine/threonine-protein kinase 35	STK35	Q8TDR2	CHEMBL5651	Kinase	0.106165761464	9/4
Ephrin type-A receptor 1	EPHA1	P21709	CHEMBL5810	Kinase	0.106165761464	9/3
Ephrin receptor	EPHB6	O15197	CHEMBL5836	Unclassified protein	0.106165761464	11/4
Receptor tyrosine-protein kinase erbB-3	ERBB3	P21860	CHEMBL5838	Kinase	0.106165761464	4/3
Serine/threonine-protein kinase MST4	STK26	Q9P289	CHEMBL5941	Kinase	0.106165761464	12/2
Eukaryotic translation initiation factor 2-alpha kinase 1	EIF2AK1	Q9BQI3	CHEMBL6029	Kinase	0.106165761464	3/3
SPS1/STE20-related protein kinase YSK4	MAP3K19	Q56UN5	CHEMBL6191	Kinase	0.106165761464	15/4
Serine/threonine-protein kinase AKT2	AKT2	P31751	CHEMBL2431	Kinase	0.106165761464	318/0
Protein kinase C gamma	PRKCG	P05129	CHEMBL2938	Kinase	0.106165761464	38/0
Serine/threonine-protein kinase AKT	AKT3	Q9Y243	CHEMBL4816	Kinase	0.106165761464	73/0
Serine/threonine-protein kinase PIM1	PIM1	P11309	CHEMBL2147	Kinase	0.106165761464	638/0
Serine/threonine-protein kinase PIM2	PIM2	Q9P1W9	CHEMBL4523	Kinase	0.106165761464	448/0
Serine/threonine-protein kinase PIM3	PIM3	Q86V86	CHEMBL5407	Kinase	0.106165761464	331/0
Cyclin-dependent kinase 2/cyclin E1	CCNE1 CDK2	P24864 P24941	CHEMBL1907605	Kinase	0.106165761464	74/0
Tyrosine-protein kinase JAK1	JAK1	P23458	CHEMBL2835	Kinase	0.106165761464	137/0
Dipeptidyl peptidase VIII	DPP8	Q6V1X1	CHEMBL4657	Protease	0.106165761464	346/0
Dipeptidyl peptidase IX	DPP9	Q86TI2	CHEMBL4793	Protease	0.106165761464	239/0
Phosphodiesterase 4B	PDE4B	Q07343	CHEMBL275	Phosphodiesterase	0.106165761464	43/0
Protein kinase C iota	PRKCI	P41743	CHEMBL2598	Kinase	0.106165761464	287/0
Cyclin-dependent kinase 2	CDK2	P24941	CHEMBL301	Kinase	0.106165761464	170/0
Cyclin-dependent kinase 1	CDK1	P06493	CHEMBL308	Kinase	0.106165761464	146/0
Cyclin T1	CCNT1	O60563	CHEMBL2108	Other cytosolic protein	0.106165761464	111/0
l elomerase reverse transcriptase	IERT	014746	CHEMBL2916	Enzyme	0.106165761464	79/0
Sodium/calcium exchanger 1	SLC8A1	P32418	CHEMBL4076	Electrochemical transporter	0.106165761464	44/0
Gonadotropin-releasing hormone receptor	GNRHR	P30968	CHEMBL1855	⊢amily A G protein-coupled receptor	0.106165761464	431/0
Amine oxidase, copper containing	AOC3	Q16853	CHEMBL3437	Enzyme	0.106165761464	19/0

TABLE 3	Lung	fibrosis-related	targets	obtained	from th	e GeneCards	database

1 OFR 35 PDFA 063 CPL AFE 1.03 HEPH 3 TERT 33 MIELT7 070 MiOT 1.004 MTAPE 3 TERT 33 MIELT7B 071 TEX1 1.005 CASP10 5 TNF 33 MIELT7B 071 TEX1 1.005 CASP10 6 STPC 340 OHAL1 074 FRA2 1.008 SASP10 7 EGFR 340 MIELTFE 074 SLD/A7 T.009 SSPAA 8 U.G. SASP MIELTA 074 SLD/A7 T.009 SSPAA 9 MIELTA SIT MIELTA 074 SIT 1.014 PRAVA 10 MIELTA SIT MIETA 691 SOLAL 1.014 MIETA 11 MIELTA SIT MIETA 892 DEFA 1.017 MAD 12 STATA MIETA BB	Number	Gene	Number	Gene	Number	Gene	Number	Gene
2 TGPE1 S36 MATE/T2 670 MAG2 1.004 MTATPS 4 TPS3 S37 MITE/T2 PI3 1.005 MITE/T2 5 INF S38 MITE/T6 671 EMMIA 1.000 CASP19 6 SITPC 340 CARD 671 EMMIA 1.000 SITCA 7 ESPR 311 MITE/T6 675 SIC/TA 1.001 SITCA 8 U.G. SIT MITE/TA 675 SIC/TA 1.012 PMACA 10 MITE/TA MITE/TA 676 BIC/TA 1.012 PMACA 11 U.D. AMA MITE/TA 676 BIC/TA 1.010 LOIA MITE/TA 12 SITPA 348 MITE/TA 830 LOIA MITA 1.010 LOIA MITA 13 SITPA 348 MITA 830 LOIA MITA 1.010 MITA MITA	1	CFTR	335	PDGFA	669	CPLANE1	1,003	HSPH1
1 TERT STR MARE TIPR PT TEXA LOBB MARE TP 5 TNF 358 MARES 672 PKB LOBB CASP TO 5 TNF 330 MARES 673 BMA4 LOBB CASP TO 7 FGFT 340 CHELL 674 STACT LOBB SCHAA 9 MALCE 342 MARETFF 676 STACT LOB SCHAA 9 MALCE 342 MARETFF 676 STACT LOB SCHAA 9 MALCE 342 MARETFF 676 STACT LOB SCHAA 10 HTD 342 MARETA 680 LAMAS LOB SCHAA 12 STFB 348 MARETA 681 SCD1 1018 RACA 14 EA SCHA 683 SCHAA SCHAA SCHAA SCHAA 15 AFAA 342 CAMA <t< td=""><td>2</td><td>TGFB1</td><td>336</td><td>MIR197</td><td>670</td><td>MKI67</td><td>1 004</td><td>MT-ATP6</td></t<>	2	TGFB1	336	MIR197	670	MKI67	1 004	MT-ATP6
1 1	2	TEDT	227	MIDI ET7D	671		1,005	MID212
4 Intel SSB MM MB2 L/2 PLA L/L L/L<	0	TEM	007		071	TBX1	1,000	
5 TMP 380 MR80 67.3 BMP4-// PMS2 1.0.28 SPH01A 7 EGFH 340 MR10-17TE 0.55 SLC7A7 1.0.08 SPH01A 7 EGFH 341 MR10-17TE 0.75 SLC7A7 1.0.01 SCH4A 7 EGFH 343 MR10-17 0.75 SLC7A7 1.0.01 SCH4A 10 MR10-13 MR10-17 0.76 TKT 1.0.11 BPH2A 11 L10 346 MR10-10 0.76 TKT 1.0.11 SPMA7 12 STTPB 346 MR10-1 620 DCEFH 1.0.11 MF1A 13 STTPA1 347 THED 681 SOCIA-1 1.0.11 MC1H 14 ELN 348 DMR15 682 DFEH 1.0.171 ADM 15 AFGCA3 940 MR163 684 SOCIA-1 1.0.19 MCPCP 16 CAV1 350	4	TP53	338	MIR195	672	PI3	1,006	CASP10
6 SFIPC 640 CHIG.1 674 PM82 10.08 SHEDNA 7 FORH 341 MRIETYC 675 EZFIH 1.019 SCHAA 8 LLC 342 MRIEGA 677 EZFIH 1.019 PSPHAA 10 RTEL1 344 MR20A 078 TKT 1.013 PSPHAA 11 LD 346 MR20A 078 TKT 1.013 PCRAP 12 STFPAT 346 MR20A 079 MR4H 1.013 PCRAP 13 FIN 346 MR20A 079 DOFAH 1.018 PSROP 14 FIN 346 MR20A 080 PLAT 1.018 PSROP 15 ACCA3 346 MR155 683 PCL1 1.018 PSROP 16 OVA 350 DYNCUIN 685 PLA1 1.020 MPR01 17 FINA 352 DYNCUIN	5	INF	339	MIR96	673	BMP4	1,007	PDE5A
7 EDFR 91 MFILETZE 075 SLC7AT 1.0.10 SCN4AA 9 MLC6B 342 MR190A1 077 S100A1 1.0.10 RSPHAA 9 MLC6B 343 MR190A1 077 S100A1 1.0.12 DNAH9 111 L10 344 MR270A 679 MRF 1.0.12 DNAH9 131 STFDA1 347 THED 681 CL2A1 1.0.16 NCFA3 131 STFDA1 347 THED 681 CD2A1 1.0.16 PSR-C3 131 ABCA3 349 MR163 683 RFB 1.0.16 PSR-C3 131 ABCA3 349 MR163 683 RFB 1.0.16 PSR-C3 131 RACA3 349 MR164 683 REFB 1.0.21 PSR-C3 131 RACA3 350 CL4A 691 CL4A 1.0.22 PSR-C3 131 RACA3	6	SFTPC	340	CHI3L1	674	PMS2	1,008	SH2D1A
8 IL6 942 MFI19A1 976 EPF1 1.010 FISPHA1 10 RTEL1 344 MP100 678 TKT 1.012 INMPS 11 IL10 345 MP20A 678 TKT 1.013 ENAPT 12 STTPB 346 MP20A 678 TKT 1.014 KTSA 12 STTPB 346 MP20A 678 TKT 1.015 STA 13 STTPA 347 MP10A 820 COL2AT 1.017 ADM 14 EIN 347 MP10A 820 DP17A 800 DOTAS 15 AECAS 348 DMR15 843 DOTAS 1.019 WD17A 16 CAVI 330 DATAS 898 DC111 1.018 WD17A 17 MP10A 350 MP10A 898 EPAS 1.021 MP10A 18 MP17A 354 MP1A	7	EGFR	341	MIRLET7E	675	SLC7A7	1,009	SCN5A
0 NUCERS 938 MIR 109A1 977 S100A1 1.011 PROPA 11 L10 343 MIR30A 679 MrFF 1.013 PNA47 11 L10 345 MIR37A 870 MrFF 1.015 CPTAA5 13 STFPA1 347 THED 881 PL51 1.016 CPTAA5 14 ELN 348 DMBT1 882 DEFB1 1.016 CPTAA5 15 AlCA3 349 MIR378A 883 PL51 1.017 ALM 16 CAV1 353 DMC1 685 SCGBA24 1.020 MR101-1 18 MLC1 353 DMC211 687 SCGA347 1.021 PROE 21 STA3 355 ICCE1 688 ICC113664105 1.021 PROE 22 CCA2 370 HLA <a< td=""> 681 ICT34 1.021 PROE 23 CCA2 360</a<>	8	11.6	342	MIR16-1	676	F2F1	1 010	RSPH4A
Prile 12 STFDS 346 MRSPA 80 LAMAS 10.14 KFA 13 STFDA 347 HeBD 81 COL2.01 10.05 COPEND 14 ELN 348 DMBT1 82 DEFB1 10.07 ADM 15 ACCA3 349 MRT80 884 SODI 10.016 LOC1167/466 16 CAVI 350 II.9 84 SODI 10.018 PSMC3 19 STFDA2 353 DYNC2.01 87 SCGABM2 10.02 II.35A2 21 STA3 365 IIC21 884 PAD 10.02 BISA2 22 TEFC 365 IIC21 884 IIC31 10.02 BISA2 23 CCN2 355 IIC21 89 KAC1 10.03 KAC2A	9	MUC5B	3/3	MIR100A1	677	S100A1	1 011	PIK3B2
10 H1E1 344 MH210 075 INI 1012 Diversity 11 L105 345 MH27A 600 LAMAS 1.014 KF3A 12 SFTPA1 347 HBD 680 COLLAN 1.016 LCOPTAA 13 SFTPA1 347 HBD 681 COLLAN 1.017 LCOPTAA 14 EN 348 DMETT 622 DEFT 1.017 ACMA 15 ALA 353 LD 623 SCARAC 1.009 MCPCP 16 CAM 353 DOTA 686 SCARAC 1.001 MCPCP 19 STATS 355 MCD1 685 SCARAC 1.002 MP101-1 19 STATS 355 MCD1 689 LOC113664106 1.026 MP102 21 STATS 355 MCD1 689 FAD0 1.025 SUP14 22 CDNA 695 MRD	10		040	MINITIONAL	070	TICT	1,011	
11 LIO 345 MR2VA 679 MYH 1.013 PSMA/ 13 STFPA1 347 THBD 681 COL2A1 1.015 CYRA6 14 ELN 348 MR3TAA 683 PL51 1.016 CYRA6 15 ARCA3 349 MR3TAA 683 PL51 1.017 ALM 16 CAV1 360 LBJ 684 SODI 1.018 PSMC3 17 FNG 551 COM1 685 PLK1 1.019 WDCPP 19 STFPAZ 353 DYNC211 687 S.CABART 1.021 PRKC2 21 STAT3 355 ICCE1 689 LCT13664103 1.023 MYH111 23 CCN2 357 HLA-A 681 CCT13664103 1.024 PRKC2 24 LI3 368 PLAA 681 CCT3664103 1.025 MH737 25 TLPA SSGEMAPA	10	RIELI	344	MIR210	678		1,012	DINAH9
12 STFPS 346 MR072A 080 LAMAS 1,014 KPAA 141 ELN 347 THBD 081 COL2AN 1,016 LCOT1677406 15 ARCAS 348 MR185 683 SQD1 1,016 LCOT11677406 16 CAVI 350 LIP 684 SQD1 1,018 PSKC3 17 IFNG 351 CTM1 086 SGB3A2 1,020 MR101-1 18 MUC1 352 CTMA 688 IGEB1 1,020 MR101-1 20 SEFRIMA1 353 NEX1 688 ILCOT13684106 1,023 MR142 21 LTAI3 356 MC24 680 HCPB1 1,026 WC2A 22 TERC 357 HLAA 691 CT95A4 1,026 WC2A 23 LTAN 350 BCA1 693 MARK14 1,026 WC2A 24 LTAN 350	11	IL10	345	MIR20A	679	MYRF	1,013	PSMA7
13 SFTPA1 347 THBD 661 COL2A1 1.015 C/PEAA5 15 ABCA3 349 MR185 663 RPL5 1.017 ADM 15 ABCA3 349 MR185 663 RPL5 1.017 ADM 16 CAV1 350 LG RPL 1.019 WDPC2 17 IFNG 351 COPA 660 SCOB3A2 1.021 MR101-1 18 MUC1 352 COPA 660 SCOB3A2 1.023 MIT01-1 19 SFTPA2 353 COCB1 669 LOC113664106 1.023 MTH11 21 STAT3 356 IOCD1 669 MAPK14 1.025 SIFG2A 23 CCM2 357 HIA-A 691 CYT3A4 1.025 SIFG2A 24 L13 358 IGA2 MAPK14 1.027 PSMC5C 25 TLR4 360 BFLA1 667	12	SFTPB	346	MIR378A	680	LAMA5	1,014	KIF3A
14 ELN 348 DMPT1 682 DEFB1 1.016 LOC111674466 15 ABCA3 349 MIR185 68 PEID 1.018 PSMC3 16 CAV1 350 LIB 644 SOD1 1.018 PSMC3 17 IPNG 350 CPMT1 686 SCGE3A2 1.020 MIR101-1 18 SFTPA2 353 DYNC2LIT 686 IFCR2 1.021 MIR101-1 21 STA13 355 IOCE1 680 IFCR2 1.022 MIR102 22 TEFC 357 HLA-A 690 FAD2 1.025 SUFU 23 CCAP 357 HLA-A 691 CTSB1 1.026 MIR13 24 LTB1 398 FILA 692 HSPB1 1.026 MIR13 25 PAFN 392 MIR15A 696 MAP14 1.030 GCAPC 26 CAPA GSS	13	SFTPA1	347	THBD	681	COL2A1	1,015	CYP3A5
15 ABCA3 349 MR185 683 PR.5 1.017 ADM 16 CAV1 350 LS 644 SOD1 1.018 PSMC3 17 FNG 351 CPM1 685 SCREA2 1.021 MR101-1 19 SFTPA2 353 CPMC2U1 687 SLGASR1 1.021 PFRCB 21 STATS 355 INCL1 689 LOCI 18664106 1.023 MYH11 22 TEFC 356 MR204 690 COT18064106 1.023 MYH17 23 CCA2 357 HIAA 691 COT18064105 1.023 MYH17 24 L13 358 IG72 692 MARCM4 1.027 PSKC2A 26 TAR 360 BC/2 693 MARCM4 1.023 MR1341 27 CTMB1 361 GAC2 696 BAP1 1.033 GACA 28 CAF6 320 MARCM4 33 MARCM4 1.034 MR1341 29 MR121<	14	FLN	348	DMBT1	682	DEFB1	1.016	LOC111674466
1 CAW SS IDO DBM NOD1 1.01% PSMC3 17 FNG SS CMT BB SCDEMA2 1.00 MFR01-1 19 SFTPA2 SS CMT BB SCDEMA2 1.00 MFR01-1 19 SFTPA2 SS DYNCCUI BB SCDEMA2 1.02 L/NP22 20 SFTPMA2 SS DYNCCUI BB REED 1.02 L/NP22 21 STATS SS NCC1 BB REED 1.02 L/NP22 22 COA2 SS NCC4 BB CATA BD FAD NCC4 SS NCC4 NCC4 NCCA NCC	15	ABCAS	3/0	MIR185	683	RPI 5	1 017	
10 CAVI 330 LD DBA SLD1 LD16 PSMC3 17 IPNG 331 CPMI 084 SLD1 LD16 Vertice 18 MUC1 322 CD7JA 086 SCGBA2 1.221 MRID1-1 19 SFIPA2 383 DVNC2L1 086 SCGBA2 1.221 PRAC6 20 SERPHAN1 384 NFK1 068 IFEB2 1.222 MIFL 21 STAT3 386 IG72 682 HSPB1 1.228 MVFL 22 TERC 386 IG72 682 HSPB1 1.228 MVFL3 23 CCNR 383 IG72 682 HSPB1 1.228 MVFL3 24 L13 380 BC2 684 MIFL3 1.228 MVFL3 25 TARIN 381 MBR15A 688 MMFL3 1.238 MIR13A 26 CARB1 386 IFFA5 </td <td>10</td> <td></td> <td>040</td> <td>10111100</td> <td>000</td> <td>0001</td> <td>1,017</td> <td>DOMOS</td>	10		040	10111100	000	0001	1,017	DOMOS
17 IPNG 351 OFMI BBS PLK1 1.019 WUPAP 18 MUC1 352 CD73A BBS SLGABSH 1.021 IPNKGE 19 SFIFPA2 353 DYNC2L11 BF SLGABSH 1.021 IPNKGE 21 STAT3 355 IOCB1 BSP ILCC113664106 1.023 MTH11 22 TERC 356 ME204 B60 FADD 1.025 SUSCA 23 CCN2 357 HLA-A B61 CYP3A4 1.025 SUSCA 24 L13 358 IGF2 B62 HSPB1 1.026 PKG2CA 25 TLA4 359 FLNA B63 MAPK14 1.027 PSMC5 26 PARN 360 BCL2 B64 CTSB 1.028 MKN13A1 27 CTNNB1 361 MR14 B67 IGAP 1.030 MR133A1 28 MAP1 363 PFA1 B68 MPR6 1.032 TMFRSP 29 CCRB	10	CAVI	350	IL9	684	SODI	1,018	PSMC3
18 MLC1 352 CD70A 686 SCGB3A2 1,020 MH:101-1 19 SFIPA/A 353 DYNC2L/I 687 SLG9ASR1 1,021 HL7A 20 SFIPA/A 354 MNEX1 688 IFEB2 1,022 L13FA2 21 STAT3 355 IGC61 689 LC13a664106 1,024 PFKC2 22 TERC 356 MR204 690 FADD 1,024 PFKC2 24 L13 388 IGP2 692 HSPE1 1,026 PFKC3 25 TLA4 389 FLNA 693 MAPK14 1,028 MF133A1 26 CAR1 380 BFA1 697 GATA2 1,031 TFAP2 27 CTNNB1 364 MAPAC2 696 BAP1 1,030 MF133A1 28 MAP1 366 PFK1 697 CATA2 1,031 MF42 29 ACF1 368 <td>17</td> <td>IFNG</td> <td>351</td> <td>CFM1</td> <td>685</td> <td>PLK1</td> <td>1,019</td> <td>WDPCP</td>	17	IFNG	351	CFM1	685	PLK1	1,019	WDPCP
19 SFIPA 353 DYNC2L11 687 SLC3A3F1 1,021 PIRKCB 21 STAT3 355 OCB1 689 LCC113664106 1,024 PMKC2 21 TERC 356 MIR204 691 CVC13684106 1,025 SUFU 23 CON2 357 HLA-A 691 CVR3A4 1,025 SUFU 24 LL3 358 GCP2 692 HSPE1 1,025 SUFU 25 TLP4 359 FLNA 693 MAPK14 1,027 PSMC3 26 PARN 360 BCL2 694 CTSB 1,028 MTR3A1 27 CTNB1 361 GSN 695 GF2R 1,030 GPC 28 ACT1 368 BPLFA1 696 MAP14 1,030 MTR3SA1 29 MK21 364 MP2K2 696 BAP1 1,030 MTR3SA1 30 MR24 368 PFFA1 696 MAP4 1,030 MTR3SA1 31 MK72	18	MUC1	352	CD79A	686	SCGB3A2	1,020	MIR101-1
20 SERPINA1 354 NEK1 688 IPER2 1.028 LISRA2 21 STAT3 355 VOCR1 689 LOC136664106 1.024 PRKG2 22 TERC 356 MIR204 690 FADD 1.024 PRKG2 23 CON2 357 HLAA 691 CMPSA4 1.025 SUFU 24 LI3 358 GS2 622 HSPB1 1.026 PRKG2 25 TLM 360 BCL2 684 MTS1A 1.029 MIR13A 26 CCR0 362 MAP2A2 686 LGF2A 1.031 TRAP2 27 CTNNB1 361 MS1A 697 GATA2 1.031 TRAP2 28 ACT1 364 MF1A 699 TGAV 1.033 MIR19 33 MAD4 367 TRAP3P1 701 MSLN 1.035 GATA2 34 MAD4 367 GA	19	SFTPA2	353	DYNC2LI1	687	SLC9A3R1	1,021	PRKCB
21 STATS 55 ICCB1 680 LCC11864106 1.023 MH11 22 TERC 365 ME204 600 FADD 1.024 PHK32 24 IL13 386 IGF2 692 HSPB1 1.026 PHK32 25 TLR4 369 FLNA 683 MAPK14 1.027 PHK35 26 PARN 360 BCL2 684 CTSB 1.028 KCMN010T1 27 CTNNB1 361 GSN 695 IGP2R 1.020 MH135A1 28 CCR6 362 MAP2K2 696 BAP1 1.030 GOPC 30 MIR21 364 MIF15A 698 MMP3 1.032 TNFR5F6B 31 NK62-1 366 FP4K1 699 ITGAV 1.038 GAD44 33 SMAD4 366 FP4K31 703 GTGAV 1.038 GAD4470 34 ADE 370	20	SERPINA1	354	NFK1	688	IBEB2	1 022	II 13BA2
1 DIAL Dia Dial Dial Dia	21	STATS	355	IOCB1	690	100112664106	1 022	
22 IERC 350 MIRCA 980 PAQJ I,024 PHAZZ 23 COR2 357 HLAA 691 C/PSA4 1,025 BUFU 24 L13 358 ICF2 692 HSPB1 1,025 PRAC PRAC 350 PRAC 1,025 PRAC PRAC 1,025 PRAC PRAC PRAC 1,025 PRAC PRAC <td>21</td> <td>JIAIJ</td> <td>050</td> <td></td> <td>009</td> <td>LOC 113004100</td> <td>1,023</td> <td></td>	21	JIAIJ	050		009	LOC 113004100	1,023	
23 CXN2 357 HLA-A 601 CYA4A 1,02b SUPU 24 L133 358 IGF2 602 HSPB1 1,02b PHKOSCA 25 TLR4 359 FLNA 603 MAPK14 1,02b PHKOSCA 26 PARN 361 GSN 605 IGF2 1,02b KCN10T0T1 27 CTNNB1 361 GSN 606 BAP1 1,029 MIP13A1 28 CCR6 383 BIPFA1 607 GATA2 1,031 TMFAP2 29 AKT1 365 EPPK1 609 ITGAV 1,033 MIP139 31 NK02-1 366 HPS5 700 PTGAV 1,034 LOC111674470 33< <mad4< td=""> 367 TAF3UP1 701 MSLN 1,033 MIP137 34 ACE 368 CFTR-AST1 702 AFFA 1,040 DNAF2 35 SPP1 368 CTR-AST</mad4<>	22	TERC	356	MIR204	690	FADD	1,024	PRKG2
24 L13 358 IGF2 692 HSP1 1.026 PHR3C2A 25 TLR4 359 FLNA 683 MAPK14 1.027 PSKC5 26 PARN 360 BCL2 664 CTB8 1.028 MCR13A1 28 CCR6 32 MAP2X2 66 B4P1 1.030 GOPC 29 AKT1 363 BPFA1 697 GATA2 1.031 TRAFF6B 30 MR21 364 MR15A 698 MMP6 1.032 TNF8F6B 31 NKQ2-1 365 EPHX1 699 TGA 1.034 LOC11167470 33 SMAD4 367 TFAF31P1 701 MSL 1.035 EGF 34 ACE 358 CFHAS1 703 CTG 1.037 PSMC6 35 SPP1 369 APB1 703 CTG 1.041 PAGE 36 CXLA 372 MR107	23	CCN2	357	HLA-A	691	CYP3A4	1,025	SUFU
25 TLR4 359 FLNA 663 MAPK14 1,027 PSMC5 26 PARN 360 BCL2 664 CTSB 1,029 KCNOTOTT 27 CTMNB1 361 GSN 665 IAFP 1,029 MIP13A1 28 CCR6 362 MAP2X2 696 BAP1 1,030 GOPC 30 MIR21 364 MIP15A 697 GATA2 1,031 TRAP2 31 NKQ2-1 366 HPS5 700 PTGAV 1,033 IGHP4P3 32 MMP1 366 HPS5 700 PTGAV 1,036 IGHP4P3 33 SMAD4 367 TRAPSIP1 701 MSLN 1,036 IGHP4P3 34 ACE 368 CPTR-AS1P1 701 MSLN 1,037 PSMC6 35 SPP1 369 AP3B1 705 KTLG 1,039 PSMA3 36 CXCLB 371 KTT19 704 ADA 1,041 EPC5 37 EGF <	24	IL13	358	IGF2	692	HSPB1	1,026	PIK3C2A
26 PARN 360 BCL2 644 CTSN 1,028 MCNC10T1 27 CTNNE1 361 GSN 665 IGP2R 1,029 MIR13A 28 CCR6 362 MAP2K2 696 BAP1 1,030 GCPC 29 AKT1 363 BPFA1 697 GATA2 1,031 TRAF2 30 MR21 365 EPHK1 698 MMPB 1,032 TNFRF6E 31 NKQ2-1 365 EPHK1 698 TGAT 1,034 LOC111674470 33 SMAD4 367 TAFSIP 701 MSLN 1,035 IGHMSP2 34 ACE 368 CFTR-AS1 701 MSLN 1,036 PSMAG 35 SPP1 368 CFTR-AS1 703 CTCF 1,037 PSMAG 36 CXCLB 370 GAPDH 703 LATA 1,041 DPATE 37 MRIN107 706	25	TLR4	359	FLNA	693	MAPK14	1,027	PSMC5
CTNNE1 361 GSN 995 IGF2R 1,029 MIR130A1 28 CCR6 362 MAP2K2 666 BAP1 1,030 GOPC 30 MIR21 364 MIR15A 696 BAP1 1,030 GOPC 30 MIR21 364 MIR15A 696 BMP8 1,032 TNFRSF6B 31 NK02-1 365 FPHX1 698 GTAAV 1,033 MIR139 32 MMP1 366 HPS5 700 PTX3 1,034 LOC111674470 33 SMAD4 367 TRAF3IP1 701 MSIN 1,035 IGHMBP2 34 ACE 368 CATLAS 703 CTCF 1,037 PSMAG 35 SPP1 369 AP3B1 703 CTCF 1,037 PSMAG 36 CXCL8 374 HIAB 706 ZNF423 1,040 DNAF2 37 DCH1 375 MMP12	26	PARN	360	BCI 2	694	CTSB	1 028	KCNQ1OT1
Chikari Constant Constant	27	CTNNB1	361	GSN	605	IGE2B	1 020	MIR133A1
20 CUMD 362 MMPARA 686 BMP1 1,000 GUPC 30 MKP21 364 MIR15A 687 GATA2 1,031 TMAP2 31 MK02-1 366 EPHX1 698 MMP8 1,032 TMFRSFGB 32 MMP1 366 EPHX1 698 MR3 1,034 LCCTI1 33 SMAD4 367 TRASIPIT 701 MSLN 1,035 IGHMBP2 34 ACE 368 CFTF-AST 702 AFF4 1,036 PSMA3 35 SPP1 369 AP381 703 CTCF 1,037 PSMA6 36 CXCL8 370 GAPD4 704 ADA 1,040 DNAF2 37 EGF 371 KR179 705 KILG 1,042 EPG3 38 CDH1 373 CP 701 LL2A 1,046 PF4 42 BRAF 376 MMP12	20	CODE	001		606		1,020	0000
29 AK 11 363 BHPA1 697 GANA2 1.031 IFARS 30 MIR21 364 MIR15A 698 MMP8 1.032 TNFRSFBE 31 NK0Z-1 365 EPHX1 699 TGAV 1.033 MIR139 32 MMP1 366 HPS5 700 PTX3 1.035 IGHMBP2 34 ACE 386 CFTR-AS11 702 AFF4 1.036 PSMC6 35 SPP1 389 AQE 370 GAPDH 704 ADA 1.039 PKRP 36 CXCL8 370 GAPDH 705 KITLG 1.040 DNAAF2 37 EGF 371 KRT19 705 KITLA 1.041 ECCS 38 FASLG 372 MIR172 707 IL12A 1.041 ECCS 41 SERPINET 373 CP 707 IL12A 1.043 PKR2 42 BRAF	20	CCRD	302	IVIAP2K2	090	BAPI	1,030	GOPC
30 MIR21 364 MIR15A 698 MIMP8 1,032 TIMERSFEB 31 NKX2-1 365 EPHX1 698 MIMP8 1,033 MIR139 32 MMP1 366 EPHX1 690 MIGA 1,034 LOC11167/47/0 33 SMAD4 367 TRASIPI 701 MSLN 1,035 IGHMBP2 34 ACE 368 CFTH-AST 702 AFF4 1,036 PSMA3 35 SPP1 399 AP3B1 703 CTCF 1,037 PSMA3 36 CXCL8 370 GAPD4 704 ADA 1,038 GAD045B 37 EGF 371 KFT19 705 KTLG 1,041 ERC5 38 CDH1 373 CP 70 IL12A 1,041 ERC5 40 KRAS 374 HLA-B 708 EGR1 1,046 PF4 41 SERPINE1 376	29	AKT1	363	BPIFA1	697	GATA2	1,031	TRAF2
31 NKC2-1 366 EPHX1 699 TGAV 1.033 MR139 32 MMP1 366 HPS5 700 PXS 1.034 LOC11167/47/0 33 SMAD4 367 TRAF3IP1 701 MSLN 1.035 IGHMEP2 34 ACE 368 CFIT-AS1 702 AFF4 1.036 PSMA3 35 SPP1 369 AP3B1 703 CTC 1.037 PSMC6 36 CKLB 370 GAPDH 704 ADA 1.038 GADD456 37 EGF 371 KRT19 705 KITLG 1.039 FKRP 38 FASLG 372 MR107 706 ZMF423 1.040 DNA472 39 CDH1 373 CP 707 IL12A 1.041 EFC5 41 SMAD3 376 MAP12 708 EGR1 1.042 FKRA 42 BRAF 376 MNP12 712 EZR 1.046 FP4 44 PTNS 379 <td>30</td> <td>MIR21</td> <td>364</td> <td>MIR15A</td> <td>698</td> <td>MMP8</td> <td>1,032</td> <td>TNFRSF6B</td>	30	MIR21	364	MIR15A	698	MMP8	1,032	TNFRSF6B
32 MMP1 366 HPSS 700 PTXS 1.034 L0111674470 33 SMAD4 367 TRAF3IP1 701 MSLN 1.035 IGHMPP2 34 ACE 688 CFIR-AS1 702 AFF4 1.036 PSMA3 35 SPP1 369 AP3B1 703 CTCF 1.037 PSMC6 36 CXCLS 371 KRT19 705 KITLG 1.039 GADb458 37 EGF 371 KRT19 705 KITLG 1.041 DMAAP2 38 FASLG 372 MIH07 706 ZNF423 1.041 DMAAP2 40 KRAS 374 HLA-B 708 PRCA 1.042 EF8 41 SMAD3 377 DR1 711 INA1 1.045 IFMAR1 43 SMAD3 377 DR1 713 LGALS3 1.047 MIR27B 44 HENSA 378 <	31	NKX2-1	365	EPHX1	699	ITGAV	1,033	MIR139
33 SMAD4 367 TRAF3IP1 701 MSLN 1.035 IGHMEP2 34 ACE 368 CFIT-AS1 702 AFF4 1.038 PSMA3 35 SPP1 369 AP3B1 703 CTCF 1.037 PSMC6 36 CXCLB 370 GAPDH 704 ADA 1.038 GADD45B 37 EGF 371 KRT19 705 KITLG 1.041 ERCF 38 FASLG 374 HLA-B 708 PRKCA 1.042 PRCS 40 SERPINE1 375 MIP12 707 EGR1 1.043 PRK3 41 SERPINE1 376 MIP12 710 DLL4 1.044 PRK3 42 BRAF 376 TNNT2 712 EZR 1.046 PFA 43 SMA02A 379 CCL18 713 LGALS3 1.047 MR27B 44 PRTN3 381 MIR141 715 TUB22B 1.048 VTN 47 HMOX1 <td< td=""><td>32</td><td>MMP1</td><td>366</td><td>HPS5</td><td>700</td><td>PTX3</td><td>1.034</td><td>LOC111674470</td></td<>	32	MMP1	366	HPS5	700	PTX3	1.034	LOC111674470
Sol Sole CFR + Sole Sole CFR + Sole Free - Sole PSMC6 34 ACE 368 CFR + Sole 1,037 PSMC6 35 SPP1 369 APB1 702 AFF4 1,036 PSMC6 36 CXCLS 370 GAPDH 704 ADA 1,038 GADdA5B 37 EGF 371 KRT19 705 KITLG 1,040 DNA4F2 38 FASLG 372 MIR107 706 ZNF423 1,041 ERCC5 40 KRAS 374 HLA-B 707 L12A 1,041 EPKC5 41 SERPINE1 376 AGER 710 DLL4 1,044 PFF1 43 SMAD3 377 DDR1 711 IPNA1 1,045 IFNAF1 44 PRTN3 376 AGER 710 DLL4 1,044 PFF1 45 PIK3CA 379 CL18 713 LGALS3<	33	SMADA	367		701	MSLN	1.035	IGHMBP2
34 ALC 360 CHINASI 712 APP4 1,030 PSMAS 35 SPP1 369 AP3B1 703 CTCF 1,037 PSMC6 36 CXCLB 370 GAPDH 704 ADA 1,038 GADD45B 37 EGF 371 KRT19 705 KITLG 1,039 FKPP 38 FASLG 372 MIR107 706 ZIN423 1,040 DNAAF2 39 CDH1 373 CP 707 LI2A 1,041 ERC5 40 KRAS 374 HLAB 708 PRKCA 1,042 EZF3 41 SERPINE1 375 MMP12 709 EGR1 1,046 PKAR1 42 BRAF 376 AGER 710 DLL4 1,046 PF4 43 SMAD3 377 DDR1 711 IFNA1 1,046 PF4 44 PRTN3 378 TNNT2	00		007		701		1,000	
35 SPP1 369 Ar361 703 C1CP 1,037 PSMC6 36 CXCLB 370 GAPDH 704 ADA 1,038 GADD45B 37 EGF 371 KRT19 705 KITLG 1,040 DNA4F2 38 FASLG 372 MIR107 706 ZNF423 1,040 DNA4F2 39 CDH1 373 CP 707 L12A 1,041 ERCC5 40 KRAS 374 HLA-B 708 PRKCA 1,042 PERC3 41 SERAF 376 MIP12 709 EGR1 1,043 PIK3R3 42 BRAF 376 MIP12 709 EGR1 1,046 PFR1 43 SMAD3 377 DDR1 711 IFNA1 1,045 IFNA1 44 PIK3CA 379 CCL18 713 LGALS3 1,047 MIR27B 45 PIK3CA 381 MIR11	34	AGE	308	GEIR-ASI	702	AFF4	1,030	PSIVIA3
36 CXCLB 370 GAPDH 704 ADA 1,038 GADDA5B 37 EGF 371 KRT19 705 KITLG 1,039 FKPP 38 FASLG 372 MIR107 706 ZNF423 1,040 DNAAF2 39 CDH1 373 CP 707 L12A 1,041 ERC5 40 KRAS 374 HLAB 708 PRKCA 1,042 EZF3 41 SERPINE1 376 AGER 710 DLL4 1,044 PRTA 42 BRAF 376 AGER 710 DLL4 1,045 IFNAR1 43 SMAD3 378 TNNT2 712 EZR 1,046 PF4 44 PRTN3 378 TNNT2 712 EZR 1,048 VTN 45 PIK3CA 379 CCL18 713 LGALS3 1,049 DNAJC5 48 L1B 382 INS 716 EPCAM 1,051 MIR455 50 FAM13A 884	35	SPP1	369	AP3B1	703	CICF	1,037	PSMC6
37 EGF 371 KRT19 705 KILG 1,039 FKPP 38 FASLG 372 MIR107 706 ZNF423 1,041 DNAAF2 39 CDH1 373 CP 707 L12A 1,041 ERCC5 40 KRAS 374 HLA-B 707 L12A 1,042 EPG3 41 SERPINE1 375 MMP12 709 EGR1 1,043 PHK3R3 42 BRAF 376 AGER 710 DLL4 1,044 PHK1 43 SMAD2 377 DDR1 711 IFNA1 1,045 IFNAR1 44 PTIN3 378 TNNT2 712 EZR 1,047 MIR27B 45 PIK3CA 379 CCL18 713 LGALS3 1,047 MIR27B 46 L1RN 383 GL3 716 EPCAM 1,050 BGL4P 47 HMOX1 383 GL3 717 APOB 1,051 MIR455 50 FAM13A 386	36	CXCL8	370	GAPDH	704	ADA	1,038	GADD45B
38 FASLG 372 MIR107 706 ZNF423 1,040 DNAAF2 39 CDH1 373 CP 707 IL12A 1,041 ERCC5 41 KRAS 374 HLA-B 708 PRKCA 1,042 E2F3 41 SERPINE1 375 MMP12 709 EGR1 1,043 PKSR3 42 BRAF 376 AGER 710 ILL4 1,044 PRF1 43 SMAD3 377 DD11 711 IFNA1 1,045 IFNA1 44 PRTN3 378 TNNT2 712 EZR 1,046 PF4 45 MIR3CA 378 CL18 T14 AFP 1,048 VTN 46 LIFN 380 MIR148 714 AFP 1,049 DNAJC5 47 HMOX1 381 JAK2 716 EPCA 1,051 MIR455 50 FAM13A 384 JAK2	37	EGF	371	KRT19	705	KITLG	1,039	FKRP
39 CDH1 373 CP 707 IL12A 1,041 ERCC5 40 KRAS 374 HLA-B 708 PRKCA 1,042 EZF3 41 SERPINE1 375 MMP12 708 PRKCA 1,043 PIK3R3 42 BRAF 376 AGER 710 DLL4 1,044 PRF1 43 SMAD3 377 DDR1 711 IFNA1 1,045 IFNAR1 44 PRTN3 378 TNNT2 712 EZR 1,046 PF4 45 PIK3CA 379 CL18 713 LGALS3 1,047 MIR27B 46 IL1RN 380 MIR148B 714 AFP 1,048 VTN 47 HMOX1 381 MIR141 715 TUBE2B 1,049 DNAJC5 48 IL1B 882 INS 716 EPCAM 1,051 MIR455 50 FAM13A 384 JAK2 <td>38</td> <td>FASLG</td> <td>372</td> <td>MIR107</td> <td>706</td> <td>ZNF423</td> <td>1.040</td> <td>DNAAF2</td>	38	FASLG	372	MIR107	706	ZNF423	1.040	DNAAF2
AL AL<	39	CDH1	373	CP	707	II 12A	1 041	FBCC5
NUS NUS NUS NUS NUS LLAD NOS FINCA 1,042 LLAD 41 SERPINETI 375 MMP12 709 EGR1 1,043 PIK3R3 42 BRAF 376 AGER 710 DLL4 1,044 PRF1 43 SMAD3 377 DDR1 711 IFNA1 1,045 IFNAR1 44 PRTN3 378 TNNT2 712 EZR 1,046 IFNAR1 45 PIK3CA 379 CCL18 713 LGALS3 1,047 MIR27B 46 LTB 380 MR148B 714 AFP 1,048 VTN 47 HMOX1 381 MR141 715 TUBB2B 1,051 MIR455 48 L1B 382 INS 716 EPCA 1,052 LOC111674471 51 FAM13A 384 JAK2 718 SPPL2C 1,054 VCL 52 PTEN	40	KDAS	274		709		1,012	E2E2
41 Sth MMMP12 709 EGH1 1,043 PHX3R3 42 BRAF 376 AGER 710 DL4 1,044 PRT1 43 SMAD3 377 DDR1 711 IFNA1 1,046 PF4 44 PHTN3 378 TNNT2 712 EZR 1,046 Pf4 45 PHX3CA 379 CCL18 713 LGALS3 1,047 MI27B 46 L1RN 380 MIR148B 714 AFP 1,048 VTN 47 HMOX1 381 MIR141 715 TUBB2B 1,049 DNAJC5 48 L1B 382 INS 716 EPCAM 1,052 MIR455 50 FAM13A 384 JAK2 718 SPP12C 1,053 CSF3R 51 FAS 385 EVC 719 CDK2 1,054 VCL 53 SFIPD 387 IL33 721 EPO 1,056 GUSB 54 ITGAM 389 SLPI	40		074		700		1,042	Ezi o
42 BRAF 376 AGER 710 DLL4 1,044 PRF1 43 SMAD3 377 DDR1 711 IFNA1 1,045 IFNAR1 44 PRTN3 378 TNNT2 712 EZR 1,046 PF4 45 PIK3CA 379 CCL18 713 LGALS3 1,047 MIR27B 46 L1RN 380 MIR148B 714 AFP 1,048 VTN 47 HMOX1 381 MIR141 715 TUBE2B 1,049 DNAJC5 48 L1B 383 GLI3 717 APOB 1,051 MIR455 50 FAM13A 384 JAK2 718 SPPL2C 1,053 CSF3R 51 FAS 385 EVC 719 CDK2 1,055 NAGLU 53 SFTPD 386 HPS3 721 EPO 1,055 NAGLU 54 ITGAM 389 SLPI	41	SERPINE1	375	MMP12	709	EGR1	1,043	PIK3R3
43 SMAD3 377 DDR1 711 IFNA1 1,045 IFNAR1 44 PRTN3 378 TNNT2 712 EZR 1,046 PF4 44 PIK3CA 379 CCL18 713 LGALS3 1,047 MIR27B 46 IL1RN 380 MIR148B 714 AFP 1,048 VTN 47 HMOX1 381 MIR141 715 TUB2B2B 1,049 DNAJC5 48 IL1B 382 INS 716 EPCAM 1,050 BGLAP 49 HLA-DRB1 383 GL33 717 APOB 1,051 MIR455 50 FAM13A 384 JAK2 718 SPPL2C 1,053 CSF3R 51 FAS 385 EVC 719 CDK2 1,054 VCL 53 SFTPD 387 IL33 721 EPO 1,056 GUSE 54 ITGAM 389 SLPI 723 HSPA8 1,057 NEAT1 55 DSP 393	42	BRAF	376	AGER	710	DLL4	1,044	PRF1
44 PRTN3 378 TNNT2 712 EZR 1,046 PF4 45 PK3CA 379 CCL18 713 LGALS3 1,047 MIR27B 46 IL1RN 380 MIR148B 714 AFP 1,048 VTN 47 HMOX1 381 MIR141 716 TUBB2B 1,049 DNAJC5 48 IL1B 382 INS 716 EPCAM 1,050 BGLAP 49 HLA-DRB1 383 GLI3 717 APOB 1,051 MIR455 50 FAM13A 384 JAK2 718 SPPL2C 1,053 CST3R 51 FAS 385 EVC 719 CDK2 1,054 VCL 52 PTEN 386 HPS3 720 GDF2 1,055 NAGLU 54 ITGAM 388 NOS2 722 VCP 1,056 GUSB 55 DSP 390 SLPI 723 HSPA8 1,057 NEAT1 56 STN1 390	43	SMAD3	377	DDR1	711	IFNA1	1,045	IFNAR1
45 PIK3CA 379 CCL18 713 LGALS3 1,047 MIR27B 46 IL1RN 380 MIR148B 714 AFP 1,048 VTN 47 HMOX1 381 MIR141 715 TUBB2B 1,049 DNAJC5 48 IL1B 382 INS 716 EPCAM 1,050 BGLAS5 49 HLA-DRB1 383 GLI3 717 APOB 1,051 MIR455 50 FAM13A 384 JAK2 718 SPPL2C 1,052 LOC111674471 51 FAS 385 EVC 719 CDK2 1,054 VCL 52 PTEN 386 HPS3 720 GDF2 1,054 VCL 53 SFTPD 387 IL33 721 EPO 1,055 NAGLU 54 ITGAM 389 SLP1 723 HSPA8 1,057 NEAT1 55 DSP 391 TCTN3 726 HBB 1,059 PSMD1 57 TGFBR1 391	44	PRTN3	378	TNNT2	712	EZR	1,046	PF4
A6 ILTRN 380 MIR14BS 714 AFP 1,048 VTN 47 HMOX1 381 MIR141 715 TUBB2B 1,049 DNAJC5 48 IL1B 382 INS 716 EPCAM 1,050 BGLAP 49 HLA-DRB1 383 GLI3 717 APOB 1,051 MIR455 50 FAM13A 384 JAK2 718 SPPL2C 1,052 LOC111674471 51 FAS 385 EVC 719 CDK2 1,053 CSF3R 52 PTEN 386 HPS3 720 GDF2 1,054 VCL 53 SFTPD 387 IL33 721 EPO 1,056 GUSB 54 ITGAM 388 NOS2 722 VCP 1,056 GUSB 55 DSP 389 SLPI 723 HSPA8 1,057 NEAT1 56 STN1 390 MIR133B 724 ATP4A 1,058 TBX4 57 TGFBR1 391	45	PIK3CA	379	CCI 18	713	LGALS3	1 047	MIR27B
40 LTMN 300 MIN 140D 714 A P 1,045 VTN 47 HMOX1 381 MIR141 715 TUBB2B 1,049 DNA.JC5 48 IL1B 382 INS 716 EPCAM 1,050 BGLAP 49 HLA-DRB1 383 GLI3 717 APOB 1,051 MIR455 50 FAM13A 384 JAK2 718 SPPL2C 1,052 LOC111674471 51 FAS 385 EVC 719 CDK2 1,053 CSF3R 52 PTEN 386 HPS3 720 GDF2 1,054 VCL 53 SFTPD 387 IL33 721 EPO 1,056 GUSB 54 ITGAM 388 NOS2 722 VCP 1,056 GUSB 55 DSP 389 SLPI 723 HSPA8 1,057 NEAT1 56 STN1 390 MIR133B 724 ATP4A 1,058 TBX4 57 TGFBR1 391 <td>16</td> <td></td> <td>380</td> <td>MID1/9R</td> <td>714</td> <td></td> <td>1 049</td> <td></td>	16		380	MID1/9R	714		1 049	
47 HNIXAT 381 MIRT4T 715 TOB22B 1,049 DNAJCS 48 IL1B 382 INS 716 EPCAM 1,050 BGLAP 49 HLA-DRB1 383 GLI3 717 APOB 1,051 MIR455 50 FAM13A 384 JAK2 718 SPPL2C 1,053 CSF3R 51 FAS 385 EVC 719 CDK2 1,054 VCL 53 SFTPD 386 HPS3 720 GDF2 1,055 NAGLU 54 ITGAM 388 NOS2 722 VCP 1,056 GUSB 55 DSP 389 SLPI 723 HSPA8 1,057 NEAT1 56 STN1 390 MIR133B 724 ATP4A 1,058 TBX4 57 TGFBR1 391 TCTN3 725 HBB 1,060 PSMD1 58 SC 392 TLR5 726 SELE 1,061 GAST 59 CDKN2A 393	40		001		714		1,040	
48 ILTB 382 INS 716 EPCAM 1,050 EGLAP 49 HLA-DRB1 383 GLI3 717 APOB 1,051 MIR455 50 FAM13A 384 JAK2 718 SPPL2C 1,052 LOC111674471 51 FAS 385 EVC 719 CDK2 1,053 CSF3R 52 PTEN 386 HPS3 720 GDF2 1,054 VCL 53 SFTPD 387 IL33 721 EPO 1,056 GUSB 54 ITGAM 388 NOS2 722 VCP 1,056 GUSB 55 DSP 389 SLPI 723 HSPA8 1,057 NEAT1 56 TGFBR1 390 MIR133B 724 ATP4A 1,058 TBX4 57 TGFBR1 391 TCTN3 725 HBB 1,061 GAST 59 CDKN2A 393 MUC4	47	HMOXI	381	MIR 141	715	TUBB2B	1,049	DINAJC5
49 HLA-DRB1 383 GLI3 717 APOB 1,051 MIR455 50 FAM13A 384 JAK2 718 SPPL2C 1,052 LOC111674471 51 FAS 385 EVC 719 CDK2 1,053 CSF3R 52 PTEN 386 HPS3 720 GDF2 1,054 VCL 53 SFTPD 387 IL33 721 EPO 1,055 NAGLU 54 ITGAM 388 NOS2 722 VCP 1,056 GUSB 55 DSP 389 SLPI 723 HSPA8 1,057 NEAT1 56 STN1 390 MIR133B 724 ATP4A 1,058 TEX4 57 TGFBR1 391 TCTN3 725 HBB 1,060 PSMD12 58 SRC 392 TLR5 726 SELE 1,061 GAST 60 ERBB2 394 MIR93 728 FGF10 1,063 CREB1 61 CTLA4 395	48	IL1B	382	INS	716	EPCAM	1,050	BGLAP
50 FAM13A 384 JAK2 718 SPPL2C 1,052 LOC111674471 51 FAS 385 EVC 719 CDK2 1,053 CSF3R 52 PTEN 386 HPS3 720 GDF2 1,054 VCL 53 SFTPD 387 IL33 721 EPO 1,055 NAGLU 54 ITGAM 388 NOS2 722 VCP 1,056 GUSB 55 DSP 389 SLPI 723 HSPA8 1,057 NEAT1 56 STN1 391 TCTN3 726 HBB 1,059 PSMD1 58 SRC 392 TLR5 726 SELE 1,060 PSMD12 59 CDKN2A 393 MUC4 727 NAT2 1,061 GAST 60 ERBB2 394 MIR93 728 FGF10 1,063 CREB1 61 CTLA4 395 MIR18A 729 BMP7 1,063 CREB1 62 NFE2L2 396	49	HLA-DRB1	383	GLI3	717	APOB	1,051	MIR455
51 FAS 385 EVC 719 CDK2 1,053 CSF3R 52 PTEN 386 HPS3 720 GDF2 1,054 VCL 53 SFTPD 387 IL33 721 EPO 1,055 NAGLU 54 ITGAM 388 NOS2 722 VCP 1,056 GUSB 55 DSP 389 SLPI 723 HSPA8 1,057 NEAT1 56 STN1 390 MIR133B 724 ATP4A 1,058 TBX4 57 TGFBR1 391 TCTN3 725 HBB 1,060 PSMD12 58 SRC 392 TLR5 726 SELE 1,061 GAST 60 ERBB2 394 MIR93 728 FGF10 1,062 MIR99A 61 CTLA4 395 MIR18A 729 BMP7 1,063 CREB1 62 NFE2L2 396 SLC11A1 730 ETS1 1,064 TRPC6 63 MMP9 397	50	FAM13A	384	JAK2	718	SPPL2C	1,052	LOC111674471
52 PTEN 386 HPS3 720 GDF2 1,054 VCL 53 SFTPD 387 IL33 721 EPO 1,055 NAGLU 54 ITGAM 388 NOS2 722 VCP 1,056 GUSB 55 DSP 389 SLPI 723 HSPA8 1,057 NEAT1 56 STN1 390 MIR133B 724 ATP4A 1,058 TBX4 57 TGFBR1 391 TCTN3 725 HBB 1,060 PSMD1 58 SRC 392 TLR5 726 SELE 1,061 GAST 60 ERB82 394 MIR93 728 FGF10 1,062 MIR99A 61 CTLA4 395 MIR18A 729 BMP7 1,063 CREB1 62 NFE2L2 396 SLC11A1 730 ETS1 1,064 TRPC6 63 MMP9 397 PSMA6 731 DEFB4A 1,065 EPAS1 64 MTOR 398	51	FAS	385	EVC	719	CDK2	1.053	CSE3B
52 FTEN 560 FTEO 720 GB/2 1,054 VOL 53 SFTPD 387 IL33 721 EPO 1,055 NAGLU 54 ITGAM 388 NOS2 722 VCP 1,057 NEAT1 55 DSP 389 SLPI 723 HSPA8 1,057 NEAT1 56 STN1 390 MIR133B 724 ATP4A 1,058 TBX4 57 TGFBR1 391 TCTN3 725 HBB 1,050 PSMD1 58 SRC 392 TLR5 726 SELE 1,060 PSMD12 59 CDKN2A 393 MUC4 727 NAT2 1,061 GAST 60 ERB2 394 MIR93 728 FGF10 1,062 MIR99A 61 CTLA4 395 MIR14A 729 BMP7 1,063 CREB1 62 NFE2L2 396 SLC11A1	52	DTEN	386	HPS3	720	GDE2	1.054	VCI
53 SFTPD 367 IL33 721 EPO 1,055 NAGLU 54 ITGAM 388 NOS2 722 VCP 1,056 GUSB 55 DSP 389 SLPI 723 HSPA8 1,057 NEATI 56 STN1 390 MIR133B 724 ATP4A 1,059 PSMD1 57 TGFBR1 391 TCTN3 725 HBB 1,060 PSMD1 58 SRC 392 TLR5 726 SELE 1,061 GAST 60 ERBB2 394 MIR93 728 FGF10 1,062 MIR99A 61 CTLA4 395 MIR18A 729 BMP7 1,063 CREB1 62 NFE2L2 396 SLC11A1 730 ETS1 1,064 TRPC6 63 MMP9 397 PSMA6 731 DEFB4A 1,065 EPAS1 64 MTOR 398 RNASE3	52		007	11-00	720		1,054	NACILI
54 ITGAM 388 NOS2 722 VCP 1,056 GUSB 55 DSP 389 SLPI 723 HSPA8 1,057 NEAT1 56 STN1 390 MIR133B 724 ATP4A 1,058 TBX4 57 TGFBR1 391 TCTN3 725 HBB 1,060 PSMD1 58 SRC 392 TLR5 726 SELE 1,061 GAST 59 CDKN2A 393 MUC4 727 NAT2 1,061 GAST 60 ERBB2 394 MIR93 728 FGF10 1,062 MIR99A 61 CTLA4 395 MIR18A 729 BMP7 1,063 CREB1 62 NFE2L2 396 SLC11A1 730 ETS1 1,064 TRPC6 63 MMP9 397 PSMA6 731 DEFB4A 1,065 EPAS1 64 MTOR 398 RNASE3	53	SFIPD	307	IL33	121	EPO	1,055	NAGLU
55 DSP 389 SLPI 723 HSPA8 1,057 NEAT1 56 STN1 390 MIR133B 724 ATP4A 1,058 TBX4 57 TGFBR1 391 TCTN3 725 HBB 1,060 PSMD1 58 SRC 392 TLR5 726 SELE 1,061 GAST 60 ERBB2 394 MIR93 728 FGF10 1,062 MIR99A 61 CTLA4 395 MIR18A 729 BMP7 1,064 TRPC6 62 NFE2L2 396 SLC11A1 730 ETS1 1,065 EPAS1 63 MMP9 397 PSMA6 731 DEFB4A 1,065 MIR125B1	54	ITGAM	388	NOS2	722	VCP	1,056	GUSB
56 STN1 390 MIR133B 724 ATP4A 1,058 TBX4 57 TGFBR1 391 TCTN3 725 HBB 1,059 PSMD1 58 SRC 392 TLR5 726 SELE 1,060 PSMD12 59 CDKN2A 393 MUC4 727 NAT2 1,061 GAST 60 ERB82 394 MIR93 728 FGF10 1,062 MIR99A 61 CTLA4 395 MIR18A 729 BMP7 1,063 CREB1 62 NFE2L2 396 SLC11A1 730 ETS1 1,064 TRPC6 63 MMP9 397 PSMA6 731 DEFB4A 1,065 EPAS1 64 MTOR 398 RNASE3 732 PRDM10 MIR125B1 (Continuent on and)	55	DSP	389	SLPI	723	HSPA8	1,057	NEAT1
57 TGFBR1 391 TCTN3 725 HBB 1,059 PSMD1 58 SRC 392 TLR5 726 SELE 1,060 PSMD12 59 CDKN2A 393 MUC4 727 NAT2 1,061 GAST 60 ERBB2 394 MIR93 728 FGF10 1,062 MIR99A 61 CTLA4 395 MIR18A 729 BMP7 1,063 CREB1 62 NFE2L2 396 SLC11A1 730 ETS1 1,064 TRPC6 63 MMP9 397 PSMA6 731 DEFB4A 1,065 EPAS1 64 MTOR 398 RNASE3 722 PRDM10 MIR125B1	56	STN1	390	MIR133B	724	ATP4A	1,058	TBX4
58 SRC 392 TLR5 726 SELE 1,060 PSMD12 59 CDKN2A 393 MUC4 727 NAT2 1,061 GAST 60 ERBB2 394 MIR93 728 FGF10 1,062 MIR99A 61 CTLA4 395 MIR18A 729 BMP7 1,063 CREB1 62 NFE2L2 396 SLC11A1 730 ETS1 1,064 TRPC6 63 MMP9 397 PSMA6 731 DEFB4A 1,065 EPAS1 64 MTOR 398 RNASE3 732 PRDM10 (Continued on following page)	57	TGFBR1	391	TCTN3	725	HBB	1.059	PSMD1
Sol Gro Sol Field	58	SBC	202	TI R5	706	SELE	1,000	PSMD12
59 CLIKNZA 393 MUC4 727 NA12 1,061 GAST 60 ERBB2 394 MIR93 728 FGF10 1,062 MIR99A 61 CTLA4 395 MIR18A 729 BMP7 1,063 CREB1 62 NFE2L2 396 SLC11A1 730 ETS1 1,064 TRPC6 63 MMP9 397 PSMA6 731 DEFB4A 1,066 MIR125B1 64 MTOR 398 RNASE3 732 PRDM10 Locationa on a following page)	50		39Z		120	SLLL	1,000	
60 EHBB2 394 MIR93 728 FGF10 1,062 MIR99A 61 CTLA4 395 MIR18A 729 BMP7 1,063 CREB1 62 NFE2L2 396 SLC11A1 730 ETS1 1,064 TRPC6 63 MMP9 397 PSMA6 731 DEFB4A 1,066 MIR125B1 64 MTOR 398 RNASE3 732 PRDM10 (Continued on following page)	59		393		121	INAT2	1,061	GASI
61 CTLA4 395 MIR18A 729 BMP7 1,063 CREB1 62 NFE2L2 396 SLC11A1 730 ETS1 1,064 TRPC6 63 MMP9 397 PSMA6 731 DEFB4A 1,065 EPAS1 64 MTOR 398 RNASE3 732 PRDM10 1,066 MIR125B1	60	ERBB2	394	MIR93	728	FGF10	1,062	MIR99A
62 NFE2L2 396 SLC11A1 730 ETS1 1,064 TRPC6 63 MMP9 397 PSMA6 731 DEFB4A 1,065 EPAS1 64 MTOR 398 RNASE3 732 PRDM10 1,066 MIR125B1	61	CTLA4	395	MIR18A	729	BMP7	1,063	CREB1
63 MMP9 397 PSMA6 731 DEFB4A 1,065 EPAS1 64 MTOR 398 RNASE3 732 PRDM10 1,066 MIR125B1	62	NFE2L2	396	SLC11A1	730	ETS1	1,064	TRPC6
64 MTOR 398 RNASE3 732 PRDM10 1,000 ELAST (Continued on following page)	63	MMP9	397	PSMA6	731	DFFB4A	1 065	FPAS1
Intervence 152 FIDURIU 1,000 MILTIZED I	64	MTOR	202	BNASES	720	PRDM10	1 066	MIR125R1
	U T		030		102		1,000 (Contin	

TABLE 3 | (Continued) Lung fibrosis-related targets obtained from the GeneCards database.

b5 HPAS 300 CMACC 734 GAL 100 PROPI 67 FORTH 400 CAM1 734 PRORD 1008 PROP 67 FORTH 401 TGFA 736 TR93 1000 TD1 68 CU1A1 422 PROR 738 TR93 1070 CD40 69 NPHR3 433 ANSAS 737 HNF18 1071 DUA1 71 DFR1 436 L 738 TD3 1072 FOS 71 DFR1 436 L 738 TD3 MANDA 1072 DAD1 73 MFE1 436 L CD17 741 BORH 1076 MAND1 74 MFE1 407 COER7 748 MANT1 1077 MAND1 74 MFE17D 411 SOS2 745 CD42 1079 COER8 75 MFE27D 411 SOS2 745 CD42 1079 COER8 76 ME127D 411 TD47 744 HASA 1080 MANT1 76 ME127D 411 TD44 1080 MANT1 1081	Number	Gene	Number	Gene	Number	Gene	Number	Gene
efs TIMI2 4101 CAM1 714 RPSR11 1008 PCR 66 CDL1A1 402 PEGR 735 LMA3 1000 CDL1A1 68 CDL1A1 402 PEGR 736 TPR3 1000 CDL3 70 F2 404 CXCR1 738 BB10 1007 PCR 71 FPE2 404 CXCR1 738 BB10 1007 PR08 72 FPE2 404 CXCR1 748 BDTA 1007 PR02 73 MFE2 FPGR 408 BH12 74 BA2 1078 PR02 74 MEE 408 BH12 744 BA2 1078 CR04 PR04 75 MGA2 410 IMMA 744 BA2 1078 CR04 PR04 76 MGA2 410 IMMA 746 CHA 1080 ACR 77 MIRLET/O <t< td=""><td>65</td><td>HRAS</td><td>399</td><td>SMAD2</td><td>733</td><td>GJA1</td><td>1,067</td><td>IFNGR1</td></t<>	65	HRAS	399	SMAD2	733	GJA1	1,067	IFNGR1
67 FORF1 401 TGFA 736 AVAS 1000 TLR 68 COLIAI 402 PROR 730 TP63 1070 COLO 69 NIFH23 403 ANDAS 735 HNS 1070 COLO 71 DFP3 404 CXCR11 738 BES10 1072 FOS 71 DFP3 404 CXCR11 738 BES10 1077 MADII 74 HFE 406 CMCR14 744 PADIA 1076 MADII 74 HFE 406 META2 742 CMARI 1076 HBADII 75 PRORB 409 SGTP1 743 CMARI 1079 RADII 76 MEL270 411 SCR2 745 CMARI 1089 MBADII 76 MEL270 411 SCR2 745 CMARI 1089 MADII 76 MEL270 411 SCR2 745 CMARI 1089 MADIII 76 MEL270 717 FRAA 1089 MADIII 1081 MADIII 76 MEL270 718 HSAA 1089 MADIIII 1081	66	TINF2	400	ICAM1	734	RPS6KB1	1,068	PGR
B6 CDL1A1 402 PPRA 780 TPB 1 1.071 CDa0 70 P2 403 CXCH1 738 BIS10 1.071 DIC1 71 DPP0 405 Ll2 738 BIS10 1.073 DNL1 72 TGFB2 405 GZ274 741 SK11 1.075 PRMD11 73 MIP11A 407 GZ274 741 DKAP1 1.075 HB2 74 HE 400 MAF142 742 DKAP1 1.075 HB2 75 MIRLETD 410 MS22 745 DKAP1 1.080 PRAR 78 MGL2 412 LMAA 746 CHKA1 1.080 MCD147474 81 TMP1 414 CPC1 724 PRKA3 1.082 KASA31 78 MR12 418 MRET 740 CHKA3 1.080 KASA31 81 TMP1 419 MRET	67	FGFR1	401	TGFA	735	JAK3	1,069	TLR1
bh NPRPB CD PA ANXAS P37 HP/FB 1.072 CD 71 DPPB 405 LI2 739 HDA/A 1.0742 FOS 71 DPPB 405 LI2 739 HDA/A 1.0742 DAVID 73 ATP11A 407 CD274 741 SK1 1.075 HSV2 74 HE 408 MR142 742 DMA/F1 1.076 HSV2 75 POGRE 400 GSTP1 743 DMA/F1 1.078 CALRA 76 MRLET/D 411 SS2 745 DMA21 1.081 MS 77 MRLET/D 413 DPP2 745 DMA21 1.081 MA11 78 MCT 413 DPP2 745 MSA21 1.081 MA311 80 MTP1 416 OPP1 746 CHAR 1.081 MA314 81 MMP2 418 MR2	68	COL1A1	402	RPGR	736	TP63	1.070	CD40
70 P2 P3 P4 P3 P3 P3 P3 P3 P3 71 DPPH 466 H2 78 HTGA2 1,13 DNA I 72 TGFH2 466 GPEM1 740 HOTAR 1,13 DNA I 73 ATP1 IA 407 GD274 741 SACL 1,17 HAD11 74 HE 408 MR142 742 DMAAF1 1,07 HAD118 75 PIGHB 409 GSIP1 743 DMAT1 1,07 HAD118 76 MGL2 411 SOS2 745 DMAT<1	69	NPHP3	403	ΔΝΧΔ5	737	HNE1B	1 071	DI K1
0 1 0 1000 10.04 10.04 72 TGFR2 466 CPEMI 740 KOTAR 10.74 MADD11 73 AFTPLIA 407 CPEMA 741 SOKH 10.74 MADD11 74 HFE 408 MRT142 742 DMAAF1 10.76 HEA2 75 FOGRER 408 GSTP1 743 DMAT1 10.76 HEA2 76 MRLETD 411 SOS2 745 COH2 10.78 AGS-AS1 78 MRL2 412 LMMAA 749 HKA1 1.080 HAT6 78 MRL2 412 CAMAA 749 CHKA1 1.081 LOC1167474 83 SCNMA 177 PLA2 751 LK 1.084 KAA11 84 MMP2 418 MRLETC 752 ADGFA2E 1.084 KAA11 85 ELANE 419 MRETC 753 SET </td <td>70</td> <td></td> <td>400</td> <td></td> <td>700</td> <td>PPC10</td> <td>1,071</td> <td>EOS</td>	70		400		700	PPC10	1,071	EOS
1 DF-P2 400 LCE_DM 7.89 HOXAC 1.974 DAVAL 74 AFFHA 407 CDT41 7.49 DAVAF1 1.974 More 75 PDGFHB 409 CDT41 7.41 DAVAF1 1.977 PDG11 76 PDGFHB 409 CDT41 7.42 DAVAF1 1.978 CCRB 77 PDGFHB 409 CDT41 7.42 DAVAF1 1.988 CCRB 78 NGL2 412 LMMA 7.49 DAVAF1 1.988 CCRB 79 NOTCH1 413 CDP11 7.49 HBFAS 1.983 CON187 80 MET 414 TOP1 7.49 HBFAS 1.985 KAAN516 81<	70		404		700	DD310	1,072	FUO DNAL1
12 (DHP2 408 CaleAn1 240 HOLAR 1,107 MADULT 74 HFE 408 MARIAT 741 DAAFT 1,075 PRADIT 75 PROFER 408 MARIAT 742 DAAFT 1,076 HEBA 76 PROFER 408 MARIAT 742 DAAFT 1,076 HABA 77 MERLET 410 HORAR 744 DAMET 1,076 HABA 78 MEL 412 LMMA 748 HAV 1,081 MAB 74 NOTCH 418 FNPP2 747 PRKAA1 1,082 GASFAST 80 MET 414 CPC 751 LK 1,084 MAA9318. 81 TMMP1 416 CPCXL 752 SAFT 1,084 MAA9318. 83 SCNNIA 417 PAA APAE 753 SFT 1,084 MAA9318. 84 ADRE2A <t< td=""><td>71</td><td>DPP9</td><td>405</td><td>IL2</td><td>739</td><td>TIGA2</td><td>1,073</td><td>DINALI</td></t<>	71	DPP9	405	IL2	739	TIGA2	1,073	DINALI
73 AIP11A 407 CD274 741 SSRI 1.075 PBMD11 74 HEE 468 MRH42 742 DNAMT1 1.075 HBA2 75 FDGFRB 460 GSTP1 743 DMMT1 1.077 RAB11B 76 MRL2 411 SOS2 748 CDVP2 1.078 CCHGR1 77 MRL2 412 LMMA 746 HAV 1.081 MRSP 78 NGTCH1 413 EMP22 747 PMACA1 1.081 MRSP 78 NGTCH1 416 CAD19 750 CMP2 1.044 CAD17474 80 SCINNIA 417 MRSP 750 CADP22 1.064 KAT474 81 MMP2 418 MRSP 754 CADP428 1.086 ASO2 82 VEGFA 420 MRSP1 756 CAD11 1.080 MAC2 83 MR1930A 422 <	72	IGFB2	406	GREM1	740	HOTAIR	1,074	MAD1L1
7.4 HFE 408 MR1/2 742 DNAF1 1.076 HEA2 75 PDGFRB 408 GSTP1 743 DNMT1 1.078 CRMB1 76 HIGA3 410 PHOK2A 744 DM22 1.079 CLCN3 77 MRLETD 411 SOS2 746 CHV 1.080 PFARA 80 MET 413 TOP1 748 HSPAE 1.081 MB 81 TMP1 416 CAL9 750 SRP2 1.084 KCN11 82 SERPINH1 416 CAL9 750 SRP2 1.086 PSMA2 83 SCM11A 417 PAL 751 ILC 1.088 RA2 84 MMP2 418 MRETC 753 SST 1.087 PSMA2 85 ELANE 419 MRR04 755 COC14 1.080 AGC2 86 VEGFA 40 MRR04 <	73	ATP11A	407	CD274	741	SGK1	1,075	PSMD11
75 PGGFBB 400 GSTP1 743 DIMNT1 1,077 RAITS 76 IGAS 410 PHOX2A 746 DAES 1,078 CCKBR 77 MRLETD 411 SOS2 745 CDP2 1,078 CCKBR 78 MGL2 412 LMNN 746 HLV 1,080 PPARA 78 MGT1 413 EMP12 747 PHOKA1 1,081 MB 80 MET 415 APEX1 749 CHUK 1,083 LOC111674747 81 TMP1 415 APEX1 749 CHUK 1,083 LOC111674747 83 SCNN1A 417 PLAU 751 LK 1,083 LOC11167473 84 MM22 418 MRIDE 755 CMB1 1,084 LOC11167473 85 ELANE 420 MR101 756 ADC11 1,080 PBOT2 86 ADE42 423	74	HFE	408	MIR142	742	DNAAF1	1,076	HBA2
TigAs TigAs Hoto Process of the source of t	75	PDGFRB	409	GSTP1	743	DNMT1	1,077	RAB11B
77 MPLLETP 111 SOS2 745 DoPl2 0.703 C.DNS 78 MBL2 412 LMNA 746 H.V. 1.081 MBL7 79 NOTCH1 413 ENPP2 747 FRKAA1 1.081 GAS5-AS1 81 TMP1 416 OPF1 748 HSPA 1.083 CAS5-AS1 81 TMP1 416 CXCL9 750 SKP2 1.084 KCNL1 83 SONNIA 417 PLAU 751 ILK 1.085 KCNL1 84 MMP2 418 MRIETC 752 COCN1 1.089 ADS12 85 ILANE 421 MRISDE 756 ADC11 1.083 BS162 86 ADFR2 423 THFSP138 757 HDAC9 1.083 BRF5 87 PLGFRA 423 MIFRP1 760 DCCH1 1.084 GLS2 89 PDGFFRA 423	76	ITGA3	410	PHOX2A	744	DAB2	1,078	CCKBR
NBL2 042 LNAN 766 LUV 1.080 PPARA 70 NOTCH1 413 EMPP2 74 PRIXA 1.081 MG 80 MET 414 TOP1 748 HSPA5 1.082 GASS-AS1 81 TIMP1 416 CACLA 750 SKP2 1.086 KAAM319L 82 SERPINH1 416 CACLA 750 SKP2 1.086 KAAM319L 84 MMP2 418 MIRLET7C 752 ADCRA22 1.086 KAAM319L 84 VEGFA 420 MIR24-1 754 CPLAF 1.088 ADC711677473 86 VEGFA 420 MIR124-1 754 CPLAF 1.088 ADC710 1.080 PSMD8 87 PLG 421 MIR124-1 756 ADCY10 1.080 PSMD8 89 ADR182 424 MIR1461 758 APG1 1.081 MIR130 91	77	MIRLET7D	411	SOS2	745	CDH2	1.079	CLCN3
70 NOTC+11 413 EMPP2 747 PRIVAN 1,081 MB 80 MET 415 APE(1 749 CHUK 1,083 LOC111674474 81 SCHNIA 417 PLAU 750 CHUK 1,085 KAA0319L 83 SCNNIA 417 PLAU 751 LK 1,085 KAA0319L 84 MMP2 418 MIRISCE 753 AOPA2B 1,085 KAA0319L 85 ELANE 419 MIRISCE 753 AOPA2B 1,087 PSM22 86 VEOFA 420 MIRISCE 756 CFLAT 1,088 AOC110 88 ADRE2 421 MIRISCE 758 ADC110 1,080 PSM22 89 MIRISDA 422 KRT7 756 ADC110 1,080 PSM26 90 KT 424 MIRISDB 758 ARC1 1,022 PSM27 91 CZD2A 425 MIRISDA 769 BAC1 1,030 RWF5 92 TGFBRZ 426 MIRISDA 769 BAC1 1,084 GLIS3 92 TGFBRZ 426 MIRISDA 769	78	MBL2	412	I MNA	746	H.IV	1 080	PPARA
of MET 111 CP1 716 HSPAC 1002 SASS-S1 101 MIN-1 416 APEST 716 HSPAC 1004 KCNL11 122 SEPRIM-H1 416 APEST 776 SKC2 1004 KCNL11 123 SCNN1A 417 PALL 751 SKC2 1005 PSMA2 124 SCNN1A 417 PALL 752 ADCAR2B 1005 PSMA2 125 HAR 410 MIRIDE 753 CALRT 1005 PSMA2 126 HAR 420 MIRIDE 754 CALRT 1005 PSMA2 127 HLG 421 MIRIDE 756 ADCY10 1002 PSM25 126 CG2DAA 424 MIRIDE 757 HACG1 1002 PSM25 127 CG2DAA 425 MIRIDE 756 ADC1 1001 QL2 PSM25 126 CG2DAA	70	NOTCH1	/13	ENIPP2	747		1,000	MB
all IMPL 4/4 IVPL 7/48 PSPAD ILB2 GRSD-ADJ 81 TIMPL 4/16 APEN 7/40 CHLK ILB3 LICH119/47/4 82 SCHN1A 4/17 PLAU 7/51 LK ILB6 KACAUI 84 MMP2 4/18 MIRIDE 7/52 ADDRAZE ILB6 KACAUI 84 MMP2 4/18 MIRIDE 7/52 ADDRAZE ILB6 KACAUI 86 VEGFA 4/0 MIRIDE 7/56 ADDCYTO 1.090 PSMD2 87 PLGS 4/21 MIRIDE 7/56 ADDCYTO 1.090 PSMD2 88 MIRIDAA 4/22 KRT7 7/56 ARC1 1.092 PSMD2 90 KIT 4/24 MIRIDA1 7/56 ARC1 1.098 MIRIDA 91 CC2DDA 4/26 MIRITA 7/56 ARC1 1.098 MIRIDA 92 TGFBR2	19		413		747		1,001	
B1 IMP1 415 APEX1 749 CHUK 1,083 LUC1116/44/4 82 SERNN11 416 CXCL9 750 SRP2 1,084 K/N11 83 SCINN1A 417 PLAU 751 LIK 1,085 K/AG319L 84 MMP2 418 MERDE 753 SST 1,087 PSMD3 85 VEGFA 420 MERDE 753 SST 1,089 ADCR2 86 WEGFA 421 MERDE 756 ADCV10 1,089 ABCF2 89 ADRE2 423 INFRSF13B 757 HDAC9 1,091 MERDO 91 CC2D2A 426 MERTHR 760 DICFR1 1,038 RMFS 92 TOFBR2 428 MERD11 759 BAK1 1,038 MERD3 93 LL4 429 MERD11 750 LKKG 1,038 MERD4 94 LL4 428	80		414		748	HSPA5	1,082	GASS-AST
82 SERPINIT 416 CXCL9 760 SRP2 1,084 KXOAT16 84 MMP2 418 MRILETCC 752 ADORA2B 1,086 PSMA2 84 LANE 418 MRIDETCC 752 ADORA2B 1,086 PSMA2 85 LANE 418 MRIDETCC 752 ADORA2 1,086 ADCT147473 86 VEGFA 420 MRIPARA 756 CALAT 1,089 ADCT2 88 MRIDSOA 422 KRT7 766 ADCV10 1,080 PSMD8 90 CZD2A 425 MRIDGR 786 ARG1 1,082 PSMD7 91 CZD2A 426 MRIDGR 786 ARG1 1,084 GLSS 92 TGFBR2 428 MRIHA 782 ADCEA 1,084 GLSS 94 LA 429 KDR1 783 ADCEA 1,088 MRIS06 97 NDP10	81	IIMP1	415	APEX1	749	CHUK	1,083	LOC1116/44/4
83 SCINIA 417 PLAU 751 LAC 1.085 KUA0319L 84 MMP2 418 MIR2DC 752 ADCRA2B 1.087 PSMD3 85 ELANE 419 MIR2DC 753 SST 1.087 PSMD3 86 VEGFA 420 MIR266-1 756 ADCN10 1.088 LCI11674473 87 PLG 421 MIR466-1 756 ADCN10 1.089 ADCR2 89 ADR82 423 TNFRSF13B 757 HDAC9 1.091 MIR30 91 CC222A 428 MIR181A1 759 BAK1 1.083 PNF5 92 TGFBR2 428 MIR181A 760 DCER1 1.084 GLIS3 93 PDGFRA 422 FTPN11 762 MAR61 1.085 MIR268 94 IL4 428 PTPN11 762 MAR11 1.096 MIR268 95 TIA1	82	SERPINH1	416	CXCL9	750	SKP2	1,084	KCNJ1
84 MMP2 418 MIRLET/C 752 ADCRA2B 1.086 PSMA2 85 ELANE 419 MIR30C 753 SST 1.087 PSM03 86 VEGFA 420 MIR496-1 754 CONE1 1.089 ADCP2 88 MIR130A 422 VRTF 766 ADCV10 1.000 PSM08 90 KIT 424 MIR106B 788 ARG1 1.082 PSM07 91 CZD20A 426 MIR11611 760 DICER1 1.084 GLS3 92 TGFBR2 428 MIR17 762 MARG 1.086 LIC111674476 93 TGFBR2 428 MIR17 763 COL4AS 1.089 MIR20B 94 ILA 428 PIPN11 762 ARAG 1.081 1.081 MIR20B 95 NTR11 430 ELMOL2 764 RQA 1.081 MIR20B 97	83	SCNN1A	417	PLAU	751	ILK	1,085	KIAA0319L
85 FLANE 419 MIR3DE 754 ST 1.0.87 PRM33 86 VEGFA 420 MIR496-1 754 CCLAR 1.0.89 ADCP11074473 87 PLG 421 MIR496-1 756 CCNB1 1.0.89 ADCP12 88 MIR3DA 422 KIT 756 ADCV10 1.0.90 PSMD3 89 ADR82 423 MIR16B 758 ARG1 1.0.92 PSMD7 91 C2C2D2A 426 MIR15A11 759 BCK11 1.0.96 CLATT 92 TGFBR2 428 MIR15A11 750 DICER1 1.0.96 CLATT 93 PDGFRA 427 STNL2 761 KERGA 1.0.96 LOT11674473 94 IL4 428 PTPN11 763 COLA3 1.0.96 MIR151A 95 STK11 430 ELMOD2 764 FGA 1.0.98 MIR151A 96 TMEM67 432 CAM1 765 ABL1 1.0.99 MIR154A	84	MMP2	418	MIRLET7C	752	ADORA2B	1,086	PSMA2
B6 VEGFA 420 MIR214 754 CPLA 1.088 LOC111674473 B8 MIR130A 422 KRT7 756 ADC70 1.080 PSMD7 B8 ADR82 423 TNFRSF13B 757 HDAC9 1.081 MIR390 90 KIT 424 MIR1066 758 ARG1 1.082 PSMD7 91 C2202A 425 MIR191A1 759 BAK1 1.083 RNF5 92 TGFBR2 426 MTNH7 760 DICER1 1.094 CLIS3 93 POGFRA 427 BTNL2 761 KK46 1.096 CLC111674476 95 STK11 430 ELMOD2 764 FGA 1.094 MIR130B 96 TK11 433 STN11 766 GLAS 1.100 LOC111674478 97 NOP10 433 STN11 766 GLAS 1.100 MIR130B 1010 MR467	85	ELANE	419	MIR30E	753	SST	1,087	PSMD3
PLG 421 MIR486-1 755 CCNB1 1.089 ABC2 88 MIR130A 422 KRT7 756 ADCY10 1.080 PSMD8 99 ADR82 423 TMFRSF13B 757 HDAC9 1.091 MIR30 90 KIT 424 MIR106B 758 ARG1 1.092 PSMD7 91 C2CD2A 425 MIR1B1A1 759 BAK1 1.094 GLIS3 92 TGFBR2 426 MTHFR 760 DICER1 1.094 GLIS3 93 POGRA 427 BTNL2 761 IKBKG 1.096 LOC111674476 94 IL4 428 PTPN11 763 COLA3 1.098 MIR130F 95 NLPP2 428 KDFN 763 ABL1 1.098 MIR130F 96 ALDS 433 STIN1 786 ABL1 1.098 MIR130F 97 NOP10 433 S	86	VEGEA	420	MIR214	754	CFLAR	1.088	LOC111674473
MIR130A 42 KRT7 756 ADCY10 1.080 PSMDB 88 ADR82 423 TNFRSF13B 757 HDAC93 1.081 MIR190 90 KIT 424 MIR106B 758 ARG1 1.082 PSMD7 91 CC2D2A 425 MIR19A1 759 BAK1 1.083 RNF5 92 TGFBR2 426 MITHFN 761 IKBK0 1.095 CHAT 93 POGFRA 427 BTNL2 761 IKBK0 1.096 LOC11167476 95 NIF22 429 KDR 763 COLAA3 1.097 MIR23B 96 STK11 430 ELMOD2 764 FGA 1.098 MIR130B 97 NOP10 431 STING1 765 ABL1 1.098 MIR154 100 CCL2 434 VCAM1 768 FCGAB 1.101 MIR42 101 MIR4C 435 C	87	PLG	421	MIR486-1	755	CCNB1	1 089	ABCE2
DD ADRE2 423 TMFRSF13B 757 HDAC3 1,027 MRES0 90 KT 424 MR106B 758 ARG1 1,022 PSMD7 91 C2D2A 425 MR191811 769 BAK1 1,034 GUS3 92 TGFBR2 426 MTHFR 760 DICEN1 1,034 GUS3 93 POGFRA 427 BTNL2 761 IKBKG 1,096 LVTT 94 L4 428 PTPN11 762 MYH6 1,096 MIF130B 95 NHP2 428 PTPN11 762 MR4 1,099 MR151A 96 STK11 430 ELMOD2 764 FGA 1,099 MR151A 97 NOP10 431 STING1 766 ABL1 1,099 MR151A 98 ALOKS 433 MR140 767 AHAGAS1 1,101 DESE2 1010 MR47 433	88	MIR130A	121	KBT7	756		1,000	PSMD8
B9 AUHB2 42.3 INFRSP1.3D 7.57 FDAGS 1,091 INFRSP1 90 KTT 424 MIR10E 758 ARG1 1.093 FNF5 91 CC2D2A 425 MIR18IA1 759 BAK1 1.093 FNF5 92 TGFBR2 426 MTHFR 760 DICEF1 1.094 GUS3 93 IL4 427 BTNL2 761 IKRG 1.095 OHAT 94 IL4 429 KDR 763 COLA3 1.097 MIR32B 96 STK11 430 ELMOD2 764 FGA 1.098 MIR130B 97 NOP10 431 STIG1 765 ABL1 1.099 MIR130F 98 TMEM67 433 MIR140 767 ABHGAPA31 1,101 CDB2 100 CCL2 434 VCAM1 768 FCGRB1 1,108 DFF103B 101 <mir34c< td=""> 423 CD</mir34c<>	00		422		750		1,000	
90 KII 424 MIRTOBE /38 ArG1 1,082 PSMD/ 91 CC2D2A 425 MIR181A1 759 BAK1 1,094 GLIS3 92 TGFBR/2 426 MTHFR 760 DICER1 1,094 GLIS3 93 PDGFRA 428 PTPN11 761 KGKG 1,095 CHAT 94 IL4 428 PTPN11 762 MVH6 1,096 LOC111574476 95 STK11 430 ELMOD2 764 RGA 1,099 MIR130F 97 NOP10 431 STING1 765 ABL1 1,00 LOC111574478 98 ALCXS 432 THY1 766 GJAS 1,101 LOD2 CD22 100 CGL2 434 VCAM1 768 PGGR30 1,103 RWF185 102 STAT1 711 PMM2 1,106 NFR186 103 ALB GSTAT4 77	89	ADRB2	423	INFROF ISB	/5/	HDAC9	1,091	MIR590
91 CC2D2A 425 MiR181A1 759 BA11 1,083 RNF5 92 CGFBR2 425 MTHFR 760 DICER1 1,084 GLIS3 93 PDGFRA 427 BTNL2 761 HKGG 1,095 CHAT 95 NHP2 429 KDR 763 COLA33 1,097 MIR23B 96 STK11 430 ELMOD2 764 FGA 1,098 MIR130B 97 NOP10 431 STING1 765 ABL1 1,009 MIR151A 98 MEM67 433 MIR140 767 ARHGAP31 1,101 CD22 100 CCL2 434 VCAM1 768 FCGR3B 1,102 EP2 101 MIR34C 436 CP144 771 PMA2 1,105 DEFB103B 102 STAT1 436 CP144 772 ACD 1,106 NRF42 103 RVERPHPL 439 <td>90</td> <td>KII</td> <td>424</td> <td>MIR106B</td> <td>758</td> <td>ARG1</td> <td>1,092</td> <td>PSMD7</td>	90	KII	424	MIR106B	758	ARG1	1,092	PSMD7
92 TGFBR/2 426 MTHFR 760 DCBP1 1,094 GLIS3 93 PDGFRA 427 BTNL2 761 KBKG 1,095 CHAT 94 LL4 428 PTPN11 762 MKHG 1,096 LC0111674476 95 NHP2 429 KDR 763 COL4A3 1,097 MR23B 96 STK11 430 ELMOD2 764 FGA 1,008 MR130F 97 NOP10 431 STING1 765 ABL1 1,009 MR130F 98 ALCX5 432 MR140 767 ABLAP371 1,101 CDE2 100 CCL2 433 MR140 767 ABLAP371 1,104 MR423 101 MR34C 435 CCR2 769 SL26A9 1,103 RNF485 102 STAT1 771 PMM2 1,106 NFK82 103 ALB GSTAT4 777 CAGP <td>91</td> <td>CC2D2A</td> <td>425</td> <td>MIR181A1</td> <td>759</td> <td>BAK1</td> <td>1,093</td> <td>RNF5</td>	91	CC2D2A	425	MIR181A1	759	BAK1	1,093	RNF5
93 PDGFRA 427 BTNL2 761 IRIKG 1.096 CHAT 94 LA 428 PTN111 762 MVH6 1.096 LCC11167476 95 NHP2 429 KDR 763 COL4A3 1.097 MIR3DB 96 STK11 430 ELMOD2 764 FGA 1.098 MIR15A 97 NOP10 431 STING1 766 ABL1 1.099 MIR15A 98 TMEM67 433 MIR140 767 ARAGAP31 1.101 COB2 100 CCL2 434 VCAM1 768 FCGR3B 1.102 E2F2 101 MIR4C 435 CCR2 769 SLC26A9 1.106 NRF82 103 ALB 437 STAT4 771 PMM2 1.105 DEF8103B 104 HOF 439 MIR128-2 773 CHIT1 1.106 NFR2 105 RPGRIP1L 439 </td <td>92</td> <td>TGFBR2</td> <td>426</td> <td>MTHFR</td> <td>760</td> <td>DICER1</td> <td>1,094</td> <td>GLIS3</td>	92	TGFBR2	426	MTHFR	760	DICER1	1,094	GLIS3
94 L4 428 PTPN11 762 MYH6 1.096 LCC111674476 95 NHP2 429 KDR 763 COL4A3 1.097 MR33B 96 STK11 430 ELMOD2 764 FGA 1.098 MR13D 97 NOP10 431 STING1 765 ABL1 1.098 MR14D 98 ALOX5 432 THY1 766 GLAS 1.100 COC111674478 99 TMEM67 433 MR140 767 APHGAP21 1.101 COC111674478 90 MEM67 433 MR140 767 APHGAP21 1.108 RNF185 101 MR34C 435 CCP2 769 SLC2649 1.108 NFR182 102 STAT1 436 CPC164 772 ACD 1.106 NFR82 103 ALB 438 CEP164 775 CSF1 1.108 AFAP1-AS1 105 NPAPI	93	PDGFRA	427	BTNL2	761	IKBKG	1,095	CHAT
95 NHP2 429 KDR 763 COL4A3 1.097 MIR28E 96 STK11 430 ELMOD2 764 FGA 1.098 MIR130E 97 NOP10 431 STNG1 766 ABL1 1.099 MIR151A 98 ALOX5 432 THY1 766 GJA5 1.100 LOC111674478 99 TMEM67 433 MIR140 768 FGGR0B1 1.102 E2F2 101 MIR34C 435 CCR2 769 SLC26A9 1.104 MIR423 102 STAT1 436 CDKN1A 770 LBAA 1.104 MIR423 103 ALB 437 STAT4 771 PMM2 1.105 DFEB103B 104 HGF 438 CEP164 772 ADC 1.106 AFA1-A51 105 PGRIP1L 439 MIR128-2 773 CMIT 1.109 PSMC2 105 TCS2 <t< td=""><td>94</td><td>IL4</td><td>428</td><td>PTPN11</td><td>762</td><td>MYH6</td><td>1,096</td><td>LOC111674476</td></t<>	94	IL4	428	PTPN11	762	MYH6	1,096	LOC111674476
96 STK11 430 ELMOD2 764 FGA 1.098 MIR130B 97 NOP10 431 STNG1 765 ABL1 1.099 MIR151A 98 ALOX5 432 THY1 766 GLAS 1.100 LOC111674478 99 TMEMØF7 433 MIR140 767 ARHGAP31 1.011 CD621 100 CGL2 434 VCAM1 768 FCGR3B 1.102 E2F2 101 MIR34C 435 CCR2 769 SLC26A9 1.104 MIR423 102 STAT1 436 CDK11A 770 LRBA 1.106 DEFB103B 104 HGF 438 CEP164 772 ACD 1.106 MIR186 105 RPGRIP1L 439 MIR18-2 773 CHIT 1.109 PSMC2 106 NPHP1 440 S100A9 776 CSF1 1.101 GAD45G 107 TSC2	95	NHP2	429	KDR	763	COL4A3	1.097	MIR23B
BOT NOP10 431 STING1 76 AL 1.02 MIR151A 98 ALOX5 432 THY1 766 GJA5 1,100 LOC111674478 99 TMEM67 433 MIR140 767 ARHGAP31 1,101 CD2 100 CCL2 434 VCAM1 768 FCGR3B 1,102 E2F2 101 MIR4C 436 CDK11A 770 LRBA 1,104 MIR423 102 STAT1 436 CDK11A 770 LRBA 1,105 DEFB103B 104 HGF 438 CEP164 772 ACD 1,106 NFKB2 105 RPGRIP1L 439 MIR128-2 773 CHIT 1,108 APAP1-AS1 107 TSC2 441 TLB3 776 ABG22 1,110 ERUN2 108 MDM2 442 SERPINA3 776 ABG21 1,111 GAD04563 110 FDR14	96	STK11	430	FLMOD2	764	FGA	1 098	MIR130B
Mon to 431 Striket Fact	07		100	STING	765		1,000	MID151A
96 ALOXS 4.22 ITT 766 GUAS 1,100 ECCT116/4476 99 TMEM67 433 MIR140 767 AFRAPA31 1,101 CDS 100 CCL2 434 VCAM1 768 FCGR3B 1,102 E2F2 101 MIR34C 435 CCRV1A 770 LIRBA 1,104 MIR423 102 STAT1 436 CDKN1A 770 LIRBA 1,105 DEFE103B 104 HGF 438 CEP164 772 ACD 1,106 NFKB2 105 RPGRIP1L 439 MIR128-2 773 CHIT1 1,107 MIR186 106 NFHP1 440 S100A9 774 CDK6 1,110 ERLN2 107 TSC2 441 TLR3 776 ABCG2 1,110 ERLN2 108 MDM2 442 SERPINA3 776 ABCG2 1,110 ERLN2 110 EDN1	91	NOF TO	401		703	ADLI	1,099	
SM INERAD/ 433 INERAD/ 767 AFREAPS1 1,101 CDS2 100 CCL2 434 VCAM1 768 FCGR3B 1,102 E2P2 101 MIR3C 435 CCR2 769 SLC26A9 1,103 RNF185 102 STAT1 436 CDKN1A 770 LRBA 1,105 DEFB103B 104 HGF 438 CEP164 772 ACD 1,106 NFKB2 105 RPGRIP1L 439 MIR128-2 773 CHIT1 1,107 MIR186 106 NPHP1 440 S100A9 774 CDK6 1,108 AFAP1-AS1 107 TSC2 441 TLR3 775 CSF1 1,110 ERLN2 109 TTC21B 443 MIR25 777 CASP1 1,111 GADD45G 111 WD119 445 MALAT1 779 ASCL1 1,114 PSME1 113 CCL11	90		432		700		1,100	LUC1110/44/0
100 CGL2 434 VCAM1 769 FCGR3B 1,102 E2F2 101 MIR34C 435 CCR2 769 SLC26A9 1,103 RNF185 102 STAT1 436 CDKN1A 770 LRBA 1,104 MIR423 103 ALB 437 STAT4 771 PMM2 1,105 DEFB103B 104 HGF 438 CEP164 772 ACD 1,106 NFKB2 105 RPGRIP1L 439 MIR128-2 773 CHIT1 1,107 MIR186 106 NPHP1 440 S100A9 774 CDK6 1,108 AFAP1-AS1 107 TSC2 441 TLR3 775 CSF1 1,110 ERLN2 108 MDM2 442 SERPINA3 776 ABCG2 1,110 ERLN2 110 EDN1 444 CD44 778 P2RX7 1,112 CS 111 WDR19 445 MALAT1 779 ASCL1 1,113 CD22 111	99		433	MIR 140	767	ARHGAP31	1,101	CD82
101 MIR34C 435 CCR2 769 SLC2RA9 1,103 RNF185 102 STAT1 436 CCR2 769 LREA 1,104 MIR423 103 ALB 437 STAT4 771 PMM2 1,105 DEFB103B 104 HGF 438 CEP164 772 ACD 1,106 NrKB2 105 RPGRIPL 439 MIR128-2 773 CHIT1 1,107 MIR186 106 NPHP1 440 S100A9 774 CDK6 1,108 AFAP1-AS1 107 TSC2 411 TLR3 776 ABCG2 1,110 ERLN2 108 MDM2 442 SEPINA3 776 ASC1 1,111 GAD45G 110 EDN1 443 MIR25 777 CASP1 1,113 CD22 112 CRP 446 COL3A1 780 WWF 1,114 PSMB1 113 CCL11 448 <td>100</td> <td>CCL2</td> <td>434</td> <td>VCAM1</td> <td>768</td> <td>FCGR3B</td> <td>1,102</td> <td>E2F2</td>	100	CCL2	434	VCAM1	768	FCGR3B	1,102	E2F2
102 STAT1 436 CDKN1A 770 LBBA 1,104 MIR423 103 ALB 437 STAT4 771 PMM2 1,105 DEFB103B 104 HGF 438 CEP164 772 ACD 1,106 NFKB2 105 RFGRIP1L 439 MIR12s-2 773 CHT1 1,108 AFAP1-AS1 106 NPHP1 440 S100A9 776 CSF1 1,108 AFAP1-AS1 107 TSC2 441 TLR3 775 CSF1 1,101 ENLN2 108 MDM2 442 SERPINA3 776 ABCG2 1,110 ENLN2 109 TTC21B 443 MIR25 777 CASP1 1,112 CS 111 WDR19 445 MALAT1 779 ASCL1 1,113 CD22 112 CRP 446 COL3A1 780 WF 1,114 PSMB1 113 CCL11 447 MIR429 783 PROM1 1,115 LOC111674467 115	101	MIR34C	435	CCR2	769	SLC26A9	1,103	RNF185
103 ALB 437 STAT4 771 PMM2 1,105 DEFB103B 104 HGF 438 CEP164 772 ACD 1,106 NFKB2 105 RPGRIPL 439 MIR128-2 773 CHT1 1,107 MIR186 106 NPHP1 440 S100A9 774 CDK6 1,108 AFAP1-AS1 107 TSC2 441 TLR3 775 CSF1 1,109 PSMC2 108 MDM2 442 SERPINA3 776 ABCG2 1,110 ENLN2 109 TTC21B 443 MIR25 777 CASP1 1,112 CS 111 WDR19 444 CD44 778 P2x7 1,113 CD2 112 CRP 445 MALAT1 780 WF 1,114 PSMB1 113 CCL11 447 CD28 781 PROM1 1,115 LOC111674467 114 AGT 448 MIR23A 782 PDN 1,114 DSMB1 115 COND1 </td <td>102</td> <td>STAT1</td> <td>436</td> <td>CDKN1A</td> <td>770</td> <td>LRBA</td> <td>1,104</td> <td>MIR423</td>	102	STAT1	436	CDKN1A	770	LRBA	1,104	MIR423
104 HGF 438 CEP164 772 ACD 1,106 NFKB2 105 RPGRIP1L 439 MIR128-2 773 CHIT1 1,107 MIR186 106 NPHP1 400 S100A9 774 CDK66 1,108 AFAP1-AS1 107 TSC2 441 TLR3 775 CSF1 1,109 PSMC2 108 MDM2 442 SERPINA3 776 ABCG2 1,110 EFLIN2 109 TTC21B 443 MIR25 777 CASP1 1,112 CS 1110 EDN1 444 CD44 778 P2RX7 1,112 CS 112 CRP 446 CD28 781 PROM1 1,115 LOC111674479 113 CCL11 447 CD28 781 PROM1 1,116 LOC11167447 116 COL1A2 450 MIR35 786 TNFRSF10A 1,120 IFNB1 117 COPA	103	ALB	437	STAT4	771	PMM2	1,105	DEFB103B
105 RPGRIP1L 439 MIR128-2 773 CHIT1 1,107 MIR186 106 NPHP1 440 S100A9 774 CDK6 1,108 AFAP1-AS1 107 TSC2 441 TLR3 775 CSF1 1,109 PSMC2 108 MDM2 442 SERPINA3 776 ABCG2 1,110 ERLIN2 109 TTC21B 443 MR25 777 CASP1 1,112 CS 110 EDN1 444 CD44 778 P2RX7 1,113 CD22 111 WDR19 446 COL3A1 780 WVF 1,114 PSMB1 113 CCL11 447 CD28 781 PROM1 1,115 LOC111674479 114 AGT 448 MIR23A 782 PDPN 1,116 LOC111674467 115 CCND1 448 MIR13A 783 PRODH 1,117 SDH3 116 COL1A2 450 HAMP 784 ALG9 1,120 IFNB1 117	104	HGF	438	CEP164	772	ACD	1,106	NFKB2
106 NPHP1 440 S100A9 774 CDK6 1,108 AFAP1-AS1 107 TSC2 441 TLR3 775 CSF1 1,109 PSMC2 108 MDM2 442 SERPINA3 776 ABCG2 1,110 EPLIN2 109 TTC21B 443 MIR25 777 CASP1 1,111 GADD45G 110 EDN1 444 CD44 778 P2RX7 1,112 CS 111 WDR19 445 MALAT1 779 ASCL1 1,113 CD22 113 CCL11 447 CD28 781 PROM1 1,115 LOC111674479 114 AGT 448 MIR23A 782 PDPN 1,116 LOC111674465 115 COND1 449 MIR19A 783 PRODH 1,117 SDHB 116 COL1A2 450 HAMP 784 ALG9 1,120 IFNB1 117 COPA <t< td=""><td>105</td><td>RPGRIP1L</td><td>439</td><td>MIR128-2</td><td>773</td><td>CHIT1</td><td>1,107</td><td>MIR186</td></t<>	105	RPGRIP1L	439	MIR128-2	773	CHIT1	1,107	MIR186
107 TSC2 441 TLR3 775 CSF1 1,109 PSMC2 108 MDM2 442 SERPINA3 776 ABGG2 1,110 ERLIN2 109 TTC21B 443 MIR25 777 CASP1 1,111 GADD45G 110 EDN1 444 CD44 778 P2Rx7 1,112 CS 111 WDR19 445 MALAT1 779 ASCL1 1,113 CD22 112 CRP 446 COL3A1 780 WWF 1,114 PSMB1 113 CCL11 447 CD28 781 PROM1 1,115 LOC111674479 114 AGT 448 MIR23A 782 PDPN 1,116 LOC111674465 115 COND1 449 MIR19A 783 PRODH 1,118 LOC111674465 117 COPA 451 MIR35 786 TNFRSF10A 1,120 IFNB1 118 CAST61	106	NPHP1	440	S100A9	774	CDK6	1,108	AFAP1-AS1
INSC INSC <thinsc< th=""> INSC INSC</thinsc<>	107	TSC2	441	TI R3	775	CSF1	1 109	PSMC2
No. N	108	MDM2	442	SERDINIAS	776	ABCG2	1,100	FBLIN2
IDS ITC2 IB 443 MIR2S ITC CASP1 I,ITI GADDASG 110 EDN1 444 CD44 778 P2RX7 1,112 CS 111 WDR19 445 MALAT1 779 ASCL1 1,113 CD22 112 CRP 446 COL3A1 780 WWF 1,114 PSMB1 113 CCL11 447 CD28 781 PROM1 1,115 LOC111674479 114 AGT 448 MIR23A 782 PDPN 1,116 LOC111674467 115 COND1 449 MIR19A 783 PRODH 1,117 SDHB 116 COL1A2 450 HAMP 784 ALG9 1,118 LOC111674465 117 COPA 451 MIR429 785 HOXD13 1,119 PSMD14 118 CASP8 452 MIR35 786 TNFRSF10A 1,120 IFNB1 120 ACT01	100		442	MIDOS	770	ADOGZ	1,110	
110 EDN1 444 CD44 778 P2HX7 1,112 CS 111 WDR19 445 MALAT1 779 ASCL1 1,113 CD22 112 CRP 446 COL3A1 780 WWF 1,114 PSMB1 113 CL11 447 CD28 781 PROM1 1,115 LOC111674479 114 AGT 448 MIR23A 782 PDPN 1,116 LOC111674467 115 CCND1 449 MIR19A 783 PRODH 1,117 SDHB 116 COL1A2 450 HAMP 784 ALG9 1,118 LOC111674465 117 COPA 451 MIR429 785 HOXD13 1,119 PSMD14 118 CASP8 452 MIR355 786 TNFRSF10A 1,120 IFNB1 119 DKC1 453 TTR 787 IL12B 1,121 PLAT 120 ACTC1 454 C2CD3 788 BES9 1,122 PSMA5 121	109	FDNH	443		770	CASEI	1,111	GADD45G
111 WDR19 445 MALA11 779 ASCL1 1,113 CD22 112 CRP 446 COL3A1 780 WWF 1,114 PSMB1 113 CCL11 447 CD28 781 PROM1 1,115 LOC111674479 114 AGT 448 MIR23A 782 PDPN 1,116 LOC111674467 115 CCND1 449 MIR19A 783 PRODH 1,117 SDHB 116 COL1A2 450 HAMP 784 ALG9 1,118 LOC111674465 117 COPA 451 MIR429 785 HOXD13 1,119 PSMD14 118 CASP8 452 MIR355 786 TNFRSF10A 1,120 IFNB1 119 DKC1 453 TTR 787 IL12B 1,121 PLAT 120 ACTC1 454 C2CD3 788 BBS9 1,122 PSMA5 121 FGFR2 455 NR1H4 789 NR3C1 1,123 NEB 122	110	EDN1	444	CD44	//8	P2RX7	1,112	CS
112 CRP 446 COL3A1 780 WWF 1,114 PSMB1 113 CCL11 447 CD28 781 PROM1 1,115 LOC111674479 114 AGT 448 MIR23A 782 PDPN 1,116 LOC111674467 115 CCND1 449 MIR19A 783 PRODH 1,117 SDHB 116 COL1A2 450 HAMP 784 ALG9 1,118 LOC1111674465 117 COPA 451 MIR429 785 HOXD13 1,119 PSMD14 118 CASP8 452 MIR335 786 TNFRSF10A 1,120 IFNB1 119 DKC1 453 TTR 787 IL12B 1,121 PLAT 120 ACTC1 454 C2CD3 788 BSS9 1,122 PSMA5 121 FGFR2 455 NR1H4 789 NR3C1 1,123 NEB 122 IL17A 456 G6PD 790 MIR122 1,124 CHGA 123	111	WDR19	445	MALAI1	779	ASCL1	1,113	CD22
113 CCL11 447 CD28 781 PROM1 1,115 LOC111674479 114 AGT 448 MIR23A 782 PDPN 1,116 LOC111674467 115 CCND1 449 MIR19A 783 PRODH 1,117 SDHB 116 COL1A2 450 HAMP 784 ALG9 1,118 LOC111674465 117 COPA 451 MIR429 785 HOXD13 1,119 PSMD14 118 CASP8 452 MIR335 786 TNFRSF10A 1,120 IFNB1 119 DKC1 453 TTR 787 IL12B 1,121 PLAT 120 ACTC1 454 C2CD3 788 BSS9 1,122 PSMA5 121 FGFR2 455 NR1H4 789 NR3C1 1,123 NEB 122 IL17A 456 G6PD 790 MIR122 1,124 CHGA 123 SCNN1B 457 MIR127 791 ITGB3 1,125 MIR157 124 </td <td>112</td> <td>CRP</td> <td>446</td> <td>COL3A1</td> <td>780</td> <td>VWF</td> <td>1,114</td> <td>PSMB1</td>	112	CRP	446	COL3A1	780	VWF	1,114	PSMB1
114 AGT 448 MIR23A 782 PDPN 1,116 LOC111674467 115 CCND1 449 MIR19A 783 PRODH 1,117 SDHB 116 COL1A2 450 HAMP 784 ALG9 1,118 LOC111674465 117 COPA 451 MIR429 785 HOXD13 1,119 PSMD14 118 CASP8 452 MIR355 786 TNFRSF10A 1,120 IFNB1 119 DKC1 453 TTR 787 IL12B 1,121 PLAT 120 ACTC1 454 C2CD3 788 BS9 1,122 PSMA5 121 FGFR2 455 NR1H4 789 NR3C1 1,123 NEB 122 IL17A 456 G6PD 790 MIR122 1,124 CHGA 123 SCNN1B 457 MIR127 791 ITGB3 1,125 MIR187 124 ATM 458 TNNI3 792 ERF 1,126 LOC113523647 125	113	CCL11	447	CD28	781	PROM1	1,115	LOC111674479
115 CCND1 449 MIR19A 783 PRODH 1,117 SDHB 116 COL1A2 450 HAMP 784 ALG9 1,118 LOC111674465 117 COPA 451 MIR429 785 HOXD13 1,119 PSMD14 118 CASP8 452 MIR355 786 TNFRSF10A 1,120 IFNB1 119 DKC1 453 TTR 787 IL12B 1,121 PLAT 120 ACTC1 454 C2CD3 788 BBS9 1,122 PSMA5 121 FGFR2 455 NR1H4 789 NR3C1 1,123 NEB 122 IL17A 456 G6PD 790 MIR122 1,124 CHGA 123 SCNN1B 457 MIR127 791 ITGB3 1,125 MIR187 124 ATM 458 TNNI3 792 ERF 1,126 LOC113523647 125 MIR155 459 CXCL1 793 CCR5 1,127 HSD3B7 126	114	AGT	448	MIR23A	782	PDPN	1,116	LOC111674467
116 COL1A2 450 HAMP 784 ALG9 1,118 LOC111674465 117 COPA 451 MIR429 785 HOXD13 1,119 PSMD14 118 CASP8 452 MIR335 786 TNFRSF10A 1,120 IFNB1 119 DKC1 453 TTR 787 IL12B 1,121 PLAT 120 ACTC1 454 C2CD3 788 BBS9 1,122 PSMA5 121 FGFR2 455 NR1H4 789 NR3C1 1,123 NEB 122 IL17A 456 G6PD 790 MIR122 1,124 CHGA 123 SCNN1B 457 MIR127 791 ITGB3 1,125 MIR187 124 ATM 458 TNNI3 792 ERF 1,126 LOC113523647 125 MIR155 459 CXCL1 793 CCR5 1,127 HSD3B7 126 SHH <td< td=""><td>115</td><td>CCND1</td><td>449</td><td>MIR19A</td><td>783</td><td>PRODH</td><td>1,117</td><td>SDHB</td></td<>	115	CCND1	449	MIR19A	783	PRODH	1,117	SDHB
117 COPA 451 MIR429 785 HOXD13 1,119 PSMD14 118 CASP8 452 MIR335 786 TNFRSF10A 1,120 IFNB1 119 DKC1 453 TTR 787 IL12B 1,121 PLAT 120 ACTC1 454 C2CD3 788 BBS9 1,122 PSMA5 121 FGFR2 455 NR1H4 789 NR3C1 1,123 NEB 122 IL17A 456 G6PD 790 MIR122 1,124 CHGA 123 SCNN1B 457 MIR127 791 ITGB3 1,126 LOC113523647 124 ATM 458 TNNI3 792 ERF 1,126 LOC113523647 125 MIR155 459 CXCL1 793 CCR5 1,127 HSD3B7 126 SHH 460 MIR424 794 ADIPOQ 1,128 LOC108491823 127 RB1 461 IFT52 795 TF 1,129 IL4R 128	116	COL1A2	450	HAMP	784	ALG9	1,118	LOC111674465
118 CASP8 452 MR335 786 TNFRSF10A 1,120 FNB1 119 DKC1 453 TTR 787 IL12B 1,121 PLAT 120 ACTC1 454 C2CD3 788 BBS9 1,122 PSMA5 121 FGFR2 455 NR1H4 789 NR3C1 1,123 NEB 122 IL17A 456 G6PD 790 MIR122 1,124 CHGA 123 SCNN1B 457 MIR127 791 ITGB3 1,125 MIR187 124 ATM 458 TNNI3 792 ERF 1,126 LOC113523647 125 MIR155 459 CXCL1 793 CCR5 1,127 HSD3B7 126 SHH 460 MIR424 794 ADIPOQ 1,128 LOC108491823 127 RB1 461 IFT52 795 TF 1,129 IL4R 128 CSF2 462 ZCCHC8 796 RXRA 1,129 IL4R (Continued on following	117	COPA	451	MIR429	785	HOXD13	1 119	PSMD14
119 DKC1 452 Min Color 760 Min Color 1,120 Min Color 119 DKC1 453 TTR 787 IL12B 1,121 PLAT 120 ACTC1 454 C2CD3 788 BES9 1,123 NEB 121 FGFR2 455 NR1H4 789 NR3C1 1,123 NEB 122 IL17A 456 G6PD 790 MIR122 1,124 CHGA 123 SCNN1B 457 MIR127 791 ITGB3 1,125 MIR187 124 ATM 458 TNNI3 792 ERF 1,126 LOC113523647 125 MIR155 459 CXCL1 793 CCR5 1,127 HSD387 126 SHH 460 MIR424 794 ADIPOQ 1,128 LOC108491823 127 RB1 461 IFT52 795 TF 1,129 IL4R 128 CSF2 462 ZCCHC8 796 RXRA Quotining on following on following on following on following on following on	118	CASP8	452	MIR335	786		1,110	IENIR1
119 DKC1 453 TH 787 IL12B 1,121 PLAT 120 ACTC1 454 C2CD3 788 BBS9 1,122 PSMA5 121 FGFR2 455 NR1H4 789 NR3C1 1,123 NEB 122 IL17A 456 G6PD 790 MIR122 1,124 CHGA 123 SCNN1B 457 MIR127 791 ITGB3 1,125 MIR187 124 ATM 458 TNNI3 792 ERF 1,126 LOC113523647 125 MIR155 459 CXCL1 793 CCR5 1,127 HSD3B7 126 SHH 460 MIR424 794 ADIPOQ 1,128 LOC108491823 127 RB1 461 IFT52 795 TF 1,120 IL4R 128 CSF2 462 ZCCHC8 796 RXRA 1,130 PSMB4	110	DKO1	452		700		1,120	
120 ACTC1 454 C2CD3 788 BBS9 1,122 PSMAS 121 FGFR2 455 NR1H4 789 NR3C1 1,123 NEB 122 IL17A 456 G6PD 790 MIR122 1,124 CHGA 123 SCNN1B 457 MIR127 791 ITGB3 1,125 MIR187 124 ATM 458 TNNI3 792 ERF 1,126 LOC113523647 125 MIR155 459 CXCL1 793 CCR5 1,127 HSD3B7 126 SHH 460 MIR424 794 ADIPOQ 1,128 LOC108491823 127 RB1 461 IFT52 795 TF 1,120 IL4R 128 CSF2 462 ZCCHC8 796 RXRA 1,130 PSMB4	119		400		707	ILIZD	1,121	FLAT
121 FGFR2 455 NR1H4 789 NR3C1 1,123 NEB 122 IL17A 456 G6PD 790 MIR122 1,124 CHGA 123 SCNN1B 457 MIR127 791 ITGB3 1,125 MIR187 124 ATM 458 TNNI3 792 ERF 1,126 LOC113523647 125 MIR155 459 CXCL1 793 CCR5 1,127 HSD3B7 126 SHH 460 MIR424 794 ADIPOQ 1,128 LOC108491823 127 RB1 461 IFT52 795 TF 1,120 IL4R 128 CSF2 462 ZCCHC8 796 RXRA 1,130 PSMB4	120	AUIUI	454	02003	788	8828	1,122	PSIVIA5
122 IL17A 456 G6PD 790 MIR122 1,124 CHGA 123 SCNN1B 457 MIR127 791 ITGB3 1,125 MIR187 124 ATM 458 TNNI3 792 ERF 1,126 LOC113523647 125 MIR155 459 CXCL1 793 CCR5 1,127 HSD3B7 126 SHH 460 MIR424 794 ADIPOQ 1,128 LOC108491823 127 RB1 461 IFT52 795 TF 1,130 PSMB4 128 CSF2 462 ZCCHC8 796 RXRA 1,00 PSMB4	121	FGFR2	455	NR1H4	789	NR3C1	1,123	NEB
123 SCNN1B 457 MIR127 791 ITGB3 1,125 MIR187 124 ATM 458 TNNI3 792 ERF 1,126 LOC113523647 125 MIR155 459 CXCL1 793 CCR5 1,127 HSD3B7 126 SHH 460 MIR424 794 ADIPOQ 1,128 LOC108491823 127 RB1 461 IFT52 795 TF 1,120 IL4R 128 CSF2 462 ZCCHC8 796 RXRA point on following page)	122	IL17A	456	G6PD	790	MIR122	1,124	CHGA
124 ATM 458 TNNI3 792 ERF 1,126 LOC113523647 125 MIR155 459 CXCL1 793 CCR5 1,127 HSD3B7 126 SHH 460 MIR424 794 ADIPOQ 1,128 LOC108491823 127 RB1 461 IFT52 795 TF 1,129 IL4R 128 CSF2 462 ZCCHC8 796 RXRA 1,130 PSMB4	123	SCNN1B	457	MIR127	791	ITGB3	1,125	MIR187
125 MIR155 459 CXCL1 793 CCR5 1,127 HSD3B7 126 SHH 460 MIR424 794 ADIPOQ 1,128 LOC108491823 127 RB1 461 IFT52 795 TF 1,129 IL4R 128 CSF2 462 ZCCHC8 796 RXRA 1,130 PSMB4	124	ATM	458	TNNI3	792	ERF	1,126	LOC113523647
126 SHH 460 MIR424 794 ADIPOQ 1,128 LOC108491823 127 RB1 461 IFT52 795 TF 1,129 IL4R 128 CSF2 462 ZCCHC8 796 RXRA 1,130 PSMB4 (Continued on following page) (Continued on following page) CSP2	125	MIR155	459	CXCL1	793	CCR5	1.127	HSD3B7
127 RB1 461 IFT52 795 TF 1,129 IL4R 128 CSF2 462 ZCCHC8 796 RXRA 1,130 PSMB4	126	SHH	460	MIR424	794		1 128	LOC108491823
128 CSF2 462 ZCCHC8 796 RXRA 1,129 IL4H (Continued on following page) (Continued on following page) (Continued on following page) (Continued on following page)	127	BB1	461	IFT52	705	TE	1 120	II 4R
120 UVIZ 4UZ ZUVIIVO 190 DADA I, ISU PONB4 (Continued on following page)	128	CSF2	160	700409	706	RYRA	1 120	
	120		702	2001100	790		(Contin	ued on following nage)

Number	Gene	Number	Gene	Number	Gene	Number	Gene
129	CEP290	463	AGTR2	797	FAT4	1,131	DRC1
130	FCGR2A	464	NSMCE3	798	PSMD4	1,132	MIR361
131	PKHD1	465	TYR	799	UMOD	1,133	COL11A2
132	NPHP4	466	ABCB4	800	TMEM107	1,134	MIR497
133	MIR200B	467	NOS3	801	BLOC1S6	1,135	SBDS
134	MKS1	468	LPAR1	802	MMP14	1,136	TLR6
135	SCNN1G	469	CXCB2	803	PTK2B	1,137	MIR339
136	FAM111B	470	ZIC3	804	PIEZO2	1 138	RECOL4
137	FNI1	471	LOC111674475	805		1,139	DEBL 2
138	INIVS	472	CCB7	806	SIRTS	1,100	SH2B3
120	STATE	472	ANKSE	807	01110	1,140	GLICADA
140		475		007		1,141	
140		474		000		1,142	DONA
141	FGFRJ	475		809	GATAD	1,143	PONA
142	REI	476	MIR224	810	EPOR	1,144	PSIVIE2
143	NRAS	477	IGF1R	811	PVI1	1,145	
144	DDR2	478	XRCC1	812	MUSK	1,146	TIC37
145	FBN1	479	CD34	813	ESR2	1,147	PSMB5
146	OFD1	480	EVC2	814	MAP1B	1,148	PRKG1
147	MAP2K1	481	CEACAM5	815	MT-CYB	1,149	LEPR
148	ENG	482	MIR338	816	TRAF6	1,150	TNC
149	NEK8	483	GATA4	817	PKD1L1	1,151	PTGS1
150	FGF2	484	MIRLET7G	818	RBPJ	1,152	IFNA2
151	MUC5AC	485	SOD2	819	DMD	1,153	DZIP1L
152	NFKB1	486	MIR191	820	FABP4	1,154	MIR296
153	RARB	487	CCR3	821	CD80	1,155	CD86
154	TNFRSF1A	488	CXCL5	822	PSMA4	1,156	MYCL
155	IL5	489	MYLK	823	IGHE	1,157	VPS45
156	APC	490	H2AC18	824	EGFR-AS1	1,158	GBE1
157	SMPD1	491	GPC3	825	DNMT3B	1 159	II 7B
158	MPO	492	TMEM138	826	MIR26A1	1,160	CYP27A1
159	ACTA2	493	MIB377	827	FI T4	1,161	PL A2G7
160	MIR126	494	CCI 22	828	CCNA2	1,162	NOTCH2
161		405	SI C34A2	820		1,162	CEACAM1
162	MID17	495		820	TUG1	1,100	MID495
162	ECE7	490		821		1,104	
164	IGI7	497		001		1,100	DECOA
104		490	DINALIJ C10044	002		1,100	
100		499	5100A4	033	IVIIVIP3	1,107	
100		500		834		1,108	LOC113033875
107	PDCD1	501		835	BLUC 153	1,109	LUC 113004907
168	VEGEC	502	MIR 137	836	SERPINBI	1,170	ZEBT
169	IF180	503	FOXJ1	837	GLA	1,171	FOXM1
170	SCGB1A1	504	BCL2L1	838	LPO	1,172	CASR
1/1	BRCA2	505	TRPV4	839	F2R	1,173	TALDO1
172	AHI1	506	CCR4	840	BIK	1,174	MIR219A1
173	TCTN2	507	CADM1	841	SOCS3	1,175	CCL26
174	BMPR2	508	TMEM237	842	COL4A2	1,176	LOC113664107
175	RAF1	509	LOC111674463	843	NBAS	1,177	CLCN4
176	CXCR4	510	GBA	844	CEP104	1,178	SNHG1
177	KIAA0586	511	EZH2	845	MAGEA4	1,179	LAMA2
178	HIF1A	512	SOX9	846	DERL1	1,180	TCF7
179	FARSB	513	MIR24-2	847	AKT3	1,181	TFRC
180	TLR2	514	SPARC	848	NPPA	1,182	PLCZ1
181	AGTR1	515	S100A8	849	BCL2L11	1,183	POMC
182	BMP6	516	LTA	850	LAMA1	1,184	ABCC3
183	CDK4	517	MKKS	851	IL3	1,185	CRYAB
184	TMEM216	518	HYDIN	852	ITGA5	1,186	LOC110806263
185	RELA	519	GLI1	853	CYP2D6	1,187	MCM4
186	CSF3	520	BIRC5	854	DOCK6	1,188	TNFSF13B
187	CCL5	521	MAPK3	855	CANX	1.189	MIR149
188	ESR1	522	PSMB8	856	AXIN2	1.190	PLA2G6
189	MIR223	523	AP3D1	857	SCARB2	1 191	KNG1
190	FOXP3	524	MIRI FT7A3	858	CDX2	1 102	HOTTIP
191	TTN	525		850	SI C9A3	1 103	AR
192	MARS1	526	CYP2F1	860		1 10/	PSMR2
		020	011 LL1	000		1,104	

TABLE 3 | (Continued) Lung fibrosis-related targets obtained from the GeneCards database.

193 MAPK8 527 TNESE10 861 DTCED	4 1.195 LSM1
	,
194 MEG3 528 PRKCD 862 SLC17/	A5 1,196 NIPBL
195 CCL3 529 MIR181C 863 CXCR5	1,197 PSMA8
196 HPS4 530 CYCS 864 TCTEX	1D2 1,198 IL16
197 BRCA1 531 IFT27 865 MXRA5	5 1,199 CCAT1
198 IL2BA 532 TUBB3 866 FOXP1	1.200 SPRY2
199 HPS1 533 HP 867 MB138	3-1 1.201 BIPK1
200 MIB34A 534 ALMS1 868 CLDN1	1 202 PHKG2
	1 1 203 MIR503
201 Mill 2000 000 Mill 10-	1 204 GSTT1
202 Depaged 527 TGLD 871 LICHI	1,204 GOTTI
203 Dilaser 337 ISLF 071 001L1	1,200 FRIXOI
204 ISCI 336 VDACI 672 DON	1,200 AGL
200 WDF30 039 UZAFT 073 APPRE	P3 1,207 RAG2
206 WIT 540 CAT 874 KRTI3	1,208 HNFTA-AST
207 INPPSE 541 CALCA 875 COMI	1,209 CCA12
208 MPL 542 DNAH11 876 EDNA	1,210 ERLIN1
209 MIR125A 543 NF1 877 CA4	1,211 MIR125B2
210 CSPP1 544 PTK2 878 HLA-DC	QA1 1,212 MIR15B
211 GRP 545 SP110 879 BBS12	1,213 CREBBP
212 MIR144 546 IL12RB1 880 KRT8	1,214 CTSL
213 RTEL1-TNFRSF6B 547 NQO1 881 CMA1	1,215 NR5A1
214 SERPINC1 548 GAA 882 AKR1B	10 1,216 MSR1
215 CD4 549 MIR409 883 LOC11	3633877 1,217 UTP4
216 DYNC2H1 550 VIP 884 CEP55	1,218 MIR301A
217 MIR145 551 GPT 885 MAP2K	(4 1,219 MUC7
218 FLT1 552 MIR708 886 CDK5	1,220 CASC2
219 TNFRSF1B 553 NFKBIA 887 P2RY2	1,221 ZNRD1ASP
220 MIR29A 554 KEAP1 888 NLRP3	1,222 PLCG2
221 HLA-DQB1 555 LOC111674477 889 PSMC4	1.223 MIR124-1
222 FHIT 556 CD36 890 HSPA4	1.224 MIB382
223 H19 557 IGEBP3 891 AVPB2	1.225 LAMP1
224 PKD1 558 NKX2-5 892 BPS27	A 1.226 CD69
225 SOS1 559 CEP83 893 MB37	5 1 227 DANCB
226 SPINK1 560 BDNE 894 MIB33	A 1 228 TP53COB1
227 MIR31 561 ABCR11 895 ATE6	1 229 MYL 3
228 IFT172 562 FGER4 896 RYB	1 230 CYSLTB2
220 MMP7 562 CTCC 807 HPC	1,200 0102112
223 ININI / 300 OTCA 037 ODO	
230 CDCA 304 IIGDI 030 NFC2	1,232 LING-HOH
201 FDG D 300 COI2NA 044 CCOI2	1,233 NOST
	1,234 II 120
233 JUN 307 ArL3 901 Milri 32	2 1,235 MIRIOB
234 DVIP2 306 WIEUF2 902 FIDGE	
233 FINGET 309 CDENTE 903 WITTE	D 1,237 ANTART
236 ERBB3 570 DINNI3A 994 SLC9A	3R2 1,238 PR552
237 MIRTIDO 571 VHL 905 H2AX	1,239 SNHG20
238 PRS1 5/2 THES1 906 PRKA	i2 1,240 MIR95
239 Mil229C 5/3 YAP1 907 SERPIN	NB3 1,241 GALC
240 MIR146B 574 IIMP2 908 LRP1B	1,242 DGCR5
241 ABCC1 575 TOLLIP 909 DNAAF	3 1,243 HNMI
242 BBS2 576 KCNK3 910 BCL10	1,244 SLCO2A1
243 ABCB1 577 NOTCH3 911 RAG1	1,245 MLH1
244 CXCL10 578 RASSF1 912 LAMA4	1,246 PLA2G2A
245 XIAP 579 SP1 913 HLA-G	1,247 MME
246 KIF21A 580 RHOA 914 PSMB3	3 1,248 TYMS
247 PIK3R1 581 ABCC2 915 SIRT1	1,249 MIR198
248 BBS1 582 IKBKB 916 MIRLET	1,250 JAK1
249 IRF1 583 GZMB 917 PLA2G	1B 1,251 PDE4D
250 IL1A 584 LEP 918 KDM40	C 1,252 LAMC2
251 PTPRC 585 BBS5 919 MUC6	1,253 AHR
252 HLA-DPB1 586 APOE 920 TUBB1	1,254 TPM1
253 ERCC6 587 NHLRC2 921 SKIV2L	1,255 MT-CO2
254 STX1A 588 NPPB 922 TPM2	1,256 ASCC1
255 SETD2 589 SYP 923 CCDC4	40 1,257 EOGT
256 CCL17 590 ACTB 924 TET2	1,258 CCL7

TABLE 3 | (Continued) Lung fibrosis-related targets obtained from the GeneCards database.

Number	Gene	Number	Gene	Number	Gene	Number	Gene
257	IDH2	591	PSMA1	925	TRIP11	1,259	TRPM4
258	CXCL12	592	PTCH1	926	ITGA2B	1,260	GPSM2
259	MIR27A	593	LOXL2	927	ENO2	1,261	TARS1
260	GSTM1	594	CEP41	928	EIF2AK3	1,262	TPM3
261	DCTN4	595	MYPN	929	RSPH9	1,263	CD14
262	PRKN	596	CR1	930	MIR193A	1,264	MIR216A
263	CXCR3	597	ERCC1	931	PXN	1.265	CTAG1B
264	MIB200A	598	IGEBP5	932	DNAAE5	1 266	MIB22HG
265	ABI 13B	599	MGMT	933	LAT	1 267	MIR10A
266	PTGS2	600	VIM	934	BSPH1	1 268	PCAT1
267	MIR1484	601	ENIO1	935	CDKN2B-AS1	1,269	SNHG15
269	MYC	602		026		1,200	BANCE
260		602		027		1,270	DANON
209	1011	604		907		1,271	F GAF
270		605	E10A1	900		1,272	
271		606		939		1,273	
272	NEK9	606	VVIN14	940	RSPU2	1,274	
273	LUX	607	NIVIE I	941	04A	1,275	UBE2L3
274	MIR30D	608	CD63	942	IFI27	1,276	FBLN5
275	MIR146A	609	RPGRIP1	943	MIR29B1	1,277	GC
276	IF1122	610	ATP8B1	944	HSPD1	1,278	IP73-AS1
277	B9D2	611	GNAS	945	CCDC39	1,279	PPBP
278	KCNQ1	612	TUBB	946	PDE4A	1,280	LINC00473
279	CYP2A6	613	IFRD1	947	TRIM21	1,281	SOX2-OT
280	MIR483	614	CASP9	948	PLCG1	1,282	MIR181B1
281	MIR183	615	LAMP2	949	IL1RL1	1,283	XIST
282	IL1R1	616	HDAC2	950	BBIP1	1,284	MIR129-1
283	SDCCAG8	617	ANXA1	951	MIR196A1	1,285	PRL
284	PTRH2	618	IFT74	952	BAD	1,286	MIR193B
285	MIR182	619	ROS1	953	MYBPC3	1,287	NR3C2
286	CDKN3	620	CLEC7A	954	ARAF	1,288	MYL1
287	GUCY2C	621	AKT2	955	VDR	1,289	SDC1
288	MIR222	622	WRN	956	MAGEA1	1,290	MIR24-1
289	LOC111674472	623	DTNBP1	957	TAC1	1.291	PHB
290	KIF7	624	CD19	958	IDUA	1.292	MYL2
291	FLNC	625	SMARCA4	959	FPX	1.293	APOA1
292	PPARG	626	ANGPT2	960	ASXL1	1 294	SNHG12
203	XBCC3	627	PARP1	961	MAGEAS	1 295	CEP57
294	SNAI1	628	BBS7	962	RAC1	1,206	IL 6R
295	POSTN	629	MIE	963	GATA1	1 297	SERPINE2
296	MIR192	630	SELP	964	GAS5	1 298	CAL B2
200		631		965	MIRQ-1	1,200	MIR152
208		632		966	RVR2	1,200	
200		633		967	IPH2	1,300	NBG1
300		634	CHRM3	968	BIOX2	1 302	MIR501
201	MID201	625		900		1,002	
301		636		909	LUCT11074404	1,000	
302	DES	627	EDCCO	970		1,304	
303	MID22	629		971		1,000	
304		030		972		1,300	FUII
305		639		973		1,307	EP300
306	IRF5	640	CLUAT	974	SINAI2	1,308	FBL
307	ALK	641	OGG1	975	ERBB4	1,309	PLOD2
308	CEP120	642	MGL1	976	ACVR1	1,310	DLL1
309	MIR451A	643	CCN4	977	NPC1	1,311	TOP2A
310	DYNC2I2	644	F3	978	LNX1	1,312	MAGEC2
311	CASP3	645	STAT5B	979	GRB2	1,313	MIR499A
312	CCL4	646	FUZ	980	TFAP2B	1,314	ENSG00000266919
313	HPS6	647	LBR	981	SLC6A4	1,315	TNFRSF11B
314	MIR143	648	CXCL2	982	IFT88	1,316	HOXA11-AS
315	ICOSLG	649	PLAUR	983	NPHS1	1,317	RASGRP1
316	CLCA4	650	ASAH1	984	MAP2K7	1,318	SPRY4-IT1
317	HLA-DPA1	651	BPI	985	PSMD2	1,319	FIP1L1
318	FOXF1	652	NPM1	986	DNAH8	1,320	GSR
319	BIRC3	653	ACTA1	987	B2M	1,321	CST3
320	SMAD7	654	ANGPT1	988	INTU	1,322	LTBP4
						(Continuec	d on following page)

Number	Gene	Number	Gene	Number	Gene	Number	Gene
321	MIR203A	655	GGT1	989	ENTPD1	1,323	ZFAS1
322	MIR30A	656	CAMP	990	PRSS8	1,324	F5
323	MIR324	657	SOD3	991	CCNE1	1,325	STMN1
324	MIR199B	658	F2RL3	992	LRRC56	1,326	AIRE
325	ACP5	659	TEK	993	MAP3K8	1,327	RETN
326	MIR205	660	LTF	994	SHC1	1,328	NTS
327	TP73	661	MT-CO1	995	CCDC114	1,329	KRT5
328	TLR9	662	LIPA	996	ACHE	1,330	F2RL1
329	MAPK1	663	WNT3	997	TBX20	1,331	TNFSF11
330	CLCN5	664	GDF1	998	AURKB	1,332	COL4A5
331	TMEM231	665	SLC40A1	999	ASL	1,333	PIK3CD
332	BBS4	666	GLIS2	1,000	MIR30C1	1,334	FGF9
333	RMRP	667	AREG	1,001	IL2RB	1,335	KRT20
334	TGFB3	668	CDKN2B	1,002	NCF2		

TABLE 4	Common targets	shared bet	ween the	potential	anlotinib	targets and		
lung fibros	3LE 4 Common targets shared between the potential anlotinib targets and glibrosis-related targets.							

Number	Gene	Number	Gene
1	AXL	38	EPHA3
2	MERTK	39	TIE1
3	ERBB2	40	CACNA2D1
4	AURKB	41	ERBB4
5	FLT1	42	MAP3K8
6	EGFR	43	ERN1
7	KDR	44	MST1R
8	SRC	45	FGFR4
9	MET	46	EPHA7
10	RET	47	MAP2K5
11	ALK	48	RIPK2
12	ABL1	49	DDR2
13	KIT	50	ACVR1B
14	ACVR1	51	DDR1
15	FLT4	52	MAP4K2
16	FLT3	53	EPHA1
17	PDGFRA	54	EPHB6
18	FGFR1	55	ERBB3
19	TGFBR1	56	EIF2AK1
20	BTK	57	MAP3K19
21	LYN	58	AKT2
22	FGFR3	59	PRKCG
23	PDGFRB	60	AKT3
24	YES1	61	PIM1
25	FGFR2	62	PIM2
26	FGR	63	JAK1
27	CSF1R	64	DPP8
28	BLK	65	DPP9
29	PLK4	66	PDE4B
30	FYN	67	PRKCI
31	MAP2K2	68	CDK2
32	HCK	69	CDK1
33	STK10	70	CCNT1
34	ABL2	71	TERT
35	TEK	72	SLC8A1
36	SLK	73	GNRHR
37	STK4	74	AOC3

PCBP3 increases the translation of PFKFB3. Overall, these results suggest that PCBP3 improves PFKFB3 expression levels by increasing its translation rather than by influencing its protein stability.

To determine the functional impact of PCBP3-mediated regulation of PFKFB3 expression in lung fibrosis, we transfected lung fibroblasts with FLAG-PCBP3. Expression of PFKFB3 was significantly increased by PCBP3 overexpression compared to that of the empty vector control. Reliable markers of the phenotypic transformation of fibroblasts into myofibroblasts, fibronectin, collagen I and a-SMA, were markedly increased in FLAG-PCBP3treated cells at the protein level (Figures 3G,H) compared with vector-treated cells. In turn, using small interfering RNA (siRNA) to silence PFKFB3, the FLAG-PCBP3-induced overexpression of fibronectin, collagen I and α-SMA was abolished (Figures 3G,H). These findings suggest that PCBP3 protein upregulation is an early and sustained event during fibroblast activation and that the profibrogenic effects of PCBP3 are mediated by PFKFB3 expression. Taken together, these data suggest that PCBP3 posttranscriptionally increases PFKFB3 expression by promoting its translation during myofibroblast activation.

AnIotinib Represses PCBP3 Expression Levels During Myofibroblast Activation

To confirm the regulation of PCBP3 by anlotinib *in vitro*, we evaluated the protein expression of PCBP3 in MLFs and IMR90 cells. We found that TGF- β 1 induced the expression of PCBP3 in MLFs and that anlotinib prevented PCBP3 expression by immunofluorescence analysis (**Figure 4A**). Western blot analysis of PCBP3 showed a similar result (**Figures 4B,C**) in MLFs, and these results were confirmed in the human IMR90 cell line (**Figures 4D,E**). Taken together, these data suggest that anlotinib can repress PCBP3 expression levels during myofibroblast activation *in vitro*.

Anlotinib Attenuates Bleomycin-Induced Pulmonary Fibrosis

To investigate the biological effects of anlotinib on pulmonary fibrosis *in vivo*, we established a bleomycin (BLM)-induced mouse model of pulmonary fibrosis. The mice were intraperitoneally injected with 1 mg/kg anlotinib daily after BLM administration (**Figure 5A**). From the first week after bleomycin instillation, the bleomycin-treated mice showed a

#	Protein D	RNA ID	Z score?	Discriminative power (%) [?]	Interaction strength (%) [?]	Domain [?]	Motif [?]	Ranking [?]
1	ELAV1_MOUSE_247-308	NC_000068.7:c11_1_5924-6036	-0.13	50	98	yes	yes	ННН
2	ELAV1_MOUSE_247-308	NC_000068.7: c11_1_26816-27008	-0.08	67	99	yes	yes	HHH
3	ELAV1_MOUSE_247-308	NC_000068.7: c11_1_15806-15983	-0.23	40	90	yes	yes	HHH
4	PCBP3_MOUSE_301-351	NC_000068.7: c11 1 41382-41564	-0.69	14	13	yes	yes	HHH
5	ELAV1_MOUSE_247-308	NC_000068.7: c11 1 77223-77340	-0.47	22	74	yes	yes	HHH
6	ELAV1_MOUSE_247-308	NC_000068.7: c11 1 10399-10532	-0.50	20	64	yes	yes	HHH
7	ELAV1_MOUSE_109-176	NC_000068.7:c11_1_5924-6036	-0.14	50	98	yes	yes	HHH
8	ELAV1_MOUSE_109-176	NC_000068.7: c11_1_45706-45815	-0.39	26	85	yes	yes	HHH
9	ELAV1_MOUSE_109-176	NC_000068.7: c11_1_26816-27008	-0.04	63	99	yes	yes	HHH
10	ELAV1_MOUSE_109-176	NC_000068.7: c11 1 15806-15983	-0.24	40	90	yes	yes	HHH
11	ELAV1_MOUSE_109-172	NC_000068.7:c11_1_5924-6036	-0.15	47	97	yes	yes	HHH
12	ELAV1_MOUSE_109-172	NC_000068.7: c11_1_45706-45815	-0.40	26	85	yes	yes	HHH
13	ELAV1_MOUSE_109-172	NC_000068.7: c11 1 15806-15983	-0.26	37	87	yes	yes	HHH
14	PCBP3_MOUSE_301-351	NC_000068.7: c11 1 77461-77636	-0.71	14	9	yes	yes	HHH
15	PCBP3_MOUSE_301-351	NC_000068.7: c11_1_66050-66214	-0.66	14	17	yes	yes	ННН

TABLE 5 | Potential proteins may interact with PFKFB3 mRNA through the catRAPID algorithm.

certain reduction in activity, accompanied by slight shortness of breath. 21 days after bleomycin administration, bleomycintreated mice showed obvious hyperventilation, accompanied by reduced activity and weight loss, but no similar symptoms were observed in the control group. A single dose of BLM (5 mg/kg) administered by intratracheal instillation successfully induced pulmonary fibrosis in C57BL/6 mice, as evidenced by a decline in pulmonary function, decreased tidal volume (TV, Figure 5B) and dynamic compliance (Cdyn, Figure 5C), and increased lung resistance (RI, Figure 5D). However, treatment with anlotinib significantly reversed bleomycin-induced pulmonary dysfunction. Moreover, we evaluated collagen deposition in the lung tissues by analyzing the hydroxyproline (HYP) content and found that anlotinib treatment reduced the amount of collagen in the lungs of bleomycin-treated mice (Figure 5E). Hematoxylin and eosin (H&E) staining indicated that anlotinib-treated mice had decreased lung inflammation and reduced lung architectural damage (Figure 5F). Accordingly, Masson's trichrome staining showed decreased collagen deposition in anlotinib-treated mice compared with vehicletreated mice (Figure 5F). Furthermore, attenuated fibrosis was supported by decreased protein levels of fibronectin and α-SMA by immunohistochemical (IHC) staining (Figure 5G). We also found that anlotinib treatment reduced fibronectin, collagen I and α-SMA expression by western blotting (Figures 5H,I). Taken together, these data show that anlotinib attenuates bleomycininduced pulmonary fibrosis in vivo.

Anlotinib Decreases PCBP3 Expression and Inhibits PFKFB3-Driven Glycolysis in Fibrotic Rodent Lungs

We next examined whether the levels of PCBP3 were regulated by anlotinib in vivo. We evaluated the expression of PCBP3 in lung tissues and found that the protein levels of PCBP3 were markedly increased after bleomycin instillation, while anlotinib treatment decreased PCBP3 expression (Figures 6A,B). Accordingly, IHC staining showed decreased PCBP3 protein levels in anlotinibtreated mice compared with vehicle-treated mice (Figure 6C). In addition, to confirm the regulation of PFKFB3-driven glycolysis by anlotinib in vivo, we measured the levels of lactate and the expression of PFKFB3 in the lungs of mice. We found that there were significantly higher levels of lactate in the lungs of bleomycin-treated mice than in the lungs of control mice, and anlotinib decreased lactate levels (Figure 6D). Western blot and IHC staining studies revealed that bleomycin-induced PFKFB3 expression in the lungs of mice was prevented by anlotinib (Figures 6E-G). Overall, these results suggest that anlotinib decreases PCBP3 expression and inhibits PFKFB3driven glycolysis in fibrotic rodent lungs.

AnIotinib Accelerates the Resolution of Bleomycin-Induced Lung Fibrosis

We demonstrated that anlotinib treatment could attenuate bleomycin-induced pulmonary fibrosis. In that *in vivo*

experiment, anlotinib was administered at approximately the same time as bleomycin instillation. We further examined whether anlotinib could postpone the progression of established fibrosis. Therefore, we performed another in vivo experiment in which anlotinib was intraperitoneally injected 7 days after bleomycin instillation (Figure 7A). As interventions beginning 7 days post bleomycin were classified as therapeutic (Izbicki et al., 2002; Moeller et al., 2008), we initially treated mice with anlotinib (1 mg/kg/day or 2 mg/kg/day) beginning on day 7 after bleomycin instillation. Pulmonary function tests showed that anlotinib treatment reversed the bleomycin-induced decline in pulmonary function, with increases in TV (Figure 7B) and Cdyn (Figure 7C) and a decrease in RI (Figure 7D). HYP measurements showed that the collagen content was significantly decreased in anlotinib-treated mice compared with vehicle-treated mice (Figure 7E). H&E staining and Masson's trichrome staining of lungs collected at day 21 showed enhanced recovery from fibrosis upon anlotinib treatment (Figure 7F). Correspondingly, IHC staining showed that anIotinib treatment reduced fibronectin and a-SMA expression in the lungs (Figure 7G). Western blot analysis also showed that anlotinib decreased the protein levels of fibronectin, collagen I and α-SMA in the lungs (Figures 7H,I). Collectively, these data clearly demonstrate that anlotinib accelerates fibrosis resolution in vivo even after the establishment of fibrosis.

DISCUSSION

Despite recent advances in our understanding of IPF pathology, there is still no curative treatment for this disease; indeed, the currently available antifibrotic treatment modalities slow but do not completely stop the progression of the disease (Spagnolo and Maher, 2017). In this study, we demonstrate that anlotinib strongly inhibits fibroblast-to-myofibroblast extracellular transdifferentiation and reduces matrix production in primary MLFs and in the human IMR90 cell line. Accordingly, preventative and therapeutic administration of anlotinib to bleomycin-administered mice resulted in accelerated resolution of fibrosis. No adverse, systemic side effects were observed. Here, we demonstrate a novel mechanism by which anlotinib exerts antifibrotic effects by downregulating PCBP3, reducing PFKFB3 translation and inhibiting glycolysis in myofibroblasts (Figure 8).

A previous study revealed that male and female C57BL/6 mice did not differ in terms of their lung fibrotic responses, including cellular infiltration, collagen deposition, and quantifiable morphological changes in the lung architecture, but that the bleomycin-induced decrease in static compliance was significantly greater in males than in females (Voltz et al., 2008). This adverse effect on lung function was found to be due to male sex hormones. So sex differences should be carefully considered when interpreting experimental models of pulmonary fibrosis in mice (Blaauboer et al., 2014). In our study, we used only female mice to avoid the sex differences. We found that anlotinib exerted the preventative effects on bleomycin model of pulmonary fibrosis. Furthermore, anlotinib can also accelerate fibrosis resolution after the establishment of fibrosis.

A recent report showed that anlotinib inhibits the profibrotic effect of TGF-B1 in lung fibroblasts by attenuating inflammation and oxidative stress (Ruan et al., 2020). Our data are in line with that report and reveal an additional mechanism by which anlotinib acts on lung fibroblasts to attenuate fibrosis. There is emerging evidence about the association between metabolic disorders and IPF (Yin et al., 2019; Cho et al., 2020; Hu et al., 2020). Similar to highly proliferative cancer cells, myofibroblasts are highly dependent on glycolysis in vitro (Bueno et al., 2020). Furthermore, glycolysis is necessary not only for fibroblast growth and migration but also for the acquisition and maintenance of a myofibroblastic phenotype (Xu et al., 2017; Para et al., 2019). A previous study revealed that inhibition of glycolysis by the PFKFB3 inhibitor 3PO or by genomic disruption of the PFKFB3 gene blunted the differentiation of lung fibroblasts into myofibroblasts and attenuated profibrotic phenotypes in myofibroblasts (Xie et al., 2015). Another study revealed that lung fibroblasts displayed augmented aerobic glycolysis through activation of the PI3K-Akt-mTOR/PFKFB3 pathway in LPS-induced pulmonary fibrosis (Hu et al., 2020). Our data, along with previous studies, demonstrated that glycolytic reprogramming was critical to lung myofibroblast activation and pulmonary fibrosis. Furthermore, we demonstrated that anlotinib could strongly inhibit glycolytic reprogramming *in vitro* and *in vivo*.

The results presented herein provide new insights into the molecular mechanisms of lung fibrogenesis. This work unveils a previously unrecognized posttranscriptional regulation in activated lung fibroblasts composed of the RNA binding protein PCBP3 and the critical glycolytic enzyme PFKFB3, which maintains fibroblasts with higher glycolytic activity in fibrotic lungs compared to normal lung fibroblasts in healthy lungs. PCBP family members perform multiple functions by binding to the poly(C) sequence in both DNA and RNA to modulate mRNA stabilization, translation silencing, or translation enhancement (Blyn et al., 1997; Andino et al., 1999; Ostareck et al., 2001). Our present findings showing that PCBP3 plays an important role in myofibroblast activation and fibrogenesis and significantly extends our previous understanding by identifying an additional node of interaction between PCBP3mediated posttranscriptional dysregulation and lung disease. We found that PFKFB3 protein overexpression was not accompanied by PFKFB3 mRNA upregulation, indicating that this increase was not transcriptionally derived. Instead, we observed that high PFKFB3 protein levels were maintained during fibroblast transdifferentiation, owing to PCBP3-mediated translational activation. Thus, the PCBP3 protein is upregulated during myofibroblast activation and binds directly to PFKFB3 during transcription. This binding activates PFKFB3 mRNA translation and generates high levels of the glycolysis activator PFKFB3. This mechanism does not exclude additional pathways of regulating PFKFB3 expression. Hence, it is not unusual for key proteins to be regulated at multiple levels, including through transcription, translation, and posttranslational modifications.

Our study is the first to report that anlotinib inhibits PFKFB3mediated glycolysis in myofibroblasts. Moreover, anlotinib attenuates glycolysis in myofibroblasts by repressing PCBP3 expression levels rather than directly regulating the expression of PFKFB3, as anlotinib treatment does not decrease the mRNA levels of PFKFB3. Our work contributes novel mechanistic insight into the action of anlotinib. However, one of the limitations of this study is that we didn't knock out PCBP3/PFKFB3 in mice to verify their effects in lung fibrosis, which may be explored in the further research. This future direction may be important to better understand how PCBP3 regulates PFKFB3-mediated glycolysis in pulmonary fibrosis. The other one is that this study only used bleomycin mice model for the research. Although the bleomycin model is the most widely used and best-characterized mouse model, the fibrosis of the bleomycin model is self-resolving, which contrasts with the progressive chronic fibrosis typical of human IPF (Liu et al., 2017). Therefore, whether anlotinib could attenuate fibrosis in human IPF still requires ex vivo models of pulmonary fibrosis.

In conclusion, our study demonstrated a clear antifibrotic role for anlotinib in the lungs. Its antifibrotic activity is mediated by its ability to decrease PCBP3 expression and attenuate PFKFB3driven glycolysis, thereby inhibiting myofibroblast activation. Anlotinib might be considered as a potential therapeutic option for IPF patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

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ETHICS STATEMENT

The animal study was reviewed and approved by Southern Medical University Institutional Animal Care and Use Committee.

AUTHOR CONTRIBUTIONS

WC, JZ, and WZ performed study concept and design; YL, YL, and ZZ performed development of methodology and writing; HH and XW provided acquisition, analysis and interpretation of data, and statistical analysis; XM and FZ provided technical and material support; SC and HD performed review and revision of the paper.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.744826/full#supplementary-material

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