

Supplementary material.

Supplementary methods

Inclusion/exclusion criteria¹

For the COPD group, exclusion criteria included a forced expiratory volume at 1 s (FEV₁) of <35%, hypercapnia, and comorbid diseases that would render bronchoscopy unsafe. Inclusion criteria were (1) chronic bronchitis as determined by history and/or emphysema as determined by chest x-ray or computed tomography; (2) 20 pack-years of cigarette smoking but smoking cessation for at least 1 year preceding enrollment; (3) the absence of other lung disease, including asthma and bronchiectasis; (4) chest x-ray findings that were normal or compatible with COPD but no other disease detected; (5) FEV₁:forced vital capacity ratio and FEV₁ both below the lower 95% confidence limit of normal on spirometry; (6) no atopy in the medical history; (7) <15% bronchodilator response with inhaled albuterol on spirometry; and (8) no antibiotic or steroid use for 4 weeks preceding enrollment. Inclusion criteria for the no-COPD group were the same as those for the COPD group, except for the absence of lung disease by clinical evaluation, normal chest x-ray, and normal spirometric results. Healthy nonsmokers met all inclusion criteria for the no-COPD group, except that all had <5 cumulative pack-years of smoking.

Supplementary tables

Table S1: Drugs commonly prescribed for stable COPD. Curated drugs currently indicated for COPD ("MESH:D029424") from the Comparative Toxicogenomics Database² and manually curated to include drugs used to treat stable COPD in the United States.

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|-----------------------------|
| beclomethasone dipropionate |
| budesonide |
| arformoterol |
| roflumilast |
| aclidinium |
| fluticasone propionate |
| dexamethasone acetate |
| prednisolone tebutate |
| prednisone acetate |
| prednisolone acetate |
| mometasone |
| fluticasone |
| methyl prednisone |
| pirbuterol |
| ciclesonide |
| erdosteine |
| terbutaline |
| fluticasone furoate |
| glycopyrronium |
| indacaterol |
| ipratropium |
| levosalbutamol |
| clarithromycin |
| olodaterol |
| salbutamol |

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|---------------|
| salmeterol |
| revefenacin |
| theophylline |
| salbutamol |
| aminophylline |
| umeclidinium |
| vilanterol |
| prednisone |
| tiotropium |

Table S2: Unique proteins upregulated in BALF (n=95), Differentially expressed proteins with at least 1.5x fold change increase in the BALF proteome in COPD versus control cohort samples.

| Uniprot ID | Symbol | Entrez Gene Name | Location | Type(s) | Fold change | Previously described association with COPD | References |
|------------|--------|-------------------------------------------------------------|-----------|------------------|-------------|---------------------------------------------------------|------------|
| P00325 | ADH1B | alcohol dehydrogenase 1B (class I), beta polypeptide | Cytoplasm | Lipid metabolism | 12.86 | NONE | |
| P46439 | GSTM5 | glutathione S-transferase mu 5 | Cytoplasm | enzyme | 11.26 | Various GST polymorphisms implicated in lung protection | 3-5 |
| O00487 | PSMD14 | proteasome (prosome, macropain) 26S subunit, non-ATPase, 14 | Cytoplasm | peptidase | 9.53 | NONE | |

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|--------|--------|---------------------------------------------------------------|---------------------|-----------|------|---------------------------------------------------|-----|
| Q86TZ1 | TTC6 | tetratricopeptide repeat domain 6 | unknown | other | 8.68 | NONE | |
| P02743 | APCS | amyloid P component, serum | Extracellular Space | pentraxin | 8.23 | Not APCS but Pentraxin 3 in COPD | 6-8 |
| Q9UBR2 | CTSZ | cathepsin Z | Cytoplasm | peptidase | 7.92 | NONE | |
| Q9NP98 | MYOZ1 | myozenin 1 | Cytoplasm | other | 7.08 | NONE | |
| Q13402 | MYO7A | myosin VIIA | Cytoplasm | enzyme | 6.84 | NONE | |
| Q49MG5 | MAP9 | microtubule-associated protein 9 | unknown | other | 6.31 | NONE | |
| Q13642 | FHL1 | four and a half LIM domains 1 | Cytoplasm | other | 5.53 | NONE | |
| P02775 | PPBP | pro-platelet basic protein (chemokine (C-X-C motif) ligand 7) | Extracellular Space | cytokine | 5.47 | Neutrophil marker increased in severe stable COPD | 9 |
| P21333 | FLNA | filamin A, alpha | Cytoplasm | other | 5.14 | NONE | |
| Q8NFC6 | BOD1L1 | biorientation of chromosomes | Extracellular Space | other | 4.43 | NONE | |

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|------------|--------|---------------------------------------------------------------------------------------------------------------|------------------------|---------------------|-------|-----------------------------------------------------------------------------------|-------|
| | | in cell division 1-like 1 | | | | | |
| P04220 | MUCB | Ig mu heavy chain disease protein | Plasma Membrane | | 4.36 | NONE | |
| P02656 | APOC3 | apolipoprotein C-III | Extracellular Space | Lipid metabolism | 4.24 | NONE | |
| P42330 | AKR1C3 | aldo-keto reductase family 1, member C3 (3- alpha hydroxysteroid dehydrogenase, type II) | Cytoplasm | enzyme | 4.11 | NONE | |
| P35749 | MYH11 | myosin, heavy chain 11, smooth muscle | Cytoplasm | other | 4.01 | Myosin heavy chain variation was noted in COPD but not specific proteins | 10-12 |
| O00522 | KRIT1 | KRIT1, ankyrin repeat containing | Plasma Membrane | other | 3.89 | NONE | |
| A6NDU 8 | CE051 | UPF0600 protein C5orf51 | unknown | other | 3.56 | NONE | |
| P04114 | APOB | apolipoprotein B (including Ag(x) antigen) | Extracellular Space | transporter | 3.556 | NONE | |

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|--------|----------|--------------------------------------------------------------------------------|---------------------|------------------|------|-----------------------------------------------|-------|
| Q5XKE5 | KRT79 | keratin 79 | Extracellular Space | other | 3.43 | NONE | |
| Q9NWS1 | PARPBP | PARP1 binding protein | Nucleus | other | 3.42 | NONE | |
| P12429 | ANXA3 | Annexin A3 | | | 3.34 | NONE | |
| P30838 | ALDH3A1 | aldehyde dehydrogenase 3 family, member A1 | Cytoplasm | Lipid metabolism | 3.33 | None, but is implicated in cell proliferation | |
| Q6NUK1 | SLC25A24 | solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 24 | Cytoplasm | other | 3.33 | NONE | |
| P00738 | HP | haptoglobin | Extracellular Space | peptidase | 3.22 | Acute phase reactant associated with COPD | 13,14 |
| Q16787 | LAMA3 | laminin, alpha 3 | Extracellular Space | other | 3.2 | Haemophilus and Moraxella binds to laminin | |

| | | | | | | | |
|--------|-------|-------------------------------------------------|---------------------|------------------------|------|---------------------------------------------------------------|-------|
| P02675 | FGB | fibrinogen beta chain | Extracellular Space | other | 3.17 | Serum fibrinogen levels in COPD associated with exacerbations | 14-20 |
| P08670 | VIM | vimentin | Cytoplasm | cytoskeleton component | 3.12 | Epithelial to mesenchymal transition | 21-25 |
| Q7KZI7 | MARK2 | MAP/microtubule affinity-regulating kinase 2 | Cytoplasm | kinase | 3.12 | NONE | |
| Q15847 | APM2 | Adipose most abundant gene transcript 2 protein | | | 3.01 | NONE | |
| Q16280 | CNGA2 | cyclic nucleotide gated channel alpha 2 | Plasma Membrane | ion channel | 3.01 | NONE | |
| O94782 | USP1 | ubiquitin specific peptidase 1 | Cytoplasm | peptidase | 2.9 | NONE | |
| Q96C24 | SYTL4 | synaptotagmin-like 4 | Cytoplasm | transporter | 2.82 | NONE | |
| P02671 | FIBA | Fibrinogen alpha chain | | | 2.78 | Serum fibrinogen levels in COPD associated with exacerbations | 14-20 |
| P02679 | FGG | fibrinogen gamma chain | Extracellular Space | other | 2.75 | Serum fibrinogen levels in COPD associated with exacerbations | 14-20 |

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|--------|--------|--------------------------------------------|---------------------|-------------------------|------|---------------------------------------------------------------|----------|
| P53004 | BLVRA | biliverdin reductase A | Cytoplasm | enzyme | 2.66 | NONE | |
| Q2TVT3 | KGFLP2 | keratinocyte growth factor-like protein 2 | unknown | other | 2.62 | NONE | |
| P23284 | PPIB | peptidylprolyl isomerase B (cyclophilin B) | Cytoplasm | enzyme | 2.55 | NONE | |
| P17931 | LGALS3 | lectin, galactoside-binding, soluble, 3 | Extracellular Space | other | 2.52 | Increased Gal-3 in small airways | 26,27 |
| P13645 | K1C10 | Keratin type I cytoskeletal 10 | | | 2.47 | NONE | |
| Q9NX58 | LYAR | Ly1 antibody reactive homolog (mouse) | Plasma Membrane | other | 2.37 | NONE | |
| O95497 | VNN1 | vanin 1 | Plasma Membrane | Enzyme/lipid metabolism | 2.34 | NONE | |
| P16152 | CBR1 | carbonyl reductase 1 | Cytoplasm | enzyme | 2.34 | NONE | |
| P23771 | GATA3 | GATA binding protein 3 | Nucleus | transcription regulator | 2.33 | NONE | |
| P01023 | A2M | alpha-2-macroglobulin | Extracellular Space | transporter | 2.31 | A protease inhibitor that has increased serum levels found in | 13,28-31 |

| | | | | | | | |
|--------|-----------|---------------------------------------------------------------------------------------------------|---------------------|-------|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| | | | | | | | patients with alpha-1 antitrypsin deficiency |
| Q15149 | PLEC | plectin | Cytoplasm | other | 2.31 | NONE | |
| P62328 | TYB6 | Thymosin beta_4 | | | 2.28 | NONE | |
| Q6UXR4 | SERPINA13 | serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 13 (pseudogene) | Extracellular Space | other | 2.26 | A serpin peptidase inhibitor that is in the same family of peptidase inhibitor as alpha-1 antitrypsin (a serpin peptidase inhibitor, clade A, member 1) implicated in protease-antiprotease homeostasis | 32,33 |
| Q14019 | COTL1 | coactosin-like 1 | Cytoplasm | other | 2.25 | NONE | |
| P03950 | ANGI | Angiogenin | | | 2.24 | Increased in induced sputum from stable COPD individuals compared to healthy smokers | 34 |
| Q9UK76 | HN1 | hematological and | Nucleus | other | 2.21 | NONE | |

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|--------|--------|--------------------------------------------------------------------------------|---------------------|-------------------|-------|-------------------------------------------------------------------------------------|----|
| | | neurological expressed 1 | | | | | |
| P02647 | APOA1 | apolipoprotein A-I | Extracellular Space | Lipid metabolism | 2.13 | COPD biomarker | 35 |
| P07108 | DBI | diazepam binding inhibitor (GABA receptor modulator, acyl-CoA binding protein) | Cytoplasm | other | 2.13 | NONE | |
| P55822 | SH3BGR | SH3 domain binding glutamic acid-rich protein | Cytoplasm | other | 2.13 | NONE | |
| P08758 | ANXA5 | annexin A5 | Plasma Membrane | Apoptosis pathway | 2.1 | Decreases macrophage efferocytosis and elastase-induced pulmonary emphysema in mice | 36 |
| P37837 | TALDO1 | transaldolase 1 | Cytoplasm | enzyme | 2.09 | NONE | |
| P04259 | KRT6B | keratin 6B | Cytoplasm | other | 2.049 | NONE | |
| P41222 | PTGDS | prostaglandin D2 synthase 21kDa (brain) | Cytoplasm | enzyme | 2.03 | Increased RNA expression in the human lung tissue of | 37 |

| subjects with moderate versus mild COPD | | | | | | |
|-----------------------------------------|----------|------------------------------------------------|---------------------|------------------|------|-----------------------------------------------------------------------------------------------|
| Q9BWM5 | ZNF416 | zinc finger protein 416 | Nucleus | other | 1.98 | NONE |
| Q9HCE9 | ANO8 | anoctamin 8 | Extracellular Space | other | 1.98 | NONE |
| Q96PP8 | GBP5 | guanylate binding protein 5 | Plasma Membrane | enzyme | 1.95 | NONE |
| Q92888 | ARHGEF1 | Rho guanine nucleotide exchange factor (GEF) 1 | Cytoplasm | other | 1.94 | NONE |
| P51884 | LUM | lumican | Extracellular Space | other | 1.93 | Extracellular matrix component 38 |
| P62937 | PPIA | Peptidyl_prolyl cis_trans isomerase A | | | 1.92 | Increased in lung tissue from smokers with COPD versus never-smokers, and non-COPD smokers 39 |
| P09972 | ALDOC | aldolase C, fructose-bisphosphate | Cytoplasm | Metabolic enzyme | 1.91 | NONE |
| Q5JYT7 | KIAA1755 | KIAA1755 | unknown | other | 1.91 | NONE |

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|--------|---------|--------------------------------------------------------------------------------------------------------------|---------------------|--------------|------|------|
| P30086 | PEBP1 | phosphatidylethanolamine binding protein 1 | Cytoplasm | other | 1.9 | NONE |
| O75368 | SH3BGR1 | SH3 domain binding glutamic acid-rich protein like | Cytoplasm | other | 1.89 | NONE |
| Q4G0N8 | SLC9C1 | solute carrier family 9, subfamily C (Na ⁺ -transporting carboxylic acid decarboxylase), member 1 | unknown | other | 1.89 | NONE |
| O75874 | IDH1 | isocitrate dehydrogenase 1 (NADP ⁺), soluble | Cytoplasm | enzyme | 1.88 | NONE |
| Q13421 | MSLN | mesothelin | Extracellular Space | other | 1.88 | NONE |
| Q9Y6W5 | WASF2 | WAS protein family, member 2 | Cytoplasm | cytoskeleton | 1.87 | NONE |

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|--------|--------|---------------------------------------------|----------------------------|--------|------|------------------------------------------------------------------------------------------------------------------|-------------|
| P50224 | ST1A3 | Sulfotransferase 1A3/1A4 | | | 1.86 | NONE | |
| Q9Y2K3 | MYH15 | myosin, heavy chain 15 | Extracell ular Space | other | 1.86 | Muscle dysfunction and aberrations of myosin composition within muscle has been associated with COPD | 10,11,40-45 |
| | | | | | | NONE | |
| Q16881 | TXNRD1 | thioredoxin reductase 1 | Cytoplas m | enzyme | 1.82 | | |
| P37802 | TAGLN2 | transgelin 2 | Cytoplas m | other | 1.73 | NONE | |
| P35527 | KRT9 | keratin 9 | Cytoplas m | other | 1.71 | NONE | |
| P09104 | ENO2 | enolase 2 (gamma, neuronal) | Cytoplas m | enzyme | 1.7 | NONE | |
| | | | | | | NONE | |
| P40925 | MDH1 | malate dehydrogenase 1, NAD (soluble) | Cytoplas m | enzyme | 1.68 | | |

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|--------|---------|-----------------------------------------|---------------------|-------------------------|------|--------------------------------------------------------------------------------------|-------|
| P30041 | PRDX6 | peroxiredoxin 6 | Cytoplasm | enzyme | 1.66 | NONE | |
| P04264 | K2C1 | Keratin type II cytoskeletal 1 | | | 1.65 | NONE | |
| P61088 | UBE2N | ubiquitin-conjugating enzyme E2N | Cytoplasm | enzyme | 1.65 | CS induces UBE2N | 46 |
| P06319 | LV605 | Ig lambda chain V_VI region EB4 | Extracellular Space | immunoglobulin | 1.64 | NONE | |
| P20962 | PTMS | parathymosin | Nucleus | other | 1.63 | NONE | |
| Q8N0Y7 | PGAM4 | phosphoglycerate mutase family member 4 | unknown | phosphatase | 1.63 | NONE | |
| P06733 | ENO1 | enolase 1, (alpha) | Cytoplasm | transcription regulator | 1.61 | NONE | |
| P09467 | FBP1 | fructose-1,6-bisphosphatase 1 | Cytoplasm | phosphatase | 1.6 | NONE | |
| P17066 | HSPA6 | heat shock 70kDa protein 6 (HSP70B') | unknown | other | 1.59 | Increased proteins levels in patients with COPD treated with Inhaled Corticosteroids | 47-49 |
| Q96PX6 | CCDC85A | coiled-coil domain containing 85A | unknown | other | 1.57 | NONE | |

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|--------|--------|---------------------------------|-----------|--------------|------|-----------------------------------------------------------------------------------------------------------------------------------|-------|
| P23528 | CFL1 | cofilin 1 (non-muscle) | Nucleus | cytoskeleton | 1.56 | NONE | |
| P63261 | ACTG | Actin_cytoplasmic 2 | Cytoplasm | | 1.56 | NONE | |
| P06703 | S100A6 | S100 calcium binding protein A6 | Cytoplasm | transporter | 1.55 | Calcium binding protein involved in neutrophil activation and protein levels elevated in sputum from COPD versus control subjects | 50-52 |

Table S3: Unique proteins downregulated in BALF (n=138). Differentially expressed proteins with at least 1.5x fold change decrease in the BALF proteome in COPD versus control cohort samples.

| Uniprot ID | Symbol | Entrez Gene Name | Location | Type(s) | Fold change | Previously described association with COPD | References |
|------------|---------|----------------------------------------------|---------------------|--------------------------------|-------------|--------------------------------------------------------------------|------------|
| Q9HCH0 | NCKAP5L | NCK-associated protein 5-like | unknown | other | -8.55 | NONE | |
| Q01995 | TAGLN | transgelin | Cytoplasm | other | -8.11 | NONE | |
| Q29865 | HLA-C | major histocompatibility complex, class I, C | Plasma Membrane | other | -7.63 | GWAS analysis in the ECLIPSE study noted a SNP in the HLA-C region | 53 |
| P14314 | PRKCSH | protein kinase C substrate 80K-H | Cytoplasm | enzyme | -6.84 | NONE | |
| B3KS81 | SRRM5 | serine/arginine repetitive matrix 5 | unknown | other | -6.06 | NONE | |
| P20142 | PEPC | Gastricsin | Extracellular Space | | -5.25 | NONE | |
| O95185 | UNC5C | unc-5 homolog C | Plasma Membrane | transmembrane receptor/ netrin | -5.11 | NONE | |
| Q9Y3P9 | RABGAP1 | RAB GTPase activating protein 1 | Cytoplasm | other | -5.04 | NONE | |

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|--------|--------|-----------------------------------------------------------------|---------------------|----------------------------|-------|--------------------------------------------------------------------------------------------------------|-------|
| Q7Z3U7 | MON2 | MON2 homolog (S. cerevisiae) | Cytoplasm | other | -5.02 | NONE | |
| Q9NWN3 | FBXO34 | F-box protein 34 | unknown | other | -4.80 | NONE | |
| O60885 | BRD4 | bromodomain containing 4 | Nucleus | kinase | -4.33 | NONE | |
| Q9UHX3 | EMR2 | egf-like module containing, Mucin-like, hormone receptor-like 2 | Plasma Membrane | G-protein coupled receptor | -4.32 | NONE | |
| Q9NSY1 | BMP2K | BMP2 inducible kinase | Nucleus | kinase | -4.03 | NONE | |
| Q9H0P7 | CF059 | Putative uncharacterized protein encoded by NCRNA00241 | | | -3.96 | NONE | |
| O75419 | CDC45 | cell division cycle 45 homolog | Nucleus | other | -3.68 | NONE | |
| P03950 | ANG | angiogenin, ribonuclease, RNase A family, 5 | Extracellular Space | enzyme | -3.59 | NONE | |
| Q8IWL2 | SFTPA1 | surfactant protein A1 | Extracellular Space | transporter | -3.59 | Imbalances of the surfactant proteins, major components of alveolar fluid have been implicated in COPD | 54-60 |
| Q1ED39 | CP088 | Protein C16orf88 | | | -3.57 | NONE | |
| P54750 | PDE1A | phosphodiesterase 1A, calmodulin-dependent | Cytoplasm | enzyme | -3.48 | NONE | |

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|--------|---------|-------------------------------------------------------|---------------------|-------------------------|-------|---------------------------------------------------------------------|-------|
| Q8ND24 | RNF214 | ring finger protein 214 | unknown | other | -3.46 | NONE | |
| Q96N16 | JAKMIP1 | janus kinase and microtubule interacting protein 1 | Cytoplasm | other | -3.41 | NONE | |
| Q14980 | NUMA1 | nuclear mitotic apparatus protein 1 | Nucleus | other | -3.26 | NONE | |
| Q9UI36 | DACH1 | dachshund homolog 1 | Nucleus | transcription regulator | -3.03 | NONE | |
| Q9UHG3 | PCYOX1 | prenylcysteine oxidase 1 | Cytoplasm | enzyme | -3.03 | NONE | |
| O14905 | WNT9B | wingless-type MMTV integration site family, member 9B | Extracellular Space | Signal transduction | -3.03 | NONE | |
| Q99996 | AKAP9 | A kinase (PRKA) anchor protein (yotiao) 9 | Cytoplasm | other | -3.02 | NONE | |
| Q9Y2P7 | ZNF256 | zinc finger protein 256 | Nucleus | transcription regulator | -3.00 | NONE | |
| P02747 | C1QC | complement component 1, q subcomponent, C chain | Extracellular Space | other | -3.00 | NONE | |
| O00750 | PIK3C2B | phosphoinositide-3-kinase, class 2, beta polypeptide | Cytoplasm | kinase | -3.00 | Associated with glucocorticoid sensitivity and inflammation in COPD | 61-63 |
| Q9P2N5 | RBM27 | RNA binding motif protein 27 | Nucleus | other | -3.00 | NONE | |
| Q9Y520 | PRRC2C | proline-rich coiled-coil 2C | Cytoplasm | other | -2.92 | NONE | |

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|--------|---------|----------------------------------------------------------------------------|---------------------|----------------------------------------------|-------|---------------------------------|-------|
| Q9P2Y4 | ZNF219 | zinc finger protein 219 | Nucleus | transcription regulator | -2.92 | NONE | |
| O43813 | LANCL1 | LanC lantibiotic synthetase component C-like 1 (bacterial) | Plasma Membrane | other | -2.92 | NONE | |
| P01714 | LV301 | Ig lambda chain V_III region SH | Extracellular Space | immunoglobulin | -2.92 | NONE | |
| O75264 | CS077 | Transmembrane protein C19orf77 | | | -2.92 | NONE | |
| A6NMX2 | EIF4E1B | eukaryotic translation initiation factor 4E family member 1B | unknown | other | -2.92 | NONE | |
| Q8IYD8 | FANCM | Fanconi anemia, complementation group M | Nucleus | enzyme | -2.92 | NONE | |
| Q8TC84 | FANK1 | Fibronectin type III and ankyrin repeat domains 1 | Nucleus | transcription regulator | -2.92 | NONE | |
| Q96NX9 | DACH2 | dachshund homolog 2 | Nucleus | other | -2.90 | NONE | |
| Q9BVG8 | KIFC3 | kinesin family member C3 | Cytoplasm | enzyme | -2.87 | NONE | |
| O14920 | IKBKB | inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta | Cytoplasm | kinase | -2.75 | Implicated in COPD inflammation | 64-66 |
| Q92738 | USP6NL | USP6 N-terminal like/ RAB5 effector RN-tre | Plasma Membrane | Cytoskeleton element involved in pinocytosis | -2.75 | NONE | |

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|--------|----------|------------------------------------------------|---------------------|------------------------|-------|-------------------------------------------------------------------------------------|----------|
| Q96JB5 | CDK5RAP3 | CDK5 regulatory subunit associated protein 3 | Cytoplasm | other | -2.74 | NONE | |
| Q9UEW3 | MARCO | macrophage receptor with collagenous structure | Plasma Membrane | transmembrane receptor | -2.74 | A macrophage scavenger receptor involved in bacterial phagocytosis in COPD | 67,68 |
| Q13724 | MOGS | mannosyl-oligosaccharide glucosidase | Cytoplasm | enzyme | -2.68 | NONE | |
| P51674 | GPM6A | glycoprotein M6A | Plasma Membrane | ion channel | -2.68 | NONE | |
| Q16651 | PRSS8 | protease, serine, 8 | Extracellular Space | peptidase | -2.63 | NONE | |
| O96009 | NAPSA | napsin A aspartic peptidase | Extracellular Space | peptidase | -2.58 | NONE | |
| Q9NVX2 | NLE1 | notchless homolog 1 (Drosophila) | Nucleus | enzyme | -2.54 | NONE | |
| P02751 | FN1 | fibronectin 1 | Extracellular Space | enzyme | -2.53 | Matrix protein involved in fibroblast proliferation implicated in COPD pathogenesis | 38,69-73 |

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|--------|---------|------------------------------------------------------------|---------------------|-----------|-------|--------------------------------------------------------------------------------------------------------|-------------|
| Q13023 | AKAP6 | A kinase (PRKA) anchor protein 6 | Nucleus | other | -2.53 | NONE | |
| Q5VWQ0 | RSBN1 | round spermatid basic protein 1 | Nucleus | other | -2.53 | NONE | |
| Q9UGM5 | FETUB | Fetuin B | Extracellular Space | other | -2.49 | NONE | |
| Q9Y2G8 | DNAJC16 | DnaJ (Hsp40) homolog, subfamily C, member 16 | unknown | other | -2.45 | NONE | |
| P35247 | SFTPD | surfactant protein D | Extracellular Space | other | -2.44 | Imbalances of the surfactant proteins, major components of alveolar fluid have been implicated in COPD | 54,56,74-79 |
| Q2TBE0 | CWF19L2 | CWF19-like 2, cell cycle control | unknown | other | -2.42 | NONE | |
| Q9BYF1 | ACE2 | angiotensin I converting enzyme (peptidyl-dipeptidase A) 2 | Plasma Membrane | peptidase | -2.41 | | 80 |
| O95969 | SCGB1D2 | secretoglobulin, family 1D, member 2 | Extracellular Space | other | -2.40 | NONE | |
| P78367 | NKX32 | Homeobox protein Nkx_3.2 | | | -2.40 | NONE | |
| Q9P275 | USP36 | ubiquitin specific peptidase 36 | Nucleus | peptidase | -2.40 | NONE | |

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|--------|--------|------------------------------|-----------|-------------------------|-------|----------------|-------|
| O43464 | HTRA2 | HtrA serine peptidase 2 | Cytoplasm | peptidase | -2.40 | NONE | |
| O60281 | ZNF292 | zinc finger protein 292 | Nucleus | transcription regulator | -2.38 | NONE | |
| Q96JM2 | ZNF462 | zinc finger protein 462 | Nucleus | other | -2.37 | NONE | |
| P27487 | DPP4 | dipeptidyl-peptidase 4 | Plasma | | | Putative | serum |
| | | | Membrane | peptidase | -2.33 | COPD biomarker | 81 |
| Q86SX3 | CN080 | Uncharacterized protein | | | | NONE | |
| | | C14orf80 | | | -2.28 | | |
| Q9UJV3 | MID2 | midline 2 | Cytoplasm | other | -2.13 | NONE | |
| Q6ZU80 | CEP128 | centrosomal protein 128kDa | unknown | other | -2.12 | NONE | |
| Q01968 | OCRL | Inositol polyphosphate | Cytoplasm | | | NONE | |
| | | 5_phosphatase | m | phosphatase | -2.11 | | |
| P42696 | RBM34 | RNA binding motif protein 34 | Nucleus | other | -2.11 | NONE | |

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|--------|---------|--------------------------------------------------------------------------|-----------|-----------------------|-------|----------------------------------------------------------------------------------------------------------------------|
| P0CB38 | PABPC4L | poly(A) binding protein, cytoplasmic 4-like | unknown | other | -2.09 | NONE |
| P49770 | EIF2B2 | eukaryotic translation initiation factor 2B, subunit 2 beta, 39kDa | Cytoplasm | translation regulator | -2.09 | NONE |
| P11678 | EPX | eosinophil peroxidase | Cytoplasm | enzyme | -2.06 | NONE, Although one reference examined EPX in subjects, it is was NOT differentially expressed in COPD |
| B1AJZ9 | FHAD1 | forkhead-associated (FHA) phosphopeptide binding domain 1 | unknown | other | -2.04 | NONE |

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|--------|------------------------------|-------------------------------------------------------------|-----------------|------------------------|------|-------|
| P54920 | NAPA | N-ethylmaleimide-sensitive factor attachment protein, alpha | Cytoplasm | other | NONE | -2.03 |
| P01771 | HV310 | Ig heavy chain V_III region HIL | Extracellular | immunoglobulin | NONE | -2.03 |
| Q9Y2H0 | DLGAP4 | discs, large homolog-associated protein 4 | Plasma Membrane | other | NONE | -2.01 |
| Q07954 | LRP1 (includes EG:16971) | low density lipoprotein receptor-related protein 1 | Plasma Membrane | transmembrane receptor | NONE | -2.00 |

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|--------|---------|-------------------------------------------------------------------------|--------------------|-----------|-------|------|
| Q13702 | RAPSN | receptor-associated protein of the synapse | Plasma Membrane | other | -2.00 | NONE |
| Q13620 | CUL4B | cullin 4B | Nucleus | other | -2.00 | NONE |
| P15291 | B4GALT1 | UDP-Gal:betaGlcNAc beta 1,4- galactosyltransferase, polypeptide 1 | Cytoplasm | enzyme | -1.99 | NONE |
| P04259 | K2C6B | Keratin type II cytoskeletal 6B | | | -1.99 | NONE |
| P14384 | CPM | carboxypeptidase M | Plasma Membrane | peptidase | -1.98 | NONE |
| Q5HYK9 | ZNF667 | zinc finger protein 667 | Nucleus | other | -1.97 | NONE |
| Q5VVM6 | CCDC30 | coiled-coil domain containing 30 | unknown | other | -1.97 | NONE |

| | | | | | |
|--------|-------|-------------------------------|-----------|----------------|-------|
| Q16181 | SEP7 | septin 7 | Cytoplas | other | NONE |
| | | | m | | -1.97 |
| | | | Extracell | | NONE |
| | HV302 | Ig heavy chain V_III region | ular | immunoglobulin | |
| P01763 | | WEA | Space | | -1.96 |
| | | | Extracell | | NONE |
| P07225 | PROS1 | protein S (alpha) | ular | other | |
| | | | Space | | -1.96 |
| | | | Extracell | | NONE |
| | HV319 | Ig heavy chain V_III region | ular | immunoglobulin | |
| P01780 | | JON | Space | | -1.95 |
| | | | Extracell | | NONE |
| | KV113 | | ular | immunoglobulin | |
| P01605 | | Ig kappa chain V_I region Lay | Space | | -1.95 |

| | | | | | |
|--------|--------|--------------------------------|-----------|----------------|-------|
| | | | Extracell | | NONE |
| | KV119 | | ular | immunoglobulin | |
| P01611 | | Ig kappa chain V_I region Wes | Space | | -1.93 |
| | | | Extracell | | NONE |
| | KV120 | Ig kappa chain V_I region | ular | immunoglobulin | |
| P01612 | | Mev | Space | | -1.93 |
| | | | Extracell | | NONE |
| Q8NB66 | UNC13C | unc-13 homolog C | Cytoplas | other | NONE |
| | | | m | | -1.90 |
| | | | Extracell | | NONE |
| A4D1S5 | RAB19 | RAB19, member RAS | Cytoplas | enzyme | NONE |
| | | oncogene family | m | | -1.90 |
| | | | Extracell | | NONE |
| Q9Y613 | FHOD1 | formin homology 2 domain | Nucleus | other | NONE |
| | | containing 1 | | | -1.89 |
| | | | Extracell | | NONE |
| Q86Y33 | CDC20B | cell division cycle 20 homolog | unknown | other | NONE |
| | | B | | | -1.87 |

| | | | | | | |
|------------|--------------|--------------------------------------------------------------------------|----------------------------|----------------|--------------------------------------------------------------------------|-------|
| P06317 | LV603 | Ig lambda chain V_VI region SUT | Extracell ular Space | immunoglobulin | NONE | -1.86 |
| Q5FWF4 | ZRANB3 | zinc finger, RAN-binding domain containing 3 | unknown | enzyme | NONE | -1.83 |
| Q0VAM 2 | RASGEF1 B | RasGEF domain family, member 1B | unknown | other | NONE | -1.82 |
| Q9HAV0 | GNB4 | guanine nucleotide binding protein (G protein), beta polypeptide 4 | Plasma Membra ne | enzyme | NONE | -1.79 |
| P16070 | CD44 | CD44 molecule (Indian blood group) | Plasma Membra ne | enzyme | CD44 HA receptor is implicated in macrophage phagocytic ability | -1.79 |

9,83-86

| | | | | | | |
|--------|----------|---------------------------------------------------------|-----------------|------------------------|-------|-------------------------------------------------------------------------------------------|
| | | | | | | and appears to be decreased in COPD |
| P16144 | ITGB4 | integrin, beta 4 | Plasma Membrane | transmembrane receptor | -1.77 | NONE |
| Q12873 | CHD3 | chromodomain helicase DNA binding protein 3 | Nucleus | enzyme | -1.75 | NONE |
| P15151 | PVR | poliovirus receptor | Plasma Membrane | other | -1.75 | NONE |
| Q08380 | LGALS3BP | lectin, galactoside-binding, soluble, 3 binding protein | Plasma Membrane | transmembrane receptor | -1.75 | NONE for the specific protein, but as a binding protein for a lectin, its associates with |

| | | | | | | |
|--------|--------------|----------------------------------------------------|----------------------------|-------|-------|------------------------------------------------------------------------------------|
| | | | | | | galectin 3 which seems to regulate macrophage efferocytosis in COPD, , |
| Q9HBR0 | SLC38A1 0 | solute carrier family 38, member 10 | unknown | other | -1.74 | NONE |
| Q6Q759 | SPAG17 | sperm associated antigen 17 | unknown | other | -1.73 | NONE |
| Q15582 | TGFBI | transforming growth factor, beta-induced, 68kDa | Extracell ular Space | other | -1.73 | NONE |
| A6NCL7 | ANKRD33 B | ankyrin repeat domain 33B | unknown | other | -1.72 | NONE |

| | | | | | |
|--------|---------|--------------------------------------------------------------------------|---------------|------------------|-------|
| Q8TEU7 | RAPGEF6 | Rap guanine nucleotide exchange factor (GEF) 6 | Plasma | | NONE |
| | | | Membrane | other | -1.72 |
| P01619 | KV301 | Ig kappa chain V_III region B6 | Extracellular | | NONE |
| | | | ular | immunoglobulin | -1.72 |
| Q8TCU6 | PREX1 | phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 1 | Cytoplasm | other | NONE |
| | | | | | -1.70 |
| P04114 | APOB | apolipoprotein B (including Ag(x) antigen) | Extracellular | | NONE |
| | | | ular | Lipid metabolism | -1.68 |
| P06314 | KV40 | Ig kappa chain V_IV region B17 | Extracellular | | NONE |
| | | | ular | immunoglobulin | -1.67 |

| | | | | | | |
|--------|-------|-----------------------------------------------------------------------------|-----------------|------------------------|-------------------------------------------------------------------|-------|
| P01859 | IGHG2 | immunoglobulin heavy constant gamma 2 (G2m marker) | Plasma Membrane | immunoglobulin | NONE | -1.67 |
| P17174 | GOT1 | glutamic-oxaloacetic transaminase 1, soluble (aspartate aminotransferase 1) | Cytoplasm | enzyme | NONE | -1.67 |
| Q02818 | NUCB1 | nucleobindin 1 | Cytoplasm | other | NONE | -1.67 |
| P05362 | ICAM1 | intercellular adhesion molecule 1 | Plasma Membrane | transmembrane receptor | Discordant of ICAM in COPD in literature compared to our findings | -1.66 |

| | | | | | | |
|--------|--------|---------------------------------|-----------|-------------------|--|---------------------------------------------------|
| Q6UX72 | B3GNT9 | UDP-GlcNAc:betaGal beta- | | | | NONE |
| | | 1,3-N- | unknown | enzyme | | |
| | | acetylglucosaminyltransferase 9 | | | | -1.65 |
| P52823 | STC1 | | Extracell | | | NONE |
| | | stanniocalcin 1 | ular | kinase | | |
| | | | Space | | | -1.65 |
| P36222 | CHI3L1 | | Extracell | | | Increased in the 97-99 |
| | | chitinase 3-like 1 | ular | Tissue remodeling | | serum and BAL of smokers with COPD |
| | | | Space | | | compared to never smokers or smokers without COPD |
| | | | | | | -1.65 |

| | | | | | | |
|------------|---------|--------------------------------------------------------------------------|----------------------------|-----------------------|------------------------------------------------------------|------------------|
| Q96JH7 | VCPIP1 | valosin containing protein (p97)/p47 complex interacting protein 1 | Cytoplas m | peptidase | NONE | -1.64 |
| O95436 | SLC34A2 | solute carrier family 34 (sodium phosphate), member 2 | Plasma Membr ne | transporter | NONE | -1.64 |
| P46199 | MTIF2 | mitochondrial translational initiation factor 2 | Cytoplas m | translation regulator | NONE | -1.64 |
| Q86SQ7 | SDCCAG8 | serologically defined colon cancer antigen 8 | Cytoplas m | other | NONE | -1.64 |
| Q8N7W 2 | BEND7 | BEN domain containing 7 | unknown | other | NONE | -1.61 |
| P01024 | C3 | complement component 3 | Extracell ular Space | peptidase | Serum levels of C3 was decreased in serum and sputum | 100-102 -1.58 |

| | | | | | of subjects with | |
|--------|--------|------------------------------------------------------------|-----------|-------------------------------|-----------------------------------------------------|---------|
| | | | | | COPD | |
| P07998 | RNASE1 | ribonuclease, RNase A family, 1 (pancreatic) | Extracell | enzyme | NONE | |
| | | | ular | | | |
| P00739 | HPR | haptoglobin-related protein | Space | peptidase | -1.58 | |
| | | | Extracell | | NONE | |
| Q76L83 | ASXL2 | additional sex combs like 2 | ular | other | | |
| | | | Space | | -1.57 | |
| Q8NFJ5 | GPRC5A | G protein-coupled receptor, family C, group 5, member A | Plasma | G-protein coupled receptor | Decreased in lung | 103,104 |
| | | | Membrane | | epithelia associated with lung adenocarcinoma | |
| | | | ne | | -1.57 | |

| | | | | | | | |
|--------|--------|--------------------------------------------------------------------------------------------------------|------------------------|-------------------------|--|-----------------------------------------------------------------------------------|-------|
| | | | | | | compared to epithelia from subjects with COPD or never smokers | |
| Q7Z7M9 | GALNT5 | UDP-N-acetyl-alpha-D- galactosamine:polypeptide N- acetylgalactosaminyltransferase 5 (GalNAc-T5) | Cytoplasm | enzyme | | NONE | -1.57 |
| P06331 | HV209 | Ig heavy chain V_H region ARH_77 | Extracellular Space | immunoglobulin | | NONE | -1.57 |
| P15941 | MUC1 | Mucin 1, cell surface associated | Plasma Membrane | transcription regulator | | Levels are affected by age and smoking in lung tissue, sputum and plasma | -1.56 |

56,105,106

| | | | | | | |
|--------|--------|----------------------------------------------------|---------------------|----------------------------|------|-------|
| P48960 | CD97 | CD97 molecule | Plasma Membrane | G-protein coupled receptor | NONE | -1.55 |
| P06681 | C2 | complement component 2 | Extracellular Space | peptidase | NONE | -1.54 |
| Q9NYQ6 | CELSR1 | cadherin, EGF LAG seven-pass G-type receptor 1 | Plasma Membrane | G-protein coupled receptor | NONE | -1.53 |
| P0CG06 | IGLC3 | immunoglobulin lambda constant 3 (Kern-Oz+ marker) | Extracellular Space | other | NONE | -1.53 |
| P06126 | CD1A | CD1a molecule | Plasma Membrane | other | | -1.52 |

| | | | | | |
|--------|-------|----------------------------------------|------------------------|--------|-------------------|
| O00560 | SDCBP | syndecan binding protein (syntenin) | Plasma Membra ne | enzyme | NONE -1.51 |
|--------|-------|----------------------------------------|------------------------|--------|-------------------|

Table S4:

See David_FuncAnnotClustering_BALF.csv for DAVID functional annotation clustering file.

Table S5:

Transcription factors associated with binding sites on genes from differentially expressed proteins in BALF. Transcription factors that have association with binding sites on genes from differentially expressed proteins in BALF as noted by DAVID [ref].

| Transcription factor with binding sites in the genes represented in BALF | Number of the differentially expressed proteins that have corresponding gene binding sites with transcription factor | % of dataset in DAVID database | p-value (Fisher exact) |
|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|--------------------------------|------------------------|
| AREB6 | 166 | 79.43 | 0.009 |
| SRF | 148 | 70.81 | 0.000 |
| AML1 | 147 | 70.33 | 0.089 |
| P53 | 127 | 60.77 | 0.061 |
| AP4 | 125 | 59.81 | 0.053 |

| | | | |
|----------|-----|-------|-------|
| LMO2COM | 122 | 58.37 | 0.004 |
| SREBP1 | 118 | 56.46 | 0.046 |
| PAX2 | 113 | 54.07 | 0.073 |
| USF | 113 | 54.07 | 0.081 |
| PAX5 | 112 | 53.59 | 0.034 |
| GCNF | 112 | 53.59 | 0.049 |
| STAT5A | 111 | 53.11 | 0.074 |
| MRF2 | 110 | 52.63 | 0.001 |
| HTF | 110 | 52.63 | 0.010 |
| TAXCREB | 109 | 52.15 | 0.021 |
| CEBPB | 109 | 52.15 | 0.041 |
| AHRARNT | 105 | 50.24 | 0.031 |
| FOXO4 | 105 | 50.24 | 0.073 |
| RP58 | 104 | 49.76 | 0.032 |
| STAT3 | 101 | 48.33 | 0.004 |
| BACH1 | 101 | 48.33 | 0.028 |
| HNF4 | 100 | 47.85 | 0.010 |
| GFI1 | 97 | 46.41 | 0.002 |
| NFKB | 97 | 46.41 | 0.071 |
| STAT1 | 96 | 45.93 | 0.000 |
| FREAC3 | 95 | 45.45 | 0.001 |
| CREBP1 | 95 | 45.45 | 0.033 |
| OCT | 94 | 44.98 | 0.025 |
| CDPCR3HD | 92 | 44.02 | 0.019 |
| HAND1E47 | 92 | 44.02 | 0.052 |
| RSRFC4 | 91 | 43.54 | 0.091 |
| SOX9 | 90 | 43.06 | 0.028 |
| HFH1 | 90 | 43.06 | 0.044 |
| CMYB | 89 | 42.58 | 0.014 |
| GATA | 89 | 42.58 | 0.050 |
| HSF2 | 88 | 42.11 | 0.012 |
| IK3 | 88 | 42.11 | 0.058 |
| HOX13 | 88 | 42.11 | 0.098 |

| | | | |
|-------------|----|-------|-------|
| RORA1 | 87 | 41.63 | 0.087 |
| HLF | 86 | 41.15 | 0.009 |
| FOXO1 | 85 | 40.67 | 0.026 |
| TGIF | 84 | 40.19 | 0.060 |
| POU6F1 | 84 | 40.19 | 0.068 |
| E4BP4 | 84 | 40.19 | 0.100 |
| MIF1 | 83 | 39.71 | 0.074 |
| STAT | 82 | 39.23 | 0.001 |
| CP2 | 82 | 39.23 | 0.020 |
| MSX1 | 81 | 38.76 | 0.098 |
| LYF1 | 80 | 38.28 | 0.032 |
| HNF3B | 80 | 38.28 | 0.091 |
| NFKAPPAB | 79 | 37.80 | 0.004 |
| NFE2 | 70 | 33.49 | 0.094 |
| FOXD3 | 69 | 33.01 | 0.061 |
| IK2 | 62 | 29.67 | 0.054 |
| TAL1BETAE47 | 61 | 29.19 | 0.041 |
| HSF1 | 61 | 29.19 | 0.087 |
| ZIC2 | 53 | 25.36 | 0.016 |
| GATA3 | 51 | 24.40 | 0.034 |
| MAX | 37 | 17.70 | 0.089 |

Table S6: Top functional networks of differentially expressed molecules in the BALF proteome. The top biological functions associated with molecular pathways imputed with IPA that are significantly associated differentially expressed molecules measured in the BALF proteome. **Red** represents upregulated, and green represents downregulated proteins. **The** networks are collections of interconnected molecules assembled by a network algorithm. Each connection represents known relationships between the molecules, found in the Ingenuity Knowledge Base. **The score is the** degree of relevance of network eligible molecules to the BALF dataset. The

score takes into account the number of network eligible molecules in the network and its size, as well as the total number of network eligible molecules analyzed and the total number of molecules in the Ingenuity Knowledge Base that could potentially be included in networks. The network score is based on the hypergeometric distribution and is calculated with the right-tailed Fisher's Exact Test: $\text{Score} = -\log(\text{Fisher's Exact test result})$. Focus Molecules are the number of proteins identified in the BALF proteome that is found in the network.

| ID | Molecules in network | Score | Focus molecules | Top biological functions associated with the molecular network |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-----------------|------------------------------------------------------------------------------------------|
| 1 | ACTG1, Actin, Akt, Alpha catenin, ANXA5, ARHGEF1, CD44, CFL1, Collagen type I, COTL1, F Actin, FLNA, HN1, Hsp27, ITGB4, Laminin, LGALS3, LUM, MARK2, MUC1, MYH11, MYO7A, PLEC, PRKCSH, PROS1, PTGDS, PVR, Rock, SDCBP, TGFBI, TMSB10/TMSB4X, TXNRD1, USP6NL, VIM, WASF2 | 51 | 27 | Cellular Movement, Inflammatory Response, Cardiovascular System Development and Function |
| 2 | AKR1C3, ANG, APCS, C3, C1q, C1QC, C4BP, CD1A, CHI3L1, Complement component 1, ENO1, EPX, ERK1/2, ETS, Fcer1, FETUB, FHOD1, Gm-csf, Ige, LAMA3, LRP1, Mac1, MARCO, PIK3C2B, PLA2, PLA2G1B, PPIA, PPIB, PRDX6, Rsk, S100A6, Sos, STC1, T3-TR-RXR, TH2 Cytokine | 36 | 21 | Cell Death and Survival, Drug Metabolism, Small Molecule Biochemistry |
| 3 | APC, BOD1L1, C10orf116, C14orf80, C5orf51, CDC37, CEP128, CUL2, DDIT3, ELAVL1, GSK3B, GSTP1, KIAA0101, MYH15, NCKAP5L, PABPC4L, PCNA, RBM27, RNF214, RPS6KA6, RSBN1, SCGB1D2, SLC38A10, SND1, TRIM28, UBC, VAV2, ZNF256, ZNF667, ZRANB3 | 27 | 16 | Cell Morphology, Cellular Assembly and Organization, Cellular Development |
| 4 | A2M, APOA1, APOB, APOC3, B3GNT9, chymotrypsin, Cytokeratin, elastase, FGA, FGB, FGG, Fibrin, Fibrinogen, GPIIB-IIIa, Growth hormone, HDL, HDL-cholesterol, HP, HPR, Kallikrein, KRT1, KRT9, KRT10, KRT6B, LDL-cholesterol, LRP, NFkB (complex), PCYOX1, PEBP1, Pro-inflammatory Cytokine, SAA, SFTPA1, SFTPD, Stat3-Stat3, VLDL-cholesterol | 27 | 18 | Developmental Disorder, Hematological Disease, Hereditary Disorder |

| | | | | |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|----|-------------------------------------------------------------------------------------------------------------------|
| 5 | ANXA3, APITD1, C1GALT1C1, C1orf86, C9orf72, CYC1, EIF2B2, EIF2B3, EMG1, FANCB, FANCE, FANCF, FANCM, GALNT2, GALNT5, GGA1, GGA3, KRT79, LANCL1, MON2, MYOZ1, NAPSA, NLE1, PNKP, RAB6B, RABGAP1, RAPGEF6, RBM34, RMI2, SH3BGRL, SLC25A24, STRA13, TOP3A, UBC, ZNF292 | 25 | 16 | Developmental Disorder, Hematological Disease, Hereditary Disorder |
| 6 | Alp, BMP2K, C16orf88, CBR1, CD3, CDC45, Cg, CHD3, CNGA2, CUL4B, DBI, ENO2, Focal adhesion kinase, Hdac, Histone h3, Histone h4, Hsp70, HSPA6, ICAM1, IDH1, IKK (complex), LDL, NADPH oxidase, P38 MAPK, Pdgf (complex), PI3K (complex), Pkc(s), PREX1, RNA polymerase II, Sod, SRC (family), TALDO1, Vegf, VNN1, WNT9B | 24 | 16 | Cancer, Gastrointestinal Disease, Cardiovascular Disease |
| 7 | AKAP6, BEND7, C11orf48, CCDC85A, CCNB1, CCND1, CDK5RAP3, CDKN1B, CMIP, DACH2, DDRGK1, DGCR14, DNAJC16, FOXO3, GSTM4, GSTM5, GSTO2, hemoglobin, LYAR, MYRIP, NANOG, PARPBP, PGAM4, PIK3R1, PRRC2C, RAB19, RSL24D1, SIX6, SLC34A2, STAT5A, TMEM55A, UBC, UBLCP1, UFC1, ZNF462 | 20 | 14 | Cardiovascular System Development and Function, Cell Cycle, Skeletal and Muscular System Development and Function |
| 8 | ADCYAP1, alcohol dehydrogenase, ALDH16A1, ALDOC, APP, ASXL2, C19orf40, CALML3, CASP6, CCL5, CRTAC1, CWF19L2, FBXO34, GSTM3, HSP90AB1, HSPA2, HSPB7, IRAK3, KIFC3, MDH1, NUCB1, PDE1A, PSMB4, PSMD1, PTMS, RAB10, RNASE1, RUSC1, SCAVENGER receptor CLASS A, SDCCAG8, SH3RF2, TAGLN2, TRAF6, USP1, ZBTB20 | 20 | 14 | Organismal Injury and Abnormalities, Cell Death and Survival, Nervous System Development and Function |
| 9 | B4GALT1, BCR (complex), Collagen(s), CTSZ, DPP4, ERK, Fc gamma receptor, GATA3, GOT1, HLA-C, HSP, Ifn, IFN Beta, Ifn gamma, IgG1, Igg3, IgG, IGHG2, Igm, Ikb, IKBKB, IL1, IL12 (complex), IL12 (family), Immunoglobulin, Interferon alpha, LGALS3BP, MHC Class I (complex), MHC CLASS I (family), MHC Class II (complex), NKX3-2, PPBP, PRSS8, Tgf beta, Tlr | 17 | 12 | Cellular Movement, Hematological System Development and Function, Immune Cell Trafficking |
| 10 | 26sProteasome, ADCY, ARHGAP24, Calmodulin, CD97, CELSR1, chemokine, Ck2, EMR2, endocannabinoid, FBP1, FSH, Gpcr, GPR4, GPR68, GPRC5A, GRM8, Insulin, MAP9, Mapk, MID2, NAPA, OCRL, Pka, PLC, Rac, RAPSN, Ras, Ras homolog, Sfk, Shc, SYTL4, Trk Receptor, UBE2N, Ubiquitin | 17 | 12 | Cellular Assembly and Organization, Cellular Function and Maintenance, Molecular Transport |

| | | | | |
|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|----|-----------------------------------------------------------------------------------------------|
| 11 | ADH1B, AKAP9, ALDH3A1, Ap1, BLVRA, C2, C/ebp, calpain, caspase, Collagen type IV, Cyclin A, Cyclin E, DACH1, DLGAP4, estrogen receptor, FHL1, FN1, Hsp90, HTRA2, Integrin, Jnk, Lfa-1, MAP2K1/2, Mek, Metalloprotease, Mmp, MSLN, NFAT (complex), Nfat (family), NUMA1, p70 S6k, PDGF BB, PSMD14, TCR, trypsin | 16 | 13 | Cell Cycle, Visual System Development and Function, Hair and Skin Development and Function |
| 12 | ADRBK2, CACNA1B, CCM2, CHRM3, CNR1, COL11A2, COL2A1, CREB3L3, D-glucose, endocannabinoid, FCHSD2, GABBR1, GBP5, GNB4, GNG5, GNG7, GNGT1, GPM6A, GPR68, ITGB1BP1, JAKMIP1, KRIT1, N-type Calcium Channel, PLA2G6, PLCB3, RGS6, SEPT4, SEPT7, SEPT8, SH3BGR, TRHR, TRPV4, UNC13C, VCPIP1, ZNF219 | 13 | 10 | Connective Tissue Disorders, Developmental Disorder, Hereditary Disorder |
| 13 | ACP5, AKAP12, BCL3, CAMP, CPM, CSF1, CYP11A1, FANK1, FPR2, Hedgehog, HLX, HSD17B1, ITGB8, JUN, mannitol, MAP2K2, MAZ, MOGS, MTIF2, NOTCH4, PGC, PROM1, PTPRO, SERPINB2, SFTPB, SIRT6, SLC8A1, SMAD5, SOD2, STAB2, Stat3-Stat3, TEAD4, TMSB10/TMSB4X, USP36, VEGFA | 8 | 7 | Cardiovascular System Development and Function, Embryonic Development, Organismal Development |
| 14 | ANO8, COQ9 | 2 | 1 | Hereditary Disorder, Metabolic Disease, Cancer |
| 15 | Spag6, SPAG17 | 2 | 1 | Cellular Assembly and Organization, Cellular Compromise, Cellular Function and Maintenance |
| 16 | ADCY10, SLC9C1 | 2 | 1 | Cellular Movement, Reproductive System Development and Function, Reproductive System Disease |

Red=upregulated proteins

Green=downregulated protein

Networks = collections of interconnected molecules assembled by a network algorithm. Each connection represents known relationships between the molecules, found in the Ingenuity Knowledge Base.

* **Score**= The degree of relevance of Network Eligible molecules to the BALF dataset. The score takes into account the number of Network Eligible molecules in the network and its size, as well as the total number of Network Eligible molecules analyzed and the total number of molecules in the Ingenuity Knowledge Base that could potentially be included in networks. The network Score is based on the hypergeometric distribution and is calculated with the right-tailed Fisher's Exact Test. $\text{Score} = -\log(\text{Fisher's Exact test result})$

^ Focus Molecules= The number of proteins identified in the BALF proteome that is found in the network

TABLE S7

Computational drug prediction CANDO

(score1= refers to the consensus score or number of times the compound shows up in the top 30 most similar drugs used to treat COPD

score2= the average of the ranks for 'score1'

probability= the binomial distribution derived probability of achieving 'score1' by chance based on the number of drugs associated with COPD, the total number of drugs in the library, and the number of most similar drugs to consider (in this case, 30).

name= generic name of the candidate drug)

CANDO= Computational Analysis of Novel Drug Opportunities

COPD= chronic obstructive pulmonary disease

| Rank | Score1 (consensus score) | Score2 (average ranks score) | Probability | Name |
|------|--------------------------------|------------------------------|-------------|-----------------------|
| 1 | 12 | 10.1 | 1.11E-16 | clobetasol propionate |
| 2 | 12 | 11.8 | 1.11E-16 | clobetasol |

| | | | | |
|----|----|------|----------|--------------------------|
| 3 | 12 | 12.7 | 1.11E-16 | rimexolone |
| 4 | 11 | 12.5 | 4.88E-15 | deflazacort |
| 5 | 10 | 7.2 | 2.07E-13 | loteprednol_etabonate |
| 6 | 10 | 10.4 | 2.07E-13 | desoximetasone |
| 7 | 10 | 13.1 | 2.07E-13 | loteprednol |
| 8 | 10 | 13.4 | 2.07E-13 | meprednisone |
| 9 | 10 | 14.4 | 2.07E-13 | amcinonide |
| 10 | 9 | 13.2 | 7.66E-12 | flucolorolone acetone |
| 11 | 9 | 15.1 | 7.66E-12 | fluorometholone |
| 12 | 9 | 17.7 | 7.66E-12 | clobetasone |
| 13 | 8 | 14.2 | 2.48E-10 | ulobetasol |
| 14 | 8 | 16.1 | 2.48E-10 | procaterol |
| 15 | 8 | 18.1 | 2.48E-10 | desonide |
| 16 | 7 | 11 | 6.95E-09 | prednicarbate |
| 17 | 7 | 11.6 | 6.95E-09 | tezacaftor |
| 18 | 7 | 16 | 6.95E-09 | cyproterone acetate |
| 19 | 7 | 24.3 | 6.95E-09 | drometrizole trisiloxane |

| | | | | |
|----|---|------|----------|-------------------------|
| 20 | 6 | 14.2 | 1.67E-07 | nadolol |
| 21 | 6 | 14.5 | 1.67E-07 | hydrocortamate |
| 22 | 6 | 19.7 | 1.67E-07 | hydrocortisone butyrate |
| 23 | 6 | 23.2 | 1.67E-07 | flurandrenolide |
| 24 | 5 | 3 | 3.39E-06 | isoprenaline |
| 25 | 5 | 4.6 | 3.39E-06 | epinephrine |
| 26 | 5 | 5.6 | 3.39E-06 | orciprenaline |
| 27 | 5 | 6.6 | 3.39E-06 | isoetharine |
| 28 | 5 | 7.6 | 3.39E-06 | carbidopa |
| 29 | 5 | 9.2 | 3.39E-06 | gemfibrozil |
| 30 | 5 | 9.8 | 3.39E-06 | phenylephrine |
| 31 | 5 | 9.8 | 3.39E-06 | methyldopa |
| 32 | 5 | 10.8 | 3.39E-06 | carteolol |
| 33 | 5 | 11.2 | 3.39E-06 | paramethasone acetate |
| 34 | 5 | 11.8 | 3.39E-06 | clocortolone |
| 35 | 5 | 12.2 | 3.39E-06 | arbutamine |
| 36 | 5 | 12.4 | 3.39E-06 | pindolol |

| | | | | |
|----|---|------|----------|------------------------------|
| 37 | 5 | 13.4 | 3.39E-06 | hydrocortisone acetate |
| 38 | 5 | 13.8 | 3.39E-06 | levobunolol |
| 39 | 5 | 14.6 | 3.39E-06 | difluocortolone |
| 40 | 5 | 17.6 | 3.39E-06 | propofol |
| 41 | 5 | 18.6 | 3.39E-06 | celiprolol |
| 42 | 5 | 18.8 | 3.39E-06 | levonordefrin |
| 43 | 5 | 20.8 | 3.39E-06 | tapentadol |
| 44 | 5 | 20.8 | 3.39E-06 | segesterone acetate |
| 45 | 4 | 9.2 | 5.72E-05 | betamethasone |
| 46 | 4 | 9.2 | 5.72E-05 | methylprednisolone aceponate |
| 47 | 4 | 10.2 | 5.72E-05 | dexamethasone |
| 48 | 4 | 11 | 5.72E-05 | naldemedine |
| 49 | 4 | 11.2 | 5.72E-05 | elvitegravir |
| 50 | 4 | 14 | 5.72E-05 | difluprednate |
| 51 | 4 | 15.8 | 5.72E-05 | deferiprone |

| | | | | |
|----|---|------|----------|-------------------------|
| 52 | 4 | 17 | 5.72E-05 | methylprednisolone |
| 53 | 4 | 17.5 | 5.72E-05 | prednisolone |
| 54 | 4 | 18 | 5.72E-05 | tamsulosin |
| 55 | 4 | 20.5 | 5.72E-05 | fluprednisolone |
| 56 | 4 | 22.2 | 5.72E-05 | canrenoic acid |
| 57 | 4 | 22.5 | 5.72E-05 | etidocaine |
| 58 | 4 | 23 | 5.72E-05 | mephenesin |
| 59 | 4 | 24.5 | 5.72E-05 | hydrocortisone valerate |
| 60 | 4 | 25.5 | 5.72E-05 | halcinonide |
| 61 | 4 | 26 | 5.72E-05 | desvenlafaxine |
| 62 | 3 | 5 | 7.80E-04 | fexofenadine |
| 63 | 3 | 7 | 7.80E-04 | pioglitazone |
| 64 | 3 | 7.7 | 7.80E-04 | laropiprant |
| 65 | 3 | 8.3 | 7.80E-04 | terfenadine |
| 66 | 3 | 8.7 | 7.80E-04 | cyclandelate |

| | | | | |
|----|---|------|----------|---------------------------|
| 67 | 3 | 9.7 | 7.80E-04 | dobutamine |
| 68 | 3 | 10 | 7.80E-04 | mometasone furoate |
| 69 | 3 | 10.3 | 7.80E-04 | fentanyl |
| 70 | 3 | 11 | 7.80E-04 | amiodarone |
| 71 | 3 | 11.3 | 7.80E-04 | siponimod |
| 72 | 3 | 12.3 | 7.80E-04 | homatropine methylbromide |
| 73 | 3 | 14 | 7.80E-04 | metaraminol |
| 74 | 3 | 14 | 7.80E-04 | flunisolide |
| 75 | 3 | 14.3 | 7.80E-04 | meradimate |
| 76 | 3 | 14.7 | 7.80E-04 | fluocinonide |
| 77 | 3 | 15 | 7.80E-04 | masoprocol |
| 78 | 3 | 15 | 7.80E-04 | fluocinolone acetate |
| 79 | 3 | 15.3 | 7.80E-04 | loperamide |
| 80 | 3 | 16 | 7.80E-04 | hydrocortisone cypionate |
| 81 | 3 | 16 | 7.80E-04 | piritramide |

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|----|---|------|----------|-------------------------|
| 82 | 3 | 16.3 | 7.80E-04 | darifenacin |
| 83 | 3 | 17 | 7.80E-04 | ebastine |
| 84 | 3 | 18 | 7.80E-04 | guaifenesin |
| 85 | 3 | 18.7 | 7.80E-04 | zolmitriptan |
| 86 | 3 | 19 | 7.80E-04 | tropium |
| 87 | 3 | 19.3 | 7.80E-04 | darolutamide |
| 88 | 3 | 19.7 | 7.80E-04 | olmesartan |
| 89 | 3 | 20.3 | 7.80E-04 | megestrol acetate |
| 90 | 3 | 20.7 | 7.80E-04 | levocabastine |
| 91 | 3 | 23 | 7.80E-04 | benserazide |
| 92 | 3 | 26 | 7.80E-04 | stiripentol |
| 93 | 3 | 27 | 7.80E-04 | dipivefrin |
| 94 | 3 | 29 | 7.80E-04 | norepinephrine |
| 95 | 2 | 1 | 8.29E-03 | oxtriphylline |
| 96 | 2 | 2 | 8.29E-03 | bromotheophylline |
| 97 | 2 | 2 | 8.29E-03 | methscopolamine bromide |

| | | | | |
|-----|---|-----|----------|--------------------------------------------|
| 98 | 2 | 2 | 8.29E-03 | butylscopolamine |
| 99 | 2 | 2.5 | 8.29E-03 | diethylamino_hydroxybenzoyl_hexyl_benzoate |
| 100 | 2 | 3 | 8.29E-03 | caffeine |
| 101 | 2 | 3 | 8.29E-03 | methscopolamine |
| 102 | 2 | 4 | 8.29E-03 | xanthinol |
| 103 | 2 | 4 | 8.29E-03 | dopexamine |
| 104 | 2 | 4.5 | 8.29E-03 | difenoxin |
| 105 | 2 | 4.5 | 8.29E-03 | scopolamine |
| 106 | 2 | 5 | 8.29E-03 | enprofylline |
| 107 | 2 | 5 | 8.29E-03 | oxyphenonium |
| 108 | 2 | 5.5 | 8.29E-03 | cortisone acetate |
| 109 | 2 | 5.5 | 8.29E-03 | labetalol |
| 110 | 2 | 6 | 8.29E-03 | pentoxifylline |
| 111 | 2 | 6 | 8.29E-03 | oxybutynin |
| 112 | 2 | 7 | 8.29E-03 | dyphylline |

| | | | | |
|-----|---|------|----------|--------------------|
| 113 | 2 | 7 | 8.29E-03 | methylphenidate |
| 114 | 2 | 8 | 8.29E-03 | temozolomide |
| 115 | 2 | 8 | 8.29E-03 | cyclopentolate |
| 116 | 2 | 8 | 8.29E-03 | dexmethylphenidate |
| 117 | 2 | 9 | 8.29E-03 | enoxacin |
| 118 | 2 | 9 | 8.29E-03 | lemborexant |
| 119 | 2 | 9 | 8.29E-03 | diflorasone |
| 120 | 2 | 9 | 8.29E-03 | fluocortolone |
| 121 | 2 | 9.5 | 8.29E-03 | apremilast |
| 122 | 2 | 9.5 | 8.29E-03 | mepenzolate |
| 123 | 2 | 9.5 | 8.29E-03 | mebeverine |
| 124 | 2 | 9.5 | 8.29E-03 | etofamide |
| 125 | 2 | 10 | 8.29E-03 | tipiracil |
| 126 | 2 | 10 | 8.29E-03 | flumethasone |
| 127 | 2 | 10.5 | 8.29E-03 | diphenoxylate |
| 128 | 2 | 10.5 | 8.29E-03 | ambenonium |

| | | | | |
|-----|---|------|----------|----------------------|
| 129 | 2 | 12 | 8.29E-03 | dexrazoxane |
| 130 | 2 | 12 | 8.29E-03 | rosiglitazone |
| 131 | 2 | 12.5 | 8.29E-03 | halofantrine |
| 132 | 2 | 13 | 8.29E-03 | daunorubicin |
| 133 | 2 | 13 | 8.29E-03 | dicloxacillin |
| 134 | 2 | 13.5 | 8.29E-03 | permethrin |
| 135 | 2 | 13.5 | 8.29E-03 | trimethaphan |
| 136 | 2 | 14 | 8.29E-03 | tinidazole |
| 137 | 2 | 14 | 8.29E-03 | penbutolol |
| 138 | 2 | 14 | 8.29E-03 | oxyphencyclimine |
| 139 | 2 | 15 | 8.29E-03 | acetazolamide |
| 140 | 2 | 15 | 8.29E-03 | methylethergometrine |
| 141 | 2 | 15 | 8.29E-03 | cloxacillin |
| 142 | 2 | 15 | 8.29E-03 | ecamsule |
| 143 | 2 | 15 | 8.29E-03 | sonidegib |
| 144 | 2 | 15.5 | 8.29E-03 | cefpirome |
| 145 | 2 | 15.5 | 8.29E-03 | zofenopril |

| | | | | |
|-----|---|------|----------|-----------------|
| 146 | 2 | 15.5 | 8.29E-03 | panobinostat |
| 147 | 2 | 16 | 8.29E-03 | methimazole |
| 148 | 2 | 16.5 | 8.29E-03 | troglitazone |
| 149 | 2 | 16.5 | 8.29E-03 | flucloxacillin |
| 150 | 2 | 17 | 8.29E-03 | levofloxacin |
| 151 | 2 | 17 | 8.29E-03 | sumatriptan |
| 152 | 2 | 17 | 8.29E-03 | pentoxifyverine |
| 153 | 2 | 17.5 | 8.29E-03 | elagolix |
| 154 | 2 | 17.5 | 8.29E-03 | hexylcaine |
| 155 | 2 | 18 | 8.29E-03 | ofloxacin |
| 156 | 2 | 18 | 8.29E-03 | alclometasone |
| 157 | 2 | 19 | 8.29E-03 | lomefloxacin |
| 158 | 2 | 19 | 8.29E-03 | ioflupane i-123 |
| 159 | 2 | 19 | 8.29E-03 | losartan |
| 160 | 2 | 19.5 | 8.29E-03 | bemotrizinol |
| 161 | 2 | 20 | 8.29E-03 | epirubicin |

| | | | | |
|-----|---|------|----------|--------------------|
| 162 | 2 | 20 | 8.29E-03 | benzethonium |
| 163 | 2 | 20 | 8.29E-03 | benazepril |
| 164 | 2 | 20 | 8.29E-03 | mepyramine |
| 165 | 2 | 20.5 | 8.29E-03 | maraviroc |
| 166 | 2 | 20.5 | 8.29E-03 | methysergide |
| 167 | 2 | 20.5 | 8.29E-03 | dextropropoxyphene |
| 168 | 2 | 20.5 | 8.29E-03 | ritodrine |
| 169 | 2 | 21 | 8.29E-03 | doxorubicin |
| 170 | 2 | 21 | 8.29E-03 | cinchocaine |
| 171 | 2 | 21 | 8.29E-03 | cefapirin |
| 172 | 2 | 21.5 | 8.29E-03 | tegaserod |
| 173 | 2 | 21.5 | 8.29E-03 | nomegestrol |
| 174 | 2 | 22 | 8.29E-03 | dacarbazine |
| 175 | 2 | 22.5 | 8.29E-03 | oxeladin |
| 176 | 2 | 23 | 8.29E-03 | deutetrabenazine |
| 177 | 2 | 23 | 8.29E-03 | tropicamide |
| 178 | 2 | 23 | 8.29E-03 | triamcinolone |

| | | | | |
|-----|---|------|----------|---------------------------|
| 179 | 2 | 23.5 | 8.29E-03 | lovastatin |
| 180 | 2 | 24 | 8.29E-03 | methazolamide |
| 181 | 2 | 25 | 8.29E-03 | pefloxacin |
| 182 | 2 | 26 | 8.29E-03 | nalidixic acid |
| 183 | 2 | 26 | 8.29E-03 | norgestimate |
| 184 | 2 | 26.5 | 8.29E-03 | gestrinone |
| 185 | 2 | 26.5 | 8.29E-03 | ergometrine |
| 186 | 2 | 27 | 8.29E-03 | dorzolamide |
| 187 | 2 | 27 | 8.29E-03 | ethylhexyl methoxycrylene |
| 188 | 2 | 28 | 8.29E-03 | lenalidomide |
| 189 | 2 | 29 | 8.29E-03 | idarubicin |

Table S8**Predicted interactions of drugs treating respiratory diseases and central node proteins**

Representative drugs treating respiratory disease from selected categories showing their predicted interactions with the most central nodes entities of Figure 4

| Drug | Category | Undesired effect | Desired effect |
|--------------|-------------------------------------------|-------------------------|-----------------------|
| azithromycin | antibiotic with anti-inflammatory effects | VIM, ICAM1 | FN1 |
| BIBF 1120 | anti-fibrotic agent | FN1 | -- |
| fluticasone | inhaled corticosteroid | ICAM1, CD44 | -- |
| pirfenidone | anti-fibrotic agent | FN1, ICAM1 | VIM |
| roflumilast | phosphodiesterase inhibitor | ICAM1, FN1 | VIM |
| salbutamol | short acting beta agonist | FN1 | -- |
| salmeterol | long-acting beta agonist | CD44 | -- |
| tiotropium | long-acting anti-muscarinic agent | FN1, ICAM1 | -- |

Supplemental Figures

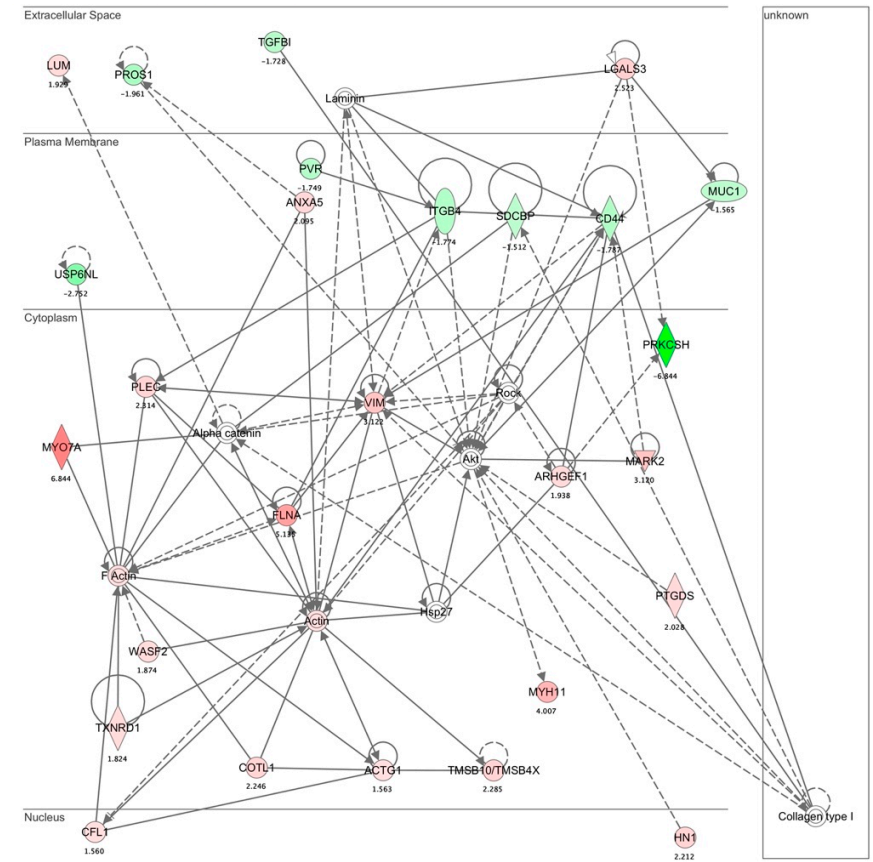


Figure S1:

IPA Network 1: Cellular Movement, Inflammatory Response, Cardiovascular System Development and Function

Functional annotation networks from IPA show relationships among the genes that in IPA's relational database are related to cellular movement, inflammatory response and cardiovascular system development and function.

Solid lines indicated a direct interaction between proteins, while dotted lines indicate an indirect association between two proteins.

Proteins upregulated in the BALF dataset are shaded in red and proteins downregulated in the BALF dataset are shaded in green. The darker shading to lighter shading corresponds to decreasing expression intensity.

IPA=Ingenuity Pathway Analysis, BALF= Bronchoalveolar Lavage Fluid

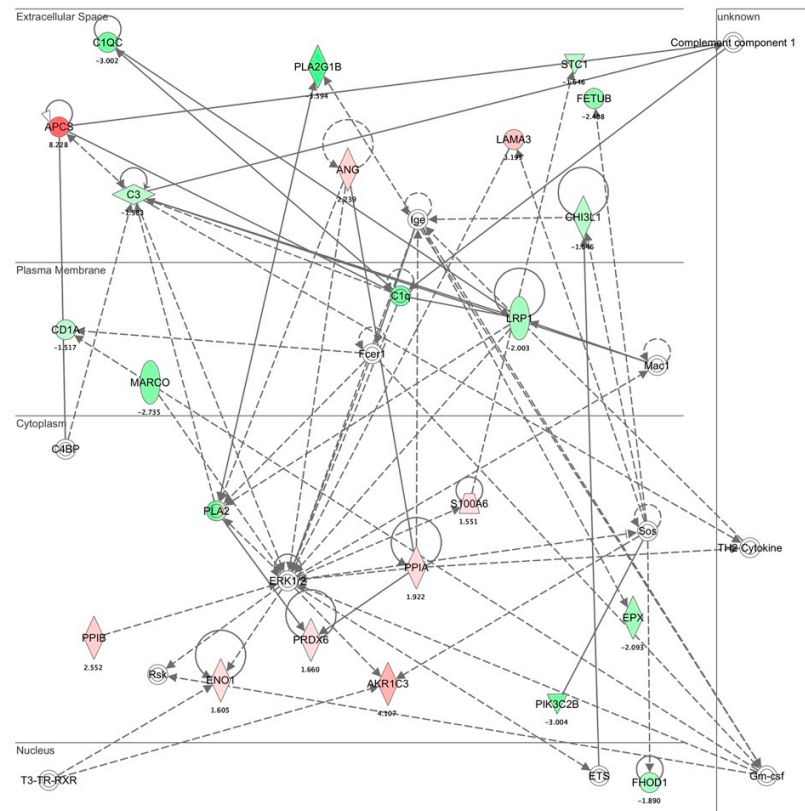


Figure S2:

IPA network 2: cell death and survival, drug metabolism, small molecule biochemistry

Functional annotation networks from IPA that show relationships among the genes that in IPA's relational database are related to cell death and survival, drug metabolism and small molecule biochemistry.

Solid lines indicated a direct interaction between proteins, while dotted lines indicate an indirect association between two proteins.

Proteins upregulated in the BALF dataset are shaded in red and proteins downregulated in the BALF dataset are shaded in green. The darker shading to lighter shading corresponds to decreasing expression intensity.

IPA=Ingenuity Pathway Analysis, BALF= Bronchoalveolar Lavage Fluid

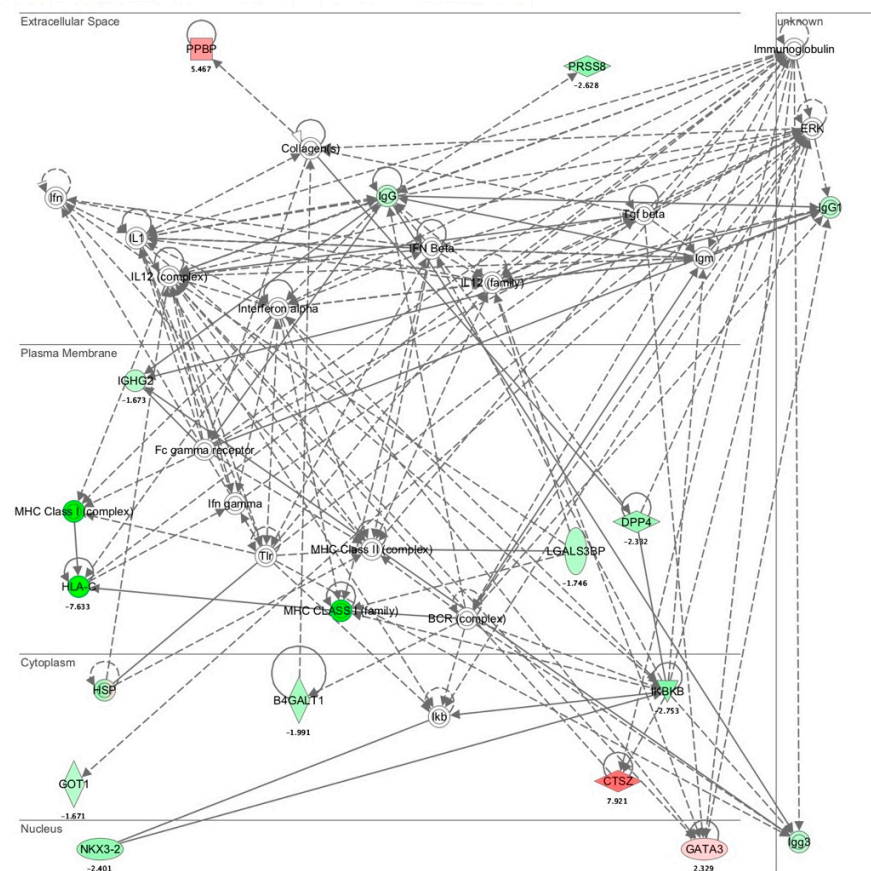


Figure S3:

IPA network 9: cellular movement, hematological system development and function, immune cell trafficking

Functional annotation networks from IPA that show relationships among the genes that in IPA's relational database are related to cellular movement, hematological system development and function, and immune cell trafficking.

Solid lines indicated a direct interaction between proteins, while dotted lines indicate an indirect association between two proteins.

Proteins upregulated in the BALF dataset are shaded in red and proteins downregulated in the BALF dataset are shaded in green. The darker shading to lighter shading corresponds to decreasing expression intensity.

IPA=Ingenuity Pathway Analysis, BALF= Bronchoalveolar Lavage Fluid

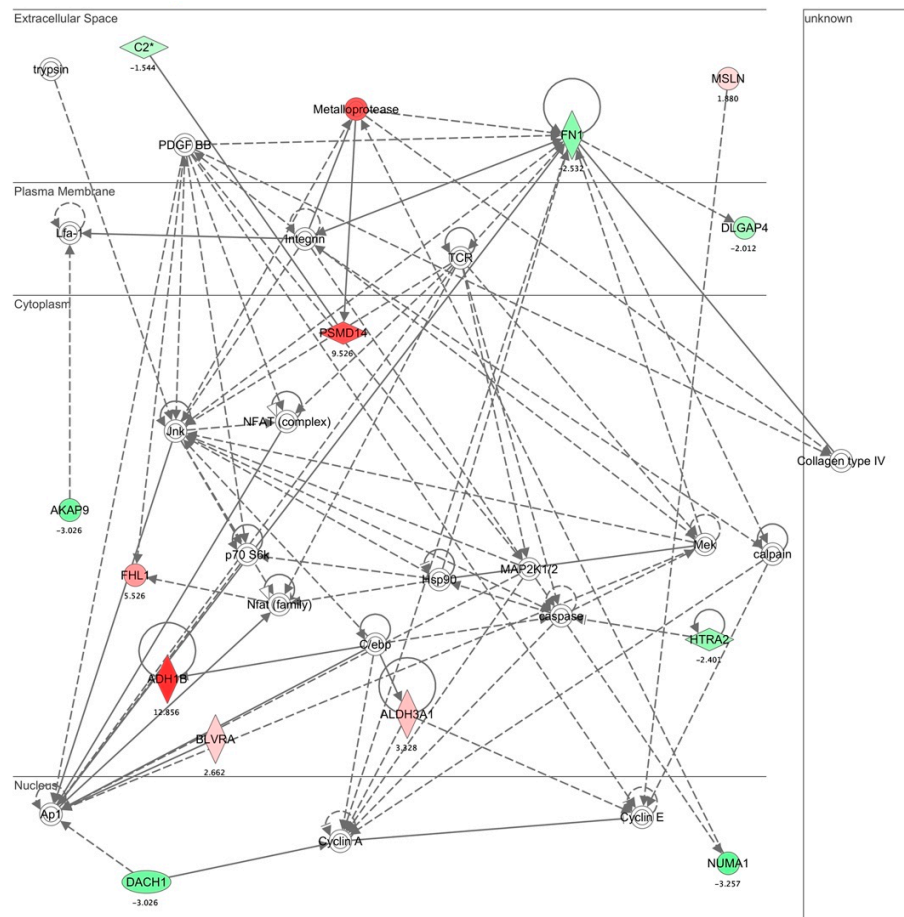


Figure S4:

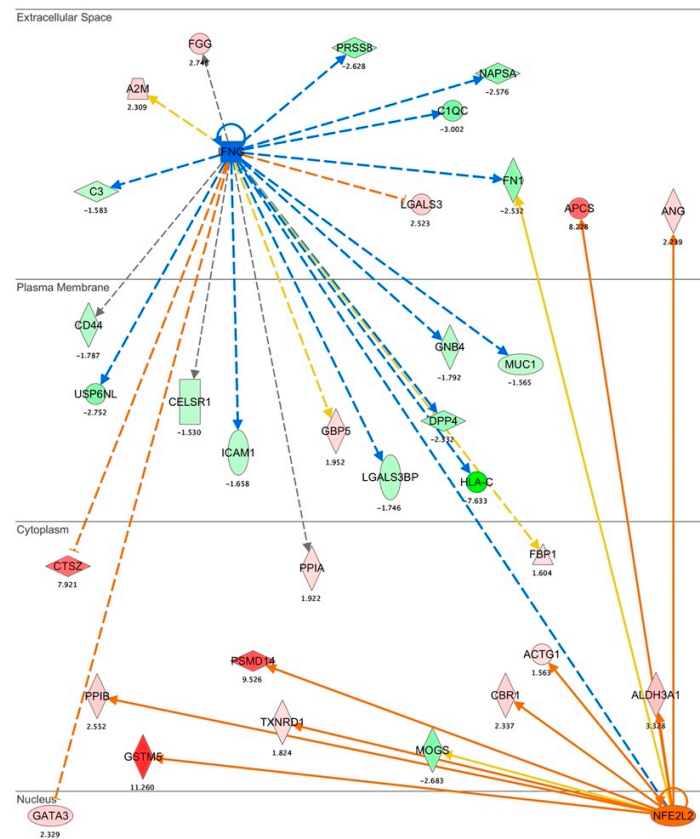
IPA network 11: cell cycle, visual system development and function, hair and skin development and function

Functional annotation networks from IPA that show relationships among the genes that in IPA's relational database are related to cell cycle, visual system development and function, hair and skin development and function.

Solid lines indicated a direct interaction between proteins, while dotted lines indicate an indirect association between two proteins.

Proteins upregulated in the BALF dataset are shaded in red and proteins downregulated in the BALF dataset are shaded in green. The darker shading to lighter shading corresponds to decreasing expression intensity.

IPA=Ingenuity Pathway Analysis, BALF= Bronchoalveolar Lavage Fluid



unknown

Figure S5:

IPA network putative upstream regulators

Putative upstream regulators of the proteins that were significantly differentially expressed between the cohorts were associated with a predicted downregulation and upregulation of interferon gamma and nuclear factor erythroid 2-related 2 (NRF2) respectively.

Solid lines indicated a direct interaction between proteins, while dotted lines indicate an indirect association between two proteins.

Proteins upregulated in the BALF dataset and are predicted are shaded in red and proteins downregulated in the BALF dataset are shaded in green. Interferon gamma is shaded in blue to denote a putative downregulation of the protein while NRF2 is shaded in orange to denote a putative upregulation of the protein based on the IPA relational database. The darker shading to lighter shading corresponds to decreasing expression intensity. The lines colored with orange shading correspond to interactions of the upstream regulator leading to increased protein synthesis of the downstream protein. The lines colored with blue shading correspond to interactions of the upstream regulator leading to decreased protein synthesis of the downstream protein. Lines colored with yellow shading indicate a downstream protein expression level that is discordant with the putative interaction from the upstream protein.

IPA=Ingenuity Pathway Analysis, BALF= Bronchoalveolar Lavage Fluid]

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