Supplemental references

S1. Lane,S., Rippon,H.J., and Bishop,A.E. 2007. Stem cells in lung repair and regeneration. *Regen.Med* 2:407-415.

S2. Wada,K., Arita,M., Nakajima,A., Katayama,K., Kudo,C., Kamisaki,Y., and Serhan,C.N. 2006. Leukotriene B4 and lipoxin A4 are regulatory signals for neural stem cell proliferation and differentiation. *FASEB J* 20:1785-1792.

S3. Beane,J., Sebastiani,P., Liu,G., Brody,J.S., Lenburg,M.E., and Spira,A. 2007. Reversible and permanent effects of tobacco smoke exposure on airway epithelial gene expression. *Genome Biol.* 8:R201.

S4. Stevenson,C.S., Docx,C., Webster,R., Battram,C., Hynx,D., Giddings,J., Cooper,P.R., Chakravarty,P., Rahman,I., Marwick,J.A. *et al.* 2007. Comprehensive gene expression profiling of rat lung reveals distinct acute and chronic responses to cigarette smoke inhalation. *Am.J Physiol Lung Cell Mol.Physiol.*

S5. Rawlins,E.L., Ostrowski,L.E., Randell,S.H., and Hogan,B.L. 2007. Inaugural Article: Lung development and repair: Contribution of the ciliated lineage. *Proc.Natl.Acad.Sci.U.S.A* 104:410-417.

S6. Majka,S.M., Beutz,M.A., Hagen,M., Izzo,A.A., Voelkel,N., and Helm,K.M. 2005. Identification of novel resident pulmonary stem cells: form and function of the lung side population. *Stem Cells* 23:1073-1081.

S7. Weibel,E.R. 2006. Morphological quantitation of emphysema: a debate. *J Appl.Physiol* 100:1419-1420.

S8. Teramoto,S. and Ishii,M. 2007. Aging, the aging lung, and senile emphysema are different. *Am.J Respir.Crit Care Med* 175:197-198.

S9. Elias,J.A., Kang,M.J., Crouthers,K., Homer,R., and Lee,C.G. 2006. State of the art. Mechanistic heterogeneity in chronic obstructive pulmonary disease: insights from transgenic mice. *Proc.Am.Thorac.Soc.* 3:494-498.

S10. Anderson,M.M., Hazen,S.L., Hsu,F.F., and Heinecke,J.W. 1997. Human neutrophils employ the myeloperoxidase-hydrogen peroxide-chloride system to convert hydroxy-amino acids into glycolaldehyde, 2-hydroxypropanal, and acrolein. A mechanism for the generation of highly reactive alpha-hydroxy and alpha,beta-unsaturated aldehydes by phagocytes at sites of inflammation. *J Clin.Invest* 99:424-432.

S11. Kamoshita,E., Ikeda,Y., Fujita,M., Amano,H., Oikawa,A., Suzuki,T., Ogawa,Y., Yamashina,S., Azuma,S., Narumiya,S. *et al.* 2006. Recruitment of a prostaglandin

E receptor subtype, EP3-expressing bone marrow cells is crucial in wound-induced angiogenesis. *Am.J Pathol.* 169:1458-1472.

S12. Zentilin,L., Tafuro,S., Zacchigna,S., Arsic,N., Pattarini,L., Sinigaglia,M., and Giacca,M. 2006. Bone marrow mononuclear cells are recruited to the sites of VEGF-induced neovascularization but are not incorporated into the newly formed vessels. *Blood* 107:3546-3554.

S13. Martorana,P.A., Beume,R., Lucattelli,M., Wollin,L., and Lungarella,G. 2005. Roflumilast fully prevents emphysema in mice chronically exposed to cigarette smoke. *Am.J Respir.Crit Care Med* 172:848-853.

S14. Wright,J.L. and Sun,J.P. 1994. Effect of smoking cessation on pulmonary and cardiovascular function and structure: analysis of guinea pig model. *J Appl.Physiol* 76:2163-2168.

S15. Tabak,C., Smit,H.A., Heederik,D., Ocke,M.C., and Kromhout,D. 2001. Diet and chronic obstructive pulmonary disease: independent beneficial effects of fruits, whole grains, and alcohol (the MORGEN study). *Clin.Exp.Allergy* 31:747-755.

S16. Machowetz,A., Poulsen,H.E., Gruendel,S., Weimann,A., Fito,M., Marrugat,J., de la,T.R., Salonen,J.T., Nyyssonen,K., Mursu,J. *et al.* 2007. Effect of olive oils on biomarkers of oxidative DNA stress in Northern and Southern Europeans. *FASEB J* 21:45-52.

S17. Culpitt,S.V., Rogers,D.F., Fenwick,P.S., Shah,P., De Matos,C., Russell,R.E., Barnes,P.J., and Donnelly,L.E. 2003. Inhibition by red wine extract, resveratrol, of cytokine release by alveolar macrophages in COPD. *Thorax* 58:942-946.

S18. Sharp,D.S., Rodriguez,B.L., Shahar,E., Hwang,L.J., and Burchfiel,C.M. 1994. Fish consumption may limit the damage of smoking on the lung. *Am.J Respir.Crit Care Med* 150:983-987.

S19. Kasagi,S., Seyama,K., Mori,H., Souma,S., Sato,T., Akiyoshi,T., Suganuma,H., and Fukuchi,Y. 2006. Tomato juice prevents senescence-accelerated mouse P1 strain from developing emphysema induced by chronic exposure to tobacco smoke. *Am.J Physiol Lung Cell Mol.Physiol* 290:L396-L404.

S20. Lee,J.H., Lee,D.S., Kim,E.K., Choe,K.H., Oh,Y.M., Shim,T.S., Kim,S.E., Lee,Y.S., and Lee,S.D. 2005. Simvastatin inhibits cigarette smoking-induced emphysema and pulmonary hypertension in rat lungs. *Am.J Respir.Crit Care Med* 172:987-993.

S21. Mancini,G.B., Etminan,M., Zhang,B., Levesque,L.E., FitzGerald,J.M., and Brophy,J.M. 2006. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am.Coll.Cardiol.* 47:2554-2560.

S22. Bry,K., Whitsett,J.A., and Lappalainen,U. 2007. IL-1beta Disrupts Postnatal Lung Morphogenesis in the Mouse. *Am.J Respir.Cell Mol.Biol.* 36:32-42.

S23. Lappalainen,U., Whitsett,J.A., Wert,S.E., Tichelaar,J.W., and Bry,K. 2005. Interleukin-1beta causes pulmonary inflammation, emphysema, and airway remodeling in the adult murine lung. *Am.J Respir.Cell Mol.Biol.* 32:311-318.

S24. Zheng,T., Zhu,Z., Wang,Z., Homer,R.J., Ma,B., Riese,R.J., Jr., Chapman,H.A., Jr., Shapiro,S.D., and Elias,J.A. 2000. Inducible targeting of IL-13 to the adult lung causes matrix metalloproteinase- and cathepsin-dependent emphysema. *J Clin.Invest* 106:1081-1093.

S25. Wang,Z., Zheng,T., Zhu,Z., Homer,R.J., Riese,R.J., Chapman,H.A., Jr., Shapiro,S.D., and Elias,J.A. 2000. Interferon gamma induction of pulmonary emphysema in the adult murine lung. *J Exp.Med* 192:1587-1600.

S26. Wert,S.E., Yoshida,M., LeVine,A.M., Ikegami,M., Jones,T., Ross,G.F., Fisher,J.H., Korfhagen,T.R., and Whitsett,J.A. 2000. Increased metalloproteinase activity, oxidant production, and emphysema in surfactant protein D gene-inactivated mice. *Proc.Natl.Acad.Sci.U.S.A* 97:5972-5977.

S27. Leco,K.J., Waterhouse,P., Sanchez,O.H., Gowing,K.L., Poole,A.R., Wakeham,A., Mak,T.W., and Khokha,R. 2001. Spontaneous air space enlargement in the lungs of mice lacking tissue inhibitor of metalloproteinases-3 (TIMP-3). *J Clin.Invest* 108:817-829.

S28. Razzaque,M.S., Sitara,D., Taguchi,T., St Arnaud,R., and Lanske,B. 2006. Premature aging-like phenotype in fibroblast growth factor 23 null mice is a vitamin D-mediated process. *FASEB J* 20:720-722.

S29. Morris,D.G., Huang,X., Kaminski,N., Wang,Y., Shapiro,S.D., Dolganov,G., Glick,A., and Sheppard,D. 2003. Loss of integrin alpha(v)beta6-mediated TGF-beta activation causes Mmp12-dependent emphysema. *Nature* 422:169-173.

S30. Bonniaud,P., Kolb,M., Galt,T., Robertson,J., Robbins,C., Stampfli,M., Lavery,C., Margetts,P.J., Roberts,A.B., and Gauldie,J. 2004. Smad3 null mice develop airspace enlargement and are resistant to TGF-beta-mediated pulmonary fibrosis. *J Immunol.* 173:2099-2108.

S31. Chen,H., Sun,J., Buckley,S., Chen,C., Warburton,D., Wang,X.F., and Shi,W. 2005. Abnormal mouse lung alveolarization caused by Smad3 deficiency is a developmental antecedent of centrilobular emphysema. *Am.J Physiol Lung Cell Mol.Physiol* 288:L683-L691.

S32. Funada,Y., Nishimura,Y., and Yokoyama,M. 2004. Imbalance of matrix metalloproteinase-9 and tissue inhibitor of matrix metalloproteinase-1 is associated with pulmonary emphysema in Klotho mice. *Kobe J Med Sci.* 50:59-67.

S33. Suga,T., Kurabayashi,M., Sando,Y., Ohyama,Y., Maeno,T., Maeno,Y., Aizawa,H., Matsumura,Y., Kuwaki,T., Kuro,O. *et al*. 2000. Disruption of the klotho gene causes pulmonary emphysema in mice. Defect in maintenance of pulmonary integrity during postnatal life. *Am.J Respir.Cell Mol.Biol*. 22:26-33.

S34. Matsuzaki,Y., Xu,Y., Ikegami,M., Besnard,V., Park,K.S., Hull,W.M., Wert,S.E., and Whitsett,J.A. 2006. Stat3 is required for cytoprotection of the respiratory epithelium during adenoviral infection. *J Immunol*. 177:527-537.

S35. Shapiro,S.D., Goldstein,N.M., Houghton,A.M., Kobayashi,D.K., Kelley,D., and Belaaouaj,A. 2003. Neutrophil elastase contributes to cigarette smoke-induced emphysema in mice. *Am.J Pathol*. 163:2329-2335.

S36. Cavarra,E., Bartalesi,B., Lucattelli,M., Fineschi,S., Lunghi,B., Gambelli,F., Ortiz,L.A., Martorana,P.A., and Lungarella,G. 2001. Effects of cigarette smoke in mice with different levels of alpha(1)-proteinase inhibitor and sensitivity to oxidants. *Am.J Respir.Crit Care Med* 164:886-890.

S37. Cantor,J.O., Cerreta,J.M., Ochoa,M., Ma,S., Chow,T., Grunig,G., and Turino,G.M. 2005. Aerosolized hyaluronan limits airspace enlargement in a mouse model of cigarette smoke-induced pulmonary emphysema. *Exp.Lung Res*. 31:417-430.

S38. Iizuka,T., Ishii,Y., Itoh,K., Kiwamoto,T., Kimura,T., Matsuno,Y., Morishima,Y., Hegab,A.E., Homma,S., Nomura,A. *et al*. 2005. Nrf2-deficient mice are highly susceptible to cigarette smoke-induced emphysema. *Genes Cells* 10:1113-1125.

S39. Ishii,Y., Itoh,K., Morishima,Y., Kimura,T., Kiwamoto,T., Iizuka,T., Hegab,A.E., Hosoya,T., Nomura,A., Sakamoto,T. *et al*. 2005. Transcription factor Nrf2 plays a pivotal role in protection against elastase-induced pulmonary inflammation and emphysema. *J Immunol*. 175:6968-6975.

S40. Foronjy,R.F., Mirochnitchenko,O., Propokenko,O., Lemaitre,V., Jia,Y., Inouye,M., Okada,Y., and D'Armiento,J.M. 2006. Superoxide dismutase expression attenuates cigarette smoke- or elastase-generated emphysema in mice. *Am.J Respir.Crit Care Med* 173:623-631.

S41. Shinohara,T., Kaneko,T., Nagashima,Y., Ueda,A., Tagawa,A., and Ishigatsubo,Y. 2005. Adenovirus-mediated transfer and overexpression of heme oxygenase 1 cDNA in lungs attenuates elastase-induced pulmonary emphysema in mice. *Hum.Gene Ther*. 16:318-327.

S42. Churg,A., Wang,R.D., Tai,H., Wang,X., Xie,C., and Wright,J.L. 2004. Tumor necrosis factor-alpha drives 70% of cigarette smoke-induced emphysema in the mouse. *Am.J Respir.Crit Care Med* 170:492-498.

S43. D'hulst,A.I., Bracke,K.R., Maes,T., De Bleecker,J.L., Pauwels,R.A., Joos,G.F., and Brusselle,G.G. 2006. Role of tumour necrosis factor-alpha receptor p75 in

cigarette smoke-induced pulmonary inflammation and emphysema. *Eur.Respir.J* 28:102-112.