Pulmonary Fibrosis:
from pathways & cytokines to molecular therapeutic targets

Melanie Königshoff, MD, PhD

Comprehensive Pneumology Center

Helmholtz Zentrum and University Hospital LMU, Munich, Germany

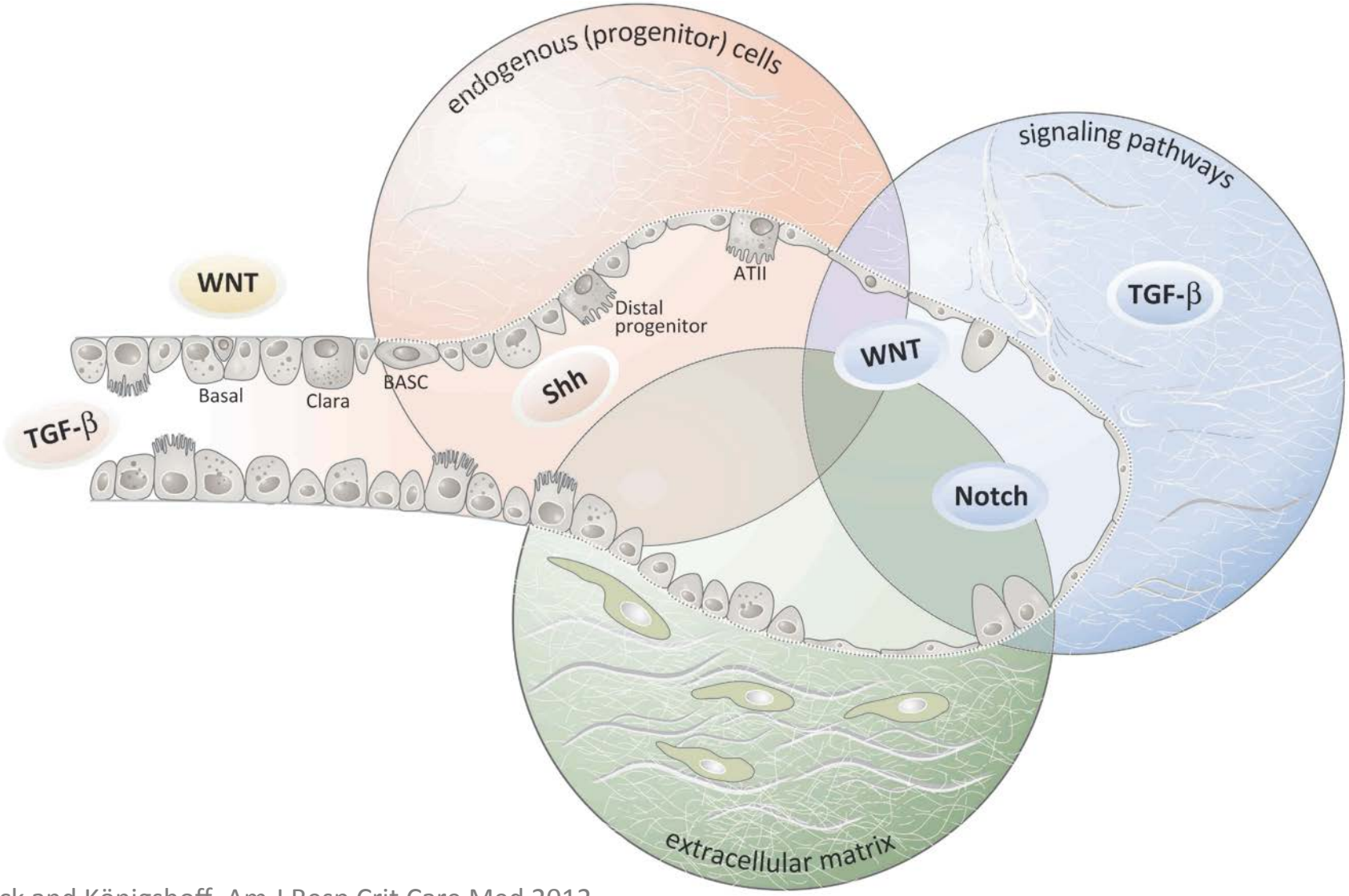
ILD Conference and Course

Prague, Czech Republic

June 21, 2014

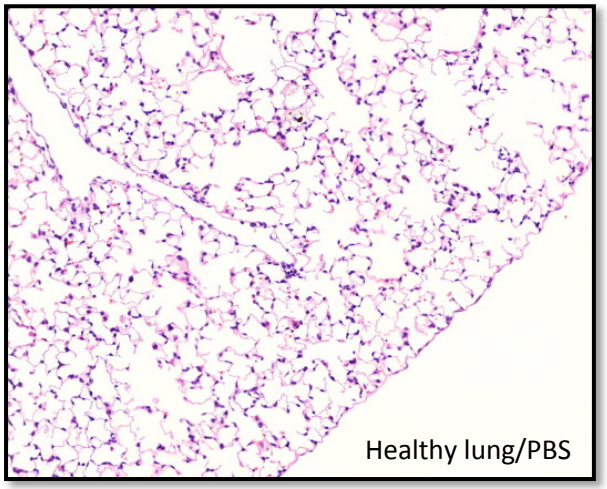
Idiopathic Pulmonary Fibrosis (IPF)

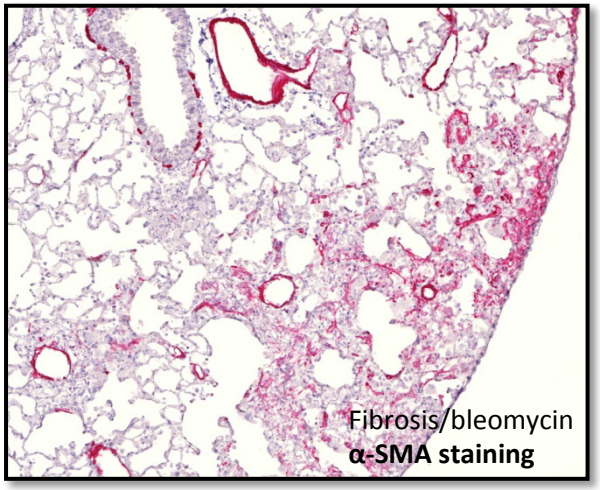
Compartments

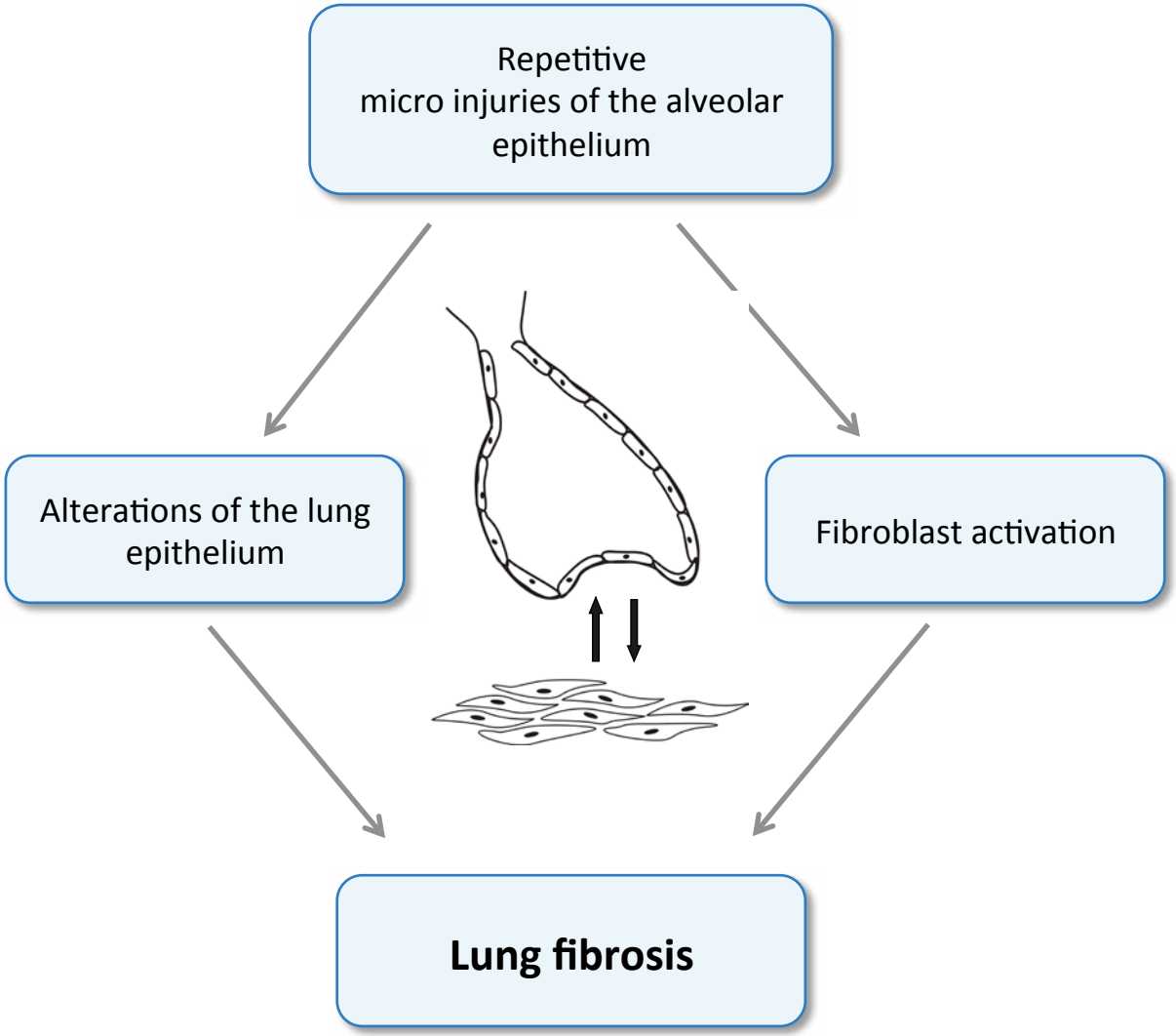


Rock and Königshoff, Am J Resp Crit Care Med 2012

Idiopathic Pulmonary Fibrosis (IPF)





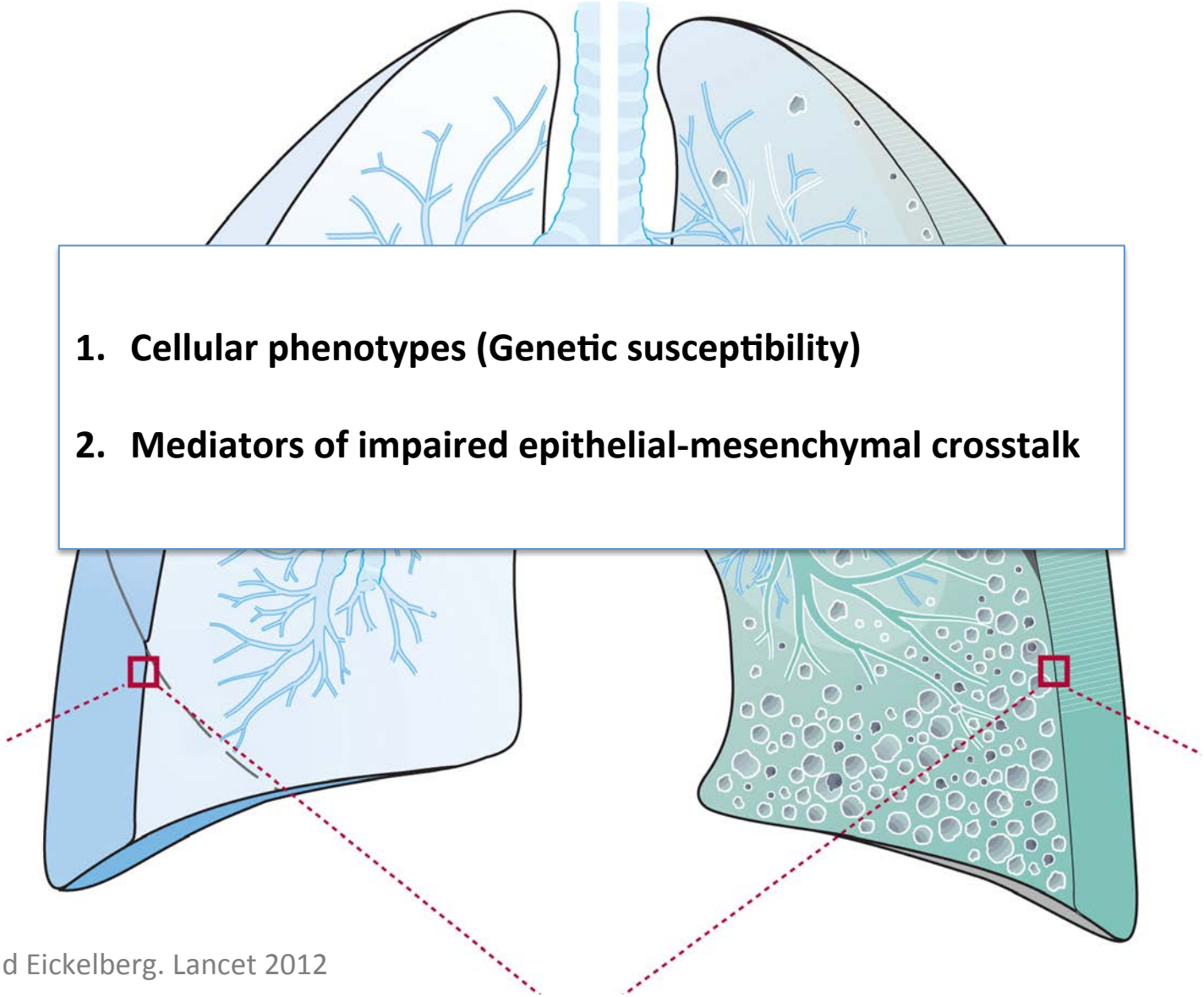


King et al., Lancet 2011
Fernandez et al., Lancet 2012
Selman et al., PLOS Med 2008

CPC Comprehensive Pneumology Center

Idiopathic Pulmonary Fibrosis (IPF)

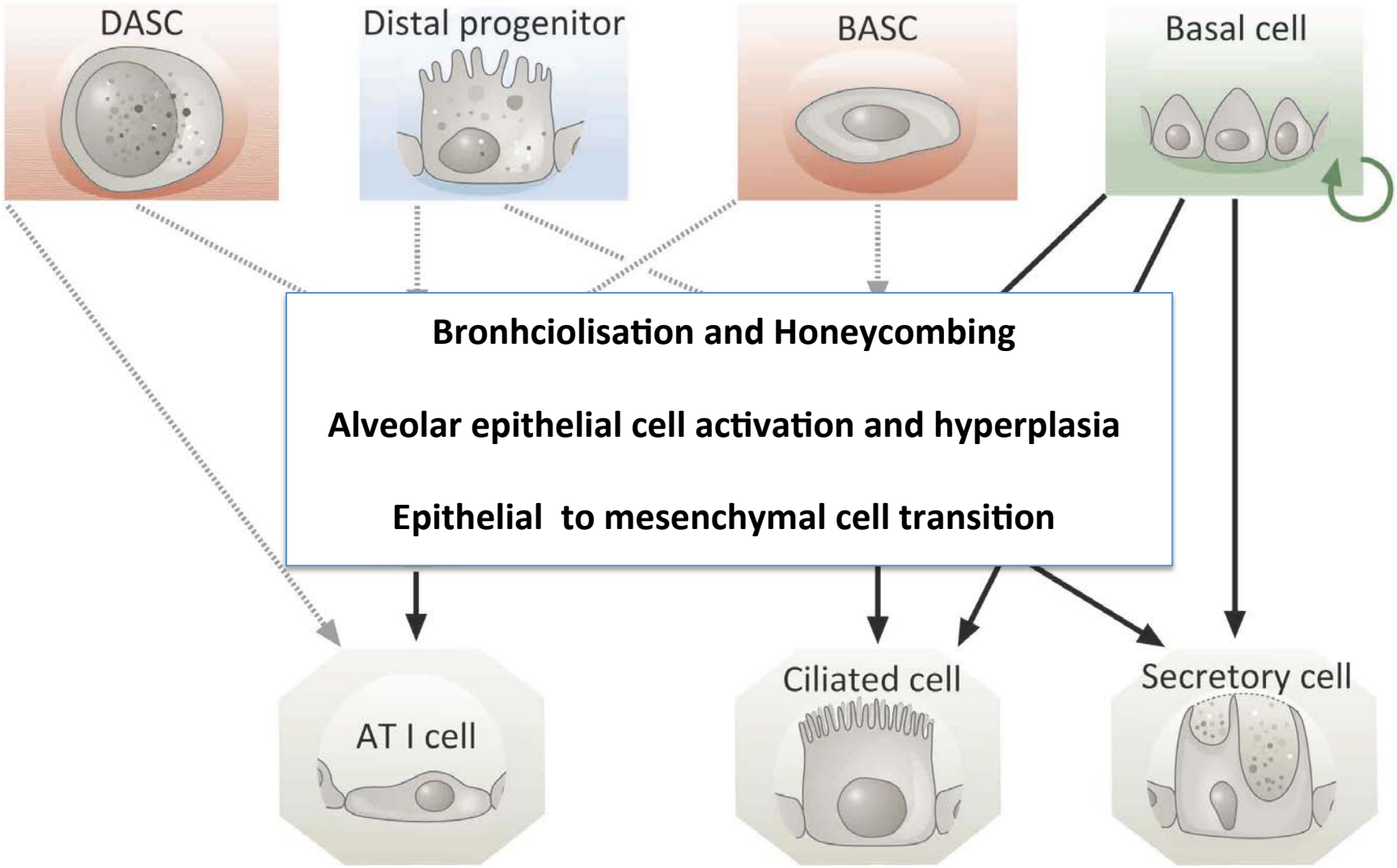
Challenges and questions



1. **Cellular phenotypes (Genetic susceptibility)**
2. **Mediators of impaired epithelial-mesenchymal crosstalk**

Fernandez and Eickelberg. Lancet 2012

The Lung Epithelial Cell Connection



Rock and Königshoff, Am J Resp Crit Care Med 2013

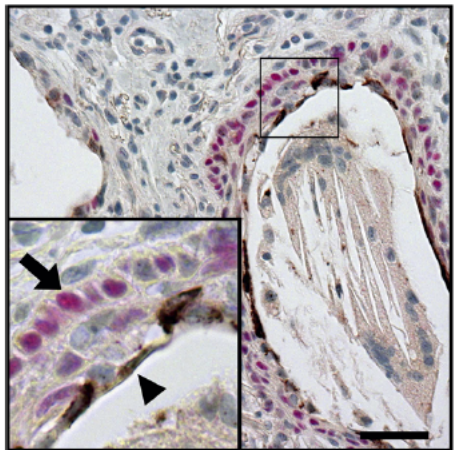
Airway/Bronchial Cell Phenotypes in IPF

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MUC5B Promoter Polymorphism and Interstitial Lung Abnormalities

Gary M. Hunninghake, M.D., M.P.H., Hiroto Hatabu, M.D., Ph.D., Yuka Okajima, M.D., Wei Gao, M.S., Josée Dupuis, Ph.D., Jeanne C. Latourelle, D.Sc., Mizuki Nishino, M.D., Tetsuro Araki, M.D., Oscar E. Zazueta, M.D., Sila Kurugol, Ph.D., James C. Ross, M.S., Raúl San José Estépar, Ph.D., Elissa Murphy, M.S., Mark P. Steele, M.D., James E. Loyd, M.D., Marvin I. Schwarz, M.D., Tasha E. Fingerlin, Ph.D., Ivan O. Rosas, M.D., George R. Washko, M.D., George T. O'Connor, M.D., and David A. Schwartz, M.D.



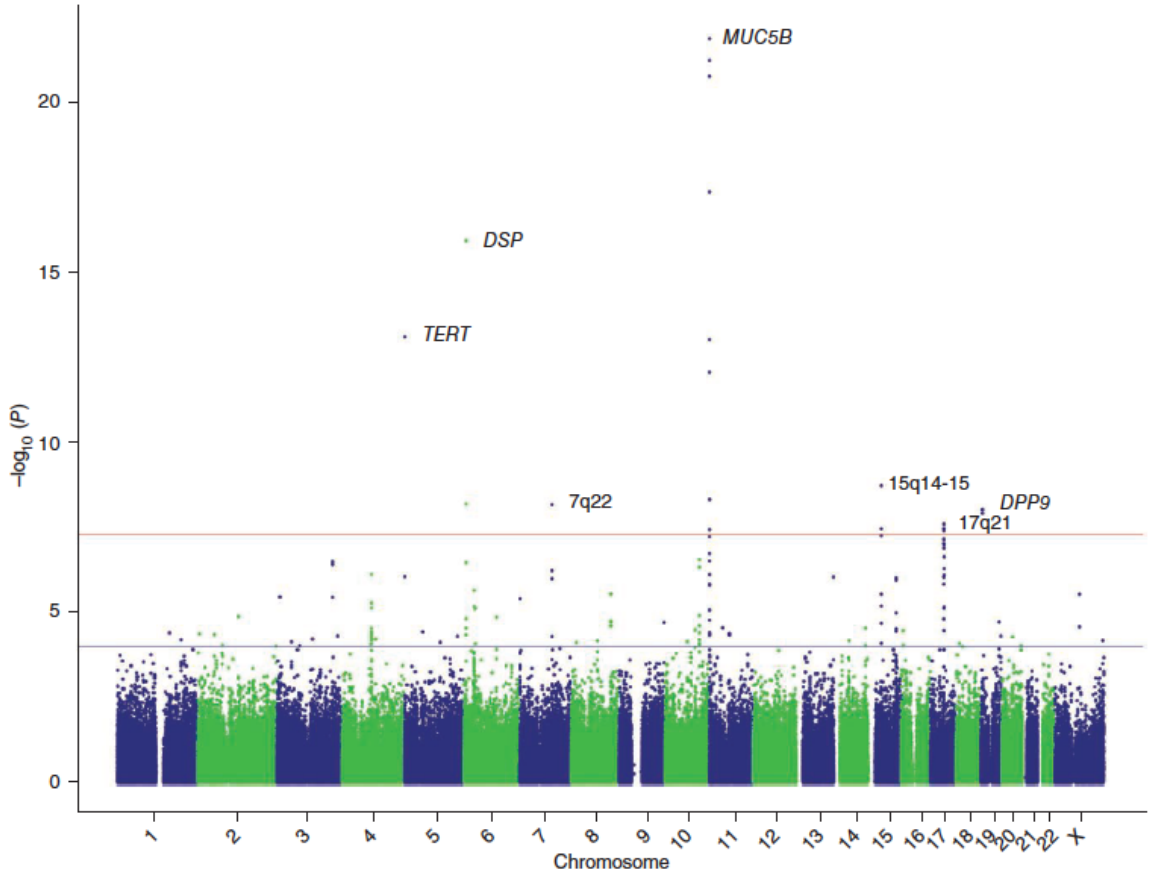
Abnormal respiratory epithelial differentiation programs contribute to the expression of MUC5B and bronchiolisation

Differential expression of cilium genes associated with honeycombing and MUC5B

Plantier et al. Thorax 2013, Yang et al. Thorax 2013

CPC Comprehensive Pneumology Center

Genetic predisposition – MUC5B



Risk allele in 3-4 % of the population

38% of sporadic IPFs
9% controls

Increased MUC5B protein expression

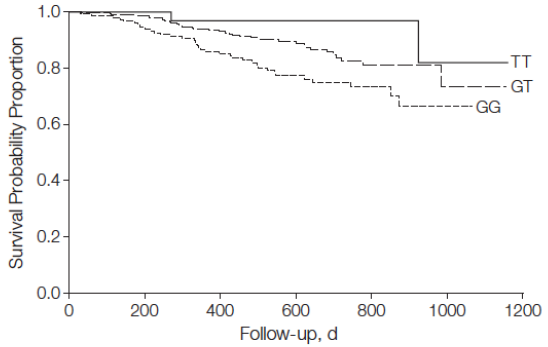
SNP in the MUC5B region – increased risk of pulmonary fibrosis

Fingerlin et al. Nat Genetics 2013

CPC Comprehensive Pneumology Center

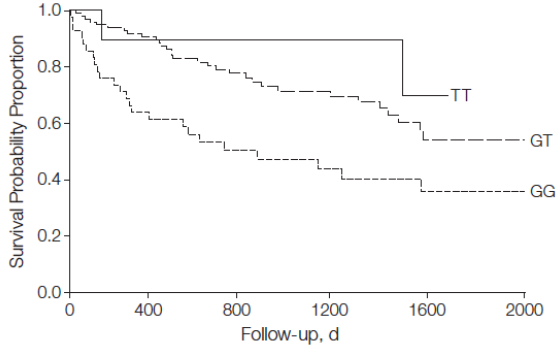
Genetic predisposition – MUC5B

Figure 1. Kaplan-Meier Survival Curves by *MUC5B* Genotypes, INSPIRE Cohort



No. at risk						
TT	31	26	21	11	3	0
GT	255	224	122	55	8	0
GG	140	115	67	36	5	0

Figure 2. Kaplan-Meier Survival Curves by *MUC5B* Genotypes, Chicago Cohort



No. at risk					
TT	7	4	4	1	0
GT	78	47	35	15	1
GG	24	16	10	7	1

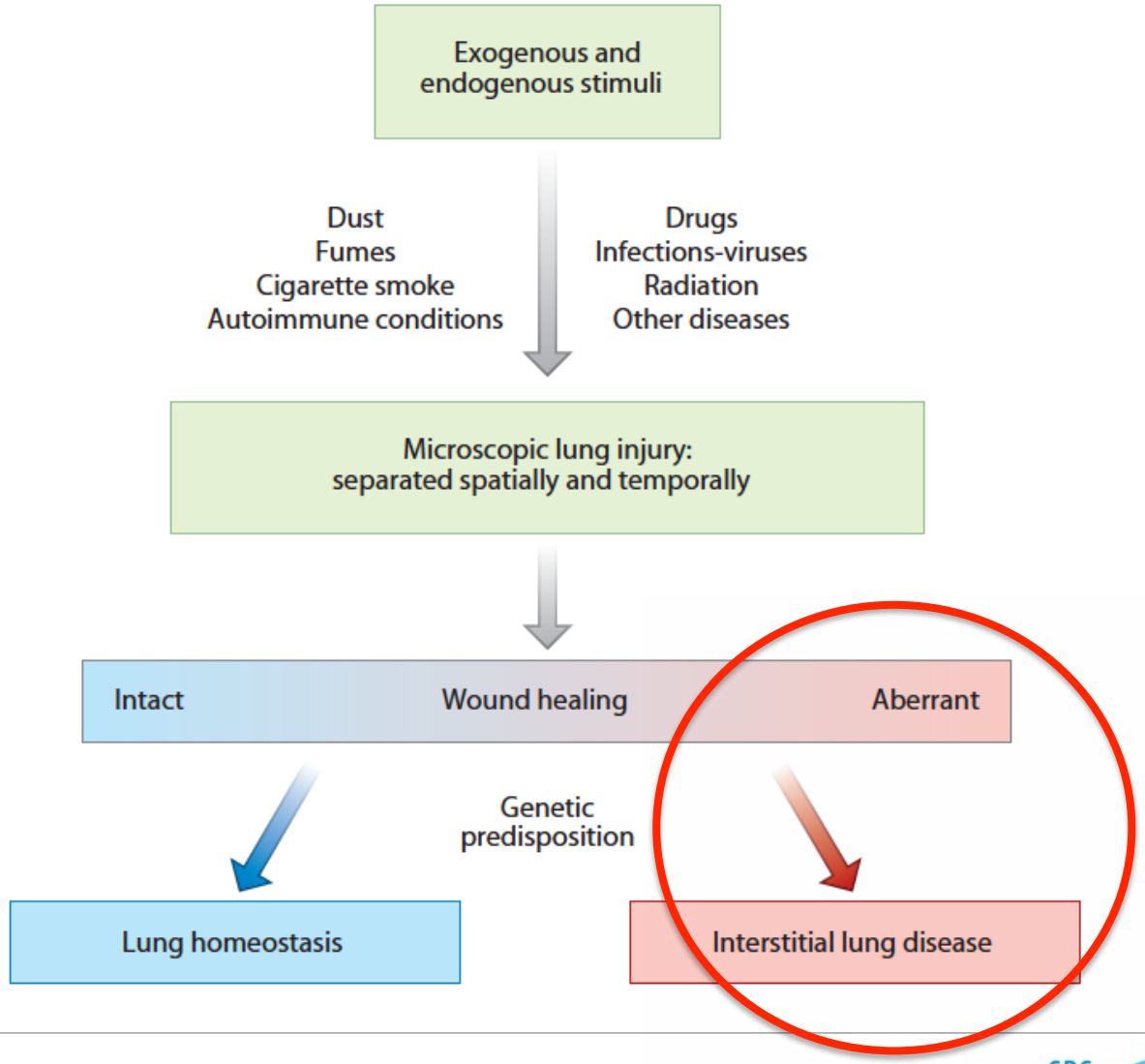
SNP in the MUC5B region – first genetic variant associated with improved survival

→ enhanced mucosal host defense, reduction in infectious complications?

Peljto et al. JAMA 2013, Roy et al. Nature 2014

CPC Comprehensive Pneumology Center

Gene X Environment Interaction

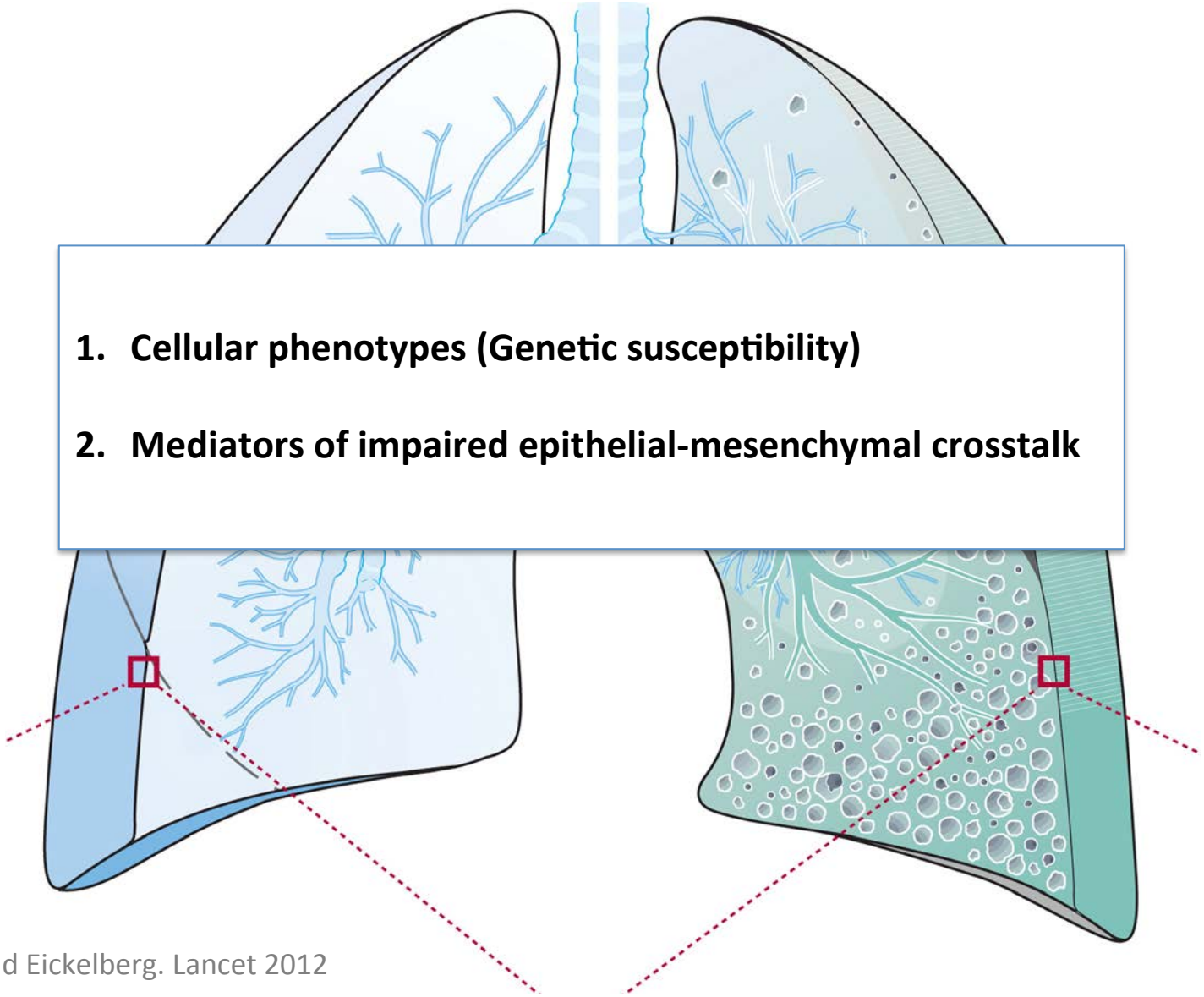


Steele and Schwartz, Annu. Rev. Med. 2013. 64:265–76

CPC Comprehensive Pneumology Center

Idiopathic Pulmonary Fibrosis (IPF)

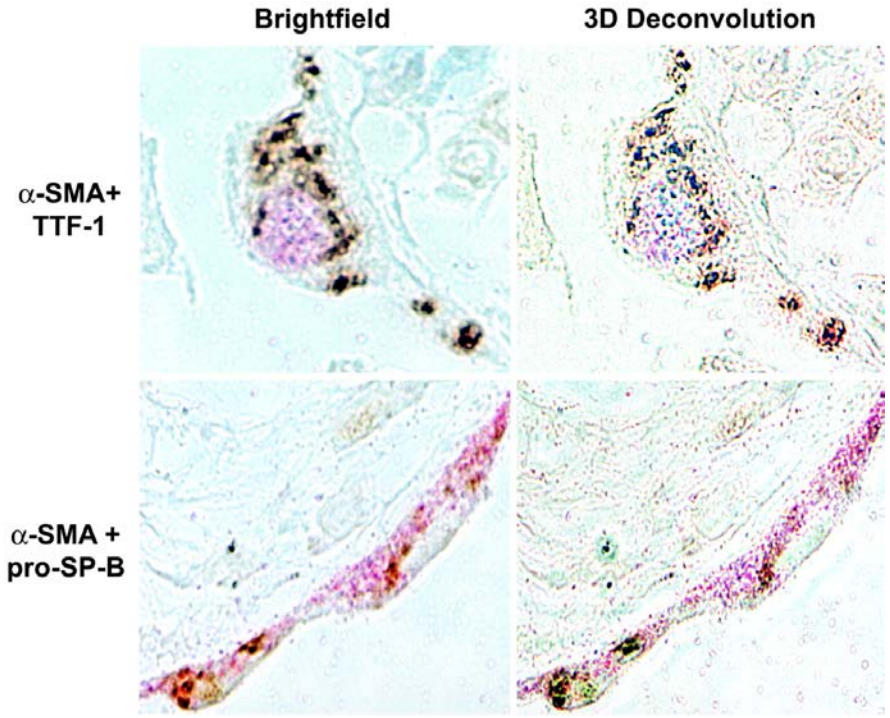
Challenges and questions



1. **Cellular phenotypes (Genetic susceptibility)**
2. **Mediators of impaired epithelial-mesenchymal crosstalk**

Fernandez and Eickelberg. Lancet 2012

Cellular plasticity – EMT ?



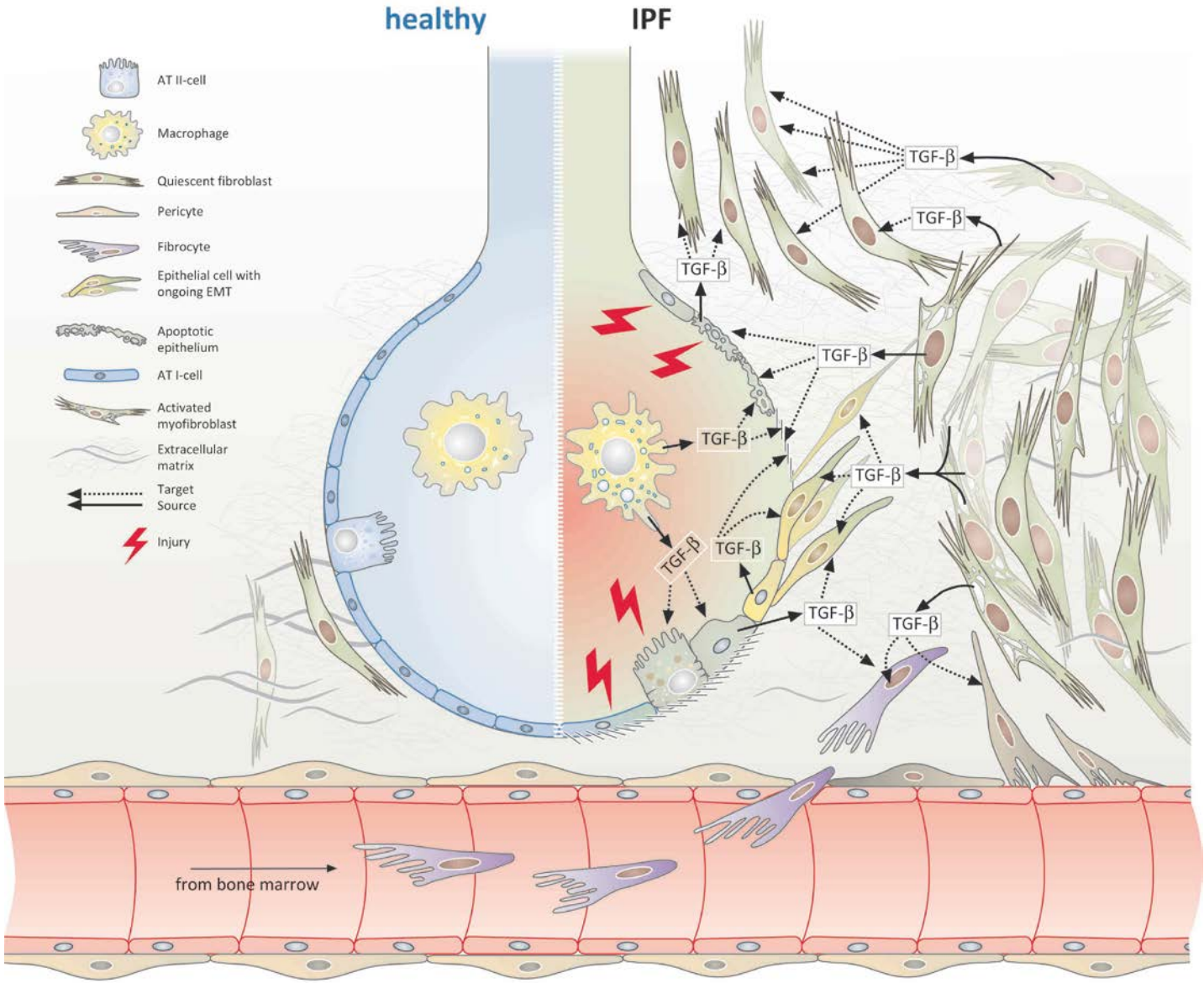
Alveolar epithelial cells

- **gain mesenchymal properties**
- **produce ECM molecules, such as col1**
- **co-express epithelial cell lineage marker, such as ATI and ATII cell marke**

Lung epithelial cell reprogramming

Willis et al. Am J Pathol 2005, Kim et al. PNAS 2006,
Wheeler et al. Am J Path 2014, Zhou ATS 2014

CPC Comprehensive Pneumology Center



Fernandez and Eickelberg. *Proc. Am Thorac Soc* 2012

CPC Comprehensive Pneumology Center

OPEN ACCESS Freely available online

PLoS MEDICINE

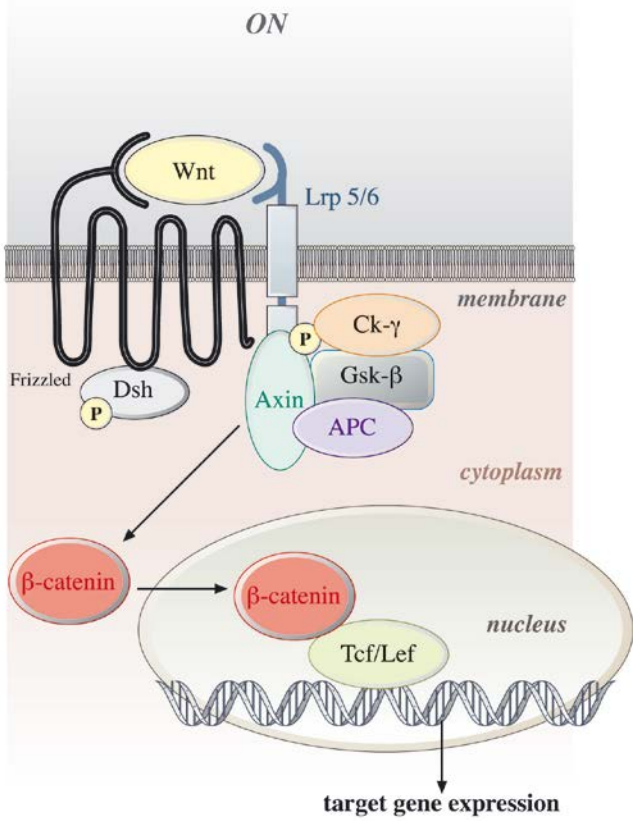
Research in Translation

Idiopathic Pulmonary Fibrosis: Aberrant Recapitulation of Developmental Programs?

Moisés Selman*, Annie Pardo, Naftali Kaminski

Pardo et al. PLoS Med. 2008, Selman et al. AJRCCM 2006,
Yang et al. AJRCCM 2007

Wnt/β-catenin signaling in the lung



Wnt/β-catenin signaling is involved in lung development

Goss et al. Dev Cell. 2009, Harris-Johnson et al. PNAS 2009, Cardoso WV. Development 2006, Shu W. et al. Developmental Biology 2005

Wnt signaling regulates stem cell function in the lung

Kim et al. Cell 2005, Stripp et al. AJRCMB 2006,, Mou et al. Cell Stem Cell 2012,Paxson et al. Stem Cells Dev. 2013, Carraro et al. Development. 2014, Huang et al. Nat Biotechnol. 2014

Wnt signaling is altered during aging

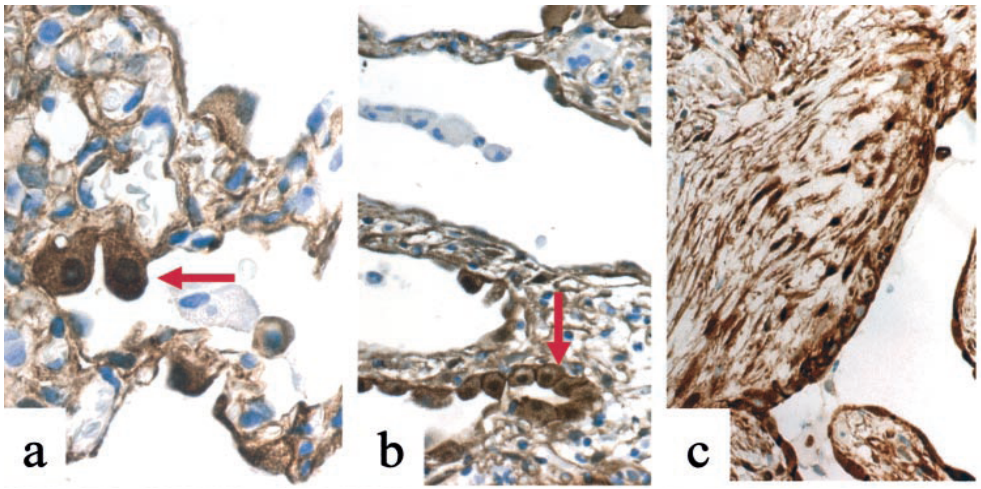
Liu et al. Science 2007, Castilho et al. Cell Stem Cell 2012, Hoffmayer et al. Science 2012, Lezzerini et al. Biogerontology 2013

Wnt/β-catenin signaling in IPF

American Journal of Pathology, Vol. 162, No. 5, May 2003

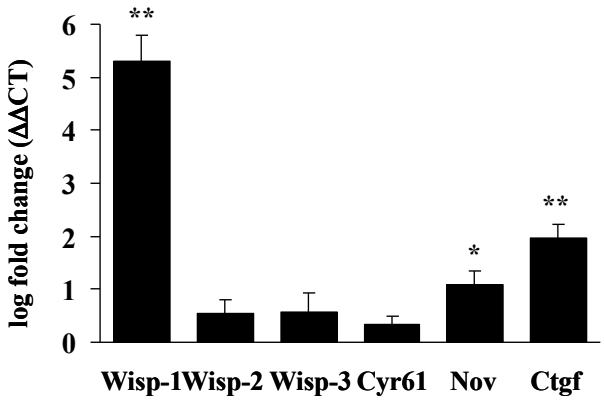
Aberrant Wnt/ β-Catenin Pathway Activation in Idiopathic Pulmonary Fibrosis

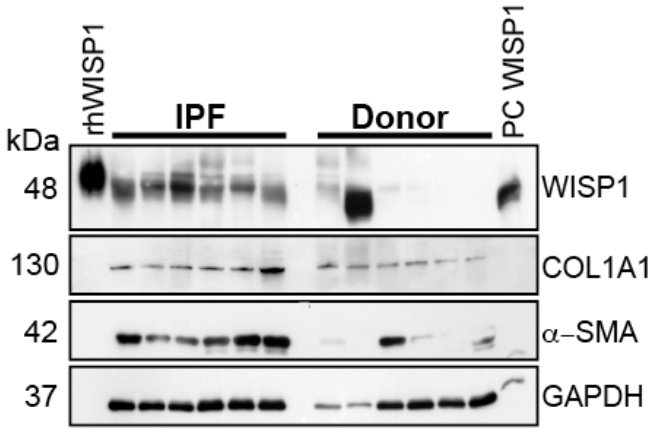
Marco Chilosi, Venerino Poletti, Alberto Zamò , Maurizio Lestani, Licia Montagna, Paola Piccoli, Serena Pedron, Manuela Bertaso, Aldo Scarpa, Bruno Murer, Alessandra Cancellieri, Roberta Maestro, Gianpietro Semenzato and Claudio Doglioni

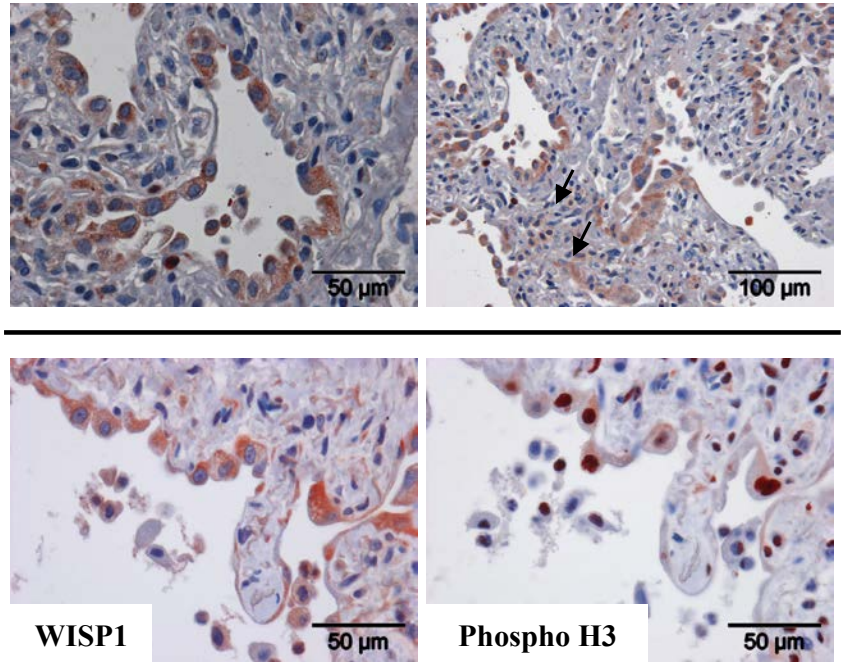


„... Chilosi and colleagues report that the Wnt signal transduction pathway is aberrantly activated in IPF.“

Altered expression of the Wnt target gene WISP1





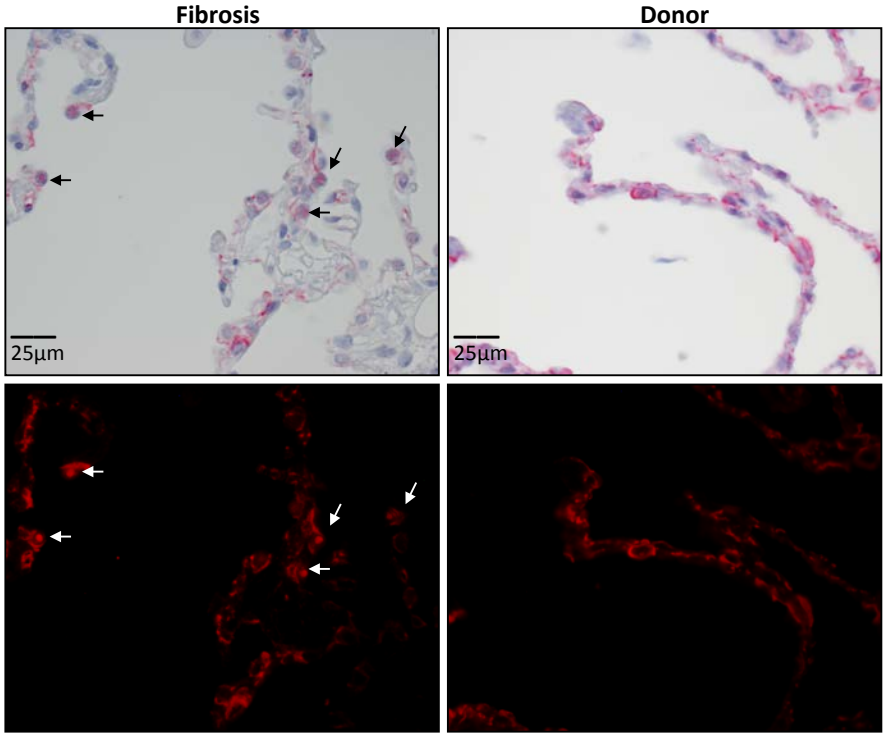


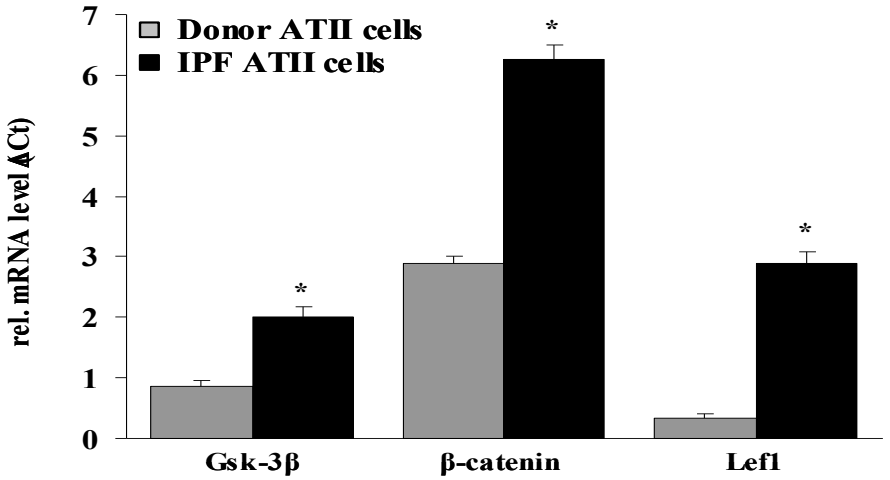
Wnt-induced signalling protein (WISP1) 1 is a Wnt target gene and CCN family member

Königshoff et al., J Clin Invest. 2009, Xu et al. Genes Dev. 2000,
Berschneider et al. 2014 *in press*

CPC Comprehensive Pneumology Center

Activation of Wnt/β-catenin signaling alveolar epithelial cells

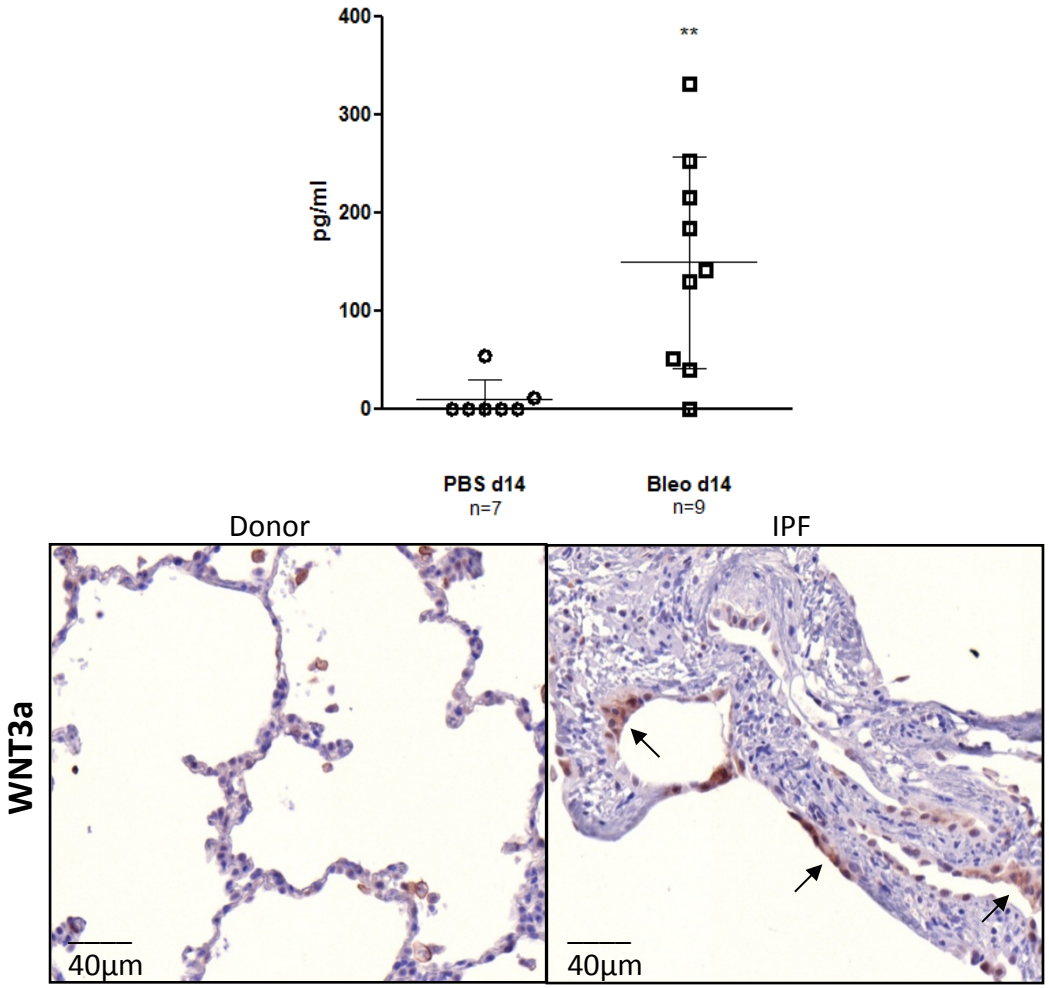




Königshoff et al PLoS One 2009

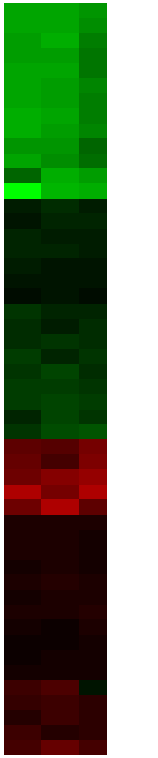
CPC Comprehensive Pneumology Center

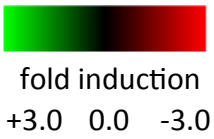
Specific Wnt ligands are increased in pulmonary fibrosis

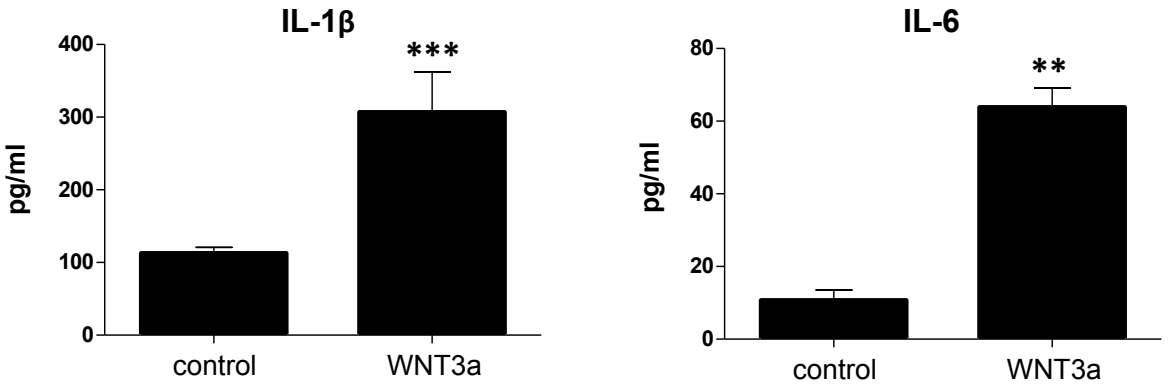


Aumiller et al. AJRCMB 2013

Wnt ligands induce IL-1 and IL-6 in pulmonary fibrosis





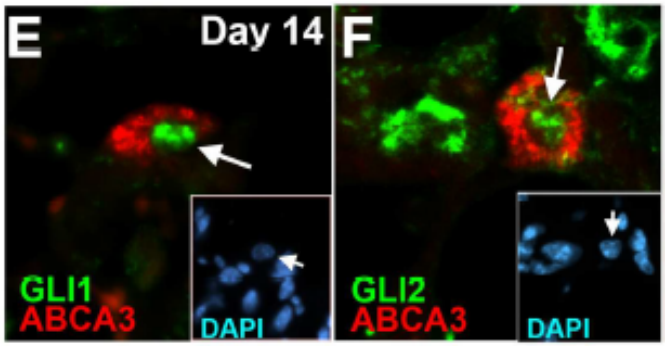


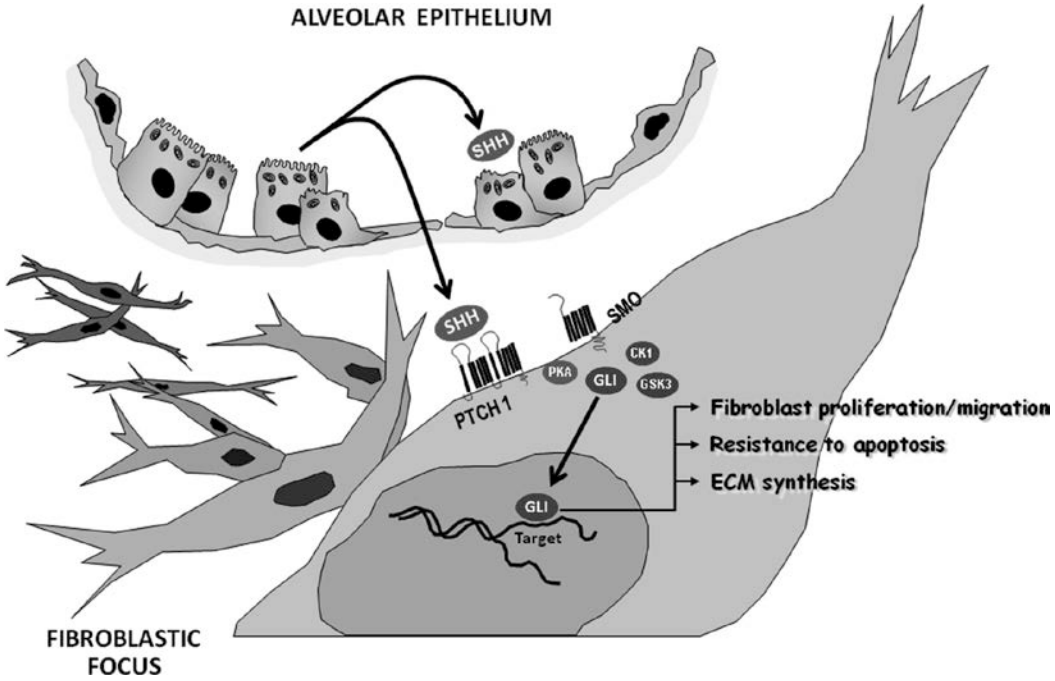
BALF from lungs treated with rhWnt3a in vivo

Link between developmental pathway reactivation and profibrotic cytokine production in IPF

Aumiller et al. AJRCMB 2013

Sonic Hedgehog Signaling in Pulmonary Fibrosis





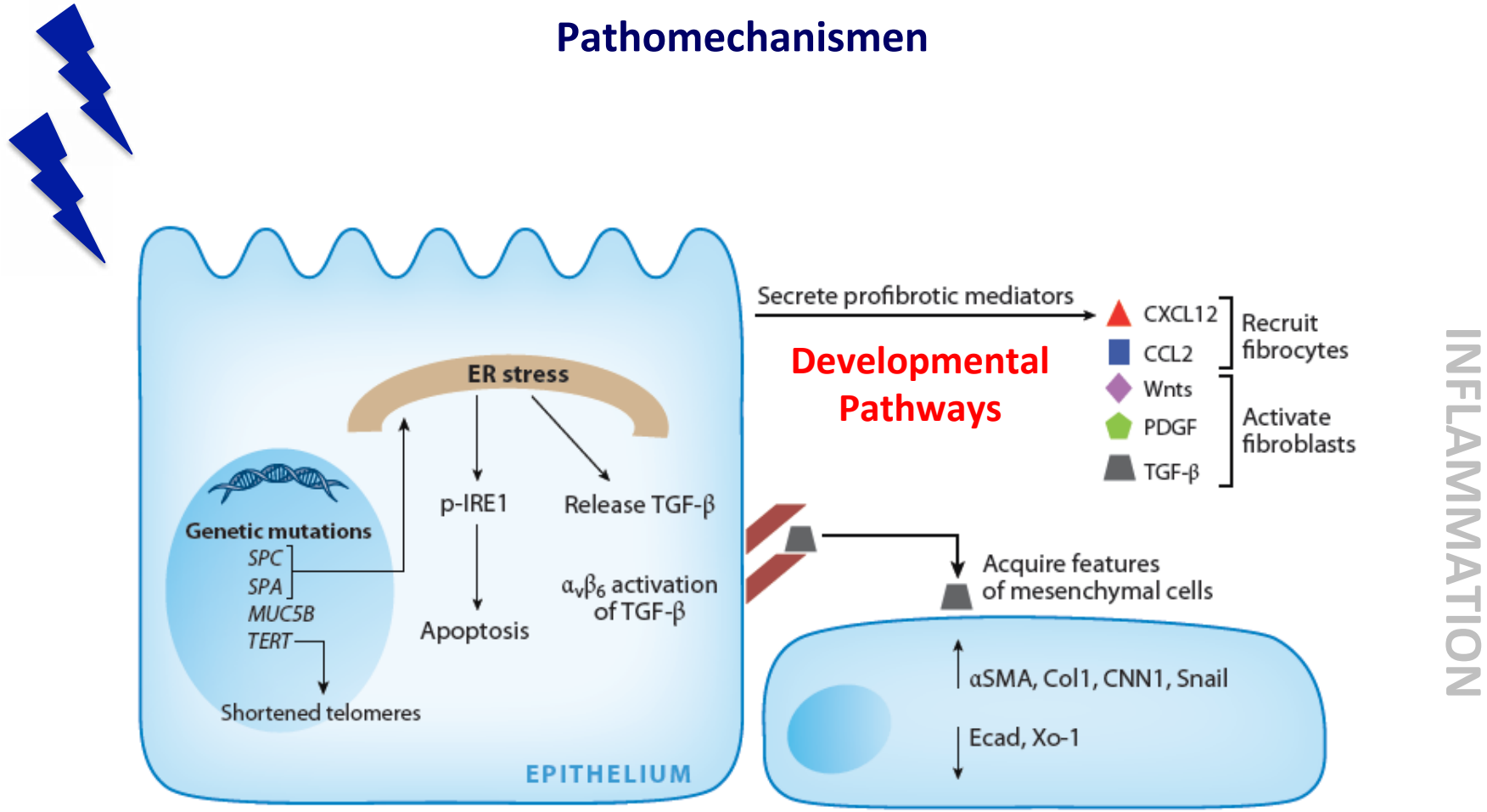
Increased lung expression of the ligand Sonic Hedgehog
Enhanced mRNA expression and nuclear localization of GLI1 and GLI2

Bolanos et al. AJP-Lung 2012, Cigna et al. Am J Pathol. 2012 Farrokhi Moshai et al. AJRCMB 2014

CPC Comprehensive Pneumology Center

Idiopathic Pulmonary Fibrosis (IPF)

Pathomechanismen



Wolters et al Annu Rev Pathol Mech Dis 2013

CPC Comprehensive Pneumology Center

How do we asses the therapeutic suitability of a pathway /cytokine?

1) experimental animal models in vivo

2) human lung tissue ex vivo

Published in final edited form as:
Int J Biochem Cell Biol. 2008 ; 40(3): 362–382.

The bleomycin animal model: a useful tool to investigate treatment options for idiopathic pulmonary fibrosis?

Antje Moeller[§,*], **Kjetil Ask**[#], **David Warburton**[¶], **Jack Gauldie**[#], and **Martin Kolb**[§,#]

§*Department of Medicine, Firestone Institute for Respiratory Health, McMaster University, Hamilton, Ontario, Canada.*

**Medizinische Klinik, Julius-Maximilians-Universität Würzburg, Germany*

#*Department of Pathology and Molecular Medicine, Centre for Gene Therapeutics, McMaster University, Hamilton, Ontario, Canada.*

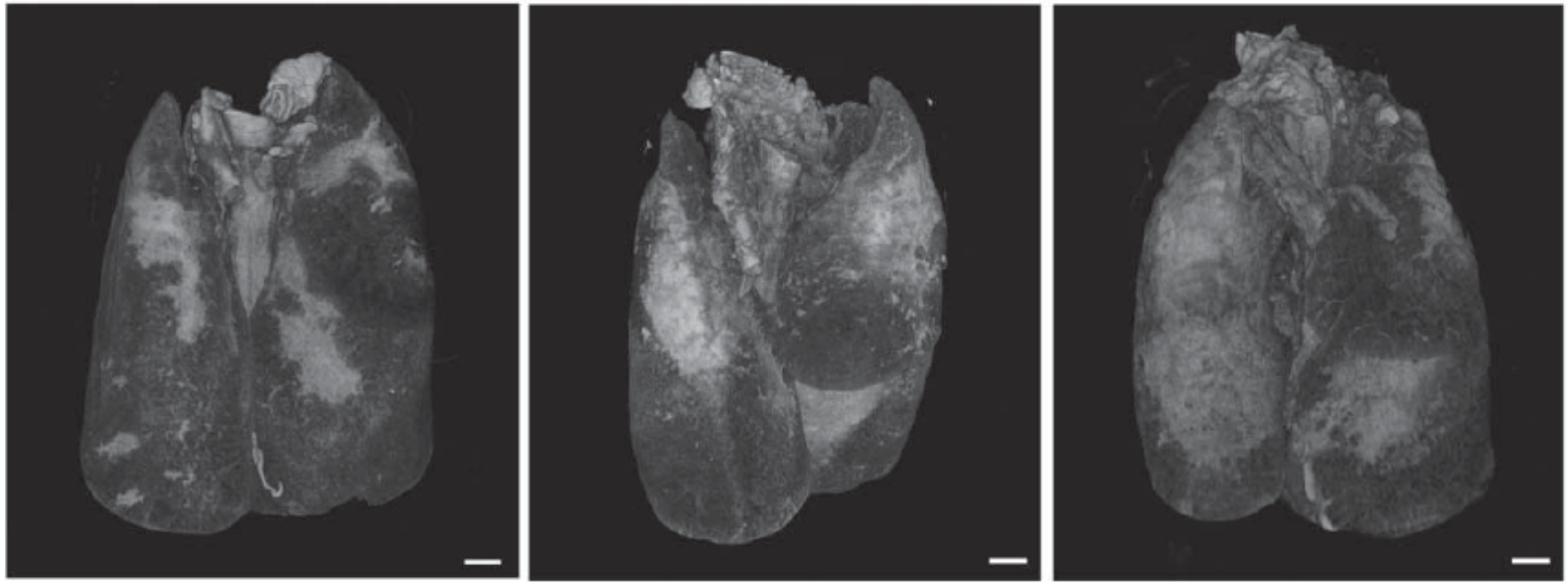
¶*Developmental Biology Program, Saban Research Institute, Children's Hospital Los Angeles, University of Southern California*

The bleomycin model of lung fibrosis

ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASES

Ex vivo micro-computed tomography analysis of bleomycin-induced lung fibrosis for preclinical drug evaluation

Chris J. Scotton[1], Brian Hayes[2], Robert Alexander[1], Arnab Datta[1], Ellen J. Forty[1], Paul F. Mercer[1], Andy Blanchard[2] and Rachel C. Chambers[1]



CPC Comprehensive Pneumology Center

The bleomycin model of lung fibrosis

OPEN ACCESS Freely available online

PLOS ONE

Bleomycin Induces Molecular Changes Directly Relevant to Idiopathic Pulmonary Fibrosis: A Model for "Active" Disease

Ruoqi Peng[1☯], Sriram Sridhar[2☯], Gaurav Tyagi[3], Jonathan E. Phillips[1], Rosario Garrido[3], Paul Harris[1], Lisa Burns[1], Lorena Renteria[1], John Woods[1], Leena Chen[1], John Allard[2], Palanikumar Ravindran[2], Hans Bitter[2], Zhenmin Liang[3], Cory M. Hogaboam[4], Chris Kitson[1], David C. Budd[1], Jay S. Fine[1¤], Carla M.T. Bauer[1], Christopher S. Stevenson[1,5*]

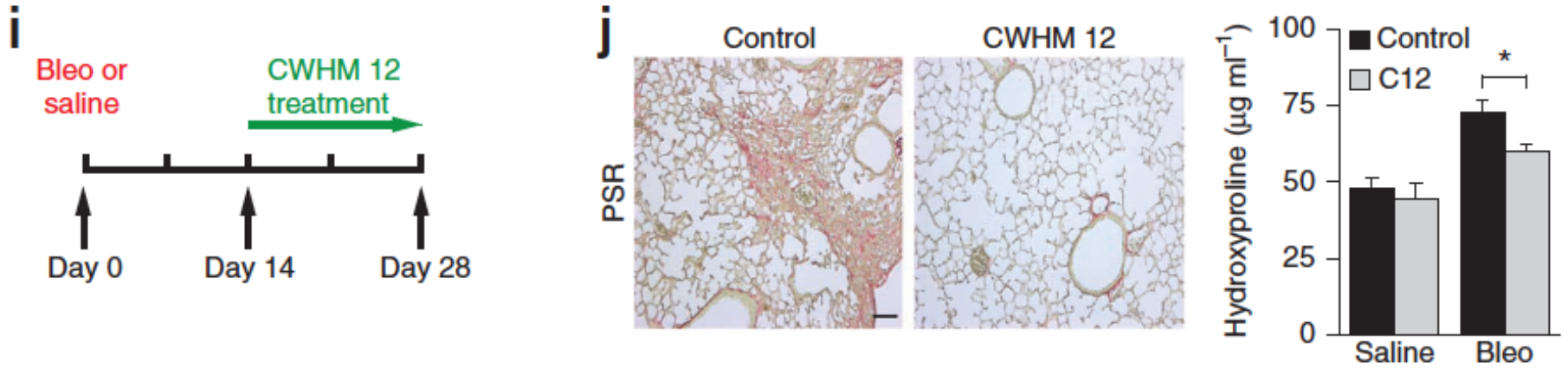
CPC Comprehensive Pneumology Center

nature medicine

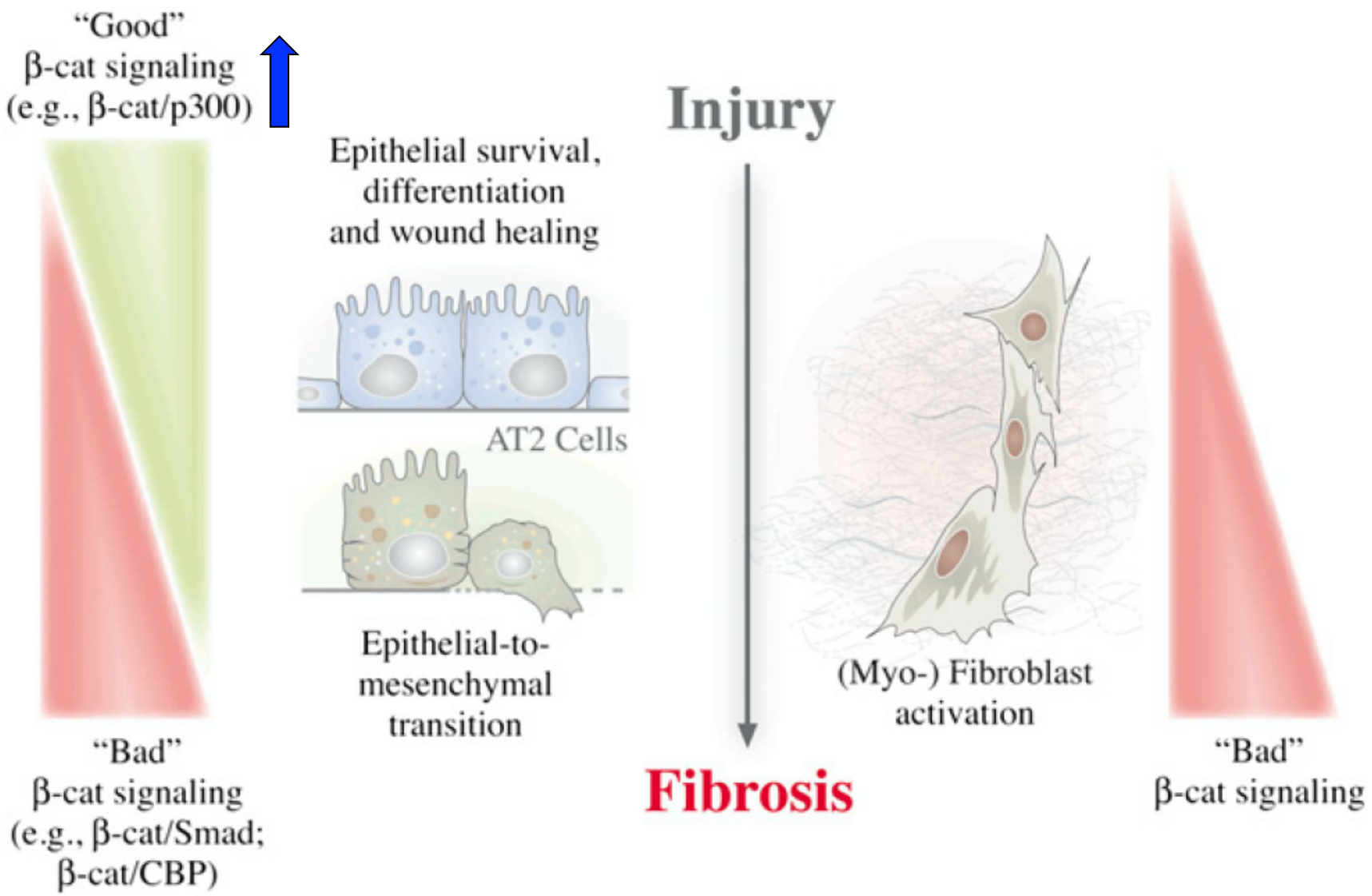
TGF-β and integrin signaling

Targeting of α_v integrin identifies a core molecular pathway that regulates fibrosis in several organs

Neil C Henderson[1,2], Thomas D Arnold[3], Yoshio Katamura[1], Marilyn M Giacomini[1], Juan D Rodriguez[1], Joseph H McCarty[4], Antonella Pellicoro[2], Elisabeth Raschperger[5,6], Christer Betsholtz[5,6], Peter G Ruminski[7], David W Griggs[7], Michael J Prinsen[7], Jacquelyn J Maher[8], John P Iredale[2], Adam Lacy-Hulbert[9], Ralf H Adams[10] & Dean Sheppard[1]



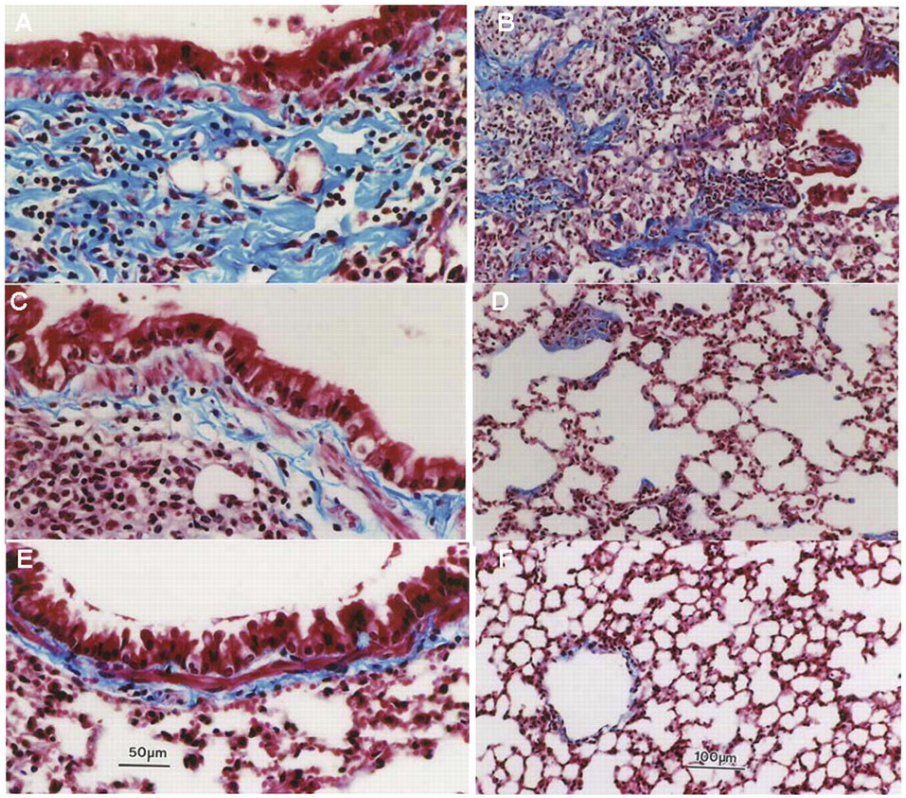
Good *versus* bad β-catenin signaling

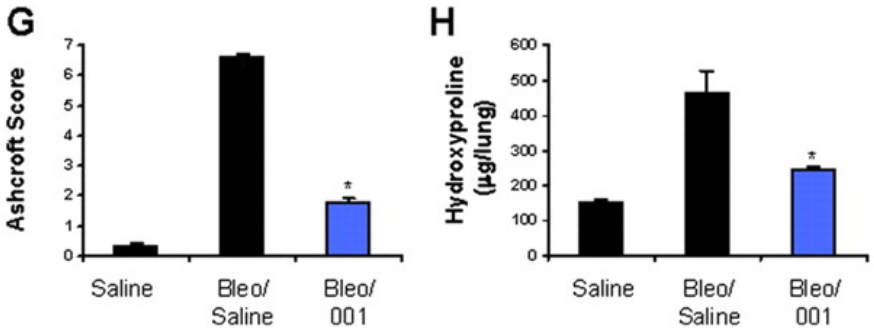


Gottardi and Königshoff, Am J Resp Crit Care Med 2013

CPC Comprehensive Pneumology Center

Inhibition of Wnt and/or β-catenin signaling attenuated experimental lung fibrosis



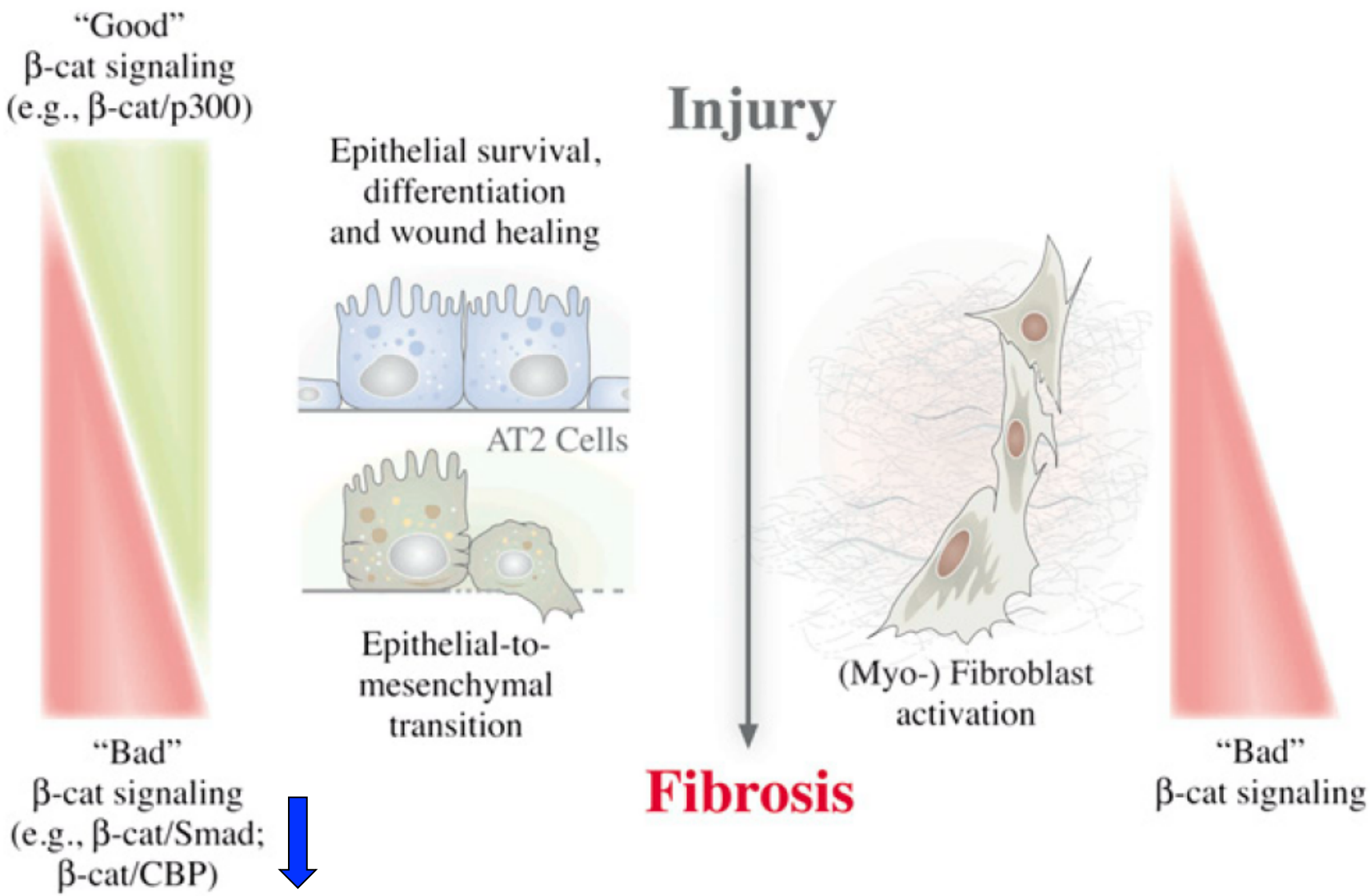


ICG001: p300 interaction

Henderson et al. PNAS 2010, Königshoff et al., J Clin Invest. 2009, Ulsamer et al. J Biol Chem 2012

CPC Comprehensive Pneumology Center

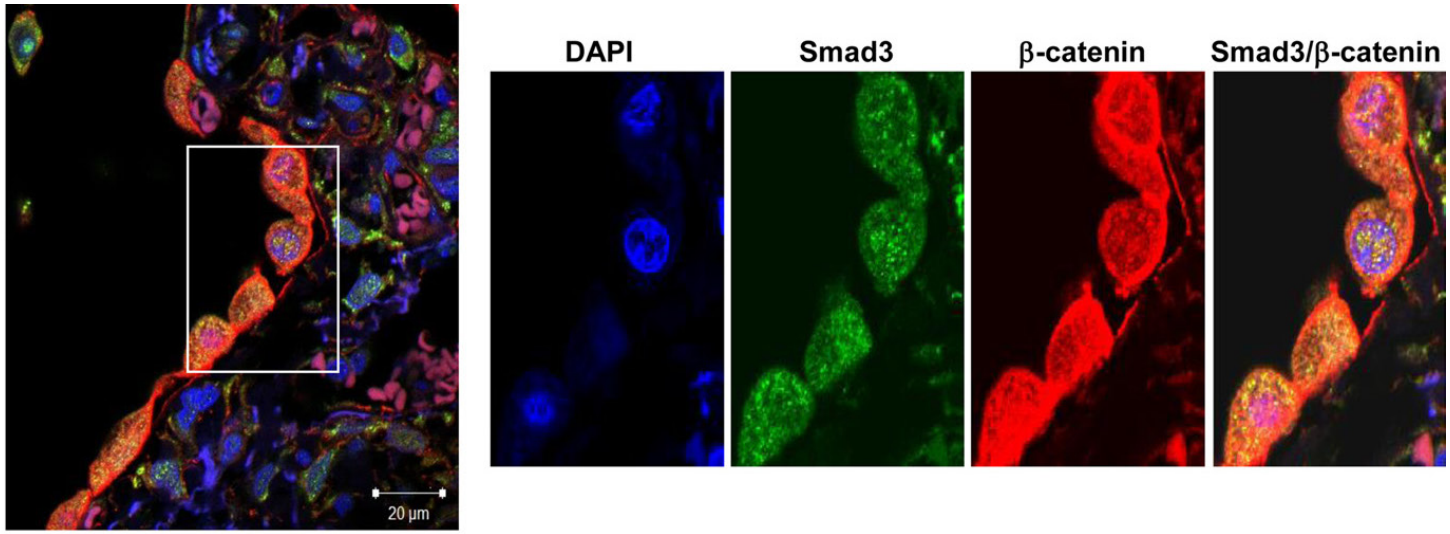
Good versus bad β-catenin signaling



Gottardi and Königshoff, Am J Resp Crit Care Med 2013

CPC Comprehensive Pneumology Center

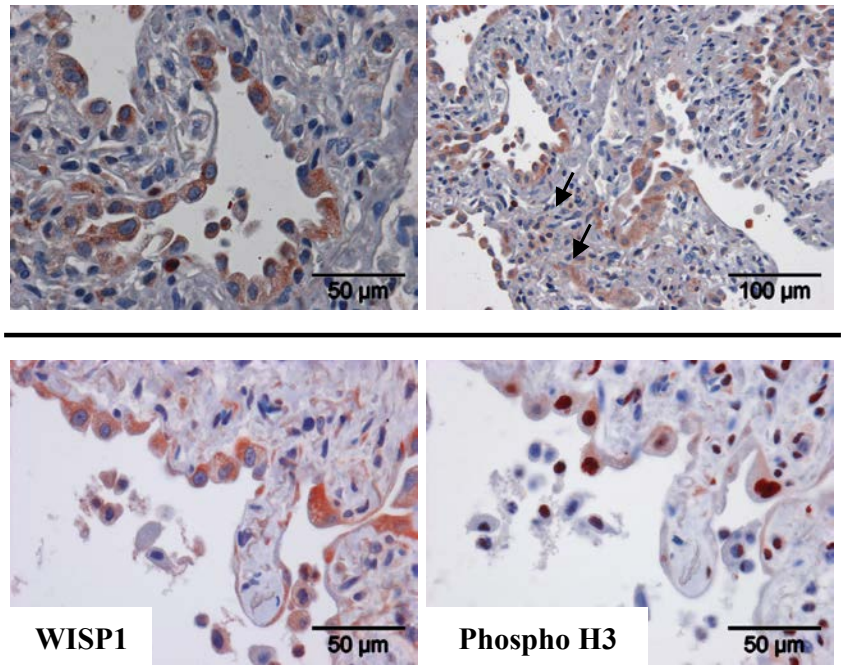
Crosstalk of TGF-β and β-catenin signaling

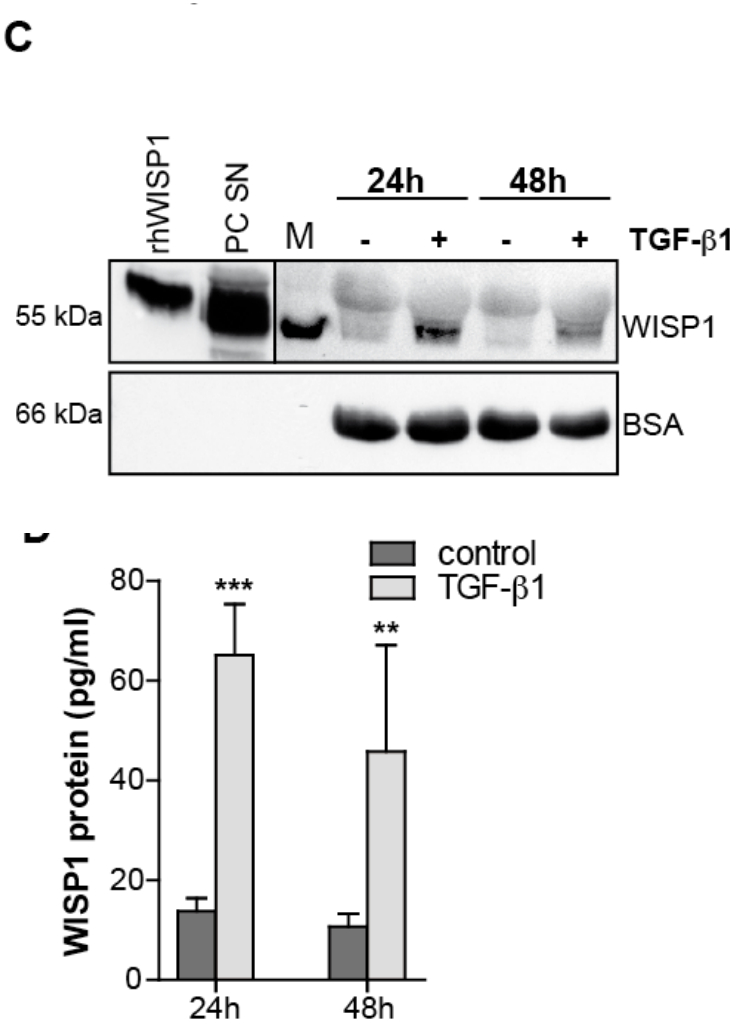


Smad3 and b-catenin co-localization in hyperplastic epithelial cells

Zhou et al. J Biol Chem 2012

WISP1 as a common downstream target of TGF-β and β-catenin signaling

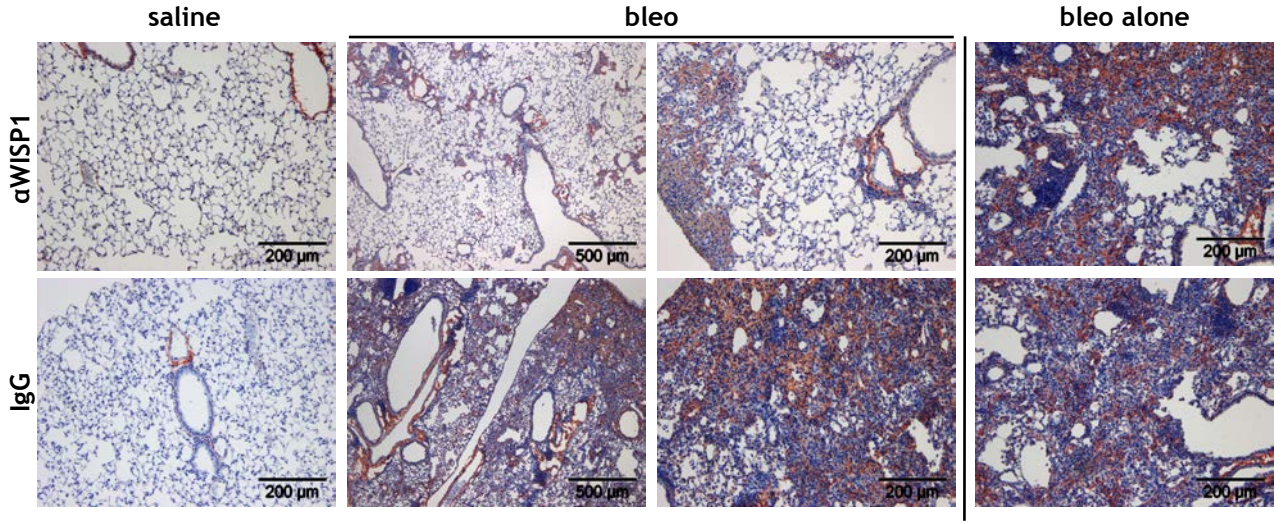




Zhou et al. J Biol Chem 2012, Berschneider et al. IJBCB, *in press*

CPC Comprehensive Pneumology Center

Inhibition of WISP1 signaling attenuated experimental lung fibrosis



- **Active Wnt and TGF signaling in IPF and during development of experimental lung fibrosis**
- **WISP1 represents a common downstream target**

Königshoff et al.,PLoSOne 2008; J Clin Invest. 2009, Flozak et al.
J Biol Chem. 2010., Henderson et al. PNAS 2010

Thank you for your attention

Organizing Committee

Prof. Dr. Oliver Eickelberg
Comprehensive Pneumology Center,
Ludwig Maximilians University Hospital Munich,
Helmholtz Zentrum München

Prof. Dr. Jürgen Behr
Comprehensive Pneumology Center,
Ludwig Maximilians University Hospital Munich,
Asklepios Hospital Munich-Gauting

Dr. Dr. Melanie Königshoff
Comprehensive Pneumology Center,
Ludwig Maximilians University Hospital Munich,
Helmholtz Zentrum München

Supported by an unrestricted educational grant by
Linde AG and Boehringer Ingelheim

and with additional support of

CPC Research School
Lung Biology and Disease

HelmholtzZentrum münchen
German Research Center for Environmental Health

ASKLEPIOS Gemeinsam für Gesundheit

LMU KLINIKUM

General Information & Application

This years Munich International Autumn School (MIAS) will offer a limited number of training positions to clinicians or scientists with a MD or PhD background. Please send your application, including a CV and a list of publications as well as a motivation letter (1/2 page), to info@atemweg-stiftung.de until June 30, 2014. The applications will be reviewed by the MIAS organizing committee. Successful applicants will be notified in due time prior to the conference via email. All costs for the MIAS (including travel and accommodation) are covered by AtemWeg – The Lung Disease Research Foundation. As an additional benefit, AtemWeg also covers the registration fee for the ERS International Congress 2014, which will take place in Munich from September 6 - 10, 2014.

Venue

Comprehensive Pneumology Center (CPC)
Max-Lebsche-Platz 31
81377 München

Contact

AtemWeg – The Lung Disease Research Foundation
Susanne Berki / info@atemweg-stiftung.de
Max-Lebsche-Platz 31 / 81377 München
P +49 (0)89 3187-2196 / F +49 (0)89 3187-4661

AtemWeg
The Lung Disease
Research Foundation

Munich International Autumn School 2014 for Respiratory Medicine

From bench to bedside and back

September 1 - 5, 2014
Munich, Germany

CPC Comprehensive
Pneumology Center