Biomarkers in IPF:

Challenges, Open questions, and strategies

Oliver Eickelberg, MD

Comprehensive Pneumology Center (CPC)

Institute of Lung Biology and Disease (iLBD)

Member, Managing Board of the German Center of Lung Research (DZL)

Helmholtz Zentrum München and Ludwig-Maximilians-Universität München (LMU)

Prague Course of Fibrosing Interstitial Lung Diseases

Saturday, June 21, 2014

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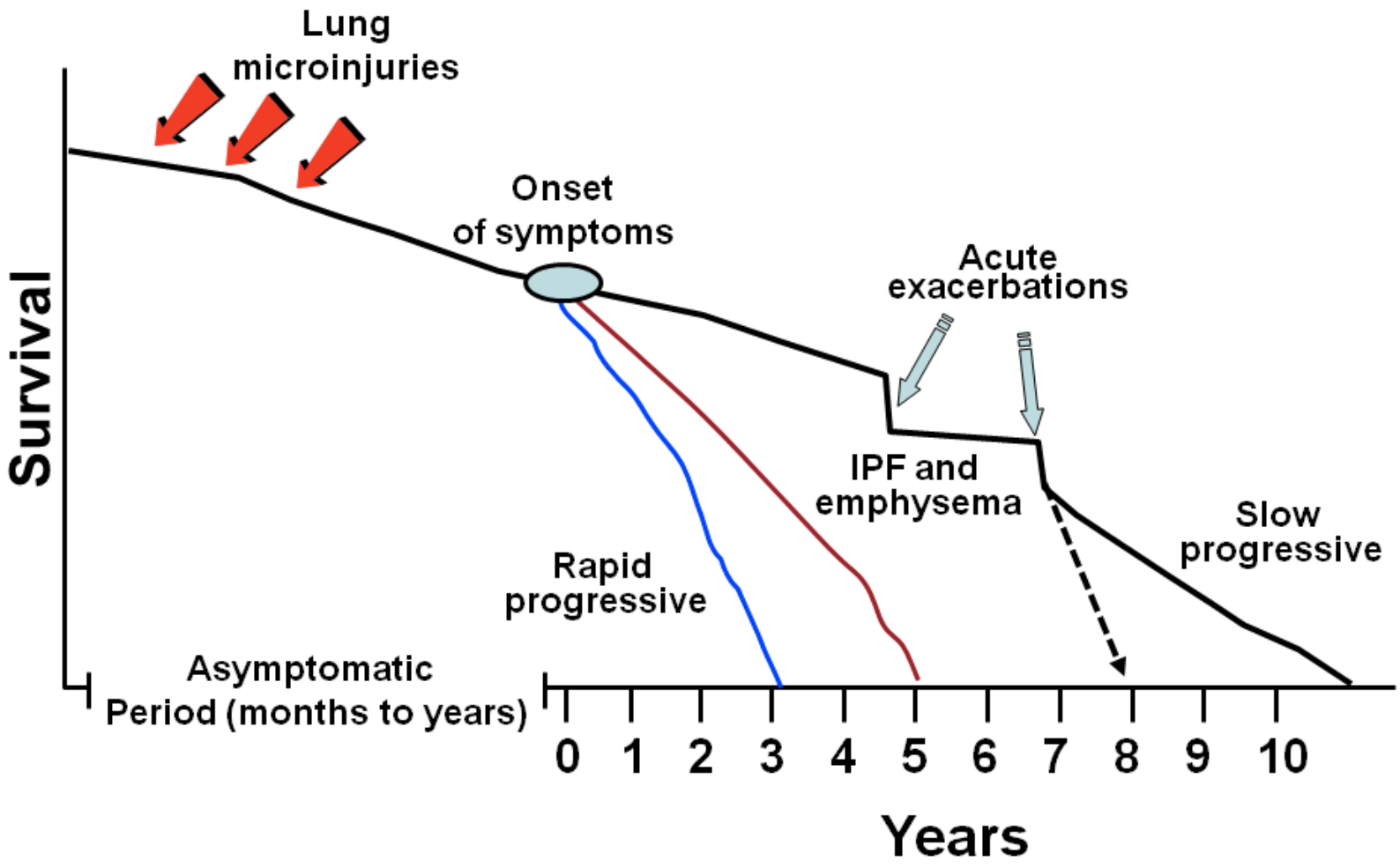
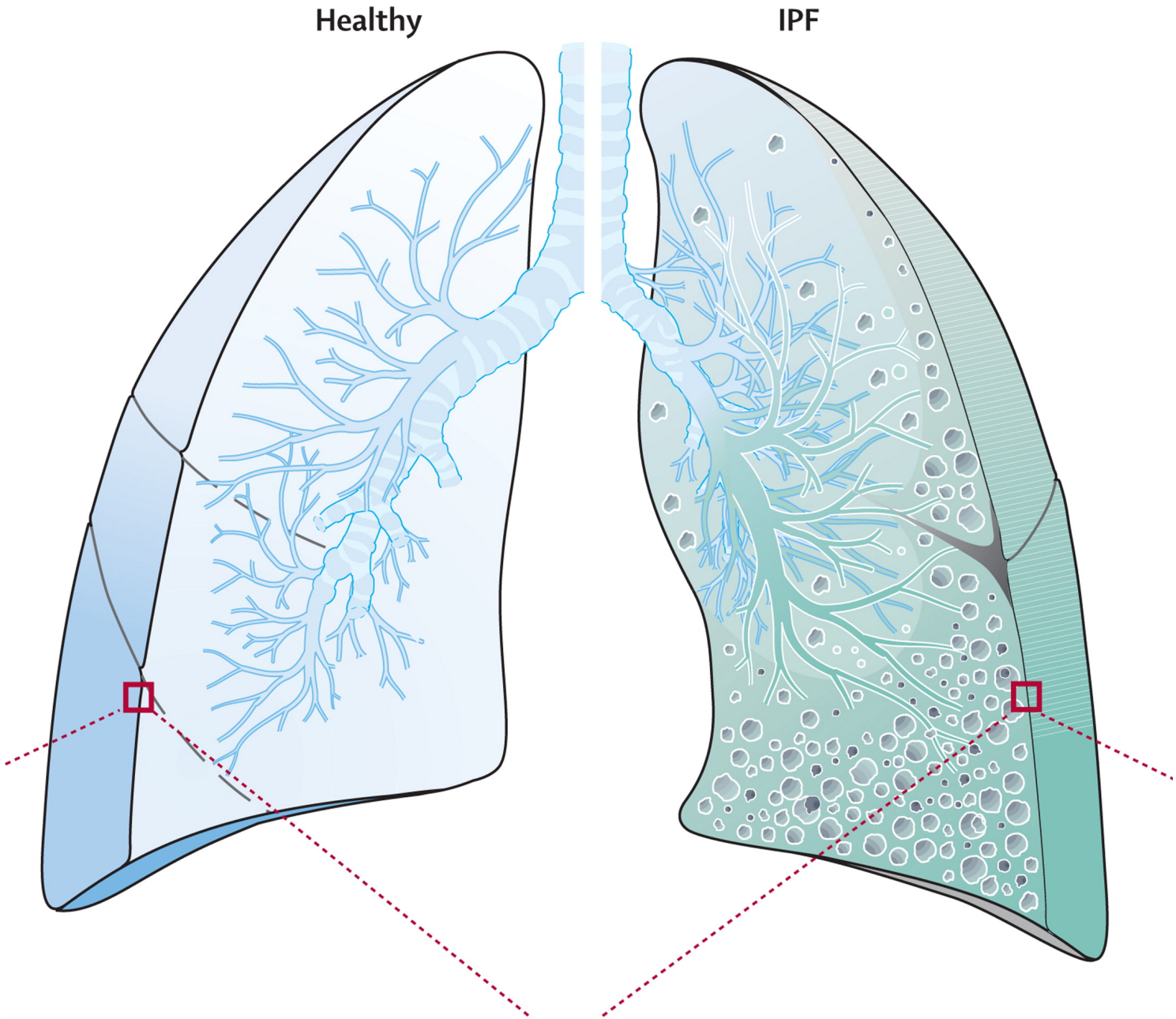
Disease trajectories



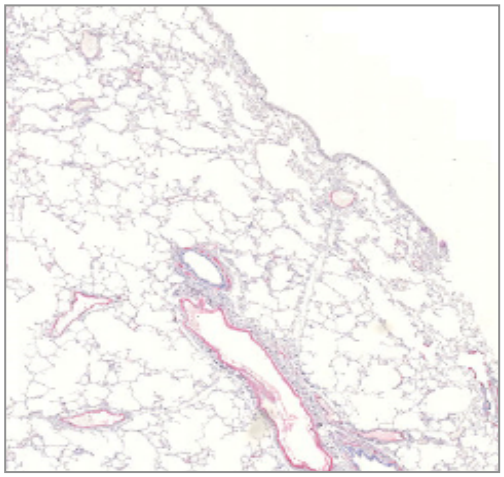
Courtesy of Moises Selman

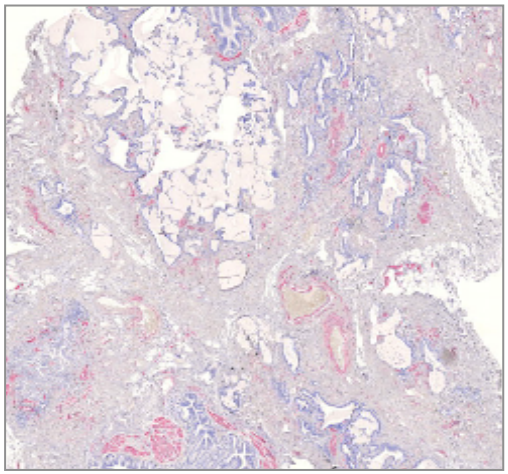


Fernandez and Eickelberg. *Lancet* 2012

Biomarkers in IPF

Possible sources





Local:

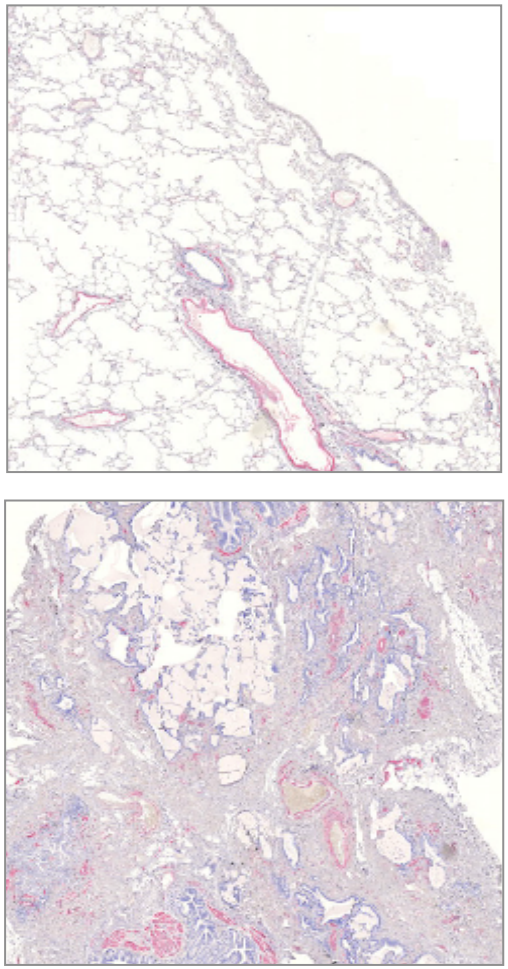
1. Lung Tissue
2. BALF
3. Exhaled Breath
4. Pleural Fluid

Systemic:

1. Serum
2. Urine
3. Faeces

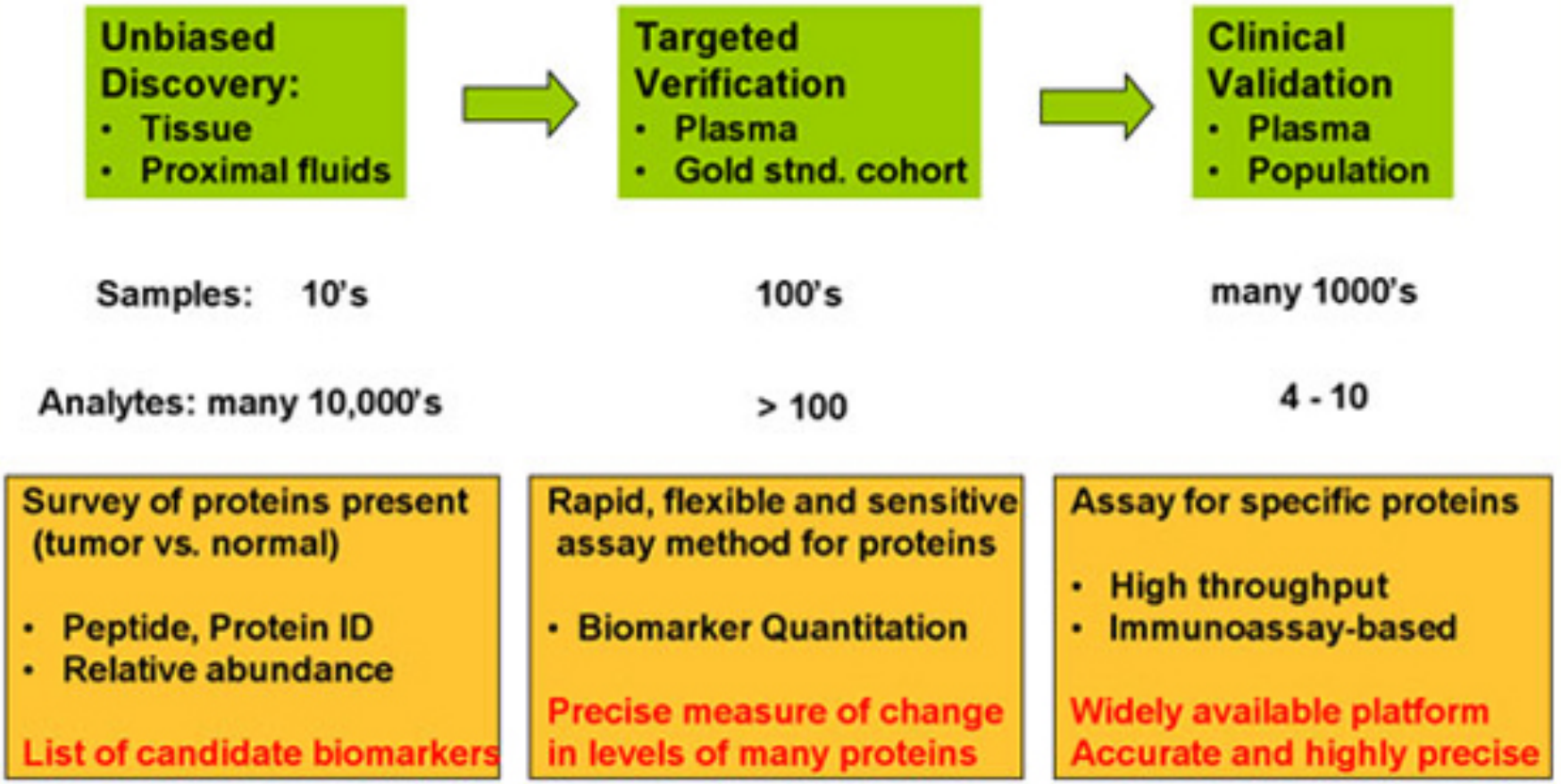
Biomarkers in IPF

Potential use/benefits

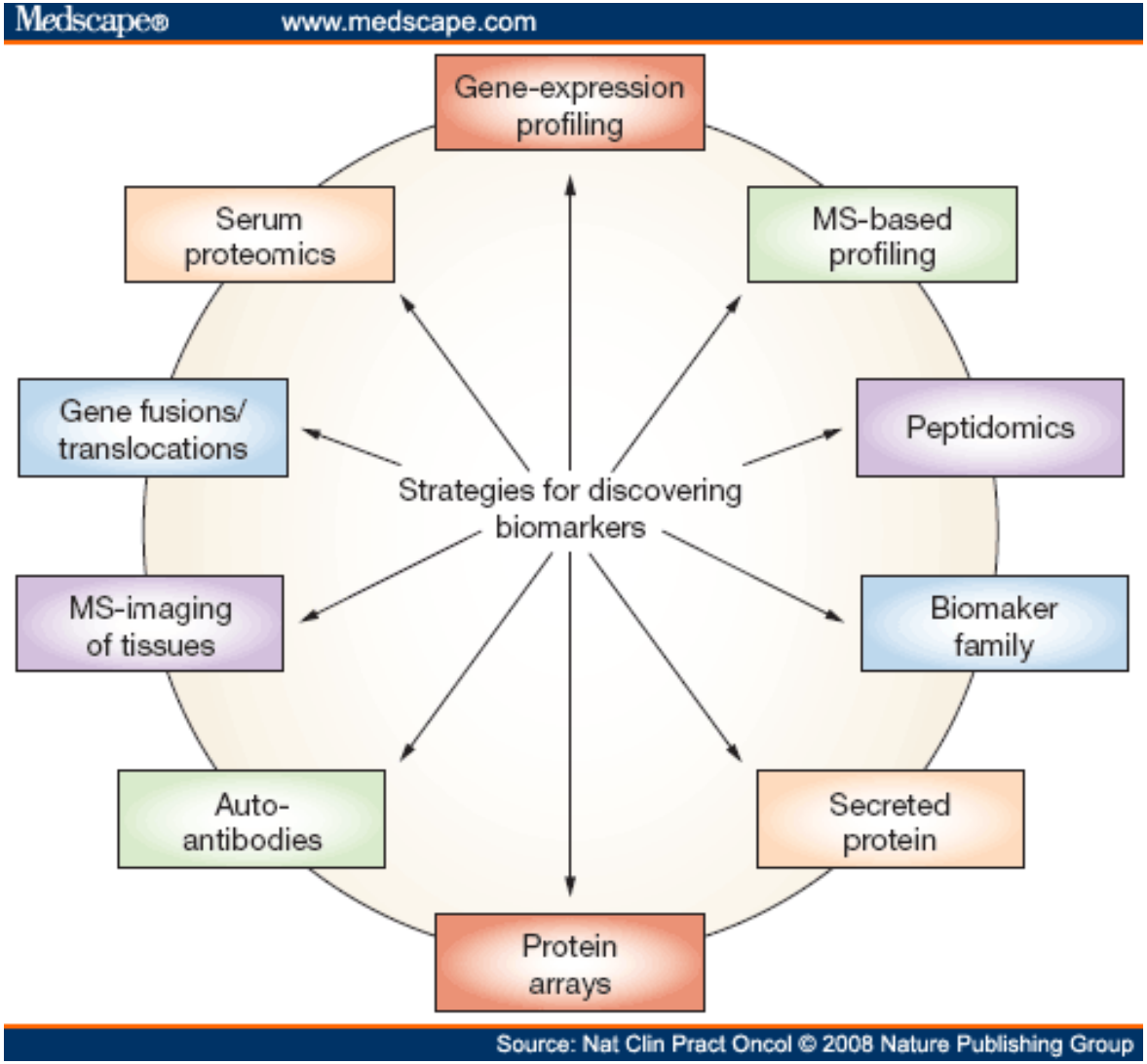


1. Diagnose accurately and early IPF
2. Predict the risk/onset of developing IPF
3. Predict the severity of IPF once diagnosed
4. Predict the response to a given therapy in IPF
5. Predict exacerbations of IPF

A refined view of the biomarker pipeline



Biomarkers in IPF



Nat Clin Pract Oncol 2008

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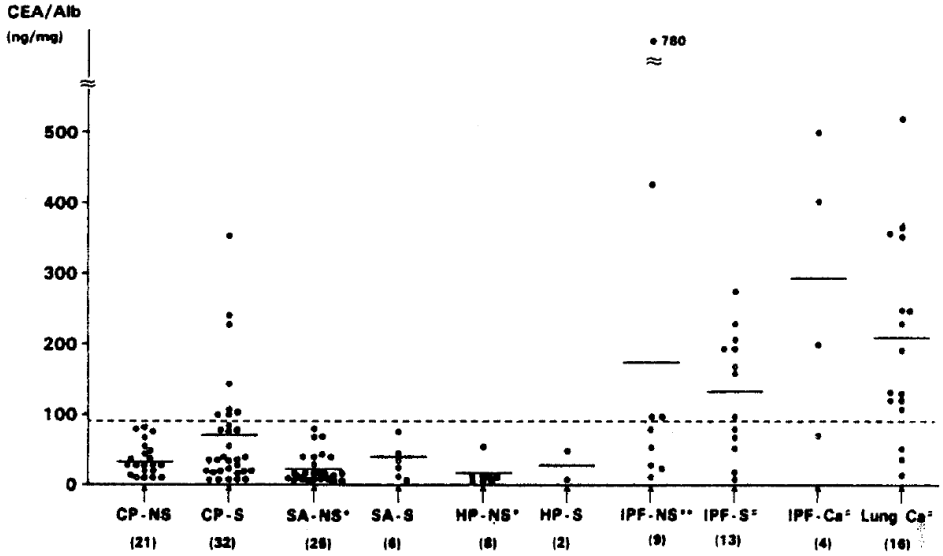
Original Article

Carcinoembryonic Antigen in Bronchoalveolar Lavage Fluid in Patients with Idiopathic Pulmonary Fibrosis

Hideki TAKAHASHI, MD, Toshihiro NUKIWA, MD, Rokuro MATSUOKA, MD, Takashi DANBARA, MD, Hiroshi NATORI, MD, Tatsuo ARAI, MD and Shiro KIRA, MD

Subjects: The subjects in this study were composed of 53 control patients, 31 patients with sarcoidosis, 10 patients with hypersensitivity pneumonitis, 26 patients with IPF and 16 patients with primary lung cancer. The consent for this study was obtained from all patients.



Takahashi et al., *Jap J Med.* 1985

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Respiratory Medicine (2014) 108, 1031–1039

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/rmed

Baseline KL-6 predicts increased risk for acute exacerbation of idiopathic pulmonary fibrosis

Shinichiro Ohshimo [a,b], Nobuhisa Ishikawa [b], Yasushi Horimasu [b], Noboru Hattori [b], Nobuyuki Hirohashi [a], Koichi Tanigawa [a], Nobuoki Kohno [b], Francesco Bonella [c], Josune Guzman [d], Ulrich Costabel [c,*]

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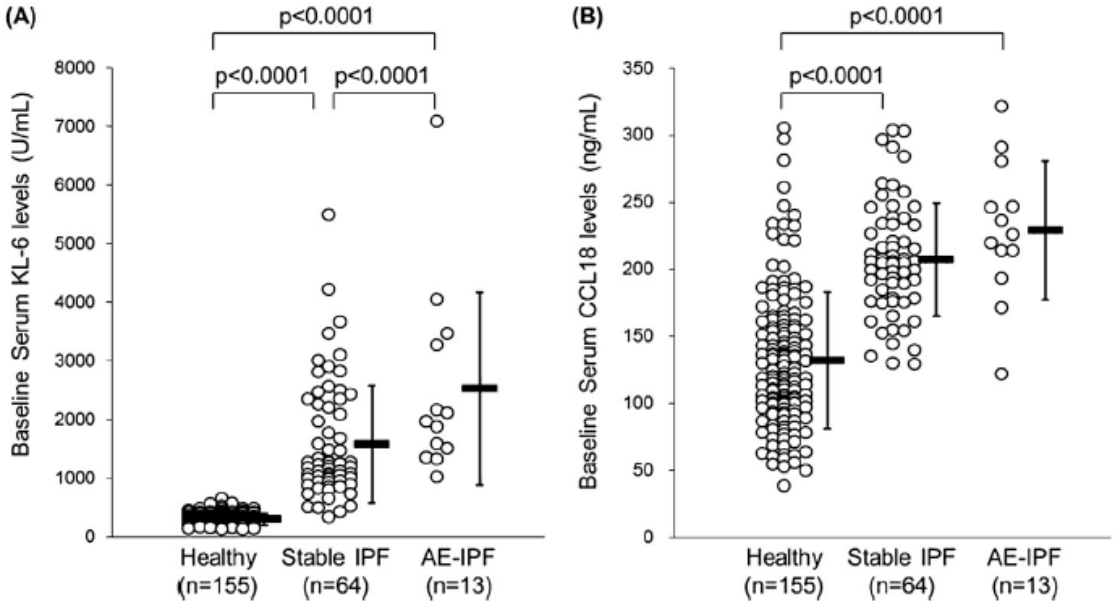

Figure 1 **Distribution of baseline serum levels of KL-6 and CCL18.** Scatter plot graphs showing the distribution of baseline serum levels of KL-6 (A) and CCL18 (B) in healthy subjects ($n = 155$), patients without AE-IPF ($n = 64$) and patients with AE-IPF ($n = 13$). IPF, idiopathic pulmonary fibrosis; AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis.

Ohshimo et al., *Resp Med.* 2014

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Ohnishi, H. et Al. Comparative Study of KL-6, SP-A, SP-D, and MCP-1 for interstitial Lung Disease. Am J Respir Crit Care Med. 2002;165(3):378-81

Circulating Fibrocytes Are an Indicator of Poor Prognosis in Idiopathic Pulmonary Fibrosis

Antje Moeller[1], Sarah E. Gilpin[2], Kjetil Ask[1,2], Gerard Cox[1], Deborah Cook[1], Jack Gauldie[2], Peter J. Margetts[1,2], Laszlo Farkas[1], Julian Dobranowski[3], Colm Boylan[3], Paul M. O'Byrne[1], Robert M. Strieter[4], and Martin Kolb[1,2]

Am J Respir Crit Care Med Vol 179. pp 588–594, 2009

Serum CC-Chemokine Ligand 18 Concentration Predicts Outcome in Idiopathic Pulmonary Fibrosis

Antje Prasse[1], Corinna Probst[1], Elena Bargagli, Gernot Zissel[1], Galen B. Toews[2], Kevin R. Flaherty[2], Manfred Olschewski[3], Paola Rottoli[4], and Joachim Müller-Quernheim[1]

[1]Department of Pneumology, [3]Department of Medical Biometry and Statistics, University Freiburg, Freiburg, Germany; [2]Division of Pulmonary and Critical Care Medicine, University of Michigan Medical School, Ann Arbor, Michigan; [4]Policlinico Le Scotte, Dipartimento di Medicina Clinica e Scienze Immunologiche, Sezione di Malattie dell Apparato Respiratorio, University of Siena, Siena, Italy

S100A9 in BALF is a candidate biomarker of idiopathic pulmonary fibrosis

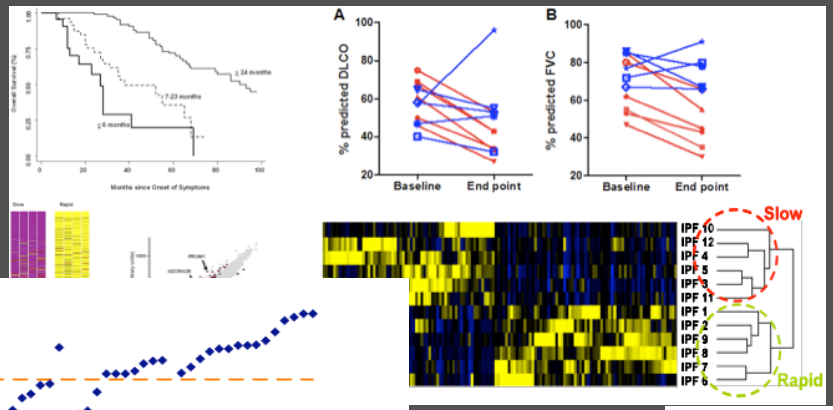
Atsuko Hara [a], Noriho Sakamoto [a,*], Yuji Ishimatsu [a], Tomoyuki Kakugawa [a], Shota Nakashima [a], Shintaro Hara [a], Misato Adachi [a], Hanako Fujita [a], Hiroshi Mukae [b], Shigeru Kohno [a]

Serum Surfactant Protein-A Is a Strong Predictor of Early Mortality in Idiopathic Pulmonary Fibrosis*

Brent W. Kinder, MD; Kevin K. Brown, MD, FCCP; Francis X. McCormack, MD, FCCP; Joachim H. Ix, MD; Alma Kervitsky, BS; Marvin I. Schwarz, MD, FCCP; and Talmadge E. King, Jr, MD, FCCP

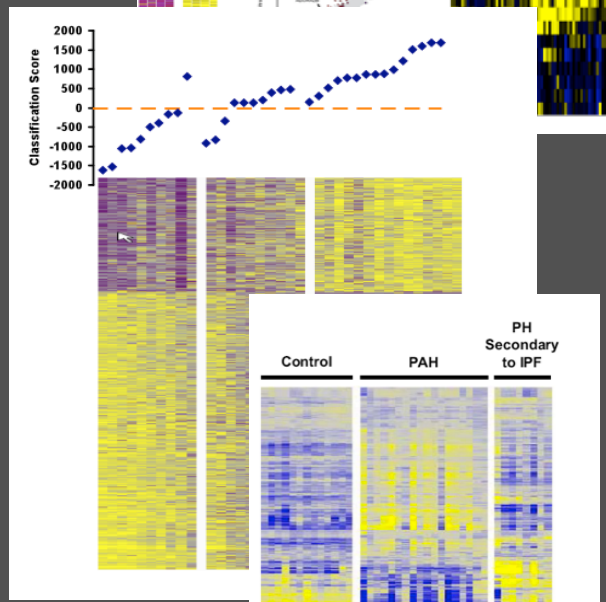
IPF lungs contain specific information about disease progression and outcome

Accelerated vs. stable

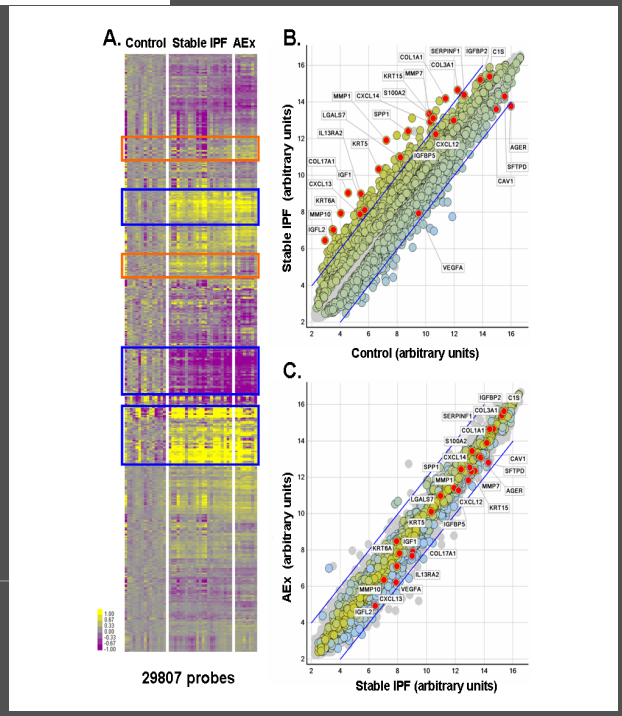


Acute exacerbations

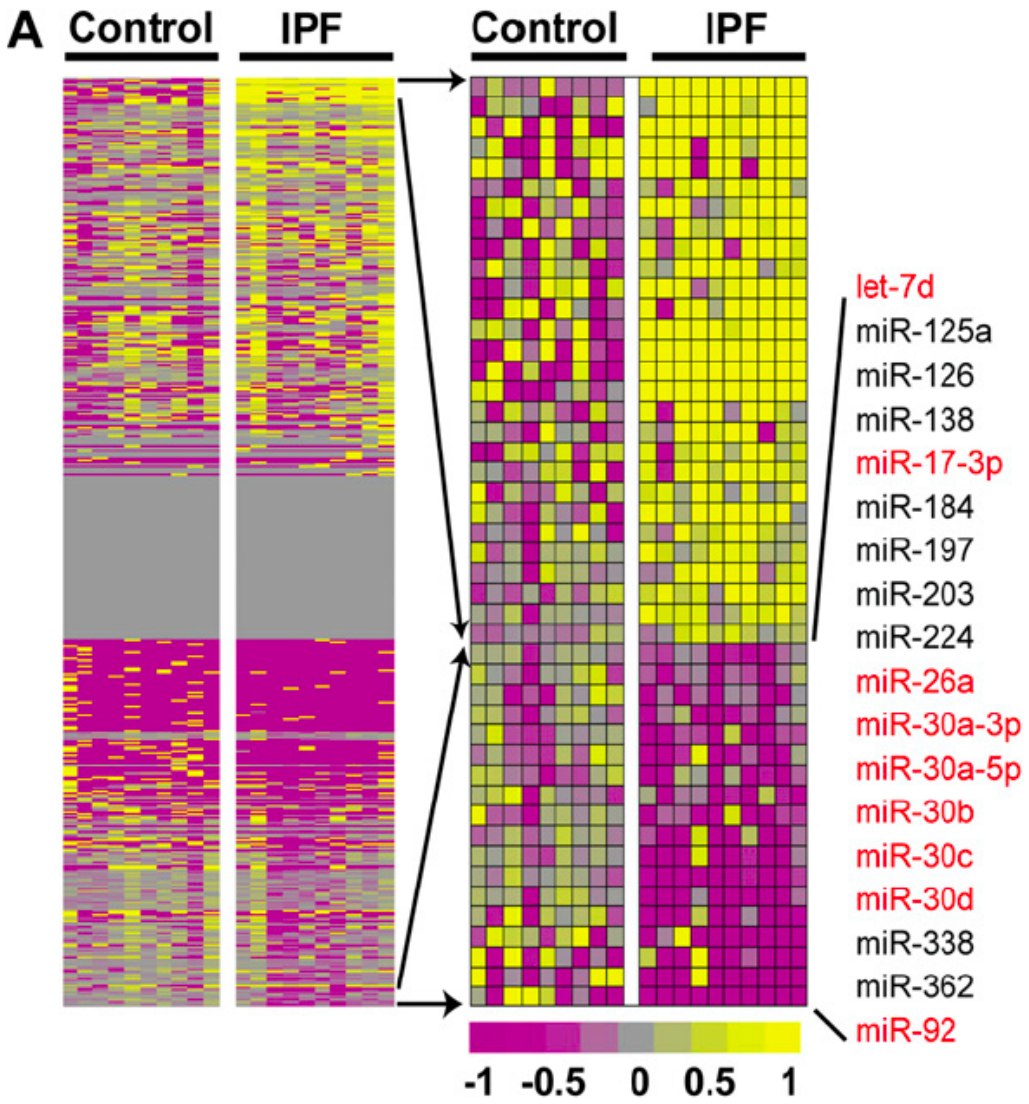
IPF vs. HP



PAH vs. Sec PAH

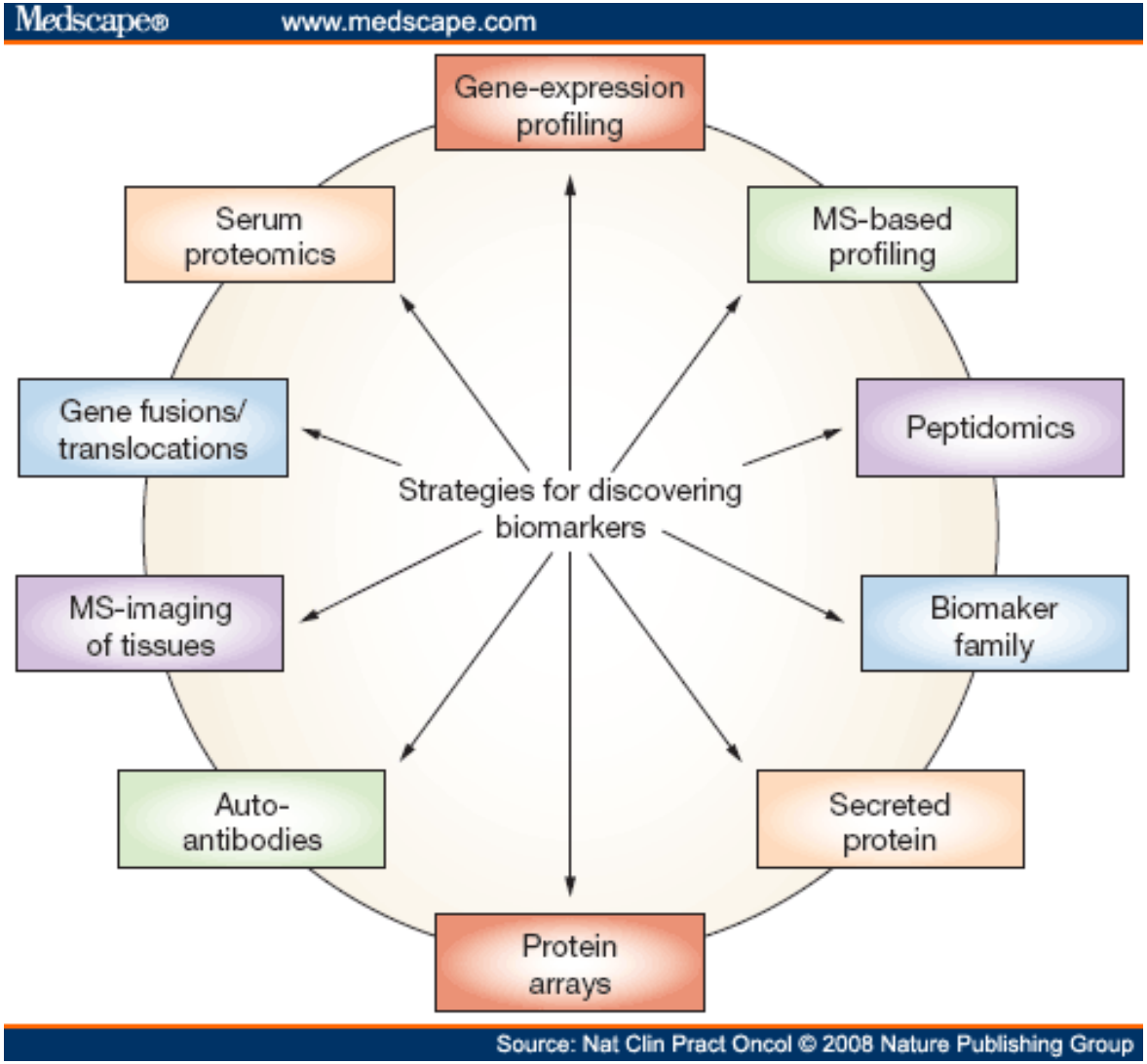


MicroRNAs are differentially expressed in IPF



Pandit et al. *Am J Respir Crit Care Med.* 2010 Jul 15;182(2):220-9

Biomarkers in IPF



Nat Clin Pract Oncol 2008

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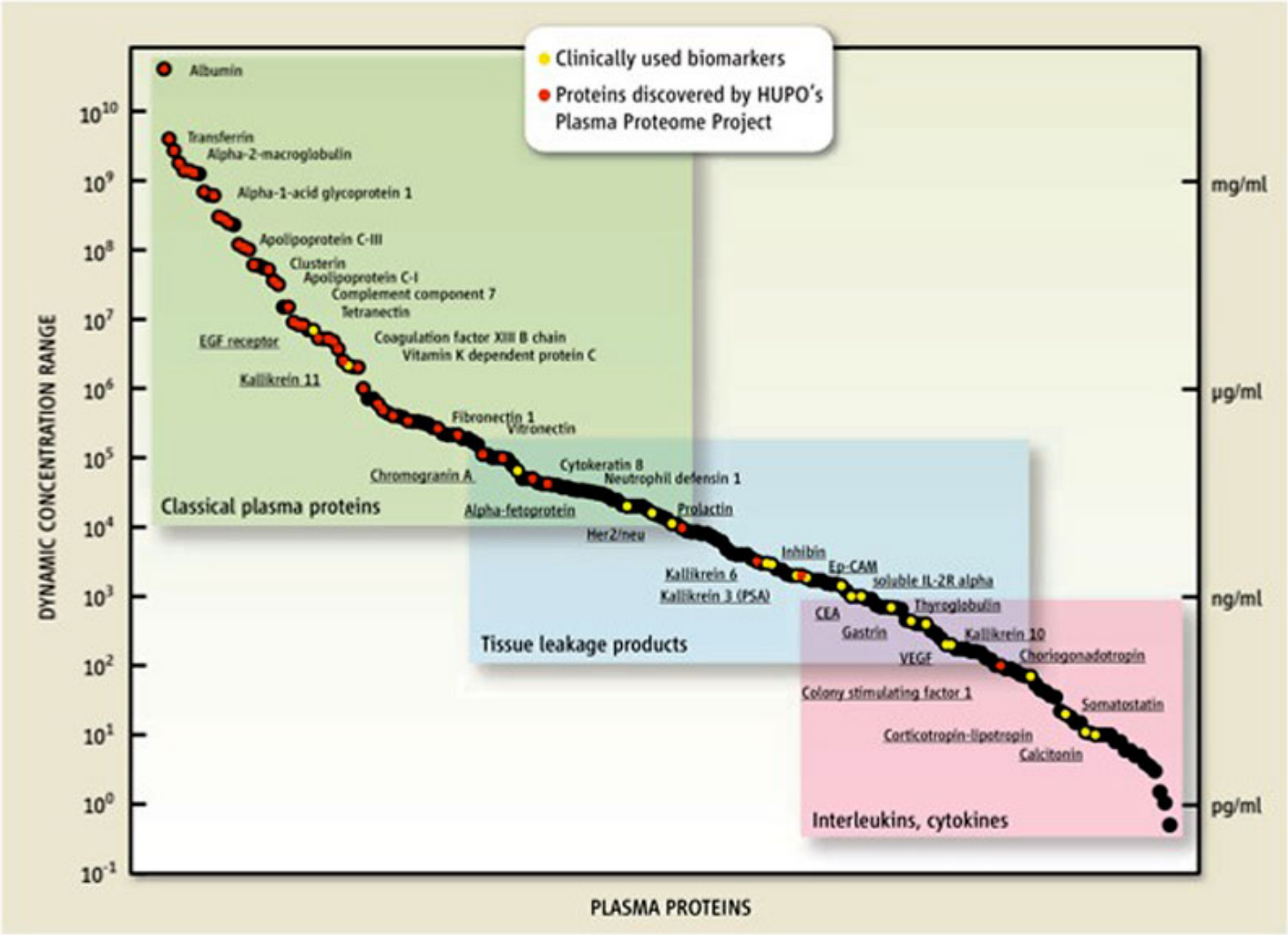
Biomarkers in IPF



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MMP1 and MMP7 as Potential Peripheral Blood Biomarkers in Idiopathic Pulmonary Fibrosis

Ivan O. Rosas[1☯], Thomas J. Richards[1☯], Kazuhisa Konishi[1], Yingze Zhang[1], Kevin Gibson[1], Anna E. Lokshin[2,3], Kathleen O. Lindell[1], Jose Cisneros[4], Sandra D. MacDonald[5], Annie Pardo[6], Frank Sciurba[1], James Dauber[1], Moises Selman[4*], Bernadette R. Gochuico[5*], Naftali Kaminski[1*]

1 Dorothy P. and Richard P. Simmons Center for Interstitial Lung Diseases, Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States of America, **2** Division of Hematology/Oncology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States of America, **3** University of Pittsburgh Cancer Institute, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States of America, **4** Instituto Nacional de Enfermedades Respiratorias, México DF, México, **5** Pulmonary-Critical Care Medicine Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, United States of America, **6** Facultad de Ciencias, Universidad Nacional Autónoma de México, México, Mexico

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Perspective

A Blood Test for Lung Fibrosis?

Peter J. Barnes

Peripheral Blood Proteins Predict Mortality in Idiopathic Pulmonary Fibrosis

Thomas J. Richards[1], Naftali Kaminski[1], Fred Baribaud[2], Susan Flavin[2], Carrie Brodmerkel[2], Daniel Horowitz[2], Katherine Li[2], Jiin Choi[1], Louis J. Vuga[1], Kathleen O. Lindell[1], Melinda Klesen[1], Yingze Zhang[1], and Kevin F. Gibson[1]

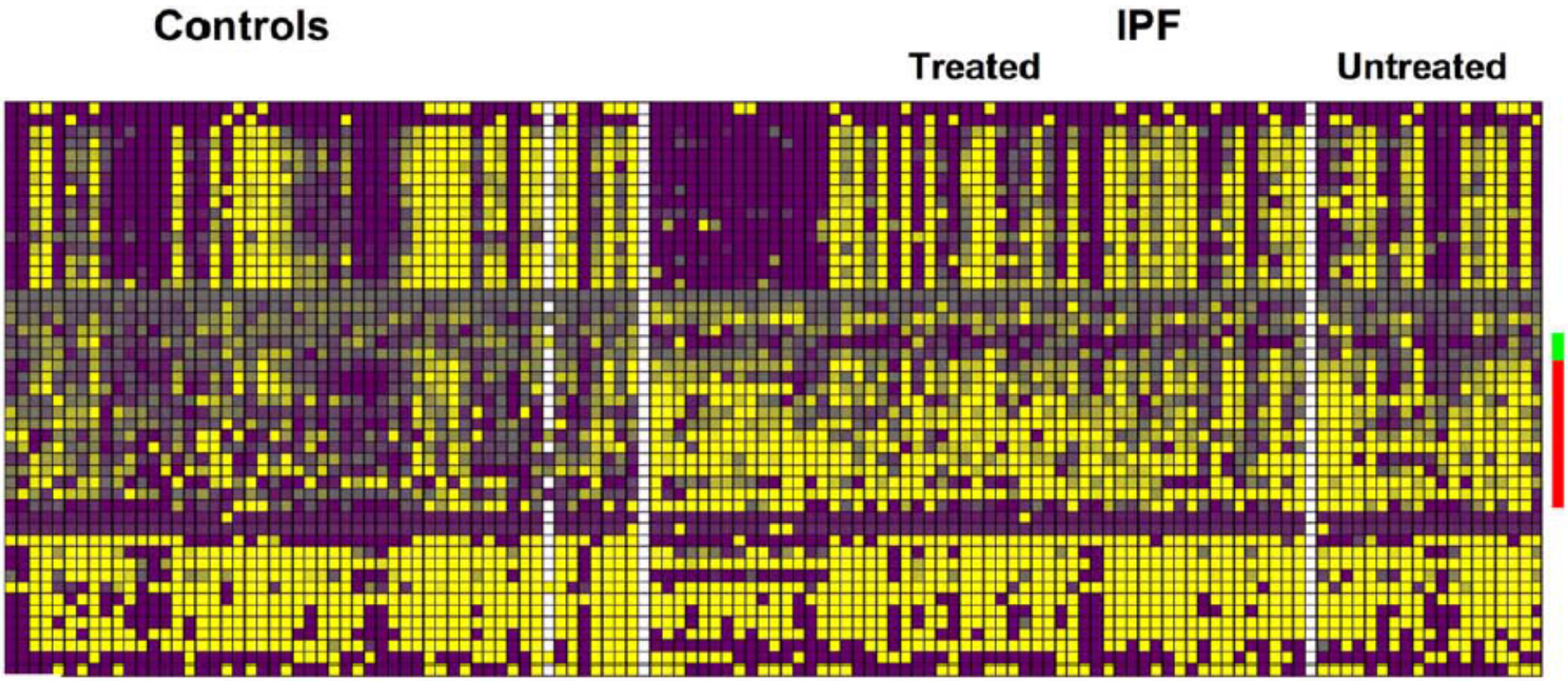
[1]The Dorothy P. & Richard P. Simmons Center for Interstitial Lung Disease, Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; and [2]Centocor R&D Inc., Radnor, Pennsylvania

Methods and Findings

We analyzed the concentrations of 49 proteins in the plasma of 74 patients with IPF and in the plasma of 53 control individuals. We identified a combinatorial signature of five proteins—MMP7, MMP1, MMP8, IGFBP1, and TNFRSF1A—that was sufficient to distinguish patients from controls with a sensitivity of 98.6% (95% confidence interval [CI] 92.7%–100%) and specificity of 98.1% (95% CI 89.9%–100%). Increases in MMP1 and MMP7 were also observed in lung tissue and bronchoalveolar lavage fluid obtained from IPF patients. MMP7 and MMP1 plasma concentrations were not increased in patients with chronic obstructive pulmonary disease or sarcoidosis and distinguished IPF compared to subacute/chronic hypersensitivity pneumonitis, a disease that may mimic IPF, with a sensitivity of 96.3% (95% CI 81.0%–100%) and specificity of 87.2% (95% CI 72.6%–95.7%). We verified our results in an independent validation cohort composed of patients with IPF, familial pulmonary fibrosis, subclinical interstitial lung disease (ILD), as well as with control individuals. MMP7 and MMP1 concentrations were significantly higher in IPF patients compared to controls in this cohort. Furthermore, MMP7 concentrations were elevated in patients with subclinical ILD and negatively correlated with percent predicted forced vital capacity (FVC%) and percent predicted carbon monoxide diffusing capacity (DL_{CO}%).

Rosas et al., *PLoS Med* 2008

Analysis of 50 proteins in Plasma of IPF patients



Rosas et al., *PLoS Med* 2008

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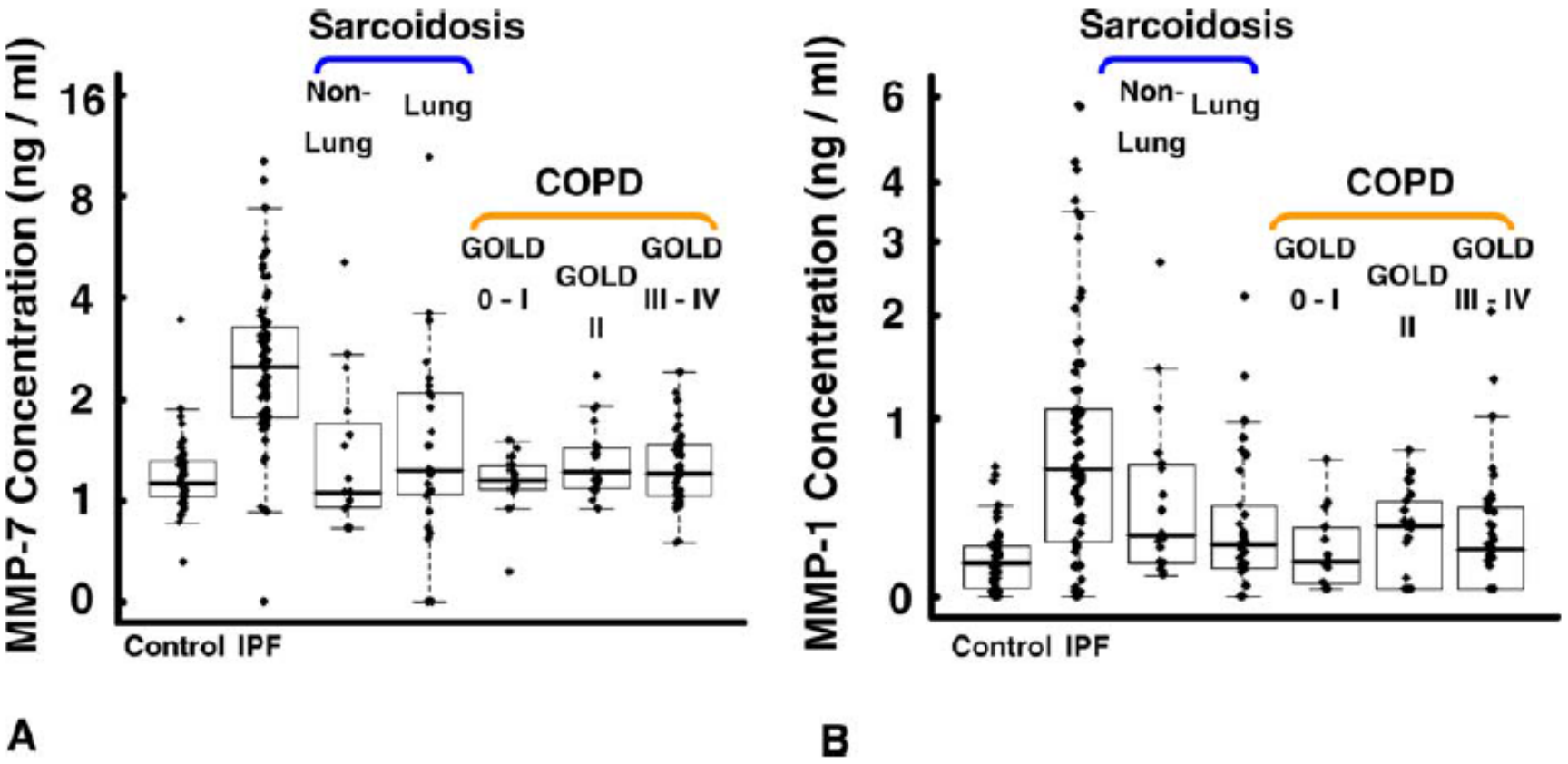

Figure 3. MMP7 and MMP1 Plasma Concentrations Are High in IPF, but Not Sarcoidosis or COPD

Rosas et al., *PLoS Med* 2008

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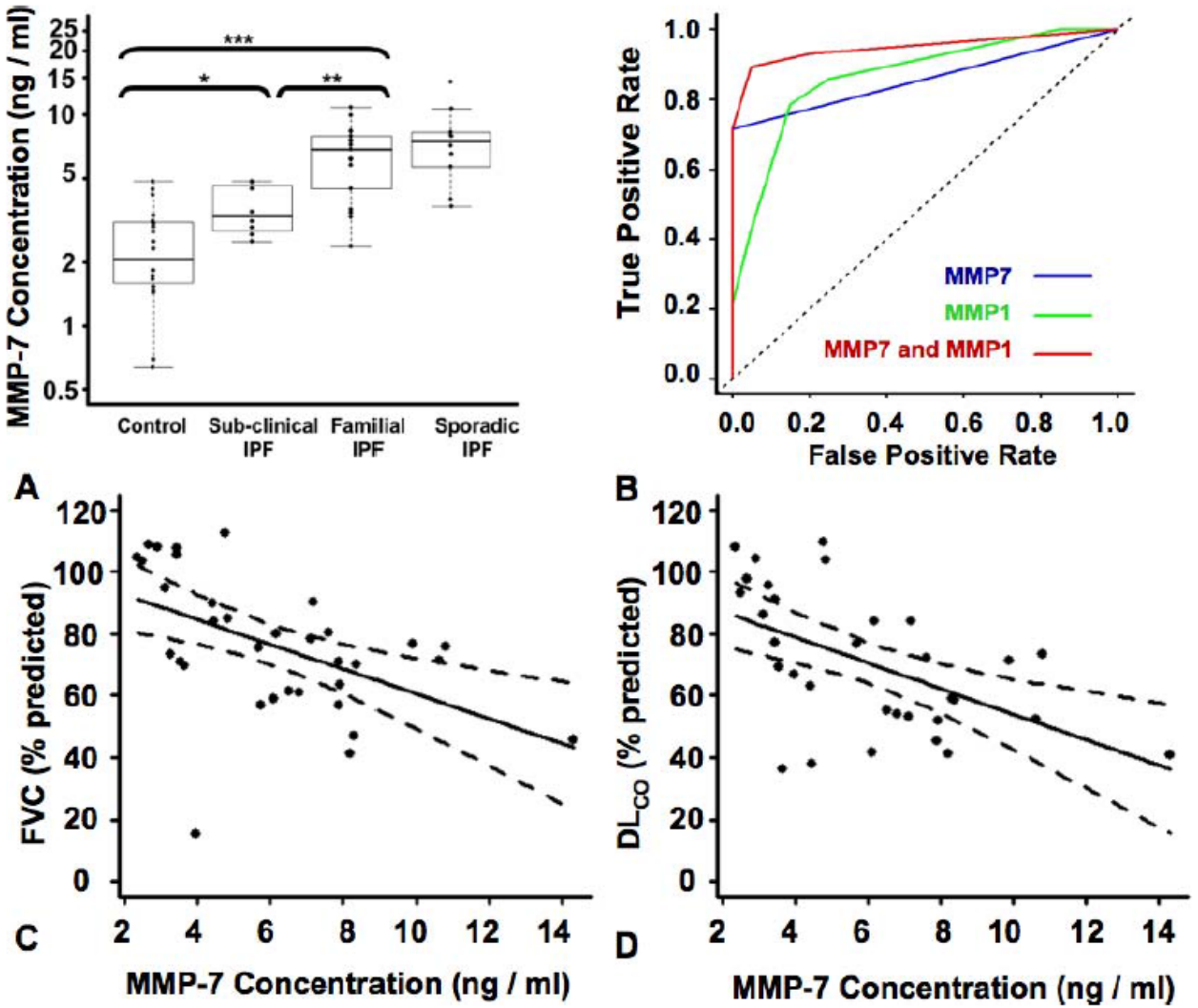
Independent NIH validation cohort MMP7 findings



Rosas et al., *PLoS Med* 2008

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Peripheral Blood Proteins Predict Mortality in Idiopathic Pulmonary Fibrosis

Thomas J. Richards[1], Naftali Kaminski[1], Fred Baribaud[2], Susan Flavin[2], Carrie Brodmerkel[2], Daniel Horowitz[2], Katherine Li[2], Jiin Choi[1], Louis J. Vuga[1], Kathleen O. Lindell[1], Melinda Klesen[1], Yingze Zhang[1], and Kevin F. Gibson[1]

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Richards et al., *AJRCCM* 2012

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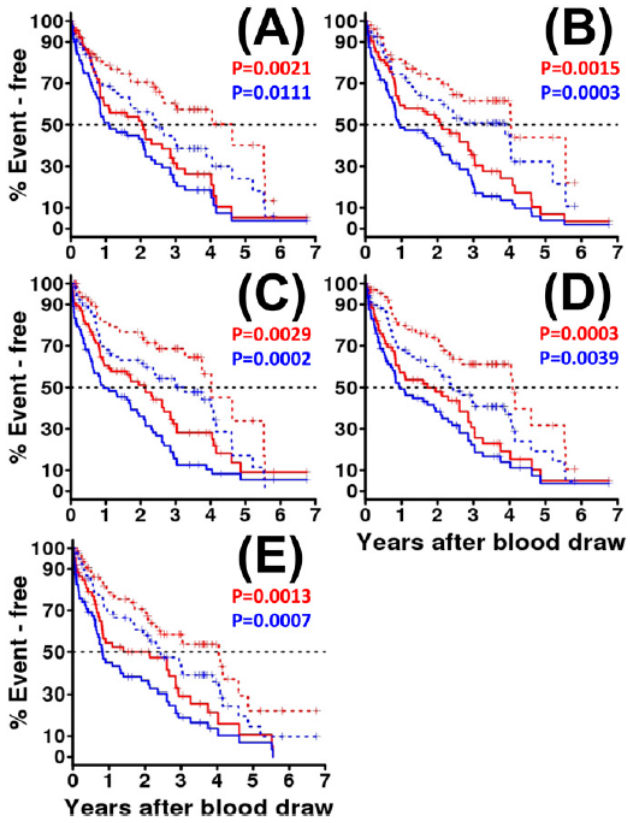

Figure 2. Peripheral blood biomarkers strongly predict idiopathic pulmonary fibrosis outcomes in the derivation cohort. For each biomarker, *red* indicates the Kaplan-Meier plot of overall survival (OS) by peripheral blood concentration dichotomized at an optimal threshold as described in the text and related to OS by the log-rank test. *Blue* indicates the Kaplan-Meier plot of transplant-free survival, by peripheral blood concentration dichotomized at an optimal threshold and related to transplant-free survival by the log-rank test. For each outcome and biomarker, high concentrations, above the threshold, are indicated by a *solid line*, low concentrations, below the threshold, by a *broken line*. The log-rank *P* values comparing high with low concentrations are shown in the appropriate color for OS and transplant-free survival are shown above each plot. The markers shown are (*A*) matrix metalloproteinase-7, (*B*) intercellular adhesion molecule-1, (*C*) IL-8, (*D*) vascular cell adhesion molecule-1, and (*E*) S100A12.

Richards et al., *AJRCCM* 2012

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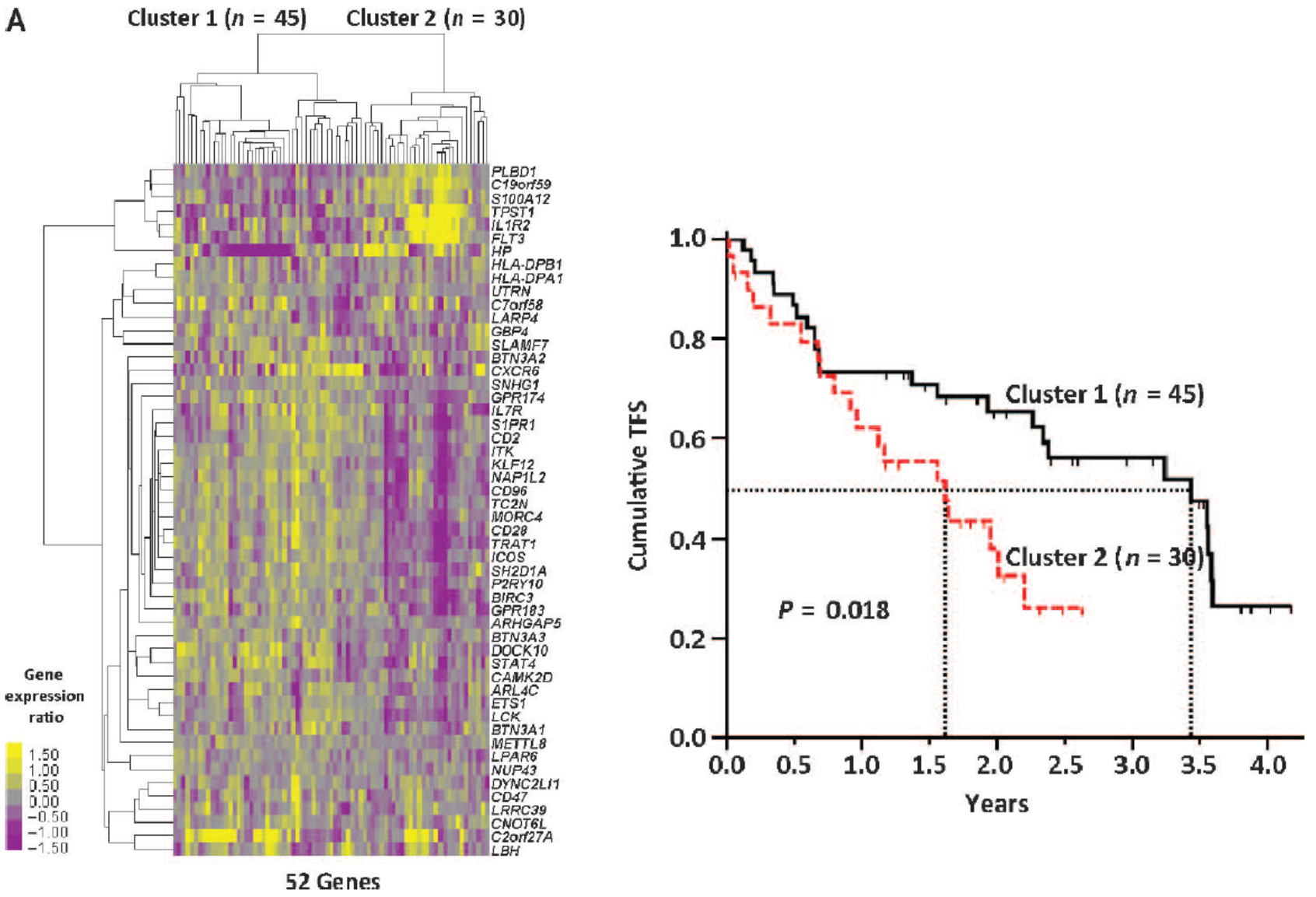
RESEARCH ARTICLE

PULMONARY FIBROSIS

Peripheral Blood Mononuclear Cell Gene Expression Profiles Predict Poor Outcome in Idiopathic Pulmonary Fibrosis

Jose D. Herazo-Maya,[1*] Imre Noth,[2*] Steven R. Duncan,[3*] SungHwan Kim,[4] Shwu-Fan Ma,[2] George C. Tseng,[4] Eleanor Feingold,[4,5] Brenda M. Juan-Guardela,[1] Thomas J. Richards,[3] Yves Lussier,[6] Yong Huang,[2] Rekha Vij,[2] Kathleen O. Lindell,[3] Jianmin Xue,[3] Kevin F. Gibson,[3] Steven D. Shapiro,[3] Joe G. N. Garcia,[7] Naftali Kaminski[1†]



Herazo-Maya et al., *Science Transl Med* 2014

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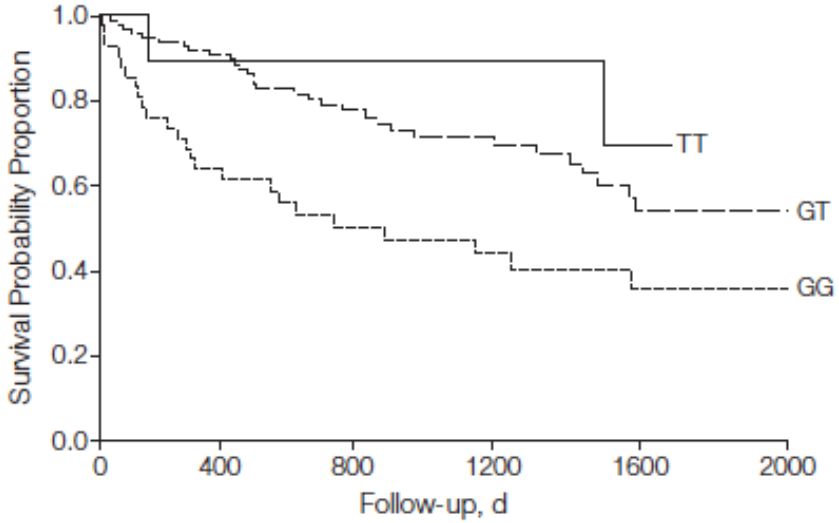
ONLINE FIRST

Association Between the *MUC5B* Promoter Polymorphism and Survival in Patients With Idiopathic Pulmonary Fibrosis

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

Peljto et al., *JAMA* 2013

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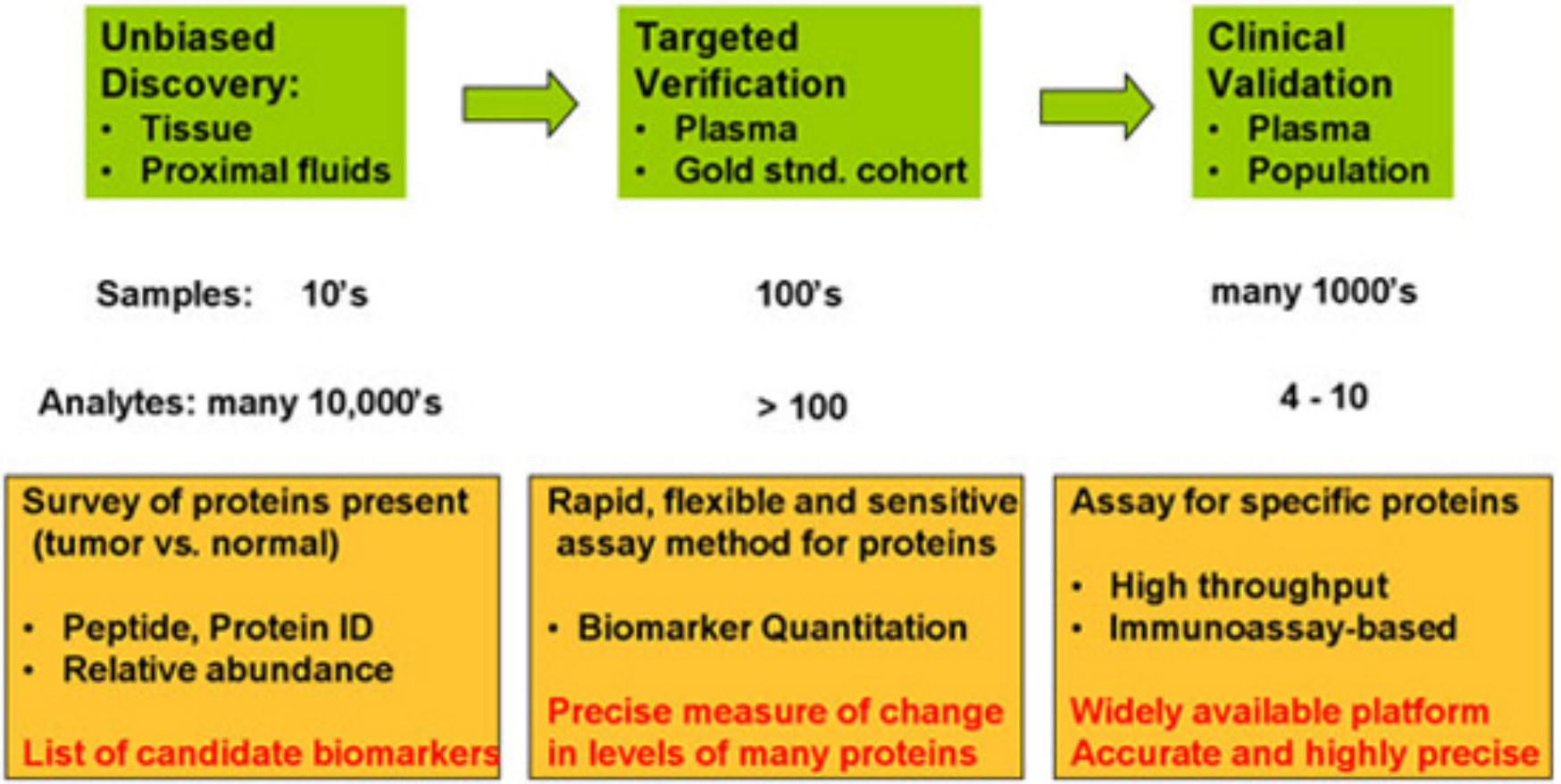
A refined view of the biomarker pipeline



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- Constanze Heise
- Elisabeth Hennen
- Katharina Lippl

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MPIB, Dept. Proteomics

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Naftali Kaminski (Yale University School of Medicine)

Martin Kolb (McMaster University, Hamilton, CA)

Ariel Munitz, Yoav Henis (Tel Aviv University)

Rachel Chambers (University College London)

Eric White, Vibha Lama (University of Michigan, Ann Arbor)

Stijn Verleden, Bart Vanaudenaerde (KU Leuven)

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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)
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81377 München

Contact

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From bench to bedside and back

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With this,

Thank you for your attention