

# Stanford

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## Edda Spiekerkoetter

Associate Professor of Medicine (Pulmonary and Critical Care Medicine)  
Medicine - Pulmonary, Allergy & Critical Care Medicine

### CLINICAL OFFICES

- **Critical Care Medicine**

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### Bio

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### CLINICAL FOCUS

- Pulmonary Hypertension
- Vasoreactivity in pulmonary hypertension as a marker of vascular remodeling
- Biomarkers
- Clinical Trial, Phase II
- Pulmonary Disease

### ACADEMIC APPOINTMENTS

- Associate Professor - University Medical Line, Medicine - Pulmonary, Allergy & Critical Care Medicine
- Member, Bio-X
- Member, Cardiovascular Institute
- Member, Maternal & Child Health Research Institute (MCHRI)

### HONORS AND AWARDS

- K08 Career development award, NIH (2011-2016)
- Postdoctoral Research Fellowship, Pulmonary Hypertension Association (2003-2005)
- Supplemental award of the Pulmonary Hypertension Association (PHA), Pulmonary Hypertension Association (2011 - 2016)
- Winner of Poster competition, Cardiovascular Institute Stanford (Sept 2012)
- Seed Grant - Small Molecule High Throughout Screen, Wall Center of Pulmonary Vascular Disease (2012)
- Seed Grant - Phase II Clinical Trial, SPARK and Spectrum Stanford (2012-2014)
- Seed Grant - Phase II Clinical Trial, Wall Center of Pulmonary Vascular Disease (2012-2014)
- Seed Grant- BMP signaling in the RV, Cardiovascular Institute Stanford (2013-2014)
- Helmholtz International Research Group Award, Helmholtz Zentrum Muenchen, Germany (2013-2016)

- Poster Award, Excellence Cluster Cardio-Pulmonary System (ECCPS) and Pulmonary Vascular Research Institute (PVRI) (Jan 2014)
- Manuscript Award, Cardiovascular Institute at Stanford (Feb 2014)
- Young Physician Scientist Award, American Society of Clinical Investigation (April 2015)

## **BOARDS, ADVISORY COMMITTEES, PROFESSIONAL ORGANIZATIONS**

- Pulmonary Circulation Program Committee, American Thoracic Society (2013 - present)
- Member at large, European Respiratory Society (2000 - present)
- Member at large, American Thoracic Society (1998 - present)

## **PROFESSIONAL EDUCATION**

- Fellowship: Stanford University Pulmonary and Critical Care Fellowship (2009) CA
- Fellowship: Stanford University (2008) CA
- Fellowship: Lucile Packard Children's Hospital (2006) CA
- Residency: Medizinische Hochschule Hannover (2002) Germany
- Medical Education: University Hospital Freiburg (1995) Germany

## **PATENTS**

- Edda Spiekerkoetter. "United States Patent 61481317 Low-Dose FK506 for the treatment of Pulmonary Arterial Hypertension", Leland Stanford Junior University

## **LINKS**

- My Lab site: <http://med.stanford.edu/spiekerkoetterlab.html>

## **Research & Scholarship**

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### **CURRENT RESEARCH AND SCHOLARLY INTERESTS**

My research focuses on the importance of the Bone Morphogenetic Protein Receptor 2 (BMPR2) signaling pathway in pulmonary, pulmonary-vascular as well as cardiac disease.

In 2000 two independent groups discovered mutations in the BMPR2 pathway as the genetic basis for pulmonary arterial hypertension (PAH). Over the past years more mutations either directly involved in the BMPR2 pathway (Endoglin, ALK1, Smad9) or indirectly linked to the BMPR2 pathway (Caveolin-1) have been discovered, emphasizing the central role of BMPR2 signaling in familial PAH. It was subsequently found that reduced BMPR2 expression and signaling seems to be a feature of other sporadic or idiopathic forms of PAH.

Hypothesizing that increasing BMPR2 signaling might improve PAH, we have performed a High-Throughput Screen of FDA approved drugs to find BMPR2 activators and have identified the immuno-suppressive drug FK506 (Tacrolimus) as the main activator.

We have subsequently shown that FK506 could rescue endothelial dysfunction in PAH, and prevent and reverse PAH in rodent models of experimental PAH (Spiekerkoetter JCI 2013).

This discovery has led to the initiation of a phase II clinical trial to test the safety, tolerability and efficacy of low-dose FK506 in PAH at Stanford (<http://www.clinicaltrials.gov/NCT01647945>)

My current research focuses on :

1. Novel ways how to modulate BMPR2 signaling (small molecule HTS screen, identifying novel modifier genes)

2. Evaluating the importance of BMPR2 signaling in the development of Right Ventricular Hypertrophy (RVH) and failure, which is the leading cause of death in PAH (Collaboration with Dres Sushma Reddy and Daniel Bernstein, Pediatric Cardiology, Stanford).
3. Evaluating the importance of BMPR2 signaling in vascular development in neonatal chronic lung disease (Collaboration with Dr. Anne Hilgendorff, Helmholtz Institute, Muenchen, Germany).

## CLINICAL TRIALS

- FK506 (Tacrolimus) in Pulmonary Arterial Hypertension, Recruiting

## Teaching

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### COURSES

#### 2020-21

- Cardiovascular and Pulmonary Sciences Seminar: MED 223 (Win)

#### 2019-20

- Cardiovascular and Pulmonary Sciences Seminar: MED 223 (Win)

#### 2017-18

- Applying Modern Techniques to Old Diseases: BIOS 269 (Win)

### STANFORD ADVISEES

#### Postdoctoral Faculty Sponsor

Md Khadem Ali, Adam Andruska, Kenzo Ichimura

## Publications

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### PUBLICATIONS

- **Repurposing of medications for pulmonary arterial hypertension.** *Pulmonary circulation*  
Toshner, M., Spiekerkoetter, E., Bogaard, H., Hansmann, G., Nikkho, S., Prins, K. W.  
2020; 10 (4): 2045894020941494
- **The left ventricle undergoes biomechanical and gene expression changes in response to increased right ventricular pressure overload.** *Physiological reports*  
Kheifets, V. O., Dufva, M. J., Boehm, M., Tian, X., Qin, X., Tabakh, J. E., Truong, U., Ivy, D., Spiekerkoetter, E.  
2020; 8 (9): e14347
- **The Hallmarks of Severe Pulmonary Arterial Hypertension: The Cancer Hypothesis - Ten years later.** *American journal of physiology. Lung cellular and molecular physiology*  
Cool, C. D., Kuebler, W. M., Bogaard, H. J., Spiekerkoetter, E., Nicolls, M. R., Voelkel, N. F.  
2020
- **A Notch3-Marked Subpopulation of Vascular Smooth Muscle Cells is the Cell of Origin for Occlusive Pulmonary Vascular Lesions.** *Circulation*  
Steffes, L. C., Froistad, A. A., Andruska, A. n., Boehm, M. n., McGlynn, M. n., Zhang, F. n., Zhang, W. n., Hou, D. n., Tian, X. n., Miquerol, L. n., Nadeau, K. n., Metzger, R. J., Spiekerkoetter, et al  
2020
- **Targeting BMPR2 Trafficking with Chaperones - An Important Step Towards Precision Medicine in Pulmonary Arterial Hypertension.** *American journal of respiratory cell and molecular biology*  
Andruska, A. n., Ali, K. n., Spiekerkoetter, E. n.  
2020
- **Targeted Proteomics of Right Heart Adaptation to Pulmonary Arterial Hypertension.** *The European respiratory journal*  
Amsallem, M. n., Sweatt, A. J., Arthur Ataam, J. n., Guihaire, J. n., Lecerf, F. n., Lambert, M. n., Ghigna, M. R., Ali, M. K., Mao, Y. n., Fadel, E. n., Rabinovitch, M. n., de Jesus Perez, V. n., Spiekerkoetter, et al

2020

- **Delineating the molecular and histological events that govern right ventricular recovery using a novel mouse model of PA de-banding.** *Cardiovascular research*

Boehm, M., Tian, X., Mao, Y., Ichimura, K., Dufva, M. J., Ali, K., Prosseda, S. D., Shi, Y., Kuramoto, K., Reddy, S., Kheyfets, V. O., Metzger, R. J., Spiekerkoetter, et al

2019

- **EXPRESS: Drug Repositioning in Pulmonary Arterial Hypertension: Challenges and Opportunities.** *Pulmonary circulation*

Grinnan, D., Trankle, C., Andruska, A., Bloom, B., Spiekerkoetter, E. F.

2019: 2045894019832226

- **Hot topics in the mechanisms of pulmonary arterial hypertension disease: cancer-like pathobiology, the role of the adventitia, systemic involvement, and right ventricular failure.** *Pulmonary circulation*

Spiekerkoetter, E. n., Goncharova, E. A., Guignabert, C. n., Stenmark, K. n., Kwapiszewska, G. n., Rabinovitch, M. n., Voelkel, N. n., Bogaard, H. J., Graham, B. n., Pullamsetti, S. S., Kuebler, W. M.

2019; 9 (4): 2045894019889775

- **EXPRESS: Myocardial Bridge - An Unrecognized Cause of Chest Pain in Pulmonary Arterial Hypertension.** *Pulmonary circulation*

Rajmohan, D. n., Sung, Y. K., Kudelko, K. n., Perez, V. i., Haddad, F. n., Tremmel, J. n., Schnittger, I. n., Zamanian, R. T., Spiekerkoetter, E. F.

2019: 2045894019860738

- **New and Emerging Therapies for Pulmonary Arterial Hypertension.** *Annual review of medicine*

Spiekerkoetter, E. n., Kawut, S. M., de Jesus Perez, V. A.

2019; 70: 45–59

- **Exome data clouds the pathogenicity of genetic variants in Pulmonary Arterial Hypertension** *MOLECULAR GENETICS & GENOMIC MEDICINE*

Abbasi, Y., Jabbari, J., Jabbari, R., Glinge, C., Izadyar, S., Spiekerkoetter, E., Zamanian, R. T., Carlsen, J., Tfelt-Hansen, J.

2018; 6 (5): 835–44

- **Consequences of BMPR2 Deficiency in the Pulmonary Vasculature and Beyond: Contributions to Pulmonary Arterial Hypertension.** *International journal of molecular sciences*

Andruska, A., Spiekerkoetter, E.

2018; 19 (9)

- **Fragile Histidine Triad (FHIT), a Novel Modifier Gene in Pulmonary Arterial Hypertension.** *American journal of respiratory and critical care medicine*

Dannewitz Prosseda, S., Tian, X., Kuramoto, K., Boehm, M., Sudheendra, D., Miyagawa, K., Zhang, F., Solow-Cordero, D., Saldivar, J. C., Austin, E. D., Loyd, J. E., Wheeler, L., Andruska, et al

2018

- **Update in Pulmonary Vascular Disease 2016 and 2017** *AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE*

Brittain, E. L., Thennapan, T., Maron, B. A., Chan, S. Y., Austin, E. D., Spiekerkoetter, E., Bogaard, H. J., Guignabert, C., Paulin, R., Machado, R. F., Yu, P. B.

2018; 198 (1): 13–23

- **New and Emerging Therapies for Pulmonary Arterial Hypertension** *Annual Reviews in medicine*

Spiekerkoetter, E., Kawut, S., de Jesus Perez, V.

2018

- **A Pro - Con debate: Current Controversies in PAH Pathogenesis at the American Thoracic Society International Meeting in 2017.** *American journal of physiology. Lung cellular and molecular physiology*

Kuebler, W. M., Nicolls, M. R., Olschewski, A. n., Abe, K. n., Rabinovitch, M. n., Stewart, D. J., Chan, S. Y., Morrell, N. W., Archer, S. L., Spiekerkoetter, E. n.

2018

- **Career Development of Young Physician-Scientists in the Cardiovascular Sciences: Perspective and Advice From the Early Career Committee of the Cardiopulmonary, Critical Care, and Resuscitation Council of the American Heart Association.** *Circulation research*

Agarwal, S. n., Spiekerkoetter, E. n., Austin, E. D., de Jesus Perez, V. n., Dezfulian, C. n., Maron, B. A., Ryan, J. J., Starks, M. A., Yu, P. B., Bonnet, S. n., Perman, S. M.

2018; 122 (10): 1330–33

- **Randomised placebo-controlled safety and tolerability trial of FK506 (tacrolimus) for pulmonary arterial hypertension** *EUROPEAN RESPIRATORY JOURNAL*

Spiekerkoetter, E., Sung, Y. K., Sudheendra, D., Scott, V., Del Rosario, P., Bill, M., Haddad, F., Long-Boyle, J., Hedlin, H., Zamanian, R. T.

2017; 50 (3)

- **RNA Sequencing Analysis Detection of a Novel Pathway of Endothelial Dysfunction in Pulmonary Arterial Hypertension** *AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE*  
Rhodes, C. J., Im, H., Cao, A., Hennigs, J. K., Wang, L., Sa, S., Chen, P., Nickel, N. P., Miyagawa, K., Hopper, R. K., Tojais, N. F., Li, C. G., Gu, et al  
2015; 192 (3): 356-366
- **Low-Dose FK506 (Tacrolimus) in End-Stage Pulmonary Arterial Hypertension.** *American journal of respiratory and critical care medicine*  
Spiekerkoetter, E., Sung, Y. K., Sudheendra, D., Bill, M., Aldred, M. A., van de Veerdonk, M. C., Vonk Noordegraaf, A., Long-Boyle, J., Dash, R., Yang, P. C., Lawrie, A., Swift, A. J., Rabinovitch, et al  
2015; 192 (2): 254-257
- **Elafin Reverses Pulmonary Hypertension via Caveolin-1-Dependent Bone Morphogenetic Protein Signaling** *AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE*  
Nickel, N. P., Spiekerkoetter, E., Gu, M., Li, C. G., Li, H., Kaschwich, M., Diebold, I., Hennigs, J. K., Kim, K., Miyagawa, K., Wang, L., Cao, A., Sa, et al  
2015; 191 (11): 1273-1286
- **Hedgehog Signaling Restrains Bladder Cancer Progression by Eliciting Stromal Production of Urothelial Differentiation Factors** *CANCER CELL*  
Shin, K., Lim, A., Zhao, C., Sahoo, D., Pan, Y., Spiekerkoetter, E., Liao, J. C., Beachy, P. A.  
2014; 26 (4): 521-533
- **Targeting the Wnt signaling pathways in pulmonary arterial hypertension.** *Drug discovery today*  
de Jesus Perez, V., Yuan, K., Alastalo, T., Spiekerkoetter, E., Rabinovitch, M.  
2014; 19 (8): 1270-1276
- **Current Clinical Management of Pulmonary Arterial Hypertension** *CIRCULATION RESEARCH*  
Zamanian, R. T., Kudelko, K. T., Sung, Y. K., Perez, V. D., Liu, J., Spiekerkoetter, E.  
2014; 115 (1): 131-147
- **Reduced BMP2 expression induces GM-CSF translation and macrophage recruitment in humans and mice to exacerbate pulmonary hypertension.** *journal of experimental medicine*  
Sawada, H., Saito, T., Nickel, N. P., Alastalo, T., Glotzbach, J. P., Chan, R., Haghghat, L., Fuchs, G., Januszyk, M., Cao, A., Lai, Y., Perez, V. d., Kim, et al  
2014; 211 (2): 263-280
- **Current clinical management of pulmonary arterial hypertension.** *Circulation research*  
Zamanian, R. T., Kudelko, K. T., Sung, Y. K., de Jesus Perez, V. n., Liu, J. n., Spiekerkoetter, E. n.  
2014; 115 (1): 131-47
- **FK506 activates BMP2, rescues endothelial dysfunction, and reverses pulmonary hypertension.** *journal of clinical investigation*  
Spiekerkoetter, E., Tian, X., Cai, J., Hopper, R. K., Sudheendra, D., Li, C. G., El-Bizri, N., Sawada, H., Haghghat, R., Chan, R., Haghghat, L., de Jesus Perez, V., Wang, et al  
2013; 123 (8): 3600-3613
- **A case of recurrent pericardial constriction presenting with severe pulmonary hypertension.** *Pulmonary circulation*  
Brunner, N. W., Ramachandran, K., Kudelko, K. T., Sung, Y. K., Spiekerkoetter, E., Yang, P. C., Zamanian, R. T., Perez, V. d.  
2013; 3 (2): 436-439
- **A case of recurrent pericardial constriction presenting with severe pulmonary hypertension** *PULMONARY CIRCULATION*  
Brunner, N. W., Ramachandran, K., Kudelko, K. T., Sung, Y. K., Spiekerkoetter, E., Yang, P. C., Zamanian, R. T., Perez, V. d.  
2013; 3 (2): 436-439
- **Loss of adenomatous polyposis coli-a3 integrin interaction promotes endothelial apoptosis in mice and humans.** *Circulation research*  
de Jesus Perez, V. A., Yuan, K., Orcholski, M. E., Sawada, H., Zhao, M., Li, C. G., Tojais, N. F., Nickel, N., Rajagopalan, V., Spiekerkoetter, E., Wang, L., Dutta, R., Bernstein, et al  
2012; 111 (12): 1551-1564
- **Safety and efficacy of transition from systemic prostanoids to inhaled treprostinil in pulmonary arterial hypertension.** *American journal of cardiology*  
de Jesus Perez, V. A., Rosenzweig, E., Rubin, L. J., Poch, D., Bajwa, A., Park, M., Jain, M., Bourge, R. C., Kudelko, K., Spiekerkoetter, E., Liu, J., Hsi, A., Zamanian, et al  
2012; 110 (10): 1546-1550

- **Safety and Efficacy of Transition from Systemic Prostanoids to Inhaled Treprostinil in Pulmonary Arterial Hypertension** *AMERICAN JOURNAL OF CARDIOLOGY*  
Perez, V. A., Rosenzweig, E., Rubin, L. J., Poch, D., Bajwa, A., Park, M., Jain, M., Bourge, R. C., Kudelko, K., Spiekerkoetter, E., Liu, J., Hsi, A., Zamanian, et al  
2012; 110 (10): 1546-1550
- **Neutrophil Elastase Is Produced by Pulmonary Artery Smooth Muscle Cells and Is Linked to Neointimal Lesions** *AMERICAN JOURNAL OF PATHOLOGY*  
Kim, Y., Haghighat, L., Spiekerkoetter, E., Sawada, H., Alvira, C. M., Wang, L., Acharya, S., Rodriguez-Colon, G., Orton, A., Zhao, M., Rabinovitch, M.  
2011; 179 (3): 1560-1572
- **BMP promotes motility and represses growth of smooth muscle cells by activation of tandem Wnt pathways** *JOURNAL OF CELL BIOLOGY*  
Perez, V. A., Ali, Z., Alastalo, T., Ikeno, F., Sawada, H., Lai, Y., Kleisli, T., Spiekerkoetter, E., Qu, X., Rubinos, L. H., Ashley, E., Amieva, M., Dedhar, et al  
2011; 192 (1): 171-188
- **S100A4 and Bone Morphogenetic Protein-2 Codependently Induce Vascular Smooth Muscle Cell Migration via Phospho-Extracellular Signal-Regulated Kinase and Chloride Intracellular Channel 4** *CIRCULATION RESEARCH*  
Spiekerkoetter, E., Guignabert, C., Perez, V. D., Alastalo, T., Powers, J. M., Wang, L., Lawrie, A., Ambartsumian, N., Schmidt, A., Berryman, M., Ashley, R. H., Rabinovitch, M.  
2009; 105 (7): 639-U37
- **Reactivation of gamma HV68 induces neointimal lesions in pulmonary arteries of S100A4/Mts1-overexpressing mice in association with degradation of elastin** *AMERICAN JOURNAL OF PHYSIOLOGY-LUNG CELLULAR AND MOLECULAR PHYSIOLOGY*  
Spiekerkoetter, E., Alvira, C. M., Kim, Y., Bruneau, A., Pricola, K. L., Wang, L., Ambartsumian, N., Rabinovitch, M.  
2008; 294 (2): L276-L289
- **Experience with inhaled iloprost and bosentan in portopulmonary hypertension** *EUROPEAN RESPIRATORY JOURNAL*  
Hoeper, M. M., Seyfarth, H. J., Hoefflken, G., Wirtz, H., Spiekerkoetter, E., Pletz, M. W., Welte, T., Halank, M.  
2007; 30 (6): 1096-1102
- **Mts1/S100A4 stimulates human pulmonary artery smooth muscle cell migration through multiple signaling pathways** *47th Annual Thomas L Petty Aspen Lung Conference*  
Spiekerkoetter, E., Lawrie, A., Merklinger, S., Ambartsumian, N., Lukanidin, D., Schmidt, A. A., Rabinovitch, M.  
*AMER COLL CHEST PHYSICIANS.2005: 577S-577S*
- **Goal-oriented treatment and combination therapy for pulmonary arterial hypertension** *EUROPEAN RESPIRATORY JOURNAL*  
Hoeper, M. M., Markevych, I., Spiekerkoetter, E., Welte, T., Niedermeyer, J.  
2005; 26 (5): 858-863
- **Increased fibulin-5 and elastin in S100A4/Mts1 mice with pulmonary hypertension** *CIRCULATION RESEARCH*  
Merklinger, S. L., Wagner, R. A., Spiekerkoetter, E., Hinek, A., Knutsen, R. H., Kabir, M. G., Desai, K., Hacker, S., Wang, L. L., Cann, G. M., Ambartsumian, N. S., Lukanidin, E., Bernstein, et al  
2005; 97 (6): 596-604
- **Interdependent serotonin transporter and receptor pathways regulate S100A4/Mts1, a gene associated with pulmonary vascular disease** *CIRCULATION RESEARCH*  
Lawrie, A., Spiekerkoetter, E., Martinez, E. C., Ambartsumian, N., Sheward, W. J., MacLean, M. R., Harmar, A. J., Schmidt, A. M., Lukanidin, E., Rabinovitch, M.  
2005; 97 (3): 227-235
- **Bosentan treatment in patients with primary pulmonary hypertension receiving nonparenteral prostanoids** *EUROPEAN RESPIRATORY JOURNAL*  
Hoeper, M. M., Taha, N., Bekjarova, A., Gatzke, R., Spiekerkoetter, E.  
2003; 22 (2): 330-334
- **Effects of inhaled salbutamol in primary pulmonary hypertension** *EUROPEAN RESPIRATORY JOURNAL*  
Spiekerkoetter, E., Fabel, H., Hoeper, M. M.  
2002; 20 (3): 524-528
- **Intravenous iloprost for treatment failure of aerosolised iloprost in pulmonary arterial hypertension** *EUROPEAN RESPIRATORY JOURNAL*  
Hoeper, M. M., Spiekerkoetter, E., Westerkamp, V., Gatzke, R., Fabel, H.  
2002; 20 (2): 339-343
- **[Long-term treatment of primary pulmonary hypertension with inhaled iloprost].** *Pneumologie (Stuttgart, Germany)*  
Hoeper, M. M., Schwarze, M., Ehlerding, S., Adler-Schuermeier, A., Spiekerkoetter, E., Niedermeyer, J., Hamm, M., Fabel, H.

2001; 55 (1): 38-43

- **Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue.** *NEW ENGLAND JOURNAL OF MEDICINE*  
Hoepfer, M. M., Schwarze, M., Ehlerding, S., Adler-Schuermeyer, A., Spiekerkoetter, E., Niedermeyer, J., Hamm, M., Fabel, H.  
2000; 342 (25): 1866-1870
- **Prevalence of malignancies after lung transplantation** *International Congress on Immunosuppression*  
Spiekerkoetter, E., Krug, N., Hoepfer, M., Wiebe, K., Hamm, M., Harringer, W., Haverich, A., Fabel, H.  
ELSEVIER SCIENCE INC.1998: 1523-24