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# Compartmentalized cAMP Signaling in COPD

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# Acknowledgements

### Don't cry because it is over, smile because it happened.

When I was 5 years old, a friend of my dad asked me what my dream was for the future. I answered seriously that I would like to help my mom in the padlock factory. Honestly, I am not sure if I really understood the meaning of "dream" at that moment, but that was my first dream, even though it did not come true. Then later on, I graduated from primary school, middle school, high school and finally entered Central China Normal University, which is one of the best universities for cultivating teachers. I believe if I did not come to the Netherlands, I would become a biology teacher in a high school since that was another dream I had when I was young. Although I am very fond of investigating the mechanisms behind a phenomenon, doing a PhD was never on my dream list. In February 2013, after finishing the experiments for my master research, I came to the Department of Molecular Pharmacology to do a master internship. After one year, I decided to join the collaborative PhD project between University of Groningen and University of Göttingen (later on moving to University of Hamburg), under the co-supervision of Prof. dr. Martina Schmidt and Prof. dr. Viacheslav O. Nikolaev. I cannot tell you more how amazing my PhD was because it was mixed 4 years with excitement, loneliness, patience, discussion, tears, happiness, relief, stress, pride.... But still I am very glad and proud that I did this PhD. Now it is time to give my special thanks to all of you, who supported me during my PhD.

First, I would like to thank my first promoter and my daily supervisor in the Netherlands, **Prof. dr. Martina Schmidt**. Martina, when I was doing my master internship in Groningen, you encouraged me several times by saying "I heard you did a great blotting yesterday". Probably you never knew how meaningful for me when I heard these compliments. You taught me how to do good research, how to make good presentations and how to take my audience with me. More than that, when I was sad because some private issues, you gave me your warm hug and told me everything would be fine. When I doubted about myself, you told me firmly that I was a smart young lady. I won't forget how excited we were when we received the confirmation that my first paper was accepted. You taught me to challenge myself and to make the best out of me. Thank you so much for everything you did for me.

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# University of Hamburg

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### University of Groningen

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Haoxiao Zuo 左浩晓

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# Curriculum Vitae

The author of this thesis was born in Laixi, Shandong Province, China, on January 19, 1989. After graduating from Laixi No.1 Senior High School, she started her Bachelor in Central China Normal Univeristy (CCNU), Wuhan, Hubei Province, China, in 2007. In 2011, she received her Bachelor degree in Biotechnology. Due to her excellent performance (research, internship, social activities) during her bachelor study, she was recommended for Master study in CCNU without taking the entrance examination. Under the supervision of Prof. MD. Xu Yang, she mainly focused on investigating the potential risk of plasticizer-induced oxidative stress in depressionlike behavior using mouse model. After two years, she finished all the required courses and experiments in her projects for her Master. Then in 2013 she went to Department of Molecular Pharmacology, Rijksuniversiteit Groningen, the Netherlands, to do another internship. During her stay in Groningen, she was involved in exploring the role of cAMP compartmentalization in epithelial-to-mesenchymal transition (EMT) during cigarette smoke exposure. After receiving her master degree in 2014, she decided to come back to Groningen for her PhD study. By joining an Ubbo Emmius sandwich project, she did her PhD in the Department of Molecular Pharmacology, Groningen, the Netherlands, under the supervision of Prof. dr. Martina Schmidt and in the Institute of Experimental Cardiovascular Research, Hamburg, Germany, under the supervision of Prof. dr. Viacheslav O. Nikolaev. Her PhD topic focused on understanding the influence of cigarette smoke in cAMP compartmentalization in pulmonary diseases. The results of her PhD study are presented in this thesis.

# List of publications

# List of Publications

**Zuo H**, Cattani-Cavalieri I, Musheshe N, Nikolaev VO, Schmidt M. (2019) Phosphodiesterases as therapeutic targets for respiratory diseases. Pharmacol Ther. pii: S0163-7258(19)30015-4.

**Zuo H**<sup>\*</sup>, Cattani-Cavalieri I<sup>\*</sup>, Valença SS, Musheshe N, Schmidt M. (2019). Function of cyclic AMP scaffolds in obstructive lung disease: Focus on epithelial-to-mesenchymal transition and oxidative stress. Br J Pharmacol.

Laudette M, <u>**Zuo H**</u>, Lezoualc'h F, Schmidt M. (2018). Epac Function and cAMP Scaffolds in the Heart and Lung. J Cardiovasc Dev Dis. 3;5(1).

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Wu Y, Li K, <u>**Zuo H**</u>, Yuan Y, Sun Y, Yang X. (2014). Primary Neuronal-astrocytic Coculture Platform for Neurotoxicity Assessment of Di-(2-ethylhexyl) Phthalate. J Environ Sci (China). 26(5):1145-53.

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Martina Schmidt, <u>Haoxiao Zuo</u>. Cyclic AMP compartments drive airway epithelial-tomesenchymal transition (EMT). European Respiratory Journal 2018; 52: PA1056.

**Haoxiao Zuo**, Bing Han, Wilfred J. Poppinga, Lennard Ringnalda, Viacheslav O. Nikolaev, Martina Schmidt. Cigarette Smoke Changes cAMP Microdomains in Lung Slices. American Journal of Respiratory and Critical Care Medicine 2017;195:A7336.

Bing Han, Wilfred J. Poppinga, <u>Haoxiao Zuo</u>, Pieter Vogelaar, Kees Van Der Graaf, Andrew J. Halayko, Herman Meurs, Martina Schmidt. Effects of the Novel

Pharmacological Compound Sul-121 on LPS-Induced Airway Neutrophilia. American Journal of Respiratory and Critical Care Medicine. 2016;193:A5801.

**Haoxiao Zuo**, Wilfred J. Poppinga, Elisabeth Zeisberg, Viacheslav O. Nikolaev, Martina Schmidt. Monitoring Local Pulmonary cAMP Levels: Combining Precision Cut Lung Slice (PCLS) and Fluorescence Resonance Energy Transfer (FRET) Technologies in Mice. American Journal of Respiratory and Critical Care Medicine. 2016; 193:A5870.

Bing Han, Wilfred J. Poppinga, <u>Haoxiao Zuo</u>, Gert-Jan Euverink, Rob H. Henning, Kees Van Der Graaf, Pieter Vogelaar, Herman Meurs, Martina Schmidt. The Anti-Inflammatory and Bronchodilating Properties of the Novel Pharmacological Compound Sul-121. American Journal of Respiratory and Critical Care Medicine 2015;191:A1353

# Presentations at conferences

**<u>Haoxiao</u>** Zuo, Viacheslav O. Nikolaev, Martina Schmidt. Inhibition of A-kinase anchoring proteins attenuated TGF-β1/cigarette smoke induced cell migration in human airway epithelial cells. 2018. British Pharmacological Society winter meeting. (oral presentation)

**Haoxiao Zuo**, Lennard Ringnalda, Melissa van der Veen, Martina Schmidt. Epithelial-to-mesenchymal transition in human airway epithelial cells: Compartmentalized cyclic AMP signaling? 2018. European Respiratory Society (ERS) Lung Science Conference, Estoril, Portugal. (poster).

<u>Haoxiao Zuo</u>, Viacheslav O. Nikolaev, Martina Schmidt. Inhibition of A-kinase anchoring proteins attenuated TGF- $\beta$ 1/cigarette smoke induced cell migration in human airway epithelial cells. 2018. FIGON Dutch Medicine Days, Ede, the Netherlands. (poster).

**Haoxiao Zuo**, Bing Han, Wilfred J. Poppinga, Lennard Ringnalda, Viacheslav O. Nikolaev, Martina Schmidt. Cigarette Smoke Changes cAMP Microdomains in Lung Slices. 2017. American Journal of Respiratory and Critical Care Medicine, Washington, United States. (oral presentation).

Haoxiao Zuo, Bing Han, Wilfred J. Poppinga, Lennard Ringnalda, I. Sophie T. Bos, Loes E. M. Kistemaker, Andrew J. Halayko, Reinoud Gosens, Viacheslav O. Nikolaev, Martina Schmidt. Cigarette Smoke changes airway cAMP by upregulation of PDE3 and PDE4. 2017. Dutch Pharmacological Society (NVF) 40th anniversary meeting, Utrecht, the Netherlands. (poster).

**Haoxiao Zuo**, Bing Han, Wilfred J. Poppinga, Lennard Ringnalda, Viacheslav O. Nikolaev, Martina Schmidt. Cigarette smoke changes cAMP microdomains in lung slices. 2017. Young Investigator Meeting, Philadelphia, United States. (poster).

**Haoxiao Zuo**. Cigarette smoke changes airway cAMP by upregulation of PDE3 and PDE4. 2017. Lund University Respiratory Network meeting, Lund, Sweden. (oral presentation).

**Haoxiao Zuo**, Lennard Ringnalda, Martina Schmidt. Epithelial-to-mesenchymal transition in human airway epithelial cells: Compartmentalized cyclic AMP signaling? 2017. FIGON Dutch Medicine Days, Ede, the Netherlands. (oral presentation).

**Zuo, Haoxiao**; Poppinga, Wilfred; Zeisberg, Elisabeth; Nikolaev, O., Viacheslav; Schmidt, Martina. Monitoring local pulmonary cAMP levels: combining precision cut lung slice (PCLS) and fluorescence resonance energy transfer (FRET) technologies in mice. 2016. American Thoracic Society International Congress, San Francisco, United States. (poster).

**Zuo, Haoxiao**; Han, Bing; Poppinga, Wilfred; Zeisberg, Elisabeth; Nikolaev, O., Viacheslav; Schmidt, Martina. Cigarette smoke changes cAMP microdomains in mouse lung slices. 2016. 5th International Meeting on Anchored cAMP Signaling Pathways, Zermatt, Switzerland. (poster).

**Haoxiao Zuo**, Wilfred J. Poppinga, Elisabeth Zeisberg, Viacheslav O. Nikolaev, Martina Schmidt. Monitoring local pulmonary cAMP levels: Combining Precision Cut Lung Slice (PCLS) and Fluorescence Resonance Energy Transfer (FRET) Technologies in Mice. 2016. Dutch Pharmacological Society (NVF) Spring Meeting, Groningen, the Netherlands. (poster).

**Haoxiao Zuo**, Bing Han, Wilfred J. Poppinga, Lennard Ringnalda, Abdul Alheraky, Elisabeth Zeisberg, Viacheslav O. Nikolaev, Martina Schmidt. Cigarette Smoke Changes cAMP Microdomains in Mouse Lung Slices. 2016. FIGON Dutch Medicine Days, Ede, the Netherlands. (oral presentation).

**Haoxiao Zuo**. Cigarette smoke changes cAMP microdomains in lung slices. 2016. Symposium of the NRS Platform animal models in pulmonary research, Utrecht, the Netherlands. (oral presentation).

# Prizes and Awards

International Trainee Scholarship award. 2017. American Thoracic Society International Congress.

Longfonds travel grant to American Thoracic Society International Congress, Washington, United States. 2017.

Netherlands Respiratory Society (NRS) travel grant to 5th International Meeting on Anchored cAMP Signaling Pathways, Zermatt, Switzerland. 2016.

Longfonds travel grant to American Thoracic Society International Congress, San Francisco, United States. 2016.