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# Host-Virus Interactions in Asthma and Chronic Obstructive Pulmonary Disease

**Akademisk avhandling**

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg
Fredagen den 16 november 2018, klockan 13:00

av

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Fakultetsopponent:
Associate Professor Lena Uller
Lunds Universitet, Sverige

Avhandlingen baseras på följande delarbeten:

**I. Lanosterol Synthase Regulates Human Rhinovirus Replication in Human Bronchial Epithelial Cells.**
McCrae C, Dzgoev A, Ståhlman M, Horndahl J, Svärd R, Große A, Großkopf T, Skujat M-A, Williams N, Schubert S, Echeverri C, Jackson C, Guedán A, Solari R, Vaarala O, Kraan M, Rådinger M.
*Accepted for publication in Am J Respir Cell Mol Biol., July 2018*

**II. INEXAS: A Phase 2 Trial of On-Demand Inhaled Interferon Beta-1a in Severe Asthmatics.**
McCrae C, Olsson M, Gustafson P, Malmgren A, Lundin C, Aurell M, Fagerås M, Da Silva CA, Randers F, Cavallin A, Paraskos J, Karlsson K, Kjerrulf M, Wingren C, Monk P, Marsden R, Harrison T.
*In manuscript.*

**III. Study on Risk Factors and Phenotypes of Acute Exacerbations of Chronic Obstructive Pulmonary Disease in Guangzhou, China – Design and Baseline Characteristics.**
Zhou Y, Bruijnzeel PLB, McCrae C, Zheng J, Nihlen U, Zhou R, Van Geest M, Nilsson A, Hadzovic S, Huhn M, Taib Z, Gu Y, Xie J, Ran P, Chen R, Zhong N.
*J. Thorac Dis 2015;7(4):720-733.*

**IV. Low Human Beta Defensin 2 Levels in the Sputum of COPD Patients Associates with the Risk of Exacerbations.**
McCrae C, Zhou Y, Bruijnzeel PLB, Muthas D, Zheng J, Nihlen U, Zhou R, Tang R, Zhang M, Qian J, Xia J, Zheng J, Hadzovic S, Taib Z, Newbold P, Xie J, Ran P, Chen R, Zhong N, Vaarala O.
*In manuscript.*

**SAHLGRENSKA AKADEMIN**
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# Host-Virus Interactions in Asthma and Chronic Obstructive Pulmonary Disease

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## Abstract

Asthma and chronic obstructive pulmonary disease (COPD) are associated with periods of worsened symptoms, known as exacerbations. Severe exacerbations can result in hospitalisation, irreversible decline of the disease and sometimes death. Thus, exacerbations are a major cause of morbidity, mortality and healthcare cost. Treatment or prevention of exacerbations is an area of unmet medical need as the current standard of care has insufficient impact on exacerbation frequency and severity.

Respiratory viral infections are hypothesized to be important triggers of exacerbations. It has been shown that 41-95% of asthma exacerbations and 22-57% of COPD exacerbations are associated with a respiratory virus infection, the most common agent being human rhinovirus (RV). Other viruses frequently associated with exacerbations include respiratory syncytial virus and influenza. Prevention or attenuation of respiratory virus infections could therefore have significant impact on exacerbation frequency and severity.

The mechanisms by which viruses trigger exacerbations are poorly understood, although there is evidence for defective anti-viral interferon (IFN) responses in cells from patients with asthma and COPD. Further investigation of host-virus interactions and their impact on underlying airway disease, may lead to novel therapeutic targets for the prevention of exacerbations.

We investigated host-virus interactions in asthma and COPD through a multi-faceted approach. First, we performed an *in vitro* functional genomics screen using RNA interference (RNAi), to identify targets that are essential for RV replication in primary normal human bronchial epithelial cells. Second, we evaluated the efficacy of inhaled IFNβ-1a for the prevention of severe asthma exacerbations in a Phase 2 trial. Finally, we performed an observational, longitudinal study in COPD patients to investigate the relationship between exacerbations, viral and bacterial infections, air pollution and anti-microbial peptides (AMPs).

In the first study, we identified lanosterol synthase (LSS) as a potential therapeutic target which, when inhibited, blocks RV replication and enhances the RV-induced IFNβ response. We discovered that the mechanism of this effect was related to the induction of a regulatory sterol, 24(S),25 epoxycholesterol.

In our phase 2 trial (INEXAS), we found that inhaled IFNβ-1a did not prevent the occurrence of severe asthma exacerbations, but improved peak expiratory flow (PEF). In an exploratory analysis, we also identified potential responder subgroups, based on blood eosinophil counts or serum interleukin (IL)-18 levels.

In our COPD cohort, we found that both viral infections and increases in ambient air pollution were associated with exacerbations. Viral exacerbations were strongly associated with upregulation of the IFN response biomarkers, CXCL10, CXCL11 and IFNγ. We went on to discover that the levels of beta-defensin 2 (hBD-2), an AMP expressed by the lung epithelium, is reduced in the sputum of patients who experienced exacerbations, and further found an association between low hBD-2 levels at exacerbation and the presence of a respiratory virus.

The studies presented in this thesis have identified and evaluated key components of host-virus interactions and applied those to the context of asthma and COPD. In all cases, we found the IFN response to be central, not only to the events that occur inside the virus-infected cell, but also to the downstream consequences of infection at the tissue and organ level, likely playing a key role in both anti-bacterial and anti-viral host defense. Despite the extraordinary complexity of the interaction between the virus and its host, this thesis demonstrates that key drivers of this interplay can be identified, manipulated and, hopefully, developed into future medicines for the prevention of asthma and COPD exacerbations.

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**Keywords:** Asthma, COPD, exacerbation, virus, interferon

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