

Propositions – Stellingen

The EGFR-ADAM17 axis controls inflammatory responses in Cystic Fibrosis and Chronic Obstructive Pulmonary Disease

1. EGFR is an equally potent regulator as ADAM17 of IL6R and AREG mRNA levels and protein shedding from human bronchial epithelial cells, which establishes the EGFR/ADAM17 axis. (this thesis)
2. Activation of ADAM17/EGFR axis is induced in COPD ALI-HBEC cells upon CS exposure, but not under basal conditions, showing that COPD human bronchial cells respond more pronouncedly to external stress factors. (this thesis)
3. Increased ADAM17/EGFR axis activity is an autonomous property of CF epithelia, and this continuous signalling may contribute to inflammation and tissue remodelling observed in CF patient bronchial epithelial cells. (this thesis)
4. The EGFR/ADAM17 axis is up regulated by oxidative stress caused by CFTR deficiency. (this thesis)
5. *“Patient-oriented research led to the development of a CFTR-dependent assay using intestinal organoids that can measure the individual efficacy of CFTR modulators in a preclinical laboratory setting (Noordhoek J, Curr Opin Pulm Med 2016)”* However, whether fully developed CF lung disease can be treated with CFTR targeted agents only or requires additional treatment to counter the lung pathology remains to be established (this thesis).
6. Two dimensional (2D) cultures do not completely recapitulate the three-dimensional (3D) organization of cells and extracellular matrix (ECM) within organs, thus development of more advanced culture models is of importance to get better knowledge about cellular processes *in vivo* and predict drug responses *in-patient*. (Shamir ER and Ewald AJ, Nat Rev 2014)
7. *“Within a tissue the individual cells respond to extracellular stimuli by regulating intracellular signaling pathways that in turn determine cell fate decisions and influence the behavior of neighboring cells”.* (D'Alessandro LA, Prog Biophys Mol Biol 2015) The further challenge is to understand how these single cell signalling pathways impact the composition and architecture of complex organs.
8. The drug response and resistance of individual patients underline the importance of *“personalized medicine that requires a different type of clinical trial that focuses on individual, not average, responses to therapy”*. (Schork NJ, Nat 2015).
9. Careful analysis of the data is important to do not overlook heterogeneity that affects statistical significance, but on the other hand provides the possibility to define a marker to predict specific outcomes in specific populations - the essence of precision medicine. (Hurst JR, Am J Respir Crit Care Med 2016).
10. The collaboration among basic scientists, translational medicine researchers, clinicians, and pharmaceutical companies is the essence of the current medical progress. (Goldblatt EM and Lee WH, Am J Transl Res 2010)
11. In the realm of ideas everything depends on enthusiasm...in the real world all rests on perseverance. (Johann Wolfgang von Goethe)