Cystic fibrosis (CF) is a rare fatal genetic protein folding disease amongst Caucasian people. The disease primarily affects the lungs which often makes transplantation in the end-stage condition of the disease inevitable. On the molecular level, CF is caused by different mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The deletion of phenylalanine (ΔF508) within the nucleotide binding domain 1 (NBD1) is exhibited by 80 % of patients (Sun et al, 2008; Boeck et al, 2014). This deletion leads to a misfolded CFTR chloride channel which is prematurely degraded by the protein quality control at the endoplasmic reticulum (ER) (Sun et al, 2008). Hence, secretory cells produce highly viscous mucus accumulating in and impairing the function of several organs. So called corrector substances should overcome the fundamental processing defect of the mutant CFTR protein, allowing an increased trafficking rate to the plasma membrane. Recent findings suggest that CFTRΔF508 might need a specialized chaperone environment for proper folding which is different from the wildtyp’s (WT) needs. Substances that change the chaperone pool, so called proteostasis regulators, are thought to modulate the cellular chaperone pool in order to augment the folding and promote the rescue of CFTRΔF508 (Wang et al, 2008). Since there are a lot of proteins involved in the recognition of the mutant CFTR protein, several intervention points are possible. Changing the level of the Hsp90 activator, Aha1, was found to stabilize CFTRΔF508 and promote its trafficking to the plasma membrane. Furthermore, decreasing the Aha1 level resulted in the partial recovery of the channel function (Wang et al, 2006).

This work focuses on the identification of innovative inhibitors of the Hsp90-Aha1 complex to modulate the protein quality control of CFTRΔF508. Using the Alpha technology, more than 14,000 small molecules were screened for their potential to inhibit the interaction between Hsp90 and Aha1. In-vitro function and efficiency of identified substances were validated in an iodide-efflux assay with CFTR expressing baby hamster kidney cells (BHK). Two inhibitors, A12 and A16, increased the channel function by about 4 % of the WT’s level. The channel’s activity could be increased even further to 40 % and 22 % respectively by combining A12 and A16 with the corrector VX-809. Immunostainings of the treated CFTRΔF508 expressing BHK cells mostly verified the positive impact of the two inhibitors on the trafficking of the mutant protein. The finding of these novel Hsp90-Aha1 inhibitors provide a basis to shed new light on the complex interactions between chaperones, co-chaperones and their client proteins. Future experiments will therefore include the investigation of the detailed mode of action of these drug like molecules. Potentially, these inhibitors impair the acceleration of the Hsp90 cycle by Aha1, allowing the protein to fold properly and traffic to the plasma membrane (Wang et al, 2006).

In this work, the initial hypothesis has been proven: Changing the composition of the chaperones of the ER protein quality control by Hsp90-Aha1 inhibitors can positively influence
the folding environment of CFTRΔF508. In future, such inhibitory molecules might pave the way for the development of new rational therapeutic drugs to cure the underlying defect of CFTRΔF508 in cystic fibrosis. However, recent findings suggest that combination therapies of several drug-like molecules might be needed to effectively overcome the processing, trafficking, and gating defect as well as the shortened lifetime of the channel at the plasma membrane. Thus, A12 in combination with VX-809 or another corrector (or potentiator) might be a rational therapy for treatment of CF.