# YOU ARE INVITED TO ATTEND THE

#  DEFENSE OF THE DOCTORAL

# DISSERTATION

**“Mechanisms involved in 1,25(OH)2D3 induction of human cathelicidin in lung epithelium and suppression of inflammatory bowel disease”**

by

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**Abstract**

Although the importance of vitamin D for maintaining calcium homeostasis is well known, recent studies have shown that 1,25(OH)2D3 is also a key regulator of the immune system. In the first project we examined the role of vitamin D as activator of lung innate immune responses. LL-37 [the C terminal domain of the human cationic antimicrobial protein 18 (hCAP18)] is the only known human antimicrobial peptide cathelicidin and is encoded by the human antimicrobial peptide (CAMP) gene. We previously demonstrated that CAMP mRNA and hCAP18 are induced by 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) in human airway epithelial cells with a resultant increase in bactericidal activity. In this study we further identify key factors that cooperate with 1,25(OH)2D3 in the regulation of CAMP. Our results show for the first time that PU.1, the myeloid transcription factor, cooperates with the vitamin D receptor (VDR) and C/EBPα to enhance CAMP transcription and mRNA expression in lung epithelial cells. We also provide evidence indicating that one mechanism of enhancement of 1,25(OH)2D3 regulation of CAMP by histone deacetylase inhibitors (HDACi) is enhanced cooperation between acetylation and chromatin remodeling through BRG1 (a component of the SWI/SNF chromatin remodeling complex). BRG1 can be an activator or repressor depending on differential recruitment of BRG1 associated factors. PRMT5, a type II methlytransferase which interacts with BRG1, was found to repress 1,25(OH)2D3 induced CAMP transcription at least in part through symmetrical dimethylation of H4R3. In summary, our findings identify key mediators involved in the regulation by 1,25(OH)2D3 of CAMP gene expression in lung epithelial cells and suggest new approaches for therapeutic manipulation of endogenous gene expression in order to increase the antibacterial capability of the airway.

Vitamin D is also a suppressor of adaptive immunity. The second project focused on the enhanced resistance to inflammatory bowel disease (IBD) by 1,25(OH)2D3. We found that transgenic mice which express VDR only in the epithelial cells of the distal intestine are more resistant than VDR null mice to DSS colitis. Our findings suggest a critical role for intestinal epithelial cells in the maintenance of epithelial cell integrity and suppression of IBD by 1,25(OH)2D3/VDR.