Abstract Group: 3.3. Mechanisms of Lung Injury and Repair
Keyword 1: Idiopathic pulmonary fibrosis Keyword 2: Animal models Keyword 3: Lung injury

Title: A transient receptor potential melastin-2 deficiency significantly worsens the fibrotic response to bleomycin in mice

Dr. Carla 32785 Bauer carlamtbauer@gmail.com 1, Dr. Davide 32786 Botta dbotta@uab.edu 2, Dr. Ruoqi 32787 Peng rochepeng@yahoo.com 1, Dr. Gaurav 32788 Tyagi gaurav.tyagi@regeneron.com 3, Dr. Jonathan 32789 Phillips jonp291@comcast.net 1, Mr. Paul 32791 Harris paul.harris@takeda.com 1, Ms. Lorena 32796 Renteria lorenarenteria@gmail.com 1, Ms. Lisa 32798 Burns lisaleon11@gmail.com 1, Dr. Frances 32799 Lund flund@uab.edu 2 and Dr. Christopher 32802 Stevenson stevenson.cs@googlemail.com 1. 1 pRED, Pharma Research & Early Development, Inflammation DTA, Hoffmann-La Roche, Nutley, NJ, United States, 07110; 2 Department of Microbiology, University of Alabama at Birmingham, Birmingham, AL, United States, 35294 and 3 pRED, Pharma Research & Early Development, Non-clinical Safety, Hoffmann-La Roche, Nutley, NJ, United States, 07110.

Body: The transient receptor potential melastin-2 (TRPM-2) is a nonselective and redox-sensitive cation channel that is expressed in a number of inflammatory cells and plays a role in sensing oxidative stress. Given the role oxidative stress plays in the pathogenesis of idiopathic pulmonary fibrosis (IPF), we tested our hypothesis that inhibiting TRPM-2 function may delay the progression of this disease using the mouse model of bleomycin-induced pulmonary fibrosis. 35% of TRPM-2-deficient mice challenged with bleomycin (2U/kg) reached endpoint compared to none of the wild-type mice. Bleomycin-challenged TRPM-2-deficient mice had significantly higher Ashcroft scores, which were associated with increased myofibroblast accumulation in the lungs of these animals. Functionally, bleomycin-challenged TRPM-2-deficient mice had significantly greater measures of tissue elastance and reduced forced vital capacity compared to controls, as assessed using the Scireq flexivent system. Finally, lung CT image analysis revealed that the fibrotic response observed in TRPM-2-deficient mice was more wide-spread than observed in wild-type mice.

Contrary to our hypothesis, these data suggest that pharmacological activation of TRPM-2 may be protective in IPF.