2017 Research Grantees/Projects: Archived

Dr. Namasivayam Ambalavanan, M.D.
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Attenuation of the Congenital Central Hypoventilation Syndrome (CCHS) Phenotype *In Vitro* and *In Vivo* by HSP90 Inhibition

Dr. Namasivayam Ambalavanan, M.D., and his team, will test the inhibition effect of new compounds on heat shock protein 90 (HSP90) in CCHS cell cultures and mouse models. These compounds have promise as potential drug candidates for CCHS. Inhibiting HSP90 can prevent the formation of protein clumps in the cytoplasm. From previous research it is known that PHOX2B mutations produce protein clumps in the cytoplasm which prevent proper functioning of PHOX2B. This project will provide preliminary efficacy and safety data in advance of studies in larger animal models and possible clinical trial investigation.

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NEWLY IDENTIFIED PHOX2B-REGULATED ION CHANNELS AS POSSIBLE DRUG TARGETS FOR THE PHARMACOLOGICAL INTERVENTION IN CONGENITAL CENTRAL HYPOVENTILATION SYNDROME (CCHS)

The missing knowledge of genes regulated by PHOX2B limits our comprehension of the pathogenic mechanisms of CCHS and of molecular targets for the development of drugs that, although may not restore the neurodevelopment defects, may improve breathing defects and other dys-autonomic symptoms, with obvious benefits for CCHS patients and their families. In our laboratory, we have recently identified new genes belonging to categories important for the Autonomic Nervous System development and maintenance. Among these there are several encoding ion channels, including those selective for K^+ and Na^+ ions, important for the modulation of respiratory activity. Preliminary findings in our lab suggested that the expression of these genes can be altered by PHOX2B mutation, indicating that

they are potential therapeutic targets for the treatment of respiratory dysfunction. Furthermore, we will exploit the role of PHOX2A as a new molecular target capable of partially rescuing the function of mutant PHOX2B. Our project, by addressing some important aspects of PHOX2B and PHOX2A function, will reveal some of the still unknown molecular mechanisms of disease pathogenesis and validate the newly identified PHOX2B target genes as therapeutic targets.