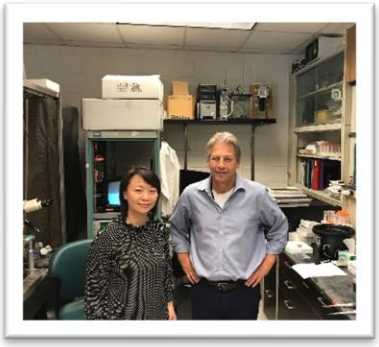
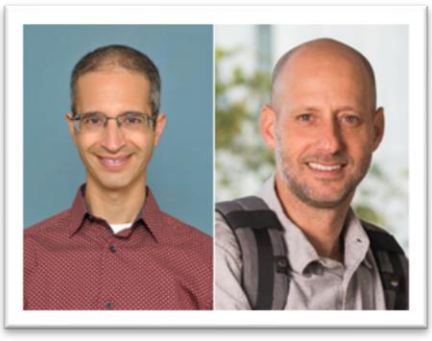
2019 Archived Research Grantees



Dr. Douglas Bayliss, Ph.D. is the Joseph and Frances Larner Professor & Chair of Pharmacology at the University of Virginia

Gene regulation by Phox2b in respiratory chemoreceptor neurons

A transcription factor called Phox2b, which controls gene expression and brain cell differentiation, is mutated in CCHS patients. In CCHS, suboptimal breathing and arousal responses to altered blood gases is a major symptom. There is evidence from CCHS patients and experimentalmouse models with Phox2b mutations that these effects arise from changes in Phox2bexpressingbrain cells that monitor blood gases (oxygen, carbon dioxide) to control breathing.Our work focuses on how these brain cells – specifically, those in the so-called retrotrapezoid nucleus, or RTN – sense and signal changes in blood gases. In work supported by CCHS Family Network, we examined gene expression in Phox2b-expressing brain cells and found a peptide messenger, named PACAP, that is made in all RTN neurons. Furthermore, we found that removing PACAP from RTN neurons blunted CO2-stimulated breathing and caused more periods of arrested breathing (apneas), with an especially prominent role at the time of birth. Notably, adding this peptide back into RTN neurons restored these deficits, suggesting that activating the PACAP system may provide a novel way to simulate breathing when RTN neurons are absent or not functioning properly. In our ongoing work, we are studying all the different genes that are regulated by Phox2b in RTN neurons, and asking what happens to those genes, and to RTN cell function, when Phox2b is mutated or eliminated. We believe this research will provide fundamental information about how Phox2b functions within this group of brain cells that is intimately associated with CCHS.



Dr. Avraham Ashkenazi, Ph.D., Department of Cell and Developmental Biology, Tel Aviv University

Dr. Gad Vatine, Ph.D., Ben Gurion University of the Negev, Department of Physiology and Cell Biology, Faculty of Health Sciences and The Regenerative Medicine and Stem Cell (RMSC) Research Center.

Investigating degradation pathways of misfolded mutant PHOX2B in neurons derived from CCHS patient-specific iPSCs

Congenital Central Hypoventilation Syndrome (CCHS) is a rare life-threatening condition affecting 1 in ~150,000 individuals. CCHS patients exhibit abnormalities in the Autonomic Nervous System (ANS), which usually present shortly after birth as hypoventilation or central apneas during sleep. Consequently, patients require lifelong support with various techniques including assisted ventilation during sleep via tracheostomy, highly impacting the quality of life of patients and their supporting families. To date, no medication was found to effectively improve spontaneous breathing during sleep. In most CCHS cases, heterozygous tri-nucleotide expansions in the PHOX2B gene lead to autosomal dominant protein mutants. However, the mechanisms underlying CCHS, are poorly understood, hindering the development of curative treatments.

Here, we propose to form an inter-disciplinary consortium consisting of two research groups and the Israeli CCHS patients' advocacy organization. Consortium participants will work together to generate patient-specific derived CCHS-disease-in-a-dish model, which will serve to test mutant PHOX2B involvement in protein homeostasis defects. Better understanding of the mechanisms and pathways affected by the mutant protein and the CCHS patient-specific models generated in our project will provide valuable platforms for future assessment of candidate treatments.

Dr. Ha Trang, MD, PhD, French Centre of Reference of CCHS, Assistance Publique Hôpitaux de Paris, Hôpital Robert Debré, Department of Physiology

Could Hypothalamic Deep Brain Stimulation improve Breathing? Pilot study determining the connectional architecture of Hypothalamic circuits controlling breathing

Deep Brain Stimulation emerges as a treatment option of motor disorders in many neurological diseases (i.e. Parkinson's disease). More recently, it is tested in different parts of the brain to address other symptoms such as hypertension, obesity or sleep disorders. In this pilot study, we aim to determine if deep brain stimulation in the hypothalamus could affect breathing, and if yes, which hypothalamic areas would be the most relevant potential targets in the treatment of central hypoventilation. In 2 non-human primates, chronic electrodes will be implanted for measurement of neurological and respiratory parameters (respiratory rate, inspiratory time, PO2 and PCO2 values). The lateral hypothalamus involvement in breathing and sleep/wake behavior will be studied by analyzing the local field potentials at baseline and after stimulation during different periods of the sleep/wake cycles. If hypothalamic deep brain stimulation improves breathing, this technique may be considered as a new treatment option of central hypoventilation for patients with CCHS. Furthermore, mapping hypothalamic areas involved in control of breathing will open up large windows of research to unknown and/or even unexpected aspects of the tangled mechanisms of brain control of breathing.