RTN and PHOX2B Research: Patrice Guyenet, Doug Bayliss, Yingtang Shi, Dan Mulkey

Background: Respiratory drive is an unconscious central nervous system process. Contraction of the diaphragm and other respiratory muscles in the chest is initiated by spontaneously firing neurons in the brain stem. This signaling is a product of complicated interactions between CNS neurons based on sensory input of CO_2, O_2 and pH (H^+). The neural control of breathing is still relatively a "black box" in systems-level physiology. While the major regions of the brain stem that are involved in respiratory drive are known, functions of the actual network components remain elusive. Research on CNS respiratory control is difficult because of the complexity of the neural networks and their anatomical locations. Today's model is: (1) respiratory neurons in the brainstem control inspiration and expiration; (2) other neurons in the same region integrate sensory information to influence ventilation; (3) the rhythmic pattern of breathing arises from brainstem neural networks with some spontaneously discharging neurons; (4) ventilation is subject to continuous modulation by various chemosensitive and mechanoreceptor-linked reflexes. The retrotrapezoid nucleus (RTN) neurons have a specific lineage and are located near the ventral surface of the rostral brainstem and consist of a bilateral cluster of glutamatergic neurons (neurons that produce the neurotransmitter glutamate, the main excitatory neurotransmitter in the mammalian central nervous system) that are non-aminergic (they don't release noradrenaline, dopamine, or serotonin at synapse) and express the homeodomain transcription factor, PHOX2B, throughout life. These neurons respond vigorously to increases in local pCO_2. RTN neurons innervate the entire ventral respiratory group, suggesting that they target many types of respiratory neurons, including those in the pre-Bötzinger complex (a neural network responsible for inspiration during the respiratory cycle).

Limitations: All of this work is done in mouse models, so it is not clear how closely the human system mimics this model. It is inconclusive that humans even have RTN neurons.

Patrice Guyenet: The retrotrapezoid nucleus, lynchpin of CO2 homeostasis

- The adult RTN produces an excitatory drive to the Respiratory Pattern Generator (RPG) that is metered to achieve CO_2 homeostasis by adjusting alveolar ventilation.
- RTN regulates breathing frequency only when the RPG is autorhythmic (i.e. slow wave sleep, quiet resting asleep and anesthesia but not during REM sleep).
- RTN operates via glutamatergic/peptidergic (producing both glutamate and peptides) neurotransmission. Its activity is regulated-via neuronal pH sensors (Task-2; GPR4) and paracrine mechanisms.
- RTN is a pH-regulated hub whose output to the RPG appears essential to match alveolar ventilation with the metabolic production of CO_2.
- At least in rodents, the absence of the RTN alone does ***not*** cause life-threatening sleep apnea or death as seen in CCHS patients.

Doug Bayliss: Molecular and cellular mechanisms for tonic activity, CO_2 sensitivity and neuromodulation in PHOX2B-expressing neurons of the retrotrapezoid nucleus

- CCHS is characterized primarily by alveolar hypoventilation, as the name implies, with reduced respiratory drive and blunted reflex regulation of breathing and arousal by elevated CO_2 or reduced O_2.
- In rodent models, substantial experimental evidence based on numerous complementary approaches has implicated a select group of PHOX2B-expressing brainstem respiratory neurons located in the RTN for the reduced respiratory drive, and especially the blunted ventilatory and arousal effects of CO_2.
- These RTN neurons are directly sensitive to CO_2 (via H^+, as proxy) and their ongoing activity reflects a host of feedforward and feedback inputs that are integrated to modulate overall respiratory drive.
- Bayliss' group has characterized the molecular phenotype of RTN neurons in mice, identifying unique markers for these cells and determining different cellular and ionic mechanisms that account for their baseline activity, intrinsic CO_2/H^+ sensitivity, neuromodulation and peptidergic excitatory transmission to respiratory centers.
- Mice with a mutated form of PHOX2B or that lack PHOX2B in the RTN have CCHS-like symptoms.

- They are also working on defining the **output** pathways of RTN neurons in wild type and CCHS mouse models, particularly the molecular characteristics of specific target neuronal groups associated with breathing and autonomic function.
- Understanding this "drive" pathway and how breathing and arousal is integrated as a cohesive process could potentially offer insights into the breathing deficiency in CCHS.

Yingtang Shi: Molecular physiology of PHOX2B-expressing brainstem neurons

- Big picture - She wants to a) understand gene expression and regulation in PHOX2B-relevant brainstem neurons, b) identify the targets of PHOX2B, c) elucidate the functional connections between PHOX2B and its targets, and d) work out the regulation of breathing and arousal in response to elevated CO_2 or reduced O_2.
- She does this using an adeno-associated virus (AAV)-mediated approach to deplete *Phox2B* expression in specific brainstem neurons based both on cell-selective expression of Cre recombinase (this is an enzyme for conditional control of gene expression) and precise neuroanatomical targeting of virus injection. Using this approach in specific gene-expressing mice, she has targeted RTN respiratory chemoreceptor neurons, the C1 adrenergic cell group, nucleus of the solitary tract (NTS), and locus coeruleus (LC) - all of these neurons have a role in breathing.
- Studying the gene regulatory functions of PHOX2B in specific brainstem cell groups relevant to CCHS may uncover novel cellular and/or molecular targets for potential therapeutic intervention.
- **Preliminary results**: PHOX2B is required for expression in the RTN of key genes involved in CO_2-stimulated breathing, specifically GPR4 and TASK-2. The rate-limiting enzyme for catecholamine synthesis, tyrosine hydroxylase, was downregulated after PHOX2B depletion in C1 and LC neurons.

Dan Mulkey: Expression of an encephalopathy-associated Kcnq2 gain-of-function variant in PHOX2B$^+$ neurons suppresses respiratory activity (He is only now starting to specifically study CCHS)

- The recurrent Kcnq2 gain of function mutation R201C has been identified in patients with neonatal epileptic encephalopathy. A primary feature of this condition is severe hypoventilation reminiscent of CCHS. Despite this, little is known about roles of Kcnq2 in control of breathing.
- Kcnq2 channels (these channels are localized to axons, where they control action potential threshold) regulate output of the RTN.
- Therefore, the RTN is considered a potential substrate responsible for Kcnq2-related breathing abnormalities.
- In support of this, Kcnq2 mutant mice exhibit a respiratory phenotype similar to humans with that same mutation including hypoventilation in room air and a blunted ventilatory response to CO_2/H^+.
- At the cellular level, chemosensitive RTN neurons showed diminished excitability.
- Mechanism of action: The function of Kcnq2 (controlling action potential threshold) in RTN neurons is regulated by a H^+-myo-inositol cotransporter (HMIT) that allows for production of phosphatidylinositol 4,5-bisphosphate (PIP2), a cofactor required for Kcnq2 channel activity.
- Moreover, at the whole animal level, conditional deletion or knockdown of Slc2a13 (the gene encoding HMIT) from PHOX2B$^+$ neurons increased the ventilatory response to CO_2/H^+, as expected for loss of Kcnq2 channel activity.
- Together, these results identify Kcnq2 channels as important regulators of RTN chemoreceptors and suggest that HMIT is a component of this mechanism.

Molecular Studies on PHOX2B: Isabella Ceccherini, Gad Vatine, Diego Fornasari, Silvia Pagliardini, Javier Oroz, Avi Ashkenazi

***Background*:** The *PHOX2B* gene provides instructions for making a protein that is important for development of nerve cells (neurons) and regulates the process by which neurons mature to carry out specific functions (differentiation). During neuronal development, the PHOX2B protein is active in the neural crest, a group of cells in the early embryo that give rise to various tissues and organs. Neural crest cells migrate to form parts of the autonomic nervous system, which controls body functions such as breathing, blood pressure, heart rate, and digestion. The protein produced from the *PHOX2B* gene contains two stretches of alanines, known as polyalanine tracts or poly(A) tracts.

Mutations in PHOX2B result in abnormal protein function and impaired gene activation. Most PHOX2B gene mutations that cause CCHS add extra alanines to the *second* polyalanine tract in the PHOX2B protein, a type of mutation that is called a polyalanine repeat expansion (PARM). The mutations that cause CCHS typically increase the number of alanines from 20 to 25 or more. Other types of *PHOX2B* gene mutations (frame shifts, stop codon mutations, insertions, deletions, substitutions…), are collectively called nonpolyalanine repeat mutations or NPARMS, and have been identified in 8 to 10 percent of individuals with this disorder. The severity of CCHS can vary, indicating the influence of other genetic factors. *PHOX2B* gene mutations that cause CCHS are believed to interfere with the PHOX2B protein's role in supporting neuron formation and differentiation, especially in the autonomic nervous system. PHOX2B regulates cellular excitability and the expression of ion channel genes, making them possible targets for pharmacological interventions in CCHS.

To study PHOX2B biology, human-induced pluripotent stem cell (hiPSC) technology is essential to overcome the limitations of current *in vivo* and *in vitro* models for CCHS and to create patient-specific cell models. Patient-specific cell models are a personalized "disease-in-a-dish" approach that allows researchers to explore molecular and cellular defects induced by CCHS-causing mutations and provide a platform for drug discovery and screening for potential therapies.

Isabella Ceccherini: Multiomics approach to identify possible PHOX2B genetic modifiers responsible for phenotypic variability in CCHS

- Cellular transcriptomics refers to a comprehensive analysis of whole sets of transcripts: mRNAs, non-coding RNAs and small RNAs from the cell. She is completing this comprehensive analysis in both normal cells and those with *PHOX2B* mutations.
- Her aim is to identify genetic modifiers of the CCHS genotype that produce different phenotypes.
- They have observed potential benefits *in vitro* (bench science) of using Hsp90 inhibitors to modulate the pathogenic cellular response.
- They are also doing whole exome (mRNA-coding DNA) sequencing in affected child-parent pairs and late-onset patients with a 20/25 genotype, with the purpose of identifying genetic variations involved in protein homeostasis, (this homeostasis ensures the proper degradation of misfolded proteins and their aggregates through protein quality control mechanisms (This is also what Dr. Ashkenazi is studying).
- This work may allow the pathways most involved in the molecular pathogenesis of *PHOX2B* PARM mutations in CCHS to be identified.

Gad Vatine: Transcriptome analysis of patient-specific iPSC-based autonomic neurons

- Creation and full characterization of induced pluripotent stem cell (iPSC) lines from three CCHS patients with 20/25 or 20/27 PARMs and two healthy control relatives (CTR).
- Findings revealed that cells derived from CCHS patients displayed a fraction of PHOX2B that did not translocate to the nucleus and instead mislocalized to the cytoplasm, indicating potential disease-relevant traits.

- Preliminary data analysis indicates that PARM-mutation and CTR lines are composed of cell clusters with differing patterns of gene expression, suggesting that PARMs may influence the differentiation process.
- They are working on creating and characterizing additional iPSC-derived neurons from other PHOX2B mutations in patients and from $CCHS^{+}$ embryos.
- Conclusion: Patient-specific platforms demonstrate biochemical and molecular distinctions between CCHS and CTR cells, making it a valuable tool for CCHS research.

Diego Fornasari: New research strategies and novel potential therapeutic targets in Congenital Central Hypoventilation Syndrome

- *In vivo* (animal work) and *in vitro* (bench work) studies indicate that CCHS results from a combination of loss of function (protein does not work anymore), dominant-negative effect (protein interferes with the normal function of the wild-type protein), and/or toxic gain of function of the mutated protein (a new function interrupts that of the wildtype protein leading to cell toxicity).
- Presently, there are no pharmacological treatments available for CCHS or its symptoms.
- However, a fortuitous clinical observation revealed that the progestin, desogestrel, might improve respiratory functions and reduce risks during sleep for CCHS patients.
- Their research demonstrated that desogestrel **downregulates** the expression of both wild-type and mutant PHOX2B proteins, along with some of their target genes. This suggests that the clinical effect may be attributed to **limiting the toxic impact of the mutant protein**.
    - ETO increases PHOX2B mRNA turnover, but does not affect protein stabilty.
    - Other progestins have the same effect as ETO.
    - ETO w/5-HT (serotonin) signaling may improve respiratory drive in CCHS.
- Recent research revealed a natural antisense long non-coding RNA, "PHOX2B-AS1" (AS1), in the PHOX2B gene locus, which influences the production of the PHOX2B protein. (Natural antisense long non-coding RNAs (lncRNAs) are regulatory RNAs transcribed from the opposite coding strand that are able to modulate their own sense (coding strand) gene expression. Their dysregulation can lead to pathologic processes).
    - There are 2 alternative transcripts of the AS1:
        - Sense = the coding DNA (gene) that is transcribed/made into a cellular protein
        - Antisense = the noncoding DNA that is transcribed but not made into a protein
    - AS1 and PHOX2B are expressed together in the same cells.
    - AS1 has a positive effect on PHOX2B expression.
    - Down-regulation of AS1 results in downregulation of PHOX2B.
    - The polyA tract might have a role in controlling the AS1 promoter (A region of DNA upstream of a gene where relevant proteins such as RNA polymerase and transcription factors bind to initiate transcription of that gene).
- The Fornasari group thinks the discovery of PHOX2B-AS1 offers the prospect of a novel therapeutic strategy targeting **antisense non-coding RNA expression** to mitigate the toxic effects of mutant proteins during *the differentiation of autonomic neurons derived from CCHS patients.*

Silvia Pagliardini: Etonogestrel promotes respiratory recovery in a model of chemoreflex impairment

- The powerful effect of hypercapnia to stimulate breathing has long been recognized and impairment of the response is one of the main symptoms in CCHS.
- The PHOX2B-expressing neurons in the RTN are critical to this response, since their ablation diminishes respiratory sensitivity to hypercapnia.
- It has long been postulated that female sex hormones have stimulatory effects on the respiratory neural networks.

- She is investigating effects of the chronic administration of a potent progestin drug (Etonogestrel - ETO) on the CO_2-chemoreflex and whether chemosensitive brainstem sites are involved.
- Major finding: Chronic administration of a potent progestin drug (Etonogestrel) restored CO_2-chemoreflexes in adult female rats ***with medium, but not large,*** RTN lesions, which may shed light on ambiguity in previous studies and supports a role of progestins in CO_2-chemoreflex potentiation.

Javier Oroz: The structure of expanded PHOX2B reveals novel pathways for its malignancy in CCHS

- Abnormal trinucleotide repeat expansions alter protein conformation causing malfunction and contribute to a significant number of incurable human diseases.
- Due to the repetitive, dynamic nature of expanded homorepeats such as polyA, their structural study is highly challenging. Only sparse structural insights are available on homorepeat-expanded proteins related to disease, which hinders the design of effective therapeutics.
- For PHOX2B, polyA repeat expansions in a 20-alanine tract are associated with CCHS.
- PHOX2B aggregation triggered by long polyA expansions is a fundamental mechanism-proposed to explain PHOX2B dysfunction in CCHS. However, the structural basis of the aggregation-prone PHOX2B mutants is still unknown.
- To help understand the pathogenic nature of polyalanine expansions in PHOX2B, Dr. Oroz' lab is determining the structure and dynamic properties of the PHOX2B C-terminal fragment. (Proteins are composed of a linear chain of amino acids linked to one another. Proteins have an amine functional group - NH_2 - at one end (N-terminal) and a carboxylic acid functional group - COOH - at the other (C-terminal).
- Interestingly, while polyA expansions do not affect the main structural conformation of PHOX2B, they **promote** nascent conformations that prompt a length-dependent **liquid to solid transition** within biomolecular condensates that capture PHOX2B (clumping/aggregration of healthy protein).
- Based on the direct observation of nascent conformations in expanded PHOX2B, Dr. Oroz proposes **unbalanced phase separation as a novel pathophysiological mechanism** in homorepeat expansion diseases (In "simple" terms, unbalanced phase separation refers to a situation where cellular proteins do not compartmentalize correctly. Think of it like oil and water not mixing as they should. This imbalance in separation can lead to problems in how cells function, potentially causing health issues or diseases).
- This paves the way towards a search for therapeutics modulating biomolecular condensates in CCHS.

Avi Ashkenazi: Regulation of proteostasis mechanisms by polyalanine expansion mutations in PHOX2B

- Background: Protein aggregation is a biological phenomenon in which aberrantly processed or mutant proteins misfold and assemble into a variety of insoluble aggregates (clumps). These aggregates can damage cells. In normal cells, "bad" proteins are marked for degradation by the attachment of ubiquitin (group of proteins) to the side chain of a residue of the amino acid, lysine. Additional ubiquitins are then added to form a multiubiquitin chain. Such polyubiquinated proteins are recognized and degraded by a large, multi-subunit protease complex called the proteasome. Proteasomes are protein complexes which degrade unneeded or damaged proteins by proteolysis, a chemical reaction that breaks peptide bonds. This process gets rid of unwanted proteins. In CCHS, mutated proteins which should be degraded are not, which leads to aggregation. Caveat: Protein aggregation has only been observed in bench models, not in "living" systems (e.g., mouse)
- Expansion mutations of trinucleotide repeats within translated sequences of either glutamine or alanine have now been linked to a growing number of neurological disorders. The exact functional or structural role of alanine repeats (polyA) within wild-type mammalian proteins is unclear.
- In the native state, a polyA sequence in the protein ubiquitin-conjugating E2 enzyme UBE2Z/USE1 contributes to USE1 ubiquitin loading by the E1 ubiquitin-activating enzyme, UBA6. This loading/activation can then mark the protein for degradation. Dr. Ashkenazi's group identified a domain (a region of the protein) in UBA6 that recognizes polyA-containing proteins (like PHOX2B).

- Under disease conditions, they have shown that UBA6 preferentially interacts with different polyA-expanded, disease-causing proteins including mutant PHOX2B, competing with USE1 binding and thereby disrupting protein degradation.
- These aberrant interactions alter downstream signaling to target proteins that are involved in neurodevelopment leading to cellular pathologies.
- Since similar effects could be seen in autonomic CCHS patient-derived neurons, they suggest that this represents a previously undescribed cellular vulnerability caused by polyA expansion mutations.

Clinical, Translational, Drug Development: Tom Keens, Ajay Kasi, Yakov Sivan, Casey Rand (Debbie Weese-Mayer), AtmosR (Nathan Bechouche)

***Background*:** The first case of CCHS reported in the literature was in 1970. PHOX2B mutations were identified as the cause of CCHS in 2003. CCHS patients are treated with mechanical venitlation - in US mostly by trach and vent, but the EU uses more non-invasive techniques. Conditions associated with CCHS include Hirschsprung's disease, cardiac asystoles, eye problems, neuroblasomas, endocrine abnormalities and inability to regulate temperature among others.

Treatment strategies in CCHS are four-pronged:

Target PHOX2B or PHOX2B regulation (ETO, PHOX2B-AS1)
Target abnormal structure of PHOX2B mutant protein (Prevent aggregation, promote correct protein folding)
Target downstream targets of PHOX2B (e.g., Ion channels)
Create new-generation technologies for ventilation and monitoring

Keynote Speaker, Tom Keens: From Discovery to Advancements: Tracing the History of Congenital Central Hypoventilation Syndrome

- Dr. Keens summarized the history of CCHS across the decades since it was first identified.
- He described the fuller understanding of CCHS phenotypes that has evolved over time.
- He listed a current set of challenges for clinicians caring for CCHS patients: Adult care; Abnormal presentations of CCHS and the need for effective medications or other treatments.

Ajay Kasi: Atypical Presentations in NPARMS

The NPARM mutations of PHOX2B are generally associated with severe phenotypes requiring full-time assisted ventilation, Hirschsprung's disease, and risk of neural crest tumors. However, recent studies have reported relatively milder phenotypes and atypical presentations in PHOX2B NPARMs including lack of hypoventilation. In this presentation, Dr. Kasi reviewed the atypical presentations and management of NPARM paitients by mean of a number of case histories

Yakov Sivan: Congenital Central Hypoventilation Syndrome in Israel - Novel Findings from a New National Center

- Dr. Sivan presented an overview of the cohort of CCHS patients that have received evaluation, follow-up, treatment, genetic counseling and family support at the Israeli National CCHS Center since its inception in 2018.
- Demographic information derived from study of CCHS pedigrees in the Israeli population suggest asymptomatic NPARM mutations may be more common than previously believed. The increased frequency of a mutated PHOX2B gene can lead to an autosomal recessive condition because of homozygous mutations (although not necessarily of the same type).
- RF cardio-neuromodulation offers a novel approach to children avoiding the need for permanent pacemaker implantation.

Casey Rand: PHOX2B Mutation-Confirmed Congenital Central Hypoventilation Syndrome (CCHS): Validating Wireless Capture of Ambulatory Biomarkers for Clinical Trial Readiness

- Currently, no pharmacologic intervention decreases the disease burden in CCHS, and the limited treatment options available are highly invasive, burdensome and offer only palliative support.
- Long considered a congenital disease with little hope for long-term improvement, mounting evidence suggests that many aspects of the CCHS phenotype, including respiratory control, cardiovascular, autonomic, and neurocognitive function, are part of ongoing disease processes that develop over time and therefore may be sensitive to intervention.
- Recent CCHS cases are known who appeared normal until a precipitating factor, such as severe respiratory infection or anesthetic exposure.
- Potential for pharmaceutical and device intervention is highlighted by reports of successful off-label drug use in CCHS case reports, cellular models indicating potential for reversing CCHS-related pathogenic processes, advances in gene editing, and development and approval of drugs and devices in diseases with shared phenotypic presentation and/or pathogenic underpinnings. These have game-changing potential for CCHS.
- The imminent potential for candidate therapeutics underscores a critical need for clinical trial readiness.
- Utilizing a suite of clinical data captured over decades of caring for CCHS patients, several potential biomarkers for CCHS have been identified that could serve as sensitive markers of disease progression and response to intervention.
- Recent advances in wireless wearable technology allow advanced monitoring of physiology during activities of daily living in the patient's own home.
- Wearable technology could validate individual and composite respiratory, cardiovascular and cerebrovascular biomarkers for stability and sensitivity to disease progression.

Nathan Beckouche/AtmosR: Drug screening discovery process for CCHS

- AtmosR has an innovative drug discovery process for CCHS.
- AtmosR employs an iterative process involving *in vitro* screening using FRAP technology to restore the molecular function of mutated PHOX2B.
- Promising compounds are evaluated in mouse models to assess their effectiveness in restoring the response to hypercapnia.
- Advanced proprietary molecules are progressing through preclinical development.
- Their goal is to develop new therapies for CCHS and improve the lives of affected individuals.

James Oakley/KeepMeBreathing: Phrenic nerve pacemaker development with biofeedback

- He has established a 5-year business plan to build the next generation phrenic nerve pacer.
- Pacer would be tied to biofeedback to "breathe" adaptively for the patient when needed.
- He reiterated the need for global cooperation across disciplines to accomplish this goal and described the anticipated roadblocks that will be encountered.

Other: Gordon Mitchel and Jan Rameriz

These two individuals spoke at the conference on aspects of breathing but are not studying CCHS directly.

Gordon Mitchell: In the translational flywheel: therapeutic acute intermittent hypoxia to improve breathing

- "Low-dose" intermittent hypoxia has beneficial effects (without detectable pathology) and is emerging as a promising therapeutic modality to restore motor function in people living with chronic spinal cord injury, ALS and other clinical disorders.
- The mechanism of intermittent hypoxia is linked to facilitation of phrenic nerve stimulation. The phrenic nerve drives the diaphragm and is the nerve stimulated by diaphragm pacemakers.
- While this may have some applications to other neuromuscular disorders, the value of intermittent hypoxia in CCHS is completely untested and its benefits are unclear given the complexity of the CCHS phenotype.

Jan-Marina (Nino) Rameriz: The pathology of dysautonomia: Lessons learned from the clinic and basic neuroscience

- In essence, he pointed out that when hypoxia is chronic or intense, it adversely affects nervous system function by triggering the formation of toxic molecules called reactive oxygen species (ROS) in cells.
- Dr. Ramirez surveyed a number of conditions characterized by disruption of the autonomic nervous system with particular emphasis on the relationship between breathing and cardiac function.

Posters

Stephen Abbott Ph.D. is the PI of a research lab based in the Department of Pharmacology at the University of Virginia. The Abbott lab aims to elucidate the central control of cardiovascular and respiratory function through neurophysiological studies in rodents.
Neuromedin B-expressing neurons in the retrotrapezoid nucleus regulate respiratory homeostasis and promote stable breathing in adult mice

Fatima Amer-Sarsour is a Ph.D. student in Dr. Avraham Ashkenazi's research group at Tel Aviv University, Israel investigating protein homeostasis mechanisms in trinucleotide repeat expansion diseases.
Investigating protein degradation pathways in cell-based models of congenital central hypoventilation syndrome

Silvia Cardani, Ph.D. is a member of the Silvia Pagliardini lab at the University of Alberta, Edmonton, Canada, investigating the site of action and mechanism of sex hormones and their use in hypoventilation syndromes.
Silencing of PHOX2B in the RTN affects chemoreflex response

Daniel Falik is a Ph.D. student in Dr. Gad Vatine's lab at Ben Gurion University, Israel. Dr. Vatine's lab studies rare neurological diseases using human iPSCs and bioengineered platforms known as Organ-on-Chip to improve the physiological relevance of iPSC-derived cells.
Uncovering mechanisms underlying CCHS using induced patient-specific pluripotent stem cells

Tayler Hedgecock is a Ph.D. candidate at the University of Tennessee Health Science center in Memphis. His thesis project is to identify transcriptional and proteomic changes attributed to CCHS mutations in PHOX2B.
PIEZO2 as a Molecular Candidate for the Respiratory Phenotype Caused by Mutations in PHOX2B

Martin Samuels, M.D. has cared for cohorts of children with CCHS at Great Ormond Street Children's Hospital in London and Staffordshire Children's Hospital for over 30 years, consults in Pediatric Respiratory Medicine, advises the UK CCHS Family Support Group, and has been guideline lead for a European Union CCHS Network project.
Modified hypoxic challenge testing in CCHS advises flying: an observational study

Jessica R. Whitaker-Fornek, Ph.D. is a postdoctoral fellow at the University of Michigan working as part of Erica Levitt's lab team. She studies the physiology of pontine, respiratory-controlling neurons in male and female Rett Syndrome mice. Rett Syndrome is a rare, severe neurodevelopmental disorder that is characterized by breathing abnormalities. Jessica is using acute brain slice electrophysiology to study the function of inhibitory synaptic transmission on KF neurons in the context of Rett Syndrome.
Inhibitory synaptic transmission in the Kölliker-Fuse of Rett Syndrome mice