JOHNS HOPKINS
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We are looking for highly motivated **postdoctoral candidates** to join the laboratory of **Charlotte Sumner, MD** at Johns Hopkins University to lead studies elucidating mechanisms of neurodegenerative disorders of motor neurons. Candidates should have a doctoral degree and strong research background. Please send statement of research experience and career goals, copy of Curriculum Vitae, and contact information of references to **csumner1@jhmi.edu**. The position is for 2 years or more and is fully funded. Candidates can start at any time. The Johns Hopkins Medical Institutions provide a stimulating and collaborative environment for biomedical research.

Research focus: The long-term goal of our research program is to advance therapeutics for spinal muscular atrophies (SMAs), early-onset motor neuron (MN) diseases causing early mortality. We focus on proximal SMA caused by recessive mutations of the survival motor neuron 1 gene (*SMN1*) and distal SMA (dSMA) caused by dominant mutations of the transient receptor potential vanilloid 4 gene (*TRPV4*) because of fundamental roles played by the encoded proteins in the nervous system and their therapeutic tractability. Our work contributed to the development of new treatments for proximal SMA (e.g. the splice-switching antisense oligonucleotide nusinersen, the splice-switching small molecule risdiplam, and the gene replacement therapy onasemnogene abeparvovec that are now at the forefront of rapidly emerging gene-targeting therapeutics. This represents a transformational success, but clinical efficacy is highly variable ranging from normal attainment of early motor milestones to no improvement in motor function. Defining the factors underlying this variability and identifying strategies to optimize therapeutic efficacy are critical to further advancing therapeutics for SMA as well as other neurological diseases. In 2010, we and others discovered that TRPV4 mutations cause dSMA and Charcot-Marie-Tooth disease 2C. TRPV4 is a promising *new* therapeutic target because it is the only ion channel known to cause MN disease and is expressed at the cell surface where it is accessible to existing small molecule antagonists that have good tolerability in humans. Currently, we are leveraging unique resources and state-of-the-art technologies to define factors limiting current SMA therapeutics, characterize molecular and cellular SMA disease mechanisms, and identify and validate novel therapeutic strategies.

Projects: In recent studies of proximal SMA, we have demonstrated that pathology begins *in utero*, before treatments are currently initiated in patients. Current projects: 1) dissect mechanisms regulating SMN expression during development and treatment, 2) identify mechanisms causing impaired maturation and degeneration of SMA MNs, and 3) develop novel and *in utero* SMA therapeutic strategies. In recent studies on dSMA, we have shown that mutations of TRPV4 disrupt regulatory protein-protein interactions, cause a gain of channel function**,** and breakdown of blood neural barriers. Current projects: 1) characterize protein interactions regulating TRPV4 channel activity, 2) evaluate the role of TRPV4 in modulating EC barrier function, and 3) assess TRPV4 antagonists as a therapeutic strategy in dSMA mice and ultimately other disorders characterized by BNB disruption. Experimental approaches include human genetics, biochemistry, cell biology, molecular imaging of human material and mouse models (including 7 new genetically engineered mouse lines in the past 5 years). Additional new experimental approaches include iDISCO, isogenic iPSC-derived 3D culture systems, and spatial and single-cell transcriptomics.

Select recent references: 1) Kong et al. Impaired prenatal motor axon development necessitates early therapeutic intervention in severe SMA. **Science Trans Med**, 2021;13:eabb6871. 2) McCray et al. Neuropathy-causing TRPV4 mutations disrupt TRPV4-RhoA interactions and impair neurite extension. **Nature Commun**, 2021;12:1444. 3) Woolums et al. TRPV4 disrupts mitochondrial transport and causes axonal degeneration via CaMKII-dependent increases of intracellular Ca^{2+}. **Nature Commun**, 2020;11:2679. 4) Sullivan et al. A dominant mutation in the notch ligand JAG1 as a novel cause of Charcot-Marie-Tooth disease type 2C. **JCI**, 2020;130: 1506-1512. 5) Ramos et al. Normal developmental, disease and post-therapy SMN expression: implications for treating SMA patients. **JCI,** 2019, 129:4817-4831. 6) D'Ydewalle et al. The antisense transcript SMN-AS1 regulates SMN expression and is a novel therapeutic target for spinal muscular atrophy. **Neuron** 2017; 93:66-79.