***{for Promotion to Associate Professor with tenure}***

**Personal Statement - Mark D. Parker, PhD**

Assistant Professor of Physiology and Biophysics

1. Research and Scholarly Accomplishments

Ever since I was an undergraduate student, I have been fascinated by membrane transport proteins. I was intrigued that one of the most fundamental physiological processes—moving ions, nutrients, and waste products across cell membranes—was among the least well understood. The solute carrier (SLC) proteins that mediate many of these processes in humans remain understudied despite their associations with disease and their potential as novel pharmaceutical targets. I studied for my PhD in the 1990s, an exciting time when genetic studies were linking SLC dysfunction to disease, the first 3D structure of a membrane protein was reported, and completion of the human genome was revealing the existence of hitherto undescribed genes that encoded SLCs whose substrates and role in health and disease had yet to be assigned. My entire scientific career has been focused on the SLC4 family of SLCs that transport acids and bases. These proteins regulate pH throughout the body, maintaining an optimal environment for all biological processes. My current research program focuses on two members of the SLC4 family: SLC4A4 (which encodes the archetypal sodium/bicarbonate cotransporter NBCe1) and SLC4A11 (an unusual member of the family that conducts protons).

# SLC4A4: The electrogenic Na+/HCO3− cotransporter NBCe1

**Background:** NBCe1 is expressed in a diverse array of cells throughout the body. For example, it is a key component of the cellular mechanisms of the kidney that supply blood plasma with sufficient HCO3− to neutralize dietary and metabolic acids and in duct-lining cells NBCe1 replenishes the intracellular HCO3− lost during secretion of HCO3−-rich fluids. Mutations in the NBCe1 gene cause proximal renal tubular acidosis (pRTA): a severe systemic disease characterized by acidic blood, stunted growth, and blindness.

**Previous experience:** Between my time as a student and postdoctoral researcher I had worked on various aspects of pH regulation and HCO3− transport for more than 15 years prior to joining UB and am considered one of the leading experts in the field. By the start of my appointment in 2013 I had published 21 peer-reviewed articles on the subject (nine as first or senior author), two book chapters, and three reviews culminating in a 153 page article in Physiological Reviews.

**Research completed at UB:** Upon starting at UB in November 2013 I began collaborating with Dr. Weibo Xia, an endocrinologist at the Peking Union Medical College in China, to determine the cause of a particularly severe case of pRTA in an individual under his care. Combining his clinical data and patient access with my molecular capabilities and familiarity with pRTA literature we determined that the individual carried two different mutations in the SLC4A4 gene and that the mutations caused NBCe1 to be withheld from the cell membrane and that individual NBCe1 molecules, although capable of normal Na/HCO3 cotransport activity, exhibit an unusual chloride leak. ***I leveraged our preliminary data to get a two-year $200,000 career development grant from the American Society of Nephrology (July 2015- June 2017) and we ultimately published two high impact manuscripts on these mutations (Myers et al,***

***J Physiol, 2016; Myers et al, Sci Rep, 2018). A modified figure of our cultured kidney cells from the first paper was selected as the cover image for the November 2016 issue of The Journal of Physiology.*** Any description of a new case of pRTA is significant because there have only been a total of 15 cases reported to date; our study was the first to report two different mutations in one patient. Besides the acidic blood and blindness, no two individuals exhibit exactly the same set of disease signs; our study added extra weight to the association between NBCe1 defects and several of these signs including dental defects and paralysis. We were also able to correctly predict that the patient would exhibit cerebral calcifications; a sign present in some other patients that had been previously overlooked in CT scans of this individual but which could underlie some of the patient’s neurological defects. Our discovery of the chloride leak through the mutant transporter was also significant as a feature that could disrupt the electrochemical balance of NBCe1-expressing cells and could in itself be pathological.

**Current focus at UB:** Presently the only therapy available to individuals with pRTA is the same as that for any form of acidosis: alkali dosing. The dogma is that correcting blood pH early enough could prevent the development of disease signs. However, there is no data to confirm that hypothesis. I suspected that at least some signs of the disease, such as blindness, could be the primary consequence of loss of NBCe1 function from cells in the eye rather than being a secondary consequence of the whole body acidosis that is caused by loss of NBCe1 from the kidney. Previous studies have tended to minimize the importance of NBCe1 expressed outside of the kidney. To test my hypothesis I developed (in conjunction with the Transgenics Center at Roswell Park) a mouse that lacked the ability to express NBCe1 outside of the kidney. The results were surprising even to me: despite a normal blood pH from birth, these mice exhibited the stunted growth, eye disease, and dental defects characteristic of pRTA. Not only does this highlight the physiological importance of non-kidney NBCe1, but also shows the inadequacy of alkali dosing as a therapy for pRTA. **The ocular defects of these mice formed one cornerstone of our application for a five year $1.9 million R01 grant that was awarded to our research team (including Dr. Michael Duffey and Dr. Sangita Patel) by the National Eye Institute in February 2018.**

**Future development:** Our first manuscript on NBCe1 mice, describing their general phenotype, is in preparation. Several more studies are underway to expand our understanding of the role of NBCe1 in specific organ systems with the plan either to convert these into streams of research support or manuscripts, depending on their promise. For example, the dental defects of these mice formed part of a 2017 R21 application to the National Institute of Dental and Craniofacial Research that was scored but not funded. We will resubmit this application once we have sufficient new data to respond to the reviewers’ comments. We also plan to study the cardiac and intestinal phenotypes of these mice and target them to the American Heart Association and Cystic Fibrosis Foundation.

# SLC4A11: A H+ conductor

**Background:** SLC4A11 is an unusual member of the SLC4 family because it does not transport bicarbonate. Mutations in SLC4A11 cause a progressive loss of vision and hearing.

**Previous experience:** During my PhD I was involved in the discovery and cloning of the SLC4A11 gene. Because the protein did not respond to our regular assays we were initially unable to ascribe a function

to SLC4A11 and I moved on to working on other aspects of the SLC4 family. Over the following decade numerous, often contradictory, papers were published by others describing new theories of SLC4A11 action. In preparing for my independent career and wishing to differentiate myself from my postdoctoral mentor’s research program, a colleague and I applied for and were awarded an R21 grant from the National Eye Institute to develop new tools (antibodies, mouse models) with which to probe SLC4A11 function.

**Research completed at UB:** Having established my new lab, I decided to repeat some of the assays that others had applied to SLC4A11 in order to reconcile the diverse theories of its operation. We were able to repeat much of the data of others and came to the novel conclusion that all of the data could be explained by a single mechanism of operation: a pH-sensitive H+ conductance. **Our findings (Myers *et al*, Am J Physiol, 2016) inspired an editorial article in the December 2016 issue of The American Journal of Physiology (Nehrke, Am J Physiol, 2016) and was the basis of my New Investigator Award from the American Physiological Society in 2017. Our remaining preliminary data formed the second cornerstone of our aforementioned R01 grant that was awarded to us in February 2018.**

**Current focus at UB:** My research program, as outlined in the R01 application, now focuses on understanding the molecular mechanism of SLC4A11 (e.g. what makes it pH sensitive, why do NBCe1 inhibitors stimulate SLC4A11 action?), developing a model of the role of this action towards maintaining ocular health, and studying the effects of SLC4A11 loss in a mouse model of the corneal disease. We have also unexpectedly found that saline eye drops reverse the corneal swelling that is characteristic of the disease and seek to understand how these drops exert their effect as a treatment for the eye disease.

**Future development:** Besides continuing to follow our interest in the role of SLC4A11 in the eye and renewing our R01, we are also in the process of studying the aural phenotype with Dr. Richard Salvi in the Department of Communicative Disorders and Sciences with the intention of applying for an R01 award from the National Institute on Deafness and Other Communication Disorders.

# Other research activities

As a leading expert in the field, I collaborate with numerous researchers around the world; as demonstrated by my co-authorships on papers from China, Denmark, the Netherlands, and the United Kingdom and acknowledgements on papers from Brazil. My local collaborations with individuals from the School of Pharmacy and Pharmaceutical Sciences and School of Exercise Sciences have also resulted in co-authorships on papers (*Jones et al, Mol Pharm, 2017; Schlader et al, Med Sci Sports Exerc, 2017*) as well as co-investigator status on several funded (IMPACT award to Morris) and pending (R01 application from Schlader [scored 4th percentile and anticipated to be funded late in 2018]; R01 application from Morris awaiting review) grant applications

1. Educational Activities and Teaching

**Academic Teaching:** Teaching is an important responsibility. As I remember from my own time as a student, a good teacher can enhance a student’s exam performance and even inspire a lifelong enthusiasm for a topic. It is the occasions when students tell me that they enjoyed a class, thank me for making a dreaded subject understandable, or ask to join my lab to undertake research projects that provide my motivation each year for wanting to do as good a job as possible for the incoming students. My goal in the classroom is to present class material in as clear and as non-intimidating a way as possible so that the students can experience the joy of understanding, rather than of just the chore of learning.

My classes are mainly mixed between small-group graduate discussions and large-class undergraduate lectures.

**PGY405/505** (**Cell and Membrane Physiology).** I have taught this class to a group of 20 undergraduate/graduate students for the last four years. During this time I developed ten new classes around the topic of epithelial transport processes. Most recently I was involved in developing and implementing a new syllabus, and acting as unofficial course coordinator. Several students from this class have gone on to do research projects in my lab.

**PGY502** (**Renal Physiology).** I have taught these classes to a group of ~90 dental students for the last three years. I present ten hours of material with a much appreciated review session at the end that narrows the focus of the material to what is required for the exam.

**BMS511 (Critiquing Literature)** and **PGY552R (Human Physiology Recitation)** are both small-groups journal-club style meeting with no more than 5 graduate students. This year is my fourth for BMS511 and second for PGY552R. As far as possible, I encourage the students to lead the discussions, interjecting only to keep discussions on track.

**PGY412 (Applied Physiology)** and **PMY302 (Introduction to Pharmacology)** are large undergraduate classes with more than 200 students each. I teach two hour-long classes related to water balance in each and have taught both for the last three years. PMY302 now runs twice per year and I have recently begun the process of converting my material for an online version of the course.

**Research Teaching:** I have hosted six **undergraduate students** from numerous departments (biological sciences, biomedical engineering, biomedical sciences, and medicine) in order to foster their interest in physiology research. They have often enjoyed their experience enough to return for several semesters and I have maintained contact with several since their graduation. In order to add value to their experience I have encouraged them to apply for funding and present posters at regional and national meetings in order to enhance their CVs and enable them to make informed decisions about their future graduate careers. Between them the six students have gathered $6,500 in awards and presented seven posters. For **graduate students**, I have hosted one Master’s student and three PhD students. One of the students has recently graduated and has taken a postdoctoral position at the University of Rochester. During his time in the lab he won three major awards from national societies, presented a talk and two posters at national meetings, was first author on three research papers in high impact journals, co-

authored one more paper, and co-authored a review. My other students have only recently started in the lab, but I intend to actively encourage them to pursue funding and other accolades.

**Commentary on Evaluations:** I have performed well in course evaluations, and typically achieve ranks of ‘good’ or ‘excellent’. In courses taught by multiple instructors, my evaluations rank my performance as being above the average.

**Program administration:** Beyond setting exam questions (all courses), proctoring exams (PGY405/505, PGY502, PMY302), and grading exams (PGY405/505), I acted as unofficial course administrator for PGY405/505 last year, assembling the syllabus, coordinating contributing faculty, and acting as the primary course contact for the students. I have also served on numerous thesis committees for Jacobs School (Departments of Physiology and Biophysics, Ophthalmology), other Schools at UB (Pharmacy & Pharmaceutical Sciences, Public Health and Health Professions), and other Institutions (New York University Langone School of Medicine).

**Future Goals:** I will continue to hone my classes with the aim of providing the students with the best possible learning experience. PMY302 is shortly to migrate to an online course for which purpose I will have to learn the tools necessary to create suitable online content. An online presence is in tune with the way that today’s students receive and process information and the migration of courses online, if done correctly, can minimize the teaching burden while maximizing tuition income by eliminating issues of schedule clashes and geographic restrictions. In the near future, we might consider creating online content for our own PGY courses. I believe that our PGY405/505 course is a unique and valuable resource for future physiologists and should be made available to as many students as possible. I would also value the opportunity to get involved in the teaching of medical students.

1. Service

I have been fortunate to have been given many opportunities to **serve the Jacobs School** and have taken them all. The two most important have been my five years on the PhD Program in Biomedical Sciences (PPBS) Admissions Committee (three years as a primary reviewer), and my two years as Secretary of the Faculty Council and Faculty Council Steering Committee. In these roles I have been able to help ensure the quality of the incoming graduate student body, learn about Medical School administration, and contribute towards Jacobs School policy development and preparation for LCME accreditation. In my role as council secretary I developed a standardized format template onto which all policy documents could be transcribed to aid with readability and inter-document consistency.

In the **wider scientific community**, I have served on the editorial advisory board for the American Journal of Physiology: Cell Physiology (Impact Factor 3.4) since 2016. I estimate that I review ~10 manuscripts per year for The American Journal of Physiology: Cell Physiology and others. I have also reviewed grant applications for the National Research Foundation of Korea and for the non-profit

vision organization ‘Fight for Sight’. I have also supported summer research placements in my laboratory for one high school student and one local Biological Sciences undergraduate student from Notre Dame.

**Future plans:** I hope to continue my service on the valuable PPBS Admissions Committee and, although my term on the Faculty Council Steering Committee is shortly to expire, I hope to return to the Steering Committee in the future in another capacity to follow the implementation of the new Jacobs School policies and bylaws and learn more about Medical School governance.