



### SSR Research Award

*(Supported by the Society for the Study of Reproduction)*

The SSR Research Award recognizes an active, regular member of the Society for outstanding research published during the previous six years. Criteria for the Award include the significance of problems under investigation, the breadth and depth of the analyses performed, and the level of originality manifested in the publications of this work. The recipient of the 2012 SSR Research Award is **Sylvie Breton, Ph.D.**

Dr. Sylvie Breton, Associate Professor of Medicine at Harvard Medical School, received her B.Sc. in Physics in 1983 and her M.Sc. in Biophysics in 1986 from the University of Montreal. She then became a research assistant in the Membrane Transport Research Group, where she worked for the next six years, gaining considerable experience in the application of electrophysiological techniques to study transepithelial ion transport processes in renal tubules. She enrolled in the Ph.D. Program at the University of Montreal in 1991 and successfully defended her thesis in 1994. She then conducted postdoctoral studies on the cell biology of acid/base transport by the kidney at Harvard Medical School. In 1996, she joined the Faculty of the Department of Medicine at the Massachusetts General Hospital (MGH) and Harvard Medical School, where she developed her laboratory in the male reproductive field.

She is the recipient of numerous awards, including the MGH Claflin Distinguished Scholar Award in 1997, the American Physiological Society Renal Section Investigator Award in 2005, and the MGH Joseph Martin Basic Research Prize award in 2008 for the best paper of the year. She is currently the Charles and Ann Sanders Scholar at MGH. She has received continuous National Institutes of Health (NIH) funding for her work since arriving at the MGH, including a prestigious NIH transformative R01 in 2009.

Dr. Breton is a leading figure in epididymal transport physiology. Her laboratory uses a variety of state-of-the-art techniques and novel animal models to study transepithelial transport processes in the epididymis, a relatively understudied organ in male reproductive physiology. Her research efforts are divided into four main research projects, each of them receiving NIH funding.

*Luminal acidification.* The lumen of the epididymis is maintained acidic compared to blood. This process is a prerequisite for keeping sperm in a dormant state during their maturation and storage. In a 1996 *Nature Medicine* paper, Dr. Breton showed that proton secretion is mediated by a subpopulation of epididymal epithelial cells, the clear cells, via the proton pumping V-ATPase. Since then, she has identified a novel pathway for the sensing and regulation of extracellular pH via the bicarbonate-activated soluble adenylyl cyclase (sAC) and the V-ATPase. She showed that activation of sAC in clear cells following elevation of luminal pH or bicarbonate concentration triggers the cAMP-PKA signal transduction pathway to increase the surface expression of the V-ATPase and increase proton secretion. As sAC is expressed in other acid/base transporting epithelia, including the kidney, this pathway may represent a widespread mechanism that allows cells to sense and modulate extracellular pH. These results highlight a

mechanism by which cAMP can be elevated in these epithelial cells without the participation of neurotransmitters or hormones.

*Water and solute transport.* The composition of the luminal environment of the epididymis and vas deferens is tightly regulated. Major fluid reabsorption occurs in the epididymis, leading to a significant increase in sperm concentration. Therefore, water movement in the excurrent duct is crucial for male fertility. Dr. Breton identified AQP9 as a major apical aquaporin in the epididymis. AQP9 is an aquaglyceroporin that can transport neutral solutes in addition to water. A major cause of male infertility in humans is cystic fibrosis (CF), and water transport linked to CFTR-dependent chloride secretion is an important step that helps control the final fluidity of the luminal content. Although the epididymis is one of the most affected organs in CF, very little is known about the mechanisms that lead to its malfunction. Dr. Breton showed that AQP9 and CFTR co-localize in the apical membrane of principal cells of the epididymis, that they co-immunoprecipitate, and that CFTR is a key regulator of AQP9-dependent permeability. Obstructive pathologies followed by atrophy of the male reproductive tract occur in men with cystic fibrosis. Her laboratory is currently examining the possibility that impairment of water transport following disruption of a functional complex between AQP9 and CFTR might contribute to the pathogenesis of male infertility in cystic fibrosis. In addition, she is examining the role of CFTR in the purinergic regulation of the epididymal epithelium.

*Cell-specific genomic and proteomic profiling and intercellular communication networks.*

Transepithelial transport in the epididymis involves a concerted interaction between the different cell types that form the epithelium

(clear, principal, and basal cells). Dr. Breton is currently dissecting the factors involved in the establishment and maintenance of the mature phenotypes of these cells, as well as factors that coordinate their ion transport activities. This information is critical to our understanding of the control of male reproductive physiology. Her laboratory uses novel molecular biology tools and transgenic model animals expressing cell-specific fluorescent proteins in an integrated approach to characterize the patterns of gene expression in clear cells and principal cells during postnatal and pre-pubertal development, under normal and pathophysiological conditions. In particular, she examines how the cellular elements for luminal acidification are established by cell-specific differentiation, and how transepithelial acid/base transport is subsequently modulated via cell signaling processes in the final differentiated epithelium. The ultimate goal of this research is to determine how abnormal acidification may impair male fertility, and how interventions to affect acidification may eventually be used to control male fertility.

*Three-dimensional modeling of basal cell function in pseudostratified epithelia.* Many organs in the body, including those of the reproductive and airway tracts, are lined by epithelial cells. The prevailing view is that so-called “basal cells” in pseudostratified epithelia are never in contact with the fluid- or air-filled lumen. Dr. Breton has recently made the paradigm-shifting discovery—published in *Cell* and featured as an Editor’s pick in *Science*—that epithelial basal cells in the epididymis and trachea in fact send out long, slender cytoplasmic projections that penetrate the tight junction barrier and scan the lumen or organ cavities like antennae in search of “signaling” molecules. They then transmit their findings to adjacent cells to modulate epithelial and, indeed, whole organ function. In the

epididymis, these basal cell sensors detect the presence of luminal angiotensin II, which upon the arrival of spermatozoa in the lumen stimulates acidification in the male reproductive tract to promote sperm maturation and storage. This transepithelial sensing apparatus is also present in other male accessory glands, including the prostate, where it may also regulate

important signal transduction processes, perhaps up to and including cell proliferation. This is literally a “breakthrough” discovery that demonstrates the continued power of innovative investigators such as Dr. Breton to re-evaluate and replace current dogma with fresh, new ideas. *(Submitted by Dennis Brown, Ph.D.)*