The Role of Tissue Barriers in Health and Disease

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Executive Summary

Multicellular organisms require maintenance of defined environments provided by tissue barriers for proper function. For example, neuronal signaling requires formation of the blood-brain and blood-retinal barriers to allow strict extracellular control of neuroactive agents and the ionic environment. Kidney function requires precise array of ion barriers through the loop of Henle to allow controlled resorption of fluids and salts. The digestive tract actively maintains a tight barrier to the gut lumen providing precise control of fluids, ions and nutrients that enter the body and preventing bacteria and viruses from entering. Nearly every organ system in the human body requires some degree of barrier formation - whether it is in epithelial sheets coating organs or lining ducts, or in endothelial tubes of vessels. Further, these barriers are often disrupted in disease conditions. Loss of the blood-brain barrier is a hallmark of stroke, brain tumors, Alzheimer's disease and traumatic brain injury. Loss of blood-retinal barrier is associated with the leading causes of blindness including diabetes and age-related macular degeneration. Loss of barrier in the intestinal epithelium is associated with inflammatory bowel diseases (IBD) like Crohn's disease and ulcerative colitis. Additionally, over 85% of cancers arise from epithelial tissues, and cancers of epithelial cells (a.k.a. carcinomas) are closely associated with loss of barrier properties. Finally, developing methods to safely and specifically deliver therapeutics across these barriers remains a major challenge, particularly for diseases of the nervous system.

Collectively, understanding how cells connect to form tissue barriers is fundamental to understanding organ system function and is central to developing effective treatment strategies for a wide range of debilitating diseases. These barriers are created by differentiation of cells to develop well-defined junctional complexes including adherens junctions, tight junctions, and desmosomes as well as communicating gap junctions. In addition, the methods of transcellular trafficking through vesicles and transporters are tightly controlled in content and polarity.

The University of Michigan boasts a wide range of experts in the area of Barriers Biology across multiple disciplines, departments, and colleges. Many of these researchers and clinician scientists have already been meeting routinely over the past 3 years to present new data, exchange ideas, and encourage collaboration and novel research strategies. The Biosciences Initiative Funding Opportunity provides an ideal chance to build upon our current strength in Barriers Biology by further developing our expertise and encouraging new collaborations among barriers researchers here at the University of Michigan. The focus of the current Exploratory Funding request will be to recruit outside experts to work alongside Michigan experts to facilitate two, 2-3 day workshops for the Michigan Barriers Biology community focusing on two specific emerging areas:

1. Using induced pluripotent stem cells to create **"organs on a dish" in order to model *in vivo* barriers** and develop potential novel stem cell therapies.
2. Using **super-resolution microscopy** for high resolution imaging of cell-cell junctions and their dynamics.

We expect these courses will not only help individual labs move their research forward in exciting new ways, but also provide a platform for investigative teams to come together to develop new initiatives (e.g. via the Biosciences Initiative and Program Project Grants) to address critical questions: understanding the role of barriers in tissue growth and differentiation, how patient specific mutations impact barrier function and therapeutic delivery, and how barrier restoration can be achieved to reduce or ameliorate disease pathology in a range of organ systems.