Research training & graduation projects in gastroenterology: 1.5 credits/week (typically 10, 20 or 30 weeks)

Course code:
Application code:
Time: 100%
Term: Spring/Fall 2019

Project Title: Gut permeability and endotoxemia: New methods to assess relationships between gut barrier function, inflammatory status and disease processes

Project type: Laboratory: Human blood, urine and tissue preparation, protein separation, enzymology and fluorescence spectroscopy

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Project description

Increased gut mucosal permeability is now a recognized early warning system for upcoming health problems. It is an early event in type 2 diabetes, inflammatory bowel disease (IBD), Parkinson's disease, post-infectious irritable bowel syndrome (PI-IBS) and colon cancer. We also suspect involvement in juvenile idiopathic arthritis (JIA), also called juvenile rheumatoid arthritis (JRA). We have initiated a series of studies to explore *in vitro* and *in vivo* regulation of tight junctions that form the gut barrier that determine the extent of permeability. The primary molecules of interest are Vibrio cholera toxin (ZOT) and zonulin. The term "zonulin" was coined to assign a name for the otherwise unknown eukaryotic protein having immunoreactivity with an antibody against ZOT. Based on amino acid sequencing analysis, zonulin was claimed to be one and the same as prehaptoglobin-2. Current models of dysregulated permeability postulate that zonulin is secreted from gut epithelial mucosal cells and targets protease activated receptor 2 (PAR2) on plasma membrane of gut epithelial cells, which through second messengers, opens tight junctions, making them more permeable. PAR2 is postulated to be the functional receptor for both ZOT and zonulin. There are now drugs stated to be based on zonulin amino acid sequence in Phase 2b clinical trials that either agonize (AT1002) or antagonize (AT1001) PAR2. AT1002 is pursued to improve drug absorption, while AT1001 is being pursued for celiac disease. This project will test several hypotheses around the concept of ZOT signaling at PAR2, envisioning a revised model to arise from experimental results. There are a number of questions permitting more than one student to enroll. There are possibilities for students to choose between a few different techniques to learn.

The candidate, most likely a biomedicine, biochemistry, pharmacy or similar major, is welcomed to take part in setting up and performing assays needed to study ZOT, zonulin and haptoglobin in humans, dogs, horses and other mammals. Western blot and 2D gel electrophoresis (including "native" gels) will be used to study serum and other samples for individual expression patterns (phenotypes) of haptoglobin. ELISA will also be performed to determine serum concentrations of zonulin. As we have a long history in immunostaining and live cell imaging, studies at the cell physiology level are planned. Gut permeability tests will also be done using probes such as lactulose, mannitol, riboflavin and sucralose. The project will be finalized by a written work in English in the general form of a manuscript and a group presentation. As such, the candidate will experience the entire scientific process by end of this project. We work with human gut tissue, blood and urine. Real blood samples from real hospitals do not always come from healthy people. Please take into consideration your status with hepatitis B vaccination.