

Disruptions of epithelial integrity in the pathogenesis of IBD: The effects of *C. jejuni*

Research findings support the hypothesis that host-microbial interactions underlie the pathogenesis of CD and UC. *Campylobacter jejuni*, may initiate and/or exacerbate IBD via mechanisms that remain unclear. *In an attempt to uncover new roads towards therapy, this project aims at understanding 1) how C. jejuni-induced epithelial disruptions may prime the intestine for subsequent inflammation in susceptible hosts, and 2) how Epidermal Growth Factor (EGF) may help protect the intestine upon such interactions.*

As IBD patients exhibit inflammatory responses to their commensal intestinal microflora, factors that induce translocation of commensal bacteria across the intestinal epithelium may contribute to IBD pathogenesis. Using animal models and human intestinal cell model systems, our findings to date indicate that 1) Strain-dependent induction of epithelial cell death by *Campylobacter jejuni* is associated with invasion ability and is independent of cytolethal distending toxin, and 2) *C. jejuni* may break the intestinal barrier and provoke the penetration of commensal intestinal bacteria, an effect that can be blocked with EGF. The mechanisms are being investigated, but they include internalization (of bystander *E. coli*) via a transcellular pathway, which may occur independently of any *C. jejuni*-induced increase in intestinal permeability. Invasion-defective *C. jejuni* mutants and *Campylobacter*-conditioned cell culture medium also induced *E. coli* translocation, indicating that *C. jejuni* does not directly 'shuttle' bacteria into enterocytes. *Campylobacter*, regardless of its own invasiveness, promotes the translocation of non-invasive bacteria across the intestinal epithelium via a newly identified lipid raft-mediated transcellular process.

To unravel the mechanisms of *C. jejuni*-induced host epithelial disruptions will help understand processes that initiate and/or exacerbate intestinal inflammation in IBD. In turn, the discovery of biological agents capable of inhibiting these events may offer insights into new therapeutic development.

## PUBLICATIONS

This CCFC grant in aid of research was awarded in 2007. Over the first year, research using these funds has yielded the following publications. Only **publications directly related to this project** are listed (names of trainees in Dr. Buret's laboratory are underscored). Funding by CCFC was duly acknowledged in each of these publications:

### Full articles:

LAMB-ROSTESKI , J.M., KALISCHUK, L.D., INGLIS, G.D., **BURET**, A.G. (2008) Epidermal growth factor inhibits *Campylobacter jejuni*-induced claudin-4 disruption, loss of epithelial barrier function, and *Escherichia coli* translocation. Infect. Immun. 76;8:3390-3398

O'HARA, J., **BURET**, A.G. (2008) Mechanisms of intestinal tight junctional disruption during infection. Front. Biosci. (1;13):7008-7021

FLYNN A.N., **BURET**, A.G. (2008) Tight junctional disruption and apoptosis in an *in vitro* model of *Citrobacter rodentium* infection. Microbial Pathogenesis. 45:98-104

MRSNY, R.J., BROWN, G.T., GERNER-SMIDT, K., **BURET**, A.G., MEDDINGS, J.B., QUAN, C., KOVAL M., NUSRAT, A. (2008) A key claudin extracellular loop domain is critical for epithelial barrier integrity. Am. J. Pathol. 172(4):905-915

FLYNN, A.N., **BURET**, A.G. (2008) Caspases 3, 8, and 9 are required for induction of epithelial cell apoptosis by enteropathogenic E. coli but are dispensable for increased paracellular permeability. Microbial pathogenesis. 44(4):311-319.

KALISCHUK, L.D., INGLIS, G.D., **BURET**, A.G. (2007) Strain-dependent induction of epithelial cell oncosis by *Campylobacter jejuni* correlates with invasion ability and is independent of cytolethal distending toxin. Microbiology 153: 2952-2963

### Oral Presentations delivered by Dr. Buret, and discussing findings from this CCFC project:

June 2008: Invited speaker (AHFMR visiting lecturer), University of Alberta (Edmonton, Canada)

June 2008: Keynote speaker, Coimbra University meeting on Advances in

Inflammatory Bowel Diseases (Coimbra, Portugal)

October 2007: Invited lecturer, Mucosal Immunity course, AGA-Sponsored (Montebello (QC), Canada)

September 2007: Invited speaker, Intestinal Disease Research, Queen's medical school (Kingston (ON), Canada)

June 2007: Invited speaker, World Congress of Inflammation (Copenhagen, Denmark )

June 2007: Keynote speaker, Symposium de physiopathologie du tube digestif (Sherbrooke, Canada)

**Abstracts:**

Note: Lisa Kalischuk's abstract (February 2008) was awarded the CAG Student Research Prize at the CDDW in Montreal.

**2008 CAG student prize:** Kalischuk L, Inglis GD, Buret AG. Campylobacter jejuni induces translocation of non-invasive intestinal bacteria in vivo and in vitro. Can. J. Gastroenterol. 2008; 22, Suppl SA: 014

Flynn AN, Buret AG. Apoptosis-inducing factor contributes to enteropathogenic E.coli epithelial cell apoptosis. Can. J. Gastroenterol. 2008; 22, Suppl SA: 134

O'Hara JR, Feener TD, Kalischuk L, Buret AG. Increased severity of DSS colitis in mice following infection with C. jejuni. Can. J. Gastroenterol. 2008; 22, Suppl SA: 135

Lisa D Kalischuk, G. Douglas Inglis, and Andre G Buret  
Plasma membrane cholesterol modulates Campylobacter jejuni-induced translocation of non-invasive intestinal bacteria *FASEB J.* 2008 22:899.12