**Role of human bar domain proteins in cell-to-cell spread of *Shigella flexneri***

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**Project:KI-1**

**Description:**

*Shigella flexneri* is a major cause of bacterial dysentery (bloody diarrhea) world- wide (1). A critical stage in *Shigella* infection is the spread of bacteria in the host intestinal epithelium (2). Cell-to-cell spread of *Shigella* involves the generation of ‘protrusions’- bacteria encased in finger-like projections of the plasma membrane of the human cell (2). How bacteria reshape the host plasma membrane into protrusions is not well understood.

This project tests the hypothesis that *Shigella* generates protrusions by exploiting a class of human membrane-remodelling proteins called ‘BAR domain proteins’ (3). The normal function of these proteins is to reshape the plasma membrane to make protrusive structures such as filopodia or neurites (3). We will test our hypothesis by addressing three specific aims.

**Aims of the project:**

* Aim 1: Identify human BAR domain proteins needed for protrusion formation by Shigella
* Aim 2: Determine if *Shigella*manipulates the subcelluar localization of these BAR domain proteins
* Aim 3: Investigate the role of BAR domain proteins in remodelling the plasma membrane during protrusion formation

**Techniques to be used:**

* RNA interference (RNAi) to inhibit expression of human BAR domain proteins
* Western blotting to assess effects of RNAi on target protein expression
* Laser scanning confocal microscopy to quantify the contributions of BAR domain proteins to *Shigella* protrusion formation and spread
* Scanning electron microscopy to examine the roles of BAR domain proteins in plasma membrane remodelling during protrusion formation

**References:**

1. Kotloff, K.L., Riddle, M.S., Platts-Mill, J.A. et al., 2018. Shigellosis. *Lancet*. 391: 801-811
2. Dowd, G.C., Mortuza, R., and Ireton, K. 2021. Molecular mechanisms of intercellular dissemination of bacterial pathogens. *Trends Microbiol*. 29: 127-141.
3. Carman, P.J. and Dominguez, R. 2018. BAR domain proteins- a linkage between cellular membranes, signaling pathways, and the actin cytoskeleton. *Biophys. Rev.* 1833: 1587-1604.