

Pathological Society of Great Britain and Ireland
Summary Of Reports of 3 Centenary Clinical Fellowships For
Pathological Society Website Publication

Centenary Clinical Fellowship #1:

Name: Dr Alistair S Easton

Project Title: The role of lipo-oligosaccharide ganglioside mimicry in the interaction of Guillain-Barré syndrome-associated strains of *Campylobacter jejuni* with the immune system.

Summary: The post infectious paralytic autoimmune disease, Guillain-Barré syndrome (GBS), has been associated with the generation of cross-reactive auto-antibodies after *Campylobacter jejuni* infection. These auto-antibodies interact with both the ganglioside mimicking *C. jejuni* lipo-oligosaccharides (LOS) and endogenous gangliosides. This study investigated novel interactions of the ganglioside mimicking LOS with immune system receptors specific for gangliosides. A novel mechanism was found by which GBS associated strains of *C. jejuni* interact with the immune system, with significant differences in the potency of ganglioside-mimicking LOS and bacteria which could account for the loss of immunological tolerance that characterises GBS.

Figure 1: Phagocytic uptake of ganglioside-mimicking *C. jejuni* by macrophages

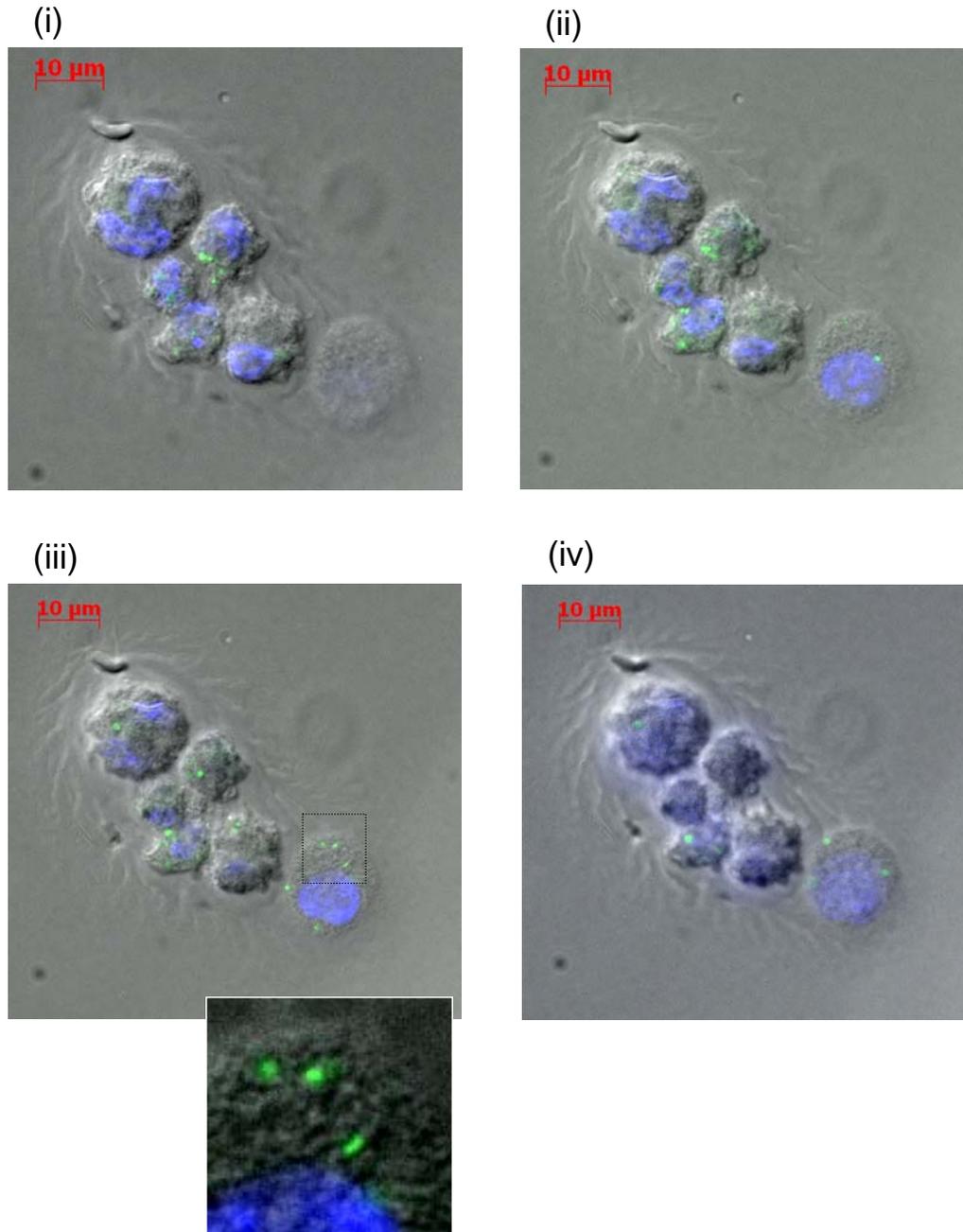


Figure 1. Bone marrow derived macrophages show enhanced phagocytosis of ganglioside mimicking *Campylobacter Jejuni* when compared with non-ganglioside mimicking control strains. *C. jejuni* have been fluorophore-labeled. Images (i) to (iv) shows a Z-stack demonstrating the intracellular location of the bacteria.

Centenary Clinical Fellowship #2:

Name: Dr Simon M L Paine

Project Title: Proteasomal Gene Targeting in Specific Brain Regions Recapitulates the Molecular Neuropathology of Parkinson's disease.

Summary: There is good evidence for dysfunction of the ubiquitin proteasome system in Parkinson's Disease. This project examined the molecular basis of Parkinson's Disease (PD) using a unique murine model, with Cre-loxP mediated knockout of *Psmc1*, an ATPase in the 19S regulatory subunit of the 26S proteasome, that was deleted in the dopaminergic neurones of the midbrains of the mice, resulting in region-specific neuronal death and intraneuronal inclusions – the hallmark pathology of sporadic PD. Using this model, proteasomal subunit expression was shown to be tightly regulated as deletion of *Psmc1* resulted in upregulation of genes encoding other subunits of the proteasome. The absence of the 26S proteasome led to up-regulation of genes involved in neuronal death and survival pathways, shown by analysing mRNA extracted from the microdissected substantia nigra of wild type and *Psmc1*-deficient mice. There was a specific topology of polyubiquitin chains present in the inclusions seen in sporadic age-related neurodegenerative diseases. The Lewy-like intraneuronal inclusions formed in the absence of alpha-synuclein, as demonstrated by crossing the mice in which there is conditional deletion of *Psmc1* with animals lacking alpha-synuclein.

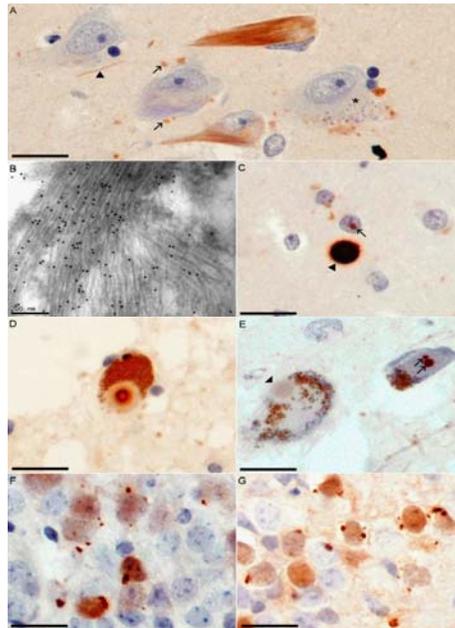


Fig. 1. (A) Section through the hippocampus in Alzheimer's disease (AD) stained with the Lys63Ub-mAb showing differential staining of neurofibrillary tangles (NFTs). Perisomatic bodies (arrows) show strong immunoreactivity but the changes seen in granulovacuolar degeneration

are negative in this case (*). Neuropil threads (arrowhead) are positive in this case. (B) Immunogold labelling transmission electron microscopy (TEM) in AD using the Lys63Ub-mAb provides further evidence that polyubiquitin with this linkage is present in NFTs. (C) Intranuclear neuronal inclusions (arrow) and neurites (arrowhead) in the neocortex in Huntington's disease (HD) show consistent, strong staining with the Lys63Ub-mAb. (D) Staining of the substantia nigra in Parkinson's disease (PD) using the Lys63Ub-mAb reveals differential immunoreactivity of Lewy bodies.

Centenary Clinical Fellowship #3:

Name: Dr Mary Gallacher

Project Title: The Oncogenic Role of WT1 and its Relationship to PTEN.

Summary: WT1 was first described as a tumour suppressor gene involved in Wilms tumour, however recent evidence has suggested it may have an oncogenic role in other tumours. PTEN is the second most common tumour suppressor gene and plays an important role in cell growth and survival, being a key negative regulator of the AKT pathway. Hence, this project investigated whether there is a relationship between WT1 expression and PTEN expression and whether WT1 overexpression reduces PTEN expression thus activating the AKT pathway. An ovarian malignancy TMA was constructed and a colorectal cancer TMA were both examined immunohistochemically for protein expression of WT1, PTEN and various downstream proteins of the AKT pathway. The data suggested that positive expression of WT1 correlates with mostly negative expression of PTEN. Analysis of 6 cultured cancer cell lines by Western blotting showed expression of WT1, however PTEN was expressed to varying degrees. The relationship between the two proteins was further investigated by knocking down WT1 using siRNA.

WT1 and PTEN expression in Colorectal, Breast and Ovarian Cell Lines

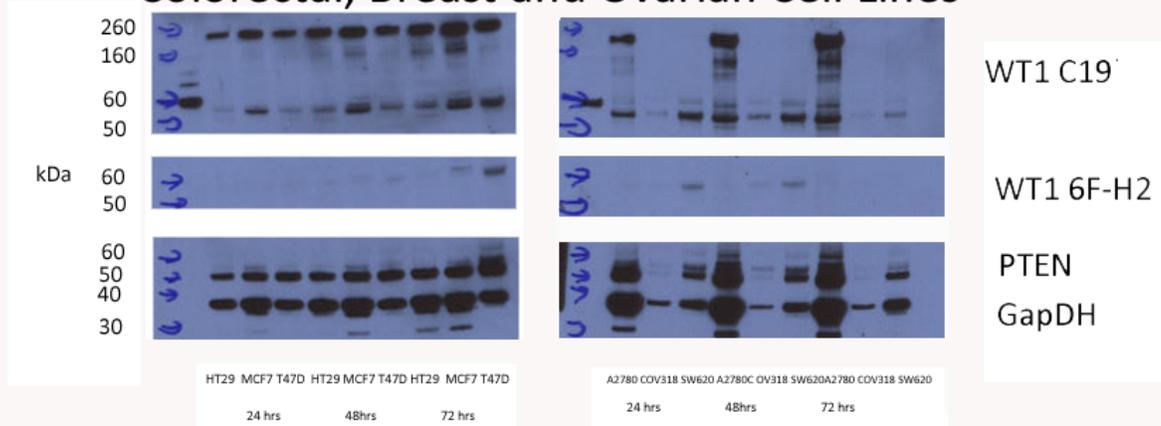


Figure 3. WT1 and PTEN expression in a variety of adult cancer cell lines: both WT1 and PTEN are expressed to varying degrees in colorectal, breast and ovarian cancer cell lines.