



# The Intensive Care Society

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## Young Investigator Award Winner

### **Exploring evidence for monocyte priming and tolerance in vivo using tumour necrosis factor-alpha converting enzyme**

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The treatment of sepsis remains challenging and places substantial morbidity and mortality burdens on the intensive care unit (ICU). There is evidence that the response to sepsis contains both a systemic inflammatory response syndrome (SIRS) and a compensatory anti-inflammatory response syndrome (CARS). Leukocytes play a key role in determining immune response and it is known that monocytes can display a state of priming or a state of tolerance when exposed to an inflammatory stimulus. These states can be considered parallels of the hyper and hypo-immune states seen in SIRS and CARS respectively.

Tumour necrosis factor-alpha converting enzyme (TACE) is a widely expressed metalloproteinase with a broad substrate base including cytokines (e.g. TNF), their receptors and adhesion molecules (e.g. L-selectin). Selective substrate shedding means that TACE activity can have both pro- and anti-inflammatory effects. TACE may play a key role in determining the cellular inflammatory balance and therefore the systemic hyper- and hypo-immune states that define sepsis pathophysiology.

This project will determine TACE activity in monocytes and macrophages obtained from patients with pneumonia and acute lung injury. Activity will be measured using a fluorometric TACE catalytic activity assay. We will look for evidence of priming and tolerance within the cells and, by comparing macrophages from infected tissue (lung) to circulating monocytes, for evidence of compartmentalisation of SIRS/CARS. Specific attention will be paid to the p38 mitogen activated protein kinase pathway.

This project may lend insights into potential therapies for sepsis aimed at suppressing or augmenting TACE activity as appropriate.