Targeting the patient with most to gain from Augmented Passive Immunotherapy with P4

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Background

- Severe sepsis is a major international public health problem

- Effective therapy limited
  - Source control
  - Antibiotics
  - Organ support (Surviving Sepsis Campaign)

- Mortality remains ~38% for septic shock
P4 Peptide

Discovered CDC Atlanta 2006: Eddie Ades & Shankar Rajam

Peptide fragment Pneumococcal surface adhesin A – PsaA

Highly conserved peptide, easily synthesized:

\[ \text{LFVESSVKRRPMKTVSQDTNIPYAIQIF} \]

Activates phagocytic cells
Augmented passive immunotherapy

P4 enhances FcγR expression on phagocyte

↑ Phagocytosis

Pathogen opsonised by antibody
P4 Translational Programme

- **In vitro testing**
  - Cell lines – HL-60, neutrophils, macrophages
    - Rajam G. Microbial Pathogenesis 44 (2008) 186–196

- **In vivo testing**
  - Murine invasive pneumonia models
    - Rajam G. JID. 2009; 199:1233–8
    - **E. Coli, Klebsiella and Pseudomonas models in progress**

- **Ex vivo testing**
  - Healthy volunteer neutrophils & alveolar macrophages
Collaboration

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GRIFOLS

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Aims & Objectives

1. Can P4 peptide augment phagocytic response in severe pneumonia?

2. Which patients are most likely to benefit from Augmented Passive Immunotherapy?

- **Work Package 1**: Proof of concept
  - 25 critically ill patients with severe community-acquired pneumonia
  - *Ex vivo* stimulation of neutrophils and alveolar macrophages to determine effect on bacterial killing
  - Completed April 2014

- **Work Package 2**: Determinants of activity
  - 75 critically ill patients with severe sepsis
  - Source (respiratory, abdominal or urogenital infection)
  - Phase (early, latent and convalescent)
  - Clinical and laboratory determinants of activity
  - Currently recruiting
Conclusions

- **WP1**: Augmented passive immunotherapy improves bacterial killing by phagocytes in patients with severe community-acquired pneumonia

- **WP2**: In progress, currently recruited 46/75 patients
  - Promising results in abdominal and urogenital sepsis

- Clear potential as a therapeutic agent moving forwards

- Work underway to define individuals and indications
Developmental programme

• WP1 → MRC Developmental Pathway Funding Scheme success
  • Commercial peptide production
  • Pre-clinical toxicology studies
  • Application for MHRA Clinical Trials Authorisation

• Future plans
  • First in human trials
    • Partnership with Royal Liverpool Clinical Research Facility
  • Commercial partnership
    • Fully flexible agreement with Grifols Inc.
Potential future applications

- **Adjunctive therapy for severe pneumonia / sepsis**

- **Multi-drug resistant organisms**
  - Antimicrobial independent mechanism of action

- **Surgical prophylaxis**
  - Orthopaedic joint surgery, resistant skin commensals
  - General surgical prophylaxis if Gram negative activity

- **Clostridium difficile diarrhoea**
  - Antibiotic avoidance