



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

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- **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**

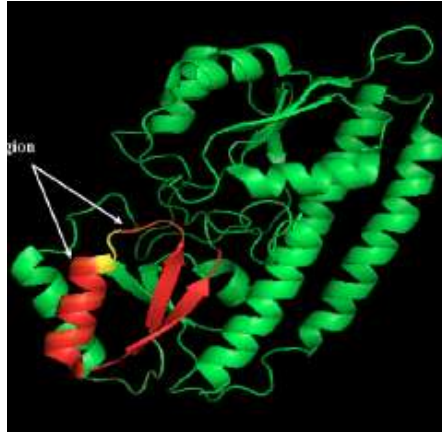
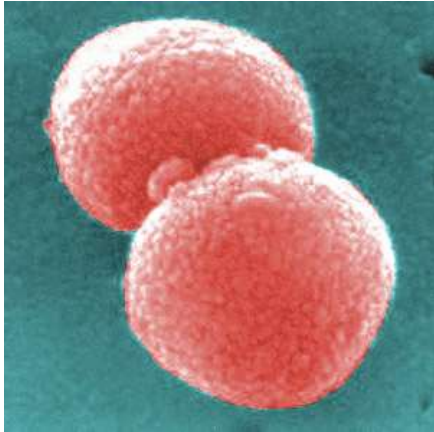


Health officials are watching in horror as bacteria become resistant to powerful carbapenem antibiotics – one of the last drugs on the shelf.

The antibiotic alarm

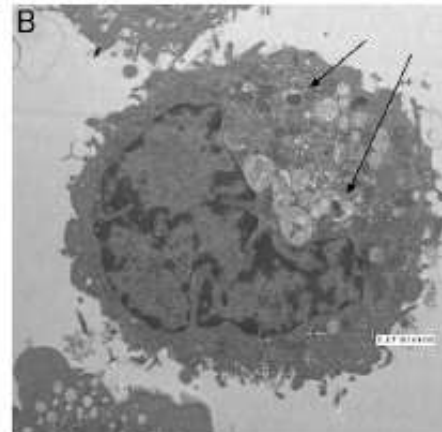
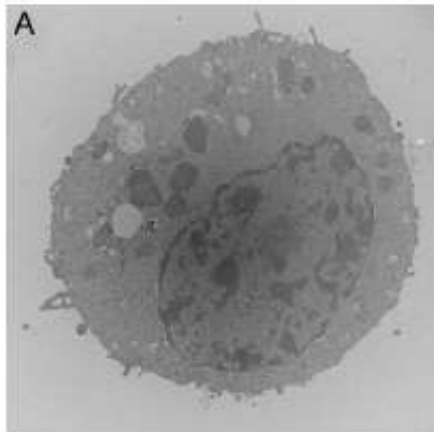
There is a growing recognition that action must be taken to deal with the alarming rise in the incidence of bacteria resistant to today's antibiotics, and its implications for global health.

P4 Peptide



Discovered CDC Atlanta 2006:
Eddie Ades & Shankar Rajam

Peptide fragment Pneumococcal
surface adhesin A– PsaA

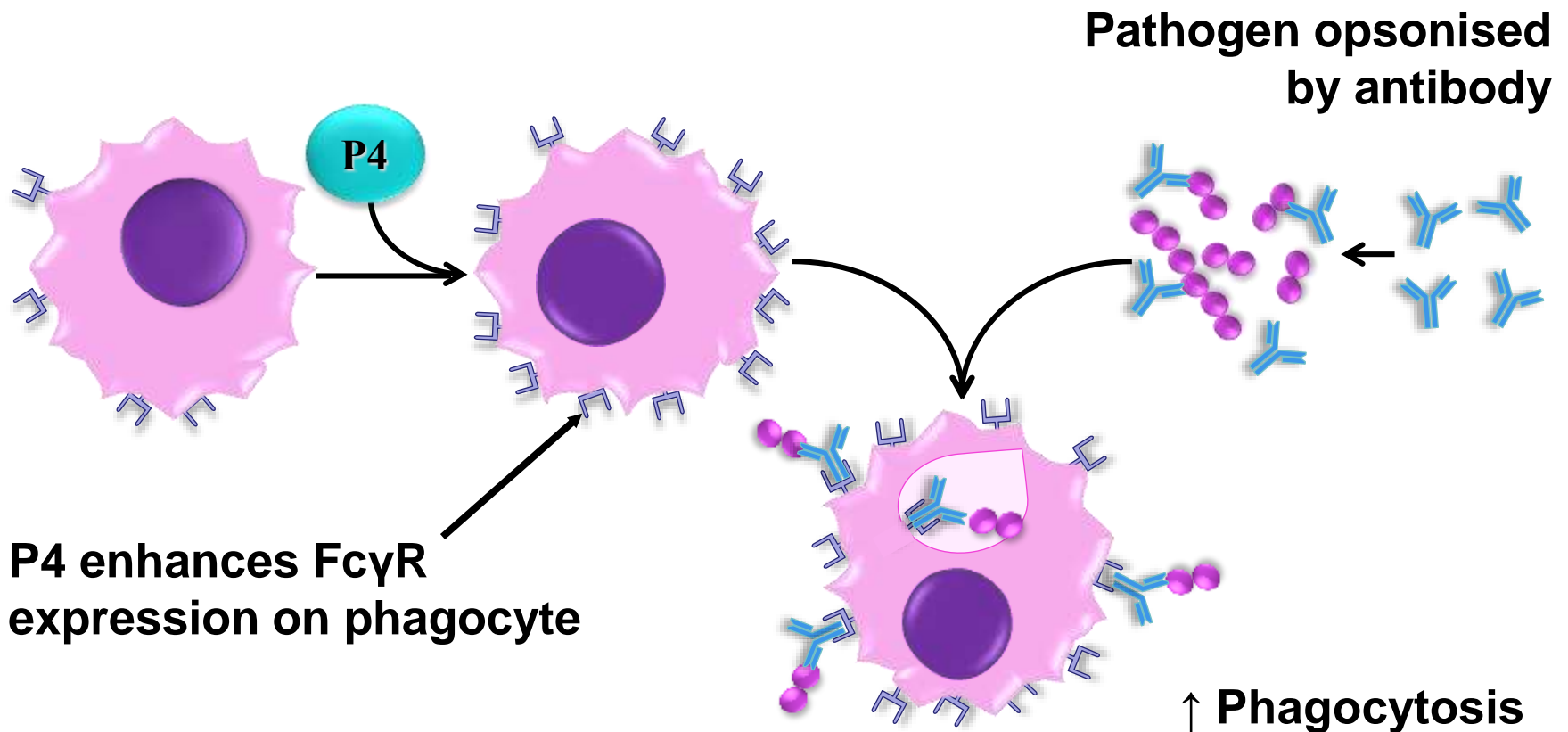


Highly conserved peptide, easily
synthesized:

251 LFVESSVKRRPMKTVSQDTNIPIYAQIF 278

Activates phagocytic cells

Augmented passive immunotherapy



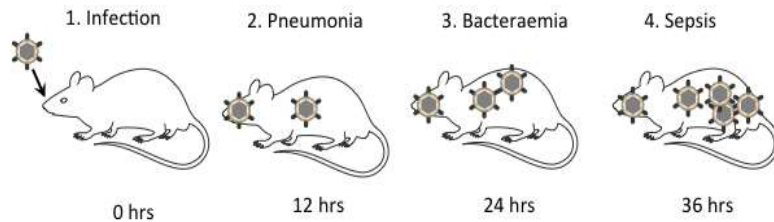
- **In vitro testing**

- Cell lines – HL-60, neutrophils, macrophages

- Romero-Steiner. *Vaccine* 24 (2006) 3224–3231
- Rajam G. *Microbial Pathogenesis* 44 (2008) 186–196

- **In vivo testing**

- Murine invasive pneumonia models



- Rajam G. *JID*. 2009; 199:1233– 8
- N Melnick. *Clin & Vaccine Immun.* 2009 (16)6: 806–810
- Rajam G. *Clin & Vaccine Immun.* 2010 (17)11:1823-1924
- Rajam, G. *Int. J. Microbiol.* 2011, 725483 (2011).
- Weeks, JN. *Antimicrob. Agents Chemother.* 55, 2276–81 (2011).
- Bangert, M. *J. Infect. Dis.* 205, 1399–407 (2012).

- **E. Coli, Klebsiella and Pseudomonas models in progress**

- **Ex vivo testing**

- Healthy volunteer neutrophils & alveolar macrophages

- Bangert, M. *Antimicrob. Agents Chemother* 2013 57(9):4566-9.

Collaboration



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Supported by:



GRIFOLS



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

- **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