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PROTECTIVE EFFECT OF QUORUM QUENCHING MONOCLONAL ANTIBODIES IN LETHAL *PSEUDOMONAS* INFECTION

Soumya Palliyil, Christina Downham, Ian Broadbent, Keith Charlton and **Andrew J Porter**
University of Aberdeen, UK

Introduction: The human pathogen *Pseudomonas aeruginosa* uses a cell-density based intercellular communication system called quorum sensing (QS) to regulate virulence gene expression and pathogenic behavior within the host. In this study, immunomodulation of QS molecules by monoclonal antibodies (mAbs) was used as a novel approach to prevent *P. aeruginosa* infections and as tools to detect these compounds in bodily fluids as a possible first clue to an undiagnosed Gram-negative infection.

Methods: Using sheep immunization and recombinant antibody technology, a panel of sheep-mouse chimeric mAbs to homoserine lactones (HSLs) was developed. Lead clones were tested in elastase and nematode slow killing assays to evaluate their quorum quenching activities and also for their ability to detect QS compounds in human urine. For survival studies in mice, lead mAbs and comparator antibiotic drugs at 10 mg/kg or vehicle-only control were co-administered with *P. aeruginosa* PA058 by the intranasal route with a second treatment dose 4 h post infection. Bacterial burden in the lung tissue 24h post infection and survival up to seven days was monitored.

Results: Specific binding of lead mAbs to QS molecules has been demonstrated by a series of *in vitro* immunoassays. In the nematode slow killing assay, the survival rates of *Caenorhabditis elegans* increased from 15% to 60%. In a non-neutropenic lung model of mice infected with *P. aeruginosa* PA058, mAb monotherapy demonstrated significant efficacy, prolonging survival up to 83%. HSL mAbs also retained functional recognition of its antigen in the presence of urine with very little reduction in sensitivity observed (IC_{50} value 4 nM in PBS vs. 10 nM in urine).

Conclusions: Antibodies are an attractive method for controlling bacterial virulence by block quorum sensing signaling as these 'antipathogenic' drugs are less likely to develop resistance in bacteria compared to conventional antibiotics. An immunoassay-based diagnostic system exploiting the high sensitivity of anti-QS MAbs could be developed to detect the presence of specific markers of infection (homoserine lactones, quinolones) in bodily fluids such as blood and urine.

Biography

Soumya Palliyil is the Principal Scientist and Facility Manager of the Scottish Biologics Facility (SBF), a biologic drug discovery unit which provides antibody and peptide hit generation services to academia and industry. She completed her PhD within Professor Andy Porter's Antibody Engineering Group, University of Aberdeen and Wyeth/Pfizer Inc Protein Therapeutics Lab, Aberdeen. Utilizing the antibody engineering experience and expertise accumulated over the years, she manages a wide range of antibody based projects in the SBF including the development of antibody therapeutic candidates in areas such as cardiovascular, neurodegenerative and infectious diseases, several antibody-fragment based diagnostics in bacterial and fungal infections and *in vivo* imaging candidates for heart disease and fibrotic conditions of the liver, pancreas, etc. She is a recipient of the prestigious Commonwealth Scholarship and has also completed the Royal Society of Edinburgh Commercialization Fellowship.

soumya.palliyil@abdn.ac.uk