CHAPTER-11

DISCUSSION

In this study the potential of Ata was investigated as a vaccine target against *A. baumannii* infections. Previous studies have shown that Ata was surface exposed on the *A. baumannii* outer membrane, mediated adherence to ECM/BM proteins and the adhesion of whole *A. baumannii* cells to collagen type IV, and was important for biofilm formation and needed for full virulence of *A. baumannii* in mice [131]. The study also demonstrated that Ata is a target for both opsonic killing and bactericidal antibodies, and passive administration to mice leads to significant reductions in bacterial burdens in the lung at 24 h post infection. Therefore, Ata represents a classic bacterial vaccine target in that expression is needed for full virulence and antibodies to Ata mediate killing.

Antibody to Ata blocked the adherence of *A. baumannii* to collagen type IV in vitro, suggesting another protective mechanism for these antibodies. Despite the fact that bacteria elaborate high numbers of different types of adhesins, which puts a constraint on their use as vaccines, several adhesins have been shown to give protection in animal models of infection. Some of them include the FimH adhesin in a complex with the FimC chaperone and the fimbrial antigen of *Escherichia coli* [144], the SafD/F adhesin chaperone complex of *Salmonella enterica serovar Enteritidis* [145], or pertactin of *Bordetella pertussis* [146]. Therefore, we speculate that the adhesion blocking activity of antisera to Ata that reduces the binding of *A. baumannii* to collagen type IV may work in vivo by decreasing the levels of bacterial tissue invasion and/or colonization.

Rabbit antibodies to Ata also mediated both phagocyte dependent and phagocyte independent killing of *A. baumannii*, indicating that immunity to Ata could be operative in both immunocompetent and immunosuppressed patients. A previous study by Goe et al. [147] reported that an IgM raised against iron regulated outer
membrane proteins of *A. baumannii* had bactericidal and opsonic properties. However, in their opsonic assays these researchers did not directly measure killing but rather bacterial uptake mediated by the IgM, so it is difficult to conclude the antibody had good killing activity, a requisite property of a protective antibody.

We also demonstrated that passive administration of immune sera to Ata reduces the CFU/g of lung tissue in *A. baumannii* infected mouse lungs regardless as to whether the animals are immunocompetent or neutropenic. Reductions in lung bacterial burdens were documented for *A. baumannii* strain ATCC 17978 and two unrelated heterologous MDR strains. Protection in the setting of neutropenia indicates that PMNs are not critical components of the protective efficacy afforded by antibody to Ata. However, it is important to caution that enhancing the bacterial clearance in a nonlethal model of infection has not been shown to be correlated with clinical benefits in humans. Since *A. baumannii* strains in general tend to exhibit low virulence in murine models of lung infection, the use of determining bacterial burdens in lung tissues was favoured as a surrogate indicator of efficacy of antibody to Ata in one of the most common clinical manifestation of *A. baumannii* infections.

Very few prior studies have pursued the research, development, and testing of novel vaccine targets to combat *A. baumannii* infections. A recent study by McConnell et al. in 2011 [148] showed that an outer membrane preparation consisting of multiple *A. baumannii* surface antigens was protective in a murine sepsis model and that the therapeutic administration of antibody could rescue mice with an established infection. That study, while promising, had the limitation of the undefined nature of the vaccine preparations. Another study evaluated OmpA as a target for vaccination against extreme drug resistant *A. baumannii* infections [116], but only a single *A. baumannii* strain was evaluated, which limits the interpretation of those findings.

Antibodies to Ata exhibited bactericidal and protective efficacy among four and three heterologous strains, respectively, which suggests that a conserved protective epitope might be shared among Ata proteins from *A. baumannii* clinical isolates. These results are consistent with the high degree of
homology of the Ata protein among the *A. baumannii* clinical strains studied here (99, 87.5, 94, and 96% amino acid identity to ATCC 17978 Ata for the strains S8, S11, I38, and S25, respectively. Alternatively, a combination of Ata proteins from various isolates might be needed in order to obtain broader protective efficacy against *A. baumannii* infections.