**Preclinical studies of anti-staphylococcal ectoslysin P128 for potential systemic hypersensitivity and evaluation of efficacy in Staphylococcus aureus bacteremia with renal abscesses in rats**

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**Abstract**

P128 is a novel recombinant chimeric bactericidal derived ectoslysin with potent antibiotic activity against Staphylococcus aureus (S. aureus), including methicillin-resistant S. aureus (MRSA), and several other bacterial species. It is designed to target bacterial membranes and cause lysis, with the potential to rescue animals from fatal Staphylococcus aureus (S. aureus) infections. This study demonstrates the efficacy of P128 in a clinically relevant model of bacteremia with renal abscesses in rats. With increasing resistance to antibiotics, there is a dire need for novel therapeutics. The use of rats rather than mice in this model allowed the assessment of in vivo efficacy of P128. Because P128 is a non-antibiotic drug with potent antibiotic activity against MRSA, this study validates the potential of P128 as a therapeutic agent for the treatment of MRSA bacteremia.

**Methods: Characterization of hypersensitivity reactions and immune response**

- **P128** is a novel recombinant chimeric bactericidal derived ectoslysin with potent antibiotic activity against S. aureus, including methicillin-resistant S. aureus (MRSA). This study reports on (i) the characterization of P128 in a clinically relevant model of bacteremia. With increasing resistance to antibiotics, there is a dire need for novel therapeutics. Use of rats rather than mice in this model allowed the assessment of in vivo efficacy of P128. Because P128 is a non-antibiotic drug with potent antibiotic activity against MRSA, this study validates the potential of P128 as a therapeutic agent for the treatment of MRSA bacteremia.

**Methods: Evaluation of efficacy in rat-model of bacteremia with renal abscesses**

The bacteremia model established was challenged with rats harboring MRSA USA300 intravenously. Animals were monitored for 14 days for mortality. Subsets of animals were euthanized at 48 hours and kidneys were examined for presence of abscesses. Bacterial load in organs was determined in kidney, liver, spleen and lung. Animals challenged at LD50 level of bacterial inoculum were administrated a single bolus dose of P128 (0.25, 0.5 or 2 mg/kg) two hours after infection. Rescue from mortality and change in the nature and number of renal abscesses signified efficacy in this model. To monitor bioavailability of P128, a subset of rats were administered P128 at 25 mg/kg and plasma levels were determined by ELISA.

**Model Development and Validation**

- **P128 treatment** (single IV bolus or 7 day course) did not result in significant loss of body weight in comparison to control group animals.

**Conclusions**

- **P128 does not elicit systemic hypersensitivity or cause tissue damage through antigen-antibody complex deposition in tissues**
- **No-abnormal clinical signs were observed**
- **No clinical signs of systemic anaphylactic reactions indicative of Type I hypersensitivity were observed following administration of P128**
- **Anti-P128 antibodies detected at relatively low titer only**
- **No-P128-related tissue injury was observed in organs**
- **A single dose of 2.5 mg/kg of P128 rescues animals from mortality and prevents formation of renal abscesses**
- **Based on its ability to rescue animals from fatal S. aureus systemic infection and absence of systemic anaphylaxis, P128 is a promising candidate for the treatment of MRSA bacteremia.**

**References**

5. All animal experiments were conducted in accordance with the guidelines of the Institutional Animal Ethics Committee, GangaGen Biotechnologies Pvt Ltd, Bangalore, India.
6. Authors have been listed in alphabetical order.