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## **IN VIVO PROTECTION WITH HUMAN MONOCLONAL ANTIBODY S315 FOLLOWING CHALLENGE WITH DIPHTHERIA TOXIN**

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**Background:** Morbidity and mortality from *Corynebacterium diphtheriae* is reduced by prompt administration of equine-derived diphtheria anti-toxin (DAT), which is in short supply worldwide. MassBiologics has developed a human monoclonal antibody (S315) to diphtheria toxin to provide a safer alternative to DAT and address critical supply issues. S315 prevents toxin binding to its putative host receptor and S315 pre-mixed with toxin increased survival in a guinea pig model of intoxication. To further evaluate the ability of S315 to provide *in vivo* protection, we established a post-exposure treatment model.

**Methods:** Female Hartley guinea pigs (300-350g) were challenged subcutaneously with diphtheria toxin (0.03 to 0.09 Lf, limit of flocculation) to identify the minimum lethal dose. To evaluate anti-toxin efficacy, DAT or S315 was administered five hours post-toxin challenge and animals monitored for 30 days for signs of illness (lethargy, dehydration, weak limbs). Serum anti-diphtheria toxin antibodies were measured by ELISA and Vero cell toxin neutralization assays.

**Results:** The minimum lethal toxin dose was 0.09 Lf. To determine the protective dose of DAT, 0.2 IU, 1.0 IU or 5.0 IU was administered intravenously post-toxin challenge (n=4/cohort). All 0.2 IU or 1.0 IU DAT-treated animals died, while one animal treated with 5.0 IU survived. DAT was subsequently evaluated at 5.0 IU, 10 IU, and 20 IU and compared to a cohort receiving 3.5 mg of S315. All untreated animals died within 72 hours and all antibody-treated animals survived. Dehydration was observed more frequently in the 5 IU and 10 IU DAT cohorts compared to the 20 IU and S315 cohorts.

**Conclusions:** Treatment with S315 after diphtheria toxin exposure is protective; further studies will define a minimum effective dose of S315. This model mimics the route and timing of anti-toxin treatment in humans and provides a rigorous preclinical evaluation of a human antibody replacement for equine DAT.

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