**Introduction:**
Previous work has shown the cytoprotective properties of antithrombin-affinity depleted heparin (AADH), by neutralization of cytotoxic extracellular histones[1], major mediators of death in sepsis[2,3]. AADH was produced from clinical grade heparin, resulting in preparations that have lost >99,5% of their anticoagulant activity. To gain insight into the mechanisms and the basic pharmacological aspects of AADH protective properties, we performed a systematic analysis of how AADH is tolerated in mice and ascertained its effects in three different in vivo models of inflammation and infection.

**Methods:**
Dose ranging studies, short term and medium term, were performed in C57BL/6 mice. The effects of i.v. administration of extracellular histones in the presence or absence of AADH were assessed in mice. We further analysed the effect of AADH in models of Concanavalin A- and MRSA-mediated lethality. In all studies we assessed clinical signs, lab parameters and histology.

**Results:**
AADH was well tolerated in both short term and intermediate term (till 7 days) experiments in mice, in the absence of any signs of tissue bleeding. AADH was able to revert the cytotoxic properties of i.v. administered histones.
In a Concanavalin A mediated model of sterile inflammation, we confirmed that AADH has protective properties that counteract the cytotoxic effects of extracellular histones. In an in vivo lethal MRSA model, for the first time, AADH was shown to induce a survival-benefit.

**Conclusion:**
We conclude that AADH contributes to the overall increased survival by means of neutralization of extracellular histones and represents a promising product for further development into a drug for the treatment of inflammatory diseases and sepsis.

**References:**