

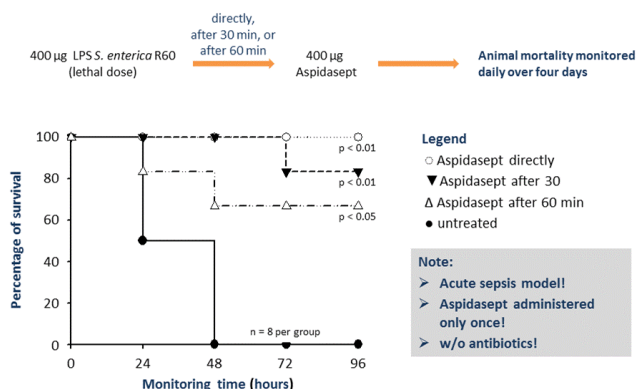
## Technology Offer

# Peptide-based antiinfectives against sepsis and other severe bacterial infections

Reference Number TO 14-00020

### Challenge

Sepsis represents one of the leading causes of death in intensive-care units worldwide, with mortality rates ranging from 20% for sepsis to over 60% for septic shock. Treatment of sepsis poses an enormous burden for the health care systems with annual costs of USD 17 bn p.a. in the US alone. Existing therapies aim at killing the bacteria or modulating the immune response. Yet, these strategies do not address the major underlying trigger for sepsis, i.e. release of pathogenicity factors (PFs; endotoxins = lipopolysaccharides [LPSs] and lipoproteins [LPs]) from bacteria. Thus, in spite of recently improved diagnostic and therapeutic options, there is a major medical need for new and efficacious drugs, which not only kill the bacteria, but also neutralize PFs.



*Aspibasept protects mice against experimental lethal septic shock.*

### Technology

Based on comprehensive biophysical studies, a novel class of polypeptide-based antiinfectives has been developed against sepsis and other severe infections. Lead compound Aspibasept possesses potent antibacterial and antiviral activities, and importantly is capable to efficiently bind and neutralize bacterial endotoxins, this way preventing the overshooting inflammation reactions induced by PFs. Aspibasept's binding leads to a structural conversion of PFs into an inactive form, preventing their interaction with the human immune system. A variety of *in vitro* and *in vivo* data are indicative of the high inflammation-decreasing activity. Protection in animal models has been demonstrated e.g. for endotoxemia and cecal ligation/punctures (CLP). Induced inflammation in lung sections could be completely inhibited, and delayed addition of Aspibasept decreases inflammation and increases survival.

### Commercial Opportunity

Aspibasept and related polypeptides are offered for in-licensing and/or co-development for the treatment of sepsis and/or bacterial and viral infections.

### Development Status

- Given their physicochemical properties, the novel antimicrobial polypeptides possess broad activity against bacteria and viruses. Various *in vitro* and *in vivo* studies revealed potent activity against MRSA and synergistic properties with other antibiotics.
- The novel polypeptides efficiently neutralize PFs *in vivo*, reducing mortality as good or better as the accepted gold standard polymyxin B.
- Protection in animal models has been demonstrated e.g. for endotoxemia and cecal ligation/punctures (CLP). Induced inflammation in lung sections could be completely inhibited, and delayed addition of Aspibasept decreases inflammation and increases survival.
- For lead compound Aspibasept, a 14-day repeated dose toxicity study in rats has been completed. The NOAEL was determined, revealing that the planned clinical dose will be 500-times lower.
- Based on animal data, SALPs possess a sufficient stability when given as permanent infusion. They are degraded within 2h, this way preventing undesired accumulation, induction of resistance and immunological/allergic reactions.

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- A protocol for GMP production has been established.
- Preclinical development of Aspidasept is well advanced. Further studies are under way, in preparation and planned.

### Patent Situation

Based on WO 2009/124721 (priority claimed: 04/2008), patents have been granted in US, JP and EP.

A second patent applications has been recently filed (WO 2017/140770; patent pending in US, JP and EP), covering e.g. the synergistic action of SALPs in conjunction with conventional antibiotics.

### Further Reading

Heinbockel et al. (2013) Preclinical investigations reveal the broad-spectrum neutralizing activity of peptide Pep19-2.5 on bacterial pathogenicity factors. *Antimicrob Agents Chemother* 57:1480-1487

Schuerholz et al. (2013) The anti-inflammatory effect of the synthetic antimicrobial peptide 19-2.5 in a murine sepsis model: a prospective randomized study. *Crit Care* 17:R3

Martin et al. (2015) Peptide 19-2.5 inhibits heparan sulfate-triggered Inflammation in murine cardiomyocytes stimulated with human sepsis serum. *PlosOne* 10:e0127583

Martinez de Tejada et al (2015) Lipoproteins/peptides are sepsis-inducing toxins from bacteria that can be neutralized by synthetic anti-endotoxin peptides. *Sci Rep* 22: 14292

Martin et al. (2016) The synthetic antimicrobial peptide P19-2.5 attenuates septic cardiomyopathy and prevents down-regulation of SERCA2 in polymicrobial sepsis. *Sci Rep* 6:37277

Yamada et al. (2017) Novel synthetic, host-defense peptide protects against organ injury/dysfunction in a rat-model of severe hemorrhagic shock. *Ann Surg epub*

Bárcena-Varela et al. (2017) Coupling killing to neutralization: combined therapy with ceftriaxone/Pep19-2.5 counteracts sepsis in rabbits. *Exp Mol Med* 40: e345