Table S1. Compilation of phage lytic enzymes that have been tested in animal models of human systemic infections.

Enzybiotic	Native / Engineered	Bacterial pathogen	Animal Model[1]	Administration route1[2]	Regimen (Dose and time of treatment)	Main results	Refs
Cpl-1	N	*S. pneumoniae*	Bacteraemia	i.p.	Single dose (0.4 or 1 mg/kg of mouse) 1 h-postinfection	0% buffer-treated and 0% enzybiotic-treated mice survived. Combination with daptamyxin resulted in ≥ 80% survival.	[89]
	N	*S. pneumoniae*	Bacteraemia	i.v.	Single or multiple dose (2 mg/mouse) 1 h-postinfection or 5 and 10-postinfection	20% buffer-treated and 100% enzybiotic-treated mice survived. In advance bacteraemia (5 and 10 h after infection) all mice died.	[73]
Cpl-1, Pal	N	*S. pneumoniae*	Sepsis	i.p.	Single dose (5 to 200 µg/mouse) 1 h-postinfection	0% buffer-treated and 100% C-treated mice survived with 200 µg of either enzyme. Survival rate was 0% with 5 µg. Cpl1 synergizes with Pal.	[48]
Cpl-771, Cpl-1	E, N	*S. pneumoniae*	Bacteraemia	i.p.	Single dose (25 to 500 µg/mouse) 1 h-postinfection	0% buffer-treated, ≥45% cpl-771-treated and ≥20% Cpl-1-treated mice survived. With highest doses, 100% and 30% survived, respectively. Cpl-771 was 50% superior than Cpl-1.	[78]
Ply30	N	*S. suis / S. equi*	Bacteraemia	i.p.	Single dose (2 mg/mouse) 1 h-postinfection	0% buffer-treated and ≥80% enzybiotic-treated mice survived within 96 h post treatment.	[90]
PlyPy	N	*S. pyogenes*	Bacteraemia	i.p.	Single dose (0.25 or 0.5 mg/mouse) 3 h-postinfection	17% buffer-treated and ≥90% enzybiotic-treated mice survived 72 h post treatment.	[91]
PlySK1249	N	*S. agalactiae*	Bacteraemia	i.p.	Single or multiple dose (22.5 to 45 mg/kg of mouse) 1 h or 2, 20 and 24 h-postinfection	No differences between buffer and treated group when administrated 1 h-postinfecton. Only consecutive doses (2, 20 and 24 h after challenge), treatment recused 60% more mice then control group.	[92]
ClyR	E	*S. agalactiae*	Bacteraemia	i.p.	Single dose (25 to 40 mg/kg of mouse) 3 h-postinfection	0% non-treated and ≥25% enzybiotic-treated mice survived. Total protection was obtained with the highest ClyR dose.	[93]
ClyS	E	*S. aureus*	Septicaemia	i.p.	Single dose (2 mg/mouse) 3 h-postinfection	0% buffer-treated and 88% enzybiotic-treated mice survived. CF-301 has a synergistic effect with oxacillin.	[54]
ClyH	E	*S. aureus*	Bacteraemia	i.p.	Single dose (450 or 900 µg/mouse) 3 h-postinfection	0% buffer-treated and ≥66.7% enzybiotic-treated mice survived. A 100% survival was reach with highest dose. Daily injections of ClyH did not cause harmful effects.	[101]
MR-10	N	*S. aureus*	Bacteraemia	subcutaneously	Single dose (50 µg/mouse) 3 h-postinfection	0% buffer-treated and 100% enzybiotic and -treated mice survived. Individual therapy (MR-10 or minocycline) resulted in 35% survival.	[102]
LysGH15	N	*S. aureus*	Bacteraemia	i.p.	Single dose (5 to 100 µg/mouse) 1, 2, 3 or 4 h-postinfection	0% non-treated and 100% enzybiotic-treated mice survived with ≥50 µg. Prolonged administrations (2, 3 and 4 h) had 40% to 0% survival rate.	[103]
CF-301 (PlySs2)	N	*S. aureus*	Bacteraemia	i.p.	Single dose (0.25 to 5 mg/kg of mouse) 3 h-postinfection	0% buffer-treated and ≥20% enzybiotic-treated mice survived for ≥2.5 mg/kg doses. A maximum 70% survival was reached with the highest dose. CF-301 synergizes with vancomycin or with daptomycin.	[104]

		S. aureus and *S. pyogenes*	Bacteraemia	i.p.	Single dose (2 to 4 mg/kg of mouse) 3 h-postinfection	0% buffer-treated and 92% enzybiotic-treated mice survived from mixed infection. PlyC or ClyS added to in the same concentrations, failed.	[105]
MV-L	N	*S. aureus*	Bacteraemia	i.p.	Single dose (500 U/mouse) 30 or 60 min-postinfection	0% buffer-treated and ≥60% enzybiotic-treated mice survived when added 60 min after challenge. Fully protection was reached at 30 min.	[45]
SAL-1	N	*S. aureus*	Bacteraemia	i.v.	Multiple dose (12.5 to 25 mg/kg of mice) 1, 25 and 49 h-postinfection	20% non-treated and ≥93.3% enzybiotic-treated mice survived. Bacterial counts were significantly reduced in the bloodstream and splenic tissue.	[106]
8 enzybiotics and lysostaphin	N, E	*S. aureus*	Bacteraemia	i.p.	Single dose (200 µg/mouse) 30 min-postinfection	30% buffer-treated and 100% enzybiotic-treated mice survived. Twort, phiSH2 and P68 had lower survival rates of 50%, 60% and 20%.	[107]
PlyG	N	*B. anthracis*	Sepsis	i.p.	Single dose (50 U/mouse) 15 min-postinfection	0% buffer-treated and 68.4% enzybiotic-treated mice survived. No toxicity was detected.	[109]
LysEF-P10	N	*E. faecalis*	Bacteraemia	i.p.	Single dose (1 to 10 µg/mouse) 1 h-postinfection	0% buffer-treated and 100% enzybiotic-treated mice survived for ≥ 5µg doses. Lowest dose (1 µg) only rescued 20% of mice. LysEF-P10 triggers antibodies but does not abolish the enzymatic activity.	[110]
PlyF307	N	*A. baumannii*	Sepsis	i.p.	Single dose (1 mg/mouse) 2 h-postinfection	10% buffer-treated and 50% enzybiotic-treated mice survived. Enzybiotic also removed biofilms in a *in vivo* catheter model.	[112]

[1] murine model unless stated otherwise;
[2] i.v., intravenously; i.p., intraperitoneal;