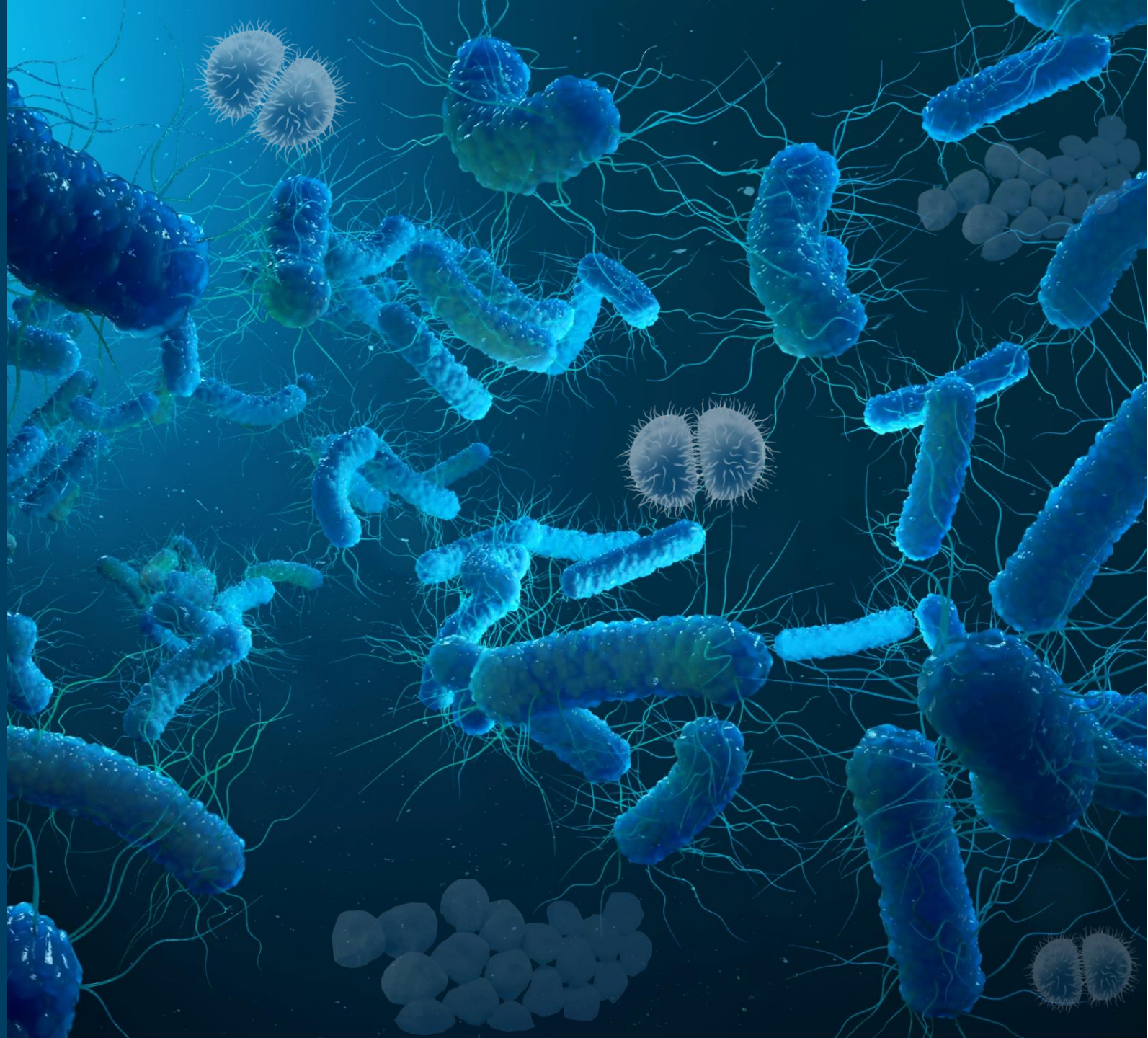
AiCuris

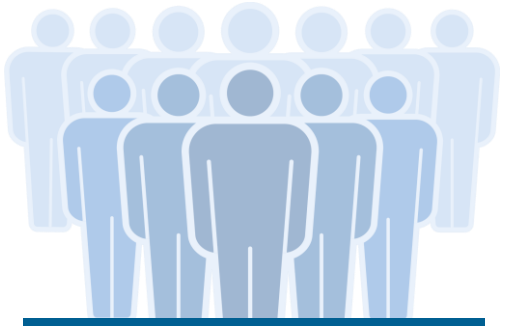
Anti-infective Cures

LpxH inhibitor

Antibacterials against Gram-negative Pathogens



GRAM NEGATIVE RESISTANCE BREAKER - MEDICAL NEED / MARKET



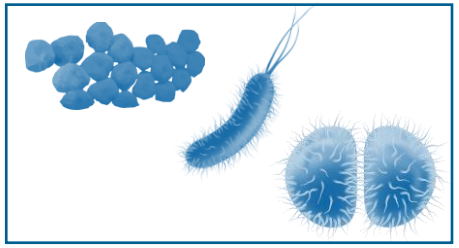
2,8M+ each year

In the US, 2019 at least 2.8 million people acquired serious infections with bacteria resistant to one or more antibiotics with more than 35,000 people dying as a result.

15% increase from 2019 to 2020

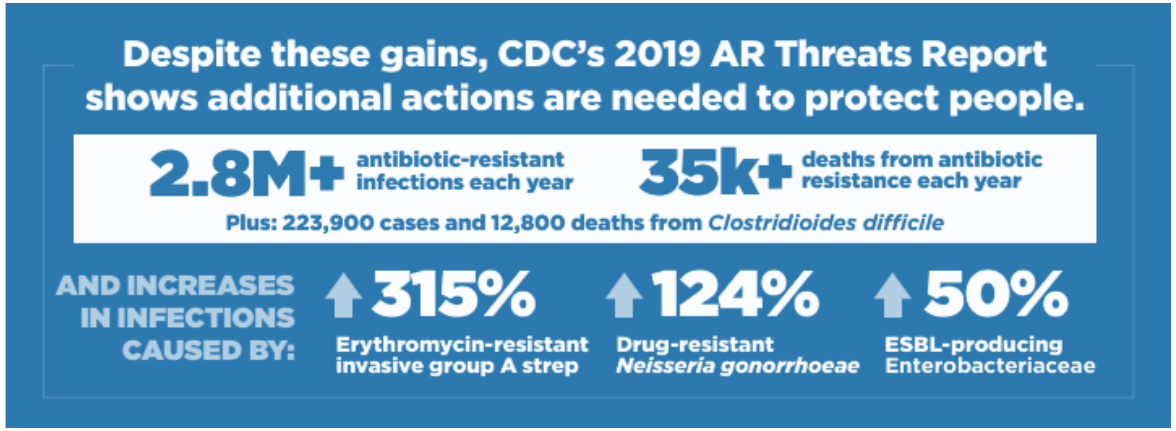
COVID-19 pandemic pushed back years of progress made combating antimicrobial resistance in the US with resistant hospital-onset infections and deaths both increasing at least 15% from 2019 to 2020.

- 3 of 5 Bacteria that require urgent and aggressive action are Gram-negative pathogens, including:



- Carbapenem-resistant *Acinetobacter*
- Carbapenem-resistant *Enterobacteriaceae*
- Drug resistant *Neisseria gonorrhoeae*

- 6 of 11 Bacteria that are deemed serious threats are gram negative



The global **antibiotics market size** was valued at **USD 49 billion in 2022** and is expected to reach **USD 62 billion in 2026**

CDC Antibiotic Resistance Threats in the Unted States 2019
COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022

AiCuris Anti-infective Cures

GRAM NEGATIVE RESISTANCE BREAKER - TPP

	Profile
Efficacy	Broad Gram-negative coverage incl. MDR strains
Administration	i.v./ oral potential
Dosing Schedule	BID/ TID/ QD (depending on PK/ PD)
Covered spectrum	▪ *Enterobacteriaceae* ▪ Extended focus on anti-Pseudomonal and *Acinetobacter* activity
Resulting indications	▪ Complicated Urinary Tract Infection (cUTI) ▪ Complicated Intraabdominal Infection (cIAI) ▪ Hospital Acquired / ventilator associated pneumonia (HAP/VAP) ▪ Blood Stream Infection (BSI) ▪ Nice to have: Cystic Fibrosis (CF) infection

Based on this TPP AiCuris has developed Lead molecules to solve the high medical need caused by resistant gram neg infections

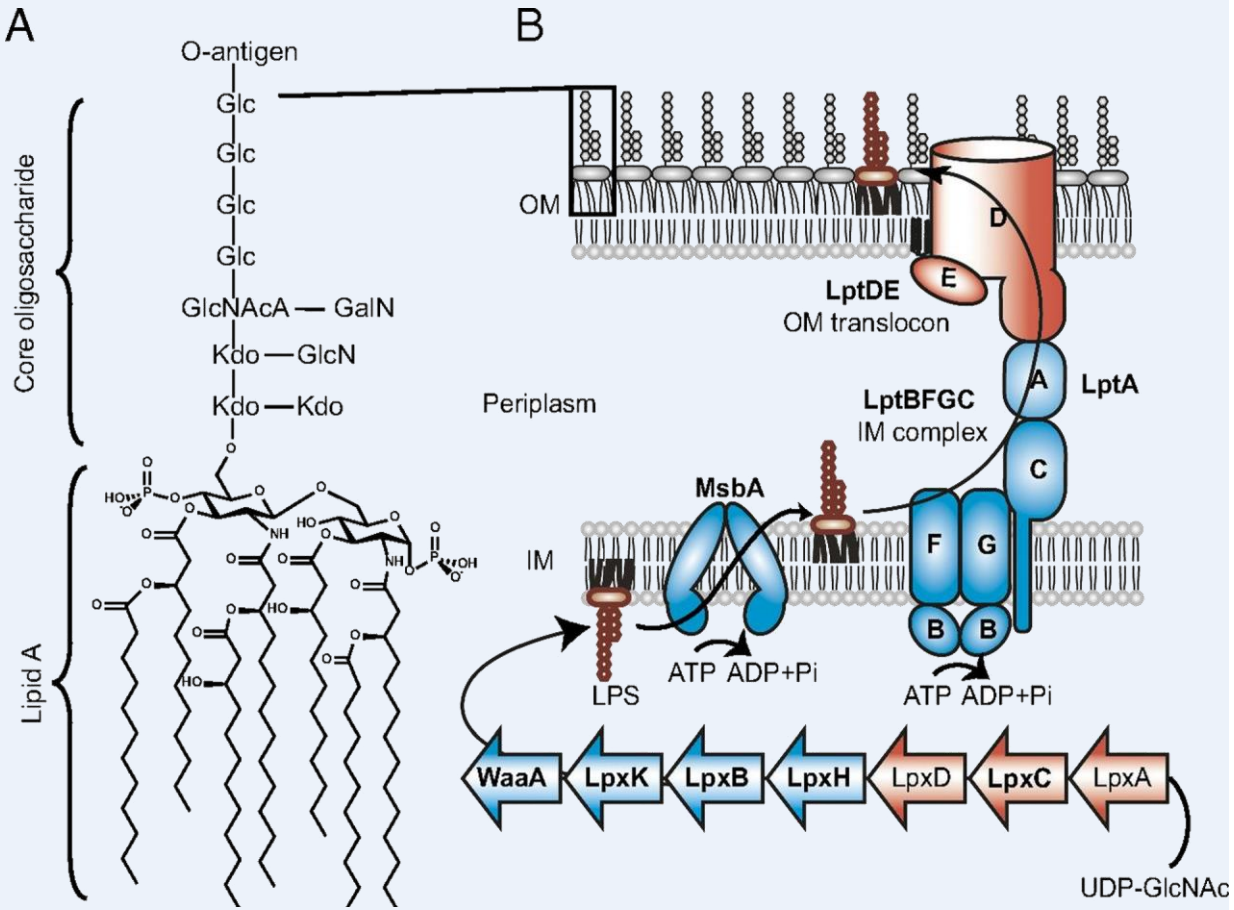
GRAM NEGATIVE RESISTANCE BREAKER – NOVEL MODE OF ACTION

Lipid A Biosynthesis as Target for Novel Antibiotics

- Lipid A is required for growth and virulence
- Inhibition of biosynthesis is lethal in *Enterobacterales* and *P. aeruginosa*
- In *E.coli* the first six enzymes synthesizing Lipid A are essential (LpxA, LpxC, LpxD, LpxH, LpxB and LpxK)

- LpxC has been extensively studied, but compounds failed

- **LpxH is an underexplored target**
- **LpxH catalyzes the fourth step to from lipid A in β- and y-proteobacteria**, which cover most of the Gram-negative human pathogens, including all CDC-listed priority bacteria



Ge Zhang et al. PNAS 2018;115:26:6834-6839

GRAM NEGATIVE RESISTANCE BREAKER – MODE OF ACTION

LpxH is an ideal target

Target LpxC	Target LpxH
In Enterobacterales LpxC production is highly regulated and inhibition is compensated by overproduction of target	Accumulation of substrate is lethal due to the detergent-like properties
LpxC is not essential for *A. baumannii*	*A. baumannii* does not tolerate loss of LpxH
Most promising LpxC inhibitors all contained moieties to bind the Zn-metals, most often hydroxamates → Off-target effects	Avoid metal binding Include off-target tests early on
Poor chemical properties	Emphasis on developing compounds with favorable drug properties

LpxC well studied, but compounds failed **– LpxH program avoids mistakes made before**

GRAM NEGATIVE RESISTANCE BREAKER – LEAD COMPOUND AIC263360

in vitro data

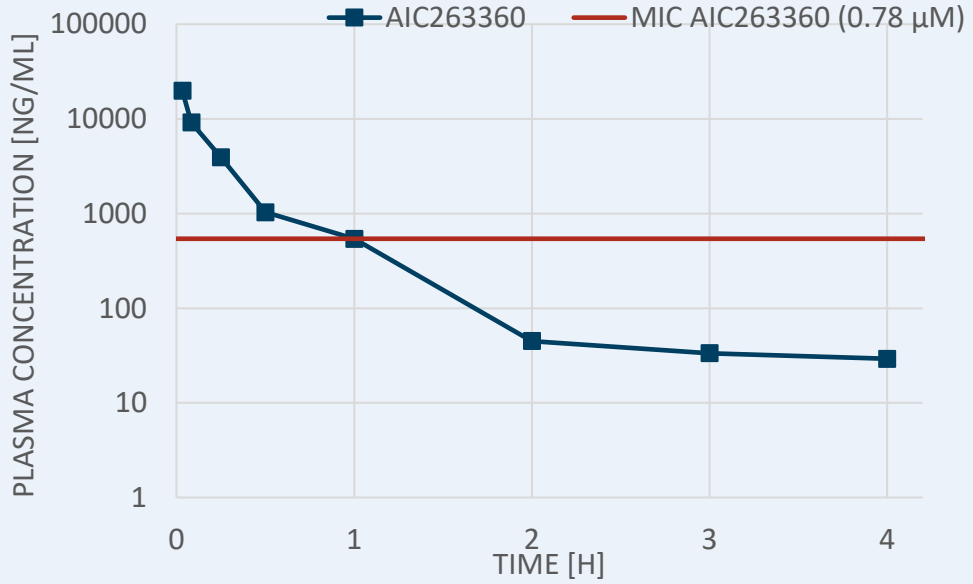
- Small molecule with sulfonyl-piperazinyl core structure
- Strong *in vitro* binding to E.coli LpxH (KD < 80nM)
- MIC values against pathogens of Enterobacterales ranging from 0.4 to 6.2µM
- Selectivity Index >50 when tested for cytotoxcity in 5 human cell lines
- No cross-resistance to other antibiotics expected due to novel target and MoA
- Favorable ADME properties with both plasma and microsomal stability >3hrs
- Our project has received acceptance for the second round of the CARB-X call for application

GRAM NEGATIVE RESISTANCE BREAKER – LEAD COMPOUND AIC263360

in vivo data

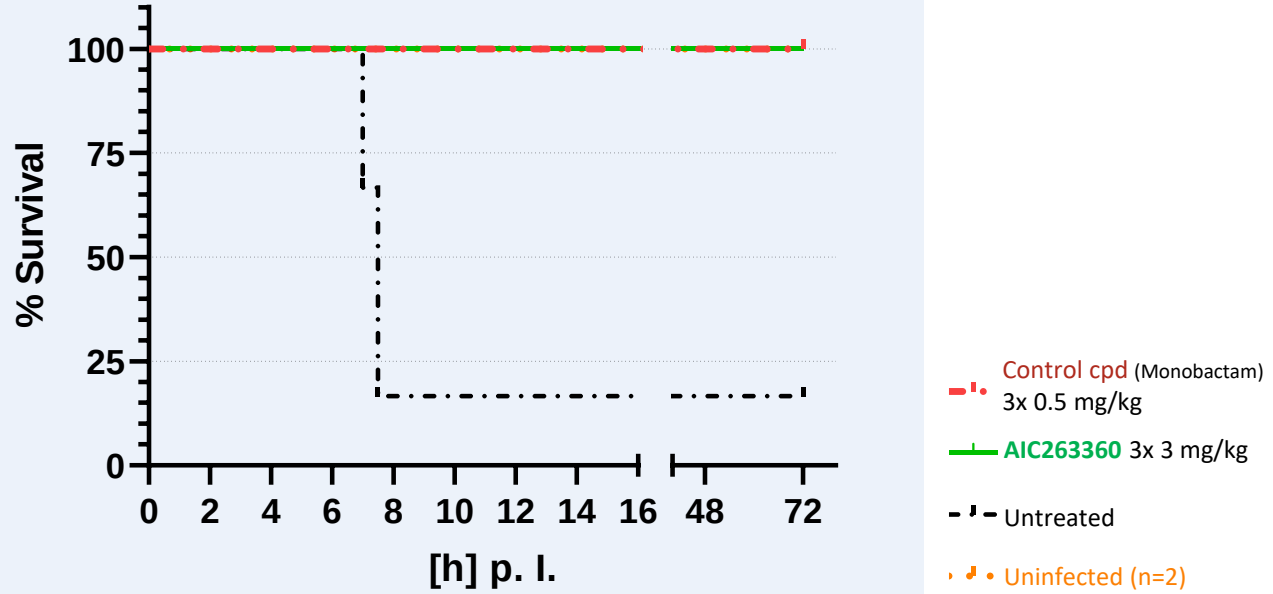
- *In vivo* PK studies in mice showed half lives up to 192 min with time above MIC of ~1h
- Treatment with 3mg/kg AIC263360 TID of infected mice in an *in vivo* mouse peritonitis infection model resulted in 100% survival while untreated mice died within the first few hours after infection with *E.coli*

In vivo PK (3 mg/kg i.v., mouse)



Sepsis in CD-1 mice with *E. coli* Neumann

(i.p. infection, i.v. treatment, n=6 per group)



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