FORGE Therapeutics

Forging New Therapies for Multidrug Resistant Infections

10578 Science Center Drive, San Diego, CA 92121 | David Puerta, Ph.D., COO & VP of Discovery

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FORGING LIFE SAVING MEDICINES

Forge Therapeutics is a biotechnology company developing novel medicines by combining bioinorganic with medicinal chemistry to target metalloenzymes.

Forge has developed a fundamentally new approach for the discovery of metalloenzyme-targeted inhibitors by focusing first on the metal in the enzyme active site.

BLACKSMITHS OF MODERN MEDICINE

Over 30% of known enzymes are metalloenzymes covering all major enzyme classes: oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases.

Metal ions, including magnesium, zinc, iron, manganese, and copper are essential to these valuable targets.

At Forge, we are the blacksmiths of modern medicine, providing the tools to address any metalloenzyme challenge.

Forge's technology is applicable to all therapeutic areas and initial focus is developing direct-acting, small molecule, novel classes of antibiotics.

BLACKSMITH PLATFORM

Forge's technology platform, BLACKSMITH comprises:

- a deep knowledge of metalloenzymes,
- bioinorganic and medicinal chemistry know-how, and
- a focused fragment library of proprietary metal-binding pharmacophores (MBPs) that provide selective & diverse chemical matter for novel inhibitor design.

Our strategy is to use the BLACKSMITH platform to discover new chemical matter for the treatment of a broad range of diseases with initial efforts in the area of infectious disease.

Forge has mined the *E. coli* genome for essential metalloenzymes and is developing novel antibiotics against these targets.

FORGE PIPELINE

Program	Indications	Discovery	Preclinical	Clinical
LPXC PROGRAM First potent and efficacious non-hydroxamate inhibitor of LpxC	Urinary tract infections	*E. coli, K. pneumoniae, P. mirabilis*		
	Intra-abdominal	*E. coli, Enterobacteriaceae*		
	Respiratory	*A. baumannii, P. aeruginosa*		
	Gonorrhea	*N. gonorrhoeae*		
	Biodefense	*Y. pestis, F. tularensis, B. mallei, B. pseudomallei*		
Program	**Indications**	**Discovery**	**Preclinical**	**Clinical**
BLACKSMITH METALLOENZYME PLATFORM Novel small molecule inhibitors of metalloenzymes	RNAP	Mg^{2+}		
	DXR	Mg^{2+}		
	IspF	Zn^{2+}		

LpxC, a Zn^{2+} deacetylase, is responsible for the production of the outer membrane of Gram-negative bacteria.

RNAP, the Mg^{2+} bacterial RNA polymerase, is essential for the synthesis of RNA.

DXR is a Mg^{2+} isomerase essential for isoprenoid synthesis, a class of organic molecules vital for a variety of biological functions in bacteria.

IspF is Zn^{2+} lyase required for the non-mevalonate pathway in bacteria.

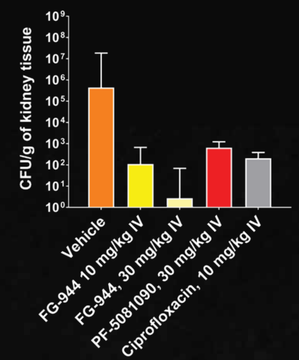
LPXC PROGRAM: IN VITRO ACTIVITY

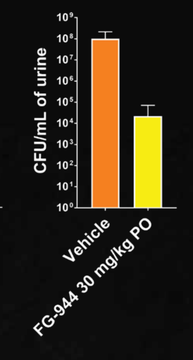
ID	MIC (μg/mL)					
	E. coli			*K. pneumoniae*		
	ATCC 25922	MDR BAA-2469	MDR BAA-2471	ATCC 13883	MDR BAA-2470	MDR BAA-2342
FG-944	0.25	0.25	0.25	1	1	2
Cipro	0.008	> 32	> 32	0.03	32	> 32
Amikacin	2	> 32	> 32	1	> 32	4
Meropenem	0.06	> 32	> 32	0.12	32	32

Due to the novel mechanism of action of inhibiting LpxC, Forge inhibitors have demonstrated antimicrobial activity against carbapenem-resistant and ESBL-producing *Enterobacteriaceae*, where traditional antibiotics are ineffective.

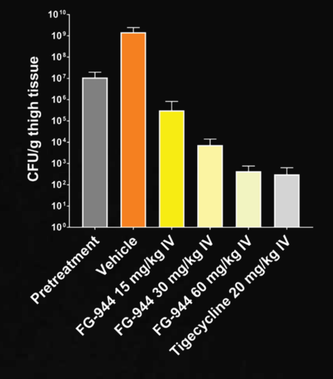
LPXC PROGRAM: IN VIVO EFFICACY

E. coli UTI89 (UTI model; IV & PO)

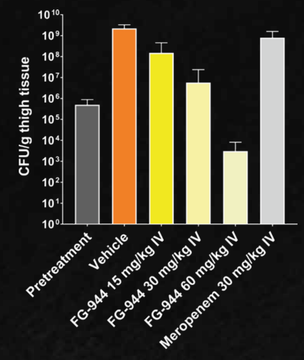




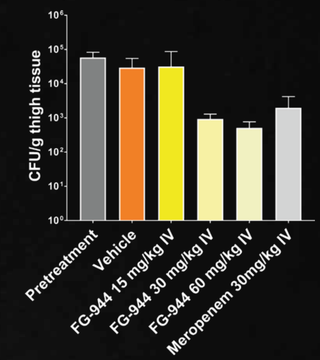
E. coli BAA-2469 (thigh)



E. cloacae KPC114 (thigh)



P. mirabilis B861 (thigh)



SUMMARY

Forge is focused on developing novel classes of antibiotics with its lead effort on LpxC.

Forge has a strategic drug discovery partnership with Evotec AG and has been awarded multiple government awards including CARB-X.

Forge has amassed a rich intellectual property estate on metalloprotein inhibitors to protect its BLACKSMITH platform and pipeline including technology licensed from UCSD.

For further information, please visit the company's website www.ForgeTherapeutics.com and follow us on Twitter @ForgeThera.

evotec

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