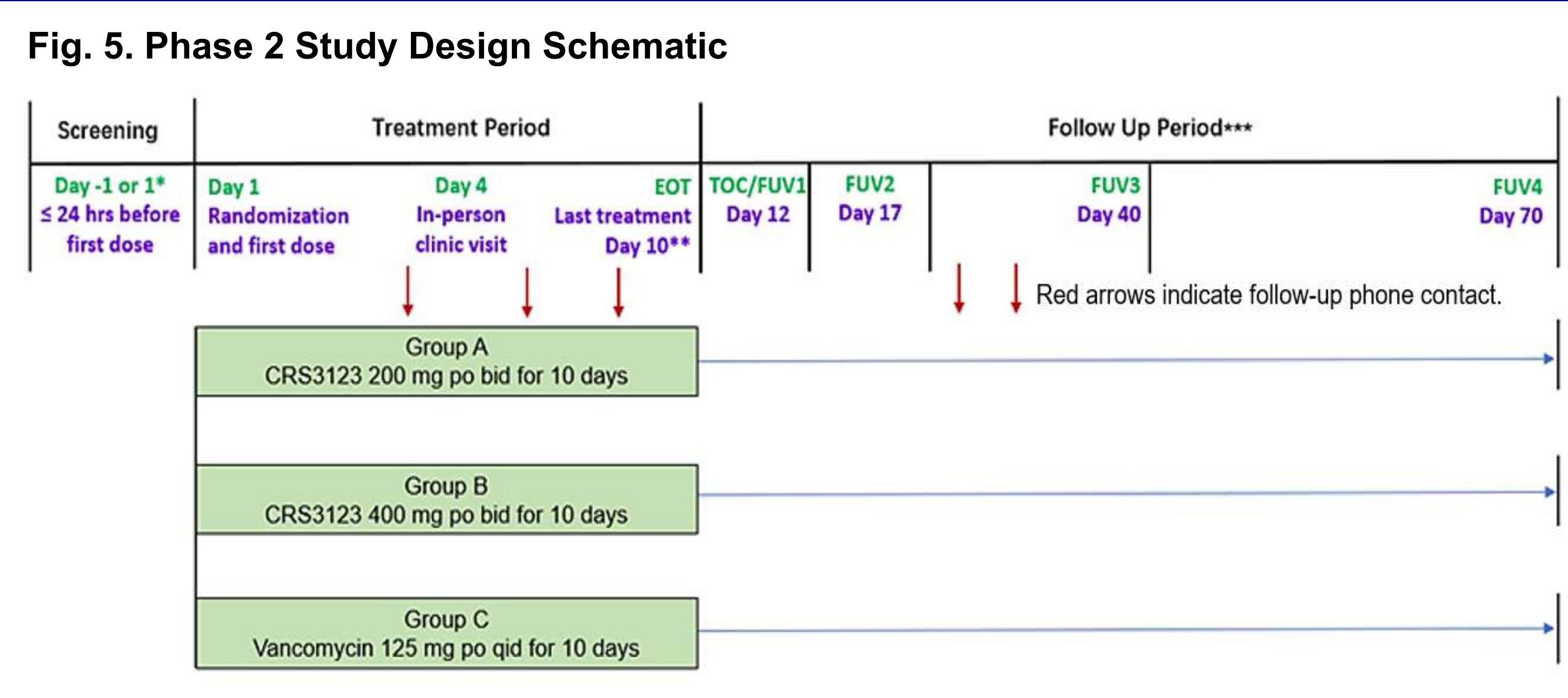
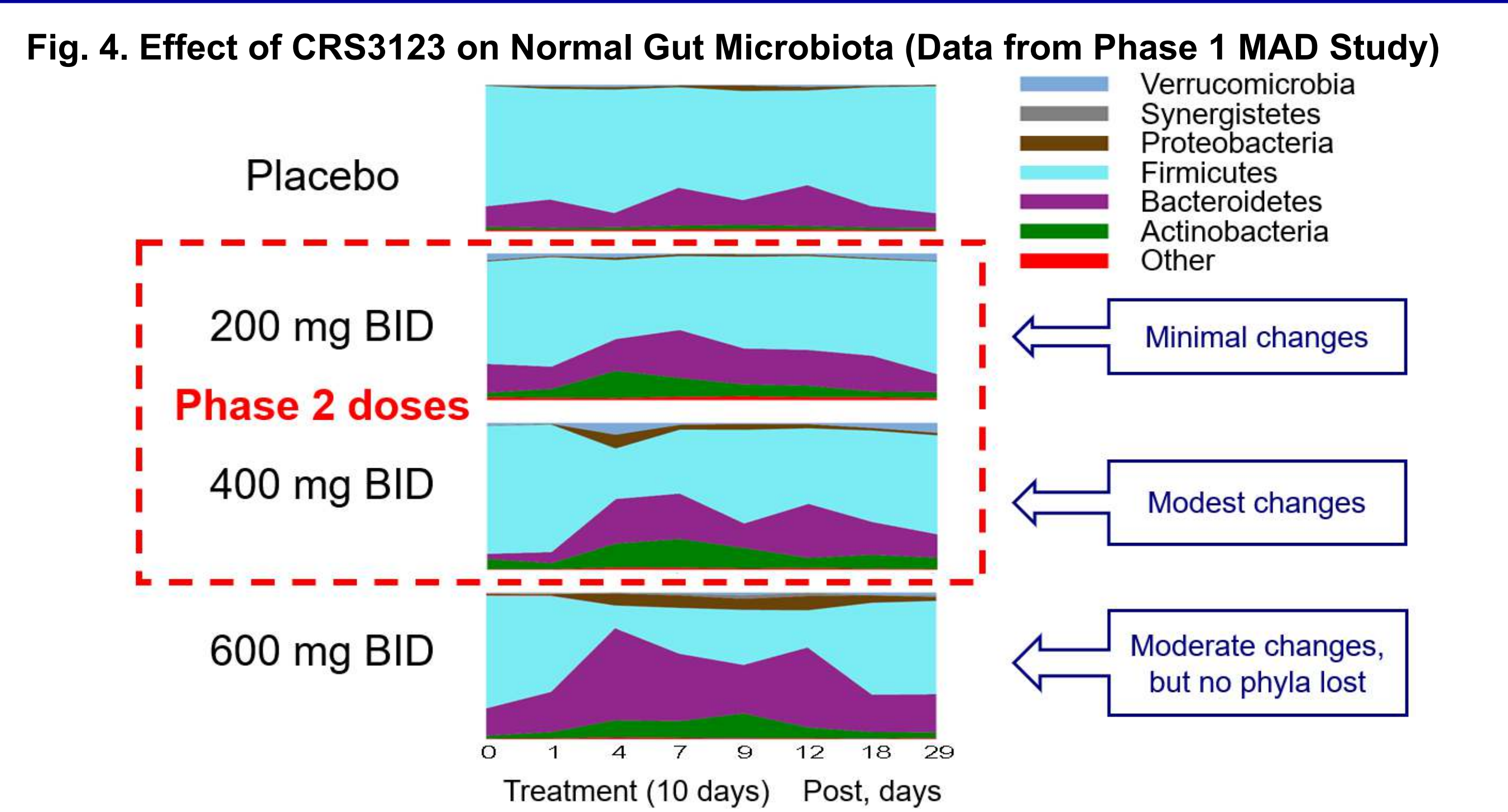
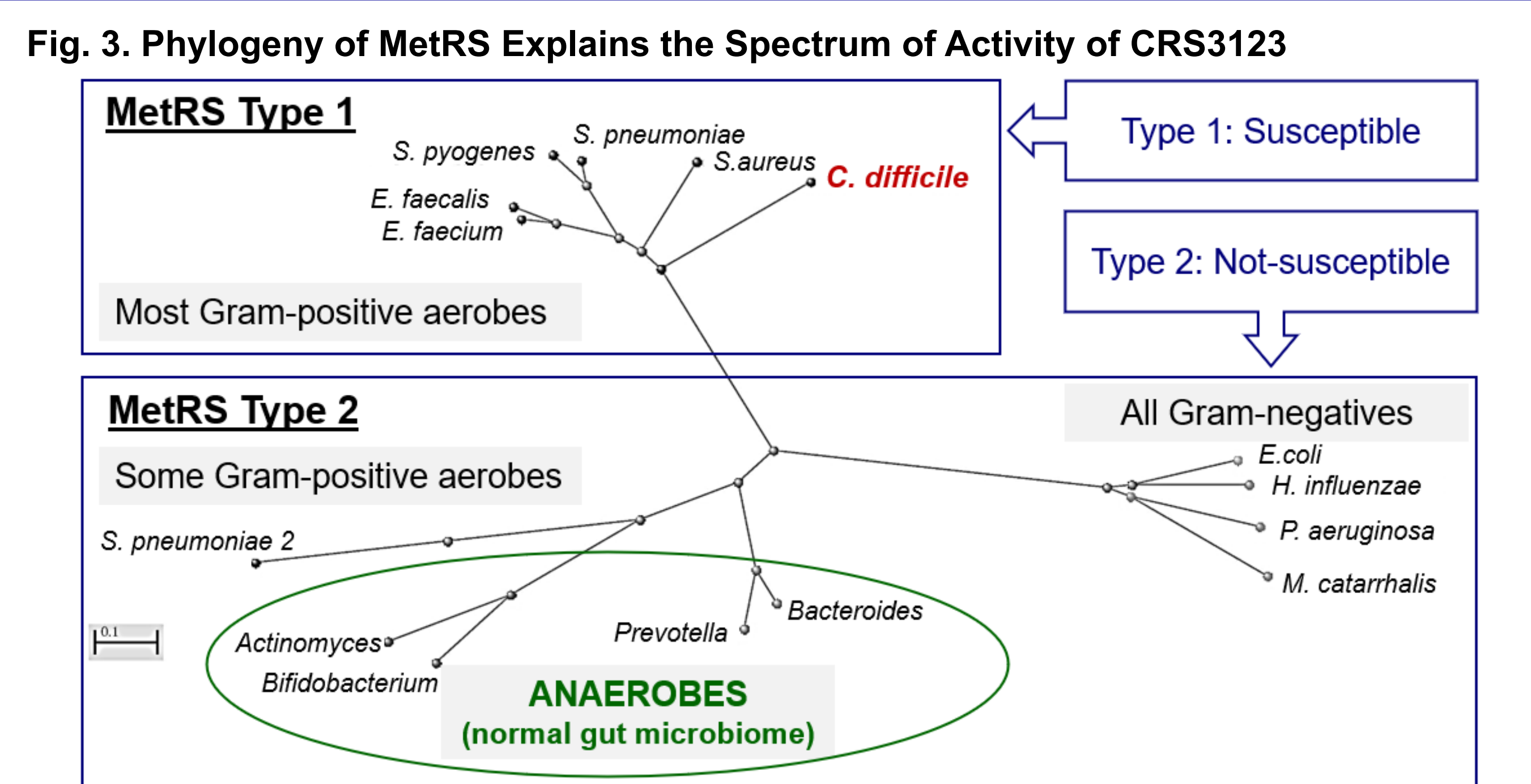
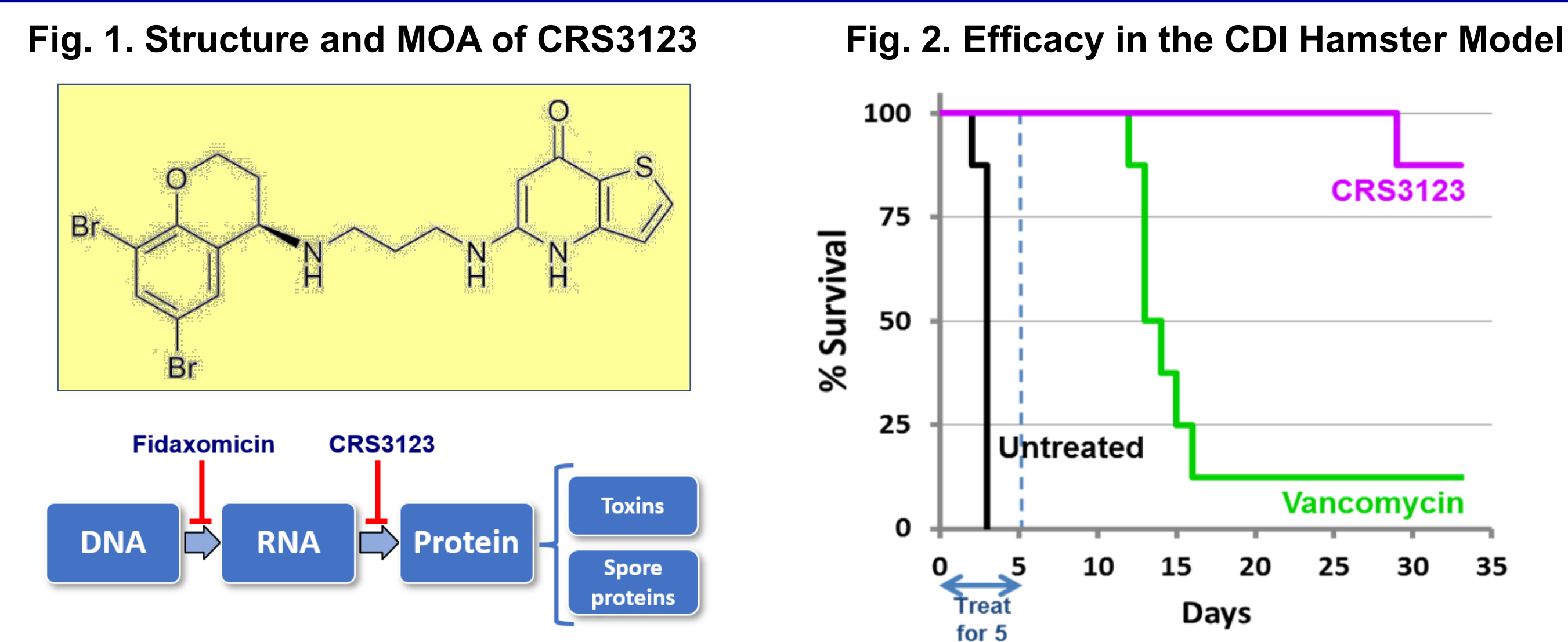


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CRS3123: *C. difficile* Infection

CRS3123 is in Phase 2 development for the treatment of *C. difficile* infection (CDI), enrolling patients (trial registration: NCT04781387). CRS3123 is a diaryldiamine that inhibits methionyl-tRNA synthetase (MetRS) and thereby blocks growth (MIC₉₀=1 µg/mL), toxin production, and sporulation. Its low oral bioavailability results in little systemic exposure but high accumulation (>1,000 µg/g) in the gut, where the drug exerts its action. CRS3123 demonstrated a favorable safety profile in Phase 1 SAD/MAD studies. An attractive feature of CRS3123 is its narrow spectrum of activity due to the phylogeny of the MetRS target, which largely spares the beneficial gut microbiota.



Funding: NIAID Contracts HHSN27220080026C (Phase I) and 75N93056C00019 (Phase II), ongoing
Acknowledgments: Dr. Cathy Lozupone and Dr. Keith Hazleton, CU-Anschutz (microbiome analysis)

CRS0540: Oral/IV Gram-positives

CRS0540 is in IND-enabling preclinical development as a novel oral/IV agent for the treatment of Gram-positive infections, including those caused by antibiotic-resistant pathogens such as MRSA, PRSP, and VRE. CRS0540 is a thiazolidine urea compound that inhibits PolC, the catalytic subunit of the DNA polymerase essential for DNA replication. It is a bactericidal agent with no pre-existing resistance and a low (10⁻⁹) spontaneous resistance frequency. CRS0540 has demonstrated efficacy in several mouse models, including MRSA soft tissue and bloodstream infection, pneumococcal and MRSA lung infection, and an anthrax nasal challenge model. AUC/MIC is the PK/PD index.

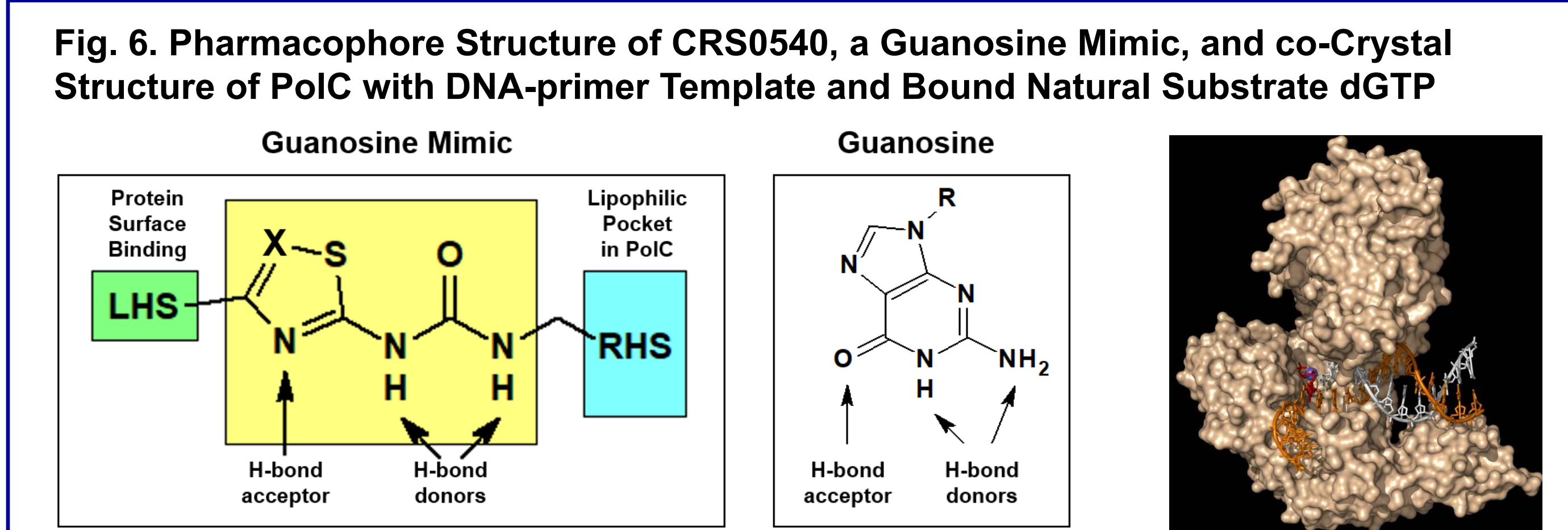
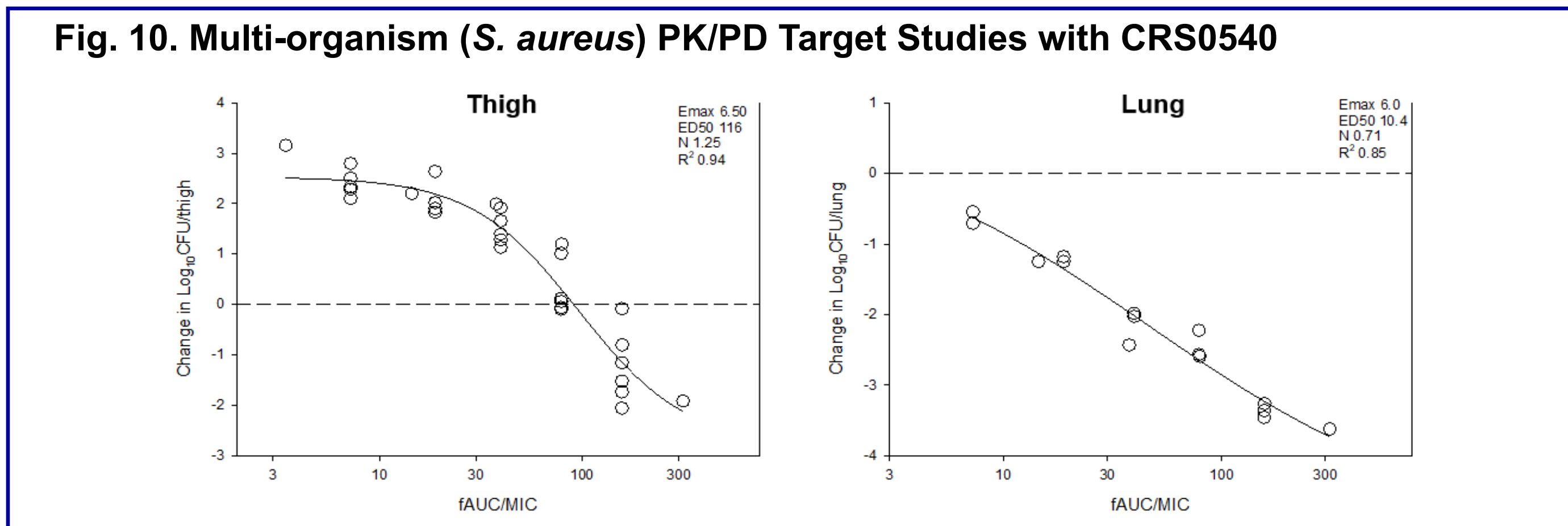
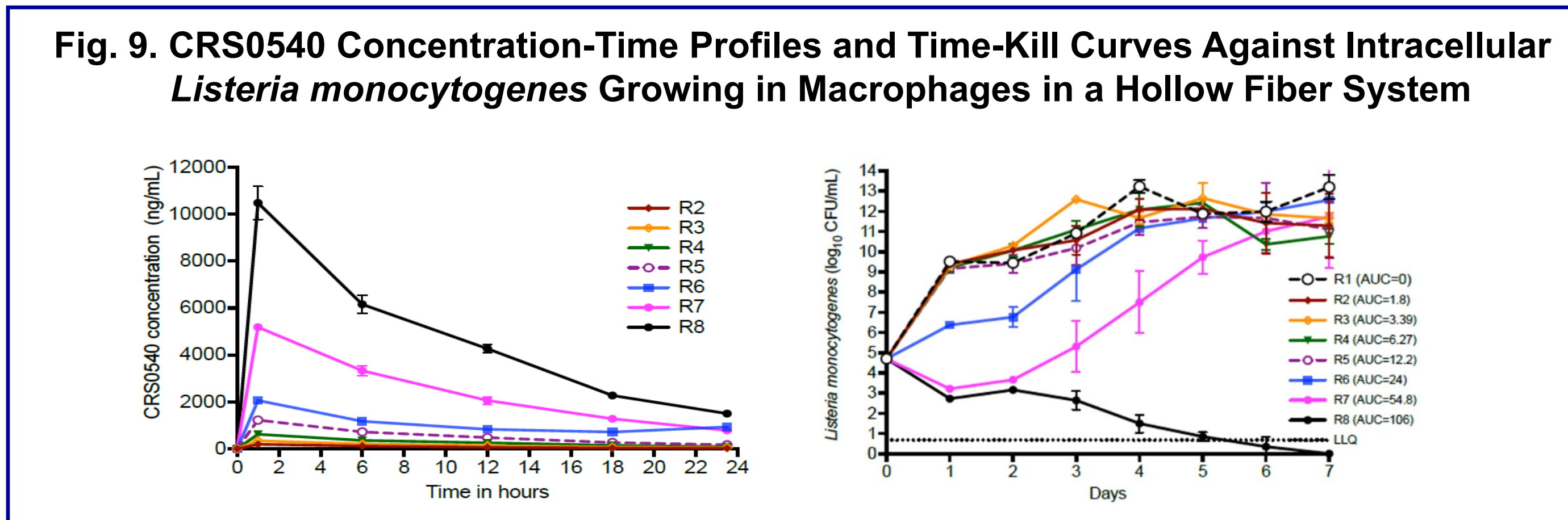
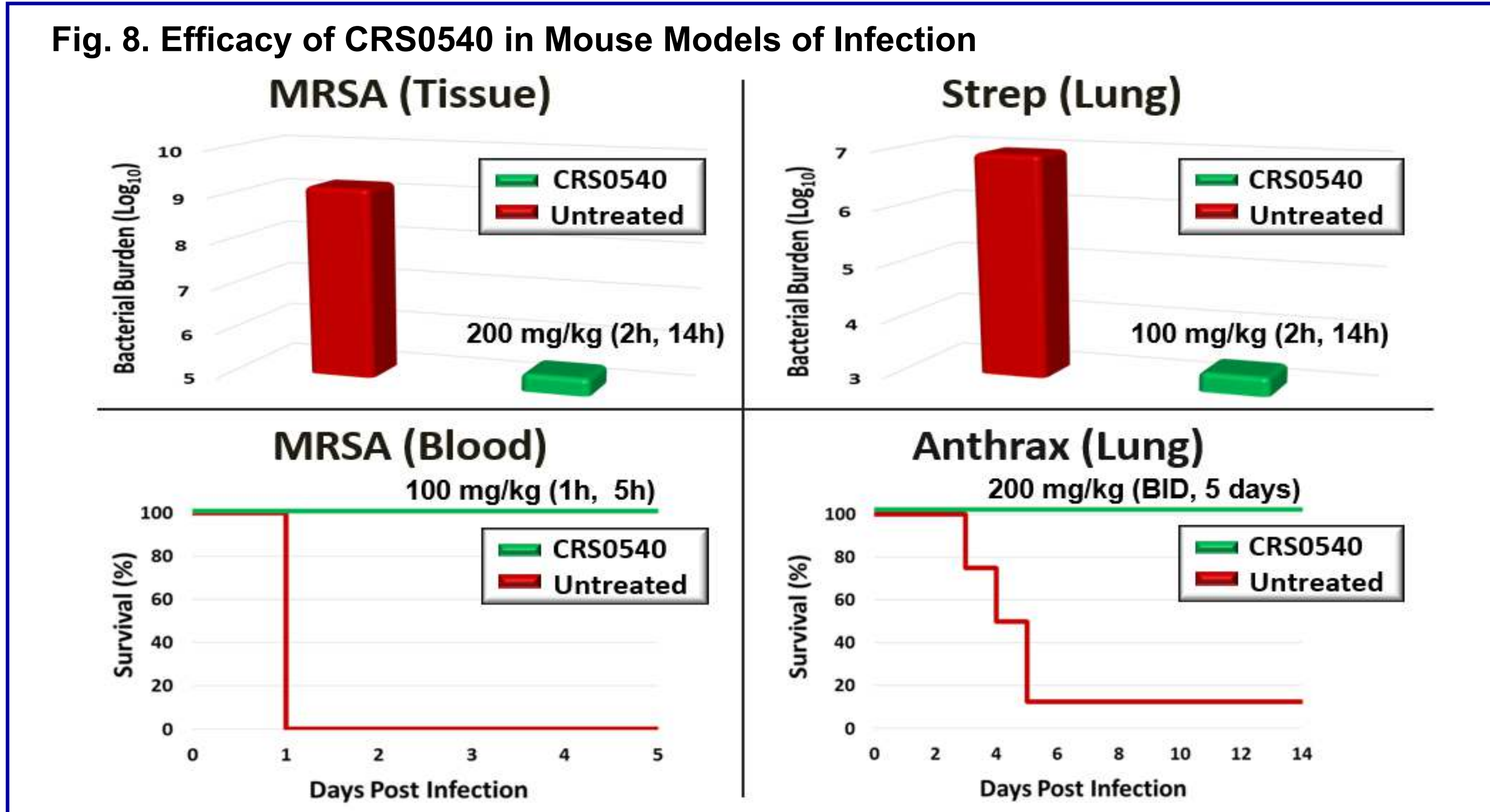


Fig. 7. Activity of CRS0540 Against Drug-resistant Gram-positive Pathogens

Strain	Minimum Inhibitory Concentration, MIC (µg/mL)									
	CRS0540	CEF	AZI	LEVO	TET	GENT	LZD	VANC	IMI	
<i>S. aureus</i> NRS384 (CA-MRSA, PVL+)	1	>16	>16	1	>16	>16	>16	2	0.5	8
<i>S. aureus</i> NRS119 (Levo-R, Lzd-R)	1	>16	1	>16	>16	>16	>16	1	>16	>16
<i>S. epidermidis</i> NRSB (MRSE)	2	>16	>16	16	0.5	>16	>16	1	8	0.5
<i>S. pyogenes</i> F758883 (AZI-R)	<0.25	1	2	0.5	>16	4	1	<0.25	<0.25	<0.25
<i>S. pneumoniae</i> MDR-1 (PRSP, MDR)	2	>16	>16	1	>16	>16	0.5	<0.25	1	<0.25
<i>S. pneumoniae</i> F1064366 (Levo-R)	1	2	16	16	>16	16	1	<0.25	<0.25	<0.25
<i>E. faecalis</i> F1111404 (VRE)	1	>16	>16	>16	0.5	>16	2	>16	>16	>16
<i>E. faecium</i> F1111434 (VRE)	1	>16	>16	>16	>16	>16	2	16	>16	>16
<i>L. monocytogenes</i> ATCC 15313	1	NT	NT	NT	NT	NT	NT	NT	NT	NT
<i>B. anthracis</i> Ames	0.5	NT	NT	NT	NT	NT	NT	NT	NT	NT



Funding: NIAID Contracts HHSN272201500012C (2015-2019), 75N93020C00020 (since 2020, ongoing)
Acknowledgments: Dr. David Andes and Dr. Alex Lepak, U Wisconsin (PK/PD), Dr. Tawanda Gumbo and Dr. David Howe, Praedicare, LLC (*L. monocytogenes* HFS model), Dr. Tim Murphy, NeoSome Life Sciences LLC (Staph and Strep *in vivo* models), Dr. Richard Bowen, CSU Fort Collins (*in vivo* anthrax model).

CRS0393: NTM/TB Infection

CRS0393 is a benzothiazole amide in preclinical development to treat NTM and TB infections. It is a bactericidal agent targeting MmpL3, a mono-mycolate transporter essential for cell wall biosynthesis in mycobacteria. CRS0393 has potent *in vitro* activity against rapid-grower NTM (MIC range <0.03 - 0.5 µg/mL) and is also active against *M. avium* and *M. tuberculosis*. CRS0393 was found effective in killing intracellular mycobacteria in human macrophages. PK data indicate that CRS0393 is suitable for oral or inhaled administration. CRS0393 was well tolerated and efficacious in a mouse lung infection model with *M. abscessus*, with a >3 Log₁₀ reduction in CFU.

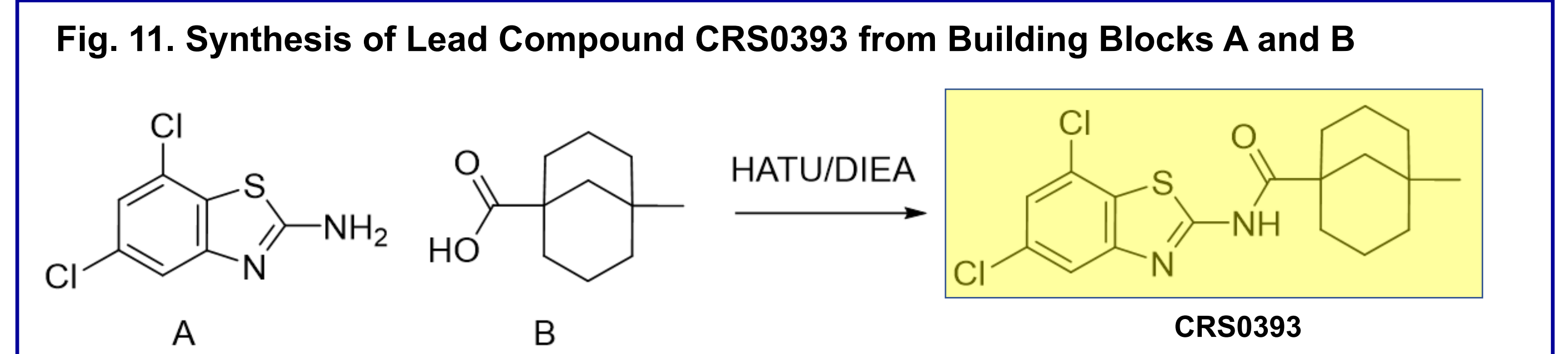
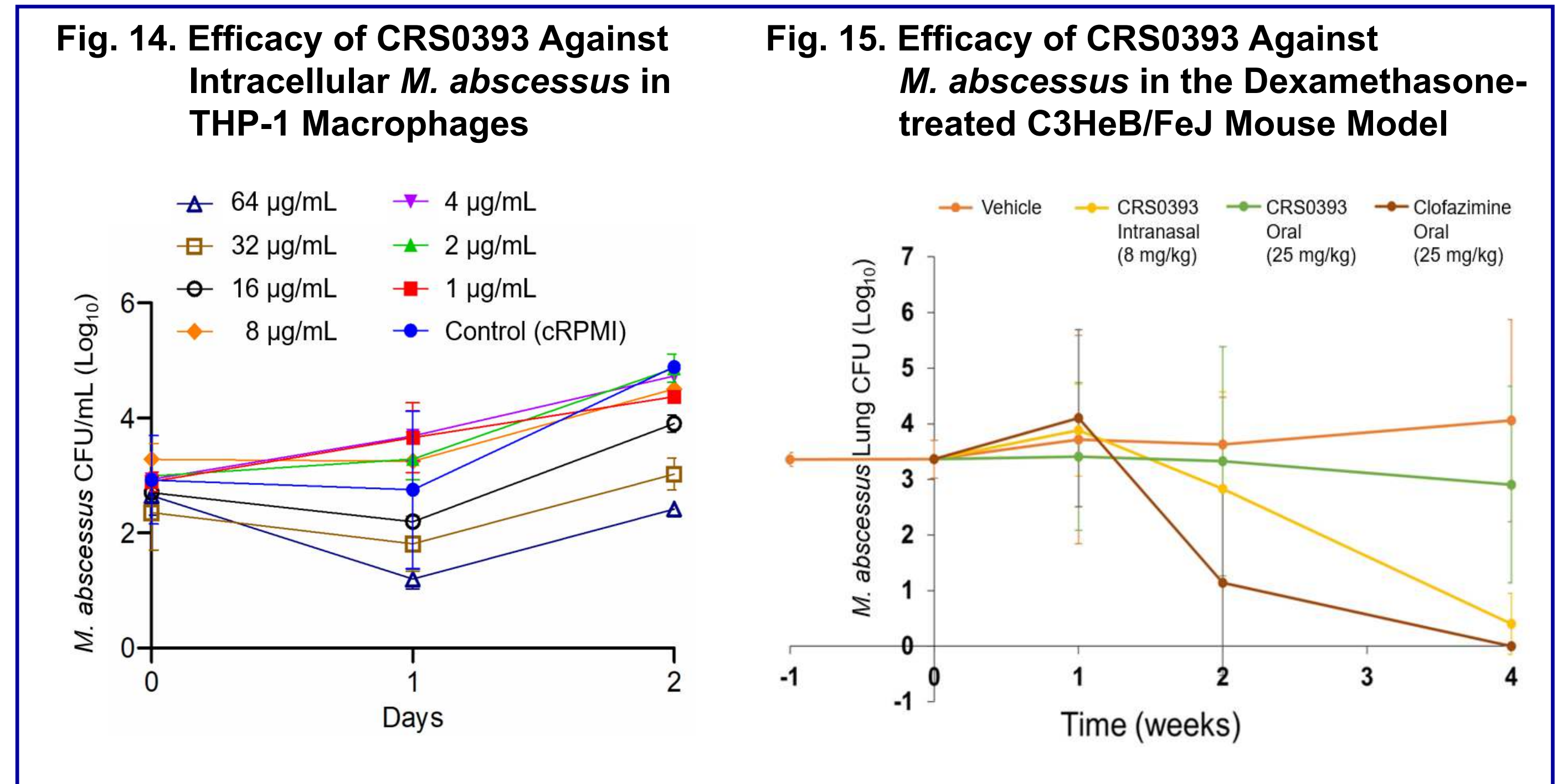
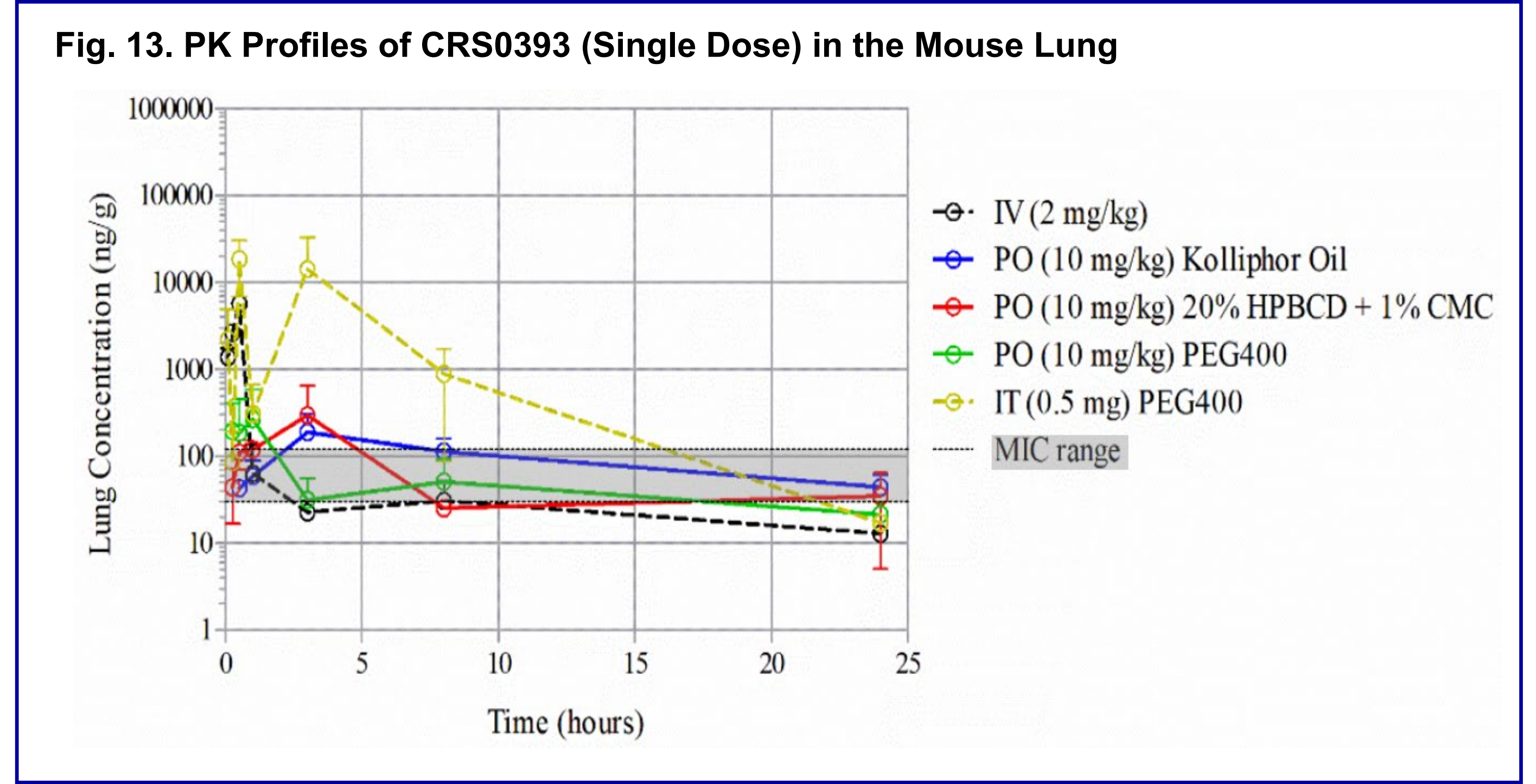


Fig. 12. MIC Profiles of CRS0393 and Closely Related Backup Compounds.

Over 100 analogs of CRS0393 have been generated and analyzed for antimicrobial activity. CRS0393 is the lead compound for development. CRS0470 is the amine version of CRS0393, on average 2-fold less active. CRS0482 is a des-methyl version of CRS0393 and is equally active against rapid-growers. CRS0499 has improved activity against slow-grower NTM strains.

Species	Minimum Inhibitory Concentration (MIC) µg/mL			
	CRS0393 ^a	CRS0470	CRS0482	CRS0499
Rapid growers				
<i>M. abscessus</i> ATCC 19977	0.015-0.06	0.06	0.03-0.06	0.12
<i>M. abscessus</i> 1	0.03-0.12	0.03-0.12	0.03-0.06	0.12
<i>M. abscessus</i> 21	0.015-0.06	0.03-0.06	0.015-0.03	0.12
<i>M. abscessus</i> 79	0.03-0.06	0.06-0.12	0.03-0.06	0.06
<i>M. abscessus</i> 103	0.015-0.25	0.06-0.5	0.015-0.25	1
<i>M. abscessus</i> massiliense 119	0.03-0.12	0.06-0.5	0.03-0.12	0.5
<i>M. chelonae</i> 93	0.015-0.25	0.015-0.5	0.03-0.12	0.25
<i>M. fortuitum</i> 41	0.06-0.25	0.12-0.25	0.12-0.25	0.25
<i>M. peregrinum</i> ATCC 700686	0.015-0.12	0.015-0.06	0.03-0.25	0.12
Slow growers^b				
<i>M. avium</i> 101	2-4	2	16	0.5
<i>M. intracellulare</i> 1956	2-4	1	>64	0.5
<i>M. chimera</i> 1501948	2-4	1	8	0.5

^a Range of 9 test occasions (different batches tested at different dates)
^b 7H9 medium used for MIC testing of slow-grower NTM contains 5 mg/mL albumin. Due to the high protein binding of the compounds, MIC values measured in this 7H9 broth for slow-grower NTM tend to be several-fold higher than in Mueller-Hinton broth used according to CLSI for rapid-grower NTM.



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