

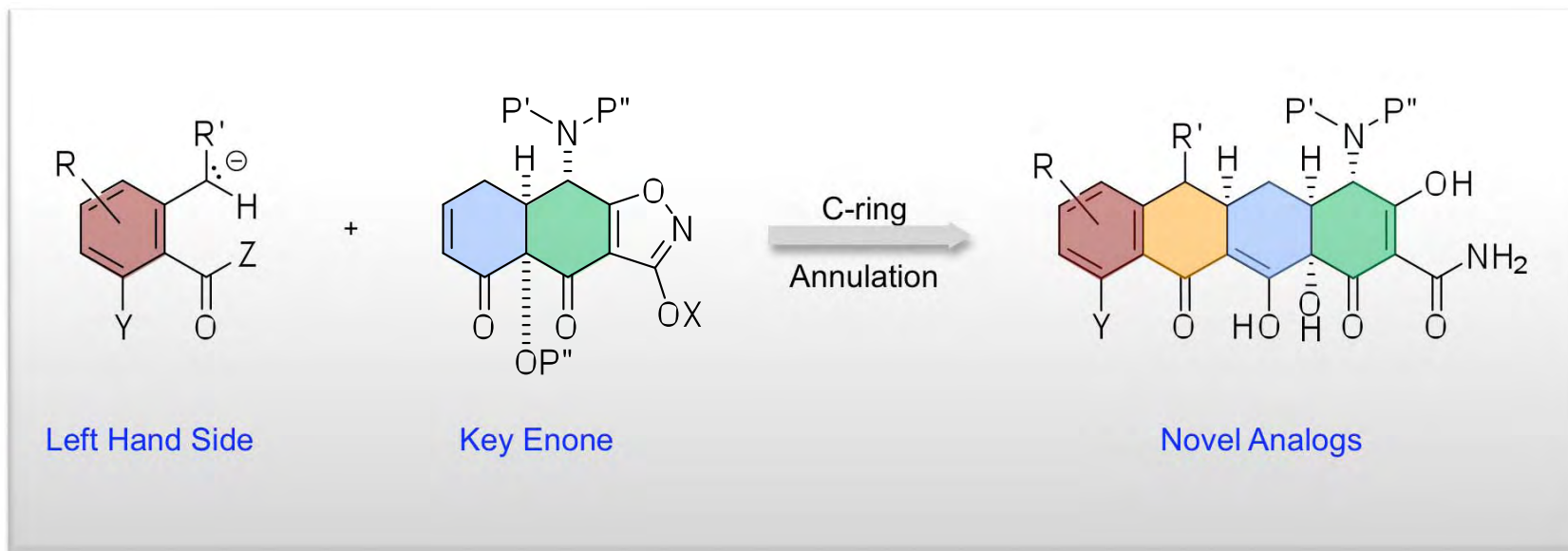
# Oral Antibacterial Activity of a Novel Pentacycline F1-1219

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Tetraphase Pharmaceuticals, Inc.  
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**Related Poster: F1-1516: Synthesis and Antibacterial Activities of  
Pentacyclines: A Novel Class of Tetracycline Analogs**

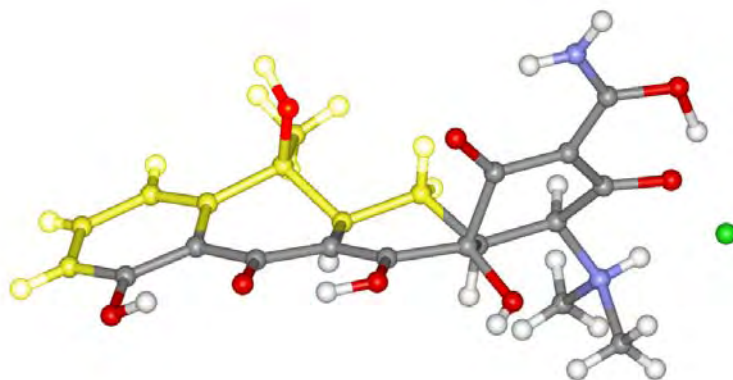
# The Tetraphase Platform

Addressing the lack of Chemical Diversity:

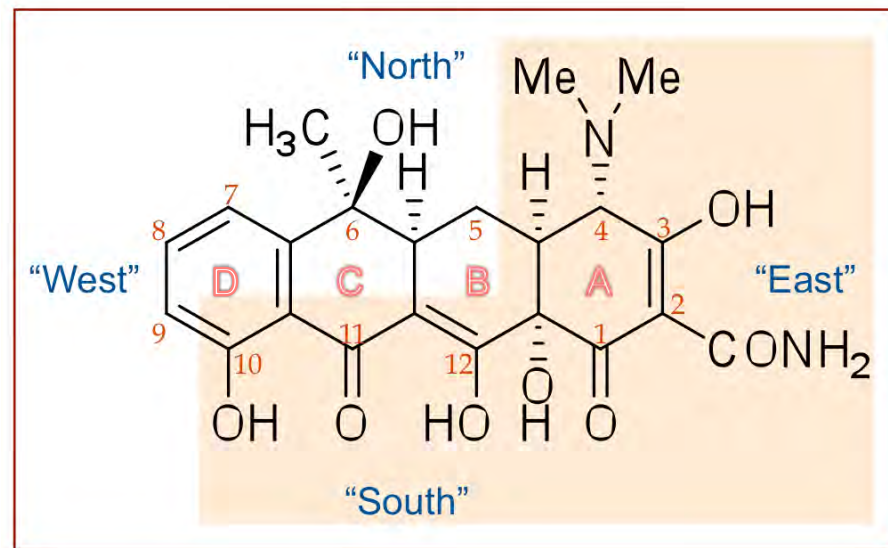


Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siegel, D. R.; Myers, A. G. *Science* **2005**, *308*, 395-398.

# Opportunity Created by The Platform



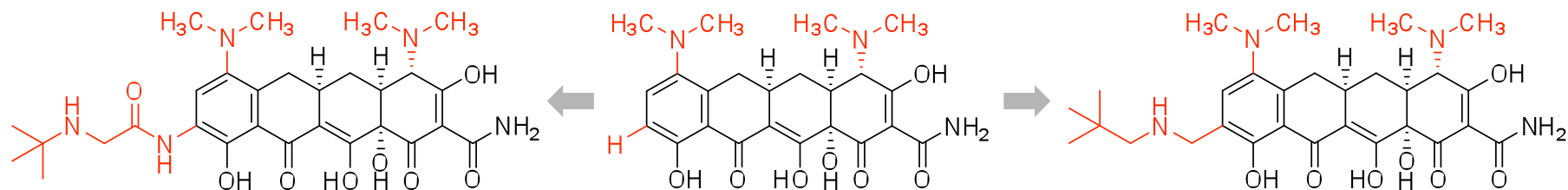
(-)-Tetracycline • HCl



- Shaded area constant in all approved tetracyclines
- Historically, majority of chemistry is at C7 and C9
- Opportunities for variation in both shaded and unshaded regions

Rogalski, W. "Chemical Modification of the Tetracyclines", In *Handbook of Experimental Pharmacology*; Hlavka, J. J.; Boothe, J. H., Eds.; Springer-Verlag: New York, NY, 1985; Vol. 78, 179-316.

# Recent Competition Has Limited Diversity



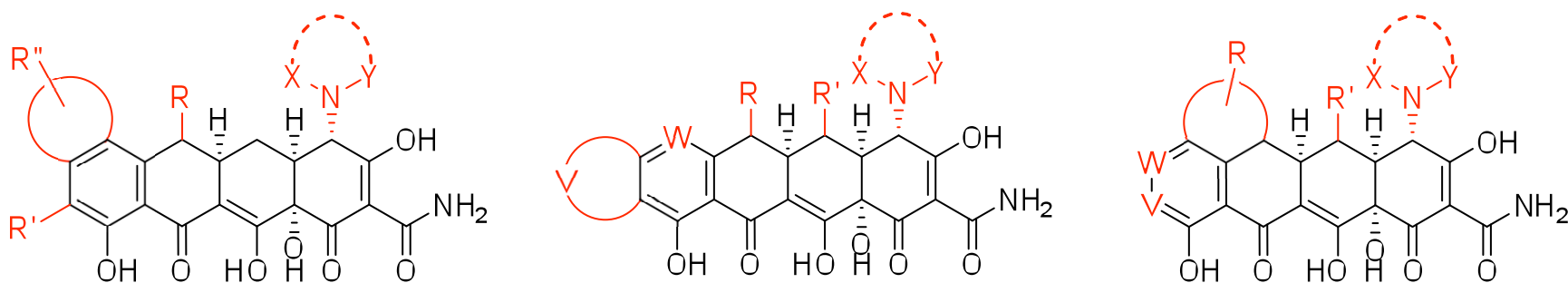
**Tigecycline**

*(Approved US: June 16, 2005)*

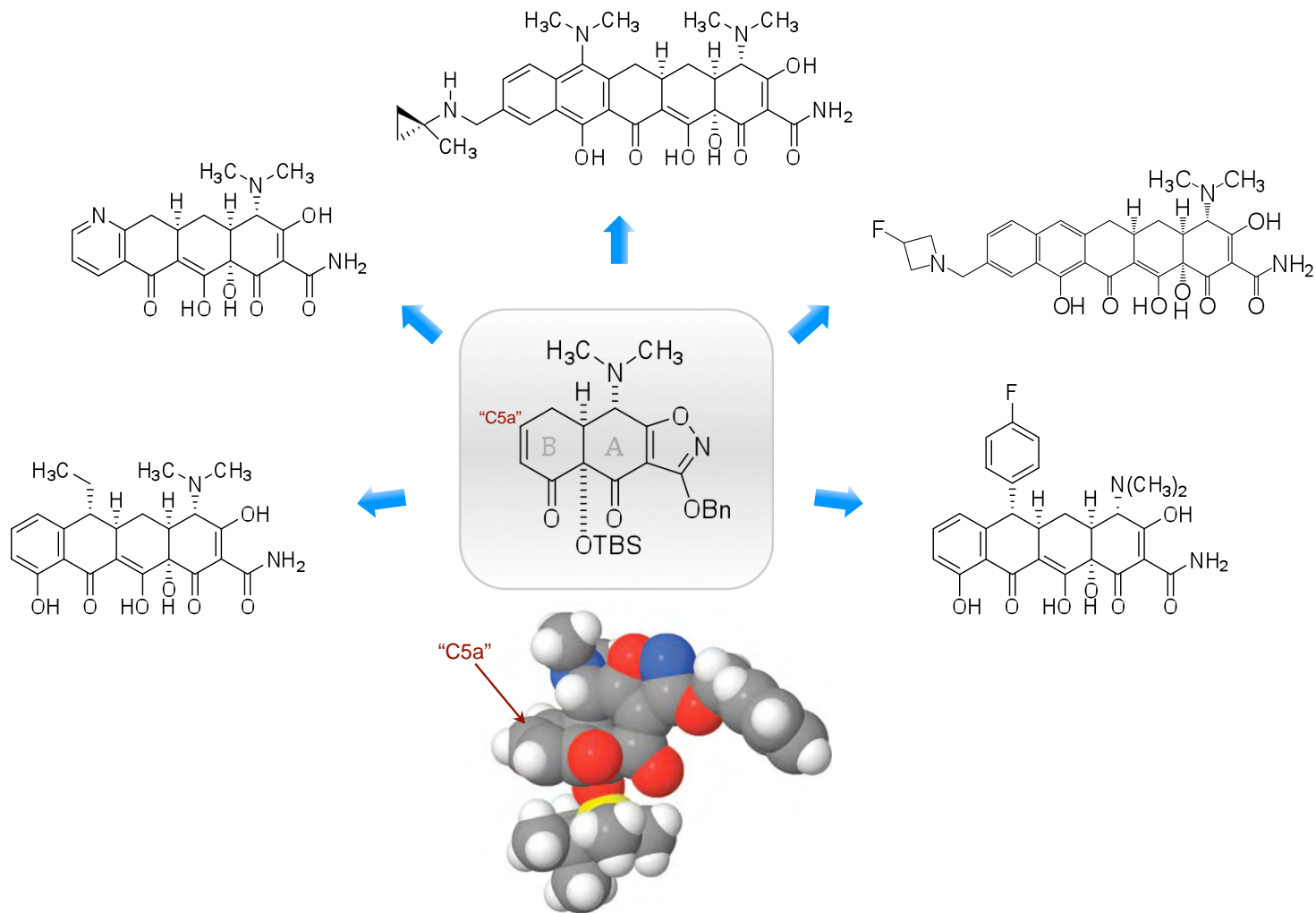
**Minocycline**

**PTK-0796**

## Tetracycline Analogs:



# Examples of Tetraphase Analogs

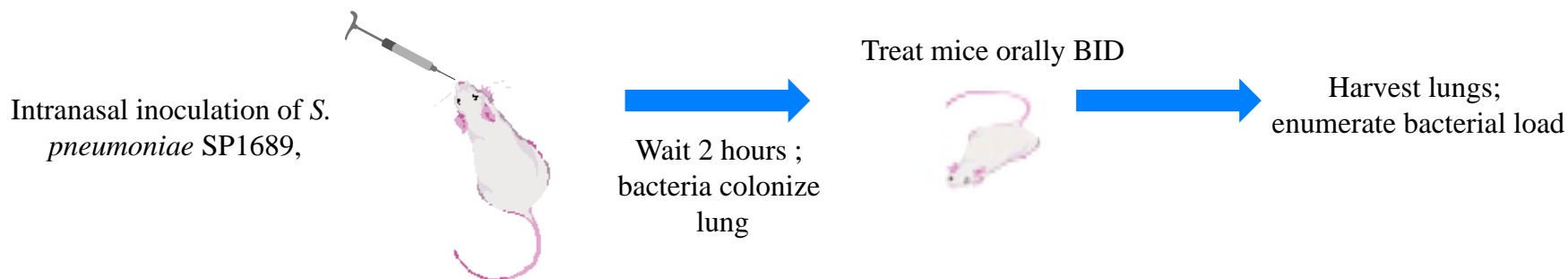


Sun, C.; Wang, Q.; Brubaker, J. D.; Wright, P. M.; Lerner, C. D.; Noson, K.; Charest, M.; Dionicio, S. R.; Wang, Y.-M.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 17913–17927

# TP-038 is Potent *in vitro* Against CAP Pathogens

Compound	<i>S. aureus</i> (n=20)			<i>S. pneumoniae</i> (n=11)			<i>H. influenzae</i> (n=11)		
	MIC range	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC range	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC range	MIC <sub>50</sub>	MIC <sub>90</sub>
TP-038	0.13 - 0.25	0.13	0.25	0.03 - 0.25	0.13	0.13	0.5 - 4	1	2
Tetracycline	0.06 - 32	0.13	0.25	0.13 - >32	32	>32	0.25 - 16	0.5	16
Doxycycline	ND	ND	ND	≤0.016 - 16	1	8	0.5 - 4	1	4
Oxacillin/ Amoxicillin	0.06 - 64	8	64	≤0.016 - 8	1	8	2 - 32	8	16

# TP-038 Protects Orally Against *Streptococcus pneumoniae* in Murine Lung Model



Cpd	Structure	SP1689 MIC ( $\mu\text{g/ml}$ )	Route, Dosing Frequency	Conc. (mg/kg)	$\text{Log}_{10}$ change from control	Standard Deviation
TP-038		0.03	PO, BID	30 mg/kg	-2.97	0.35
				15 mg/kg	-2.46	0.42
Tet		0.13	PO, BID	30 mg/kg	-0.80	0.40
				15 mg/kg	-0.57	0.16

# TP-038 Protect Orally Against *Staphylococcus aureus* 13709 in Murine Septicemia Model

Intraperitoneal inoculation of *S. aureus* 13607 at  $2 \times 10^6$  cfu/mouse  
n=6



1 hour

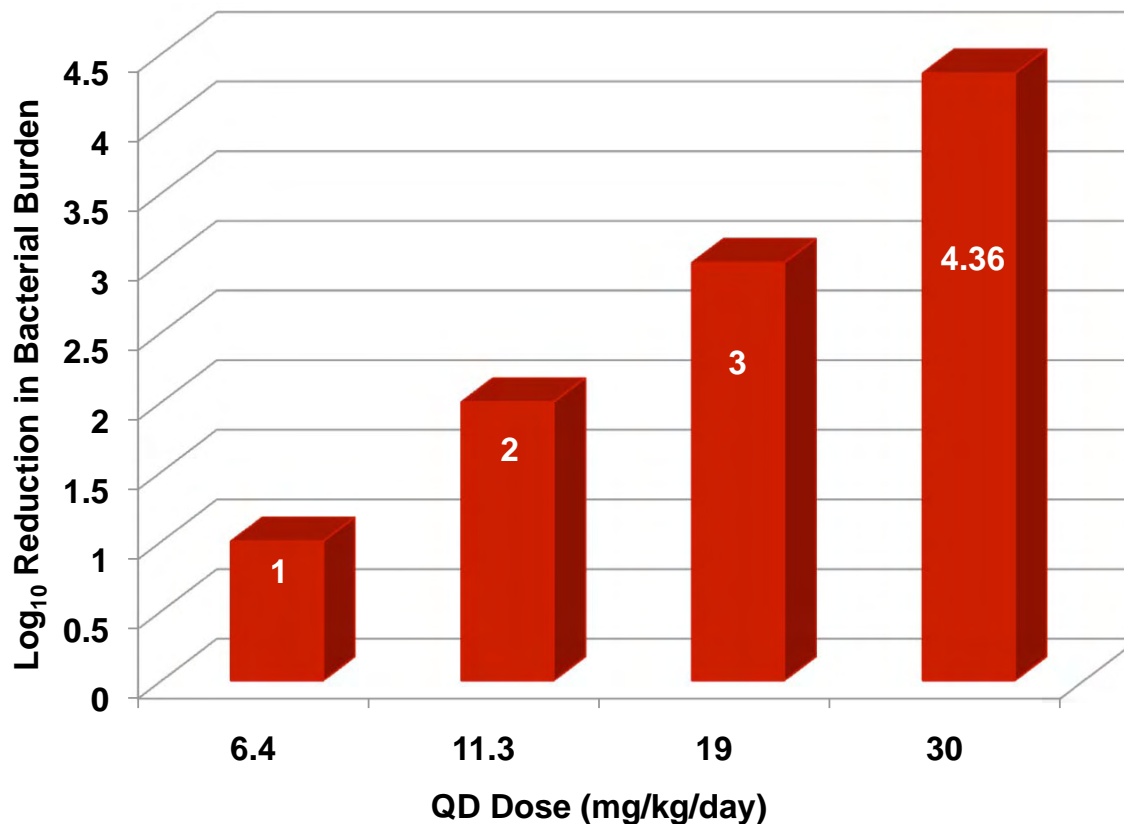
Treat mice with a single dose PO or IV

48 hours

Record % survival; calculate PD<sub>50</sub> in mg/kg

Compound	Structure	Route	PD <sub>50</sub> (mg/kg)	95% CI
TP-038 MIC = 0.5 µg/ml		IV	0.36	0.17 – 0.55
		PO	12.2	3.6-20.8
Tetracycline MIC = 0.5 µg/ml		IV	0.35	0.34 – 0.37
		PO	8.1	0.25-16.0

# TP-038 Has Bactericidal Activity In *S. aureus* Smith Neutropenic Thigh Model



# Pharmacokinetics of TP-038 in Rats and Monkeys

## *PK Parameters in Sprague-Dawley Rats (n=3)*

Compound	Dosage (mg/kg)	Route	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	CL <sub>obs</sub> (mL/hr/kg)	V <sub>ss_obs</sub> (mL/kg)	AUC <sub>inf</sub> (ng·hr/mL)	T <sub>1/2</sub> (hr)	F %
TP-038	1	IV	814	0.083	289	1400	3436	3.4	
	10	PO	460	2.00	---	---	6032	3.9	17.6%
Tetracycline	1	IV	501	0.083	1232	3676	813	4.5	
	10	PO	238	0.500	---	---	982	4.1	12.1%

## *PK Parameters in Cynomolgus Monkeys (n=2)*

Compound	Dosage (mg/kg)	Route	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	CL <sub>obs</sub> (mL/hr/kg)	V <sub>ss_obs</sub> (mL/kg)	AUC <sub>inf</sub> (ng·hr/mL)	T <sub>1/2</sub> (hr)	F %
TP-038	0.5	IV	414	0.083	222	3740	2251	11.6	
	5	PO	141	6	---	---	4238	23.9	18.8%
Tetracycline	0.5	IV	106	0.083	1632	20749	311	8.9	
	5	PO	118	4	---	---	208	20.1	6.7%

# Summary

- Unique, fully synthetic platform is highly versatile, providing compounds with novel structures and multiple dosing routes
- TP-038 is a novel pentacycline that has oral/IV activity in lung, septicemia, and thigh murine models
- TP-038 has a microbiological spectrum useful for CAP, including coverage of MRSA
- TP-038 has PK parameters, including oral bioavailability, better than tetracycline in two animal species



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PHARMACEUTICALS

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