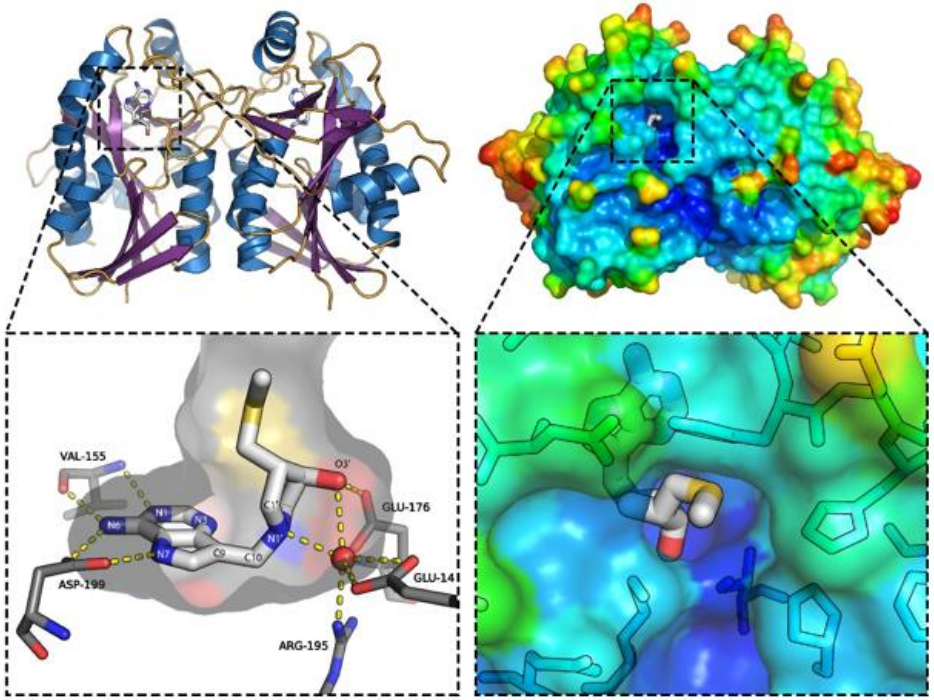
The Discovery and Development of Next Generation Antimicrobials

Prof. Gary Evans, Ferrier Research Institute

One Health Aotearoa, December 14th 2017



Capital thinking. Globally minded.

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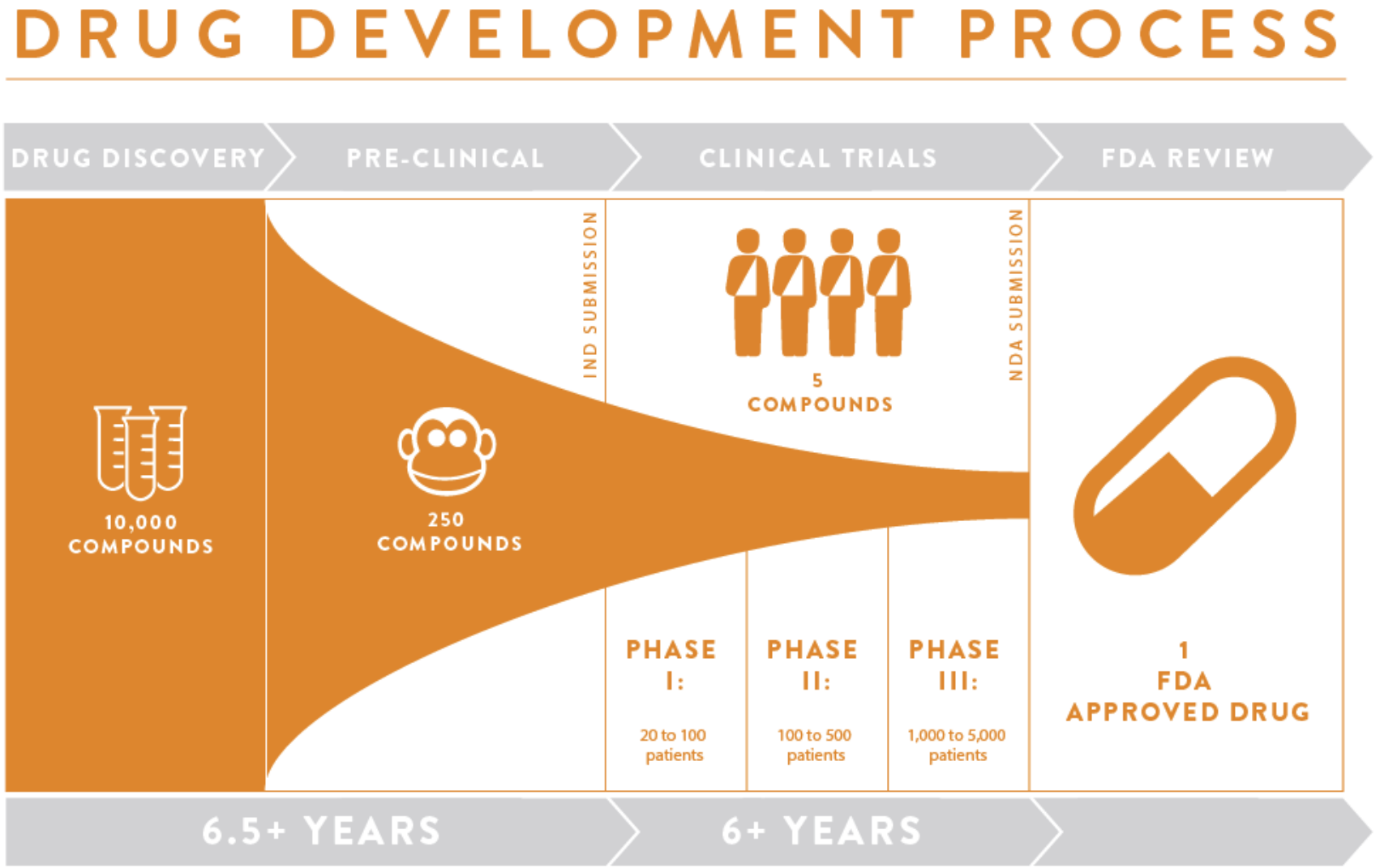
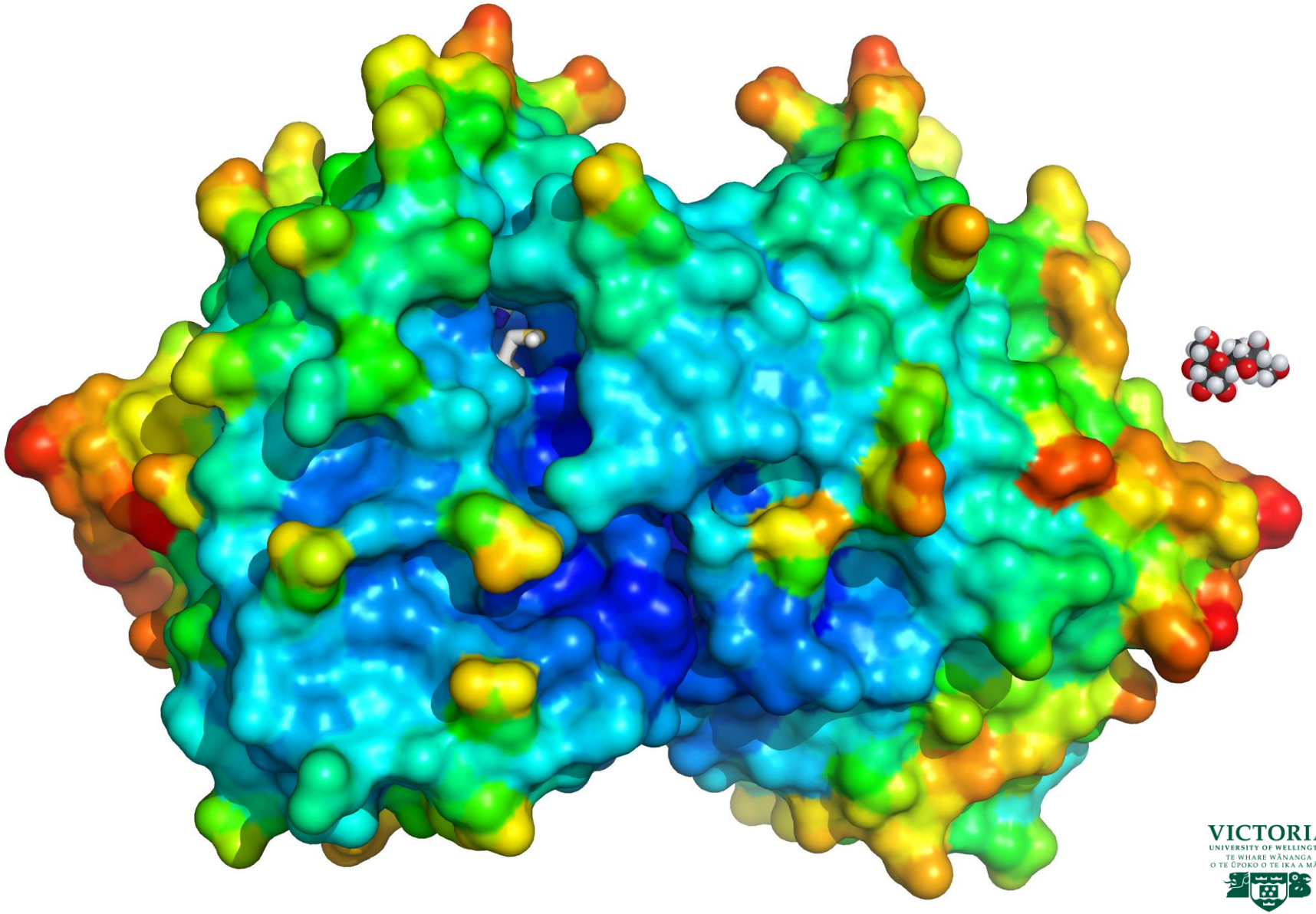
Drug Development– All it Takes is Time & Money



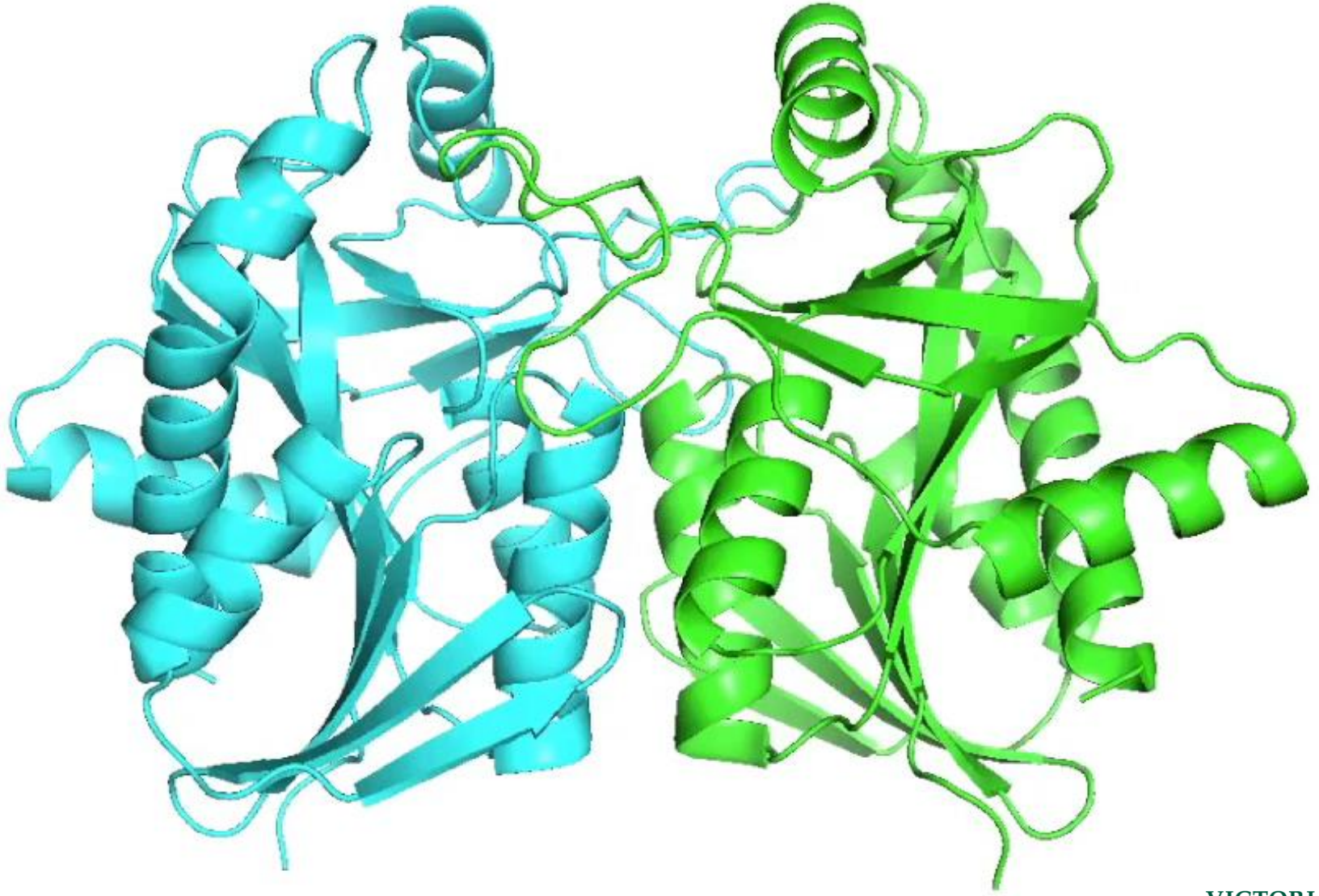
Paul Ehrlich the Father of Modern Drug Discovery

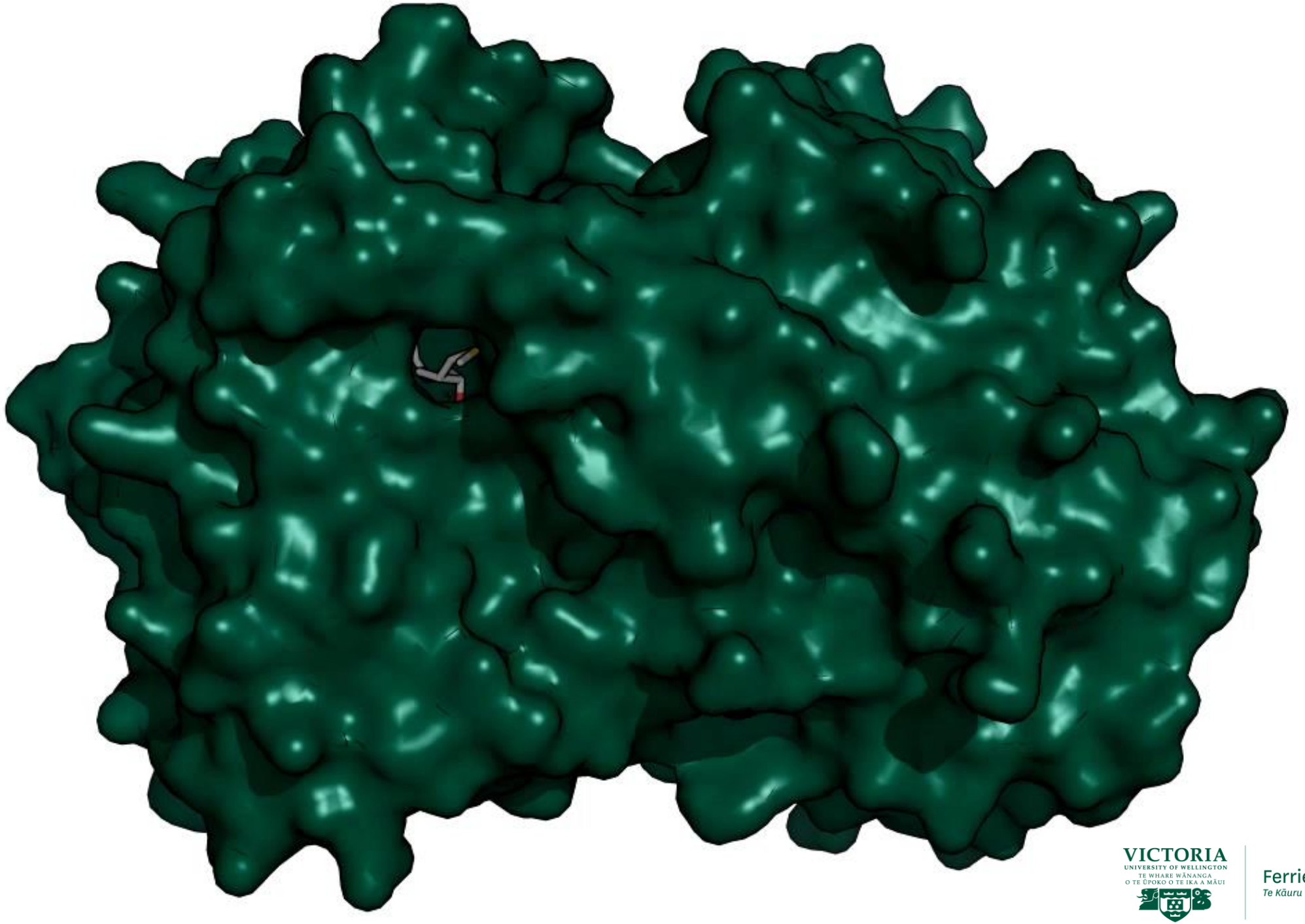
- coined the term magic bullet with regards to drugs

Enzymes as Drug Targets – Taking Aim with Chemistry

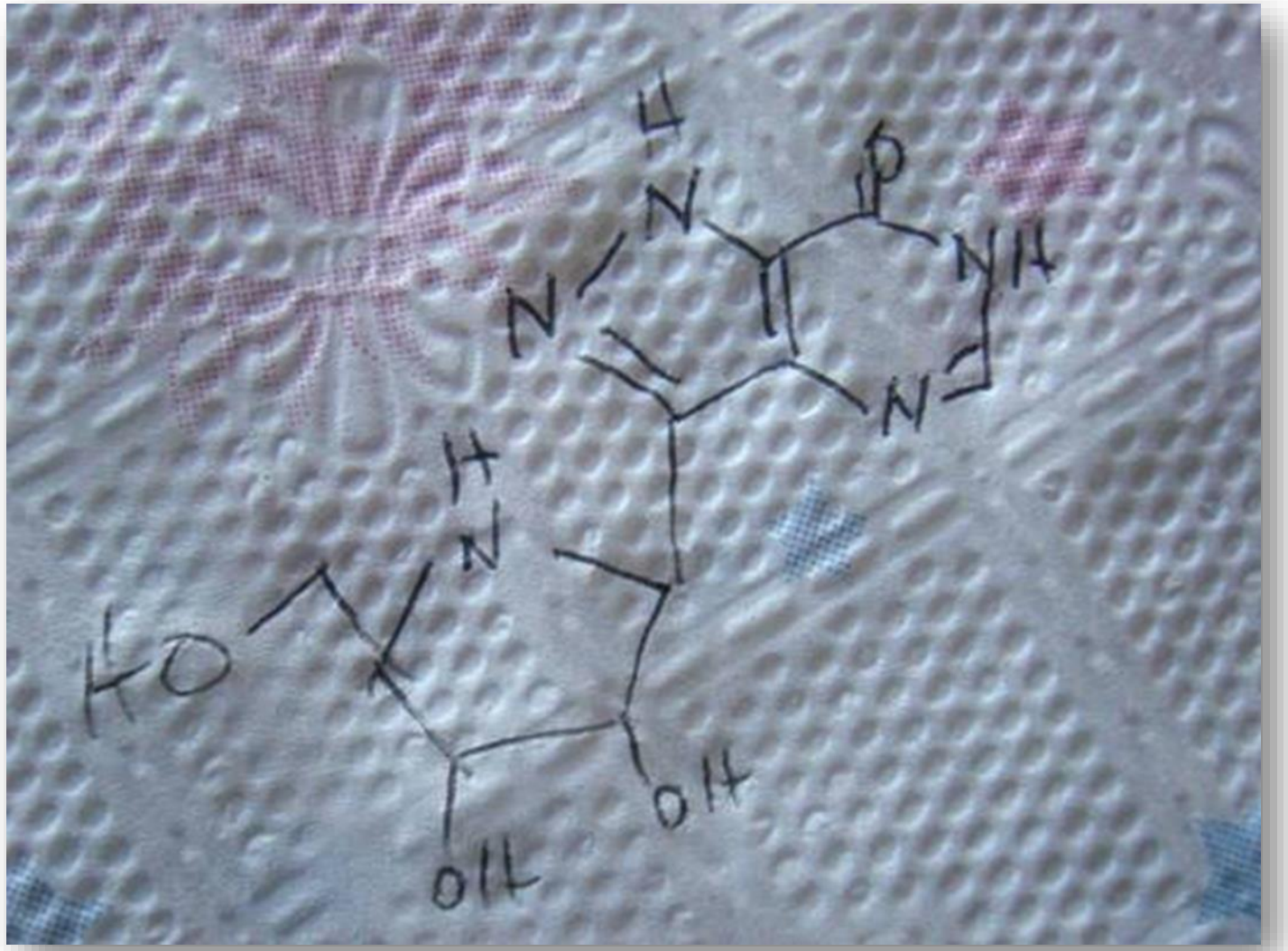


Enzymes – Nature’s Chemists

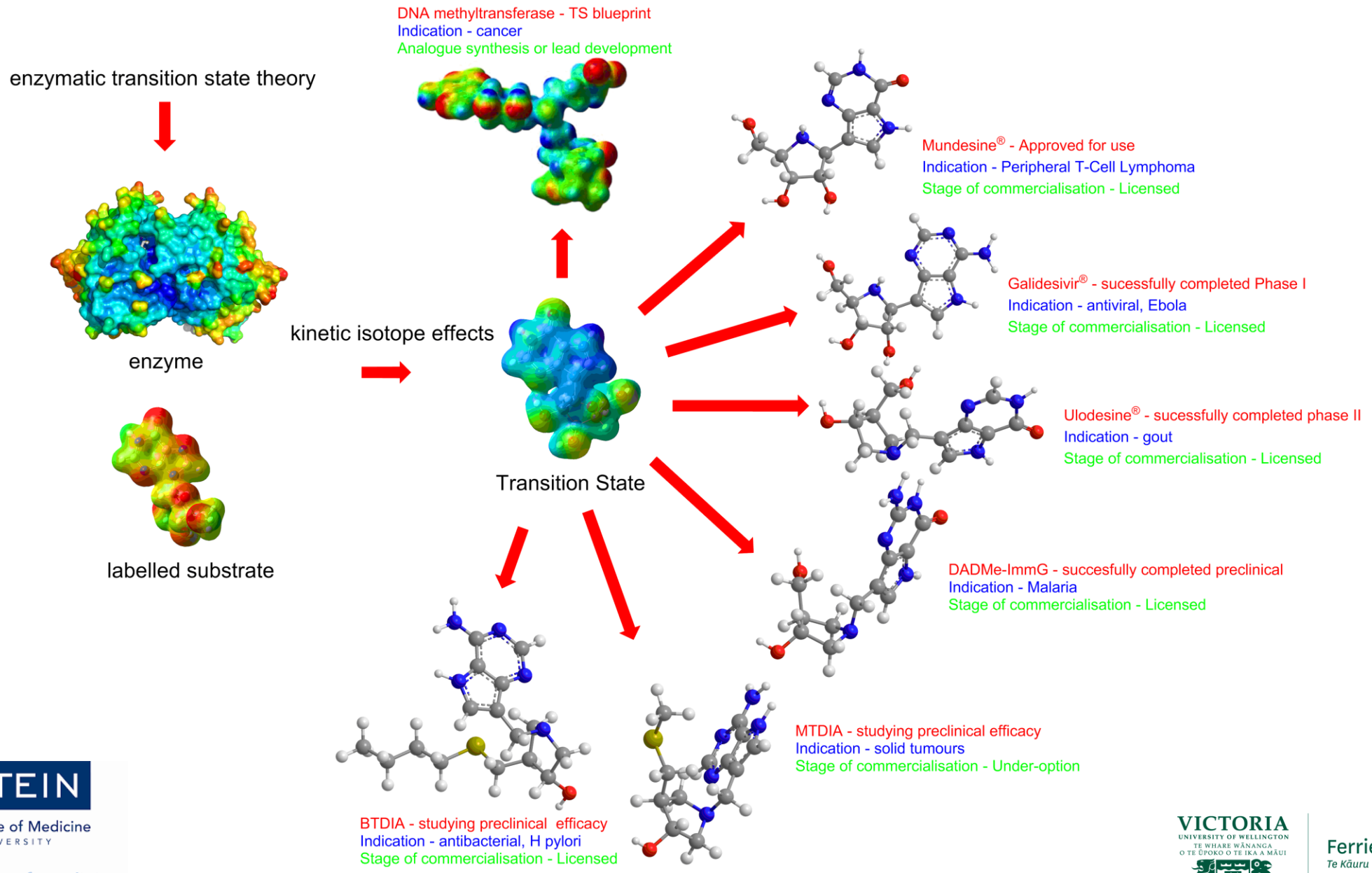




The Blueprint



Transition State Analogue Drug Design



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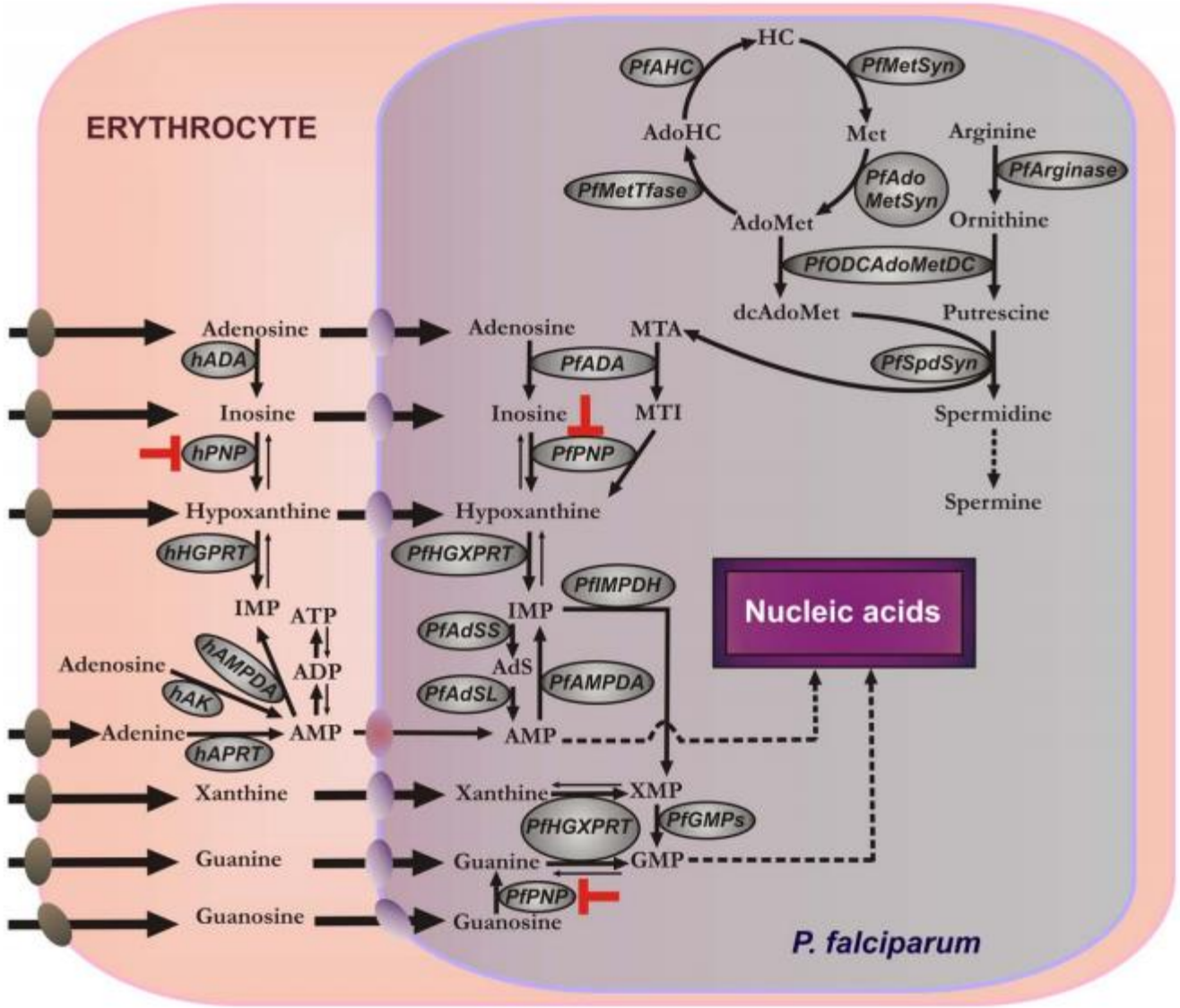
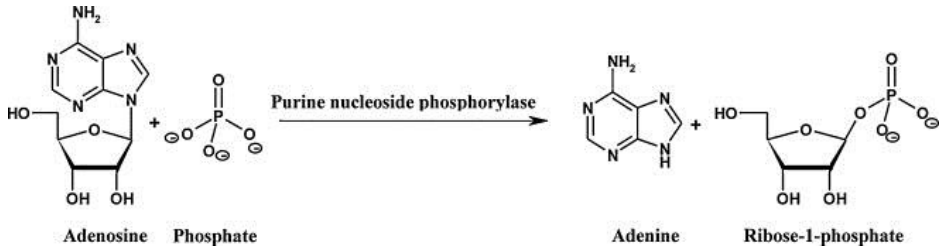
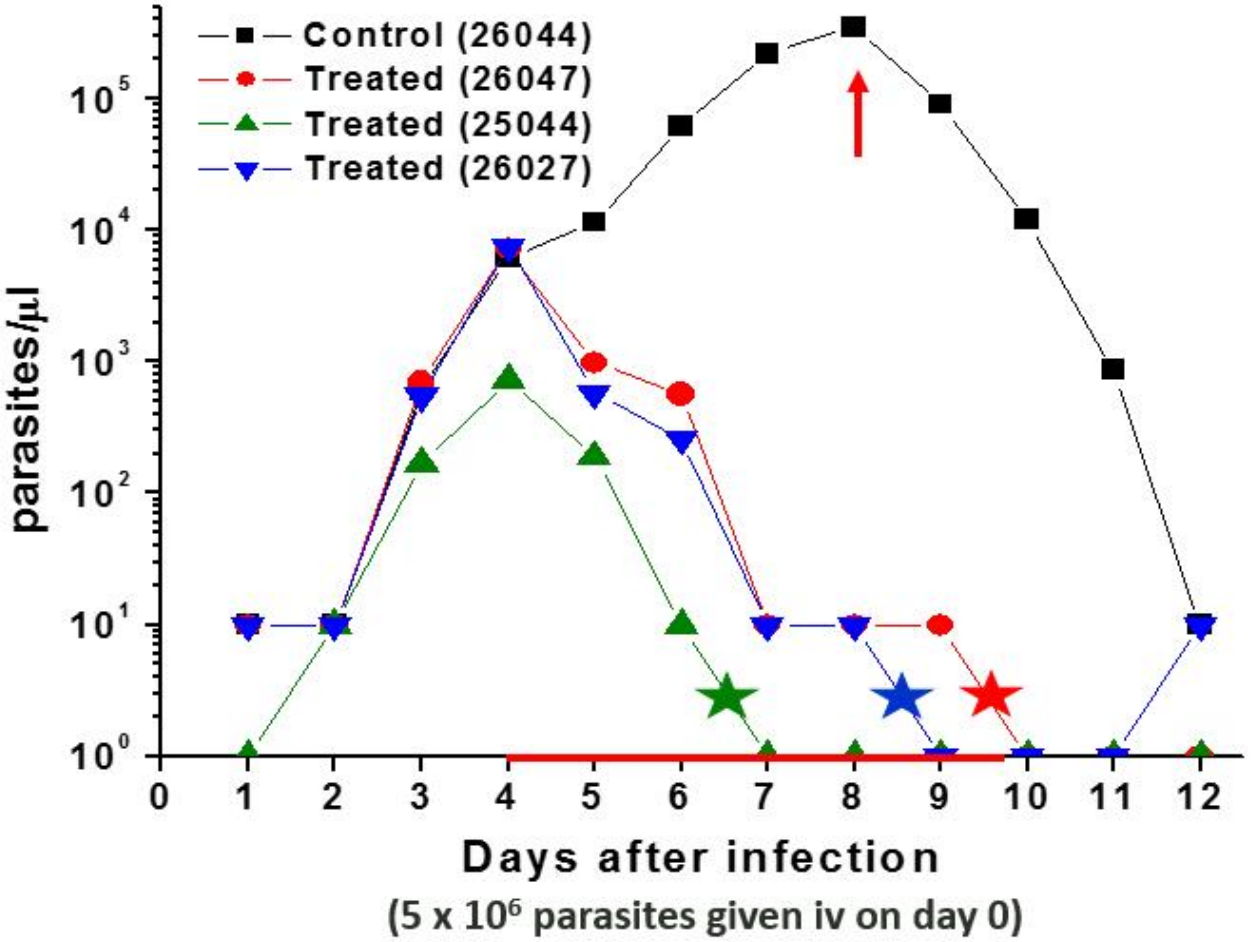
Purine and Polyamine Metabolism in Malaria





BCX4945 is Effective in a Non-Human Primate



BCX4945 dosing

Rescued with mefloquine + artesunate

★ Infection cleared (no parasites, thick blood smears)

MMV Medicines for Malaria Venture

BioCryst Pharmaceuticals, Inc.

Under approvals by CITES USA, CITES Panama, Einstein Animal Use Committee, Gorgas Research Institute Animal Use Committee, US Fish and Wild Life Division, CDC Atlanta. Supported by NIH, MMV, Einstein College of Medicine and BioCryst Pharmaceuticals.

Einstein Albert Einstein College of Medicine of Yeshiva University

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Cassera, M. B., et al. *PLoS ONE* **2011**, *6*, e26916.

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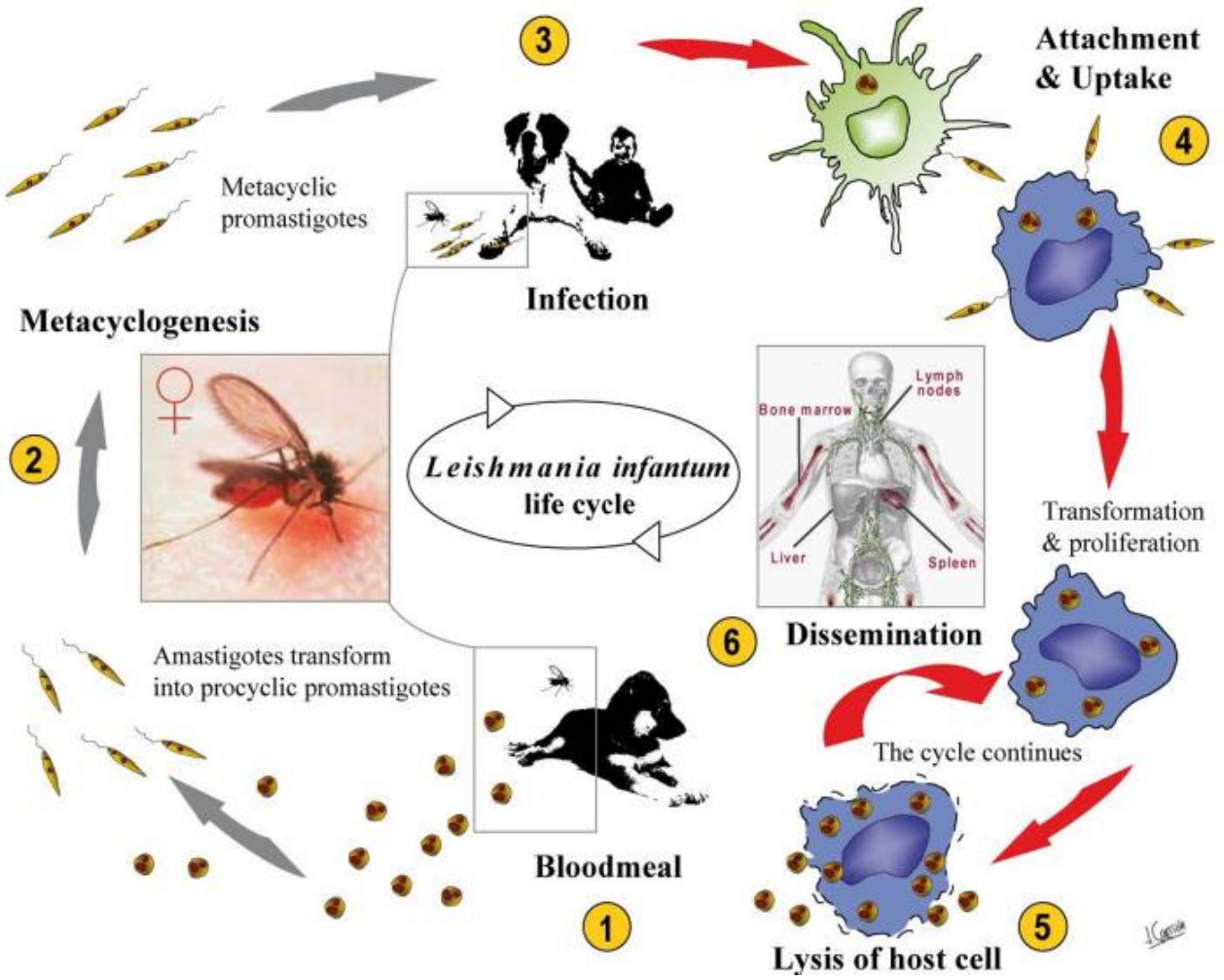
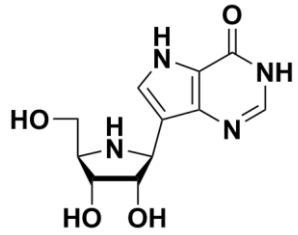
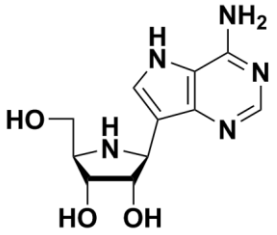
Visceral Leishmaniasis





Forodesine



BCX4430

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Freitas, E. O., et al. *PLOS Negl Trop Dis* **2015**, *9*, e0004297.

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Visceral Leishmaniasis

PLOS | NEGLECTED TROPICAL DISEASES

Efficacy of Immucillins in the Therapy of Visceral Leishmaniasis

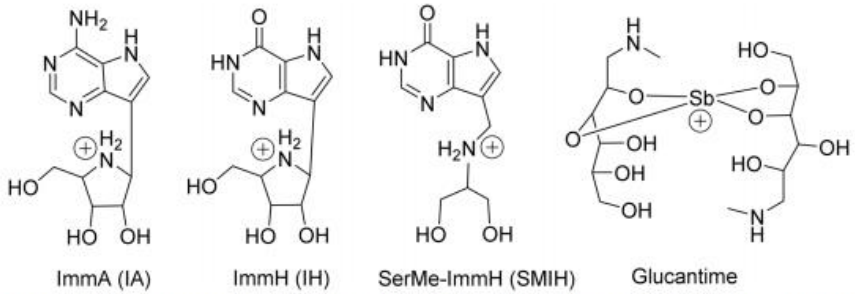
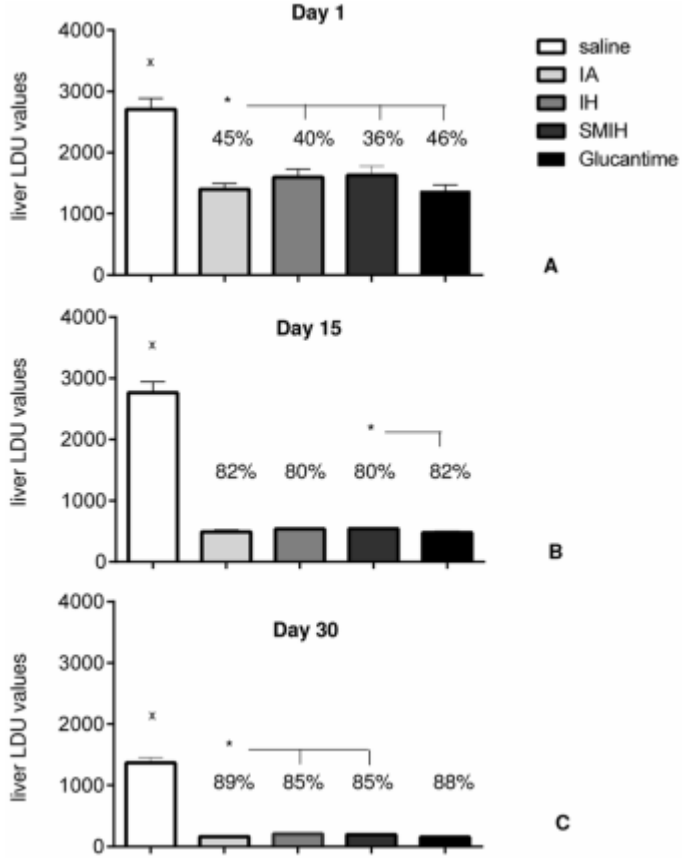


Fig 1. Structures of the compounds used in this study. The structure shown for Glucantime is one of several related antimony chelates found in the drug, which is formed from the reaction between pentavalent antimony and *N*-methyl-D-glucamine.



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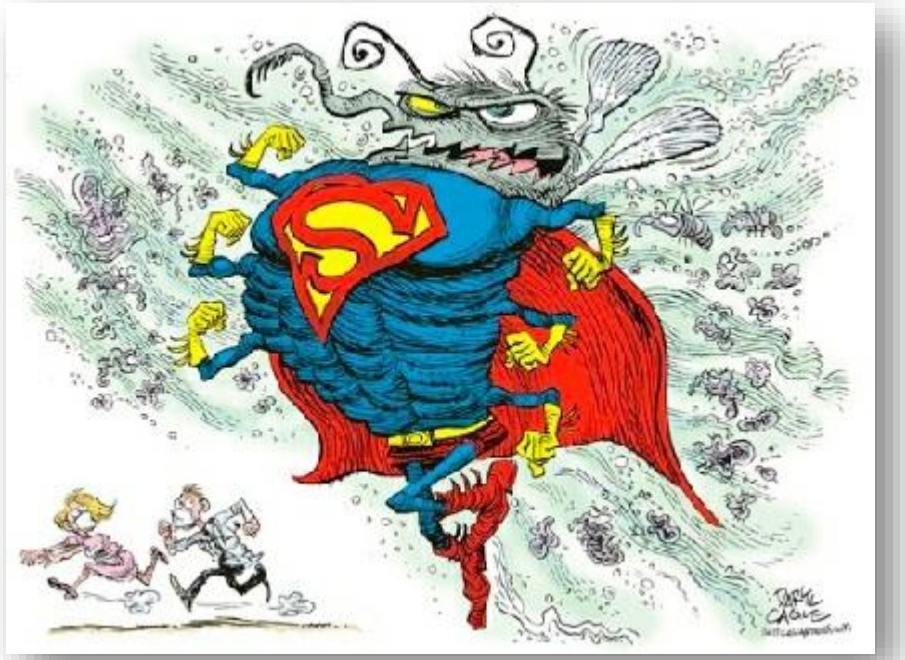
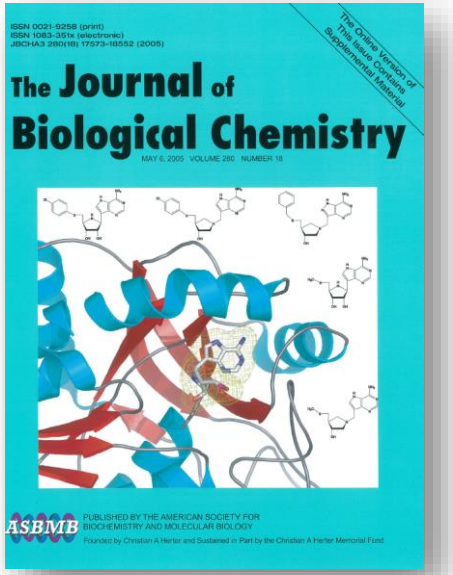
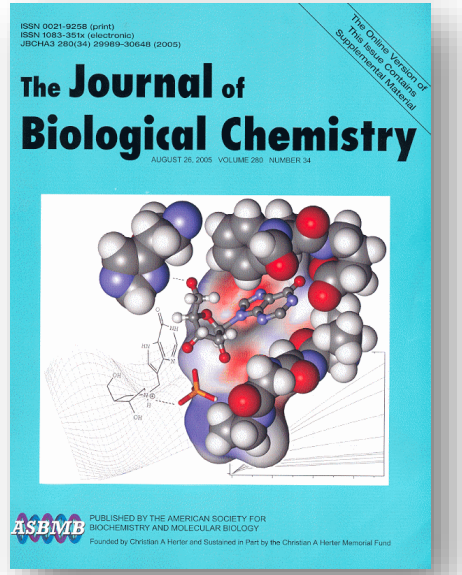
Antibiotic Resistance

- the rise of the super bug







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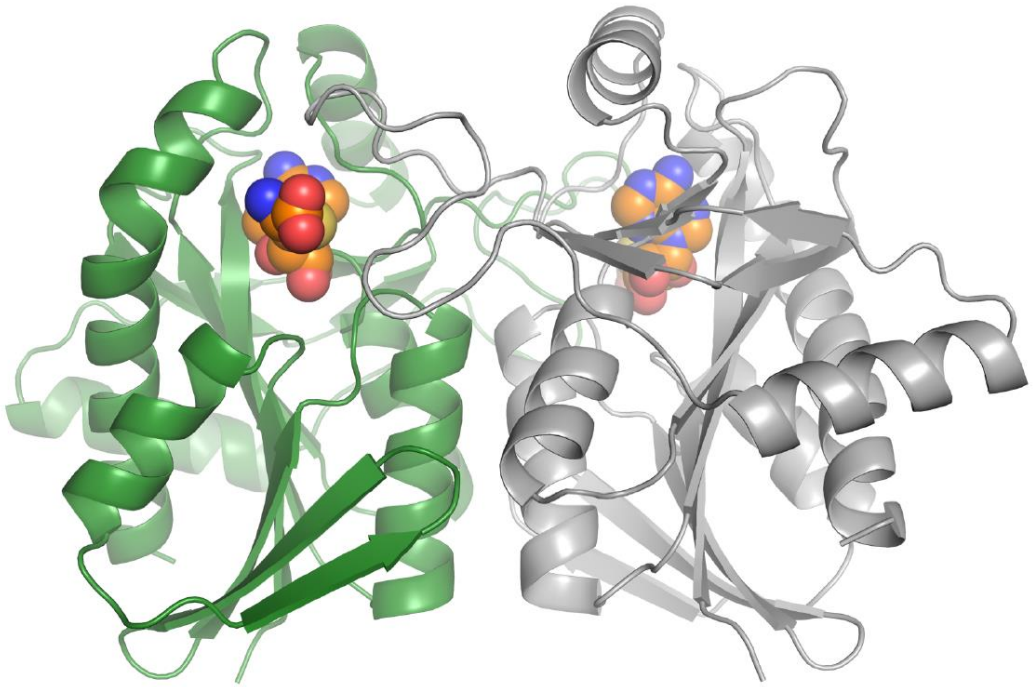
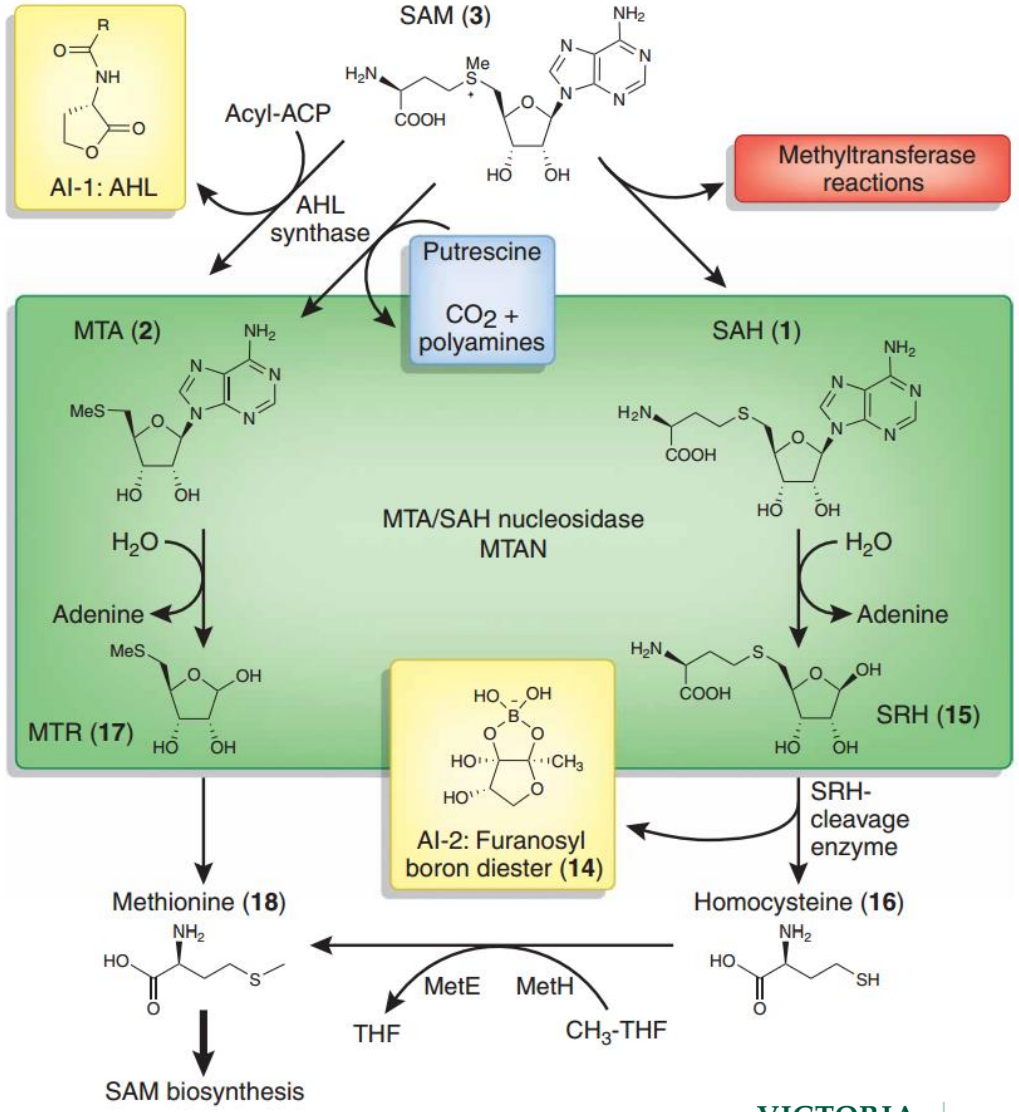
Methylthioadenosine Nucleosidase (MTAN)





Gutierrez, J. A. et al *Nature chemical biology* **2009**, *5*, 251.

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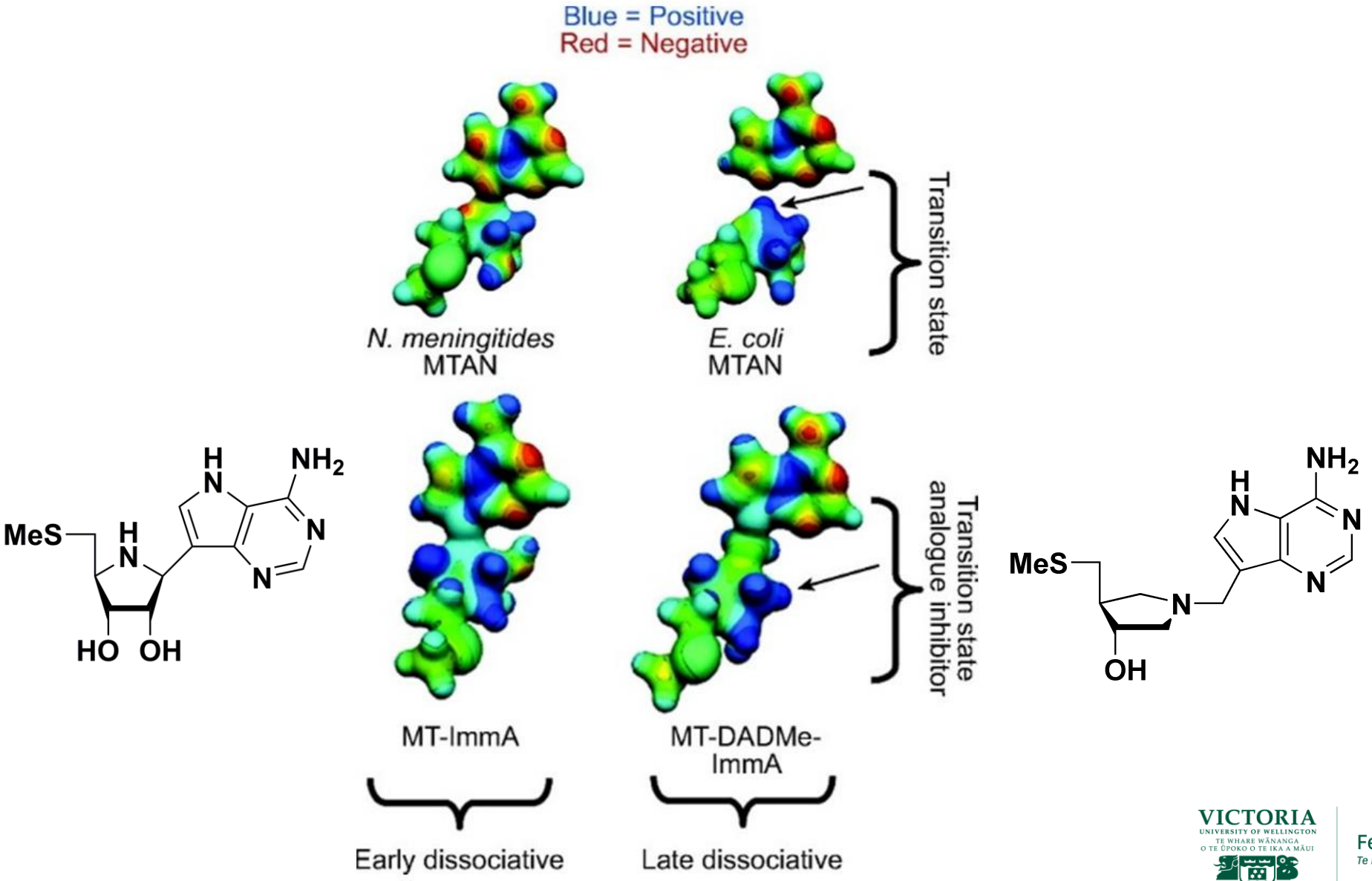
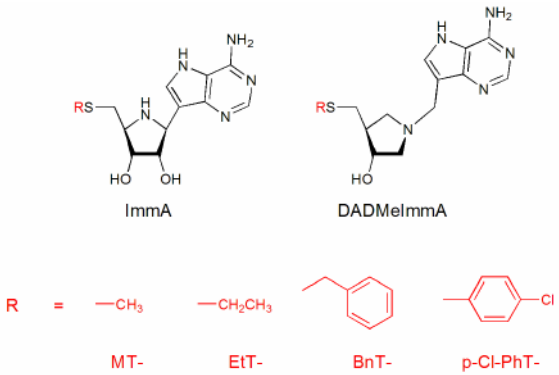
MTAN - Transition State Analogue Design



MTAN Inhibitors

- Impact on autoinducer production
- Impact on biofilm formation



	K_d ImmA (nM)	K_d DADMe-ImmA (nM)	K^{ImmA}/K^{DADMe}
MT-	10 ± 1	0.073 ± 0.005	137
EtT-	1.6 ± 0.3	0.070 ± 0.004	23
BnT-	2.1 ± 0.1	0.064 ± 0.006	33
p-Cl-PhT-	2.2 ± 0.3	0.33 ± 0.08	6.7

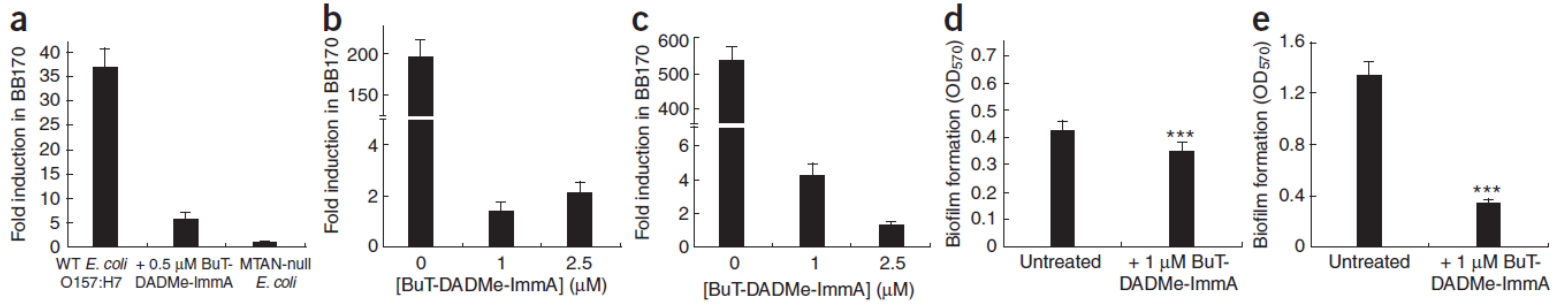


Figure 4 Effect of BuT-DADMe-ImmA on AI-2 production in pathogenic *E. coli* and *V. cholerae* upon short-term and long-term inhibitor treatment, and on static biofilm formation. (**a**) *E. coli* O157:H7 ± 0.5 µM BuT-DADMe-ImmA and an MTAN knockout strain were grown static in AB medium for >5 generations before the spent medium was assayed for AI-2 production. (**b**,**c**) *E. coli* O157:H7 (**b**) and *V. cholerae* N16961 (**c**) were grown shaken in LB for 26 generations, and AI-2 in the spent media was measured. Cultures were prepared in triplicate, and data represent mean values ± s.d. from at least six replicates. (**d**,**e**) Biofilm formation studies on *E. coli* O157:H7 (**d**) and *V. cholerae* N16961 (**e**) ± 1 µM BuT-DADMe-ImmA grown static in LB medium at 25 °C for 24 h on 96-well format. Data represent mean values ± s.d. The observed difference in biofilm formation due to BuT-DADMe-ImmA was statistically significant at $t = 5.044$, $^{***}P < 0.001$, d.f. = 14 for *E. coli*; and $t = 26.689$, $^{***}P < 0.001$, d.f. = 14 for *V. cholerae*.

Gutierrez et al *Nat. Chem. Biol.* **2009**, *5*, 251.

Biofilm Inhibition

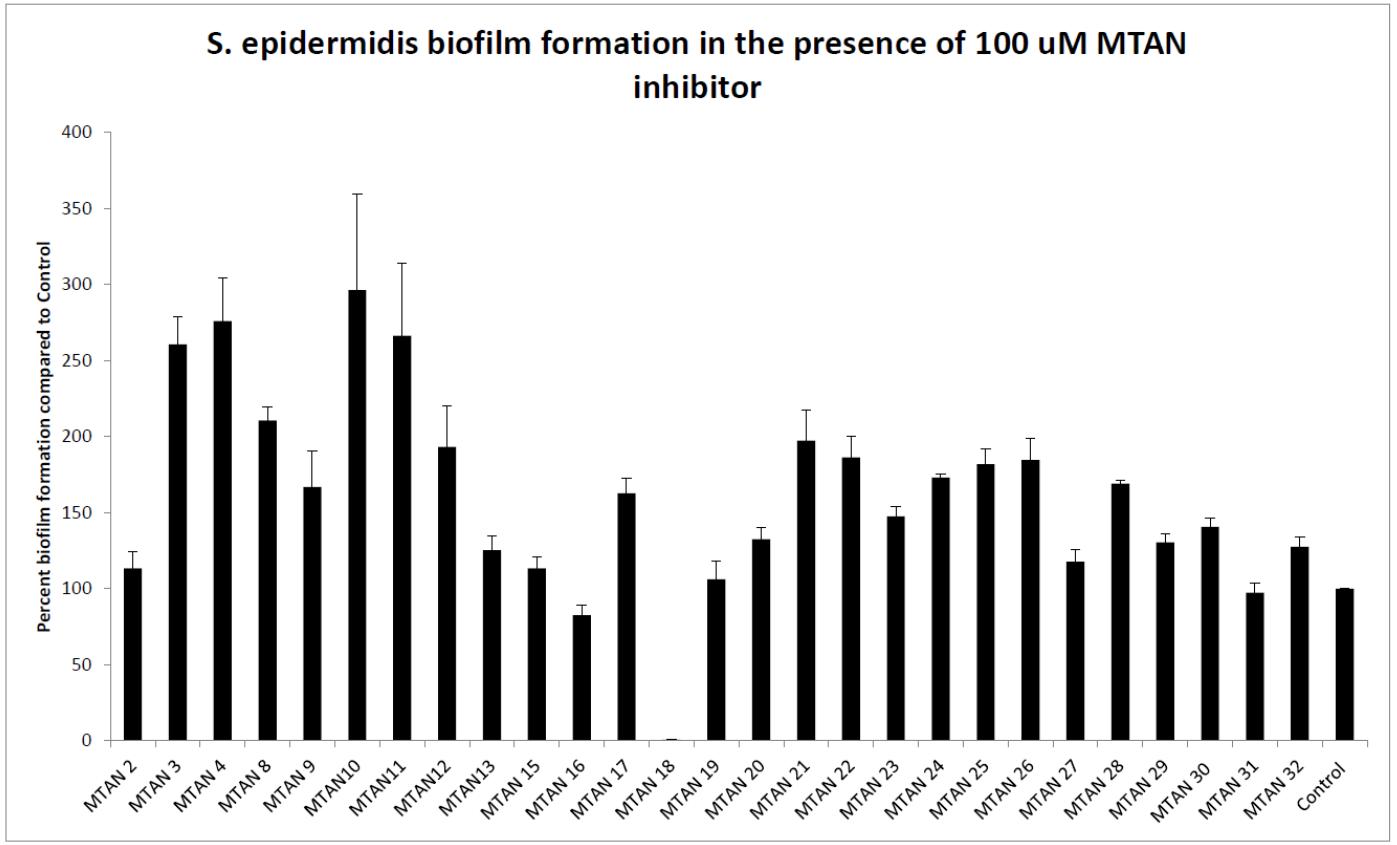
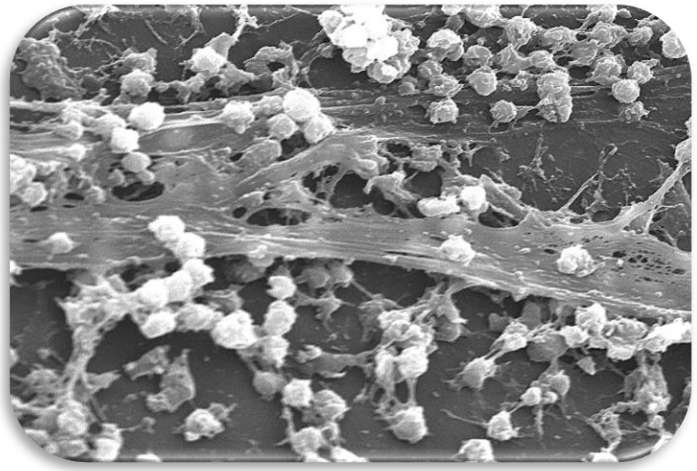


Figure 3: *S. epidermidis* biofilm formation in the presence of 100 µM of MTAN inhibitors. Each bar represents an average of 3 independent experiments containing n=6 replicates/treatment. Error bars = standard error of the mean



Miller, A. et al *unpublished*.

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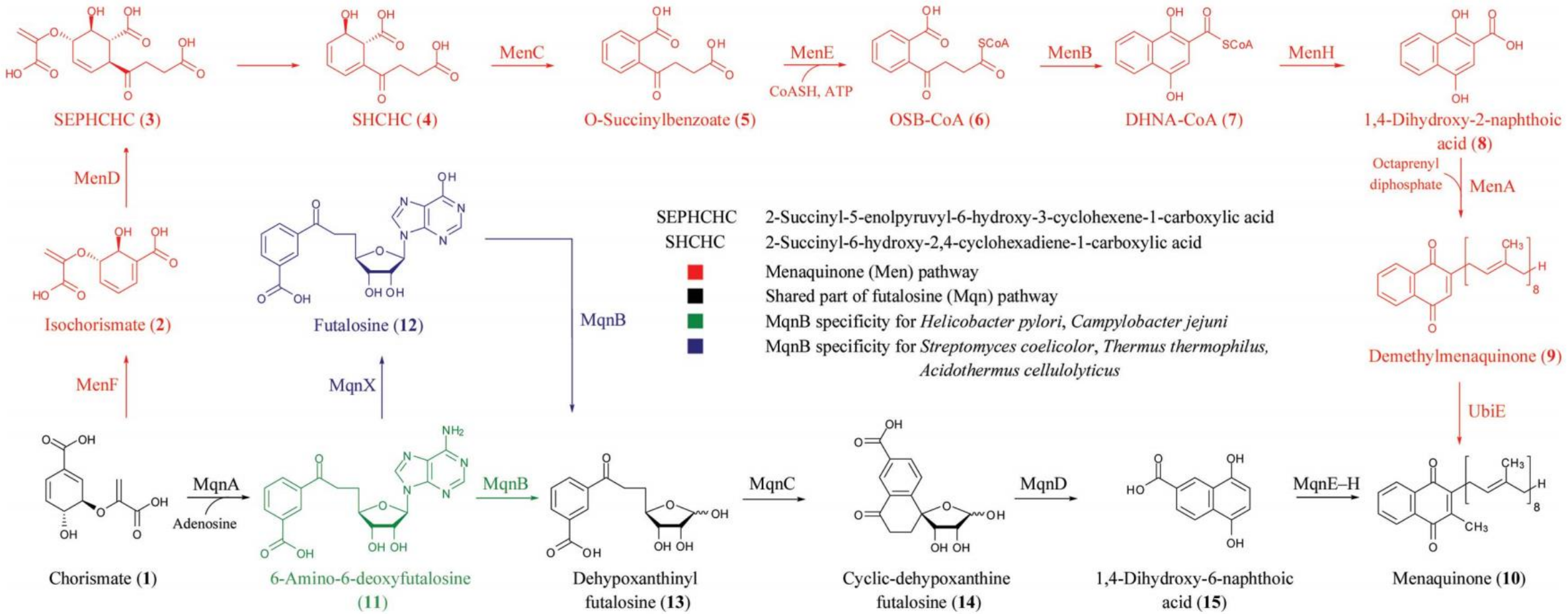
Methylthioadenosine Nucleosidase



Wang, S. et al *J. Am. Chem. Soc.* **2015**, *137*, 14275.

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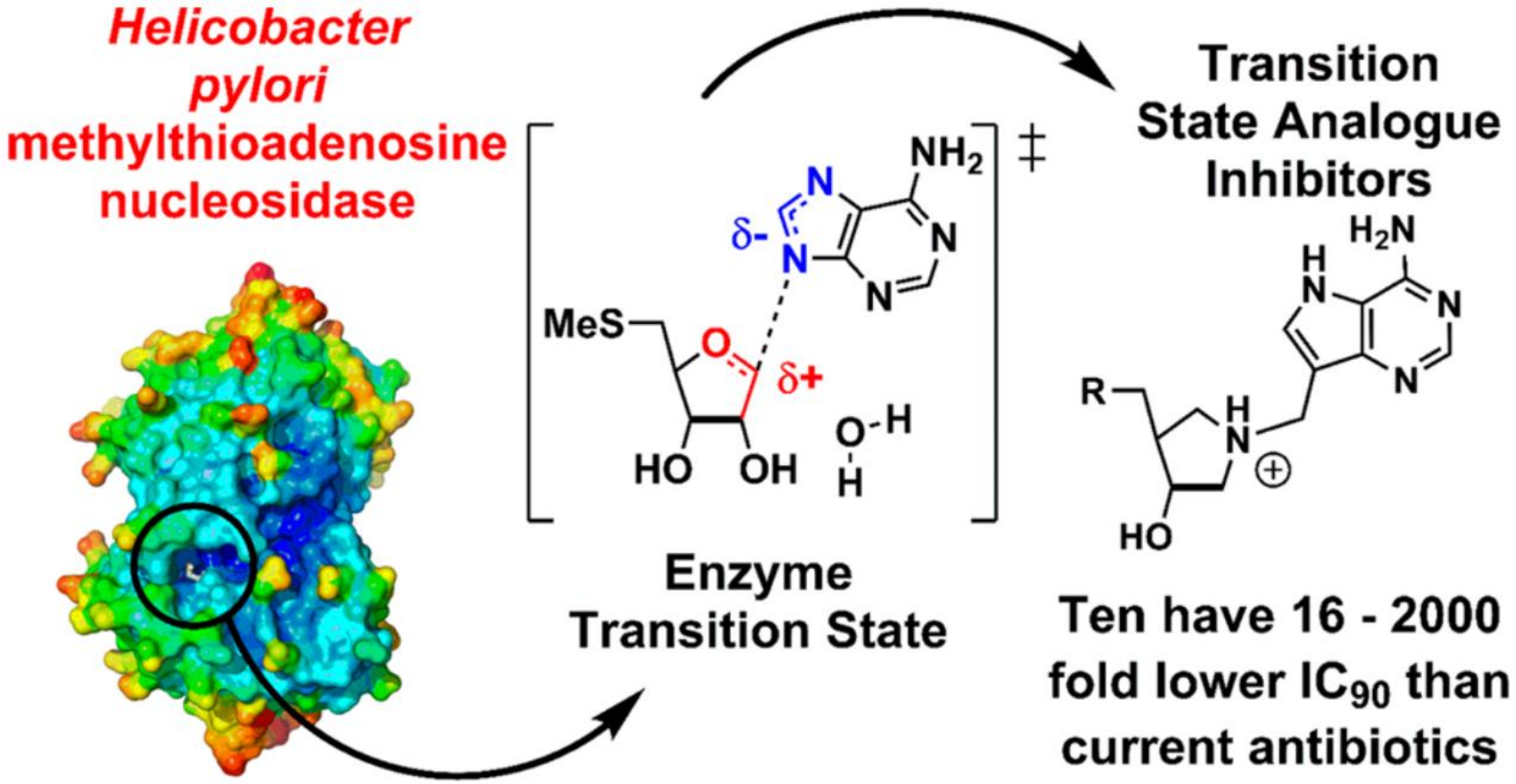
Helicobacter pylori MTAN



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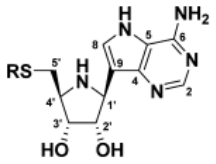
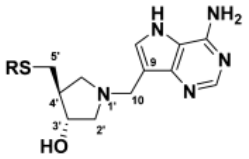
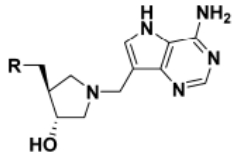


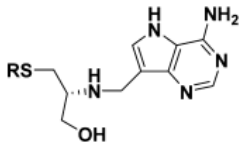
1, R = Me
4, R = *n*-Pr
5, R = *n*-Bu
6, R = 4-chlorophenyl
7, R = 3-methylphenyl
8, R = 4-methylphenyl
9, R = 2-naphthyl



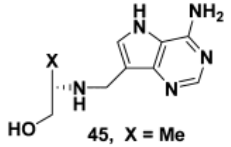
2, R = Me
3, R = *n*Bu
10, R = Et
11, R = *n*Pr
12, R = cyclobutyl
13, R = cyclopentyl
14, R = cycloheptyl
15, R = cyclohexylmethyl
16, R = Bn
17, R = 4-chlorophenyl
20, R = 2-hydroxyethyl
21, R = 3-hydroxypropyl
22, R = 4-hydroxybutyl
23, R = (2-hydroxyethoxy)ethyl
24, R = *n*Hexyl
25, R = Hex-5-yn-1-yl
26, R = Pyridin-2-yl
27, R = 2-(R/S)Ethylhex-1-yl
28, R = 5-(Pyridin-4-yl-1*H*-1,2,4-triazol-3-yl
29, R = *n*Dodecyl
30, R = 1-Adamantyl
31, R = Heptadecylfluorodecyl
32, R = Pyrazin-2-yl
33, R = 1,3-Thiazol-2-yl



18, R = Bn
19, R = Et
34, R = (3-carboxyphenyl)acetyl
35, R = 2-Hydroxyethylthiomethyl
36, R = (2-Hydroxyethoxy)ethylthiomethyl
37, R = *n*Hexylthiomethyl
38, R = (2-Hydroxyethoxy)ethoxymethyl



39, R = Me
40, R = *n*Butyl
41, R = *n*Heptyl
42, R = Benzyl
43, R = 4-Chlorophenyl
44, R = Pyrazin-2-yl



45, X = Me
46, X = Et
47, X = *n*Pr
48, X = *n*Bu
49, X = ^{i}Pr
50, X = ^{i}Bu
51, X = (1S)-1-Methylpropyl
52, X = Ph
53, X = *n*Pentyl
54, X = *n*Hexyl
55, X = *n*Nonyl
56, X = Imidazol-4-ylmethyl

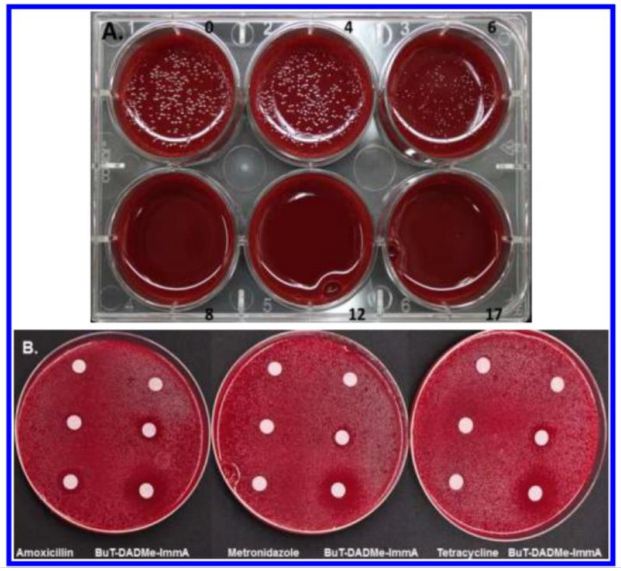


Table 1. Data of Selected Compounds for the Inhibition of *H. pylori* MTAN and IC_{90} values for *H. pylori* Growth on Blood Agar

	H. pylori MTAN inhibition (nM)		
compd	K_i	K_i*	inhibition of *H. pylori* growth IC_{90} (ng/mL)
1	0.16 ± 0.07[a]	0.04 ± 0.02[a]	80
2	0.19 ± 0.03	0.089 ± 0.019	6–12
3	0.79 ± 0.04	0.036 ± 0.002	6–8
4	0.79 ± 0.15	0.021 ± 0.004	16
11	0.058 ± 0.014	0.007 ± 0.002	10
12	0.27 ± 0.04	0.04 ± 0.01	16
13	0.78 ± 0.15	0.17 ± 0.01	7–14
15	0.56 ± 0.27	0.045 ± 0.004	18–35
19	0.17 ± 0.06	0.053 ± 0.007	16
20	0.43 ± 0.12	0.04 ± 0.01	40
22	0.34 ± 0.07	0.11 ± 0.04	9
23	0.96 ± 0.16	0.015 ± 0.004	35–70
24	0.21 ± 0.03	0.005 ± 0.002	4–8
25	0.5 ± 0.2	0.09 ± 0.02	4–8
26	0.32 ± 0.07	0.041 ± 0.002	40
27	0.16 ± 0.02	0.04 ± 0.01	>80
32	0.043 ± 0.001	0.006 ± 0.001	8
33	0.24 ± 0.07	0.016 ± 0.005	20
44	0.10 ± 0.01	N/O[b]	8
53	0.10 ± 0.01	N/O[b]	8
54	0.030 ± 0.003	N/O[b]	8

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Wang, S. et al *J. Am. Chem. Soc.* **2015**, *137*, 14275.

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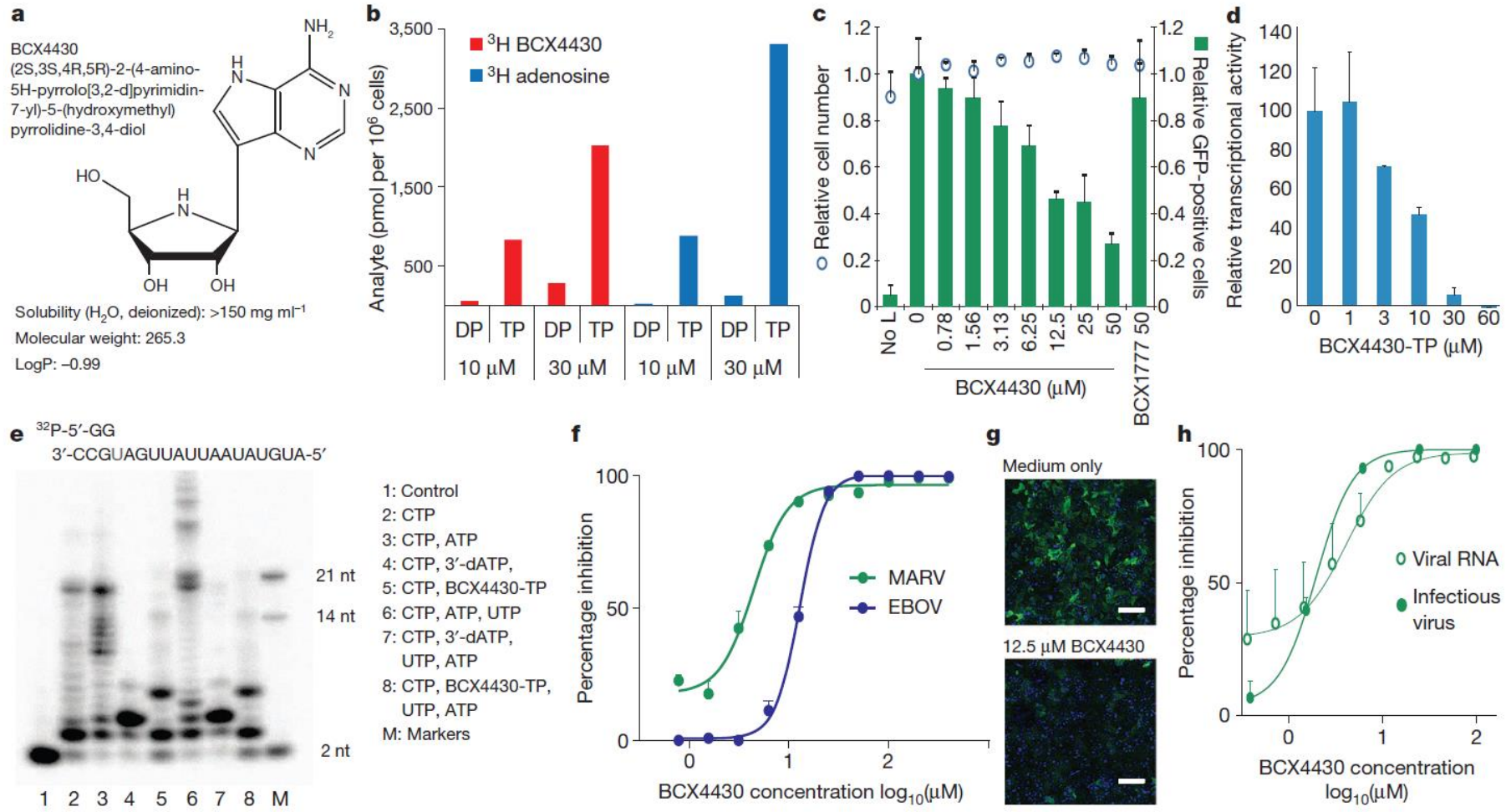

Warren, T. K. et al *Nature* **2014**, *508*, 402.

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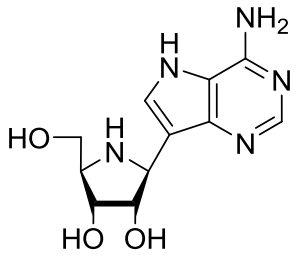

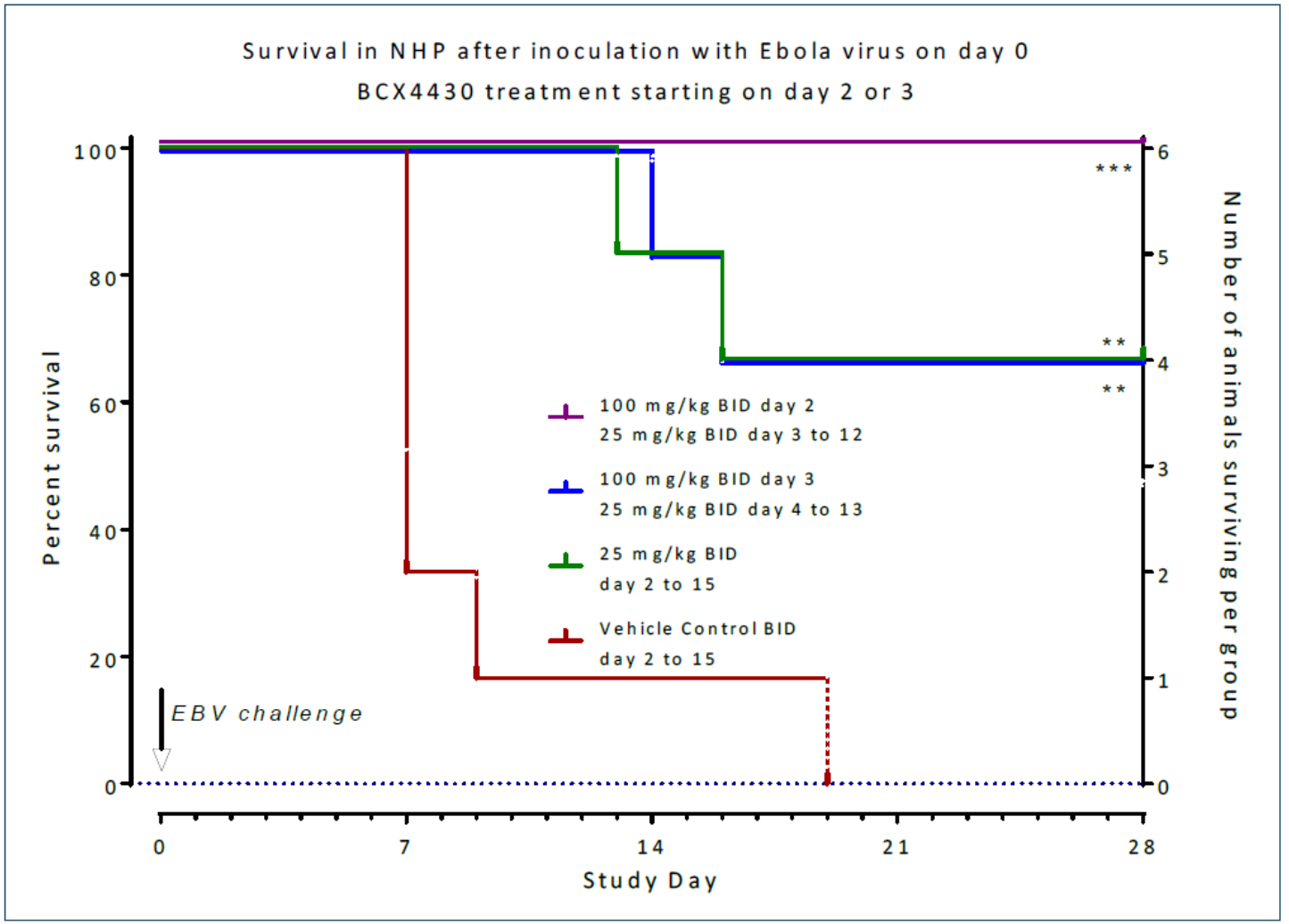

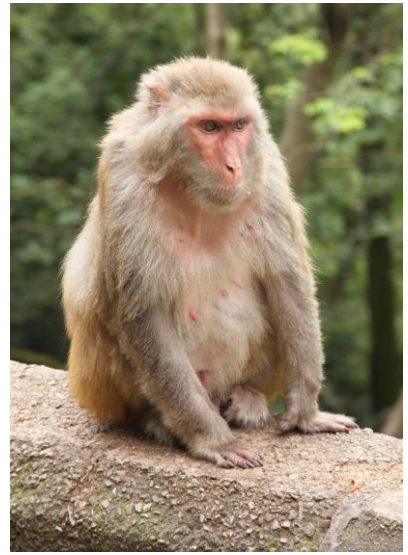

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National Institute of Allergy and Infectious Diseases

USAMRIID United States Army Medical Research Institute of Infectious Diseases
Biodefense solutions to protect our nation

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Galidesivir® *In Vivo* Activity

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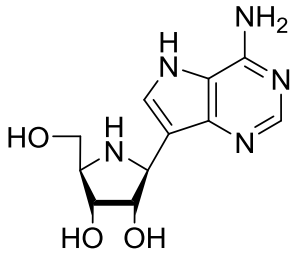
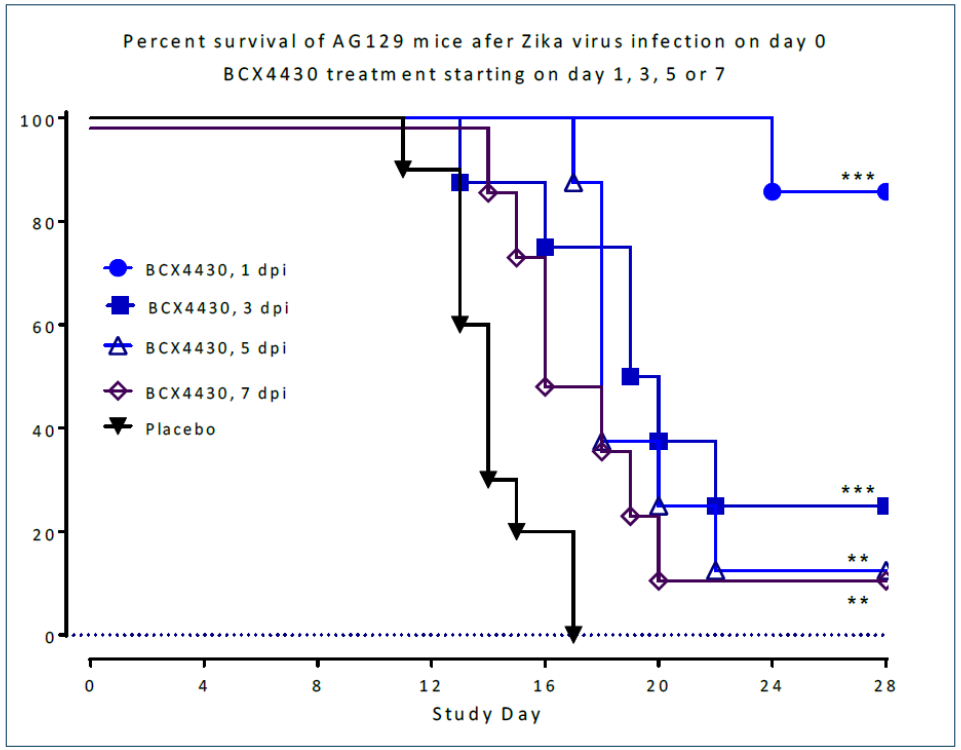
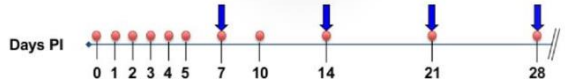




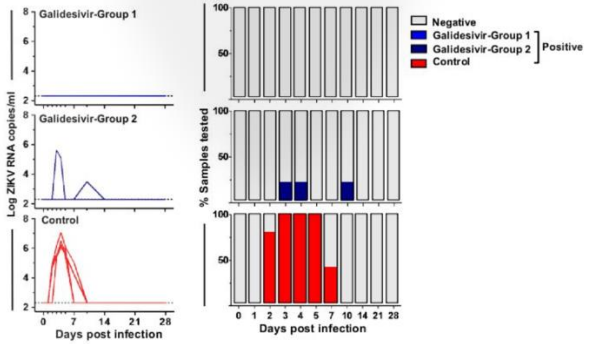
Galidesivir (BCX4430) Study Design

- 15 Indian origin rhesus monkeys (n=5 per group)
- Primary infection: 10e5 TCID50 PR Isolate, SC, monitor 1 month
- Followed ZIKV dynamics in blood, saliva, urine (daily)
- ZIKV in CSF (lumbar puncture, weekly)
- Heterologous challenge: 10e5 PFU Thai Isolate, (n=15, Day 72 PI)

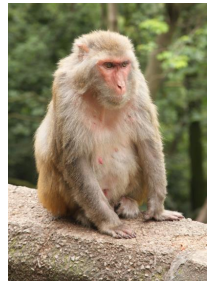


Group	Treatment	
	Dose (mg/kg)	Route
Galidesivir-Group 1	200 mg/kg, then 25 mg/kg b.i.d. for 9 days	IM
Galidesivir-Group 2	200 mg/kg on day of ZIKV infection	IM
Control	Vehicle only	IM

Post-exposure Protection of RMs Following ZIKV Infection by Galidesivir



- Group 1- All five animals have undetectable plasma ZIKV up to days 28 post-infection.
- Group 2- One animal was viremic between days 3 to 4 post-infection another animal had a single positive ZIKV blip (on day 10).



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Galidesivir® First in Humans Phase I

- the study achieved all of its objectives
- Galidesivir was generally safe and well tolerated
- 88 UK volunteers, two dosing regimens
- these results support the continued development of Galidesivir®

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Galidesivir® - Future Trials

BioCryst Pharmaceuticals, Inc.

Antiviral Program	Indication	Development funding	Additional capital infusions
	First and only one-dose IV treatment for influenza	Over $200M US Government funding to support development and approval	• Over $90M in milestones and royalty monetization • Over $25M in Government stockpiling (Japan/US)
Galidesivir (BCX4430)	• Ebola is lead indication • Broad-spectrum activity observed in Zika, Marburg and several other virus families	Approximately $80M US Government contract development funding	• Potential for Government stockpiling prior to FDA approval • Potentially eligible for FDA priority review voucher upon approval

Broad-spectrum activity increases attractiveness of Galidesivir for Government stockpiling

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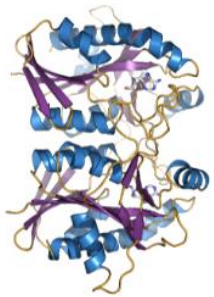
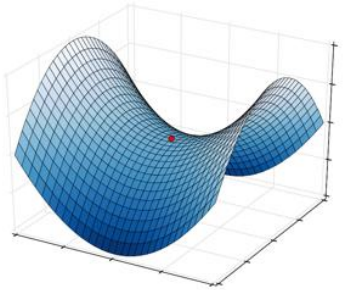
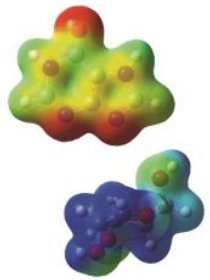
Future Work

- Transition state analogue design - Professor Emily Parker and Dr Scott Cameron







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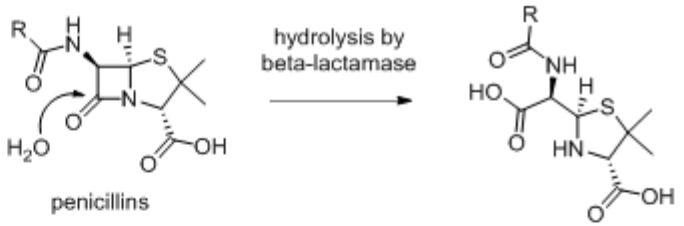
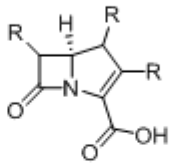
Future Work

- Inhibitors of β-lactamases and carbapenamases - New Delhi metallo-beta-lactamase

  - Hydrolyses most beta-lactam antibiotics
    - Including carbapenems (often used as “drugs-of-last-resort”)
  - Not susceptible to traditional lactamase inhibitors (e.g. clavulanic acid)
  - No FDA-approved inhibitors
  - Plasmid-bound gene
    - Readily passed between bacteria
  - Antibiotic resistance is rapidly spreading





FDA Priority Review Voucher Programme

- Voucher programme incentivises the development of treatments for neglected diseases.
- In 2014 Congress added Ebola and Filovirsuses.
- These vouchers can be traded.

Precedent voucher purchases

Disease	Drug	Seller (Buyer)	Price
Morquio A syndrome	Vimizim (elosulfase alfa)	BioMarin (Sanofi)	$67.5M
Leishmaniasis	Impavido (miltefosine)	Knight (Gilead)	$125M
High-risk neuroblastoma	Unituxin (dinutuximab)	United Therapeutics (Abbvie)	$350M
Rare bile acid synthesis disorders	Cholbam	Retrophin (Sanofi)	$245M

acknowledgements

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Albert Einstein College of Medicine

Prof Vern Schramm