




**Global TB Epidemic, HIV
and PolyMedix Solutions**

September 2008


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Developing drugs is risky, expensive, and time-consuming. All timelines and projections are based on data currently available. Advancement to each next step of development is contingent on positive data from previous work supporting such progress. Additional required experiments and studies can add significant time and cost. Substantial delays and additional costs typically occur in drug development, and should be expected. You should consider these risks carefully before making any investment. This discussion is permitted by the Private Securities Litigation Reform Act of 1995.


TB/HIV: Global View

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- **2.1 Billion people WW infected w/ TB**
 - 1/3 world's population
 - TB transmitted through **AIR:**
 - coughing, sneezing, talking
 - Transmission increased in closed environment (bus, train, plane)
 - Between now and 2020:
 - 1 billion newly infected with TB
 - >150mm become sick
 - 2006- **9.2 mm new TB cases WW, expect this to grow exponentially**
 - **33%-50% people with HIV WW have TB**
 - US TB rate for those with HIV **40X** those w/o HIV
 - TB rate increasing WW due to HIV disease
 - TB makes HIV multiply faster and makes HIV worse
 - TB and HIV make each other worse

HIV/TB Death Rates

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- **>3mm die yearly from TB**
 - **Between now and 2020, 40mm will die from TB**
 - **TB is #1 killer of people with HIV**
 - **~30-50% AIDS deaths WW due to TB**
 - **1980, US goal for TB elimination in US=2010**
 - **1985 – HIV epidemic begins**
 - **2000, revised US goal TB ‘elimination’ >2040**
 - **Those with active TB infect avg 10-15 new people each year they remain infectious and untreated**


MDR/XDR Tuberculosis

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- MDR= Multi Drug Resistant, isoniazid and rifampin (1st line drugs)
 - XDR= Extensively Drug Resistant, resist virtually all TB drugs
 - XDR TB ww threat to public health and TB control, raising concerns of future epidemic of virtually untreatable TB.
 - Up to 30% MDR isolates now XDR
 - MDR TB can cost up to \$1mm to treat
 - 45 states and DC report diagnosing and caring for MDR TB patients
 - MDR TB now found on 6 continents
 - XDR-TB found in 45 countries in 2007
 - 3/99, Man with MDR TB traveling to US via plane infected 13 of the 40 people in his immediate seating area

Costs and Spending on TB


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- US alone \$1.054 billion spent on handling TB
 - \$703mm direct health care costs
 - \$351mm indirect costs
 - WW 2006 direct TB costs **\$2.0 billion**
 - TB robs developing countries of \$12 billion a year, ~4-7% of their GDP.
 - In 2007, NIH spent \$166mm on TB research
 - Same yr, NIH spent \$2.9b on HIV/AIDS research
 - TB exacerbates HIV and HIV exacerbates TB
 - HIV can't be eliminated without TB being eliminated

TB Therapy

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- **Currently, Active TB treatment:**
 - Combination of 4 drugs (>40 years old), 6-9 months duration
 - Cause liver & kidney damage, as do ARVs
 - Can't treat HIV and TB at same time, TB first
 - **MDR TB:**
 - Duration of treatment 12-24 MONTHS
 - Add 2-4 additional drugs to susceptible treatment
 - **In the Pipeline for TB:**
 - Macrolides (old drugs- inhibit protein synthesis)
 - Oxazolidinones (old drugs- inhibit protein synthesis)
 - Nitroimidazoles (old drugs- inhibit cell wall synthesis + cell respiration)
 - Diarylquinolones (version of old drug- inhibit ATP synthase)

The Answer: PolyMedix Anti- Infective Agents

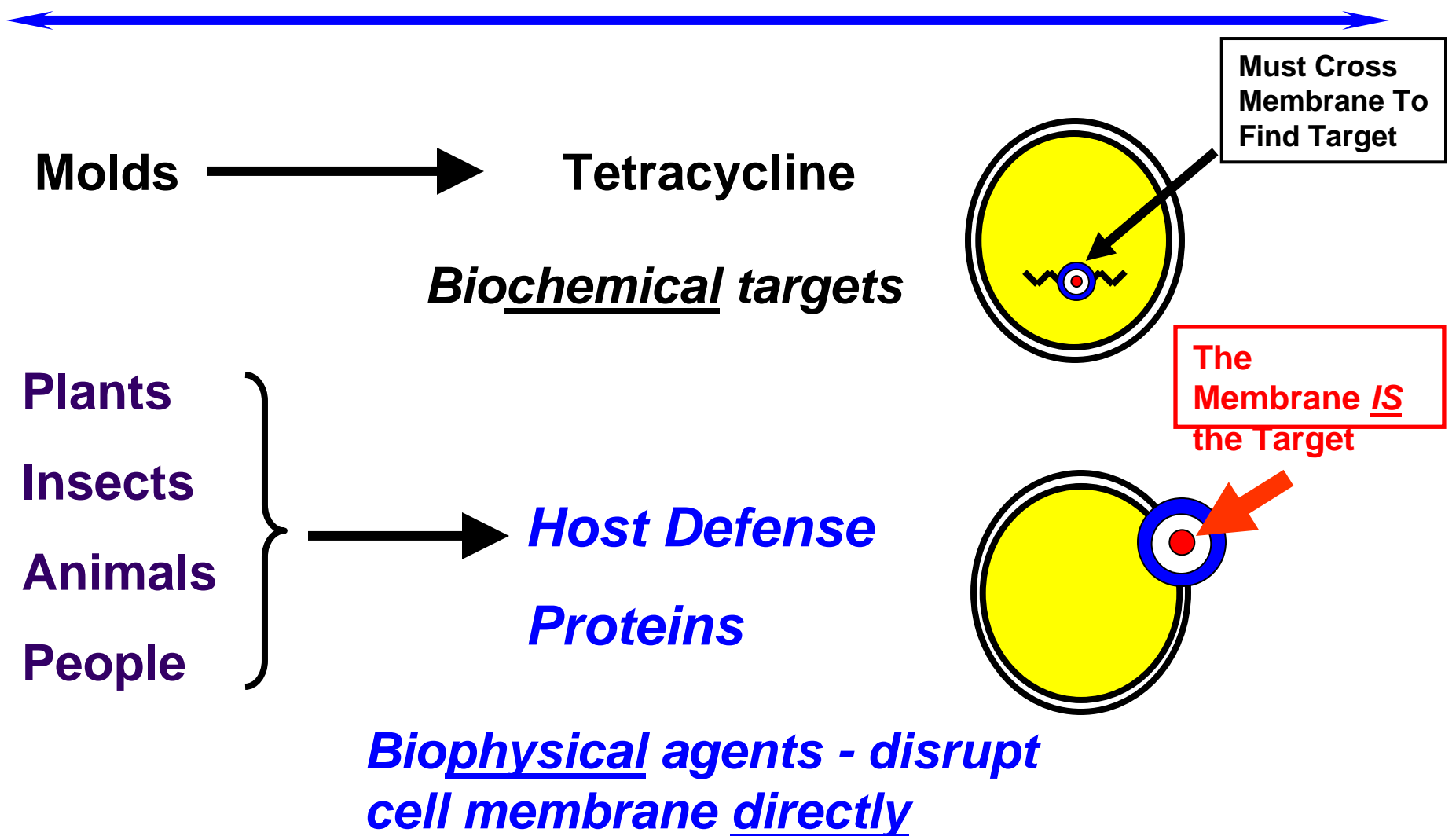


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- PolyMedix's Novel Antimicrobial Drugs
Novel antibiotic drugs : no other drugs on the market or in development work via this mechanism of action, *bacterial resistance is unlikely to develop*

Small molecule mimetics of host-defense proteins

- **Broad-spectrum** - Gram-positive, Gram-negative, anti-fungal, antiviral
- **Active against drug resistant strains**
- **Rapid acting** – *cidal in seconds to minutes*
- **Resistance demonstrated unlikely to develop**
- **Phase I clinical study for iv pan Staph antibiotic began August 2008**

Learning from Nature's Defenses Against Bacteria

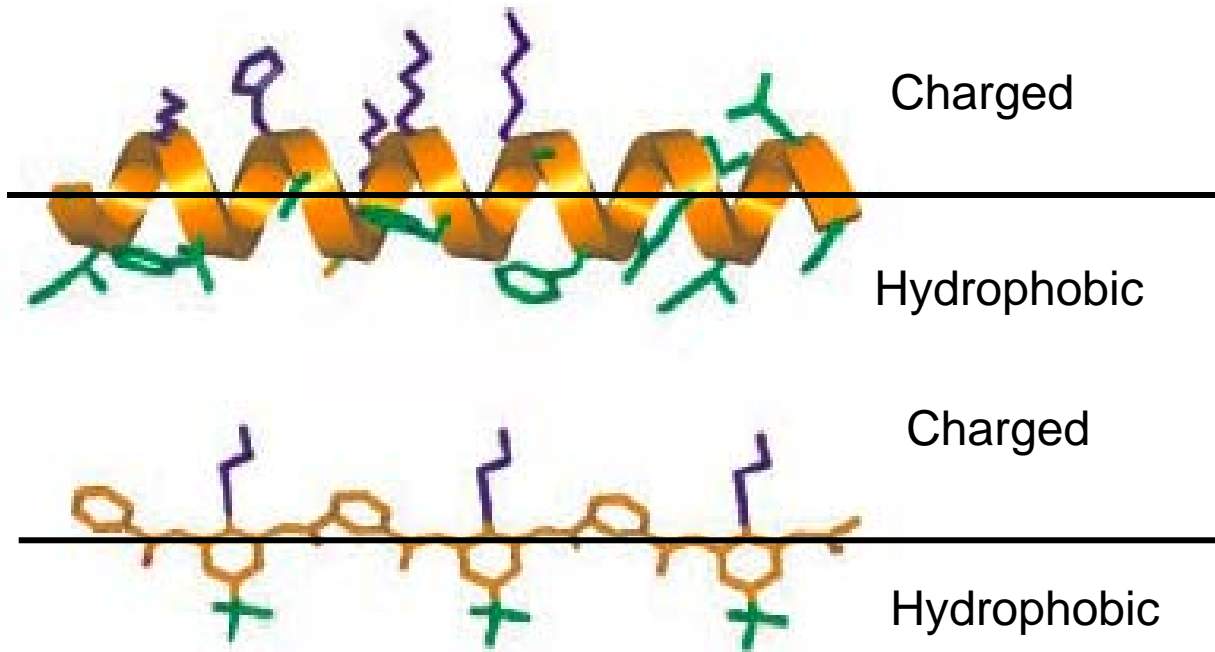


How it Works



The biological activities of host defense proteins depend on an *amphiphilic helix*:

Natural host defense protein



Novel approach:
imitate nature
with
small molecule
mimetics of host
defense proteins

PolyMedix synthetic mimetic

Completely different from all other antibiotics

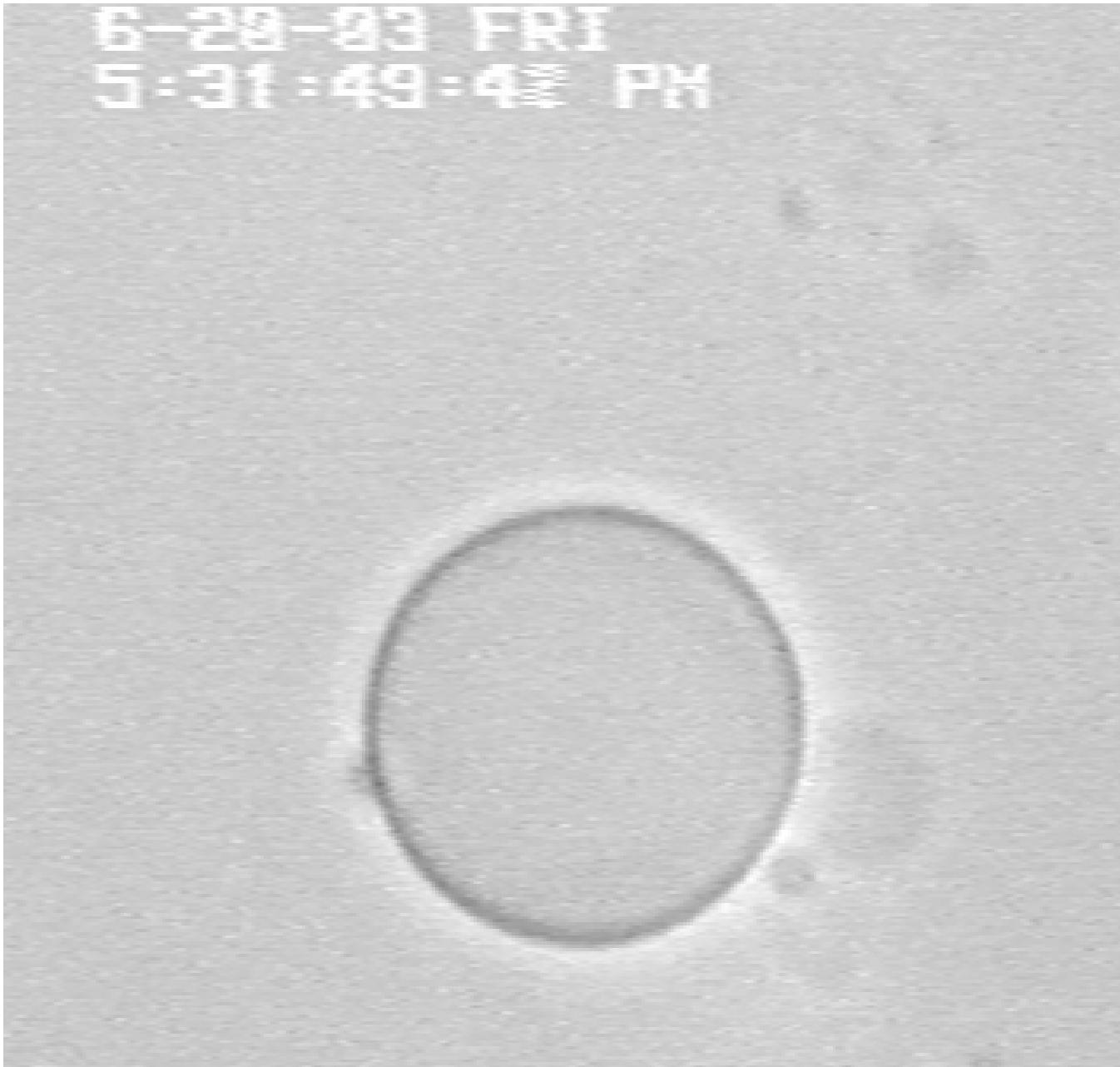
Highly Selective for Bacteria, Non-toxic to Human Cells



<u>Compound</u>	<u>MIC100</u> (µg/mL) Staph aureus	<u>Cytotoxicity</u>		<u>Selectivity</u>	
		<u>3T3</u>	<u>HepG</u>	<u>3T3</u>	<u>HepG2</u>
PMX-10129	0.05	>2000	>2000	>40,000	>40,000
PMX-30016	0.05	147	341	2,940	7,020
PMX-30063	0.098	430	1031	4,388	10,520
Host defense proteins	2 - 5	-- 20 - 50 ---		---- 10 - 20 -----	
	Concentration to kill bacteria (lower = better)	Toxic levels (higher = better)		Selectivity ratio (higher = better)	


- 1/10 the size of proteins
- 100x more potent
- 1000x more selective

Rapid Action



Activity against MDR-human clinical isolates

(MIC $\mu\text{g/ml}$)



<u>Gram positive</u>	PMX-30016	PMX-30063	Vancomycin
<i>Enterococcus faecium</i>	1	1	1
VR- <i>Enterococcus faecium</i>	1	1	>128
MR- <i>Staph aureus</i> (MRSA)	0.5	0.5	1
<i>Staphylococcus epidermidis</i>	0.5	0.5	2
<i>Staphylococcus saprophyticus</i>	0.5	0.5	1
<i>Streptococcus pyogenes</i>	1	1	0.5
<u>Gram negative</u>			
<i>Escherichia coli</i>	2	1	>128
<i>Haemophilus influenzae</i>	8	4	>128
<i>Klebsiella pneumoniae</i>	2	1	>128
<i>Enterobacter cloacae</i>	2	2	>128
<i>Citrobacter</i> species	4	2	>128
<i>Acinetobacter</i> species	4	8	>128
<u>Anaerobes</u>			
<i>Clostridium difficile</i>	2	4	-----
<i>P. acnes</i>	0.25	0.5	-----

Anti-TB activity:

Activity of selected PMX compounds in susceptibility assays (IC₉₀) versus *M. tuberculosis* (H37Rv strain) and cytotoxicity assays (EC₅₀) versus monkey VERO cells.

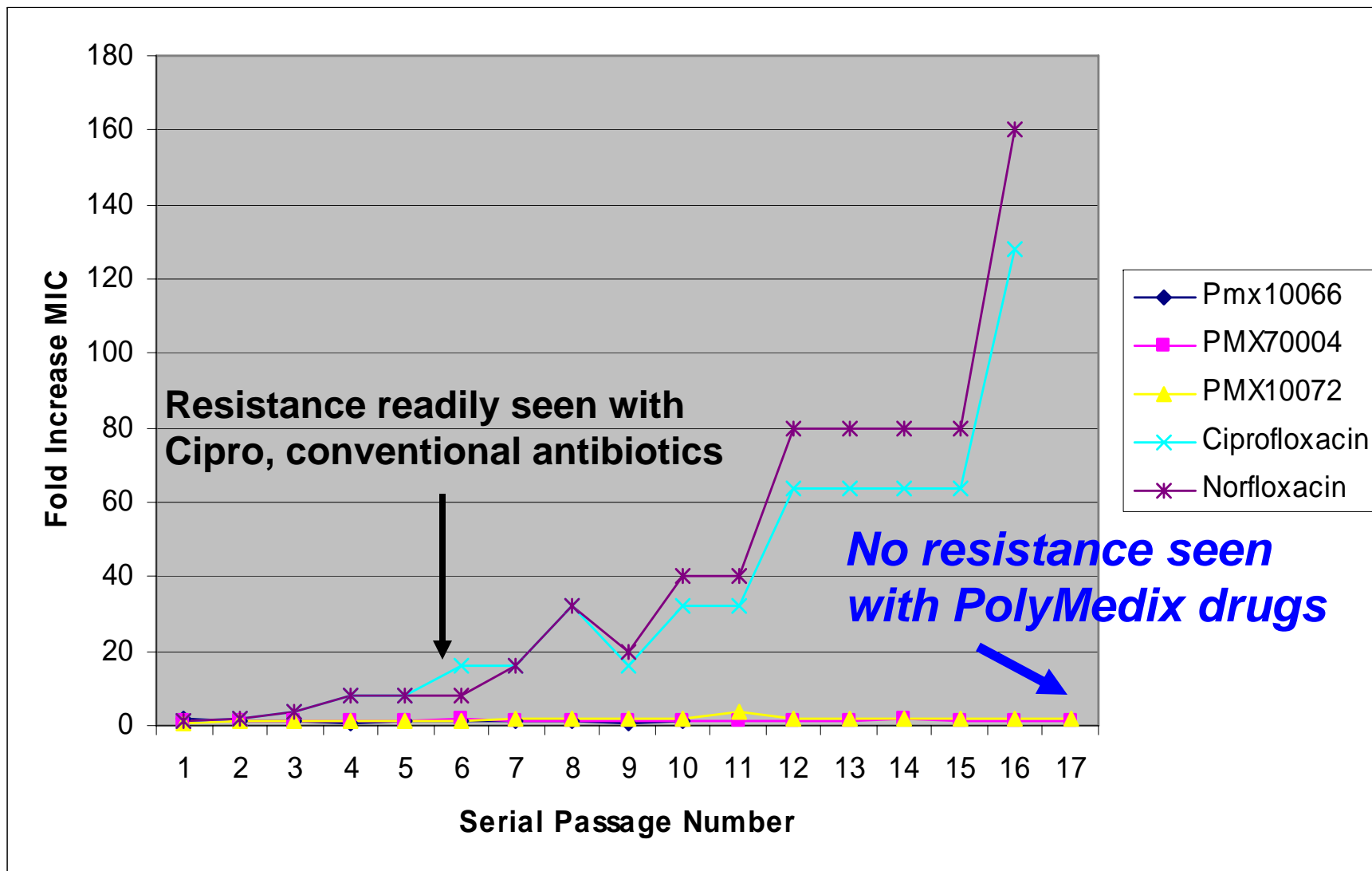
<u>PMX compound</u>	<u>IC₉₀</u> (<u>ug/ml</u>)	<u>EC₅₀</u> (<u>uM</u>)	<u>SI</u> (<u>EC₅₀/IC₉₀</u>)
PMX10072	4.49	>300	>66.82
PMX10070	2.2	>300	>66
PMX30053	3.57	>100	>28
PMX10138	18.4	>300	>16.3
PMX30024	57.6	129.8	2.25
PMX30006	60.4	39.67	0.66
PMX30063	100	120.4	1.20
PMX30016	100	55.0	0.55
PMX10129	100	251.7	2.52
PMX10166	100	110.37	1.10
PMX70004	40	12.4	0.31

Resistance: Mechanism of Action



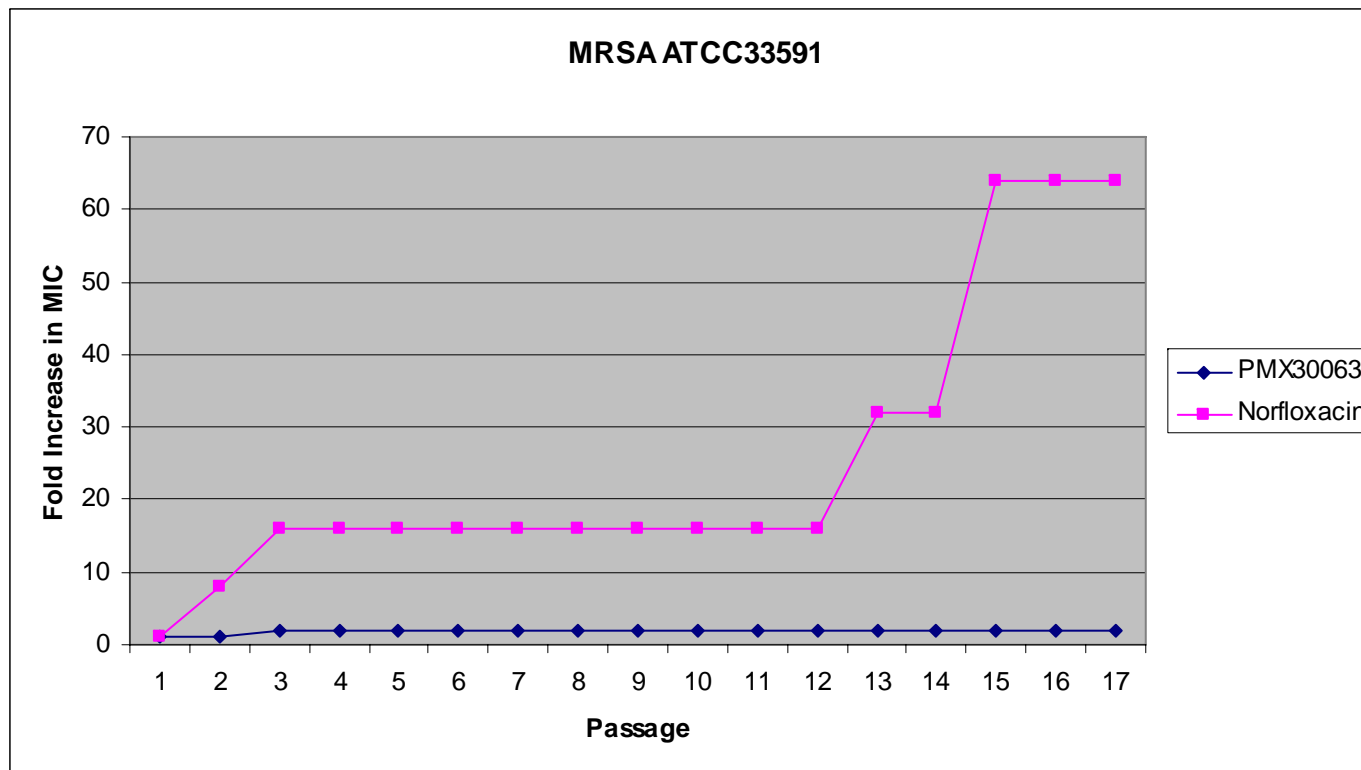
- ***Limited opportunity for efflux -***
 - targets cell membrane, not an internal biochemical target
- ***Complex target -***
 - Changes in bacterial membrane likely to affect viability in natural environment
- ***Host defense proteins still effective despite millions of years of evolution***
- ***PolyMedix compounds effective against drug resistant bacterial strains***
- ***Experimental evidence***

No Experimental Bacterial Resistance with PolyMedix Compounds – *Staph aureus* vs. Ciprofloxacin, Norfloxacin



Serial Passage Resistance: PMX30063 vs MRSA

No significant increase (2x) in 30063 MIC over 17 passages
Robust resistance apparent for the fluoroquinolone, Norfloxacin

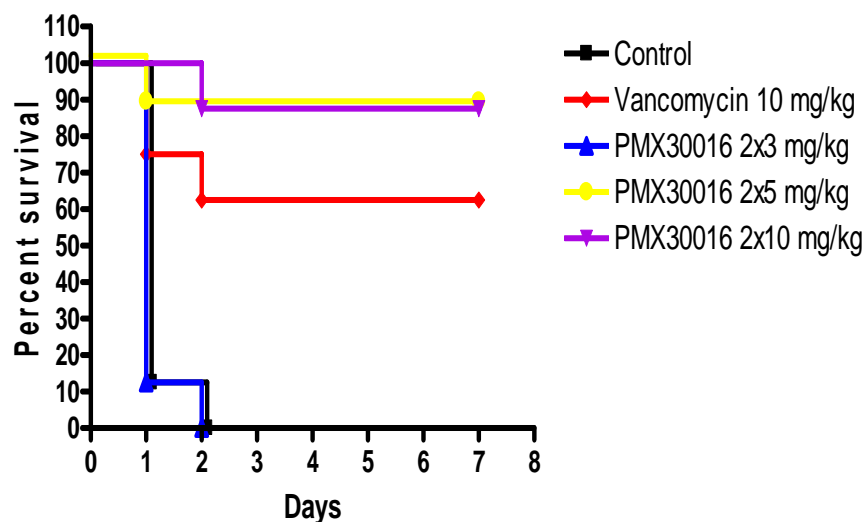


Efficacy PMX30063 and PMX30016

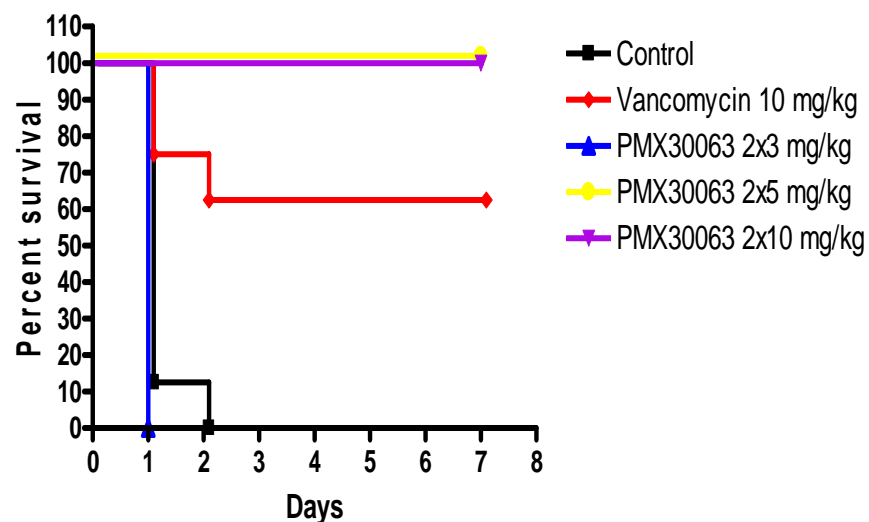
Mouse Sepsis Model: *S. aureus* infection

PMX lead compounds are highly protective in mouse peritonitis/sepsis model

Survival of PMX30016: *S. aureus*



Survival of PMX30063: *S. aureus*



Next Steps



- In vitro TB testing of wider groups of PYMX compounds
- In vivo TB testing- not many labs have this capability
- Generate interest to begin clinical trials
- The Alternative:
 - TB becomes the next plague, with HIV patients on the front lines



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