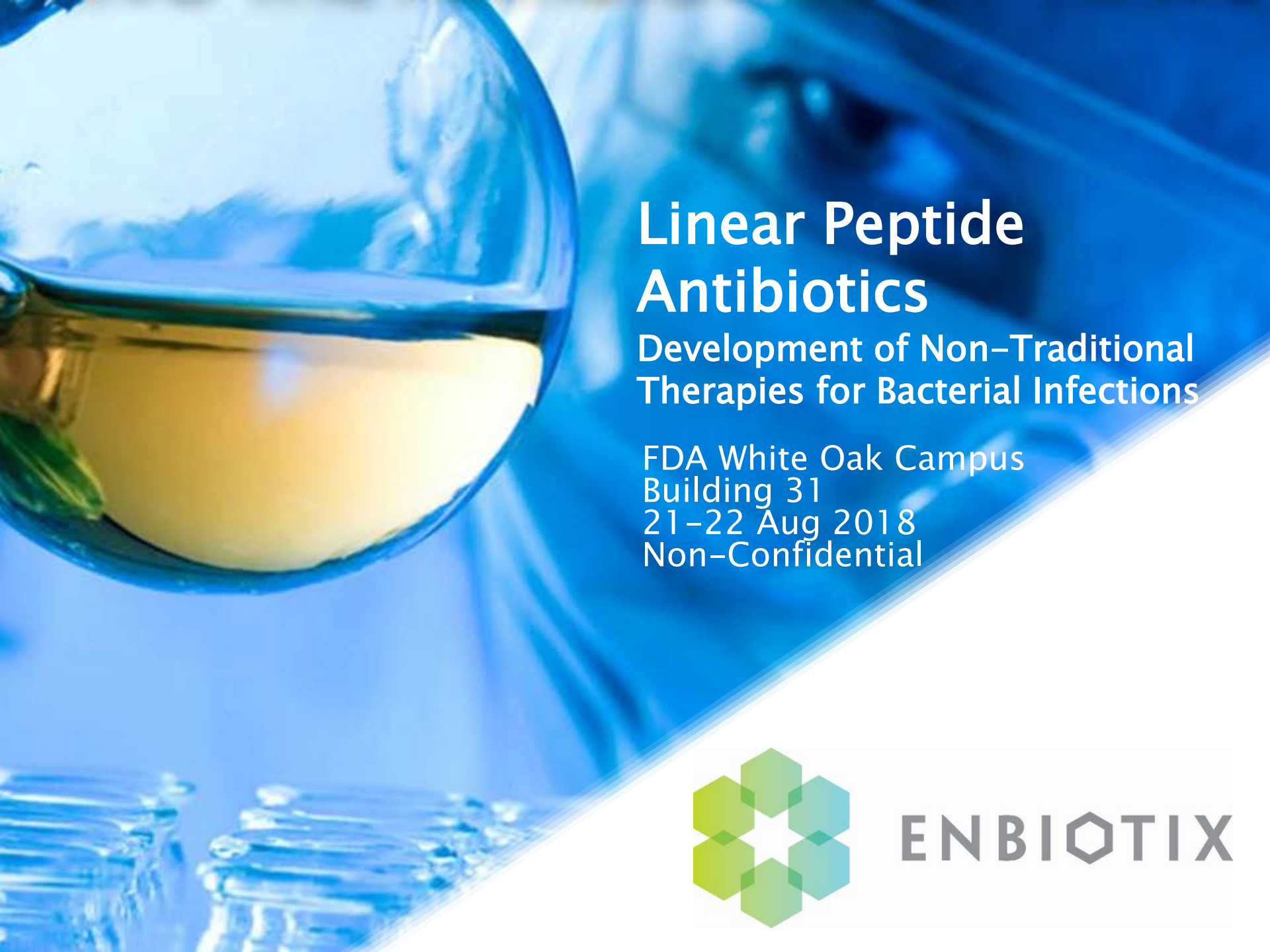


Linear Peptide Antibiotics

Development of Non-Traditional Therapies for Bacterial Infections

FDA White Oak Campus
Building 31
21-22 Aug 2018
Non-Confidential

ENBIOTIX

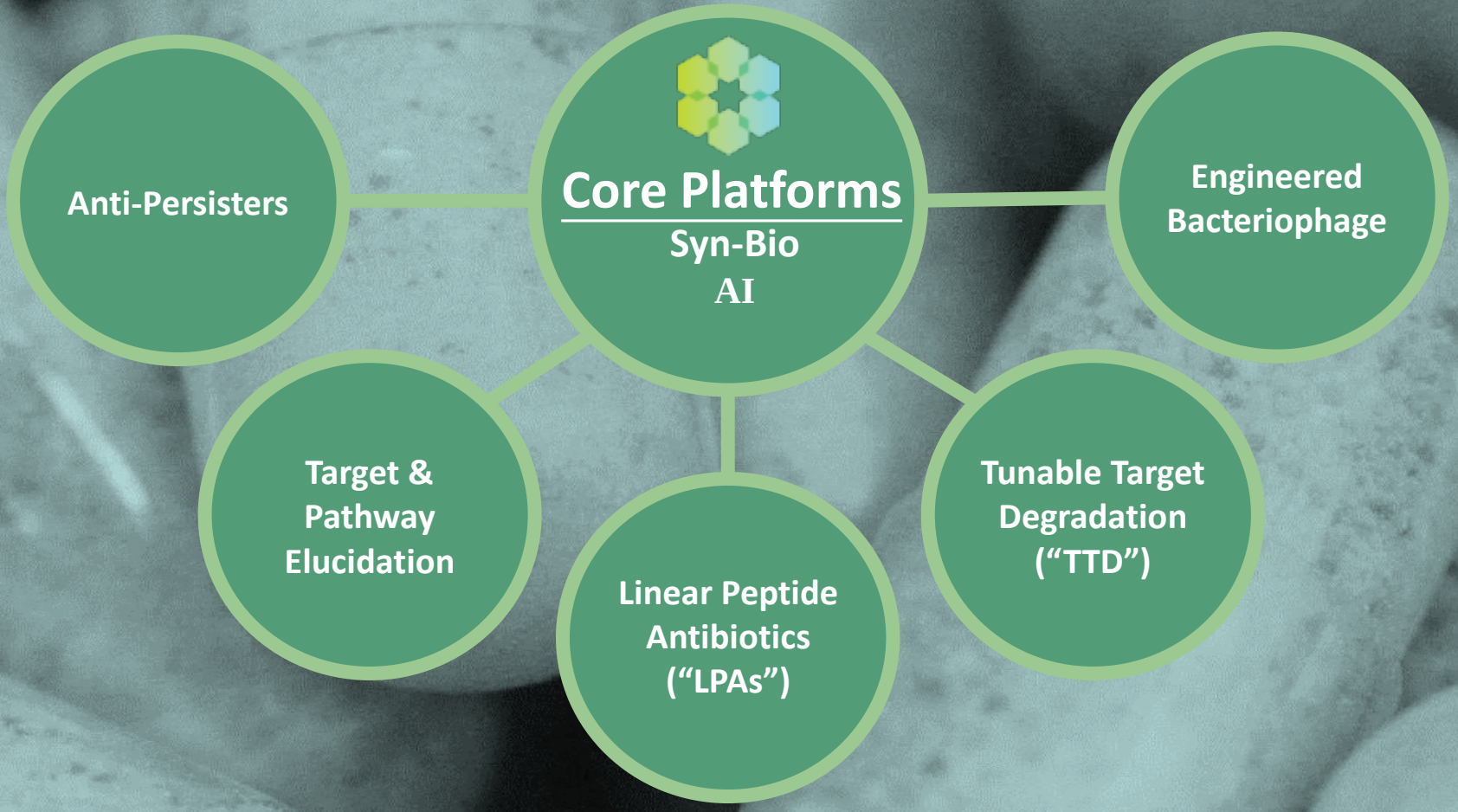
The EnBiotix Focus

Engineered antibiotics to address the global antibiotic resistance & tolerance crisis: a $40B market, projected to grow to $57B by 2024

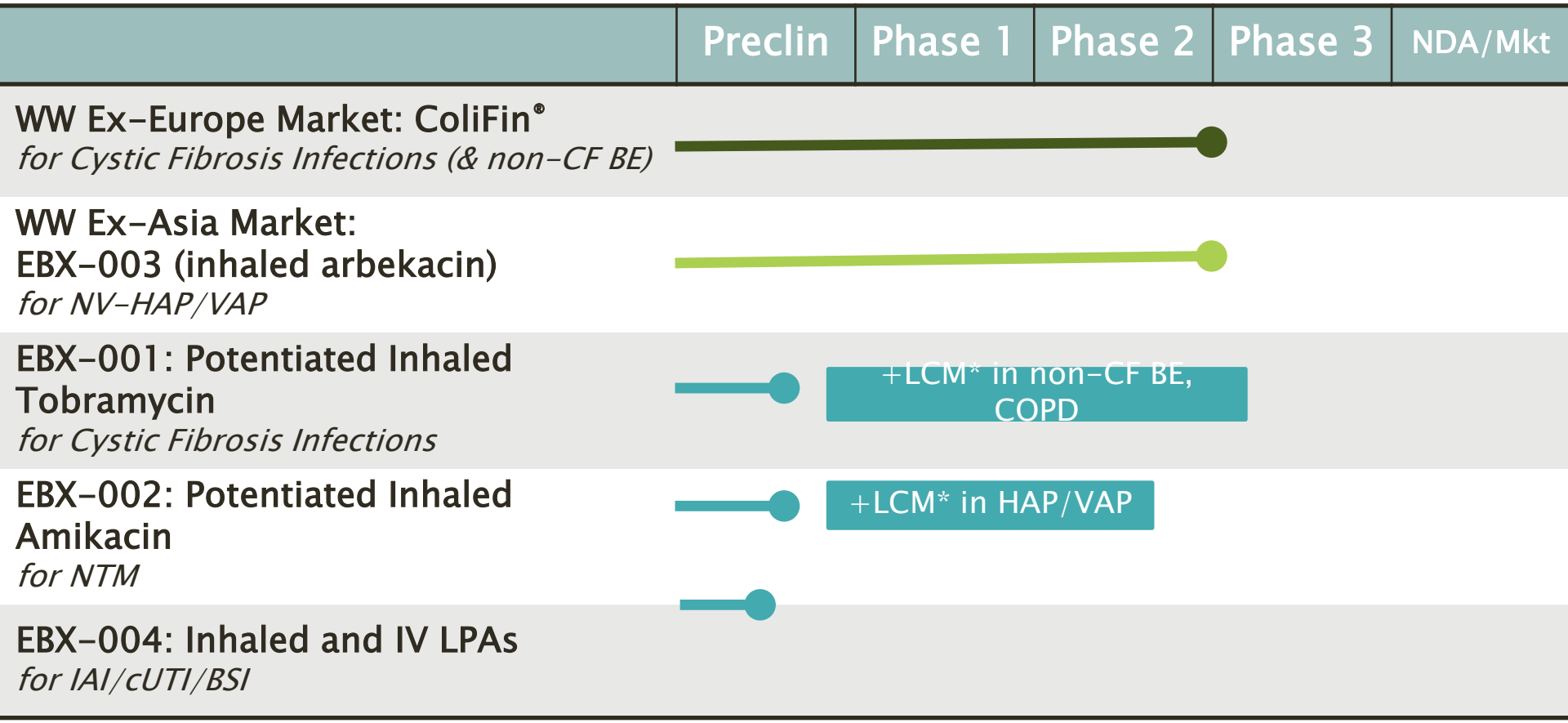
Based On Syn-bio/AI Work Of Co-founder James Collins, PhD

- MIT, Harvard, Wyss, Broad
- Member, National Academies of Science, Engineering, Medicine & Inventors; American Academy of Arts & Sciences
- 2012 Sanofi-Pasteur Award, HHMI, Rhodes Scholar
- Co-founder of Sample 6, Synlogic

EnBiotix Platforms



EnBiotix Product Pipeline



*LCM = Life Cycle Management

Product Value Proposition

Product	Value Drivers	Market Potential
ColiFin® (inhaled colistin) for CF & nCFBE	✓ Approved in EU, significant off-label use in nCFBE ✓ New Class for CF Treatment (Polymixins) ✓ Replaces off-label IV colistin usage (FDA discourages) ✓ Highly active against MDR CF pathogens	$250 – 300M
EBX-003 (Inhaled arbekacin) for NV-HAP & VAP	✓ i.v. formulation approved in Japan for MRSA ✓ Potentially first approved antibiotic for non-ventilator hospital-acquired pneumonia ✓ Greater potency & broader spectrum than amikacin	$400 – 500M $250 – 300M
EBX-001: Potentiated Inhaled Tobramycin	✓ Next-gen TOBI TIP/Podhaler® (Novartis) (front-line CF ABX, peak sales >$400M) ✓ Highly active against persisters: cause of chronic, recurrent infections	$500 – 700M
EBX-002: Potentiated Inhaled Amikacin	✓ Next-gen ARYKACE® (driving $2B Insmed market cap) ✓ Highly active against persisters: cause recurrent infections	$1 Billion
EBX-004: Inhaled and IV LPAs: IAI/cUTI/BSI	✓ New ABX class, blockbuster potential ✓ Novel Mechanism of Action ✓ Broad Spectrum, Highly Potent ✓ Very low mammalian toxicity	

LPAs Have Blockbuster Potential

Proven Class	Some of today's most successful antibiotics are peptides: Daptomycin, Dalbavancin, Colistin
Externally Validated	Acquired from AMP Therapeutics GmbH; funded by Boehringer Ingelheim Ventures & Novartis Ventures
Strong Rationale	Novel mechanism of action, excellent potency, broad spectrum G+/G- activity, favorable safety profile
Vast Potential	In vitro & in vivo data support a broad range of potential indications: VAP, cUTI, IAI, SSTIs

LPAs Possess Advantages Over AMPS for Therapeutic Use

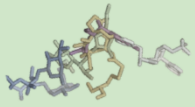
LPAs		Classical AMPs
Low mammalian cell toxicity	+ -	High mammalian toxicity
Non-helical, cationic		Alpha-helical, amphipathic
Do not cause membrane damage & cell lysis	+ -	Interact with bacterial membranes & lyse cells
Lethally targets bacterial intracellular mechanisms	+ -	Targets membranes leading to narrow therapeutic index

Two Families of LPAs: Apidaecins and Oncocins

- Apidaecins (Api) and Oncocins (Onc): proline-rich antimicrobial peptides derived from insect defensin peptides

Apidaecin 1b	GNNRPVYIPQPRPPHPRL-OH
Api88	gu-ONNRPVYIPRPRPPHPRL-NH_2
Api134	gu-ONNRPVYIPRPRPPHPOL-NH_2
Api137	gu-ONNRPVYIPRPRPPHPRL-OH
Api155	gu-ONNRPVYIPRPRPPHPHL-NH_2

Insect defensin peptide-derived



SAR to Improve Potency/Spectrum

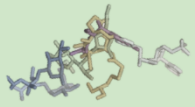
Broad Spectrum Gram- Activity

gu = tetramethylguanidinium, O=L-ornithine, H=L-homoarginine

Apidaecins

Ofa ABP4	VDKPPYLPRPPPPRRIYNNR-OH
Onc18	VDKPPYLPRPRPPRRIYNR-NH_2
Onc72	VDKPPYLPRPRPPROIYNO-NH_2
Onc112	VDKPPYLPRPRPPRrIYNr-NH_2
Onc143	VRKPPYLPRPRWPRRIYNR-NH_2
Onc158	VRKPPYLPRPRWPROIYNO-NH_2
Onc166	VrKPPYLPRPRWPRrIYNr-NH_2

Oncopeltus fasciatus peptide-derived



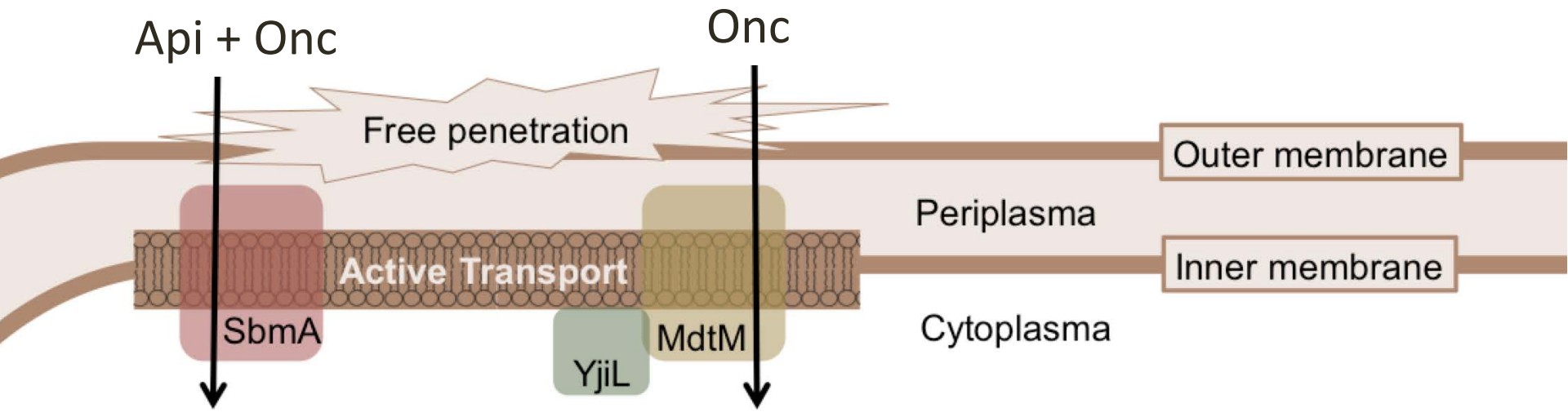
SAR to Improve Potency/Spectrum

Broad Spectrum Gram- & Gram+ Activity

Oncocins

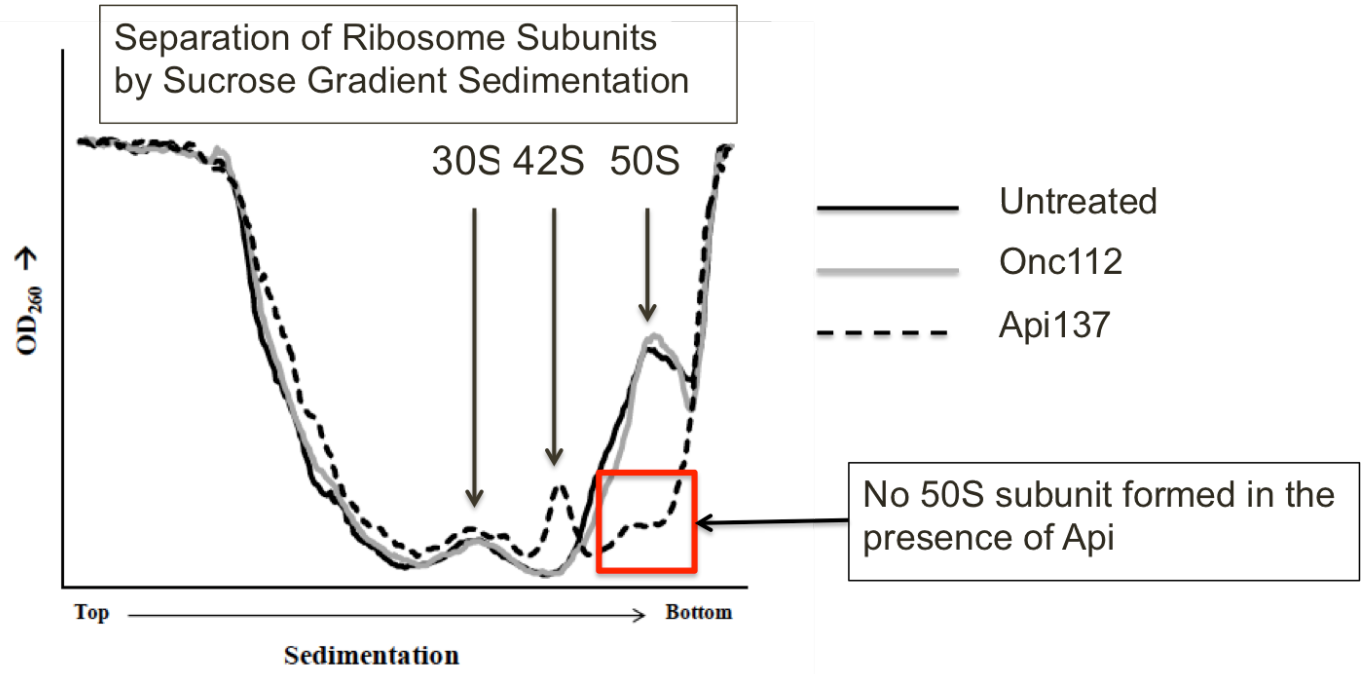
Mechanism of Action: Uptake Mediated by Specific Transporters

LPAs freely penetrate the outer membrane and have specific transporters in the inner membrane



Apidaecin Prevents Ribosome Assembly, A Unique Mode of Action

- Large Ribosome Subunit Assembly
  - 30S → 42S →50S large ribosomal subunit
- Api137 treatment accumulates 42S intermediate, preventing assembly of 50S large ribosomal subunit[1]

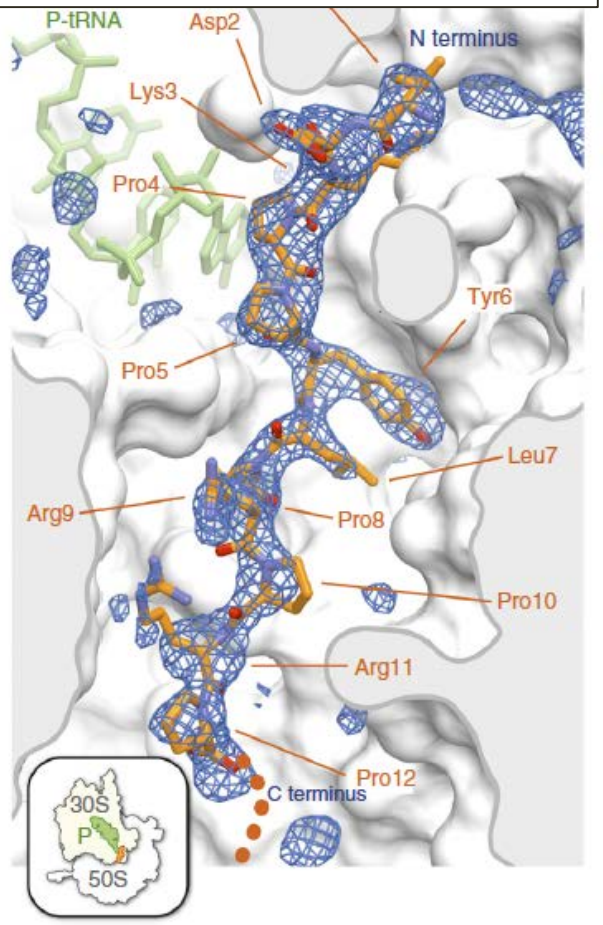


[1]Krizsan, A., et al., Short Proline-Rich Antimicrobial Peptides Inhibit Either the Bacterial 70S Ribosome or the Assembly of its Large 50S Subunit. Chembiochem, 2015. 16(16): p. 2304, PMID: 26448548

Oncocin Blocks the Entire Exit Tunnel of the Intact Ribosome

- **No other antibiotic blocks entire ribosome exit tunnel; very significant because….**
- Interaction with multiple binding sites reduces likelihood of resistance development
- Prevents elongation of nascent protein chain by the ribosome & destabilizes initiation complex
- In contrast to other antibiotic MOAs, Onc binding in tunnel overlaps several known binding sites:
  - macrolides
  - chloramphenicol
  - streptogramins
  - pleuromutilins
  - clindamycin

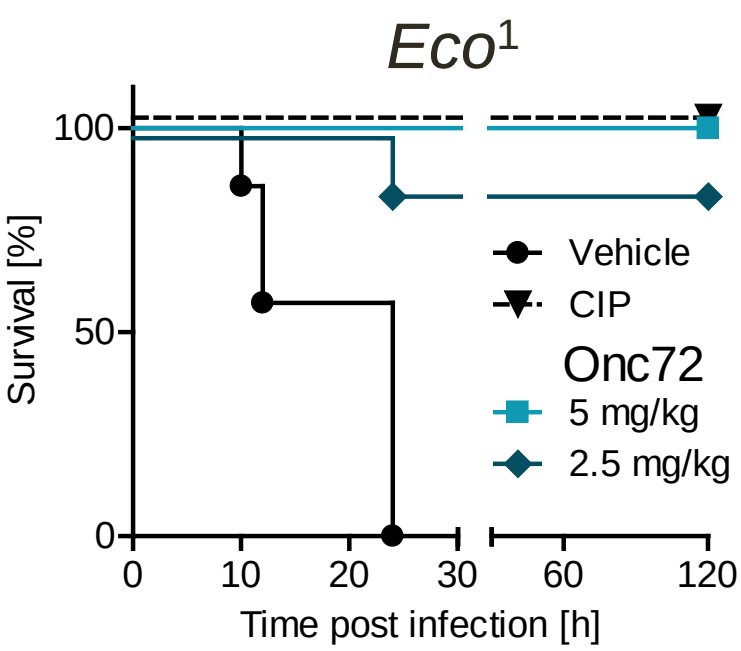
Crystal structure of Onc112 in Exit Tunnel[1]

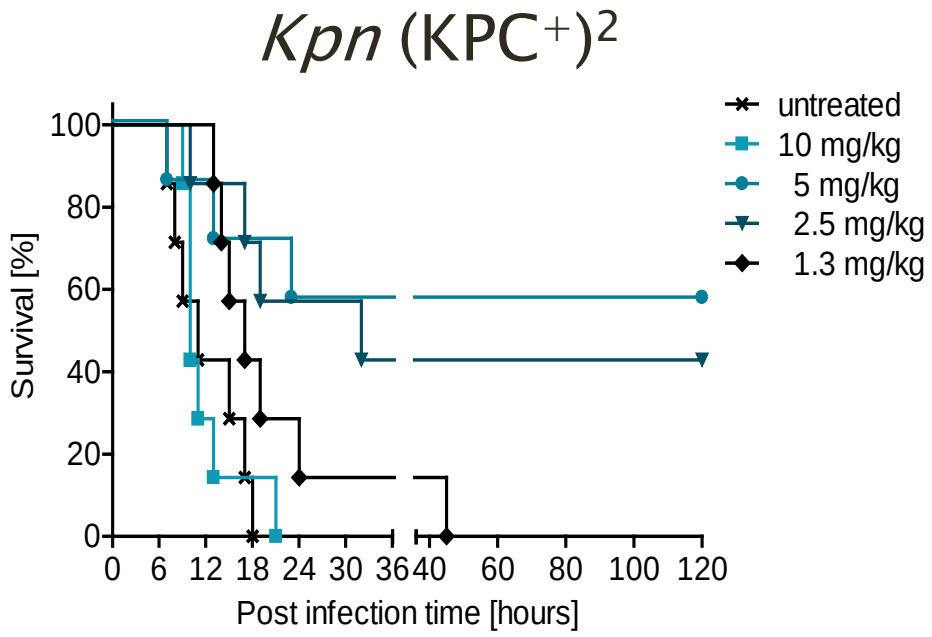


[1]Seefeldt, A.C., et al., The proline-rich antimicrobial peptide Onc112 inhibits translation by blocking and destabilizing the initiation complex. Nat Struct Mol Biol, 2015. 22(6): p. 470, PMID: 25984971

Oncocins Have Excellent Efficacy In Two Intraperitoneal Infection Models

- Onc72 shows efficacy towards *E. coli* and carbapenemase-resistant *K. pneumoniae*

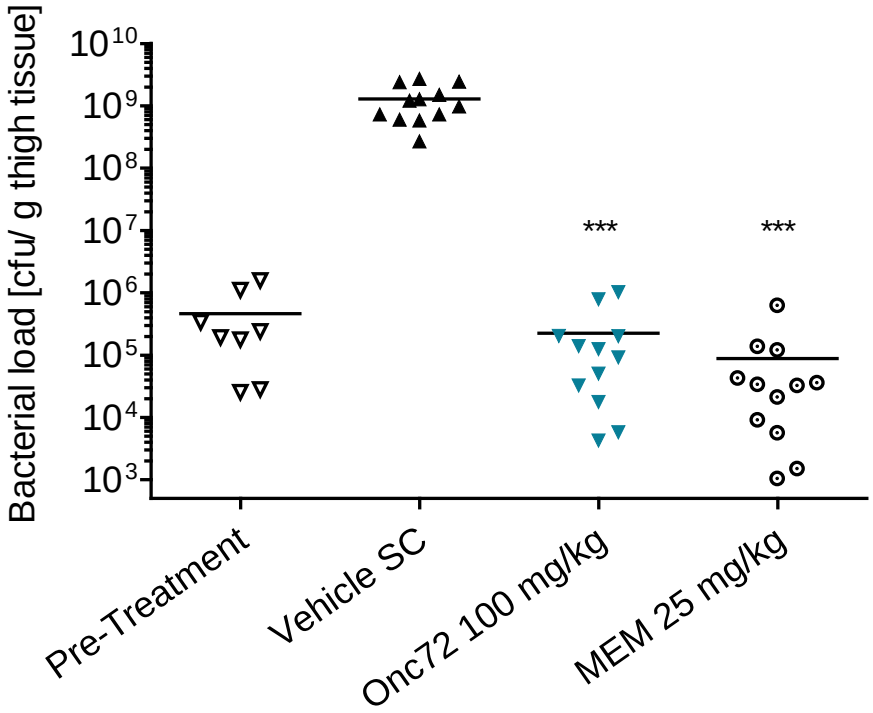




[1]Infection with *E. coli* ATCC 25922; CIP, ciprofloxacin
[2]*K.pneumoniae* K97/09 MDR strain

Onc72 Shows Strong Efficacy In *Kpn* Thigh Burden Model

- Onc72 reduces CFU recovery by ~ 4 log in thigh infection model

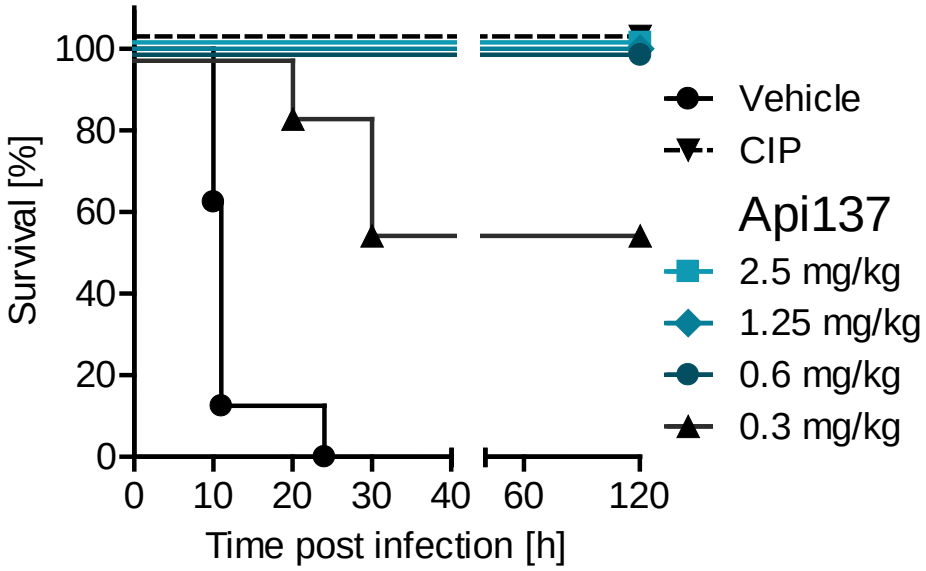


K. pneumonia ATCC 43816; MEM meropenem (IV), Onc72 (SC)

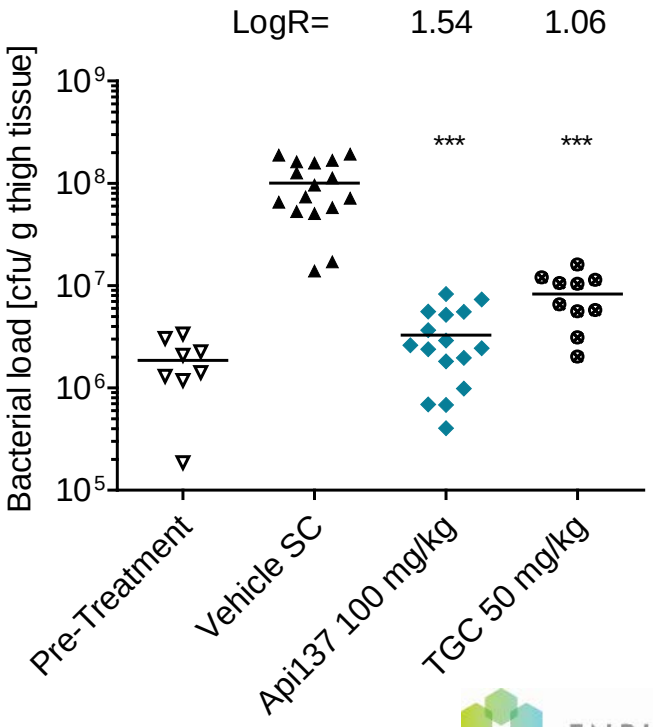
Apidaecins Have Excellent Efficacy In Two Different Infection Models

- Api137 shows efficacy towards *E. coli* and carbapenemase-resistant *K. pneumoniae*

Eco[1]



Kpn (NDM−1$^+$)[2]



[1]Infection with *E. coli* ATCC 25922; CIP, ciprofloxacin
[2]*K.pneumoniae* BAA 2146 (NDM−1$^+$); TGC, tigecycline

LPAs' Broad Spectrum Addresses Need for Empirical Therapy

Compound	S. aureus	K. pneumoniae	P. aeruginosa	A. baumannii
Ceftazidime		✓	✓	
Meropenem		✓	✓	✓
Colisitin		✓	✓	✓
Amikacin	✓	✓	✓	✓
Api137		✓	✓	✓
Onc72		✓	✓	✓
Onc143	✓	NT	✓	NT
Onc166	✓	✓	✓	✓

NT = not yet tested

LPAs Molar Potency Similar to Most Approved Antibiotics

Organism	Compound	MIC (ug/ml)[1]	MIC (uM)
S. aureus	Ceftobiprole	<2 ug/ml	3.74
	Meropenem	< 4 ug/ml	10.43
	Vancomycin	<2 ug/ml	1.38
	Daptomycin	<1 ug/ml	0.62
	Onc143	0.5 ug/ml	**0.20**
	Api137	NA	**-**
P. aeruginosa	Ceftazidime	< 8 ug/ml	14.6
	Meropenem	< 2 ug/ml	5.21
	Colisitin	< 4 ug/ml	3.16
	Amikacin	< 8 ug/ml	13.7
	Onc143	4 ug/ml	**1.59**
	Api137	16 ug/ml	**6.98**

[1]Clincalc EUCAST sensitivity breakpoints for approved drugs
[2]NA=not active

Acknowledgments

- EnBiotix, Inc., Boston, MA
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Thank You!