Cellceutix Corporation
Beverly, MA USA
www.cellceutix.com

A New Class Of Antimicrobials—The HDP Mimics
Cellceutix Corporation

QIDP Educational Breakfast

May 21, 2015

Cellceutix Presentations
ECCMID 2015

cellceutix

Cellceutix Corporation
Beverly, MA USA
www.cellceutix.com

ECMIID 2015
Copenhagen, Denmark
25 – 28 April 2015

Synthetic Novel Host Defense Protein Mimetics for the Treatment of Gram-Negative Bacterial Infections

Presentation 0169, Hall C, 12:00pm

April 26, 2015

cellceutix

Cellceutix Corporation
Beverly, MA USA
www.cellceutix.com

ECMIID 2015
Copenhagen, Denmark
25 – 28 April 2015

A Randomized, Double-Blind Study Comparing Single-Dose and Short-Course Brilacidin to Daptomycin in the Treatment of Acute Bacterial Skin & Skin Structure Infections (ABSSSI)

Presentation 2969, Hall J, 4:00pm

April 27, 2015

Full presentations available on company website: www.cellceutix.com

cellceutix

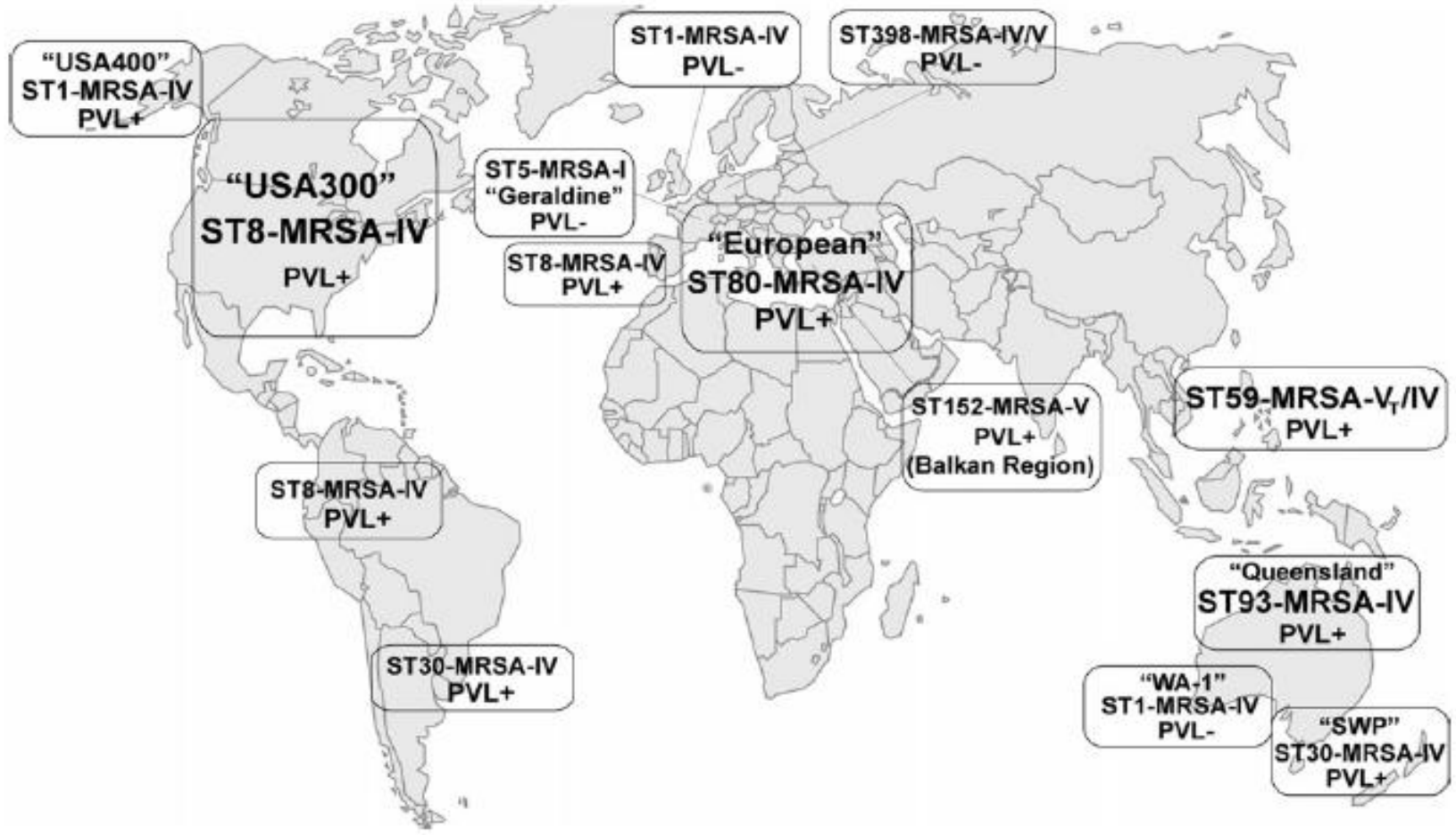
Background & Rationale

- **Develop small non-peptidic, fully synthetic mimics of Host Defense Proteins (HDPs) as systemic and topical agents**
  -Novel approach for bactericidal activity
- **HDPs are small antimicrobial peptides**
  -Expressed widely in the animal kingdom
  -Produced in skin, mucosal surfaces, neutrophils
  -Target microbial membrane
- **First line of defense against bacterial invasion**
  -Part of innate immunity
  -Maintenance of epithelial barrier function
  -Regulate microbiota
  -Immuno-modulatory activities – link innate and adaptive immunity
- **HDP dysfunction implicated in inflammatory disorders of skin and mucosal surfaces**
  -Inflammatory bowel disease (BID), atopic dermatitis, acne, skin infections, cystic fibrosis…
- **Address Global Problem of Antimicrobial Resistance**
  - Gram-positive (e.g., MRSA) and Gram-negative (e.g., CRE) development programs
  - Identified by CDC and FDA as high priority pathogens

cellceutix

CA-MRSA—A Global Public Health Problem

Major Cause of Skin and Soft Tissue Infections (ABSSSI)



Global distribution of dominant community methicillin-resistant *Staphylococcus aureus* (MRSA) clones and Panton Valentine leukocidin (PVL)

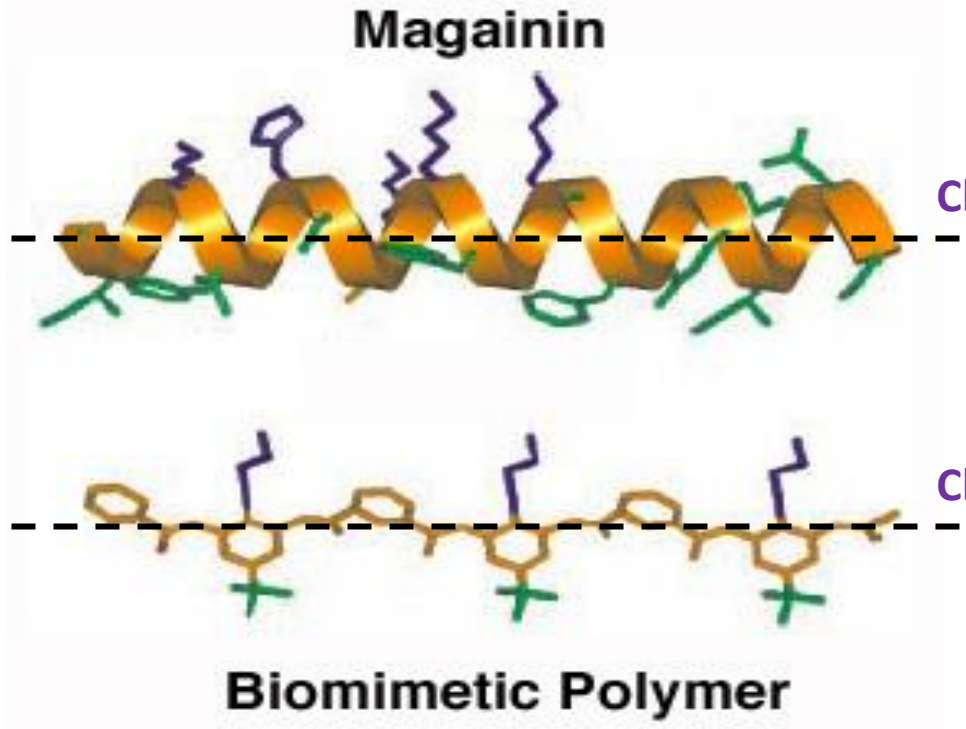
Clinical Infectious Diseases 2011;52(1):99–114

cellceutix

Background & Rationale

Design Approach

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



Capture structural and biological properties of HDPs using fully synthetic, nonpeptidic scaffolds and sidechains

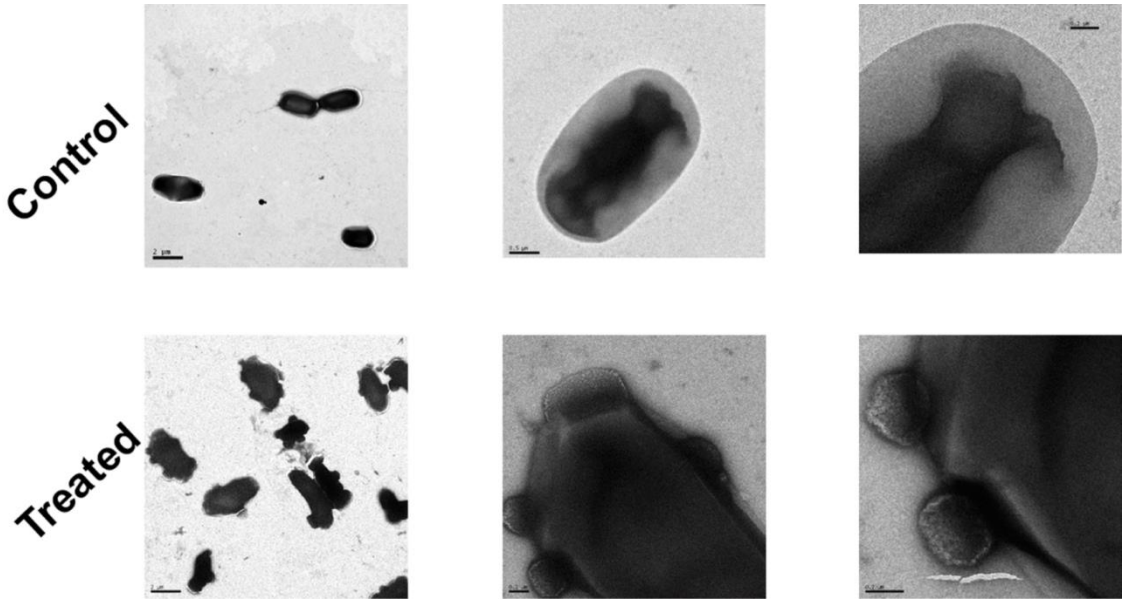
Not peptidomimetics

cellceutix

Mechanism of Action: Membrane Target

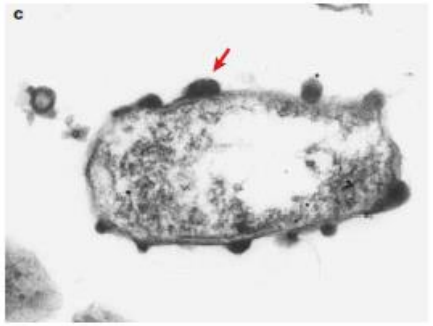
Membrane activity in Gram-positive and Gram-negative organisms supported by

- **Coarse grain molecular dynamic simulations**
- **Vesicle leakage assays**
- **Membrane permeabilization and potentiation assays**
- **Transcriptional profiling, proteomics and deep sequencing**
- **Transmission electron microscopy (TEM)**



60 minutes; 10x MIC concentrations

TEM of *P. aeruginosa* on SMAP29 (3 hrs)



Brogden, K. 2005. Nature Reviews, Microbiology *3*: 238 (2005)

Cidal concs. of a HDP mimic cause visible signs of vesiculation (blebbing) at the E. coli membrane.

Similar morphological response reported for SMAP29 and P. aeruginosa.

cellceutix

Advantages of Mimic Approach

Narrow and broad-spectrum antimicrobial agents have been produced

- 0.5 to 2 µg/ml MICs vs Gram-positives
- 0.5 to 8 µg/ml MICs vs Gram-negatives

Wide selectivity for bacteria over mammalian cells

- Significant improvements in cytotoxicity versus HDPs
- >100 to 1,000 fold selectivities

Medicinal chemistry enables "fine-tuning" for specific activities

Straightforward synthesis

- Common starting materials

Share important antimicrobial properties with HDPs

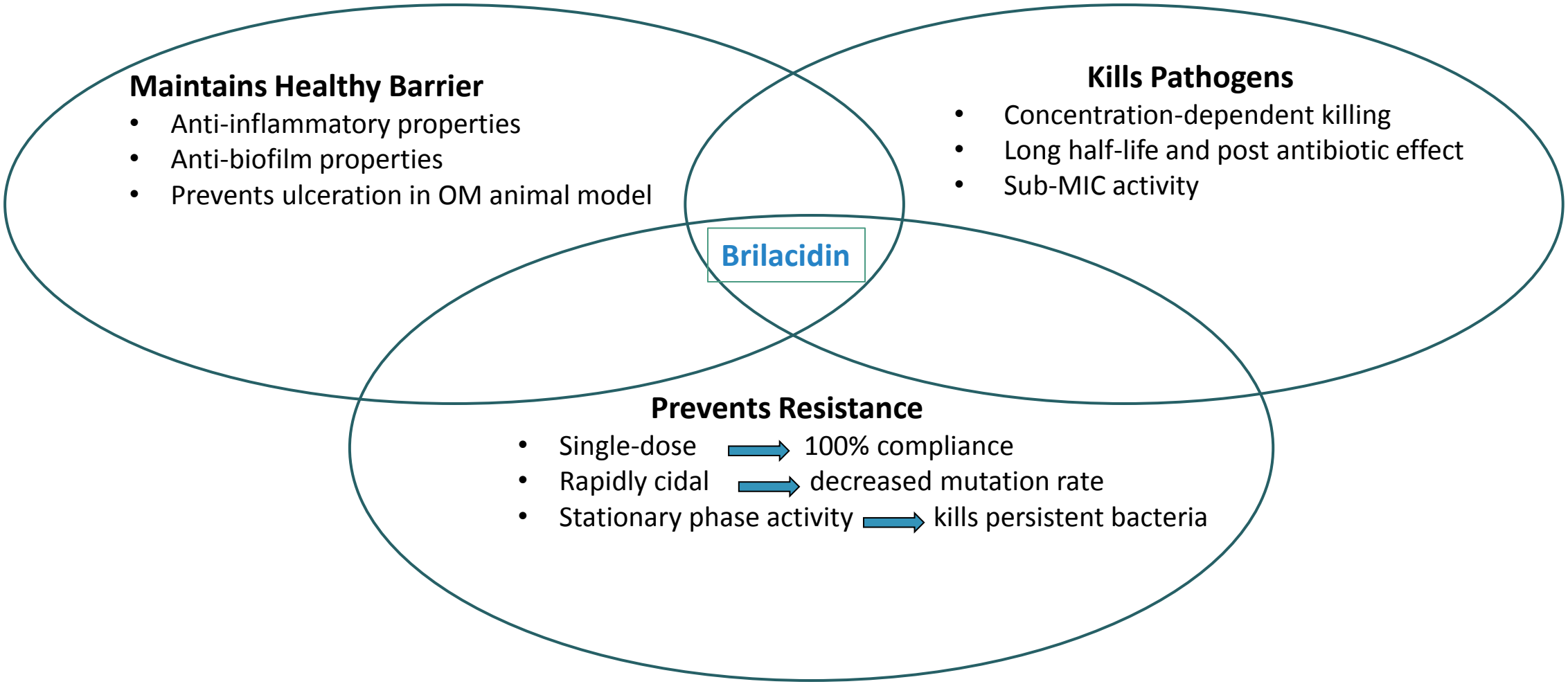
- Rapidly bactericidal; time-kills 0.5 to 6 hrs
- Low potential for resistant development; 20 serial passage assays and fsr < 10^{-11}

Metabolically stable and active *in vivo*

Lead compound: Brilacidin

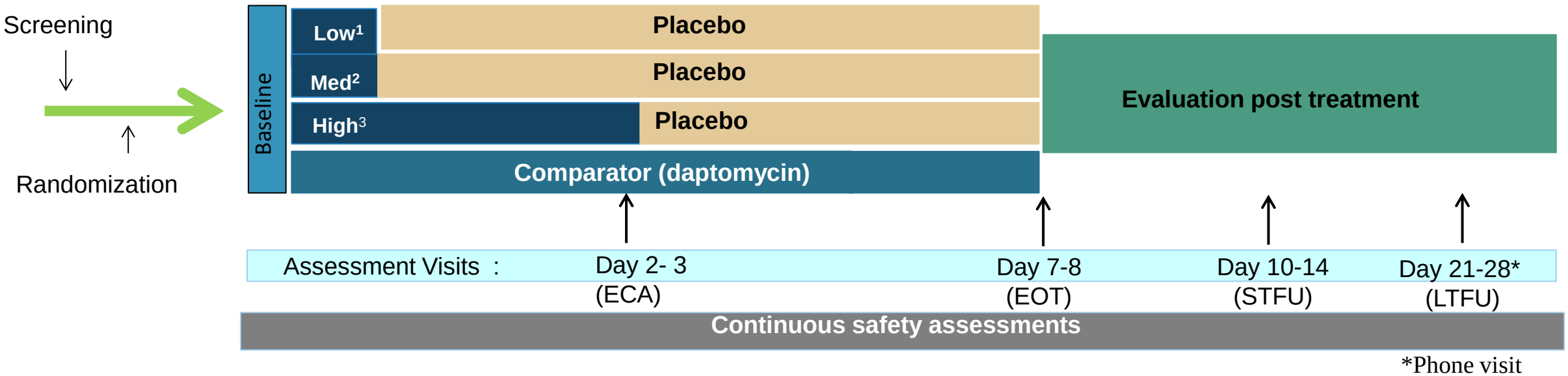
cellceutix

Lead Compound--Brilacidin



CTIX-BRI-204 Study (Phase 2b)

Study Design for ABSSSI (Skin Infections)



[1]**Low** (0.6mg/kg single dose)
[2]**Med** (0.8mg/kg single dose)
[3]**High** (0.6 mg/kg D1; 0.3 mg/kg D2 & D3)*

**Highest total dose 1.2 mg/kg is less than lowest total dose of 1.6 mg/kg in 203 study*

- **Trial conducted at 4 sites in U.S.**
- **Dosing: IV infusion 1x/day for 7 days**
  - 1or 3 days on BRI + 4 or 6 days on placebo; or 7 days on daptomycin
- **215 patients, 4 arms, ~50 patients per arm**
- **ABSSSI definition (FDA Guidance, Oct 2013)**
  - ≥ 75 sq. cm^2 (redness, edema, and/or induration)
  - Wound, major cutaneous abscess, cellulitis/erysipelas
- **Early Clinical Response (48-72 hours)—FDA endpoint**
- **Clinical Response (Day 7-8; Day 10-14)—EMA endpoint**

cellceutix

Primary Endpoint--United States
Early Clinical Response at 48-72 hours

FDA ABSSSI Guidance (Oct, 2013):

> *"Clinical response should be based on the percent reduction in the lesion size at 48 to 72 hours compared to baseline, measured in patients who did not receive rescue therapy and are alive. A clinical response in a patient generally is defined as a percent reduction in lesion size greater than or equal to 20 percent compared to baseline".*

"Clinical Response" if all of the below criteria are fulfilled:

- Did not receive rescue therapy
- Alive
- ≥ 20% reduction in lesion area (lesion length x lesion width)

cellceutix

Primary Endpoint--United States

Early Clinical Response at 48-72 hours

	0.6 mg/kg IV x 1 day (N=53)	0.8 mg/kg IV x 1 day (N=53)	Brilacidin x 3 days (N=53)	Daptomycin (N=50)
N assessed	51	48	52	48
Clinical Response (%)	47 (92.2)	46 (95.8)	51 (98.1)	45 (93.8)
95% C.I.	(84.8, 99.5)	(90.2, 100)	(94.3, 100)	(86.9, 100)

ATS = All Treated/Safety Population
Pre-specified analysis population in statistical analysis plan (SAP) for primary endpoint

Per FDA Guidance—ABSSSI (Oct, 2013)

cellceutix

Primary Endpoint—Europe

Investigator Clinical Response at EOT and STFU

Study Timepoint		0.6 mg/kg IV x 1 day	0.8 mg/kg IV x 1 day	Brilacidin x 3 days	Daptomycin
EOT	N assessed	30	31	29	38
(D7-8)	Clinical Response (%)	29 (96.7)	26 (83.9)	26 (89.7)	35 (92.1)
	95% C.I.	(90.2, 100)	(70.9, 96.8)	(78.6, 100)	(83.5, 100)
	Non-clinical Response*	1	5	3	3
STFU	N assessed	30	29	25	36
(D10-14)	Clinical Response (%)	29 (96.7)	24 (82.8)	24 (96.0)	34 (94.4)
	95% C.I.	(90.2, 100)	(69.0, 96.5)	(88.3, 100)	(87.0, 100)
	Non-clinical Response*	1	5	1	2

mITT Population

*Includes PI response of “Clinical Failure” and “Indeterminate”

cellceutix

Investigator Clinical Response at EOT and STFU

By Baseline Pathogen

Baseline Pathogen	PI Clinical Assessment at Day 7/8: EOT				PI Clinical Assessment at Day 10-14: STFU			
	Brilacidin				Brilacidin			
	0.6 1 day	0.8 1 day	0.6/0.3 3 days	Daptomycin 7 days	0.6 1 day	0.8 1 day	0.6/0.3 3 days	Daptomycin 7 days
Staphylococcus aureus								
MSSA only	16/17 (94.1)	15/18 (83.3)	12/13 (92.3)	11/13 (84.6)	16/17 (94.1)	14/17 (82.4)	12/12 (100.0)	11/12 (91.7)
+ *S. lugdunensis*	1/1 (100.0)		1/1 (100.0)		1/1 (100.0)		1/1 (100.0)	
+ *S. anginonsus-milleri*		1/1 (100.0)	1/1 (100.0)			1/1 (100.0)	1/1 (100.0)	
+ *S. pyogenes*				2/2 (100.0)				2/2 (100.0)
MRSA only	9/9 (100.0)	7/8 (87.5)	10/11 (90.9)	12/13 (92.3)	9/9 (100.0)	6/7 (85.7)	8.8 (100.0)	11/12 (91.7)
+ *E. faecalis*				1/1 (100.0)				1/1 (100.0)
+ *S. agalactiae*				1/1 (100.0)				1/1 (100.0)
Streptococcus								
agalactiae				1/1 (100.0)				1/1 (100.0)
anginonsus-milleri	2/2 (100.0)	2/3 (66.7)	2/3 (66.7)	3/3 (100.0)	2/2 (100.0)	2/3 (66.7)	2/3 (66.7)	3/3 (100.0)
pyogenes	1/1 (100.0)				1/1 (100.0)			
Staphylococcus								
lugdunensis		1/1 (100.0)		1/1 (100.0)		1/1 (100.0)		1/1 (100.0)
Enterococcus								
faecalis				1/1 (100.0)				1/1 (100.0)
Group C Beta-hemoloytic streptococci				2/2 (100.0)				2/2 (100.0)

mITT Population

cellceutix

PK-PD Modeling for Dose Selection
May Accelerate Development Program

ICPD® INSTITUTE FOR CLINICAL PHARMACODYNAMICS

Efficacy predictions consistent across two PK/PD models for microbiologically evaluable subjects

Data on File (2015) ↓ ICPD, ECCMID (2013)* ↓

Brilacidin Single Dose (mg/kg)	Average predicted % probability of Sponsor-defined clinical success (2015 pooled analysis, Studies 203 & 204)		Average predicted % probability of Sponsor-defined clinical success (2012 analysis for Study 203 alone)	
	EOT	TOC/SFTU	EOT	TOC
0.4	84.33	86.40	89.0	88.8
0.6	88.92	89.23	91.6	90.9
0.8	92.03	91.40	93.5	92.6
1.0	94.16	93.08	94.9	93.9

* Use of Pharmacokinetics-Pharmacodynamics and Monte Carlo Simulation Analyses to Support Brilacidin Dose Selection for Patients with Acute Bacterial Skin and Skin Structure Infections

cellceutix

Brilacidin Program Summary

HDP Mimics for MRSA in Skin Infections (ABSSSI)

- Brilacidin was safe and effective in two phase 2 studies
- Convenient single-dose regimen
  - Pharmacoeconomic advantages
- Efficacy comparable to 7-day regimen of robust comparator (daptomycin x 7 days)
- QIDP designation (Nov 2014) under the GAIN Act
  - Eligible for Fast Track and Priority Review
- Minimal potential for development of resistance
  - Novel class, with no cross-resistance
  - Novel mechanism of action confers fitness disadvantage for bacterial resistance
  - Single dose removes non-compliance as driver for resistance
- Immunomodulatory, with anti-biofilm properties
  - May accelerate the healing process
- Phase 3 planning in progress

cellceutix

Carbepenem-Resistant Enterobacteriaceae (CRE)

Urgent Public Health Threat in U.S, Europe, and the World

CDC, Antibiotic Resistance Threats in The United States, 2013

International dissemination of *Klebsiella pneumoniae* carbapenemase (KPC)–producing *Enterobacteriaceae*.

Clinical Infectious Diseases 2011;53(1):60–67

Expansion of healthcare-associated carbapenem-non-susceptible *Enterobacteriaceae* in Europe: epidemiological scale and stages by country, as of July 2010

Country	Stage	Epidemiological scale	Documented introduction from abroad	Dominant class	Underreporting
Greece	5	Endemic	Yes	KPC/VIM	
Israel[a]				KPC	
Italy	4	Interregional spread	Yes	KPC	
Poland					Likely
France	3	Regional spread	Yes	KPC	
Germany				OXA-48/VIM	Likely
Hungary				KPC	Likely
Belgium	2b	Independent hospital outbreaks	Yes	VIM	Likely
Spain				KPC/VIM/IMP	Likely
England and Wales				NDM	

Eurosurveillance: http://www.eurosurveillance.org

cellceutix

Activity of Lead Compounds vs. MDR *K. pneumoniae*

Cmpd	MIC (µg/ml)											
	Kpn UNT180-1 (KPC isolate)			Kpn UNT153-1 (KPC isolate)			Kpn UNT024-1 (Drug-susceptible strain)			Kpn UNT127-1 (ndm-1 isolate)		
	MHB	MHB + 40% MS	MHB + 5% MS	MHB	MHB + 40% MS	MHB + 5% MS	MHB	MHB + 40% MS	MHB + 5% MS	MHB	MHB + 40% MS	MHB + 5% MS
1807	2	2	2	2	2	4	1	2	2	1	4	2
1741	2	2	2	4	8	4	2	2	8	4	4	8
1278	4	16	2	> 16	> 16	> 16	1	4	4	> 16	2	4

UNT180-1: KPC producer; UNT153-1: KPC producer; UNT024-1: ATCC43816; UNT127-1: ndm-1 producer. Kpn: Klebsiella pneumoniae. MHB: Mueller Hinton broth. ms: mouse serum. All MIC assays were conducted under CLSI guidelines.

-Compounds are active vs. Drug-S and CRE organisms

-Serum has little impact on activity of 1807 and 1741

cellceutix

Clinical Isolate Screen-- CC-1807 vs. *Enterobacteriaceae* spp.

Activity vs. recent collection of clinical isolates

Organism (20 isolates)	MIC_{90} (µg/ml, CLSI)			
	CC-1807	Levofloxacin	Gentamicin	Meropenem
Escherichia coli	0.25	>4	32	0.015
Klebsiella pneumonia	1	>4	1	4
Enterobacter spp.	1	0.5	0.5	0.25

Activity vs. MDR* *Enterobacteriaceae* clinical isolates

Organism	MIC_{90} (µg/ml, CLSI)			
	CC-1807	Levofloxacin	Gentamicin	Meropenem
Escherichia coli (4 isolates)				
MIC range	≤0.06 – 0.12	>4	1 - >64	0.008 - 0.03
Klebsiella pneumonia (8 isolates)				
MIC range	0.25 – 1	>4	≤0.06 – >64	0.06 - >4
Enterobacter cloacae (3 isolates)				
MIC range	0.25 - 2	2 - >4	0.25 – >64	0.25 - >4
MDR *Enterobacteriaceae* (15 isolates)				
MIC range	**≤0.06 – 2**	**2 - >4**	**≤0.06 – >64**	**0.008 - >4**
MIC_{50}	**0.5**	**>4**	**64**	**0.5**
MIC_{90}	**2**	**>4**	**>64**	**>4**

* resistant to ≥ 3 antibiotic classes

cellceutix

Gram-Negative Program Summary

HDP mimics for CRE infections

- **Gram-negative activity evident in several structural series of small non-peptidic mimetics of host defense proteins**
- **2 series show low cytotoxicity, favorable PK properties and robust efficacy *in vitro* and *in vivo* against *Enterobacteriaceae* organisms**
- **CC-1807 is potently active against clinical isolates of *E. coli, K. pneumoniae* and *E. cloacae*, including MDR CRE strains**
- **Additional preclinical efficacy studies with CC-1807 are in progress**
  - **Dose optimization in lung infection models**
  - **UTI and bacteremia**
- **Chemical optimization of CC-1807 and additional analogs is continuing**
  - **Expand coverage to *Pseudomonas* and *Acinetobacter* spp.**

Cellceutix Corporation
Beverly, MA USA
www.cellceutix.com

A New Class Of Antimicrobials—The HDP Mimics
Cellceutix Corporation

QIDP Educational Breakfast

May 21, 2015