Session 1

Alternatives to Antibiotics: Lessons from Nature

Antimicrobials in animal health – Lessons from nature

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Alternatives to Antibiotics

Begin at the End

- **Is there a need?**

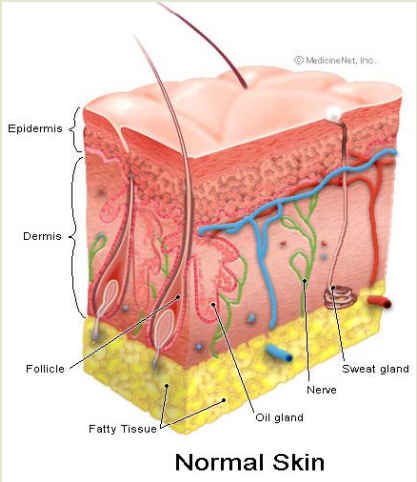
O is for Outbreak
When a drug-resistant salmonella struck a Vermont farm, health officials knew it might be just the beginning
Troubled paradise
& WORLD REPORT
U.S.News
November 24, 1997

Alternatives to Antibiotics

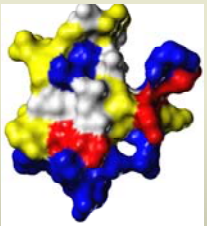
Begin at the End

- **Is there a need?**
- **Does it work?**
- **Is it cost effective?**
- **Will it be accepted?**

Host Defense Against Microbes



Physical barriers



Cells

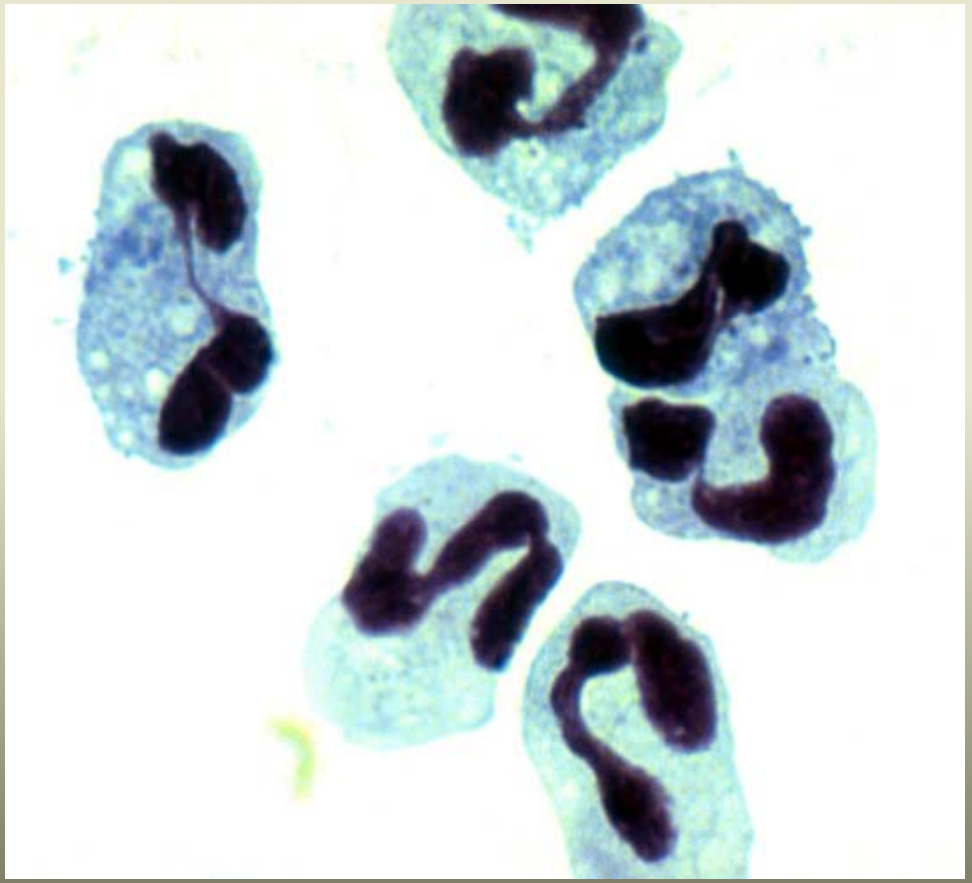
Antimicrobial peptides

Adapted from Ganz T, 2003

What are Antimicrobial Peptides?

PMNs

Neutrophils

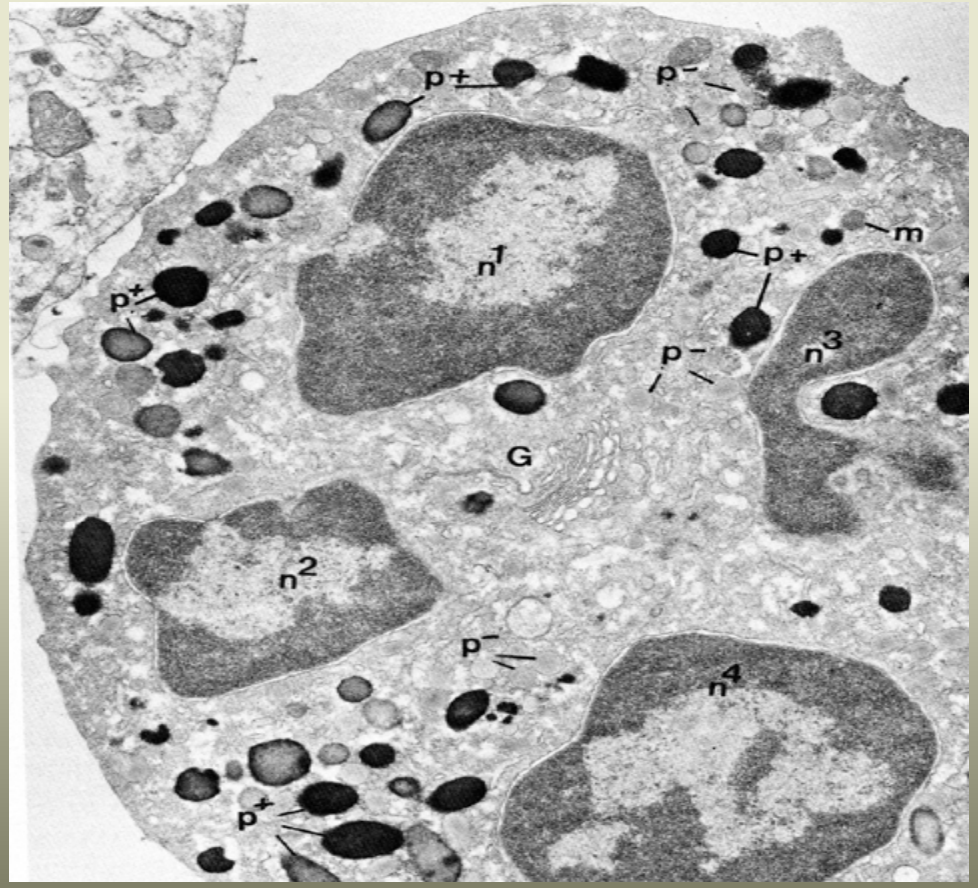


Host Defense Against Microbes

Antimicrobial peptides:

PMN

Neutrophils



Bainton, 1992

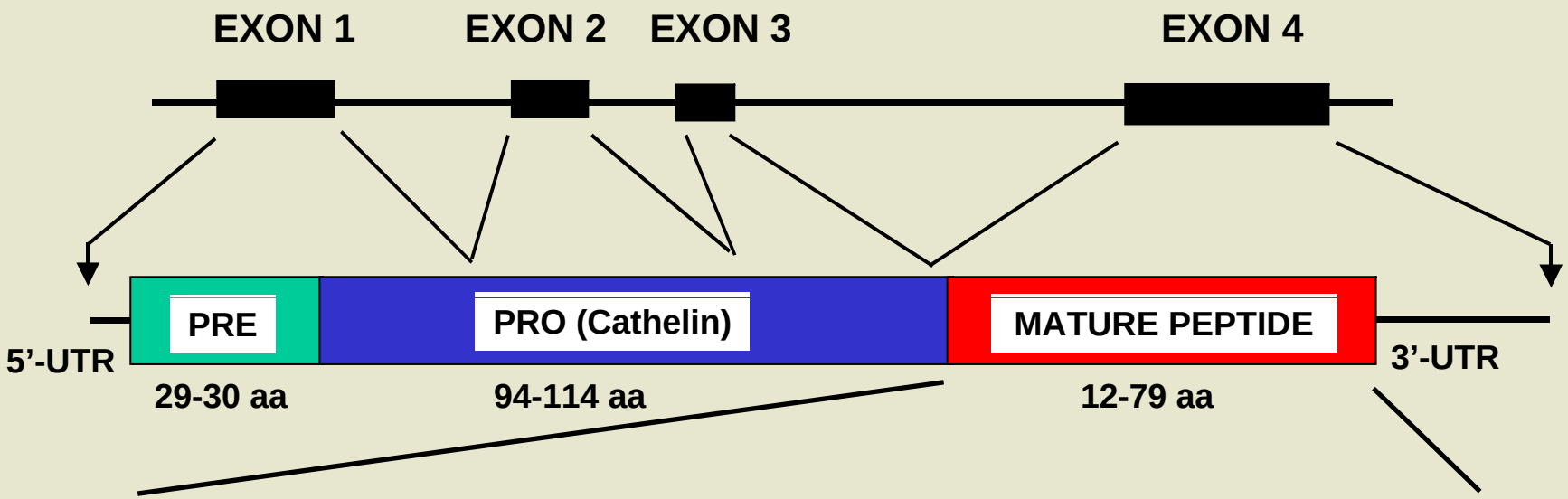
AMP Classification

Cathelicidins

Defensins

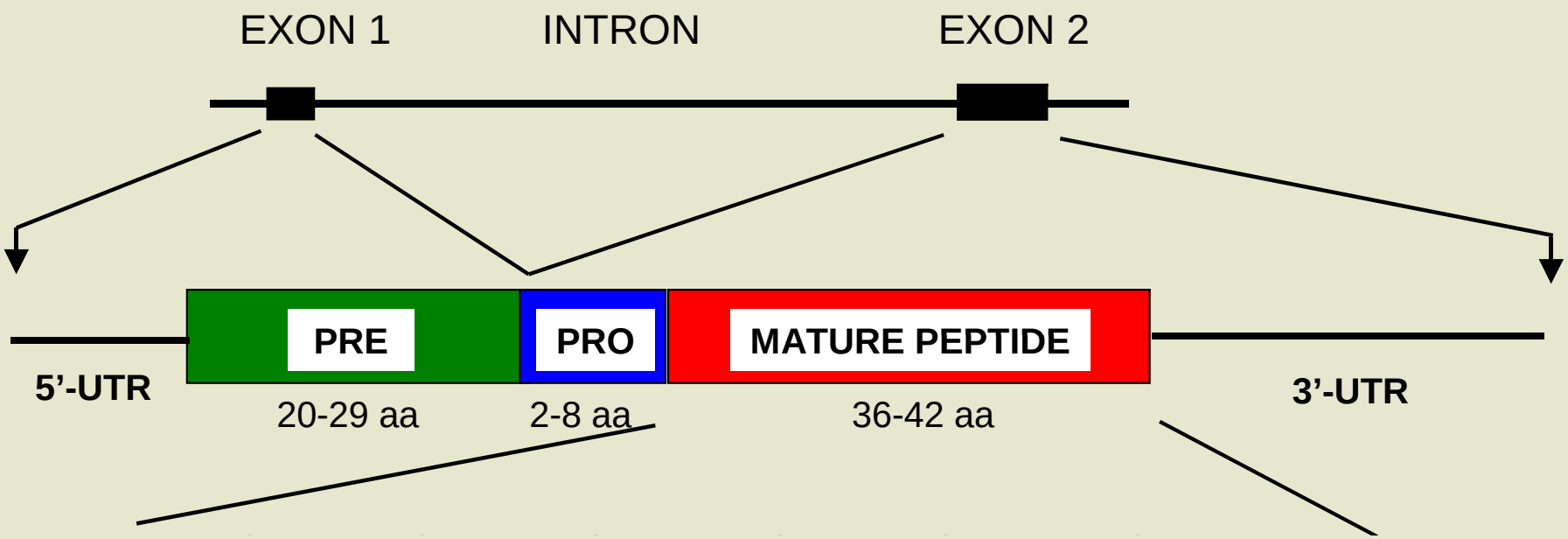
- alpha
- beta
- theta

Cathelicidins



Porcine	Bovine	Ovine	Lapine	Human	Equine	Murine
PR-39	Bac-5	SMAP-29	CAP-18	LL-37/	eCATH 1-3	CRAMP
PG 1-5	Bac-7	Bac-7.5	p-15s	hCAP-18		
PF 1-2	BMAPs	Dodecapeptide				
PMAPs	Indolicidin					
	Dodecapeptide					

Beta Defensins

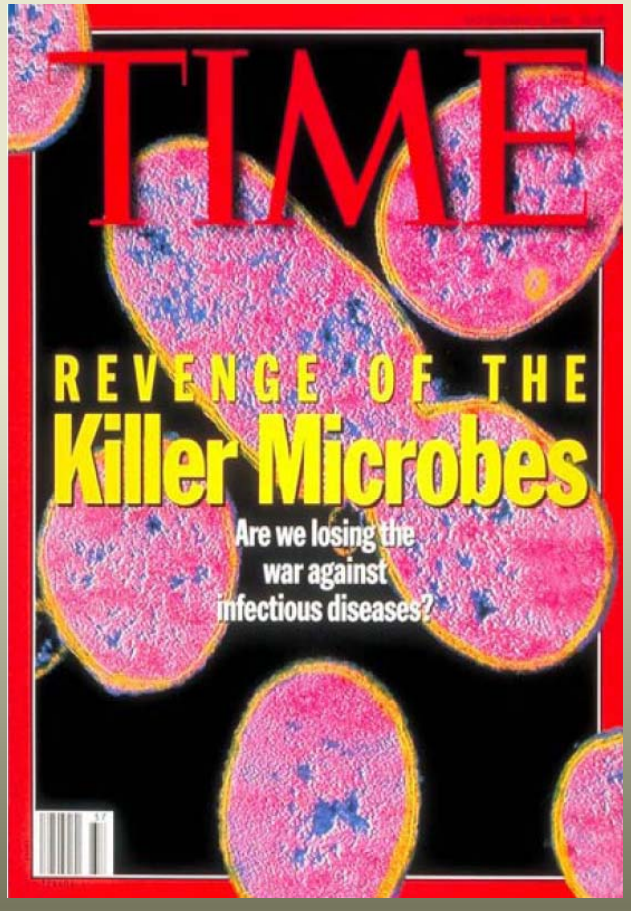


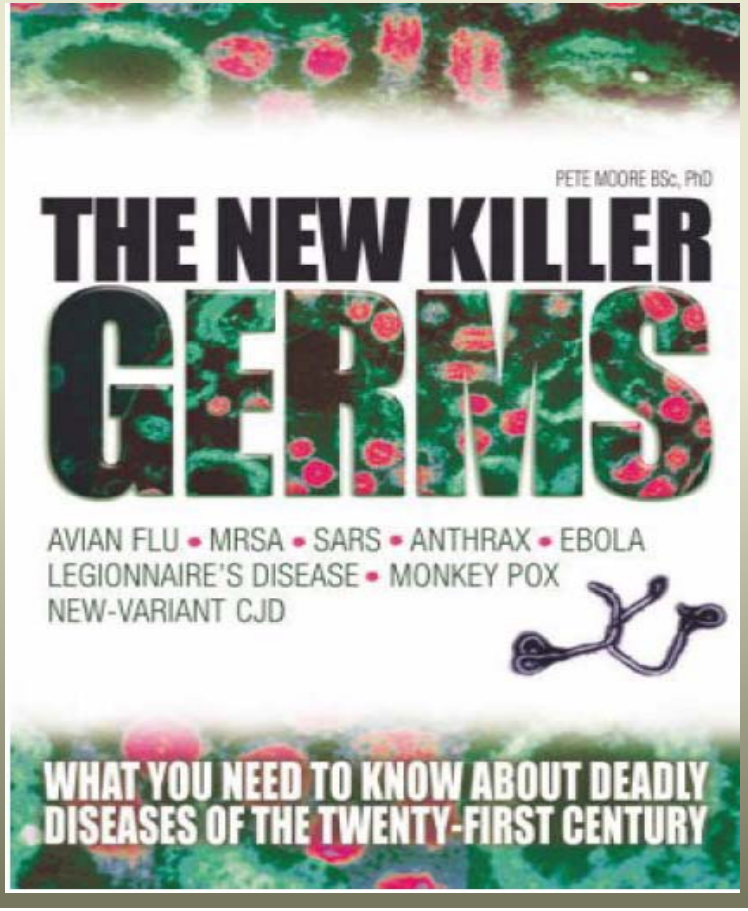
Porcine	Bovine	Avian	Murine	Ovine	Caprine	Human
pBD-1	TAP	GAL 1-2	mBD 1-6	sBD 1-2	gBD 1-2	hBD 1-4
	LAP	THP 1-2	rBD 1-2			
	EBD					
	BNBD 1-13					

Sang et al., Mamm. Genome, 2006, 17:332

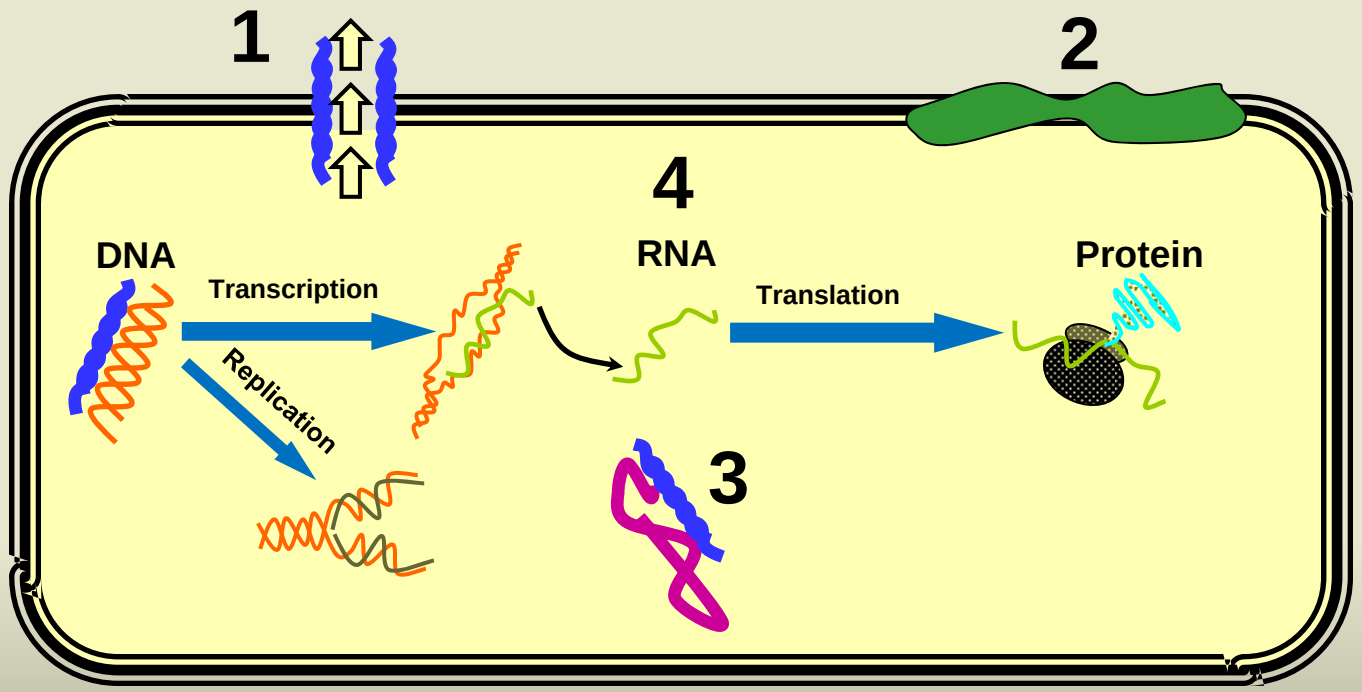
Why AMPs?

- Potential for novel antimicrobials
- Active against a broad spectrum of microbes
- Difficult for microbes to develop resistance



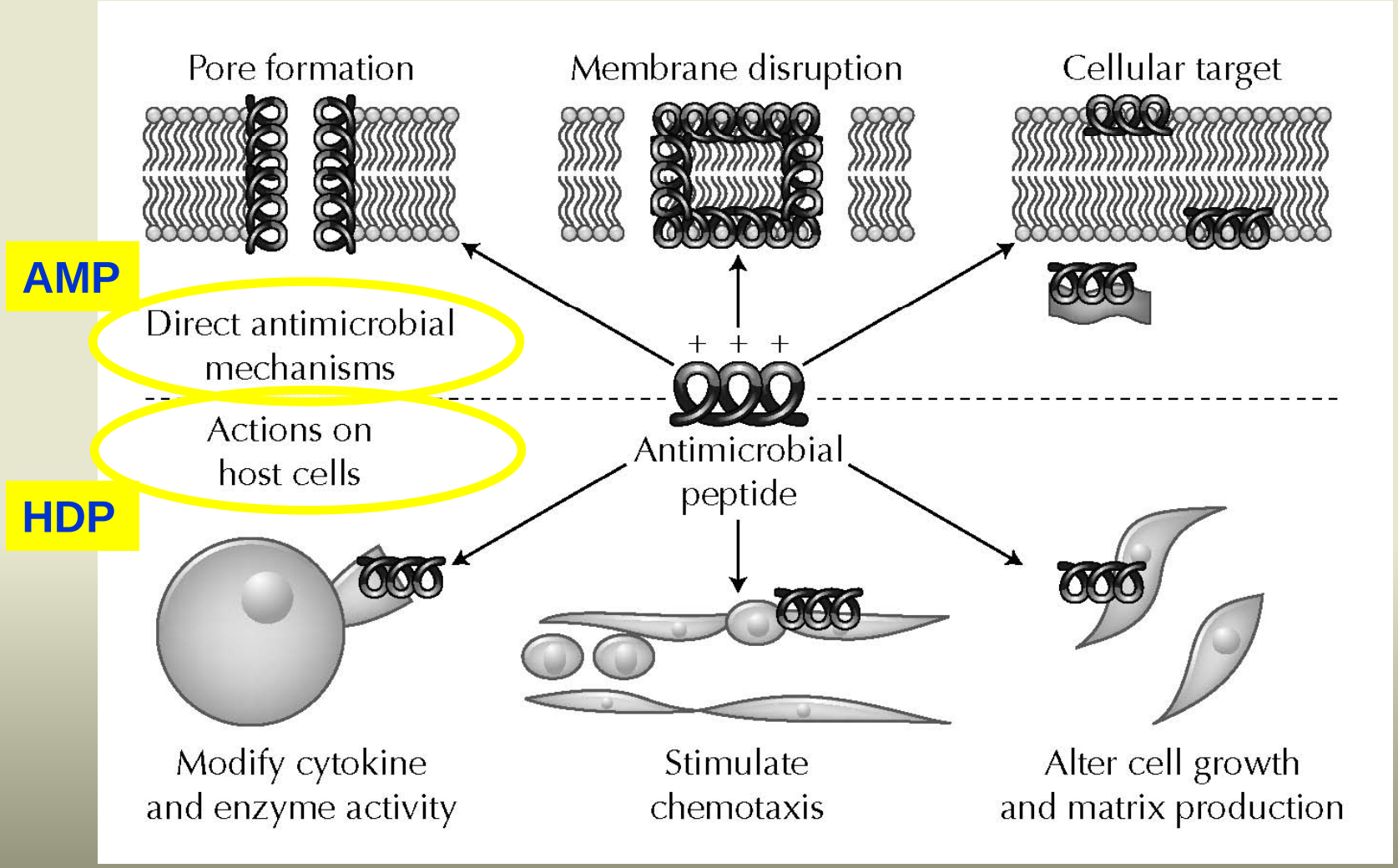


AMP Mechanism of Action



Adapted from Radek and Gallo, Semin Immunopathol 2007, 29:27-43

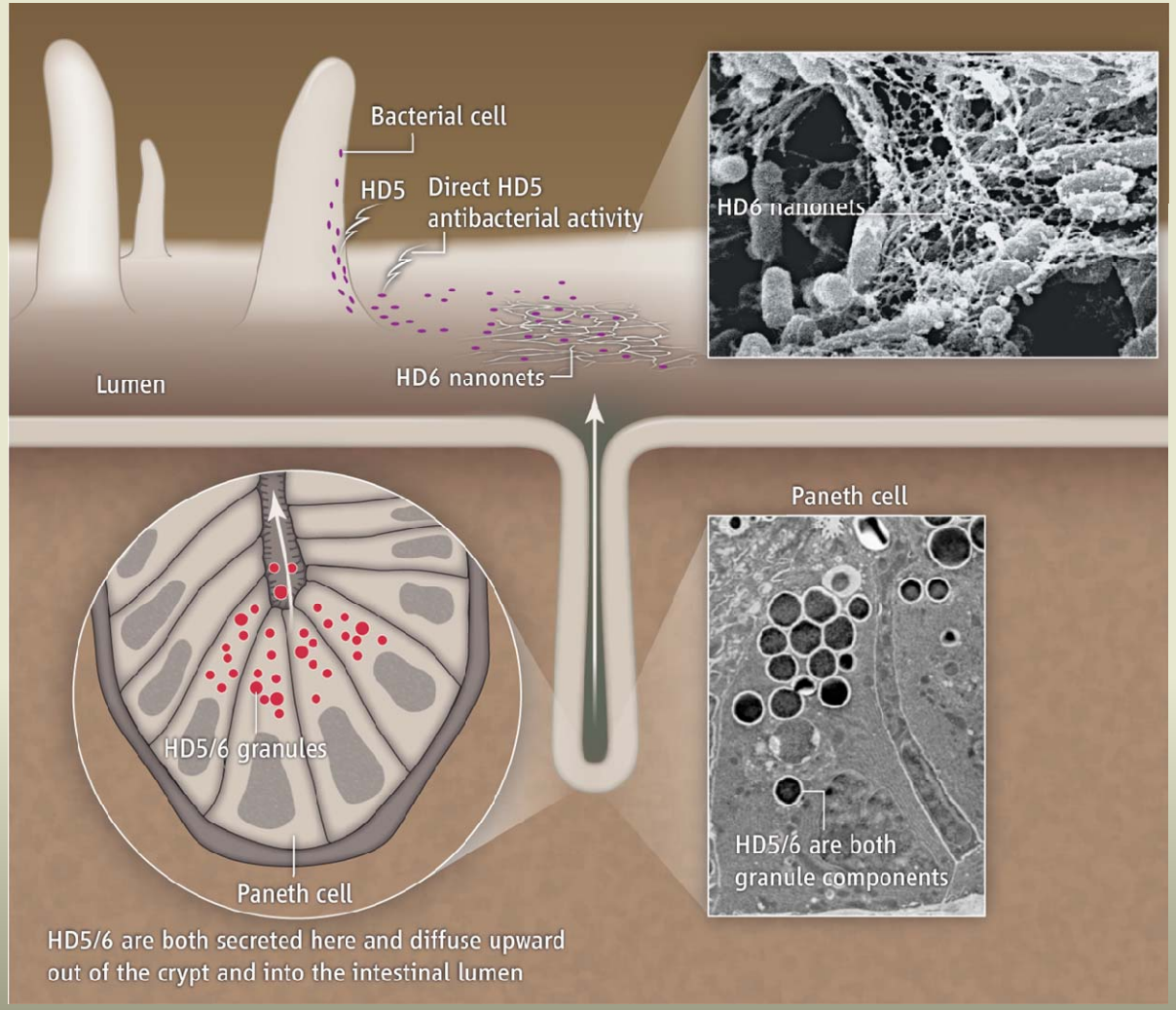
AMP or Host Defense Peptide



Modified from Gallo and Nizet, Curr Allergy Asthma Rep. 2003, 3:402-9.

In Vivo Activity?

HD6 nanonets confer mucosal immunity



Ouellette and Selsted, Science 2012;337:420-421

Lessons from the Pig

PR-39, an Amphipathic Peptide

RRRPRPPYLPRPRPPPFFPPRLPPRIPPGFPPRFPPRFP

Proline = 48.7% Arginine = 25.6%

Basic, Neutral Polar, Nonpolar

PR-39 and Analogues

PR-14(1-14) RRRPRPPYLPRPRP

PR-16(11-26) RPRPPPFFPPRLPPRI

PR-15(25-39) RIPPGFPPRFPPRFP

PR-27(13-39) RPPPFFPPRLPPRIPPGFPPRFPPRFP

PR-39 RRRPRPPYLPRPRPPPFFPPRLPPRIPPGFPPRFPPRFP

1 10 20 30 39

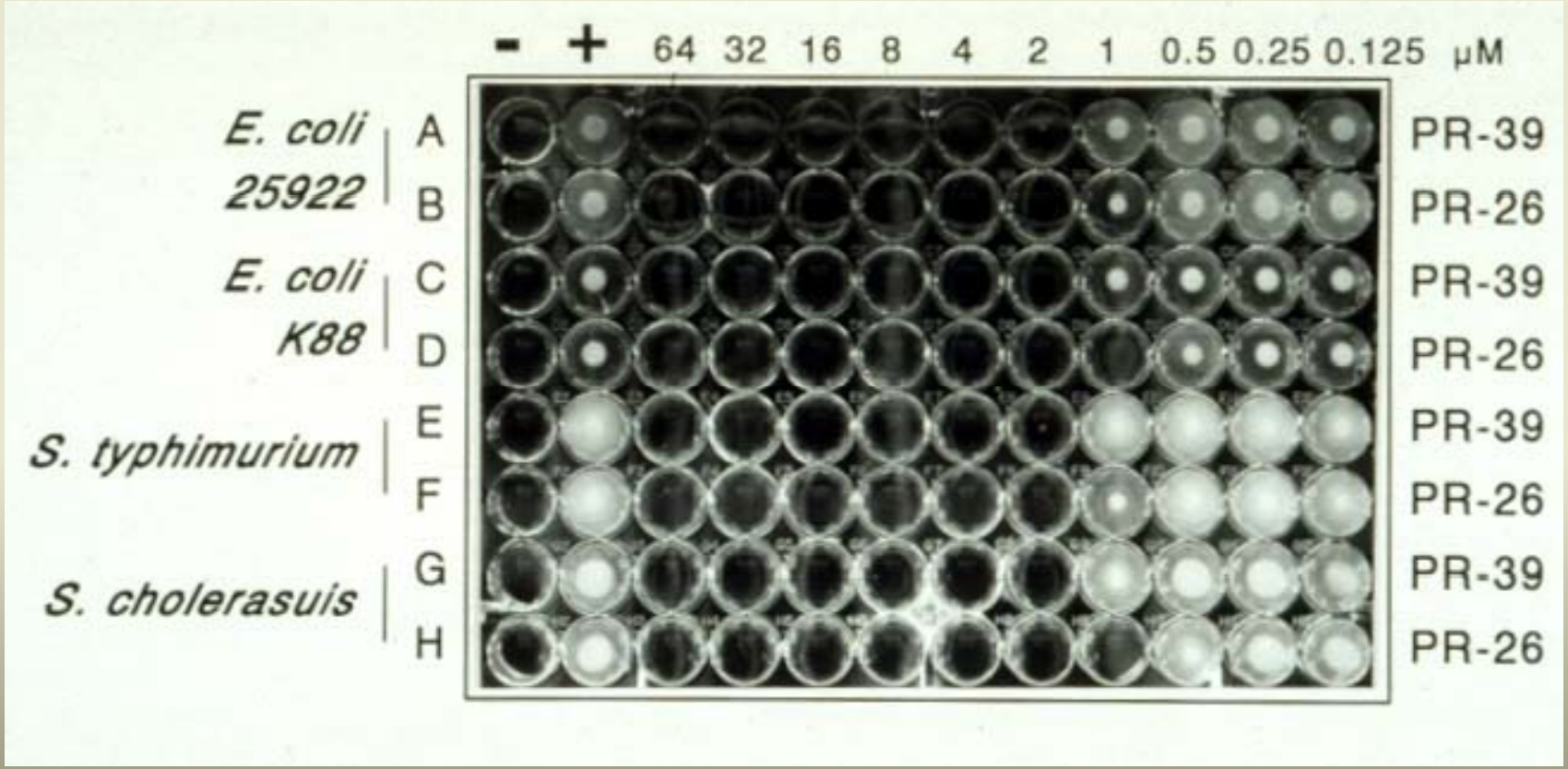
PR-26(1-26) RRRPRPPYLPRPRPPPFFP PRLPPRI

PR-19(1-19) RRRPRPPYLPRPRPPPFFP

PR-23(4-26) PRPPYLPRPRPPPFFPPRLPPRI

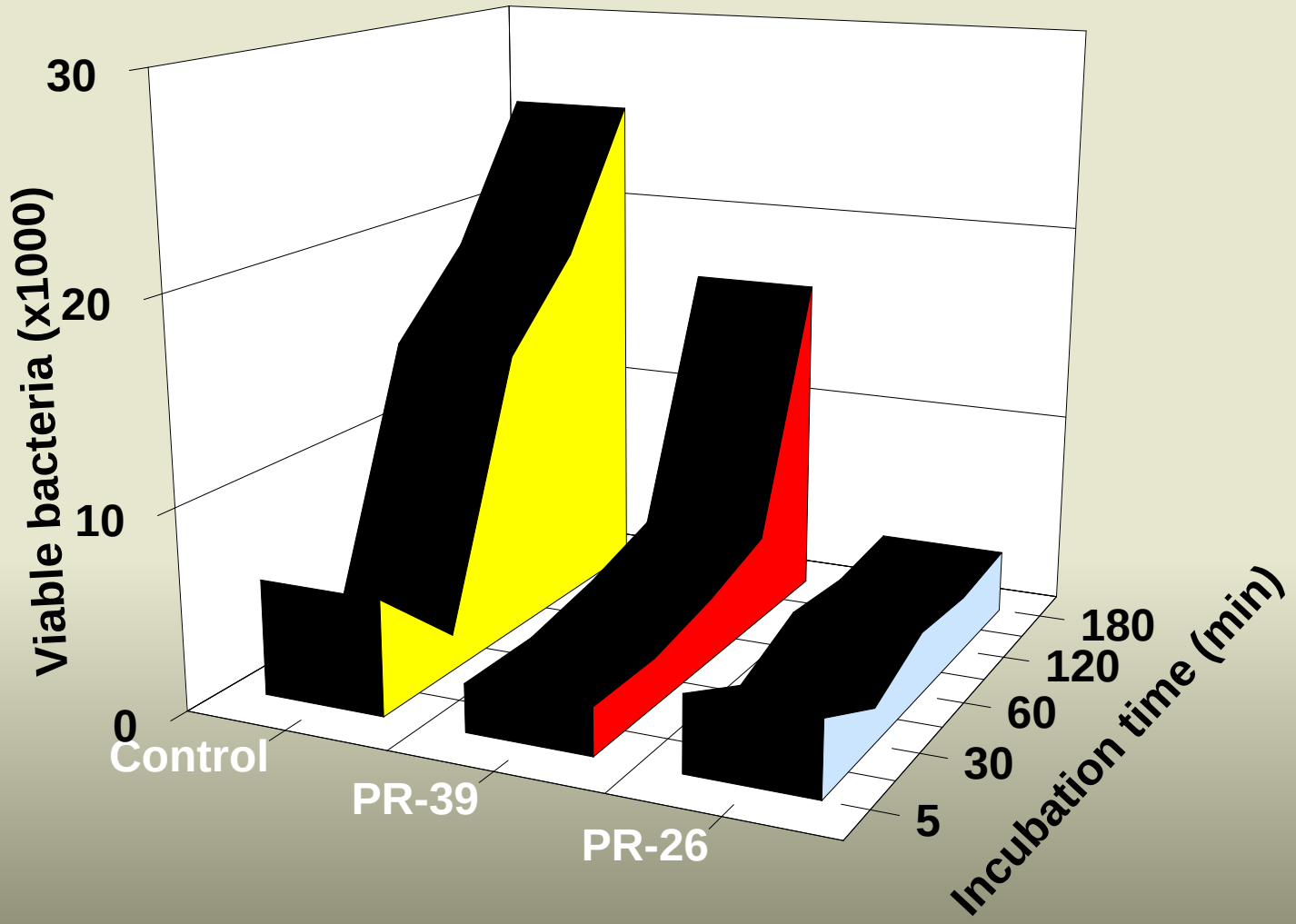
PR-26^{G}(1-26) RRRPRGPYLPRPRPPPFFPPRLPPRI

Minimal Inhibitory and Bactericidal <u>Concentrations of PR-39 & PR-26</u>



Shi et al., Antimicrobial Agents Chemotherapy 1996, 40:115-121

Inhibition of *Salmonella* Typhimurium Invasion



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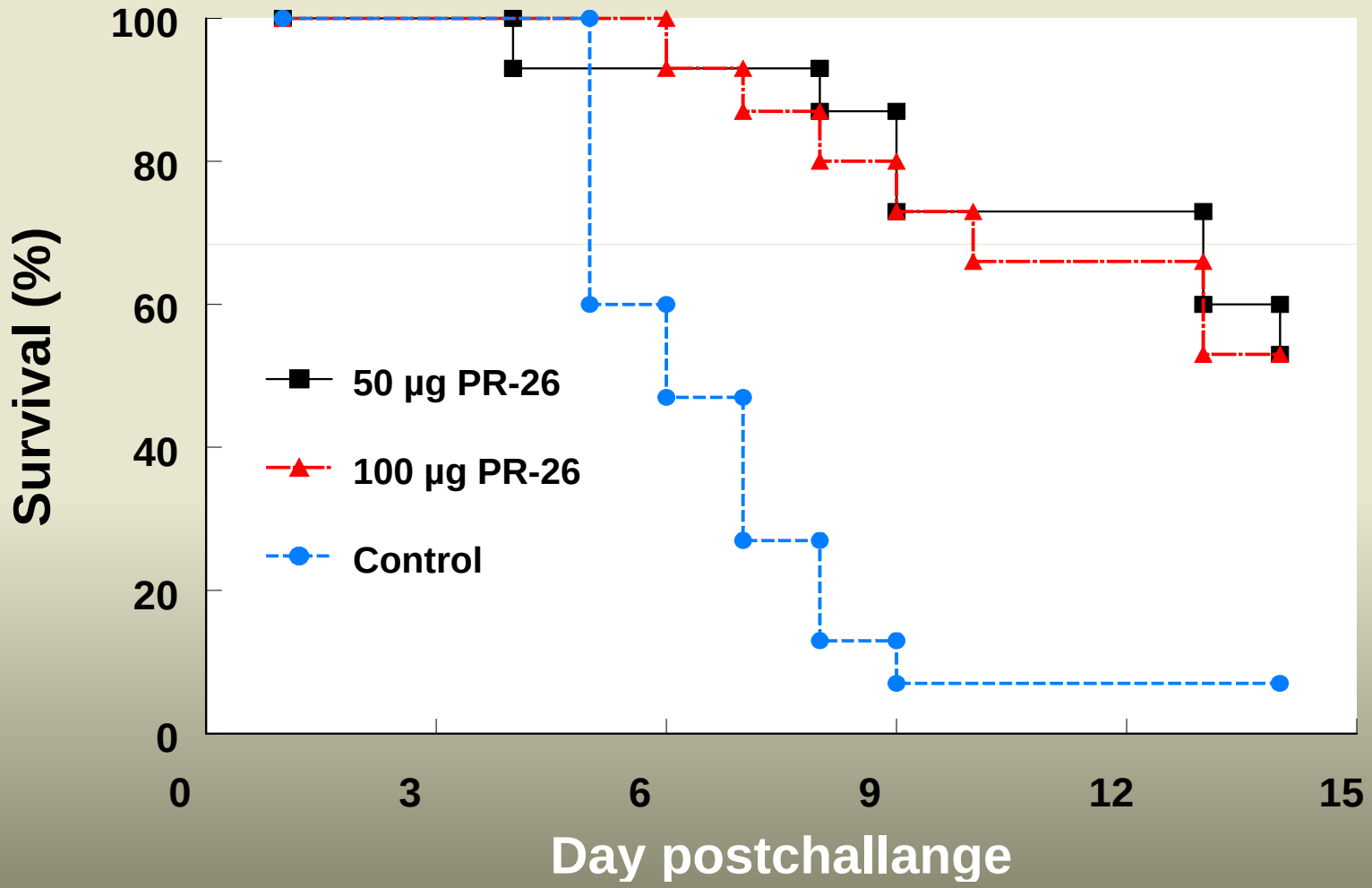
Increased Resistance to *Salmonella* Typhimurium



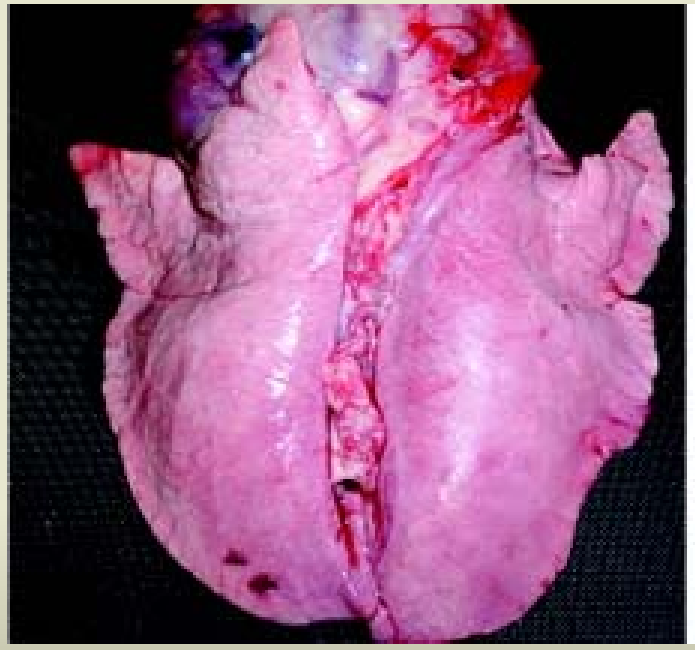
Shi et al., Antimicrobial Agents Chemotherapy 1996, 40:115-121

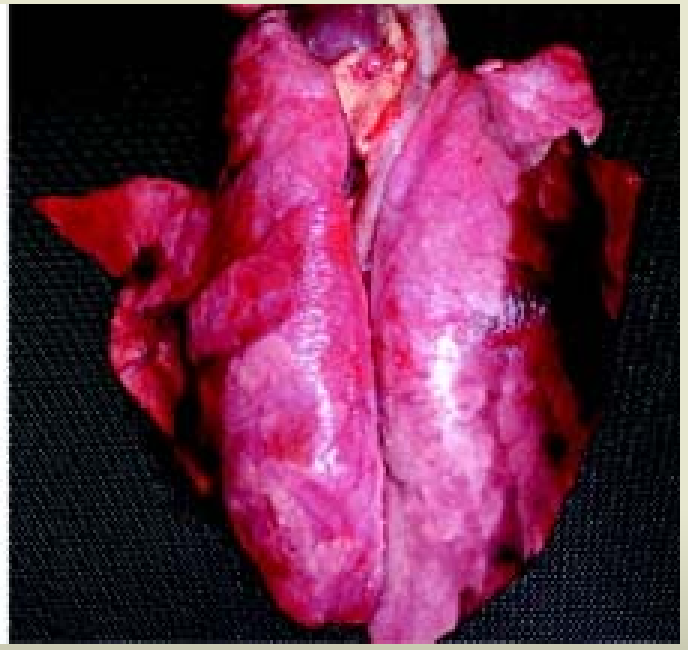
pBD-1 Protects against *B. pertusis*

Treated with pBD-1 **Non-treated**

Days Post Challenge

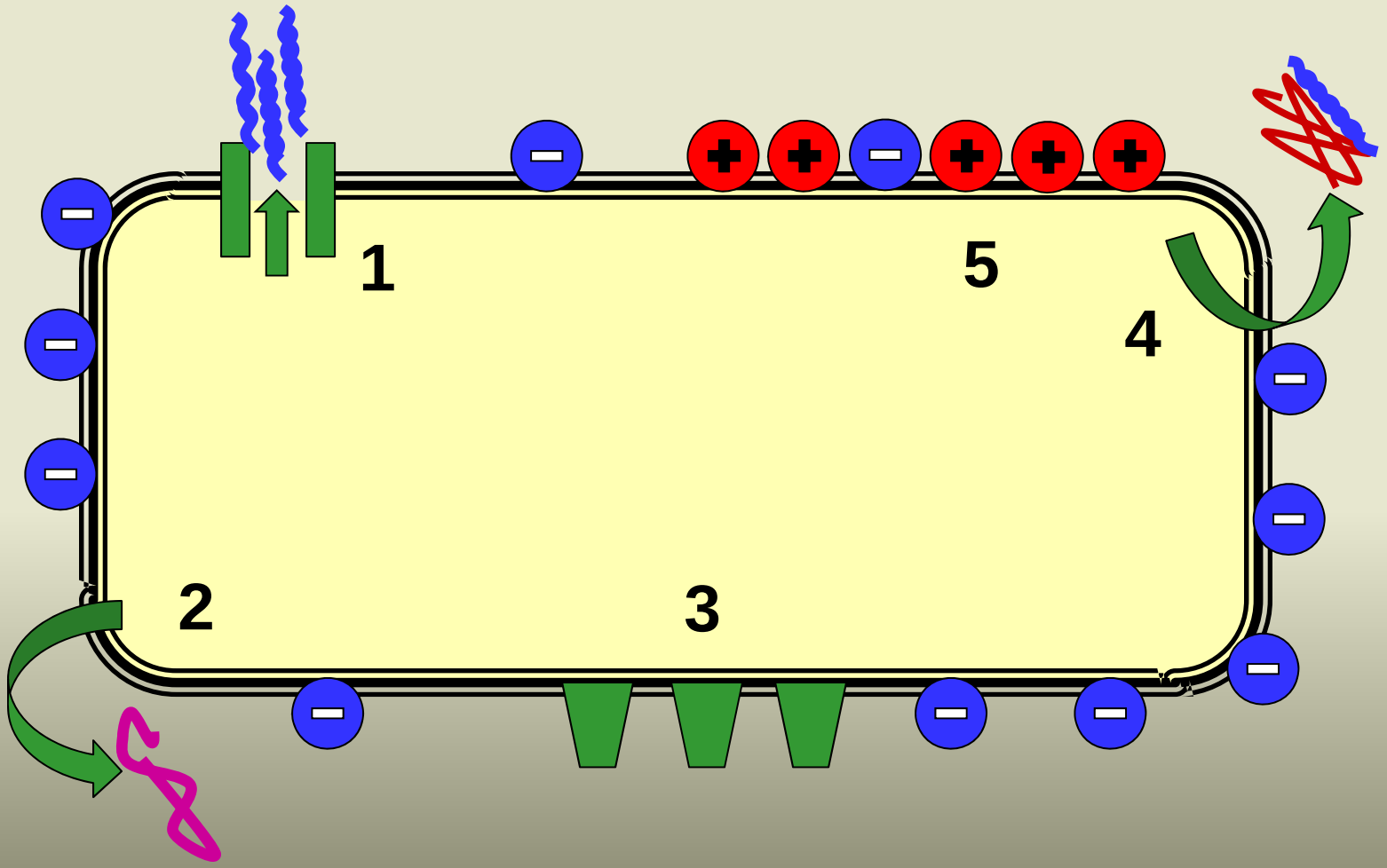
4





Elahi et al., Infect Immun 74:2338, 2006

Bacterial Resistance to AMP?



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Acknowledgments

K-State

Yongming Sang
Chris Ross
Bob Rowland
Danielle Goodband

UCLA

Bob Lehrer
Piotr Ruchala

USDA & NIH

Thank You