

Pfizer Animal Health

State of Antibiotic Development – Staying one step ahead?

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Disclosures

- Conflict of Interest Disclosure
 - Employee of Pfizer Animal Health
 - Pfizer Animal Health is engaged in the discovery, development and marketing of antibacterials used in companion animals and livestock

Presentation Topics

- Overview of the Antibacterial Drug Discovery Processes
- Antibacterial Drug Discovery in Human Health
- Antibacterial Drug Discovery in Veterinary Medicine
- The Search for Novel Substrate
- Summary

The Antibacterial Discovery Process



Human and Animal Health R&D Processes



↑ **First in Man Studies**
(Requires IND or Equivalent)

12–15 years
800M - 1.5 B

Human Health Discovery

↓ **First Target Animal Studies**
(Does not require INAD)



8–12 years
100 – 125 M

Animal Health Discovery

Initiating the Discovery Process – Beginning with the end in mind

Begins with a Target Profile

- Label Claim (treatment of X disease caused by X organisms)
- Market differentiators (single dose, oral, etc.)
 - Requires knowledge of current and future market conditions
- Market value

Key Points

- Investment is made at risk
- Assumes a defined regulatory process for that class of agent
- Timeline for process is 10 – 15 for HH and 8–12 years for AH

Innovation is driven by the profile

- Profile should reflect the markets needs at time of approval
- No incentive for “me too” drugs
 - Primary differentiators
 - Convenience
 - Cost
 - Compliance
 - Cures (Efficacy)
- Antibacterial Discovery Scientist must be keenly aware of usage patterns, shortcomings of current products, and emerging resistance trends to predict future needs

Current State of Antibacterial Discovery

- Many large pharmaceutical companies have exited the area
 - Short term use compared to chronic use
 - Older, cheaper agents are still useful for many infections
 - Reserving drugs due to resistance limits markets
 - Restricting use of new drugs limits markets
 - Identification of novel targets/leads becoming more difficult
 - Lower ROI for Antibacterials compared to other drugs
 - Shift to external programs have changed the cost structure

Miller and Miller, Emerging Trends in Antibacterial Discovery, 2011

Talent Loss is at a Critical Point!

- **E** How many people know a person that is an expert in antimicrobial agents? **cused**
On developing new programs
 - Little focus on retaining experienced talent
- **H** How many people know someone that has taken a new compound from discovery to an approved antibacterial?
 - External attitude that any well trained microbiologist can do it

As programs are closed, the talent disperses and must be reconstituted for any new program. The reality is that even a short term program pause will result in a 12-15 year delay in new compounds reaching the market place.

AB Discovery Size and Expertise (per molecule)

Assumes a core group of scientists that have experience in successful programs

Early Discovery

- Microbiologists (4-6)
- Medicinal Chemists (4-8)
- Screening Scientists (3-5)

Late Discovery

- Microbiologists (4-6)
- Pharmacologists (1-3)
 - Toxicologists (1-3)
 - Pathologists (1-2)
 - EA Scientists (1-2)
- Formulation (1-2)
 - Pharm Sci (1-3)
- Manufacturing (1-3)

Development

- Microbiologists (4-6)
- Pharmacologists (1-3)
 - Toxicologists (1-3)
 - Pathologists (1-2)
 - EA Scientists (1-2)
- Formulation (1-2)
 - Pharm Sci (1-3)
- Manufacturing (1-3)
- Clinical Research Scientists (3-5)
- Regulatory (1-2)

10-15 years

Oxazolidinones – A Successful Program Example

- 1985: Dr. Charles W. Ford initiated an Antibacterial Program targeting resistant Gram-positive pathogens
 - Based on resistance trends from Asia
 - Differentiated from vancomycin
- 1987: Dr. Steve Brickner identified the DuPont oxazolidinones as potential substrate for the new program
- 1988: Team realized that toxicity was driver for program.
 - Instituted 30 day rodent tox screen as part of early lead identification
- 1994: Linezolid and Eperezolid synthesized
 - Linezolid chosen as lead based on Phase I Pharmacokinetics data
- 1995: VRE and MRSA emerge as major problem
 - Linezolid receives fast track status with FDA-CDER
- 2000: Linezolid approved

Antibacterial Discovery in Human Health



Current Resistance Issues in Human Health

Methicillin-resistant *Staphylococcus aureus*

Carbapenamase-producing Enterobacteriaceae

MDR/XDR *Mycobacterium tuberculosis*

MDR *Streptococcus pneumoniae*

MDR *Neisseria gonorrhoea*

Methicillin-Resistant *S. aureus*

- Resistance conferred by the *mecA* gene carried as part of the staphylococcal cassette chromosome (*SCCmec*)
 - Resistant to all beta-lactams except newer MRSA cephalosporins
 - Human associated MRSA
 - Hospital acquired strains (HA-MRSA) emerged in 1980s
 - Community acquired strains (CA-MRSA) emerged in mid-1990s
 - Animal associated MRSA
 - Livestock associated MRSA (LS-MRSA) emerged in 2000s
 - Primarily associated with pigs
 - Host adapted unique clonal type (CC398)
 - Companion animals
 - Transmitted from Humans to dogs (humanosis)

Treatment Options for MRSA in Human

- Current treatment options for MRSA
 - NLTi: SXT, clindamycin, doxycycline or minocycline, linezolid
 - LTI: Vancomycin, linezolid, daptomycin
- New compounds in the pipeline
 - Oxazolidinones:
 - Profile: broader spectrum, improved dosing, improved safety
 - Radezolid, Tidezolid (torezolid)
 - Beta-lactams
 - Profile: MRSA active cephalosporin
 - Ceftalorine, ceftobiprole
 - New compounds:
 - Depsipeptide (WAP-8294A), rugulosins

Carbapenamse-producing Enterobacteriaceae (CRE)

- CREs were rare prior to 1992
 - *Klebsiella pneumoniae* carbapenamase (KPC) emerged in 2000s and is most common in US.
 - Metallo- β -lactamases (MBL)
 - Originally described in *Pseudomonas* spp.
 - In 2009, the New Delhi MBL was first recognized in *K. pneumoniae*
 - Rapidly worldwide dissemination
 - Resistant to all β -lactams including carbapenamams
 - Commonly resistant to agents used to treat Gram-negative infections including fluoroquinolones and aminoglycosides

International dissemination of New Delhi metallo- β -lactamase (NDM)–producing Enterobacteriaceae.



Gupta N et al. Clin Infect Dis. 2011;53:60-67

Clinical Infectious Diseases

Treatment Options for CRE in Human

- Current therapeutic options
 - Tigecycline, polymyxins (colistin), Aztreonam
- Rapid emergence/dissemination of NDM-1 strains has left a gap in the antibacterial discovery pipeline
 - Renewed interest in polymyxins
 - Profile: Better safety profile, Improved dosing
 - Novel carbapenems
 - Profile: active against CRE
 - Razupenem
 - Monobactams
 - Profile: active against CRE
 - Tigemonam

Antibacterial Discovery in Animal Health



Past and Future Sources of AH AB Substrate

2000s – HH and AH targets have diverged

1980s

- Fluoroquinolones
- 3rd Gen Cephs
- Florfenicol

1990s

- 4th Gen Cephs
- Novel Macrolides

Human Health Programs

- MRSA
- MDR Pneumococci
- MDR Gram-Negatives
- MDR TB

Animal Health Programs

- Livestock
 - Respiratory Disease
 - Enteric Disease
- Companion Animals
 - SSTI
 - UTIs

This severely limits the ability of AH to leverage substrate!

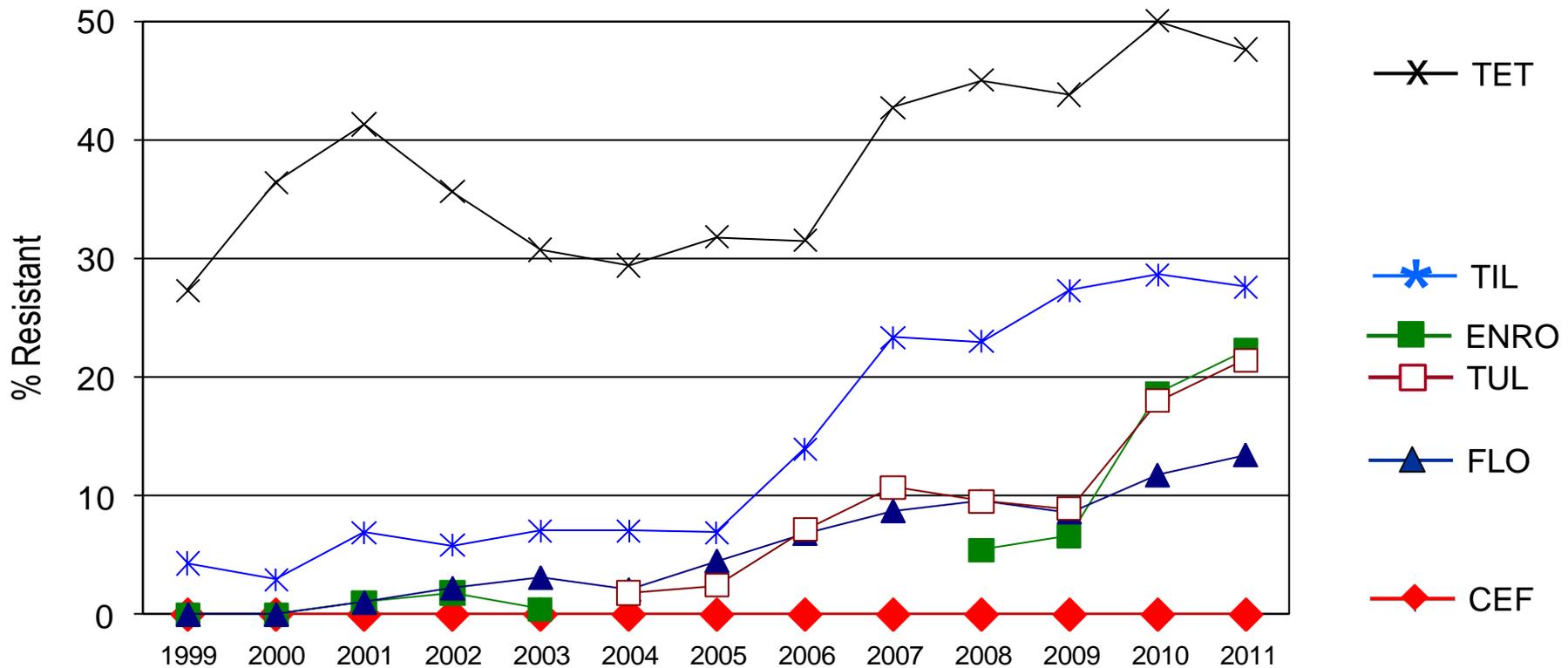
Will Resistance in Target Pathogens become a driver in AH?

- Resistance has not be a primary driver in AH for past two decades
 - Primary drivers have been convenience and cost
 - In Livestock, antibacterials are part of an overall disease management program that includes biosecurity and vaccination programs
- Resistance may be emerging as a primary reason in several animal species
 - Companion animals
 - Methicillin resistant *Staphylococcus pseudintermedius*
 - Beef Cattle
 - MDR *Mannheimia haemolytica*

MRSP in Companion Animals

- *Staphylococcus pseudintermedius* is the normal, resident coagulase-positive staphylococcus in dogs and cats
 - Formerly classified as *S. intermedius*
 - MRSP first reported in 1996
 - Resistance mediated by the *mecA* gene
 - Prevalence has been reported as 0-30%
 - Highest rates in referral hospitals
 - Community rates appear to be increasing
- Treatment Options:
 - Clindamycin, SXT, fluoroquinolones, chloramphenicol
 - Reserved: vancomycin, linezolid

Bovine *Mannheimia haemolytica* % Resistant 1999-2011



2011 results are preliminary
Total isolates in graph: n=3827

TET- Tetracycline
TIL- Tilmicosin
TUL- Tulathromycin

FLO- Florfenicol
ENRO- Enrofloxacin
CEF- Ceftiofur

ICE *Pmu1* and resistance gene regions from multi-drug resistant *P. multocida* 36950

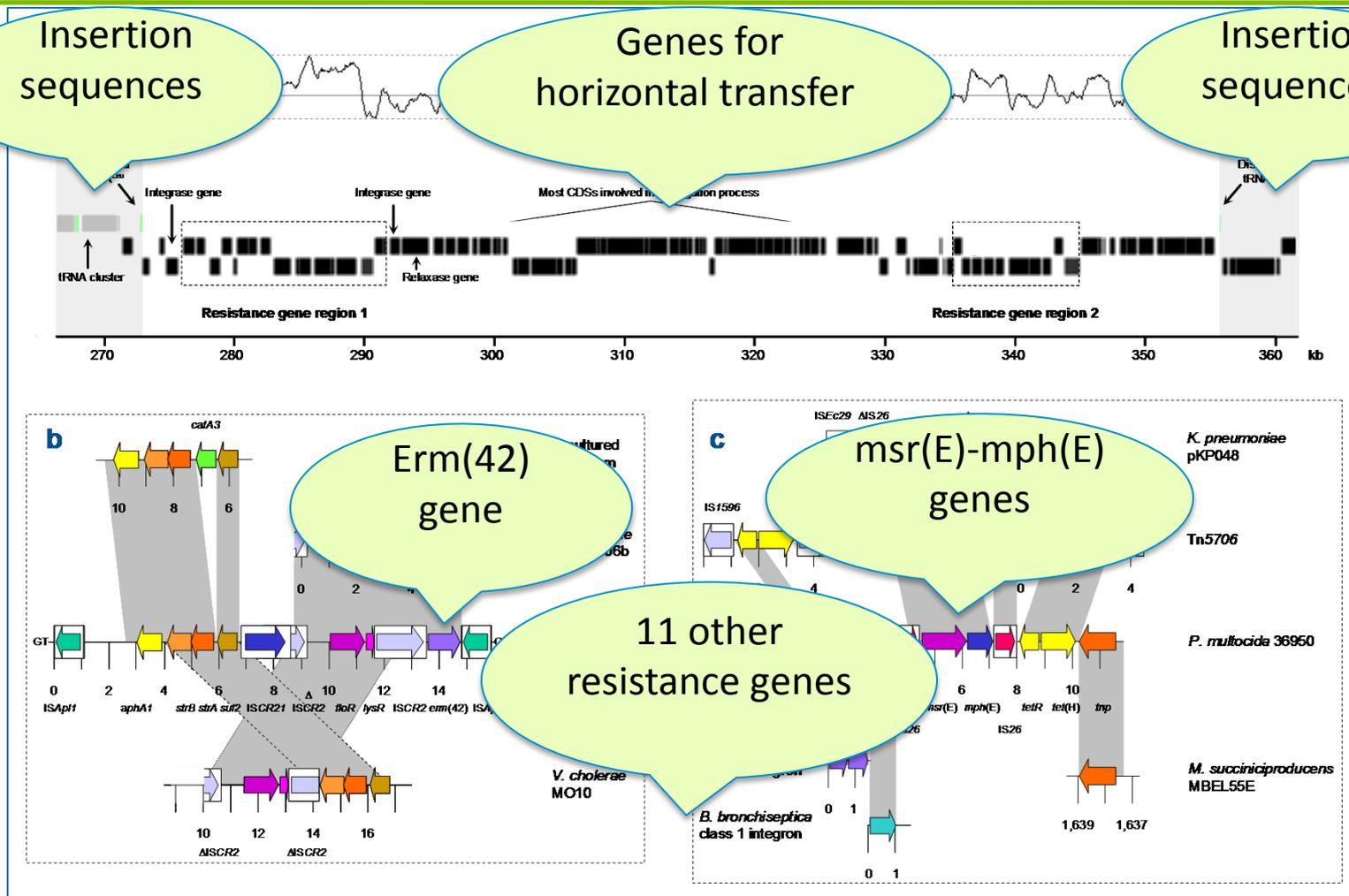


Fig. 2: Schematic presentation of ICE *Pmu1* (a) and the resistance gene regions 1 (b) and 2 (c). Genes are presented as arrows with the arrowhead indicating the direction of transcription. Insertion sequences and ISCR elements are shown as boxes with the arrows inside the boxes indicating the transposase genes. Grey shaded areas indicate areas of >95% sequence identity.

The Search for Novel Substrate



Novel Substrate Sources for AB Discovery

Antibacterial programs are dependent upon novel targets and substrate to fill the pipeline

- Substrate: may be new class or novel analog within a class. Usually active against a known target. Most amenable to rapid development against a recently emerged resistant pathogen. Usually obtained from startups, smaller companies, or from other programs (internal and external)
- Targets: Novel targets that have been recently defined. Most often within an existing bacterial process such as the ribosome but may be an entirely new target. Usually obtained through academic alliances or literature
- Approaches: Systematic process to define a novel target to exploit. Most often obtained through academic alliances. Longer term process

Traditional Sources of Novel Substrate

- Novel Classes
 - May exploit an existing target or novel target
 - Longest total program time
 - AH may be able to utilize compounds discarded by HH programs due to delivery or safety issues that are not of concern in AH
- Re-exploration of older generations of existing classes
 - Initiate chemistry program to develop novel analogs within an older class
 - Resource intensive due to chemistry needs
 - Resistance more likely to emerge more quickly
 - AH will need to tune spectrum for veterinary use

New Antibiotics approved since 2000

Year	Name	Class	Lead (source)
NP-derived			
2002	Biapenem	b-Lactam (carbapenem)	Thienamycin
2002	Ertapenem	b-Lactam (carbapenem)	Thienamycin
2005	Doripenem	b-Lactam (carbapenem)	Thienamycin
2009	Tebipenem pivoxil	b-Lactam	(carbapenem)
2008	Ceftobiprole medocari	b-Lactam	(cephalosporin)
2010	Ceftaroline fosamil	b-Lactam	(cephalosporin)
2001	Telithromycin	Macrolide (ketolide)	Erythromycin
2003	Daptomycin	Lipopeptide	(actinomycete)
2005	Tigecycline	Tetracycline	(actinomycete)
2007	Retapamulin	Pleuromutilin	(fungus)
2009	Telavancin	Glycopeptide	(actinomycete)
Synthetically-derived			
2000	Linezolid	Oxazolidinone	Oxazolidinone
2002	Prulifloxacin	Fluoroquinolone	Quinolone
2002	Pazufloxacin	Fluoroquinolone	Quinolone
2002	Balofloxacin	Fluoroquinolone	Quinolone
2004	Gemifloxacin	Fluoroquinolone	Quinolone
2007	Garenoxacin	Quinolone	Quinolone
2008	Sitafloxacin	Fluoroquinolone	Quinolone
2009	Antofloxacin	Fluoroquinolone	Quinolone
2009	Besifloxacin	Fluoroquinolone	Quinolone

Compounds in Phase III or Under Evaluation

Name	Lead	Mode of Action
Fidaxomicin	Tiacumicin	RNA Synthesis Inhibition
Amadacycline	Tetracycline	Protein Synthesis Inhibition
Torezolid phosphate	Oxazolidinone	Protein Synthesis Inhibition
Oritavancin	Glycopeptide	Cell Wall Inhibition
Dalbavancin	Glycopeptide	Cell Wall Inhibition
Cethromycin	Macrolide (Ketolide)	Protein Synthesis Inhibition

Compounds in Phase II

Name	Lead (Source)	Mode of Action
ACHN-490	Aminoglycoside	Protein Synthesis Inhibition
BC-3781	Pleuromutilin	Protein Synthesis Inhibition
CB-183,315	Daptomycin	Membrane Depolarization
Ramoplanin	Ramoplanin	Protein Synthesis Inhibition
TP-434	Tetracycline	Protein Synthesis Inhibition
Solithromycin	Erythromycin	Protein Synthesis Inhibition
CXA-101	Cephalosporin	Cell Wall Inhibition
GSK1322322	Actinonin	Peptide Deformylase
PMX-3006381-86	Defensin	Cell Membrane Lysis
NVC-422	N-chlorotaurine	Oxidation
ACT-179811172	Unknown	Unknown
Bedaquiline	Diarylquinoline	Mycobacterial ATP Synthase
SQ109	Ethambutol	Cell Wall Inhibition
OPC-67683	Nitroimidazole	Mycolic Acid Inhibitor
PA-824	Nitroimidazole	DNA and Cellular Damage
Delafloxacin	Fluoroquinolone	DNA Gyrase and Topo IV
Finafloxacin	Fluoroquinolone	DNA Gyrase and Topo IV
JNJ-32729463	Fluoroquinolone	DNA Gyrase and Topo IV
Zabofloxacin	Fluoroquinolone	DNA Gyrase and Topo IV
Nemonoxacin	Quinolone	DNA Gyrase and Topo IV
Iclaprim	Trimethoprim	Dihydrofolic Reductase
Radezolid	Oxazolidinone	Protein Synthesis Inhibition

Compounds in Phase I

Name	Lead	Mode of Action
BAL30072	Monobactam	Cell Wall Inhibition
BC-7013	Pleuromutilin	Protein Synthesis Inhibition
BC-3205	Pleuromutilin	Protein Synthesis Inhibition
Lotilibcin	WAP-8294A2	Phospholipid Binding
XF-73	Porphyrin	Membrane Perturbing
AZD9742	Unknown	Unknown
GSK2251052	AN2690	Aminoacyl t-RNA synthetase
AZD5847	Oxazolidinone	Protein Synthesis Inhibition
PNU-100480	Oxazolidinone	Protein Synthesis Inhibition
AFN-1252	Synthetic Lead	FabI Inhibition
FAB-001	Triclosan	FabI Inhibition
CG400549	Triclosan	FabI Inhibition

Non-Traditional Substrate

- Distinguished from traditional small molecules
 - Targeting virulence or other mechanisms that affect an organisms ability to cause disease but does not inhibit growth.
 - Large molecule substrate (i.e., peptides)
 - Bacteriophages (Phage Lysin Constructs)
- Sometimes referred to as “Alternatives to Antibiotics”
 - Not classic small molecule antibiotics (Biopharmas)
 - Are novel anti-infectives (antibacterials)
- Will be regulated using same pathways as traditional agents

Anti-Virulence as a Drug Target

- Goal is to inhibit specific mechanisms that promote infections and essential in the pathogenic cascade or cause disease symptoms
 - Adherence factors
 - Invasion
 - Host defense avoidance
 - Chemical signaling
 - Toxin production

Cegelski et al, Nature Rev. Microbiol. 2008

Adherence Factors

- Adherence/adhesion is an essential early step in the establishment of an infection
 - Mediated by pili or fimbriae
 - >15 different types
- Two basic strategies for inhibiting adherence
 - Blocking ligand adherence (CHO mimetics)
 - Blocking pilus/fimbriae assembly
 - Chaperone-usher system described in many Gram-Negative bacilli
 - Pilicides target chaperone function and inhibit pilus assembly

Cegelski et al, Nature Rev. Microbiol. 2008

Inhibition of Toxin Formation

- Toxins can cause devastating local and systemic effects
 - Host immune evasion (RTX toxins in *Mannheimia*)
 - Nutrient acquisition (α -toxin in *S. aureus*)
- Three potential strategies for targeting toxins
 - Transcription factors
 - Neutralizing antibodies
 - Toxin trafficking and function

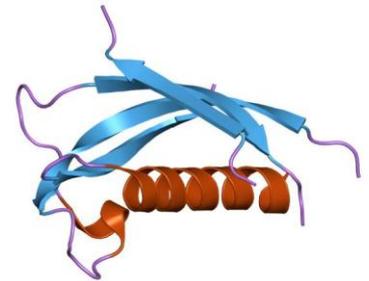
Cegelski et al, Nature Rev. Microbiol. 2008

Issues with Anti-Virulence as a target

- In vitro potency may be difficult to demonstrate due to lack of an MIC value
- Efficacy relies on host immune system to clear infection
 - Use as a standalone agent may be limited to mild infections
 - Design of efficacy studies will be critical
- Potential use with traditional small molecule antibiotics as a potentiator
 - Traditional agents are available that inhibit growth and toxin production
 - Clindamycin and erythromycin inhibit *S. aureus* growth equally
 - Clindamycin inhibits α -toxin product by 98%
 - Mechanism for this differential toxin inhibition has not be defined.

Antimicrobial Peptides

- Important component of host innate immune system
 - Not to be confused with peptide antibiotics (e.g., Nisin)
- Broadly categorized into two major families in mammals
 - Defensins
 - Found in both vertebrates and invertebrates
 - Produced in PMNs and epithelial cells
 - 18-45 AA
 - Cathelicidins
 - Contain a highly conserved cathelin region
 - Produced in PMNs and macrophages
 - 12 – 80 AA



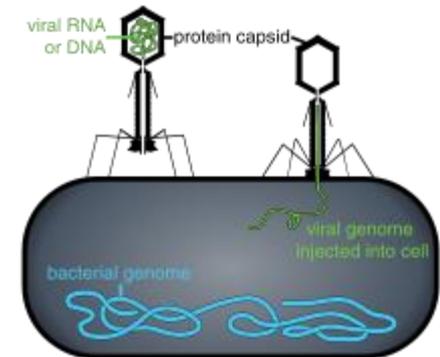
Ramanathan et al., Microbe Inf. 2002

Antimicrobial Agents as Therapeutic Agents

- Activity against both Gram-Positive and Gram-Negative bacteria depending on sequence
- Primary mechanism of action is pore formation in bacterial membranes
 - Other MOA for these agents has been described including protein synthesis and DNA synthesis
- Challenges to the development of these agents
 - Target animal toxicity
 - Systemic delivery can be problematic
 - Manufacturing of pharmaceutical grade API
 - May be relegated to use as topical agent

Bacteriophages

- Bacterial viruses
 - Act by attaching to specific receptors on host bacterial cell
 - Very specific (“narrow spectrum”)
 - Phage resistance develops quickly due to changes in the receptor or by changes in host cell strain populations
 - Governed by predator-prey dynamics
 - Due to resistance development, phage monotherapy is not considered optimal
 - Phage cocktails will most likely be required to reduce resistance development
 - Phages are inherently very safe
 - FDA-CFSAN has approved phages for food safety applications
- Development challenges
 - Delivery may limit these to “topical “ indications
 - Manufacturing



Summary - I

- Resistance is a consistent driver in HH and an emerging issue in AH
 - While prudent use programs may extend the life of existing compounds, there is a renewed need for novel agents
- The preservation of Antibacterial Discovery programs are key to refilling the pipeline with novel agents
 - The cost structure for the development of novel agents must be restructured to allow pharmaceutical companies to re-enter this area
 - Retention of experienced antibacterial discovery scientists is key to the success of these programs
 - Recognition of the unique skill set required for AB discovery is needed for survival of these programs within the pharmaceutical industry
 - Uncoupling from Marketing is key due to difficulty in valuing emerging resistance

Summary - II

- Antibacterial programs will continue to rely on traditional small molecule agents as the primary target
 - Large knowledge base
 - Existing Infrastructure
 - There is no reason to exclude any substrate that can be effectively exploited for therapeutic uses
 - Non-traditional agents will continue to attract interest but may be more difficult to bring to market

The time for a program to deliver a novel agent is 10-15 years. This emphasizes the need for continuous, well maintained antibacterial discovery programs headed by experience AB Discovery Scientists that actively promote the training of new scientists in this unique discipline

Thank You!

