Current State of Antibacterial Drug Discovery and What's Next for Antibacterial Drug Discovery

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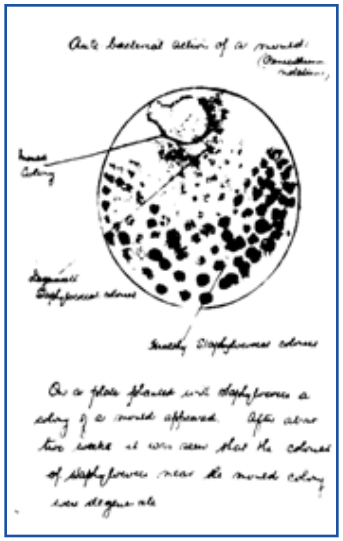
AGENDA

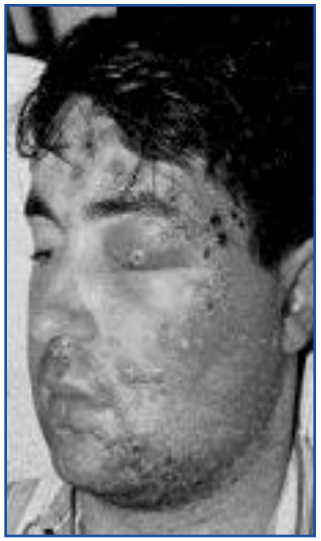
- Historical perspective – impact of discovery of penicillin
- Discovery during the “Golden Era”
- Successfully exploited antibiotic targets
- Genomics-based discovery in the 1990s
- Factors that led to the decline in antibiotic discovery
- What’s next?
- Economics and overcoming the “profitability barrier”

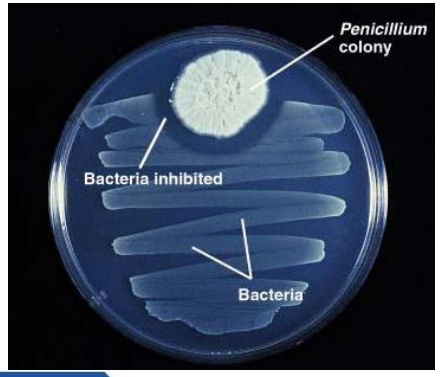
Impact of Fleming's Accidental "Discovery" of Penicillin

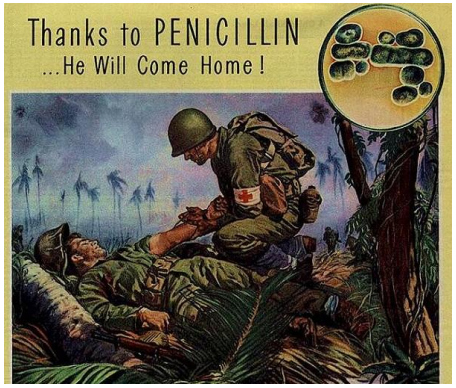
Fleming, 1928



Florey and Chain, 1940







How were the antibiotics we use today discovered?

Nearly all antibiotics used today belong to classes discovered before 1970.

- Derivatives of naturally produced antibiotics from soil streptomycetes and fungi

Only new classes to reach the market since 1970

- Oxazolidinones (discovered 1978, launched 2000)
- Lipopeptides (discovered 1986, launched 2003)

Advances from improvements within antibiotic classes yielding analogs with:

- Increased potency
- Broader spectrum of activity
- Activity against resistant phenotypes

The First in Class Antibiotics: 1940–1969

Decade	Year	Agent	First in Class
1940s	1942	Benzyl penicillin	Penicillin
		Gramicidin S	Peptide
	1944	Streptomycin	Aminoglycoside
	1948	Chlortetracycline	Tetracycline
1950s	1952	Erythromycin	Macrolide
	1955	Vancomycin	Glycopeptide
	1958	Colistin	Polymyxin
1960s	1960	Methicillin	Penicillin active vs Staph β-lactamase
		Metronidazole	Nitroimidazole
	1961	Trimethoprim	Dihydrofolate reductase inhibitor
	1964	Cefalothin	Cephalosporin
	1967	Nalidixic acid	Quinolone

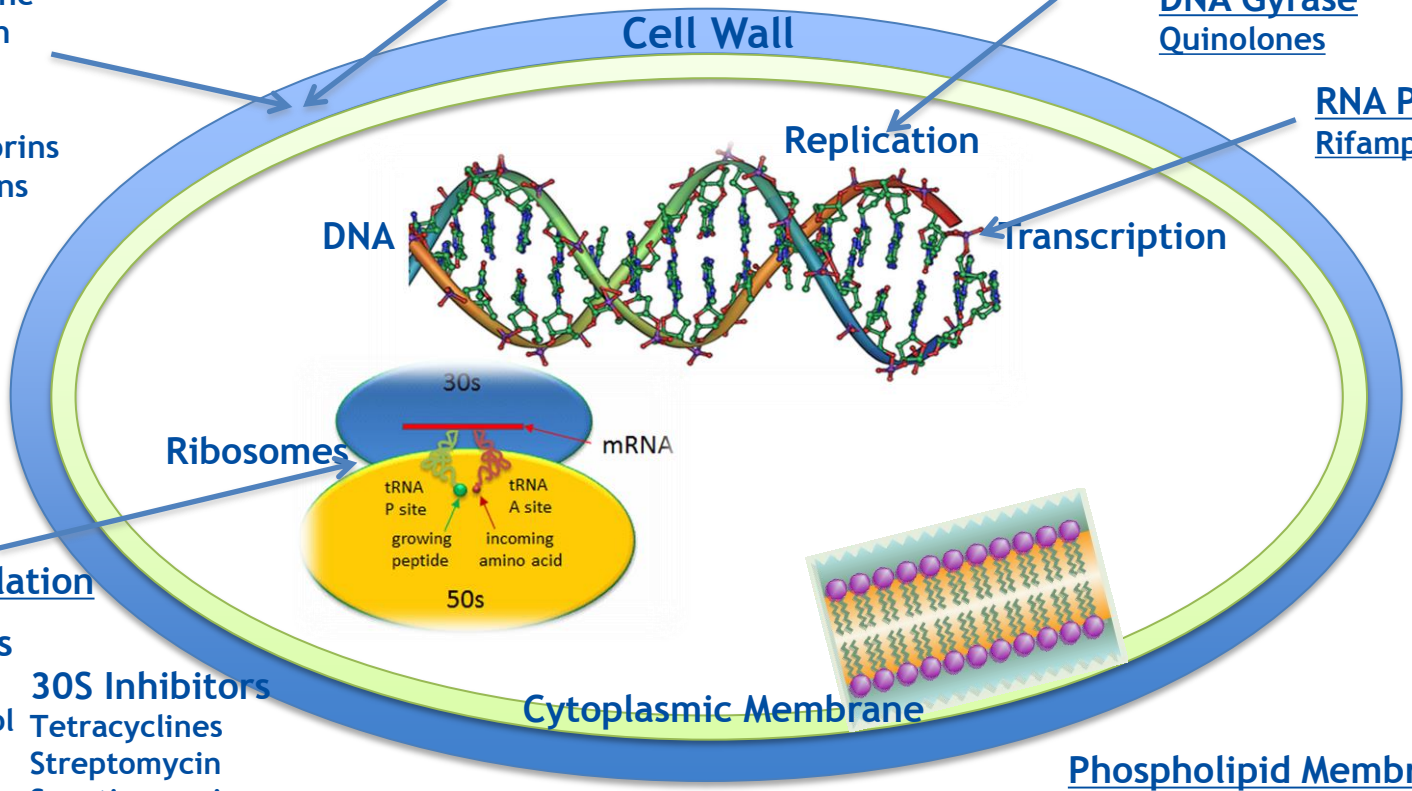
Many Antibiotics Developed in the Golden Era – Little Innovation (Me Too Analogs)

Decade	Year	Agent	
1970s		Cephalexin, pivampicillin, amoxicillin, cefradine, minocycline, pristinamycin, fosfomycin, tobramycin, becampicillin, ticarcillin, amikacin, azlocillin, cefadroxil, cefamandole, cefoxitin, cefuroxime, mezlocillin, pivmecillinam, cefaclor, cefmetazole	
1980s		Cefotaxime, cefsulodin, piperacillin, amoxicillin/clavulanate, cefoperazone, cefotiam, latamoxef, netilmicin, apalcillin, ceftriaxone, ceftazidime, ceftizoxime, norfloxacin, cefonicid, cefotetan, temocillin, cefpiramide, oxfloxacin, ampicillin/sulbactam, cefixime, roxithromycin, sultamicillin	
	1985	Imipenem/cilastatin	**Carbapenem**
	1986	Mupirocin	**Monoxycarbolic acid**
	1987	Ciprofloxacin	**2nd-generation quinolone**
		Rifaximin	**Ansamycin**
1990s		Arbekacin, clarithromycin, cefdinir, cefetamet, cefpirome, cefprozil, ceftibuten, fleroxacin, loracarbef, piperacillin/tazobactam, rufloxacin, brodimoprim, dirithromycin, levofloxacin, nadifloxacin, panipenem/betamipron, sparfloxacin, cefepime, quinupristin/dalfopristin	

The 21st Century Antibiotics

Decade	Year	Agent	First in Class
2000s	2000	Linezolid	Oxazolidinone
	2001	Telithromycin	Ketolide
	2003	Daptomycin	Lipoglycopeptide
	2005	Tigecycline	Glycylcycline
	2005	Doripenem	
	2009	Telavancin	
2010s	2010	Ceftaroline	Cephalosporin with activity against MRSA
	2011	Fidaxomycin	Macrocyclic
	2014	Tedizolid	
	2014	Oritavancin	
	2014	Dalbavancin	
	2014	Ceftolozane/tazobactam	
	2015	Ceftazidime/avibactam	First in class BLI

Successfully Exploited Antibiotic Discovery Targets



Cell Wall Synthesis
D-cycloserine
Vancomycin
Bacitracin
Penicillins
Cephalosporins
Cephamycins

Cell Wall Integrity
β-Lactamases

DNA Synthesis
Metronidazone

DNA Gyrase
Quinolones

RNA Polymerase
Rifampicin

Ribosomes

Translation

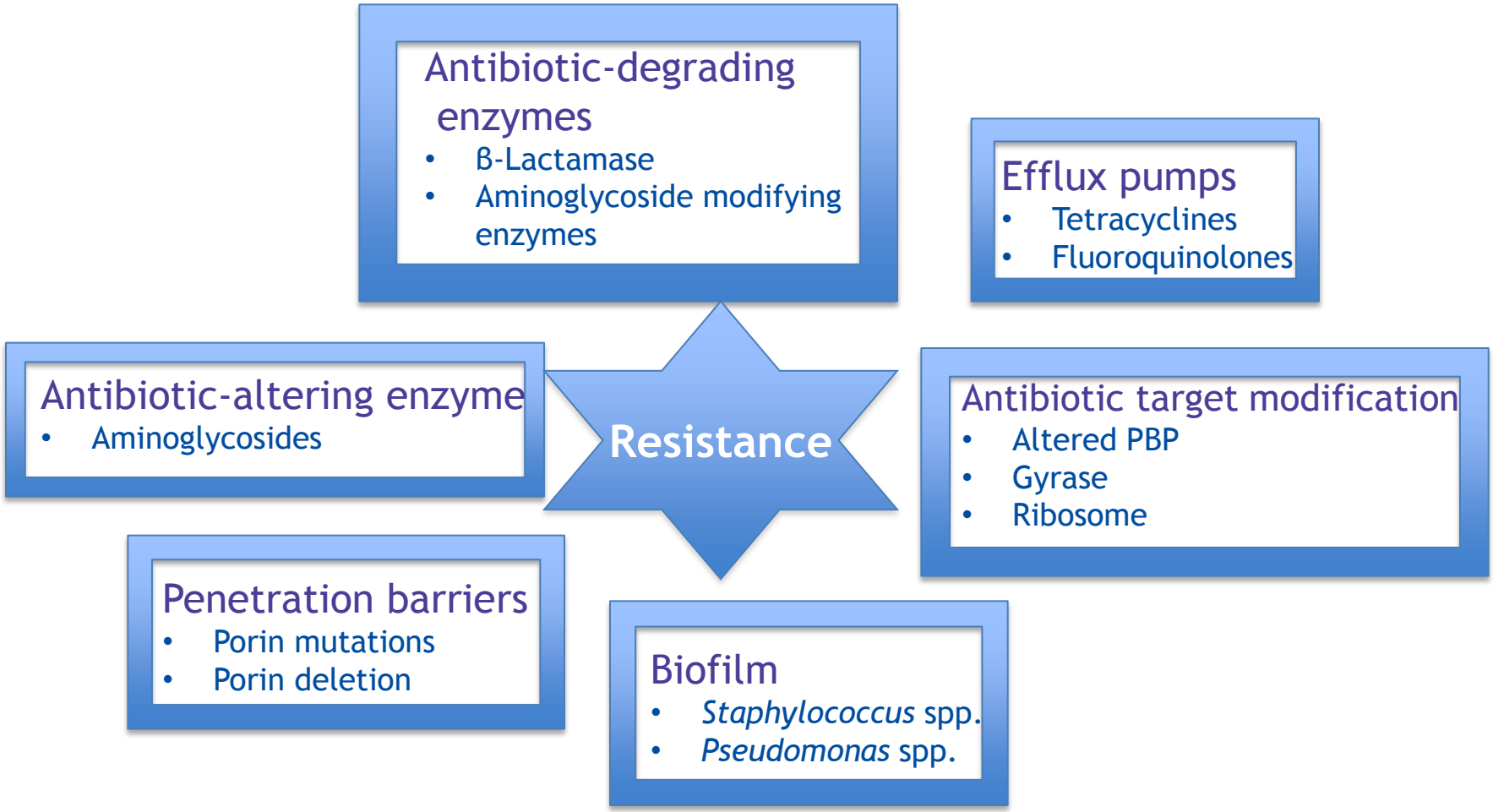
50S Inhibitors
Erythromycin
Chloramphenicol
Clindamycin
Lincomycin

30S Inhibitors
Tetracyclines
Streptomycin
Spectinomycin
Kanamycin

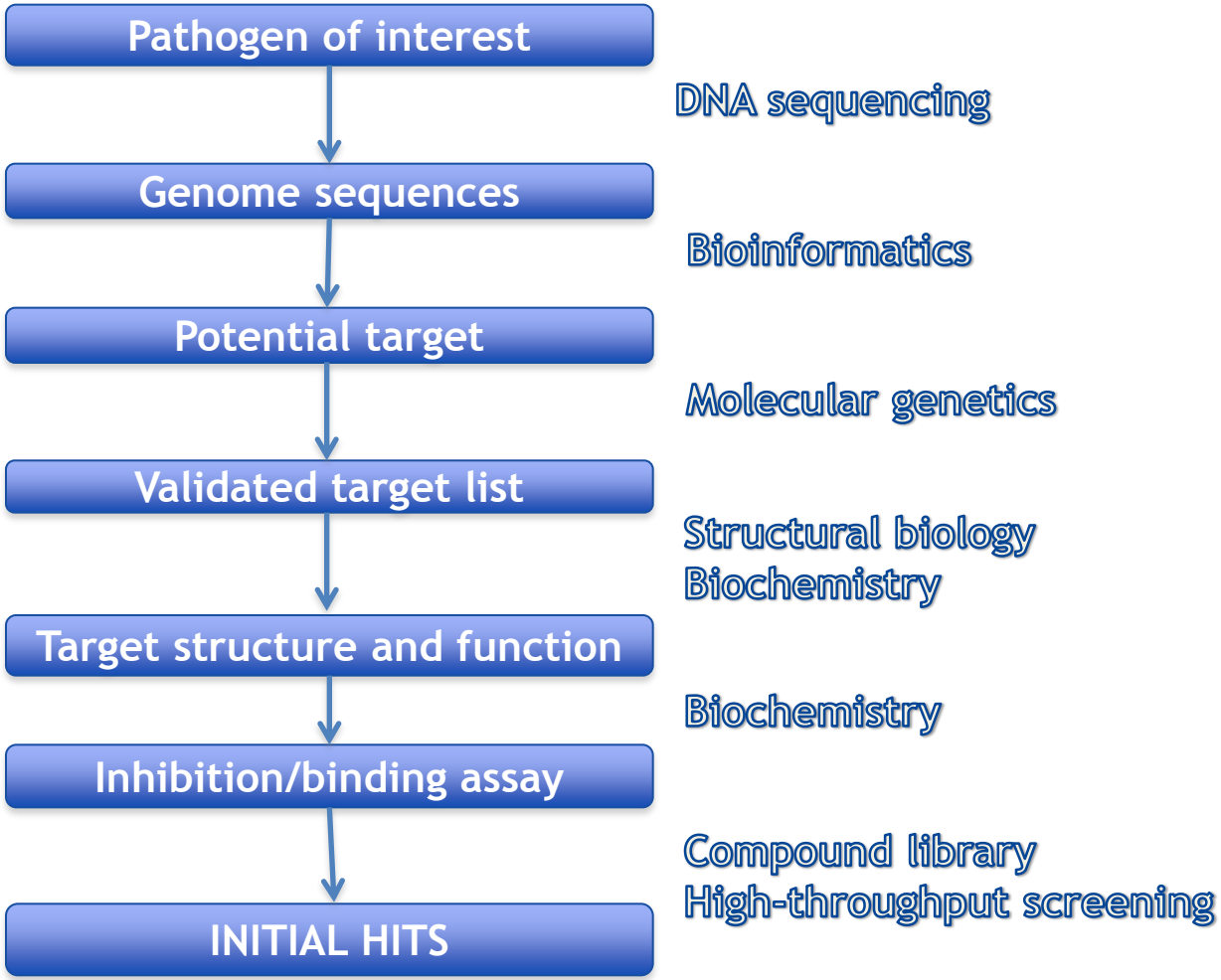
Cytoplasmic Membrane

Phospholipid Membranes
Polymyxins

Mechanisms of Resistance

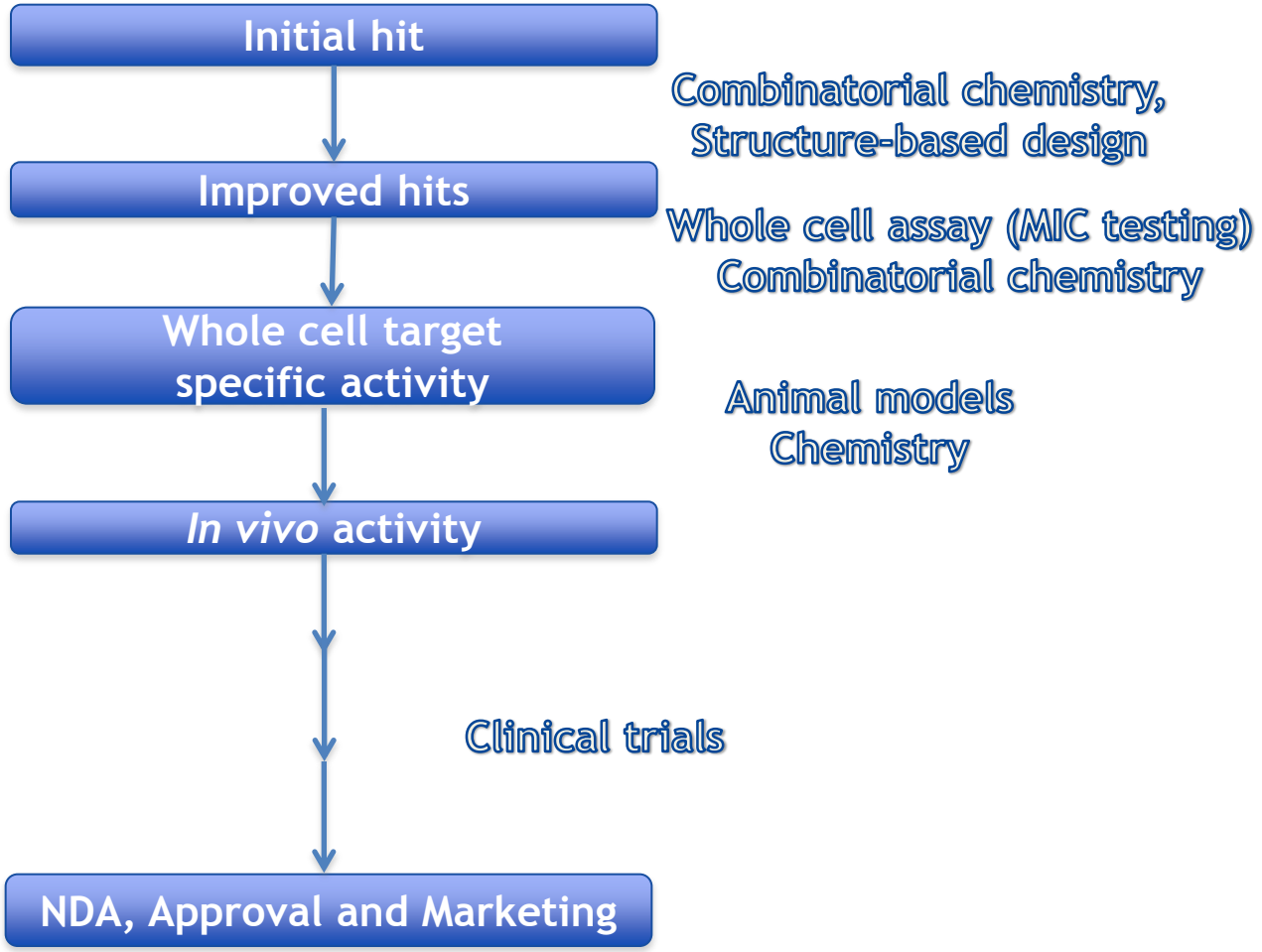


Genomics-Based Antibacterial "Hit" Discovery in the 1990s



Adapted from Dermaid Hughes, *Nature Reviews Genetics*. June 2003;4:432-441

Antibacterial "Hit to Lead" Discovery in the 1990s



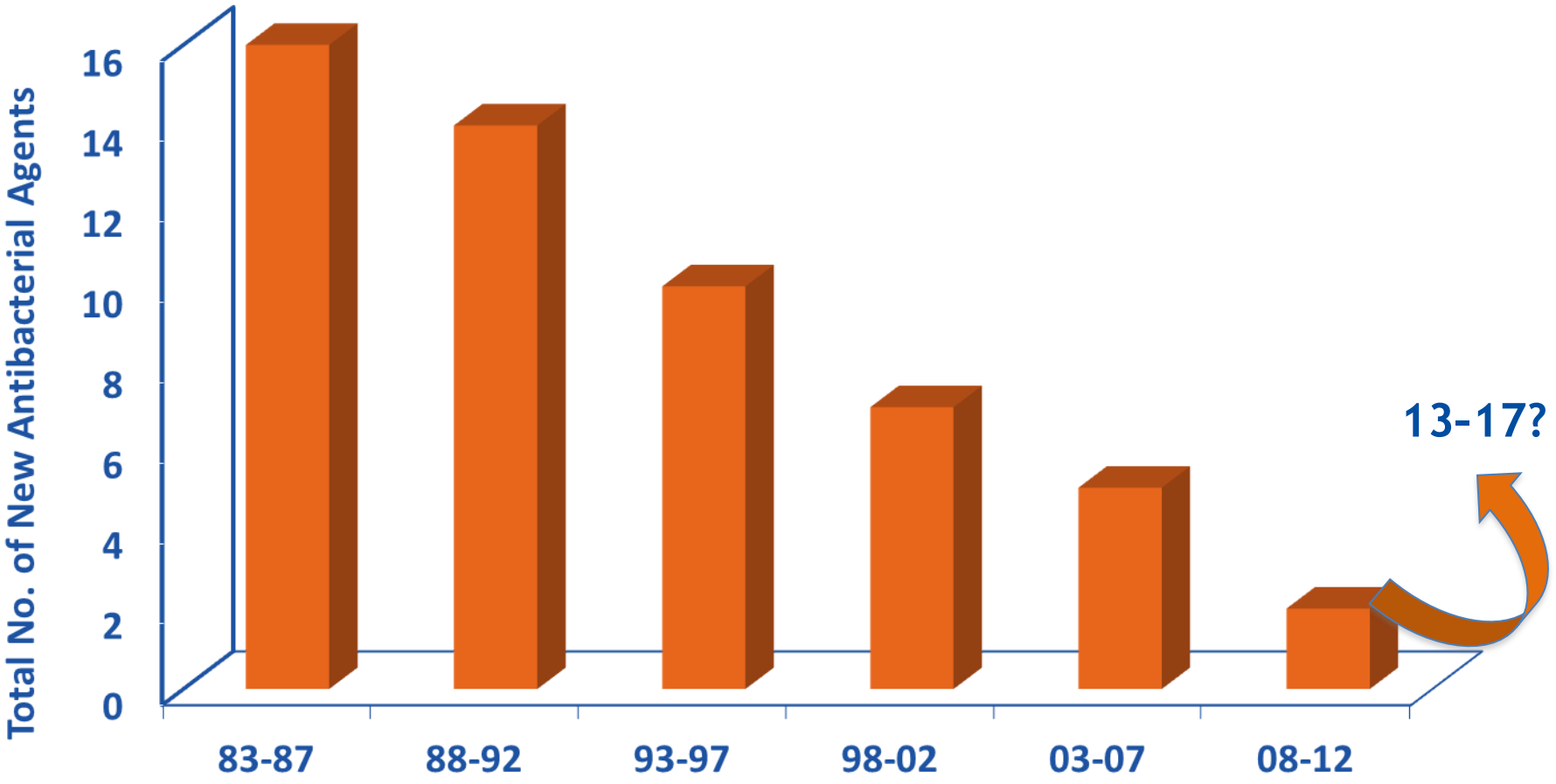
Adapted from Dermaid Hughes, *Nature Reviews Genetics*. June 2003;4:432-441

Genomics-Based Antibiotic Discovery in the 1990s

- Genomes of multiple pathogens sequenced to identify essential genes that lacked mammalian counterparts
- High-throughput screens of existing compound libraries to identify "druggable" molecules that bound to or inhibit the target (enzyme)
- Compound libraries yielded 5-fold fewer hits than for other therapeutic areas
  - Few hits translated into lead candidates
- GSK Experience
  - 300 targets and 67 HTS screens (260,000–530,000 compounds)
  - Only 16 screens gave "hits" and 5 lead compounds
- No antibiotic developed by this approach made it to the market

Payne et al., *Nat Rev Drug Discov.* 2007;6:29-40

New Antibacterial Drugs Approved in the US Per 5-Year Period (1983–2012)



Infectious Diseases Society of America (*CID* 2011:52:S397-S428)

Infectious Diseases Society of America

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

What Factors Have Led to the Decline of Antibiotic Discovery?

The Challenges of Genomics-Based Discovery

Lack of chemical diversity among compound libraries

- Biased toward molecules meeting Lipinski's rule of five (chemical algorithm)

Binding to or inhibiting cell-free targets in a screen did not always translate into antibacterial activity (MICs)

- Efflux and penetration barriers

Compounds that inhibited single targets are very prone to mutational resistance

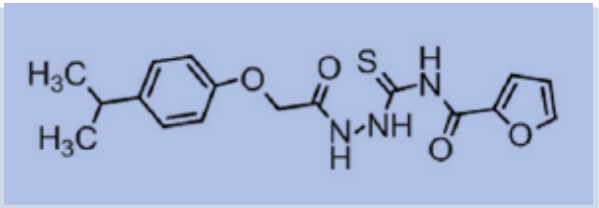
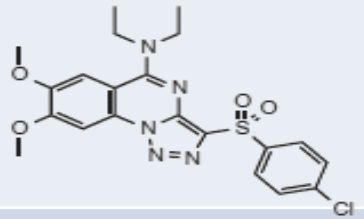
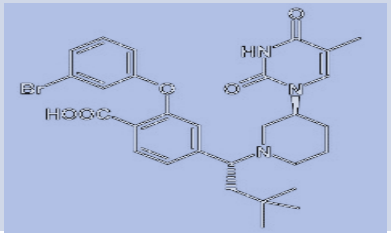
Antibacterial Drug Discovery and Development: Other Recent Challenges

- It's difficult—with a very high attrition rate
- Finding molecules that can get to their intended target(s), especially gram-negatives
- Many bacterial infections are becoming increasingly difficult to treat with existing agents
- Low returns on investment "Profitability Barrier"
- Restricted use on formularies/antimicrobial stewardship
- AST device development—way too long for new drugs
- Unpredictable and challenging regulatory pathways resulted in many companies exiting the field—but this one seems to be changing. Are companies getting back in?

What's Next?

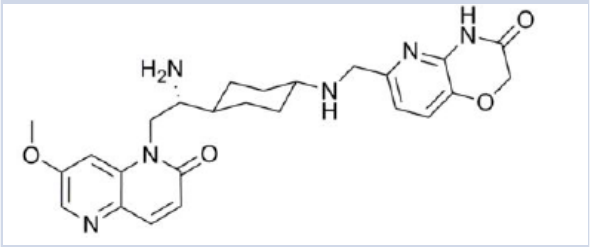
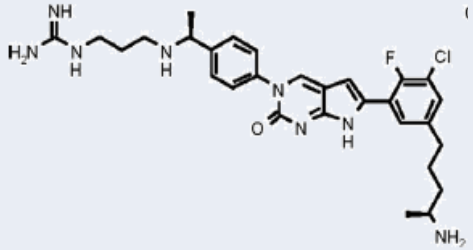
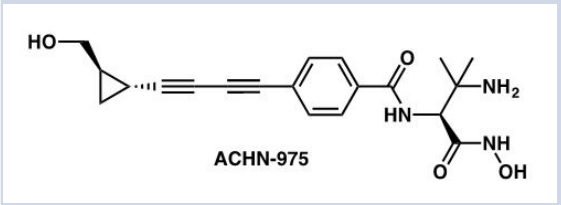
- Target-based discovery continues…
- Natural product screening strategies….
- Transport/translocation strategies (gram-negative bacteria)
- Inhibition of resistance mechanisms (eg, ß-lactamase, efflux mechanisms)
- Antivirulence/pathogenesis strategies
- Bacteriophage/lysins
- Economic strategies to "spur" antibacterial discovery

Gram-Positive Discovery (Preclinical) – Target-Based Examples

Target	Pathogen(s) and compounds	Structure
RNA degradosome[a]	*S. aureus* Small molecule inhibitors (RNPA2000)	
Teichoic acid biosynthesis (TarG)[b]	*S. aureus* (Targocil) (1835F03)	
Thymidylate kinase (Nucleoside kinase, essential for DNA synthesis)[c]	Potent broad spectrum activity vs. MRSA and VRE (TK-666)	

[a]Eidem et al, 2015 (*AAC* 59:2016)
[b]Suzuki et al, 2011 (*AAC* 55:767)
[c]Keating et al, 2012 (*ACS Chem Biol* 7:1866)

Gram-Negative Discovery (Preclinical) – Target-Based Examples

Target	Pathogen(s) and compounds	Structure
Novel bacterial topoisomerase inhibitors (NBTI)[a]	Series active vs. gram-negative bacteria Different mechanism to FQs – avoids target-mediated cross-resistance (NBTI 4563)	
Ribosomal Inhibitors[b]	NDM-1 *Enterobacteriaceae*, *P. aeruginosa*, *A. baumanii* ESKAPE Pathogens Multiple compound classes (RX-P873)	
LpxC First step in biosynthesis of Lipid A[c]	*Enterobacteriaceae* and *P. aeruginosa* ACHN-975 and LpxC-4 (PF-5081040)	

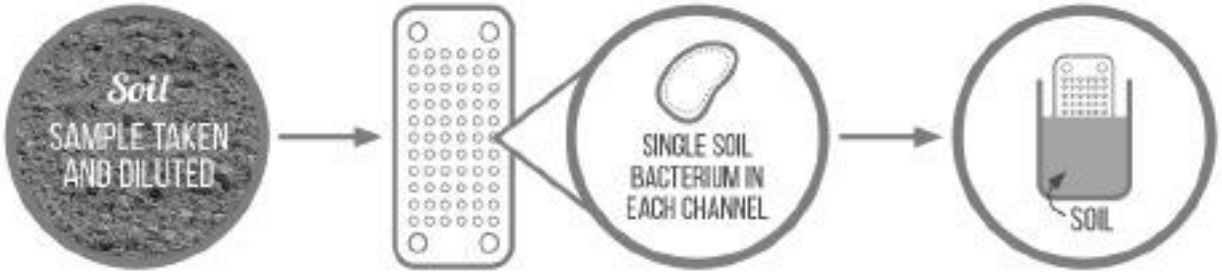
[a]Dougherty et al, 2014 (*AAC*. 58:2657) [b]Flamm et al, 2015 (*AAC*. 59:2280) [c]Castenheira et al, ICAAC 2013 F-122

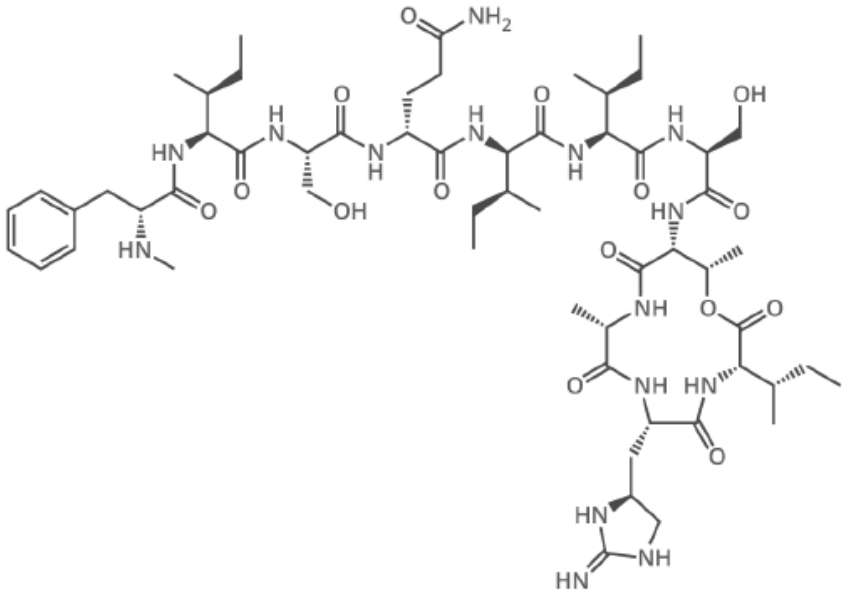
In Vitro Activity of RX-P873 (Pyrrolocytosine) *vs.* Gram-negative Pathogens

Pathogen (N)	MIC (µg/mL)		
	Range	50%	90%
Enterobacteriaceae (657)	0.06–>32	0.25	0.5
E. coli (202)	0.06–2	0.12	0.25
K. pneumoniae (202)	0.12–2	0.25	0.5
E. cloacae (50)	0.12–1	0.5	0.5
E. aerogenes (50)	0.12–1	0.25	0.5
C. freundii (51)	0.12–2	0.25	0.5
Proteus spp. (51)	0.12–>32	1	2
S. marcescens (51)	0.12–2	0.5	0.5
P. aeruginosa (200)	0.25–8	2	4
A. baumanii (202)	0.12–4	0.5	1

Flamm et al, 2015

Antibiotics on a Chip From the Soil!
Teixobactin – Natural Product Based





Ling et al, *Nature*. 2015;517:455

Translocation Strategies "Trojan Horse" – S-649266 an Iron Chelating Cephalosporin

Class	Strain	Enzyme	MIC (µg/mL)			
			S-649266	Ceftazidime	Cefepime	Meropenem
A	*K. pneumoniae* VA391	KPC-3	0.063	>32	>32	16
	E. coli SR34199	CTX-M-15	0.125	>32	>32	0.031
B	*P. aeruginosa* SR27001	IMP-1	1	>32	32	>32
	P. aeruginosa NTU	VIM-2	0.25	>32	32	>32
	S. maltophilia	L1	0.5	>32	>32	>32
	K. pneumoniae NCTC13443	NDM-1	0.5	>32	32	>32
C	*E. cloacae* ATCC13047	P99	0.5	8	0.125	0.063

Tsuji et al, 2014 ID Week Poster 256 (Table 4)

Antivirulence Strategies

QseC (Membrane-bound histidine kinase)[a]

- Responds to stress hormones
- Signaling cascade to promote virulence
- LED-209, a selective inhibitor that binds to lysines in QseC impairing function and prevents activation of virulence in gram-negative bacteria *in vitro* and *in vivo*
- Does not inhibit growth

Spero Therapeutics (Cambridge, Massachusetts)

- Antivirulence compounds
- Persistence – bacteria tolerate existing antibiotics
- Recent alliance with Roche

[a]Curtis et al, 2014 mBio 5:02165

Inhibition of Resistance Mechanisms

β-Lactamase Inhibitors

- Avibactam, relebactam
- RPX7009
- Next-generation RPX7282
  - Binds serine carbapenemases and metallo-β-lactamases

Efflux pump inhibitors

Bacteriophage and Lysins: Alternative Solution?

Review Article

Bacteriophage therapy: a potential solution for the antibiotic resistance crisis

Zhabiz Golkar, Omar Bagasra, Donald Gene Pace

South Carolina Center for Biotechnology, Claflin University, Orangeburg, United States

Abstract

The emergence of multiple drug-resistant bacteria has prompted interest in alternatives to conventional antimicrobials. One of the possible replacement options for antibiotics is the use of bacteriophages as antimicrobial agents. Phage therapy is an important alternative to antibiotics in the current era of drug-resistant pathogens. Bacteriophages have played an important role in the expansion of molecular biology and have been used as antibacterial agents since 1966. In this review, we describe a brief history of bacteriophages and clinical studies on their use in bacterial disease prophylaxis and therapy. We discuss the advantages and disadvantages of bacteriophages as therapeutic agents in this regard.

Key words:. antibiotic resistance; bacteriophage; infectious disease

J Infect Dev Ctries 2014; 8(2):129-136. doi:10.3855/jidc.3573

REVIEW

Bioengineered Bugs 1:1, 9-16; January/February 2010; © 2010 Landes Bioscience

Recombinant bacteriophage lysins as antibacterials

Mark Fenton,[1] Paul Ross,[2] Olivia McAuliffe,[2] Jim O'Mahony[1] and Aidan Coffey[1,*]

[1]Department of Biological Sciences; Cork Institute of Technology; Bishopstown, Cork; [2]Teagasc; Moorepark Food Research Centre; Fermoy, County Cork, Ireland

Key words: lysin, endolysin, bacteriophage, pathogen, antibacterial, infection, lytic, enzyme

Major Pharma Discovery Players – Who Is In and Not so In?

- **Roche/Genentech** – Recent investment
- **AstraZeneca** – Discovery R&D spin out discovery into new company
- **GlaxoSmithKline** – Little publicly available information
- **Novartis** – Little publicly available information
- **Merck** – Little publicly available information
  - Closed the Cubist discovery effort

Other Pharmaceutical Players – Not Exhaustive

- Achaogen
- Basilea
- Crestone
- Curza
- Cempra
- Discuva
- Enanta
- The Medicines Company
- Melinta Therapeutics
- Nabriva Therapeutics
- MicurX
- VenatorX
- Macrolide Pharmaceuticals
- Theravance

Overcoming the Economic Challenges

BARDA (Biomedical Advanced Research and Development Authority)

- Developing and procuring needed therapeutics against a broad array of public health threats
- Research areas of interest includes antimicrobial drugs

PCAST (Presidents Council of Advisors on Science & Technology)

- Combating antibiotic resistance
  - Increased surveillance
  - Increasing longevity of current antibiotics

IMI (Innovative Medicine's Initiative in European Union)

ND4BB (New Drugs for Bad Bugs)

ENABLE (European Gram-negative Antibacterial Engine)

- Drug discovery platform for antigram-negative antibiotics
- Launched in early 2014
- 6-Year program (€85m, $115.3m)
- 32-Partner project (EFPIA, SME, Research, Universities)
  - Manage a drug discovery engine for testing and optimizing molecules in earlier stages of drug discovery that have potential to become future drug candidates
  - Fast track development of promising candidates

GAIN Act

US Food and Drug Administration (FDA) Safety and Innovation Act

- Legislation reauthorizing the Prescription Drug User Fee Agreements (PDUFA)
- Incentives to spur antibacterial and antifungal R&D
- Provisions modeled after the Generating Antibiotic Incentives Now (GAIN) Act
- Recognition of the serious problems posed by antibiotic resistance and the dry antibiotic pipeline

GAIN Act (Continued)

Title VII (Sections 801–806) of FDASIA provides incentives to develop new treatments for life-threatening infections caused by drug-resistant pathogens.

Qualifying pathogens are defined by GAIN to include the following examples:

- Multidrug-resistant gram-negative bacteria
  - *Pseudomonas aeruginosa*
  - *Acinetobacter*
  - *Klebsiella*
  - *Escherichia coli*
- Resistant gram-positive pathogens
  - Methicillin-resistant *S. aureus*
  - Vancomycin-resistant *S. aureus*
  - Vancomycin-resistant Enterococcus
  - *Clostridium difficile*

Qualified Infectious Disease Product (QIDP) Benefits

Advancement of critically needed antibiotics

- Eligibility for fast-track status
- Priority review

If approved, a 5-year extension of Hatch Waxman exclusivity

Summary

- What we all know:
  - "Bacterial pathogens will continue to evolve mechanisms to "resist" the new agents with which we challenge them. It's only a matter of time."
- Novel agents that are effective against novel targets that lack cross-resistance to existing agents will continue to be important.
- New products are now exiting the pipeline and becoming available to the patients who need them, and we will need to ensure that new products continue to enter to keep it flowing to tackle the new pathogens that will continue to threaten public health.