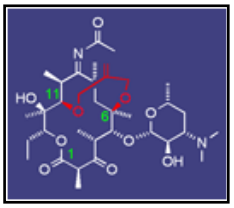
Syllabus

Chemistry 259

Medicinal Chemistry of Modern Antibiotics



Winter 2015/16

Instructor: Thomas Hermann, Pacific Hall 5222A, tch@ucsd.edu

Lecture Hours and Place: M/W/F 12:00 pm – 12:50 pm, in YORK 4080A
Office Hours: by appointment

Web: http://tch.ucsd.edu/CHEM259.html

Useful Textbooks:
- *Antibiotics: Actions, Origins, Resistance*, by C. Walsh, ASM Press
- *The Organic Chemistry of Drug Design and Drug Action*, 3rd ed. by R.B. Silverman & M.W. Holladay, Academic Press/Elsevier

Examination (for credits): Midterm: paper selection & abstract (30% of grade)
Final: paper report (70% of grade)

Tentative Course Schedule:

- **Jan 4:** **Introduction** (Lecture 1)
- **Jan 6 – 11:** **History of Antibiotics** (Lecture 2)
- **Jan 13 – Feb 10:** **Drug Discovery, Development & Approval** (Lectures 3 – 5)
- **Feb 12 – Mar 11:** **Antibiotics Classes & Targets** (Lectures 6 – 10)

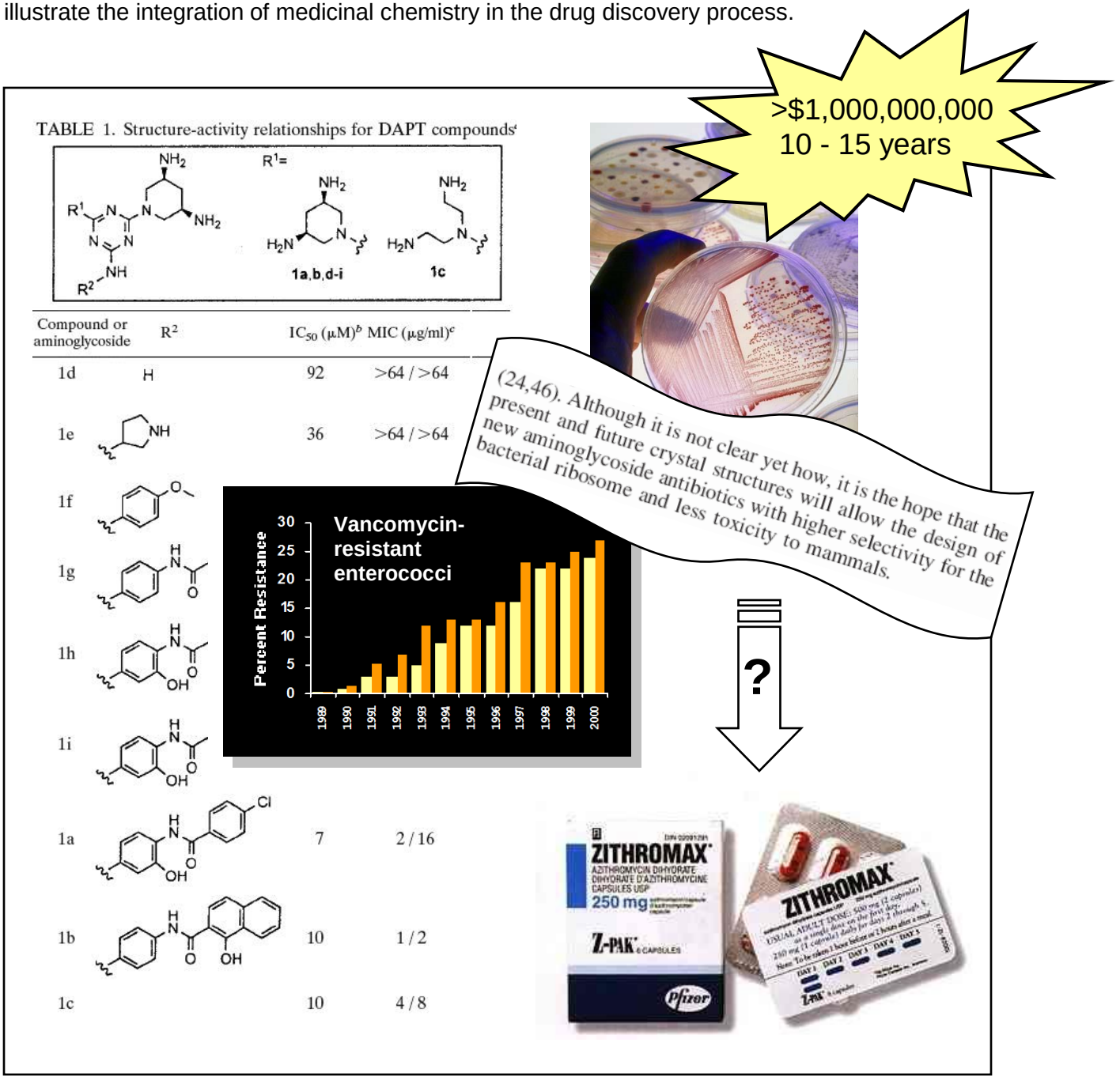
Midterm: Select a recent publication (2010 or later, from a PubMed-referenced journal) that describes any aspect of discovery or development of an antibiotic or antibiotic target. Examples are papers dealing with compound discovery by screening, medicinal chemistry elaboration, mechanism of action studies, target validation, etc. Journal suggestions include (but are not limited to) *Nature, Science, Cell, Molecular Cell, PNAS, J. Med. Chem., Nature Chemical Biology, ACS Chemical Biology, ChemBioChem, Antimicrobial Agents and Chemotherapy*.
For the midterm credit, write a ~ 1 page summary of the paper that you selected and describe why this is an interesting publication that you want to cover in a report.
This abstract is due to TH on Feb 10, 1pm! It counts for 30% of the grade. If you need help with selection or are not sure about the suitability of an article, talk to TH.

Final: Write a report of the paper that you selected, using the following structure:
1) Background, 2) Summary of the Findings, 3) Perspective for future research/application, 4) Critique. Use select figures/illustrations from the publication to convey the key points (but don't copy indiscriminately). Item 1) will require you doing some background reading of reviews and/or other publications in the field. Item 4) should reflect your thoughts on the paper.
This report is due on Mar 11, 5pm! It counts for 70% of the grade. You may turn in the report by e-mail to TH or printed out on paper.

1. Introduction & Overview; Scope of the Course

The Special Topics Course will focus on the medicinal chemistry of modern antibiotics. We will discuss the discovery, mechanism of action, and synthesis of antibacterials that are currently being used in therapy. Emphasis will be given to compounds approved over the last three decades and investigational drugs that are in clinical trials.

The process of antibacterial drug discovery and development will be outlined as an introduction. The optimization and preclinical development of antibiotics serve as transparent models to illustrate the integration of medicinal chemistry in the drug discovery process.

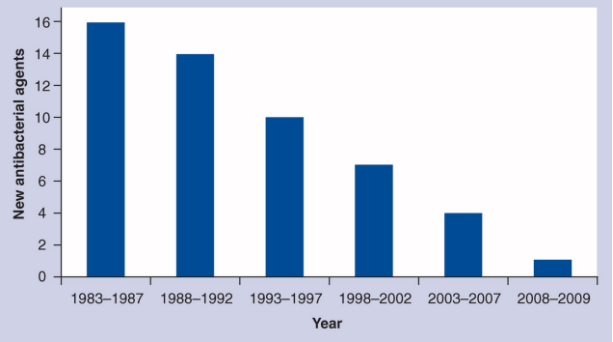


The Need for New Antibiotics:

Bad Bugs, No Drugs

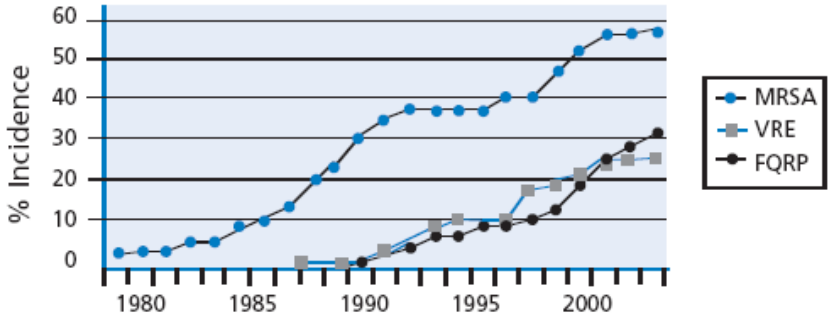
As Antibiotic Discovery Stagnates ...
A Public Health Crisis Brews

- About 2 million people acquire bacterial infections in U.S. hospitals each year, and 90,000 die as a result. About 70 percent of those infections are resistant to at least one drug. The trends toward increasing numbers of infection and increasing drug resistance show no sign of abating.
- Resistant pathogens lead to higher health care costs because they often require more expensive drugs and extended hospital stays. The total cost to U.S. society is nearly $5 billion annually.
- The pipeline of new antibiotics is drying up. Major pharmaceutical companies are losing interest in the antibiotics market because these drugs simply are not as profitable as drugs that treat chronic (long-term) conditions and lifestyle issues.
- Drug R&D is expensive, risky, and time-consuming. An aggressive R&D program initiated today would likely require 10 or more years and an investment of $800 million to $1.7 billion to bring a new drug to market.



(*Source:* Spellberg B, Guidos R, Gilbert D *et al.* The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. *Clin. Infect. Dis.*46(2),155–164 (2008).)

Chart 1: Resistant Strains Spread Rapidly



Source: Centers for Disease Control and Prevention

This chart shows the increase in rates of resistance for three bacteria that are of concern to public health officials: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and fluoroquinolone-resistant *Pseudomonas aeruginosa* (FQRP). These data were collected from hospital intensive care units that participate in the National Nosocomial Infections Surveillance System, a component of the CDC.

Why is Big Pharma getting out of antibacterial drug discovery?

- Urgent need for new antibiotics
- Antibiotics market in 2009 > $42 billion globally (Nature Reviews Drug Discovery 9, 675-676 (September 2010))

But:

- Market growth is considered "flat" ("the antibiotics market[…] showed an average annual growth of 4% over the past 5 years, compared with a growth of 16.7% and of 16.4% for antiviral drugs and vaccines, respectively" (IMS Health. IMS MIDAS (2009)))
- Market is highly fragmented
- Availability of generic forms of large selling antibiotics (for example, Amoxicillin/clavulanate = Augmentin; Ciprofloxacin = Cipro)
- Regulatory pressure to curtail "unnecessary use" of antibiotics
- Approval sets high standards for safety and superiority

And:

- Antibiotics use is for short courses of therapy (in contrast to therapy of chronic diseases)
- Therefore, prices for new antibiotics have to be high
- Antibiotics are subject of price control because they are considered "life-saving" drugs

Pharma companies prioritize projects relative to each other using risk-adjusted net present value (rNPV). (Stewart et al., Nature Biotechnol. 2001, 19, 813)

NPV: Value of a given project after projecting expenses and revenues into the future and discounting for the potential investment value of the money spent on the project.
rNPV: risk adjustment by assigning increased risk to projects at earlier stages

The risk-adjusted value, *rV*, of an endeavor in which the risk changes is the payoff (*P*) times the current risk (R_0), minus each associated cost (C_i) times the likelihood (R_0/R_i) of having to pay each cost.

$$rV = PR_0 - \sum_{i=0}^{n} C_i R_0 / R_i \qquad \text{Equation (1)}$$

Table 1

Project therapeutic class	Risk adjusted NPV x$1,000,000
Musculoskeletal	1,150
Neuroscience	720
Oncology	300
Vaccines	160
Injectable Antibiotic (Gm+)	100
MS- Psoriasis	60
Liver Transplant	20
Oral Contraceptive	10

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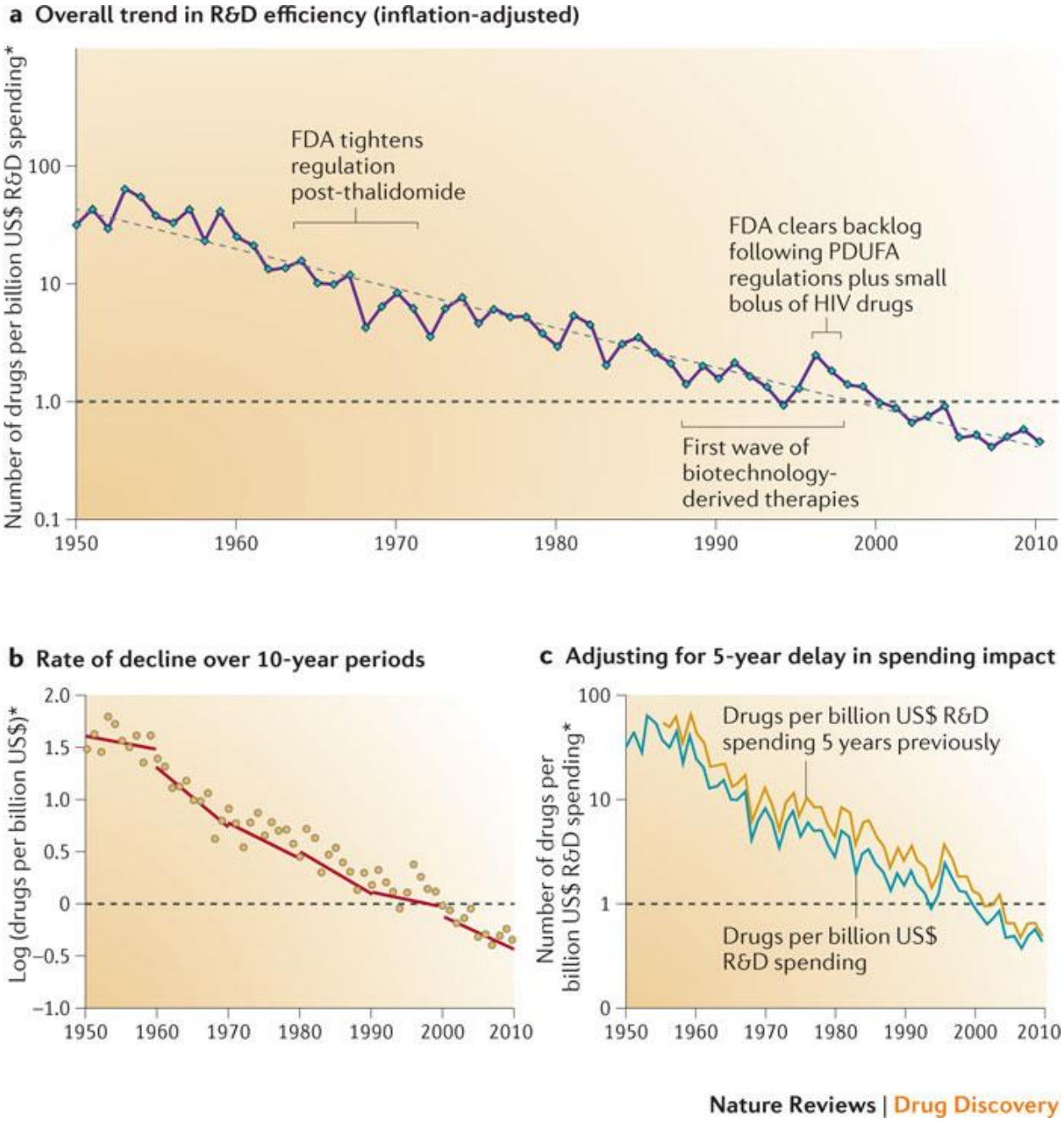

(Nature Reviews Drug Discovery 11, 191-200 (March 2012)