BIOGRAPHY:
Marieke Kruidering-Hall is Associate Professor in the Department of Cellular & Molecular Pharmacology. She was born in the Netherlands. She did her undergraduate training in Biopharmaceutical Sciences at Leiden University, where she also did her graduate training in Cellular Toxicology. The focus of her PhD was mechanisms of cisplatin-induced cell death. She joined Dr. Gerard Evan’s lab at the Imperial Cancer Research Fund (ICRF) in London to study c myc-induced apoptosis, and continued her postdoctoral studies in this field with him at the UCSF Cancer Center. She participated in the UCSF Postdoctoral Teaching Fellowship Program (PTF) in the spring of 2002, facilitating small groups for first-year medical students at UCSF. She joined the faculty of Cellular and Molecular Pharmacology in the fall of 2002. Her position at UCSF is dedicated full time to teaching and facilitation of teaching Pharmacology to students in the Schools of Medicine, Pharmacy and Dentistry. She teaches and directs courses in all three schools. In addition, together with her colleagues, Dr. Fulton and Dr. Hyland from the Department of Biochemistry, she directs the PTF program and is active in educational research. She has won numerous teaching awards, is a member of the prestigious Academy of Medical Educators and holds the Academy Chair in Pharmacology Education.
We need an immune system to live.

The immune system is complex and awesome.

We have tons of bacteria on our skin and in our gut.

Bug names: Anthrax, E. coli, pneumococcus, H. influenza, Staph. aureus (video of neutrophil chasing the Staph. aureus).

Last week......you learned

Sometimes the immune system has trouble:
We met Elizabeth!

CVID: Problem making antibodies
T cells (lymphocytes) HIV infection

The question is

Did your immune system ever have trouble?

How antimicrobial drugs work

Questions we will address

1. How do antimicrobial drugs work?
2. Why do antibiotics give you diarrhea?
3. Why do you always have to finish a prescription?
4. Why was Elizabeth sometimes not helped completely by antibiotics?

Microorganisms

1. Bacteria
2. Fungi
3. Protozoa
4. Helminths
5. Viruses

Differ from human eukaryotic cells

Drugs target these differences: affect microbe without affecting host
Overview of Drug Targets
1. Inhibition of cell wall synthesis
   - Penicillins, cephalosporins, vancomycin
2. Inhibition of protein synthesis
   - Aminoglycosides, macrolides, tetracyclines
3. Inhibition of nucleic acid synthesis
   - Antiviral agents, fluoroquinolones
4. Inhibition of folic acid synthesis
   - Sulfonamides, trimethoprim
5. Disruption of cell membrane function
   - Antifungal agents

How to pick the correct antimicrobial drug?
Identity of infecting organism & its drug susceptibility

Minimal Inhibitory Concentration (MIC):
Lowest concentration of an antimicrobial agent that inhibits the growth of an organism isolated from a patient.
Determined by tube dilution of disc diffusion assay

How antimicrobial drugs work
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Drug Resistance by “selection”

Drug A stopped too soon
Our defense cannot kill high number of microbes!

How to pick the correct antimicrobial drug?

Identity of infecting organism & its drug susceptibility
Bacterial or bacteriostatic drug?

Patient:
- Severity of illness
- History of drug allergies (NKA)
- Patient age
- Pregnancy

Everywhere I go people want to thank me for saving their lives. I really don't know why... Nature created penicillin, I only found it.
- Alexander Fleming, c. 1955

Prokaryote has CELL WALL

Inhibitors of cell wall synthesis

Penicillins, cephalosporins, vancomycin

Outside

Inside

Inhibitors of cell wall synthesis

Penicillins, cephalosporins, vancomycin

Courtesy of Gary Kaiser
Inhibitors of cell wall synthesis
Penicillins, cephalosporins, vancomycin

Bactericidal
1. Bind to penicillin binding proteins (PBPs)
2. Inhibit transpeptidation: “cross-link”
3. Activate autolytic enzymes: bactericidal

Resistance to Penicillins
I. Formation of beta-lactamases chewing up the beta-lactam ring
II. Changed PBPs preventing antibiotic binding
III. Changed porin structure preventing access of antibiotic

Adverse drug reactions:
I. Opportunistic Infections (dose dependent)
   Suppression of normal “flora” allows “overgrowth”
   Oral/vaginal candidiasis
   Diarrhea Bacterial colitis (C. difficile)
II. True allergy to Penicillins (5 % of population)
   Degradation products of beta-lactams are “antigenic”:
   rash, swelling, itching
   anaphylaxis (occurs fast: within minutes to 4 hrs)

Inhibitors of cell wall synthesis
Penicillins, cephalosporins, vancomycin
- Beta-lactam ring structure required
- Resistance through “beta lactamases”

inhibitors of cell wall synthesis
Clinical use of Penicillins
Fleming with Anne Schaeffer Miller, the first patient whose life was saved with penicillin, 1942.

Penicillin in Action

Penicilin in Action

Penicilin in Action
Adverse Drug Reactions PCNs:
True allergy to Penicillins is not an ampicillin rash

maculopapular rash – ampicillin
Rash is not life-threatening
PCN use can be safe (test)

Inhibitors of cell wall synthesis
Penicillins
Cephalosporins
Vancomycin

Inhibitors of cell wall synthesis: Historical perspective
S. aureus
PCN 1940
Penicillin resistant S. aureus 1950s
Methicillin 1959
Methicillin resistant S. aureus (MRSA) 1960s-1970s
Vancomycin resistant S. aureus (VRSA) 2002
Daptomycin, linezolid, quinupristin-dalfopristin

Pharmaceutical Industry
Number of New Molecular Entities (NMEs) submitted to FDA by world’s 15 largest pharmaceutical companies

Overview of Drug Targets
1. Inhibition of cell wall synthesis
   Penicillins, cephalosporins, vancomycin

   2. Inhibition of protein synthesis
      Aminoglycosides, macrolides, tetracyclines
Inhibition of protein synthesis
Aminoglycosides, macrolides, tetracyclines

1. Single strand copy of DNA
2. RNA modified to mRNA
3. mRNA travels out of nucleus
4. Ribosomes make protein based on mRNA
5. Ribosomes differ between bacteria and humans!!

Inhibitors of protein synthesis

Aminoglycosides (IV)
Streptomycin, gentamicin, tobramycin, amikacin and neomycin
Use: Tuberculosis, plague, endocarditis

Adverse drug reactions:
GI upset
Nephrotoxicity (6%)
Ototoxicity
Vestibular dysfunction (0.5%)

Macrolides
Erythromycin, clarithromycin, azithromycin
Use:
Respiratory tract infections, chlamydia, Bordetella

Adverse drug reactions
GI upset

Tetracyclines
Doxycycline, tetracycline
Use:
Community acquired pneumonia (CAP)
Chlamydia, cholera, H. Pylori, acne

Adverse Drug reactions
GI upset
Tooth discoloration
Photosensitivity

Inhibitors of protein synthesis

Selman Abraham Waksman,
Rutgers University
Nobel Prize 1952 "for his discovery of streptomycin, the first antibiotic effective against tuberculosis"
Summary

1. Inhibition of cell wall synthesis
   - Penicillin, cephalosporin, vancomycin

2. Inhibition of protein synthesis
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