The search for new tools: 
the R&D challenge

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Background

• Well-known (and often lamented) that the pharma industry has significantly reduced antibiotic R&D

• Reasons include:
  – Difficult to find novel activity compounds
  – Older drugs (often generic) have very broad labels
  – Therapy is brief, not chronic
  – New agents are held in reserve

• All true, but this misses the core problem
  – We (society) fundamentally undervalue antibiotics
  – Let me explain…
Lesson One

Antibiotics do Amazing Things

“Pneumonia is captain of the men of death”

(Sir William Osler)
Antibiotics do amazing things

- Simple infections: Often fatal in pre-antibiotic era
- Mortality benefit of antibiotics for pneumonia
  - You are aged < 30: 12% → 1%: 11% benefit
  - You are aged 30–59: 32% → 5%: 27% benefit
  - You are aged ≥ 60: 62% → 17%: 45% benefit
  - For all ages: A brief course of therapy is curative
- Contrast: aspirin + streptokinase in acute MI
  - 5% decrease in 5-week mortality (13% → 8%)
  - You still have heart disease

Modern care requires antibiotics

- Without reliable antibiotics, you can’t:
  - Have heart surgery
  - Take care of premature infants
  - Replace a joint
  - Treat cancer
- In serious infections, must get it right at the start
  - Delays to effective therapy of as little as a few hours measurably increase morbidity and mortality
  - Diagnostics helpful but unlikely to have adequate speed or sensitivity to eliminate fully the role of reliable broad-spectrum empirical therapy

Lesson Two

Discovery of Antibiotics is Hard

“Genius is 1% inspiration and 99% perspiration”

(Thomas Edison)

Discovery of antibiotics is hard

- Easy to find: Targets
  - Multiple bacterial genomes are fully sequenced

- Easy to find: Things that kill bacteria
  - Bleach works quite well, as do steam and fire

- Hard to find: Kills bacteria, is drug-like/relatively safe
  - Failures: physical properties, pharmacology or safety
    - Site/organism penetration require high levels → high doses
      - Typical lipid-lowering agent: 5-20 mg/day
      - Typical antibiotic: 100-2000 mg/day
    - Those high levels really stretch the safety margin

- To succeed? Be patient & be persistent

Lesson Three

Discovery & Development is Iterative

“The lesson of history is that we need a pipeline”

(John Bartlett)

Discovery of antibiotics is iterative

• The hierarchy of microbiology: A brief lesson
  – Gram-positive (S. aureus, MRSA): one cell membrane
  – Fermentative Gram-negatives (E. coli): two cell membranes
  – Non-fermentative Gram-negatives (P. aeruginosa): more genomic complexity

• Resistance mechanisms follow this hierarchy
  – Gram-positives have a limited range of resistance mechanisms
  – Non-fermentative Gram-negatives can have many mechanisms

• Discovery programmes must follow this ladder
  – This explains the current paucity of novel Gram-negative agents
  – You must walk before you run
  – Supporting early steps leads to later opportunities
Development is also iterative

- The first drug in a class
  - Platform for further development in a class
  - Penicillin G → oxacillin → piperacillin

- Insights about a given drug grow with time
  - Ciprofloxacin: Urinary tract infection → anthrax
  - Azithromycin: CAP → *Mycobacterium avium* (AIDS), malaria and GI infection (*Campylobacter*)

- Simple gateway indications provide entry vehicle
  - A path to CAP (Community-Acquired Pneumonia)…
  - … makes possible much more than just CAP

Lesson Four

The Paradox of Resistance

“*You can’t always get what you want*”

(*The Rolling Stones*)
The paradox of resistance

- Bacterial resistance drives need
  - New drugs are needed for bad bugs

- But, consider methicillin-resistant S. aureus (MRSA)
  - And, imagine Drug X: novel & active in vitro for MRSA

- What is the one study I must not do in man?
  - Drug X vs. methicillin
  - Also cannot do a placebo-controlled superiority study

- Rather, must use non-inferiority design vs. active agent
  - This confuses and has driven huge anxiety
    - Non-inferiority is more difficult to implement than superiority designs
    - New drug only seen as ‘non-inferior’ rather than superior
  - Real value (activity when other drugs not active) is not visible
  - **We have to get past this confusion:** We must not let the perfect be the enemy of the good

Lesson Five

The Paradoxes of Antibiotic Value

“Our heads are round so that thoughts can change direction”

*(Francis Picabia)*
The paradoxes of antibiotic value

• New antibiotic usage
  – “Congratulations! Well done! Important for us all!”
  – “Indeed, it is so important that let’s not use it”

• New antibiotic pricing
  – “New drug was only non-inferior to old (generic) drug”
  – “Why should anyone pay more than cost of old drug?”

• But if new antibiotic not available when needed?
  – “We have an outbreak NOW!”
  – “How can it possibly take 10 years to find a new drug?”

Conclusions
Lessons learned

• Effective antibiotics do amazing things
  – Modern medical care is not possible without them

• Discovery of antibiotics is hard
  – Start early. You can’t just open the taps

• Antibiotic discovery & development is iterative
  – Stay with it. Must support through early steps

• The paradox of resistance
  – Don’t expect direct superiority. Indirect proofs are key

• The paradoxes of antibiotic value
  – Must recognise & reward the true value of innovation

Resistance never sleeps: Perennial need

US hospital discharges with diagnosis of infection with drug-resistant microorganisms (ICD9 code V09), 1993-2005

1993–2005: A dramatic increase

Data from US Healthcare Cost and Utilization Project
The heart of the matter

“... the countermeasure that saves the day during a quick-hitting public health emergency can often take years to discover, develop, manufacture, and distribute.”

Kathleen Sebelius, Secretary DHHS
1 Dec 2009
AMA 3rd National Congress on Health System Readiness

Recommendations (1 of 2)

• Take a broad view on what is needed
  – Create conditions for a diverse long-term pipeline
  – Recognise that the true value of an antibiotic (or antibiotic class) emerges slowly
  – Continuous innovation is the best way to have options

• Increased dialogue on regulatory issues
  – Regulatory pathways: Consistent, stable, feasible
  – Ensure that gateway indications (e.g., CAP, skin) are accessible for both oral-only and IV drugs
  – Support creation and use of diagnostics for both the regulatory approval process & routine care
Recommendations (2 of 2)

• Reward the innovation of antibiotics
  – Early rather than late; more push than pull
  – Early: Orphan drug-like rules for antibiotic R&D
    • Tax incentives or credits; Research grants; Awards
  – Late: Patent extensions & exclusivity
  – Innovative: Product development partnerships, call options

• Recent EU discussions on antibiotics
  – Sept 2009: EU Conference on Innovative Incentives
  – Sept 2010: Follow-up conference
  – April 2011: WHO World Health Day

Exciting events

IDSA Initiative, Dec 2009

European Union Council: 1 Dec 09
...within 24 months, develop a comprehensive action-plan, with concrete proposals concerning incentives to develop new effective antibiotics...

US legislative activity:
GAIN Act
(Generate Antibiotic Incentives Now)

World Health Day: 7 April 2011

Antimicrobial resistance: no action today, no cure tomorrow