Antibiotics case study: How can re-studying old drugs improve existing ones?

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Slides are available on http://www.facm.ucl.ac.be → Lectures
What it's all about?

- Discovery of really novel antibiotic (new mode of action) is difficult due to the limited number of useful targets.

- In the past, several antibiotics of various classes were left undeveloped because of the success of blockbusters.

- Several “old antibiotics” are active against strains that have now become resistant to blockbusters.

- Revisiting these old molecules and tailoring them for use in specific situations of resistance may be much rewarding (“bacteria-personalized drugs...”) and help sparing the other ones.
The antibiotic crisis *

* A pictorial view using 4 paintings of Van Gogh (who stayed briefly in Belgium when moving from Holland to France) and with selected Belgian and International data…
Are antibiotics following a path to madness?

discovery in soil bacteria and fungi

1928 - …
Are antibiotics following a path to madness?

and then we all saw the blooming tree of semi-synthetic and totally synthetic antibiotics

1950 – 1980 …
Are antibiotics following a path to madness?

and the US General Surgeon told us that the fight was over

1970 …
Are antibiotics following a path to madness?
Extent of resistance of *P. aeruginosa* (International data – EUCAST breakpoints)

The hidden risk of therapy (at the corner of your street ...)

In vivo development of antimicrobial resistance in *Pseudomonas aeruginosa* strains isolated from the lower respiratory tract of Intensive Care Unit patients with nosocomial pneumonia and receiving antipseudomonal therapy

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Question #1: are you effective?

<table>
<thead>
<tr>
<th>Assessment of adequateness of initial therapy</th>
<th>No. of patients</th>
<th>No. of adequate antibiotics/total</th>
<th>% (no.) of patients with adequate therapy (EUCAST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>26</td>
<td>1/1</td>
<td>57.7 (15)</td>
</tr>
<tr>
<td>2 antibiotics</td>
<td>14</td>
<td>2/2</td>
<td>71.4 (10)</td>
</tr>
<tr>
<td>3 antibiotics</td>
<td>13</td>
<td>3/3</td>
<td>38.5 (5)</td>
</tr>
<tr>
<td>4 antibiotics</td>
<td>1</td>
<td>3/4</td>
<td>100(1)</td>
</tr>
</tbody>
</table>

Message #1: many patients receive ineffective antibiotics
Question #2: do you remain effective while treating?

- D0: initial isolate
- DL: last isolate obtained
- individual values with geometric mean (95 % CI)
- S (lowest line) and R (highest line) EUCAST breakpoints

* p < 0.05 by paired t-test (two-tailed) and Wilcoxon non-parametric test

a p < 0.05 by Wilcoxon non-parametric test only

Note: stratification by time between D0 and DL gave no clue (too low numbers)

Message #2: for all antibiotics, we see global increases of MIC during treatment
Question #3: Can you still treat patients?

• In North-America / Western Europe", we may still work with available antibiotics but we are reaching the limit…

A well known Belgian politician…

• heart attack during his holidays (in Europe) …
• transfer to hospital Intensive Care Unit
• nosocomial pneumonia …
• dying a few days later (multi-resistant organism)

• The situation becomes hopeless in several other countries for hospitals (Russia, Vietnam, …) and, for some countries, even in the community…
Resistance IS a problem ...

Has the era of untreatable infections arrived?

David M. Livermore*

Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections,
61 Colindale Avenue, London NW9 5EQ, UK

• The choices of effective therapies is narrowing dangerously for several important pathogens

• Good faith people try acting by
  – Rationalizing the choice among the remaining ones
  – Optimizing those "remaining antibiotics
  – decreasing the inappropriate use of antibiotics whenever possible and improving hygiene with close follow-up of the epidemiology
The problem is the lack of new compounds...

The drying pipeline?
So, what are the hurdles for new compounds?

• **Discovery:**
  – Remains (very) difficult especially for Gram-negative…

• **Clinical development:**
  – Remains costly (especially for new chemical entities) and will probably command (initially) a smaller market

• **Registration of new compounds:**
  – Provisional registration of really innovative compounds (at phase II level) may, in the future, be warranted … if solving unmet medical needs
  – Safety issues will remain of paramount importance but should not deter honest efforts (no drug is harmless !)
Why are Gram-negative so difficult?

1. Drug penetration requires porins
2. The drug must avoid efflux
3. The drug must avoid degradation
4. The drug must bind to its target
5. The drug must not harm eucaryotic cells
Amphiphilic aminoglycosides: an example of "dead" end?
Amphiphilic aminoglycosides: derivatives from neamine

## Amphiphilic aminoglycosides (methylnaphthyl neamine derivatives)

Table 1. Minimum Inhibitory Concentrations against Different *Staphylococcus aureus* Strains for the Neamine Derivatives, Neomycin B, and Neamine

<table>
<thead>
<tr>
<th>aminoglycosides</th>
<th>ATCC 25923</th>
<th>pump</th>
<th>NorA</th>
<th>pump</th>
<th>MsrA</th>
<th>enzyme</th>
<th>APH2′-AAC6′</th>
<th>enzyme</th>
<th>APH3′</th>
<th>enzyme</th>
<th>ANT4′</th>
<th>ATCC 33592</th>
<th>VRSA-VRS-2</th>
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<tr>
<td>neomycin B</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>&gt; 128</td>
<td>32</td>
<td>&gt; 128</td>
<td>&gt; 128</td>
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<td>neamine 1</td>
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<td>16</td>
<td>16</td>
<td>&gt; 128</td>
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<td>3′,4′,6-triPM 10c</td>
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<td>3′,4′,6-tri2QM 10d</td>
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</tbody>
</table>

Amphiphilic aminoglycosides
(methylnaphthyl derivatives)

- no significant inhibition of bacterial protein synthesis at 10 x the MIC
- decreased cell thickness decreased by 50% (Atomic Force microscopy) suggestive of intra-bacterial content leakage
- depolarization of bacterial membrane (DiSC$_3$(5) probe)
- binding to LPS (displacement of BODIPY-TRcadaverine)
- permabilization of liposomes mimicking *P. aeruginosa* membranes (POPE:POPG:CL; 60:21:11) (calcein release)

BUT ...

- cytotoxicity to eucaryotic cells at 2 to 10 x the MIC!
Amphiphilic aminoglycosides
(lipid derivatives of tobramycin)

Amphiphilic aminoglycosides
(lipid derivatives of tobramycin)

- MICs are between 4 (Staphylococci, Enterococci…) and 256 (Acinetobacter)
  → preferential anti-Gram + spectrum
- amphiphilicity is critical for antibacterial activity
- the pentacationic tobramycin-based headgroup appears to be optimal
  (vs. kanamycin, e.g.)
- MICs are increased (4 to 8 x) by addition of 4% albumin (binding)

BUT

- concentration-dependent hemolytic activity (37% at 100 mg/L)
  [can be reduced by replacement of the lipid tail by a fluorinated lipid tail (C₂H₄C₈F₁₇)
  but is still 27 % at 500 mg/L]
So, what are the hurdles?

- Discovery!
  - More efforts must be made with both public and private funding

Today, several new antibiotic programs are financed by the US DOD…

But NIH (and EU…) programs are catching up…
Why using "old" antibiotics?

- Clinical development!
  - Preclinical data are well known
  - Phases I and phase II are reasonable fast
  - The major weakness remains is in phase III

Currently, phase III studies are "controlled" (i.e. with a comparator) as per Regulatory Authorities requests…

Almost all antibiotic therapies are still initiated empirically (i.e. without documentation of the causative organism)

For ethical reasons, the comparator must be active

Therefore, most if not all studies follow a "non-inferiority" design
An example of success with daptomycin...

- Original molecule with a novel mode of action!

- Very bactericidal (membrane destabilization; no need of proteinaceous receptor!) and potent (MIC S. aureus = 0.5mg/L)

- Spare eucaryotic cells because they lack phosphatidylglycerol (critical for binding to Gram(+) membranes)

4-Step Intoxication Model

- Step 1: Calcium-dependent PG binding/insertion
- Step 2: Oligomerization (micelle formation)
- Step 3: Membrane distortion and ion leakage, depolarization
- Step 4: Lethal downstream events
Daptomycin: historical landmarks....

**1987**
Discovery of daptomycin as a novel anti-Gram + lipopeptide
In vitro and in vivo activity of LY 146032, a new cyclic lipopeptide antibiotic.

**1993**

**1997**

**2003-2006**

**2009-...**

**Development halted**
- lack of efficacy
- toxicity

“Lilly was not satisfied with the overall clinical results observed with the twice-daily dosing regimen utilized in these studies”

**Taking over by CUBIST**

or "pharmacodynamics in action ....."

**Once-daily** dosing in dogs optimizes daptomycin safety.

Daptomycin dose-effect relationship against resistant gram-positive organisms.
Cha et al, 2003, AAC 47:1598-603

**Approval at 4 mg/kg (skin)**
**and 6 mg/kg (bacteremia, endocarditis) by FDA and EMA**

- large success in the US
- problematic commercialization elsewhere
Temocillin

Temocillin revived

David M. Livermore\textsuperscript{1*} and Paul M. Tulkens\textsuperscript{2}

\textsuperscript{1}Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK; \textsuperscript{2}Unité de Pharmacologie Cellulaire et Moléculaire & Centre de Pharmacie Clinique, Université Catholique de Louvain, Bruxelles, Belgium
Resistance in Gram-negative pathogens is an increasing concern, with carbapenems often appearing as the only acceptable treatment option in serious infections. Reviving older compounds that have fallen into disuse may help to alleviate this burden. Temocillin (6-α-methoxy-ticarcillin) is resistant to most if not all classical and extended-spectrum β-lactamases and to AmpC enzymes. It is also chemically stable, allowing administration by continuous infusion.

Temocillin’s weaknesses, explaining its limited previous use, are a lack of activity against Gram-positive organisms, anaerobes and *Pseudomonas*. 
## Temocillin and efflux

<table>
<thead>
<tr>
<th>Strain</th>
<th>Origin</th>
<th>Description</th>
<th>MIC (mg/L)</th>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>temocillin</td>
<td>ticarcillin</td>
<td>- PAβN</td>
<td>+ PAβN</td>
<td>- PAβN</td>
</tr>
<tr>
<td>PAO1</td>
<td>ATCC</td>
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<td>1024</td>
<td>64</td>
<td>32</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>clin</td>
<td></td>
<td>512</td>
<td>64</td>
<td>32</td>
<td>16</td>
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<tr>
<td>168B</td>
<td>clin</td>
<td></td>
<td>256</td>
<td>32</td>
<td>16</td>
<td>16</td>
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<tr>
<td>PAO1</td>
<td>eng.</td>
<td>$\Delta(mexAB::FRT)$</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
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<td>2</td>
<td>0.25</td>
<td>2</td>
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<td></td>
</tr>
</tbody>
</table>

Fusidic acid...

Fusidic acid is bacteriostatic but may be bactericidal at high concentrations. Although fusidic acid has been used in many countries for years, it has never been approved in the US so far. In view of the mounting epidemic of community-acquired MRSA, a clinical development of fusidic acid in the US is presently under way.


**TAKSTA™ (CEM-102)**

Fusidic acid (TAKSTA™, CEM-102) is an antibiotic with a long history of safety and efficacy outside the United States. Cempra has exclusive rights to the supply of the compound for the U.S. market. Fusidic acid is orally active against gram-positive bacteria, including all *S. aureus* strains such as HA-MRSA and CA-MRSA. A novel dosing regimen has been successfully evaluated in a Phase II trial in patients with acute bacterial skin and skin structure infections (aBSSSI). Cempra is conducting a Phase II trial of TAKSTA for patients with prosthetic joint infections.
Colistin: History

- Isolated in Japan in 1949 from *Bacillus polymyxa var. colistinus* and indentified as **polymyxin E** (discovered in 1947 among polymyxins A to E).
- Differs from **polymyxin B** by only one aminoacid (D-Phe replaced by D-Leu)
- Exists under at least 2 components (**E1** and **E2**, also called colistin A and colistin B) differing by the length of the fatty acid chain
- Supplied as the
  - methylsulphonate derivative (often called methane sulfonate and also known as **colistimethate sodium**), which is a prodrug
  - sulfate (**colistine sulfate**)
Colistin Microbiology: morphological aspects

A recent prospective clinical study

Effectiveness and safety of colistin: prospective comparative cohort study

Mical Paul1,2*, Jihad Bishara1,2, Ariela Levcovich1,2, Michal Chowers2,3, Elad Goldberg1,2, Pierre Singer2,4, Shaul Lev2,4, Perla Leon5, Maria Raskin1,2, Dafna Yahav2,6 and Leonard Leibovici2,6

1Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; 2Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; 3Unit of Infectious Diseases, Meir Medical Center, Kfar Saba, Israel; 4Intensive Care Unit, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; 5Department of Anesthesiology, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; 6Department of Medicine E, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel

*Corresponding author. Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital, Petach Tikva, 49100, Israel. Tel: +972-3-9377512; Fax: +972-3-9377513; E-mail: paulm@post.tau.ac.il

Received 6 January 2010; returned 14 January 2010; revised 9 February 2010; accepted 12 February 2010

**Background:** Colistin has re-entered clinical use by necessity. We aimed to assess its effectiveness and safety compared with newer antibiotics.

**colistimethate:** 6–9 MU (million units) divided in 3 doses/day (if hemodialysis: 1–2 MU twice daily) if Gram (-) carbapenem resistant vs. beta-lactams (if susceptible)

**Conclusions:** The need for colistin treatment is associated with poorer survival. Adjusted analyses suggest that colistin is less effective and more toxic than β-lactam antibiotics.

*J Antimicrob Chemother* 2010; 65: 1019–1027
doi:10.1093/jac/dkq069 Advance publication 18 March 2010
Solving the problem of "uninteresting phase III studies"?

- Address a real problem … and look for the **correct target** (the bacteria)
  - Look for infections caused by multi-resistant RESISTANT organisms (or organisms you cannot fight with available antibiotics)
    (infections need NOT be necessarily severe…)

- Run the study in a **non-controlled fashion**
  - By definition, you cannot have a comparator if you aim at resistant organisms

- Target your study for non-inferiority against **historical controls**
  - Control = same type of infection caused by the same organisms but when it was still susceptible to the best-in-class antibiotic **at that time**

- By definition, **you will be superior** since the "control antibiotic" will not longer be acceptable.
Why not avoiding phase III altogether?

- Provisional registration could be warranted at phase II for really innovative compounds or compounds that solve unmet medical needs at phase II level if helping to solve unmet medical needs (and be accepted for that)!

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European Medicines Agency
Evaluation of Medicines for Human Use

London, 22nd March 2007

New antimicrobials are required to demonstrate non-inferiority to a licensed control. This can require hundreds, even thousands of patients across a development programme. Requirements for evidence of efficacy in phase III might be re-considered. It should be further discussed whether it might be preferable to relax the currently tight requirements for active comparator trials, so that less stringent demonstration of non-inferiority could be acceptable (especially) if absolute efficacy is clearly established (i.e. versus placebo).
Why not avoiding phase III altogether?

New antimicrobials are required to demonstrate non-inferiority to a licensed control. This can require hundreds, even thousands of patients. Efficacy in phase II is often insufficient to make it preferable to an existing licensed control. Demonstration of non-inferiority is difficult in a rapidly evolving situation and criteria for non-inferiority may be difficult to establish (i.e., data from phase II studies may be mute).

Exploring options for new and effective antibiotic treatments

Reviewing existing options to promote development of new antibiotics to treat multi-resistant bacteria including adaptation of clinical guidance documents, consideration of the balance between the amount of prior data needed with enhancing post-marketing surveillance, use of orphan legislation, etc.
What about safety?

- Registration: old scheme
  - Progression through phase I – II - III …
  - Until reaching the number of patients required for safety …
How to combine this with safety?

• Registration: proposed new scheme
  – Provisional registration at phase II level (solving the unmet medical need with compounds we know about …)
  – Continue evaluation through commercialization until reaching a number of patients equivalent to a phase III to get full registration

![Diagram of drug development phases with numbers of patients for each phase: preclinical (~50), phase I (~300), phase II (~6000), phase III (~6000).]
But there is still another problem?

- Discovery **IS** difficult…
- Preclinical development **IS** challenging…
- Clinical development and registration are **not easy** …
- But, will you recoup your investment?

This is a main part of the problem (in our current situation)
Why is economy important?

• Can you work without support? …
  – You need investors
  – Those will ask some return at some point…
  – And none ignores what is a ROI

This is what every economist will tell you (and you know it!)
Let us take a simple comparison …

• Pricing
  – Antibiotics are cheap…
  – And now, the Belgian pharmacist must deliver the cheapest one (generic)…
  – Why would Industry make an effort?

Allow me to take a simple example…

Pneumonia (> 60 years)

- Levofloxacin high dose: < 200 € / 10 days
- Survival of many years

Breast cancer (> 50 years)

- Trastusumab: > 20,000 € / year
- Survival of a few years
This may be saving lives … but at which price?


**Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study.**


Ludwig Center for Cancer Immunotherapy, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA. wolchokj@mskcc.org

*Figure 2: Kaplan-Meier estimate for overall survival, by treatment arm*

- gain in lifetime over dose (phase II trial)
- price of a **reimbursed** treatment: 77,000 euros/year
Do you remember having seen this?

Penicillin saves lives (in 1944)!

It is no longer true!

The Emerging Threat of Untreatable Gonococcal Infection

Gail A. Bolan, M.D., P. Frederick Sparling, M.D., and Judith N. Wasserheit, M.D., M.P.H.

Gonorrhea, which disproportionately affects marginalized populations, is the second most commonly reported communicable disease in the United States. Over the past 3 years, the gonococcus has shown decreased susceptibility to our last line of antimicrobial defense.
Old antibiotics may help …

Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia

Céline Pulcini,1 Karen Bush,2 William A. Craig,3 Niels Frimodt-Møller,4 M. Lindsay Grayson,5 Johan W. Mouton,6 John Turnidge,7 Stephan Harborth,8 Inge C. Gyssens,9,10 and the ESCMID Study Group for Antibiotic Policies

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In view of the alarming spread of antimicrobial resistance in the absence of new antibiotics, this study aimed at assessing the availability of potentially useful older antibiotics. A survey was performed in 38 countries among experts including hospital pharmacists, microbiologists, and infectious disease specialists in Europe, the United States, Canada, and Australia. An international expert panel selected systemic antibacterial drugs for their potential to treat infections caused by resistant bacteria or their unique value for specific criteria. Twenty-two of the 33 selected antibiotics were available in fewer than 20 of 38 countries. Economic motives were the major cause for discontinuation of marketing of these antibiotics. Fourteen of 33 antibiotics are potentially active against either resistant Gram-positive or Gram-negative bacteria. Urgent measures are then needed to ensure better availability of these antibiotics on a global scale.
But you may learn how to use them properly

Conserving antibiotics for the future: New ways to use old and new drugs from a pharmacokinetic and pharmacodynamic perspective

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\textsuperscript{j} SA Pathology at the Women's and Children's Hospital, North Adelaide, SA, Australia
Why not?