Antibiotic Discovery

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The decline in new classes of antibiotics reaching the market

THE ANALOGUE AGE

FADING OF THE ANTIBIOTIC AGE

THE GOLDEN AGE OF DISCOVERY

Number of new classes marketed
## ANTIBIOTIC PIPELINE

<table>
<thead>
<tr>
<th></th>
<th>Phase II</th>
<th>Phase III</th>
<th>Market</th>
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<tbody>
<tr>
<td>GRAM Positive</td>
<td>6 (1)</td>
<td>4</td>
<td>? 3-4</td>
</tr>
<tr>
<td>Broad Spectrum</td>
<td>4</td>
<td>0</td>
<td>? 1</td>
</tr>
<tr>
<td>GRAM Negative</td>
<td>3 (1)</td>
<td>2</td>
<td>?2</td>
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A peptide deformylase inhibitor and a leucyl-tRNA synthase inhibitor


What can we do?

Make new classes of antibiotics

Rebuild the infrastructure of antibiotic discovery
Why make new classes?

NEW CLASSES

VERSUS

ANALOGUES
New classes are needed to seed extensive antibiotic analogue development

Class Examples

\textbf{β-Lactams}

Penicillins: Penicillin G, penicillin V, methicillin, oxacillin, cloxacillin, dicloxacillin, nafcillin, ampicillin, amoxicillin, carbenicillin, ticarcillin, mezlocillin, piperacillin, azlocillin, temocillin

\textbf{Aminoglycosides}

Streptomycin, neomycin, kanamycin, paromomycin, gentamicin, tobramycin, amikacin, netilmicin, spectinomycin, sisomicin, dibekacin, isepamicin
Many new classes needed

<table>
<thead>
<tr>
<th>Marketed</th>
<th>Needed</th>
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<tr>
<td>[-----20-----]</td>
<td>[-2--]</td>
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| 19- | 20- | 21 |
| 40—50—60—70—80—90—00—10—20—30—40—50—60—70—80—90—00—10 |

Discovery of new classes requires a different approach to the discovery of analogues

New class: Structure of class unknown
Structure of target unknown
Genomics have not been successful so far
Whole cell testing early

New analogue: Structure of class known
Structure of target known
Genomics is useful
Whole bacterial cell testing later
Where do we start?

New Classes
Marketed

Whole bacterial cell assay

Multiplying (Fleming)  20+
Non-multiplying  0
Bacteriophages  0

Metagenomics  0
Genomic targets  0
Genomic-New TB targets


New class development

Whole bacterial cell target
Lessons from the past

Lessons from tuberculosis
Tuberculosis
A story of persistence
The life cycle of *Mycobacterium tuberculosis*
TB PERSISTS

Dormant  Disease  Chemotherapy

2 Billion  2 months  4 months  6 months
In TB patients, the initial fall in number of bacteria in sputum at the beginning of treatment (fast), is followed by a slow decline in bacterial counts (slow).

Tuberculosis persisters

Survive antibiotic therapy and immune system

Traditional antibiotics

Bacteria Numbers

FAST Multiplying

SLOW Non-multiplying PERSISTERS

Time
Are antibiotic resistant/tolerant persistent *Mycobacterium tuberculosis* metabolically active?

After rifampicin treatment, *M. tuberculosis* continues to incorporate [3H]uridine into RNA.

Radioactive Uridine Update
persistent *Mycobacterium tuberculosis*
Persisters in the murine Cornell Model

Viable counts of M. tuberculosis in mice treated with isoniazid and pyrazinamide (Cornell model)

In mouse, non-multiplying M. tuberculosis is slowly killed by antibacterials. After 14 weeks, a population of persistent organisms remains, which is highly resistant to antibacterials, cannot grow on culture plates or in liquid broth, and cause tuberculosis after cessation of therapy.
After treatment with antibacterials, *M. tuberculosis* mRNA is present although colony forming units are zero.

<table>
<thead>
<tr>
<th></th>
<th>rRNA</th>
<th>mRNA</th>
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<tbody>
<tr>
<td></td>
<td>16S</td>
<td>sigA</td>
</tr>
<tr>
<td><strong>in vitro</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>After</td>
<td>++</td>
<td>-</td>
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<tr>
<td><strong>in vivo</strong></td>
<td></td>
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<td>++</td>
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</tr>
<tr>
<td>After</td>
<td>++</td>
<td>-</td>
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Detection of *M. tuberculosis* RNA by RT-PCR before and after treatment with antituberculous agents

Is it possible to make new antibiotics against persisters?
Screen compound libraries from the beginning of the discovery process against dormant bacteria

THE FUTURE CHALLENGES FACING THE DEVELOPMENT OF NEW ANTIMICROBIAL DRUGS

Anthony Coates*, Yunnin Hu*, Richard Bax* and Clive Page*

The emergence of resistance to antibacterial agents is a pressing concern for human health. New drugs to combat this problem are therefore in great demand, but the past experience of antibacterial drugs indicates the time for resistance to new drugs to develop is often short. Conventionally, antibacterial drugs have been developed on the basis of their ability to inhibit bacterial multiplication, and this remains at the core of most approaches to discover new antibacterial development that could potentially alleviate the current situation of drug resistance — targeting non-multiplying latent bacteria, which prolong the duration of antimicrobial chemotherapy and so might increase the rate of development of resistance.

The market size of antimicrobial agents is now greater than US $25 billion per year. However, the global emergence of resistance to antimicrobial agents is increasing and limiting the effectiveness of current drugs. This review covers four approaches to the development of new systemic antibacterial agents: class-specific screening of structural changes to existing agents; genome hunting and a new route to targets; the non-multiplying, latent bacterial. To provide a background for the reader, elementary information about antibacterial agents and the first three of these developmental approaches is included, but they are not covered in depth, and references to more comprehensive reviews are provided. The primary focus of this review is the last, and relatively novel, approach targeting non-multiplying latent bacteria — which is hoped to lead to new drugs that will reduce the rate of emergence of resistance to antibacterial agents. For example, CLINICALLY LATENT BACTERIA prolong therapy, as they are not killed or are killed only slowly or partially by existing antibacterial agents. New drugs that target latent bacteria could reduce the duration of chemotherapy and thereby probably reduce the rate of chemotherapy of resistance as well as increase patient compliance, which would lower the rate of emergence of resistance further. In addition, these drugs might reduce the potential period of suboptimal therapy that is associated with the emergence of resistance to antibacterial agents, and could diminish the rate of emergence of chromosomal mutations that could lead to resistance in clinically latent bacteria.

Background

Before the introduction of antibiotics in the 1940s and 1950s, patients who had bacteremia — for example, with Staphylococcus aureus — had a low chance of survival, and the mortality from tuberculosis was 50%. Antibiotics radically changed this bleak prognosis, and new classes of antimicrobial agents rapidly entered the market in the 1950s and 1960s. Unfortunately, this led to over-confidence that infectious diseases would be eradicated. In addition, the large costs of research, combined with difficulties in discovering new, broad-spectrum antimicrobial drugs with previously unexploited modes of action, discouraged pharmaceutical companies from investing in this area, and many left the field.

No new classes of antibiotics were produced in the 37 years between the introduction of nalidixic acid in 1962 and linezolid in 2000: all of the antibacterial agents that entered the market during this period were modifications of existing molecules. To make
2002-2012
Antibiotic Discovery Centre

University
St George’s

Industry
Helperby Therapeutics
Antibiotic Discovery Platform
The History of Helperby’s Antibiotic Discovery Program

Helperby has a novel patented screening platform to select compounds which are active against multi-drug resistant bacteria.

These compounds (new class) have been shown to **enhance** the effect of old antibiotics against resistant bacteria.
Industrial

• £12 million raised
• 10 years
• 300 small chemical molecules
• 49 patent applications
• Clinical trials with lead product
• Seven programs
Comparison of kill of non-multiplying *Staphylococcus aureus* (MSSA) HT61 v marketed antibiotics

![Graph showing the comparison of kill of non-multiplying *Staphylococcus aureus* (MSSA) HT61 v marketed antibiotics. The x-axis represents concentrations (microgram/ml) and the y-axis represents log CFU/ml. The graph compares Augmentin, Azithromycin, Levofloxacin, Linezolid, Mupirocin, and HT61.](image)
HT61 triggers depolarization of bacterial cell membrane and breakage of cell wall.
The first antibiotic developed against persisters is in clinical trials

No resistance development to HT61 has been observed in *S. aureus* so far.
Development of Enhancer Program

By attacking the cell membrane, Helperby’s new generation enhancers, in combination with known antibiotics, kill resistant bacteria.

- Old antibiotics
  - Development of resistance
  - Relapse of disease
  - Prolonged treatment times

- Helperby’s Enhancer
  - No resistance generation so far
  - Low relapse
  - Fast kill

- Helperby’s Enhancer + Old antibiotic
  - Revive many old antibiotics
  - Low development risk
  - New patents for combinations with old drugs
Enhancer increases the potency of Antibiotic

(E = Enhancer; A = old antibiotic)

![Graph showing the effect of Enhancer on Antibiotic potency over time. The graph compares the log CFU/ml of Bacteria under different conditions: E (Enhancer), A (old Antibiotic), and A + E (Enhancer + old Antibiotic). The graph shows a significant decrease in CFU/ml when Enhancer is used, indicating increased potency.]
The Importance of Enhancers

- Rejuvenate old and existing antibiotics
- Source of new patents for combinations
- Wide spectrum of clinical indications
- Relatively low development risk
Third party opinion of the Helperby approach

- Paper in Nature: Hurdle et al. 2011# - membrane-active agents form an important new means of eradicating recalcitrant, non-growing bacteria.

- National Institute of Health (NIH) – presented Helperby approach at NIH meeting in Washington D.C. in April 2011 and had considerable interest from them.

- NIH has indicated its intention to set aside money for grants in this area##.

- NDAs signed with two Pharmaceutical Companies interested in possible partnering arrangements with Helperby.

## NIH has issued a "cleared council concept" on latent/dormant infections, which means that there will likely be a solicitation released on that topic (in the next few months).
Regulators

**FDA**
Clinical endpoint (4000 patients)

**EMA(MHRA)**
Microbiological endpoint (300-600 patients) eg number of Staphylococcus aureus in nose
## Microbiological versus Clinical endpoint for market authorisation

<table>
<thead>
<tr>
<th>Microbiological</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>300-600 patients</td>
<td>4,000 patients</td>
</tr>
<tr>
<td>Colony Forming Units</td>
<td>Death/SSI</td>
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<td>$4.5-9 million</td>
<td>$70 million</td>
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MA Cooper and Schlaes – Nature, April 2011
Rebuild Antibiotic Discovery infrastructure in universities and industry
University

ANTIBIOTIC DISCOVERY

SRF
Tech
Tech
PD
PhD
PhD
University

ANTIBIOTIC DISCOVERY

SRF
Tech
Tech
PD
PhD
PhD

Industry
ANTIBIOTIC DISCOVERY

PhD
SRF
Tech
Tech
PD
PhD

University

Industry

KI
CNRS
DTI
MPI
UG
UAM
UCL
UL
WI
LEMI
ISS
US
Antibiotic Discovery UK

ANTIBIOTIC DISCOVERY UK

SA
UL
SGUL
KC
What would be the cost of marketing 20 new classes of antibiotics?

Research Spending Per New Drug

$43.4 million* - $11.79 billion**

Research Spending for 20 New Drugs

$1-200 billion***


**Sources: InnoThink Center For Research In Biomedical Innovation; Thomson Reuters Fundamentals via FactSet Research Systems

*** Does not take into account rebuilding antibiotic discovery in Universities and Industry, or the increased costs associated with a new class rather than an analogue
Revolving loan system

Bank

Revolving door

SMEs

Conclusion

• New classes of antibiotics are needed
• Lessons from tuberculosis
• Importance of whole cells in the discovery of new classes
• The Antibiotic Discovery Centre at St George’s
• Antibiotic Discovery UK
• European Antibiotic Recovery Plan
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