Overcoming Resistance Through Novel Drug Targets

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There is an urgent need for new antibiotics

The number of new marketed antibiotics has fallen

The golden age of discovery
The analogue of the antibiotic age
Fading of the antibiotic age

- Resistance has arisen to every marketed antibiotic – urgent need for more antibiotics
Why are so few antibiotics reaching the market?

Tree of antibiotics

Low lying fruit has already been picked – few remain

Pharmaceutical companies leave the antibiotic research arena

Diminished net present value;
Discovery problems;
Increasing market restrictions;
Increasing regulation

Targets

- Bacterial molecules
- Bacteriophages
- Whole bacteria
  - Multiplying
  - Non-culturable
  - Non-multiplying
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TARGET – bacterial molecules (genomics)

Identification of an essential gene not shared by humans

Inhibition of essential gene product activity

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Kill of bacteria by inhibitor

Problems with the genomic approach
- Poor penetration through bacterial cell wall
- Efflux
- Difficult to translate into bacterial kill
- Resistance due to target of single bacterial molecule
- Resistance
- No marketed antibiotics

TARGET – bacteriophage
- Kill half of world’s bacteria every two days
- Head
- Collar
- Sheath
- Base plate
- Tail fibres
Treatments with bacteriophages and products (e.g. Endolysin Cpl-1)

- Bacteriophage therapy – in use for decades; However, no adequate clinical trials of efficacy

Problems
- Patent
- Standardisation
- Resistance
  - Formulation
  - Mode of administration
  - Safety
  - Immunogenic
  - Toxic shock
  - Clinical trials subject to agreed standards are needed
  - Regulatory requirements need to be clarified

TARGET – whole bacteria

1. Conventional – multiplying bacteria
2. Non-culturables
3. Non-multiplying bacteria
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TARGET – conventional-multiplying bacteria

Natural compounds (most marketed antibiotics)
Most “natural” antibiotics already discovered, and resistance now widespread

Chemical-derived compounds (few marketed antibiotics)
Diversity of libraries insufficient
Combinatorial chemistry or equivalent needs to be improved

Most metabolic pathways have already been targeted by marketed antibiotics

TARGET – non-culturable bacteria

Productive DNA fragments may be too infrequent to be detected by cloning

DNA fragments may not contain all the genes needed for antibiotic expression
Culture difficult

TARGET – non-multiplying bacteria

Multiplying

Non-multiplying

Infected tissue
Infectious diseases that contain non-multiplying persistent bacteria

- Tuberculosis

Bacteria lie dormant
Time to cure – 6 months

Bacterial endocarditis
Vegetations on valves
Time to cure – weeks

Catheter infections (biofilms)

- Intravenous
- Urinary

Time to cure – indefinite
(Until removal of the catheter)
Prosthesis infections (biofilms)

Biofilm on prosthesis
Pacemaker
Hip
Hand
Metal plate
Knee

Time to cure – indefinite
(Until removal of prosthesis)

Current antibiotics kill or inhibit multiplying bacteria, but are bacteriostatic for non-multiplying organisms

Multiplying

Antibiotic

Non-multiplying

PERSISTERS

The consequences of survival of non-multiplying bacteria

Multiplying

Antibiotic

Non-multiplying

Genetic resistance

Poor compliance
Clinical relapse
Antibiotic
Antibiotic
Antibiotic
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Ways of making new antibiotics against whole live bacteria

- The Fleming method: produced all the current marketed antibiotics
- Coates-Hu method (no marketed antibiotics yet)

Feasibility of making new antibiotics against non-multiplying bacteria
Helperby therapeutics

Potential advantages of new antibiotics which kill non-multiplying and multiplying bacteria
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Problems

Many different subpopulations
One antibiotic cannot kill them all

Antibiotic A
→ Kill
Antibiotic A
→ No kill
Antibiotic A
→ No kill
Antibiotic A
→ No kill

Fewer molecular targets
in non-multipliers than multiplying bacteria

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Low penetration, high efflux

- Low penetration

High local concentration of bacteria

- Kill
- Kill

Standardisation

- Bacterial molecules: enzyme inhibition or equivalent
- Bacteriophages: plaque-forming units
- Whole bacteria
  - Multiplying: MIC (minimum inhibitory concentration)
  - Non-culturable: MIC
  - Non-multiplying:
    - MSC (minimum stationary-cidal concentration)
    - MDC (minimum dormicidal concentration)
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Minimum stationary-cidal concentration

![Graph showing concentration of drug vs. log CFU for MSC and MDC concentrations.]

Minimum dormicidal concentration

![Graph showing concentration of drug vs. log CFU for MSC and MDC concentrations.]

Conclusion

- Increasing resistance and decreasing numbers of antibiotics reaching the market signal that the antibiotic era is fading away

<table>
<thead>
<tr>
<th>TARGETS</th>
<th>R&amp;D</th>
<th>Marketed</th>
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</thead>
<tbody>
<tr>
<td>Bacterial molecules</td>
<td>Phase II</td>
<td>No</td>
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<tr>
<td>Bacteriophages</td>
<td>-</td>
<td>Yes</td>
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<tr>
<td>Whole bacteria</td>
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<td></td>
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<tr>
<td>Multiplying</td>
<td>Phase IV</td>
<td>Yes (all)</td>
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<tr>
<td>Non-culturable</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>Non-multiplying</td>
<td>Phase II</td>
<td>No</td>
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