Alternatives to Antibiotics

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Antimicrobial peptides

- Some plants, animals and fungi make peptides, small proteins that destroy bacteria.
- Peptides from amphibians and reptiles (unusually resistant to infection), could yield new therapeutics.
- Peptides with antibacterial activity have been isolated from:
  - Frogs,
  - Alligators
  - Cobras,
Antimicrobial peptides

• These peptides can be modified to increase their potency, and several are in clinical trials.
• Pexiganan, based on a peptide from frog skin, is now in phase III clinical trials to treat diabetic foot ulcers.
• But synthesizing peptides can be expensive.

Gene-editing enzymes

• CRISPR, (Clustered regularly interspaced short palindromic repeats) a gene-editing technique that has taken the scientific world by storm.
• It is based on a strategy that many bacteria use to protect themselves against phages.
• Researchers are turning that system back on itself to make bacteria kill themselves.
Gene-editing enzymes

- Normally, the bacteria detect and destroy invaders such as phages by generating a short RNA sequence that matches a specific genetic sequence in the foreign body.
- This RNA snippet guides an enzyme called Cas9 to kill the invader by cutting its DNA.
- Scientists are now designing CRISPR sequences that target genomes of specific bacteria, and some are aiming their CRISPR kill switches at the bacterial genes that confer antibiotic resistance.

Metals

- Metals such as copper and silver are the oldest antimicrobials.
- They were by ancient Persian kings to disinfect food and water.
- Researchers beginning to understand how metals kill bacteria.
- The use of metal nanoparticles as antimicrobial treatments is a popular research, although little research has been done in people.
Metals

- Because metals accumulate in the body and can be highly toxic, their use may be restricted mostly to topical ointments for skin infections.

- An exception is gallium, which is toxic to bacteria that mistake it for iron, but is safe enough in people to be tested as an intravenous treatment for lung infections.

- Researchers at the University of Washington will soon start a phase II clinical trial of gallium in 120 patients with cystic fibrosis.

- Pilot studies found that the metal was moderately successful at breaking down microbial biofilms in the lungs and improving patients’ breathing.
Phages

- Of all the alternatives to antibiotics, phages have been used the longest in the clinic.
- Scientists in the Soviet Union began developing phage therapies in the 1920s, and former Soviet countries continue the tradition.
- Phages have several advantages over antibiotics.
- Each type attacks only one type of bacterium, so treatments leave harmless (or beneficial) bacteria unscathed.
- And because phages are abundant in nature, researchers have ready replacements for any therapeutic strain that bacteria evolve to resist.
Phages

- Antibiotic resistance is driving more Western patients to phage-therapy clinics in Eastern Europe.
- Phages research is regarded as a priority for addressing the antibiotic crisis.
- A clinical trial of a phage treatment for infections associated with burns is on the run.

**Table 2**

<table>
<thead>
<tr>
<th>Bacteriophages vs. Antibiotics</th>
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<tbody>
<tr>
<td><strong>Advantages</strong></td>
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<tr>
<td>- Very specific (affect only targeted bacterial species)</td>
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<tr>
<td>- Replicate at the site of infection</td>
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<tr>
<td>- Occur naturally (easy to locate)</td>
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<tr>
<td>- Safe (no reports of serious adverse effects)</td>
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<tr>
<td>- Active against antibiotic-resistant bacteria</td>
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<tr>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>- Additional research required (lack of studies)</td>
</tr>
<tr>
<td>- Development of phage resistance and phage-neutralizing antibodies</td>
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<tr>
<td>- Not accessible to intracellular pathogens</td>
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<tr>
<td>- Difficult to administer (special training required)</td>
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<tr>
<td>- Can transfer toxin genes between bacteria</td>
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*Source: References 4, 7, 12-14.*

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**ClinicalTrials.gov**

A service of the U.S. National Institutes of Health

**Evaluation of Phage Therapy for the Treatment of Escherichia Coli and Pseudomonas Aeruginosa Wound Infections in Burned Patients (PHAGOBURN)**

This study is currently recruiting participants. (see Contacts and Locations)

- Sponsor: Pherecydes Pharma
- ClinicalTrials.gov Identifier: NCT02118010
  - First received: April 1, 2014
  - Last updated: July 23, 2015
  - Last verified: July 2015

[Click here for more details on ClinicalTrials.gov]
Predatory bacteria

- Bacteria cause infection, but some can also fight it by preying on fellow microbes.
- Several researchers are beginning to test these predatory bacteria in animal models and cell cultures.
- The best-known species, *Bdellovibrio bacteriovorus*, is found in soil.
- It attacks prey bacteria by embedding itself between the host’s inner and outer cell membranes, and begins to grow filaments and replicate.
- The host bacterium eventually explodes and releases more *B. bacteriovorus* into the environment.

Predatory bacteria

- Researchers are also studying the therapeutic potential of the predatory bacterium *Micavibrio aeruginosavorus*.

- The Vampire bacteria
• Antisense drugs are based on the fact that antisense RNA hybridizes with and inactivates mRNA.
• These drugs are short sequences of RNA that attach to mRNA and stop a particular gene from producing the protein.

Antisense technology

Biofilm disruption
• Biofilm is defined a structured community of bacterial, algal, or other types of cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface.
• Advantages
  • Nutrients tend to concentrate at surfaces
  • Protection against predation and external environment
  • Pooling of resources (enzymes) from varying bacterial species in biofilm
Biofilm disruption

- Chemicals
- Laser
- Enzymatic
- Detergents
- others

Quorum sensing inhibitors

- Quorum sensing is the regulation of gene expression in response to fluctuations in cell-population density
Quorum sensing inhibitors

- Quorum sensing bacteria produce and release chemical signal molecules called autoinducers that increase in concentration as a function of cell density.

Natural Products
New antibiotics

- Teixobactin and iChip Promise Hope Against Antibiotic Resistance
- Teixobactin is the first new class of antibiotic announced in decades

The Most Effective alternative is to prevent infection

Eat healthy food and keep your normal flora happy
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