Healed by a crocodile: The search for new antibiotics.

TEDx GMU

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We need new antibiotics.

- Rampant Antibiotic Resistant Infections emerging globally.
- Common infections becoming untreatable.
We need new antibiotics.

- Very few new antibiotics in the drug development pipeline.
- Entering the Dark Ages of antibiotic resistance.
We need new antibiotics.

- Resurgence of “old” infections: Tuberculosis – a modern plague
Lest we forget…

- June of 1924 a young man developed a blister on his toe while playing tennis.
- A week later he was dead from a bacterial infection.
- The young man was President Calvin Coolidge's son.

- When he heard the news, Coolidge wept and asked what was "the power and the glory of the presidency" worth if he could not prevent the death of his son from a simple blister?

- That is the world we are heading back to…

Calvin Jr., Calvin Sr., Grace, and John Coolidge, and their dog. This photo was taken on the same day that Calvin Jr. got a blister while playing tennis and later died from the infection.
The “Dark Ages”

- 4 y.o. girl in excellent health suddenly developed facial skin infection
- Spread relentlessly, fever to 104°F
- Could not sleep because her face and neck so swollen she could not swallow her own saliva
- Began gasping for breath

Herrell. 1943. Proc Staff Meetings Mayo Clinic 18:65-76
On arrival to the hospital

After 14 days of penicillin

“Moribund” (on the verge of death)

Totally fine...
Antibiotics: A Global Resource in Need of Protection

- Prior generations of scientists gave us the gift of antibiotics
- Today, we have to ensure this global treasure is available for our children and future generations.

Infectious Diseases Society of America campaign
Where can we find new antibiotics?
Two types of immunity

“Specific” immunity
- based on antibodies.
- (for example, vaccines).
- Takes 21 days to develop.
- Very focused on one microbe (such as this year’s flu shot).

“Innate” immunity
- “broad-spectrum” general protection.
- Not specific to one microbe.
- Not based on antibodies.
- Keeps you alive for the 21 days until Specific Immunity kicks in.
How does innate immunity work?

- Partly through Antimicrobial Peptides.
  - Very small proteins that can kill bacteria.
  - Made by most higher organisms.

Structural classes of antimicrobial peptides.
(A) Mixed structure of human β-defensin-2
(B) looped thanatin
(C) β-sheeted polyphemusin
(D) rabbit kidney defensin-1
(E) α-helical magainin-2
(F) extended indolicidin.

Antimicrobial peptides kill bacteria.
Bacteria make biofilm

http://7bigspoons.com/wp-content/uploads/2012/05/Bacteria-wearing-an-acid-resistant-rain-coat.png
We can make “anti-biofilm” antimicrobial peptides


Where else can we find new antibiotics?
We can take antimicrobial peptides and make them better

*Naja atra*, the Chinese cobra

<table>
<thead>
<tr>
<th>Anti-microbial peptide</th>
<th>Sequence</th>
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<tbody>
<tr>
<td>NA-CATH</td>
<td>KRFKFFKKLKNVKKRKKFKKPKVIGVTFPF</td>
</tr>
<tr>
<td>NA-CATH:ATRA1-ATRA1</td>
<td>KRFKFFKKLKNVKKRFFKKKLVIGVTFPF</td>
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Crocodiles & Alligators

Why crocodiles?

Seem resistant to skin/wound infection, despite living in swamps.

Evolutionarily ancient
- have had millennia to select the best ways of fighting off infection.

Crocodile/Alligator Blood is known to have antimicrobial properties.

The genome is not sequenced yet.

Attempts have been made to find antimicrobial peptides – mostly unsuccessful.
How to purify an antimicrobial peptide.

One precious tube of alligator or crocodile blood.

Now what?
BioProspecting: A new way to purify an antimicrobial peptide

- obtain antimicrobial peptides from many kinds of natural samples.
  - Blood, urine, saliva, etc.
- “Bio-prospecting”.
- quickly capture new antimicrobial peptides from samples
- use advanced modern biochemical technologies
  - Nanomaterials & Nanoparticles
  - Advanced Mass Spectrometry to identify antimicrobial peptides.
BioProspecting

Large Volume Complex Sample (e.g., Crocodile Blood)

Small peptides trapped (and protected)

Sieving Shell

Binding core

Concentrated, Isolated Peptides

Recover particle w/ harvested peptides.
New Crocodile Peptide

- Using multiple techniques, we identified a new Crocodile Antimicrobial peptide.
- We called it “CHOMP”
  - It kills lots of different bad bacteria in the lab.
  - It is similar, but not identical, to a known “class” of antimicrobial peptides.

http://ars.els-cdn.com/content/image/1-s2.0-S1074552110004813-gr1.jpg
Our Dream....

"CROCOSILLIN"

Thanks to
...He Will Come Home!
Summary:

- It is critical to conserve antibiotics as a precious resource.
- We have to work urgently to develop new antibiotics.
- We have to be creative in how we find new antibiotics.
RESEARCH ARTICLE

Bioprospecting the American Alligator (Alligator mississippiensis) Host Defense Peptidome

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