Bacteriophage Therapy

Dr. Sarica Cernohous, L.Ac.
Naturallylivingtoday.com
Funkykitchenfresh.com

Goals for Today

Importance

Comparison to antibiotics

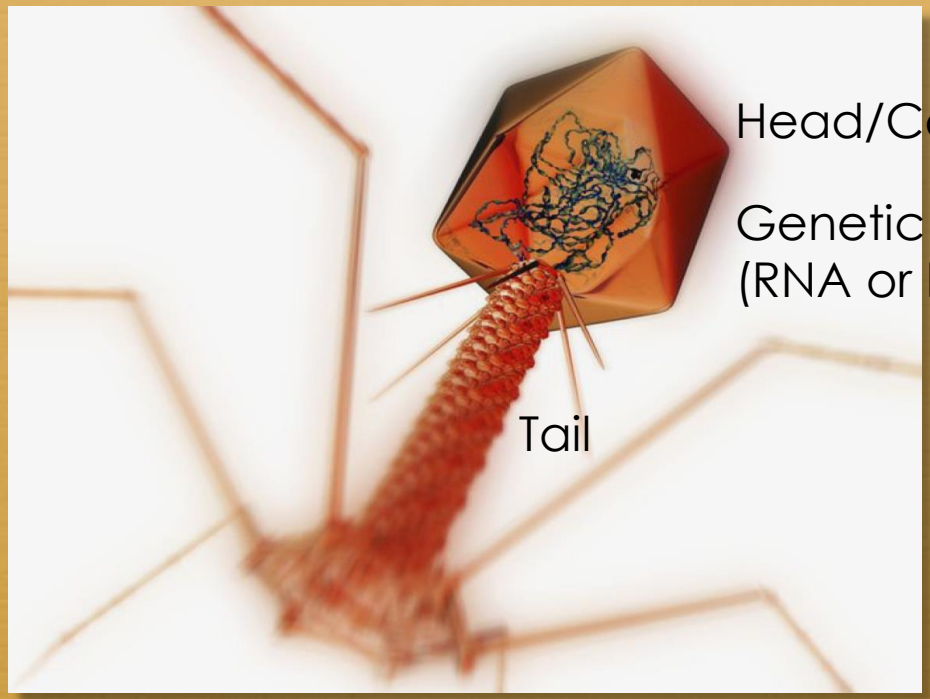
History of therapeutic use

Definition of propagation cycles

Use and concerns with food

Practical application in your practice

Bacteriophage



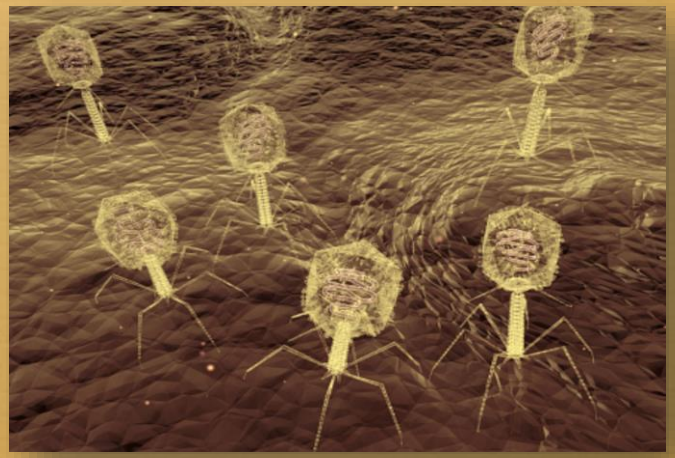
Bacteriophage in the Natural World

Sea Water

Animal Intestines

Soil

Dental Plaque and Saliva

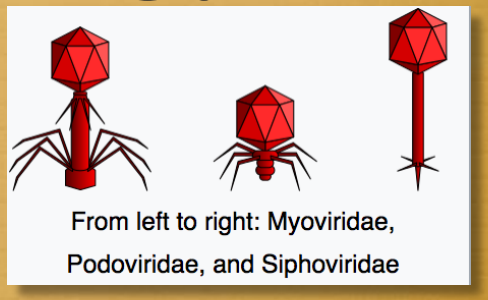


"Humans and bacteriophages, which are ubiquitous in the environment, have coexisted since humans arrived on the Earth, and thus they are very safe."

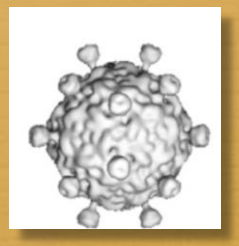
Chris Smith, CEO Phage International

Bacteriophage in the Human Inner Ecology

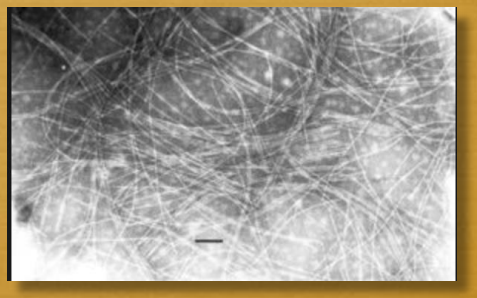
1st days and months: *Caudovirales*



In the first 2 years: *Microviridae*



Adults: *Caudovirales* (*Podoviridae*, *Siphoviridae* and *Myoviridae*), or *Microviridae* and *Inorviridae*



Bacteriophage Replication

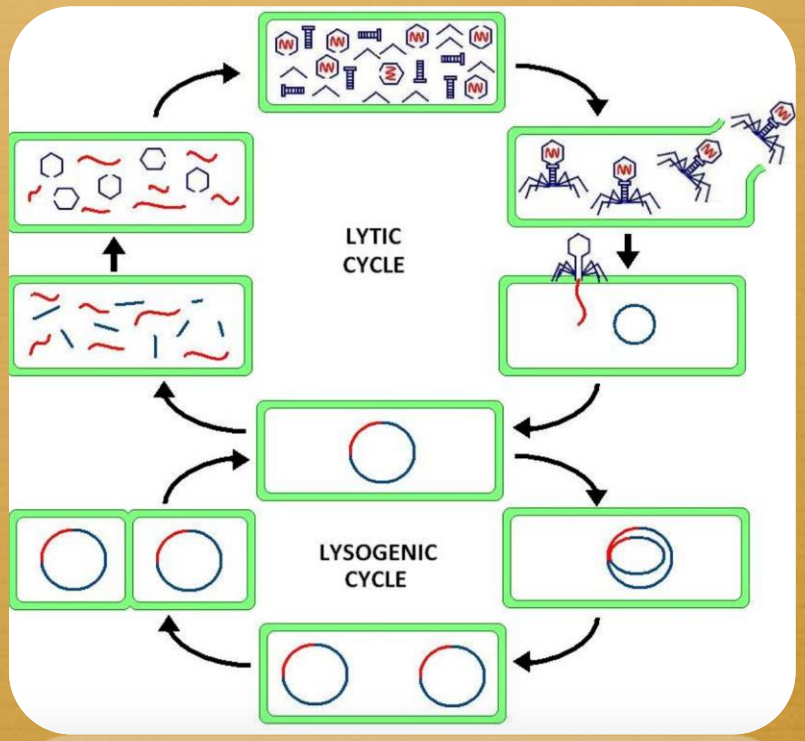
Viruses are acellular—host required for replication

Lysogenic

- Zombie
- New genetic material passed into the bacterial host

Lytic

- Inject—Fill—Explode/Destroy—Repeat




Bacteriophage T4 Virus
Life Cycle

Antibiotic Resistance

Urgent (CDC-deemed)

Clostridium Difficile (CDIFF)

Carbapenem-Resistant Enterobacteriacae (CRE)

Neisseria gonorrhoeae

Serious

Acinetobacter Campylobacter Candida

Enterobacteria Enterococcus Pseudomonas

Salmonella Shigella Staph Aureus

Strep Pneumonia Tuberculosis

Expected to kill 10 million people annually by 2050

History of Bacteriophages

France

Poland

Russia

Georgia

US

French Bacteriophage Highlights

1919: Isolation and use of phage against dysentery in children's hospital by Felix d'Herelle

1921: published seminal work citing therapy for dysentery, energizing the world of microbiology

Recognized there were virus that were capable of parasitizing bacteria, and suggested use of cocktails

Later years, commercial production allowed for thousands treated for cholera and bubonic plague in India—phage prep in wells of cholera stricken

Historical Commercial Production

d'Herelle in Paris
Marketed by predecessor to L'Oreal

- *Bacte-coli-phage*
- *Bacte-rhino-phage*
- *Bacte-intesti-phage*
- *Bacte-pyo-phage*
- *Bacte-staphy-phage*

Eli Lilly in US
Products for American market

- *Colo-lysate*
- *Ento-lysate*
- *Staphylo-lysate*
- *Neiso-lysate*
- *Colo-jel*
- *Ento-jel*
- *Staphylo-jel*

Eli Lilly Products in the US Market 1940's

The Elements

OF

Biologics

Prepared by the Biologic Department of Eli Lilly and Company for Lilly Representatives, Pharmacists, Students of Pharmacy and Medicine

What Lysates are marketed?

Colo-Lysate (Combined)
Ento-Lysate
Staphylo-Lysate
Strepto-Lysate

What are the clinical indications for each?

Staphylo-Jel and Staphylo-Lysate are useful in the treatment of localized epithelial surface staphylococcus infections. The lysate may be used parenterally or intraspinally, as well.

Ento-Jel and Ento-Lysate are indicated in the treatment of nasopharyngeal infections.

Colo-Jel (Combined) and Colo-Lysate (Combined) are indicated in the mixed infections of the abdominal and pelvic regions.

Strepto-Jel and Strepto-Lysate are indicated in localized epithelial surface streptococcus infections. The lysate may be used parenterally or intraspinally.

Pasteur Institute Highlights

Especially useful in **Staph**, Pseudomonas, Proteus and Coliform infections

Staph of bone, cardiac, respiratory, septicemia, skin lesions, kidney were commonly treated with either a phage cocktail or adapted phage, where AB had failed

Multiple modes of administration for Staph infections

local application

injection

IV injection

GI dispersion into blood

Phages in Poland

Hirszfeld Institute of Immunology and Experimental Therapy

Founded 1954

Specific preparations from Institute collection

550 patients 1981-86, articles and discussions

75-100% cure rate
http://blogs.evergreen.edu/phage/

Phages in Georgia

Eliava Institute

- Pathogenic strains from throughout Soviet Union
- 1200 staff, creating 2 tons/week
- Predominately for soldiers for diarrhea and wounds
- Public use (no Rx):
  - *Intestiphage*
  - *Pyophage*
  - Both updated regularly

Phages in Russia

- Extensive use, notably for soldiers, children and infants
- Language, national security concerns challenges to sharing information
  - Much focus on diarrheal concerns, gangrene and other battle issues
  - Creams, injections, liquids for enemas and tampons, aerosols and the first tablet-stable format

Phages and Food

"Despite advances in modern technologies, the food industry is continuously challenged with the threat of microbial contamination.

The overuse of antibiotics has further escalated this problem, resulting in the increasing emergence of antibiotic-resistant foodborne pathogens.

Accordingly, bacteriophages and their derivatives have emerged as novel, viable, and safe options for the prevention, treatment, and/or eradication of these contaminants in a range of food and food processing environments"

Phage Therapy in the Food Industry--*Annual Review of Food Science and Technology (2014)*

"Towards a food safety perspective, strictly lytic phages are possibly one of the most harmless antibacterial approaches available."

Bacteriophages and Their Role in Food Safety--*International Journal of Microbiology ()2012)*

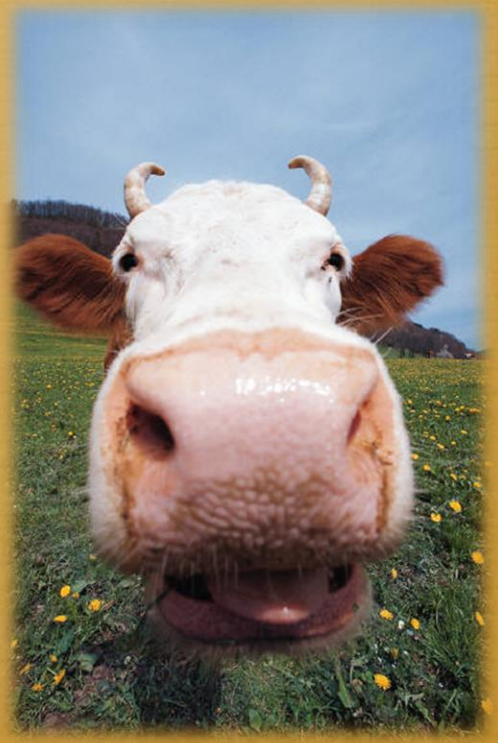
Most common foodborne pathogens of animal origin

Listeria

E coli

Campylobacter

Salmonella



Listeria

- Gram Positive, Motile Intracellular Bacterium
- Grows in many food matrices and storage conditions
- Often transmitted in ready to eat foods, poultry and dairy products
- Very minimal incidence, but has a high mortality rate if infected (255 deaths averaged in US alone)
- **Phage applications are based on post-harvest use**
- Phages for listeria are most influenced by contact time and dose, more than temperature

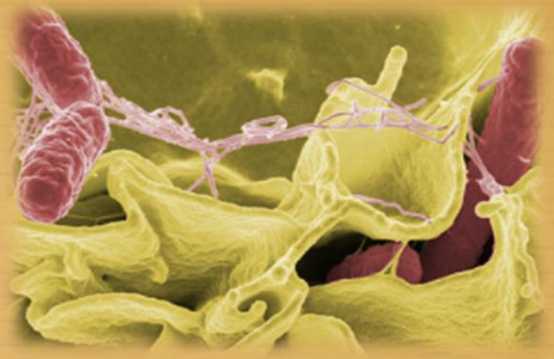
E Coli

- Gram-negative bacterium
- Prolific in ruminant intestines, fecal matter or dust on the animal's hide
- Contamination through undercooked meats, or raw milk or water that have had cross-contamination with fecal matter
- Highly virulent
- Phage therapy has mainly focused on poultry and ruminants, with mixed success when administered pre-harvest; **all post-harvest applications since 2000 have proven effective, both on the meat and on production and serving equipment**

Campylobacter

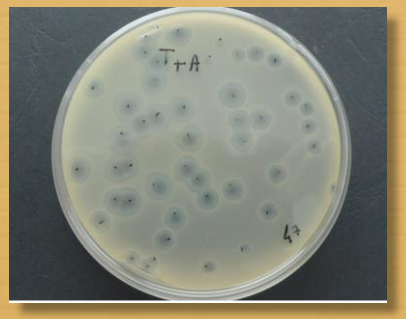
- Gram-negative, Spiral, Motile Bacterium
- Very low-dose ingestion (400-500 cells) can cause bloody diarrhea, fever and abdominal pain, averaging about 845,000 hospitalizations and 76 deaths each year in the US
- Capable of colonizing in the bowels of poultry and cattle, with human infection mostly through fecal-oral contact, contaminated raw foods and drinking water (feces in both)
- **Pre-harvest phage application has shown reduction in bacterial numbers, and post-harvest application has shown positive effect in two separate scenarios**

Salmonella



- Gram-negative bacterium, considered to be one of the principal causes of human-animal cross-interaction diseases in the world
- Can colonize and persist within the GI tract, and so human salmonella poisoning is often associated with consumption of contaminated animal foods, notably eggs, poultry, pork and beef (in that order)
- Can present with fever, abdominal cramps, diarrhea and life-threatening aspects
- **2 pre-harvest phage applications have been approved by the FDA (either sprayed on the animals, or on their feed)**
- **All post-harvest phages have shown effect on raw meats, ready to eat foods, and produce**

Bacteriophage Isolation



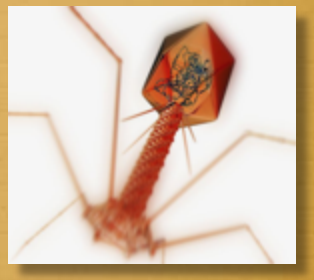
Enrichment of chosen sample

Nutritional medium is infected with bacteria; the medium turns opaque

The bacteria are infected with phages and die, producing new phages; the medium clears up

The medium is filtered through chosen filter, holding back bacteria and larger objects-- only the smaller phages pass through

Phage Challenges



Generation and isolation of lytic phages

Lysogenic phages can convert phage-sensitive bacteria to insensitive ones, and can encode toxins

Ability to maintain and deliver their formulations

Need for sequencing to ensure no undesirable genes which might be toxic

Because is protein-based and biologically-active, may cause reaction in subjects

Phages and/or AB's

Bactericidal

Lytic phages remove bacterial viability--dead

Some AB's are bacteriostatic (tetracycline), allowing for potential resistance

Auto "dosing"

Phages increase their density more in areas of high infection

AB's lose their potency as they penetrate into areas of infection

Phages and/or AB's

Toxicity

Phage toxicity is very low, though may possibly occur with anaphylactic responses to lysed bacterial components

AB toxicity has been reviewed extensively, notably to the nervous system, and can be very severe

Flora Disruption

Phage are specific and only minimally impact health-protecting flora

AB tend to be broad-spectrum and are prone to inducing superinfections (C Diff, Candida overgrowth)

Phages and/or AB's

Resistance Concerns

Phages have low host range, so resistance range shorter

AB's affect a broad range of bacteria, so greater chance of mutated resistance (can also impact phage potency)

Lack of cross-resistance with phage because they kill differently than AB's and so can be used when AB's lose effectiveness

Phages and/or AB's

Discovery Time Frame

Phages are easily located, usually in sewage

Isolation can be difficult though, notably to culturing specific bacteria—however, the phage present no toxicity, while AB's can be toxic

Versatility

Both therapies have versatility in application (creams, ingestibles, liquids, etc.) and can be formulated to "cocktails"

Phages and/or ABs

Biofilms

Phages have the ability to clear at least some biofilms

AB's are hindered by biofilms, lending toward bacterial mutation and resistance

Dosing

Phages, because amplify, generally need fewer doses for clearance—they only increase in the infection site if they are killing and do not linger

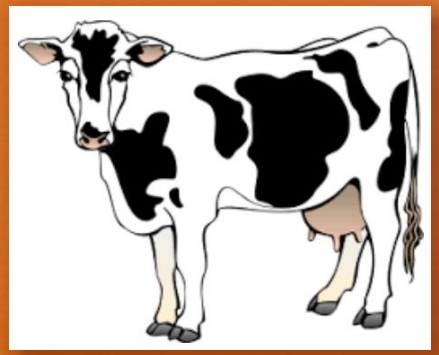
AB's generally require a course of dosing

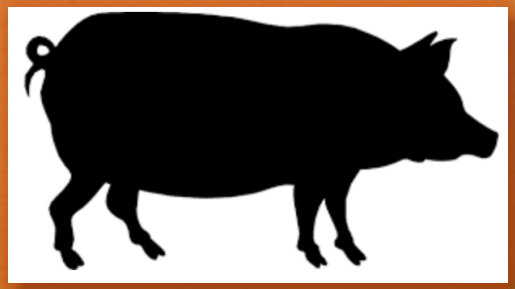
Phages and/or AB's

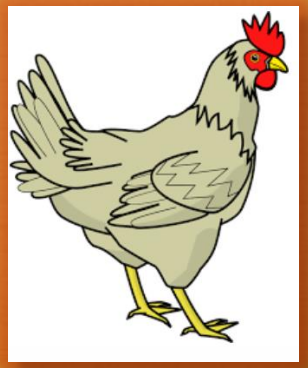
Transfer of Effect

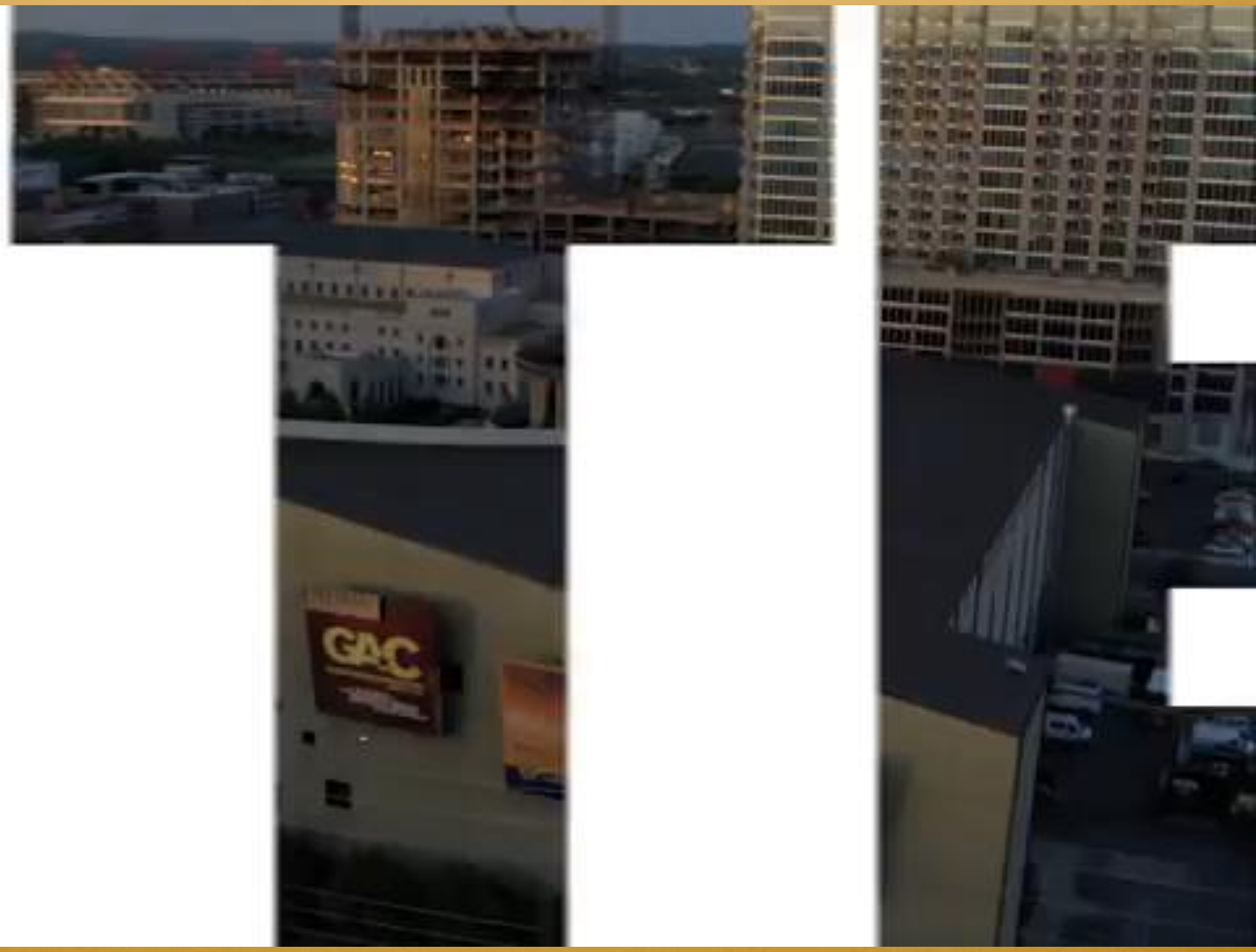
Phages' effect can be carried from one host to another, notably useful in agriculture, but no harm if not needed

AB's in industrial food production are one of the main factors in AB resistance








GAC

Sourcing Phages for Your Practice

Life Extension

InnoVita

Designs for Health

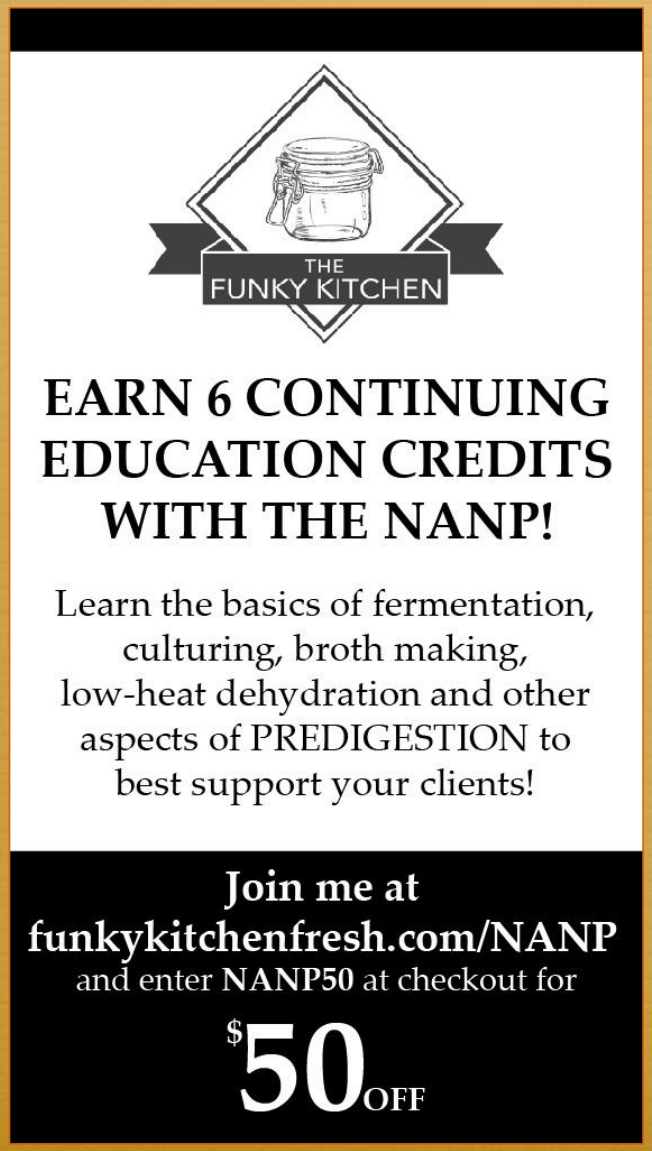
Systemic Formulas of Ogden, Utah

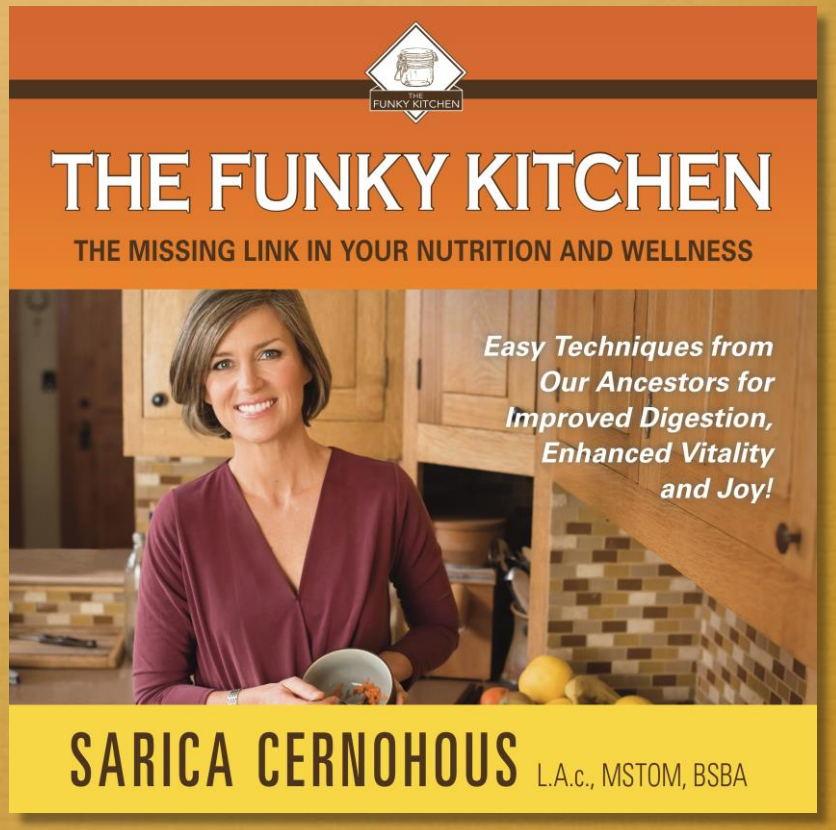
Pseudomonas

Salmonella

E Coli

More Learning!





References

Abedon, S., Blasdel, B., K., & SJ Kuhl. (n.d.). Phage treatment of human infections. Retrieved March 11, 2018, from http://europepmc.org/articles/PMC3278644/

Bacteriophage therapy: current hurdles to successful drug development. (n.d.). Retrieved March 11, 2018, from http://resistancecontrol.info/rd-innovation/bacteriophage-therapy-current-hurdles-to-successful-drug-development/

Grill, M. F., & Maganti, R. K. (2011). Neurotoxic effects associated with antibiotic use: management considerations. British Journal of Clinical Pharmacology, 72(3), 381–393. http://doi.org/10.1111/j.1365-2125.2011.03991.x

Loc-Carrillo, C., & Abedon, S. T. (2011). Pros and cons of phage therapy. *Bacteriophage*, *1*(2), 111–114. http://doi.org/10.4161/bact.1.2.14590.

McGrady, M. (n.d.). News - Bacteriophage Therapy Grows as Alternative to Antibiotics. Retrieved March 11, 2018, from https://www.heartland.org/news-opinion/news/bacteriophage-therapy-grows-as-alternative-to-antibiotics

Ramsey, L. (2017, October 15). Viruses discovered a century ago may be our best defense against a threat that could kill 10 million people a year by 2050. Retrieved March 10, 2018, from http://www.businessinsider.com/ampliphi-phage-therapy-treatment-bacterial-infections-2017-10

Sulakvelidze, A., Alavidze, Z., & Morris, J. G. (2001, March). Bacteripphage Therapy. Retrieved March 11, 2018, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC90351/

World eBook Library. (n.d.). Félix d'Herelle. Retrieved http://worldebooklibrary.net/articles/eng/F%C3%A9lix_d%27Herelle.