A multipronged attack on Latent, Active and Resistant strains of Mycobacterium tuberculosis

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Abstract

The bacterium *Mycobacterium tuberculosis,* also referred to as *MTb*, infects individuals in latent, active and resistant forms. There are recommended regimens for the delivery of established antibiotics to infected individuals. These regimens focus on the oral administration and involve relatively large doses that often result in significant side effects. This invention is a biodegradable implant composed primarily of an inert saturated fatty acid, namely stearic acid. The antibiotic is incorporated into the stearic acid matrix along with other constituents. The composition also includes a salt to regulate the release rate of the antibiotic, a metal-stearate structure to provide additional toxicity against *MTb*, ascorbic acid, and unsaturated fatty acids in low concentrations. As the fatty acid implant dissolves it forms a micelle that encapsulates the antibiotic. The micelle is transported to the infected area by serum and, since it is a primary energy source for the bacterium, is consumed. The antibiotic is hidden in the matrix (micelle). The biodegradable implant, which can be inserted as a single component or a as spheres of different sizes (i.e. micrometer) does not have to be removed.

Background

Tuberculosis

- Causative agent is *Mycobacterium tuberculosis*
- Strikes in the lungs and slowly dissolves the tissues
- Diagnosed via Sputum Test, Tuberculin Skin Test, or TB Blood Test
- Easily spread by airborne transmission through coughing or sneezing

Figure 1. Computer generated image of drug-resistant *Mycobacterium tuberculosis*

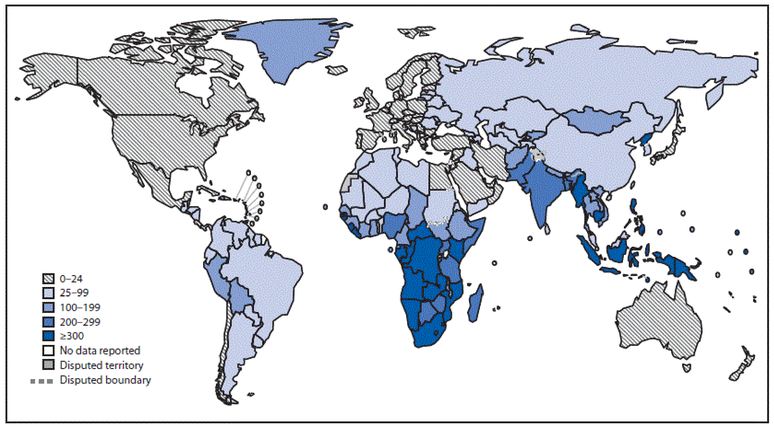


Figure 2. Annual tuberculosis incidence(per 100,000), by region–worldwide in 2017

Strain	Drug	Side Effects
Active	• Isoniazid • Rifampin • Pyrazinamide • Ethambutol • Streptomycin	• Hepatitis • Jaundice • Dizziness and loss of balance • Nausea and vomiting • Seizure • Hallucinations
Latent	• Rifampin • Isoniazid • Isoniazid and Rifapentine	
Resistant	• Capreomycin • Fluoroquinolones	• Nephrotoxicity • Renal Damage

Implant

Existing Drugs	Our Implant
• Expensive • Oral administration • Large dosages • Must be removed	• Cost effective • Biodegradable • Lower dosage • Does not have to be removed

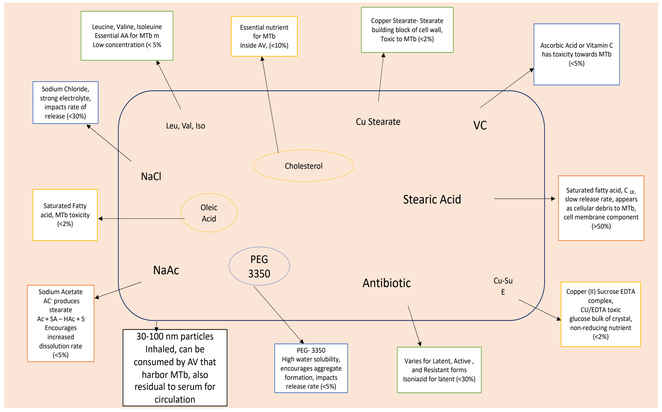


Figure 3. Composition of the implant

Composition	Significance
Amino Acids	Essential nutrients for MTb survival.
Cholesterol	Survival of MTb is based on the accumulation of cholesterol
Copper Complexes	Used to increase water solubility, block unwanted hydrogen bonding, increase structural rigidity and help to escape detection in the immune system
Vitamin C	Used to protect the implant from redox reaction that can naturally occur in human serum
Stearic Acid	Mimics the cell membrane of *Mycobacterium tuberculosis*
PEG 3350	Used for solubility, aggregate formation and release rate
Sodium Acetate	Encourages dissolution rate
Oleic Acid	Low toxicity decrease the survival rate
Sodium Chloride	Strong electrolyte impacts rate of release

Name of acid	Type of Fatty Acid	# of Carbons	Melting point (°C)	Water Solubility (mg/L)
Oleic Acid	Unsaturated	18	13.4	Insoluble
Stearic Acid	Saturated	18	69.3	0.597

Electrolyte Name	Type Electrolyte	Function
Sodium Chloride (NaCl)	Strong	• Regulates drug release rate
Sodium Acetate (NaAc)	Strong	• Increase water solubility and faster release rate
Calcium Carbonate ($CaCO_3$)	Weak	• Dissolves at slower rate • Longer drug release rate • Negative effects

Figure 5. Stearic acid is used as a matrix to contain a dozen molecular species used to attack/weak *Mycobacterium tuberculosis.* Tablets and dust of different sizes and shapes have been used to date. A tablet containing the medicinal species will be emerged in water for almost a month, and then molecular species will slowly leach out into the aqueous phase. This replicates what would take place in in vivo.

Experimental Data

Vial Composition	Hour 1	Hour 2	Hour 3	Hour 4
50 mls RO water 1 g CuCl2*2H2O 0.01 gram ETH				
50 mls RO water 1 g CuCl2*2H2O 1 gram INH 0.5 gram Stearic acid				

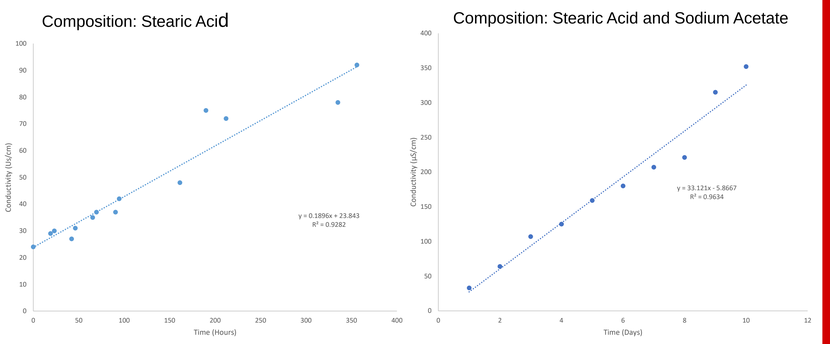
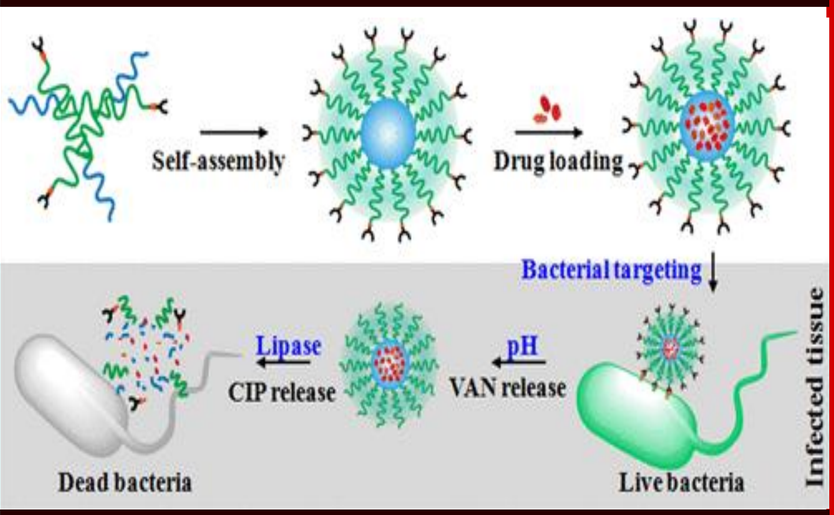


Figure 4. Conductivity comparison of Stearic Acid (left) vs Stearic Acid and Sodium Acetate (right). Hundreds of measurements were made by our group, this is representative data.

Mechanism of Action



Future

Currently writing a patent application. Experiments planned for spring include a complex series of measurements at THE NATIONAL HIGH FIELD MAGNET LAB to study the release rate of the different components.

References

MacNeil A, Glaziou P, Sismanidis C, Maloney S, Floyd K. Global Epidemiology of Tuberculosis and Progress Toward Achieving Global Targets — 2017. MMWR Morb Mortal Wkly Rep 2019;68:263–266.

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