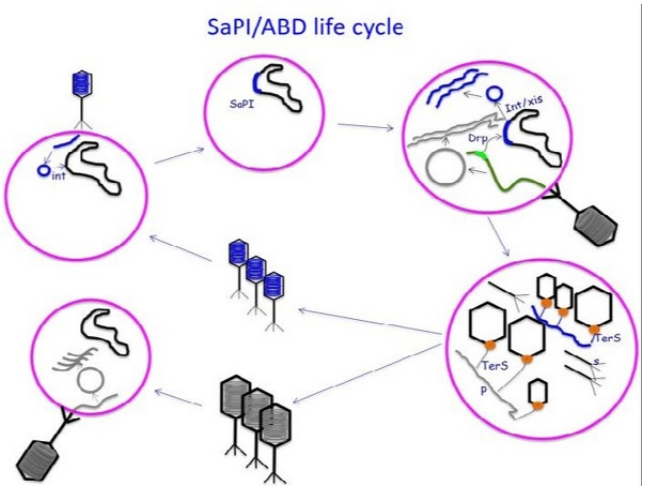
Non-Antibiotic Treatment of Staphylococcal Infections

Using re-engineered genetic elements of bacteria as antibacterial drones to block bacterial genes involved in virulence/viability.



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Life Sciences/Therapeutics/Antibacter

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Technology Overview

Researchers in NYU Langone Health's Novick Lab have developed a novel non-antibiotic method for treating staphylococcal infections. This method is based on the naturally-occurring, highly mobile staphylococcal pathogenicity islands (SaPIs). SaPIs are ~15 kb genetic elements that are stably inserted in the staph chromosome but can be induced by "helper" phages to excise and replicate. The replicated SaPI DNA is packaged in infectious phage-like particles which are released from the bacterial cell upon phage-induced lysis, resulting in high frequency SaPI transfer. The SaPIs carry and consequently disseminate genes encoding toxins and other virulence factors.

The lab has designed a unique strategy to exploit and harness SaPI spread by converting these agents of disease into agents of therapy – antibacterial drones (ABDs). To create the ABDs, the group re-engineered the SaPIs, deleting their natural cargo (toxin genes), increasing their packaging capacity from 15 to >40 kb, and inserting any of variety of antibacterial modules. They also modified the helper phage so that ABD particles are produced in the absence of functional phage. The ABD particles are administered to an infected animal (or plant), where they reach the infecting bacteria and thus abrogate the infection.

As proof of principle, the researchers incorporated into ABDs either CRISPR/cas9 or CRISPR/dcas9 modules with spacers targeting a chromosomal gene or the promoter region of a global virulence regulator, respectively. Subsequent studies showed that ABDs kill S. aureus in vitro by DNA cleavage, block the development of a subcutaneous S. aureus abscess, and rescue

mice given a lethal dose of intraperitoneal S. aureus. Most recently, the researchers incorporated a module expressing the potent staphylolytic enzyme, lysostaphin, into the ABD, and demonstrated that the lysostaphin- expressing ABD cures a murine subcutaneous abscess with 100% efficacy. This system is currently also effective against many Listeria strains and is being expanded to include other S. aureus strains.

Background

Staphylococcus aureus, long considered a dangerous, antibiotic resistant pathogen, has become even more virulent, contagious and resistant, especially to b-lactams (MRSA) and glycopeptides (VRSA). Today, it causes a wide variety of life-threatening infections, many of which cannot be treated effectively with conventional antibiotics, and there are currently few new antibiotics being developed. The main reason for this is that staphylococci rapidly acquire resistance to new antibiotics, making their development commercially unattractive and leading to a global crisis of drug resistance and rise of almost untreatable infections.

Benefits

- Wide versatility in antibacterial activity (as opposed to the use of conventional bacteriophages)
- Efficacy with many strains that are resistant to therapeutic bacteriophages
- Great capacity for attaching DNA cargo
- Ability to prevent the development of bacterial resistance

Applications

- Treating infections involving antibiotic resistant bacterial pathogens
- Preventing infection of and/or biofilm formation on surgical implants
- Preventing staphylococcal food poisoning by blocking enterotoxin production
- Preventing staphylococcal infections
- of slaughterhouse workers by treating instruments with ABDs
- Coating feminine hygiene products with ABDs to prevent staphylococcal toxic shock syndrome
- Treatment of staphylococcal wound infections
- Incorporation of ABDs into coatings for catheters, hemodialysis tubes, central nutrition lines, etc.
- Treatment of staphylococcal mastitis of milk-producing livestock

Intellectual Property

US patent issued - 11,149,269

References

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2. Ram G, Ross HF, Novick RP, Rodriguez-Pagan I, Jiang D.(Nov, 2018) , https://pubmed.ncbi.nlm.nih.gov/30247487/