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Physical & Life Sciences
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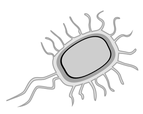
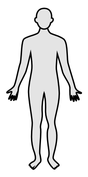
Northeastern University

ADVANCEMENTS IN AMINOGLYCOSIDES

APPLICATIONS OF AMINOGLYCOSIDES

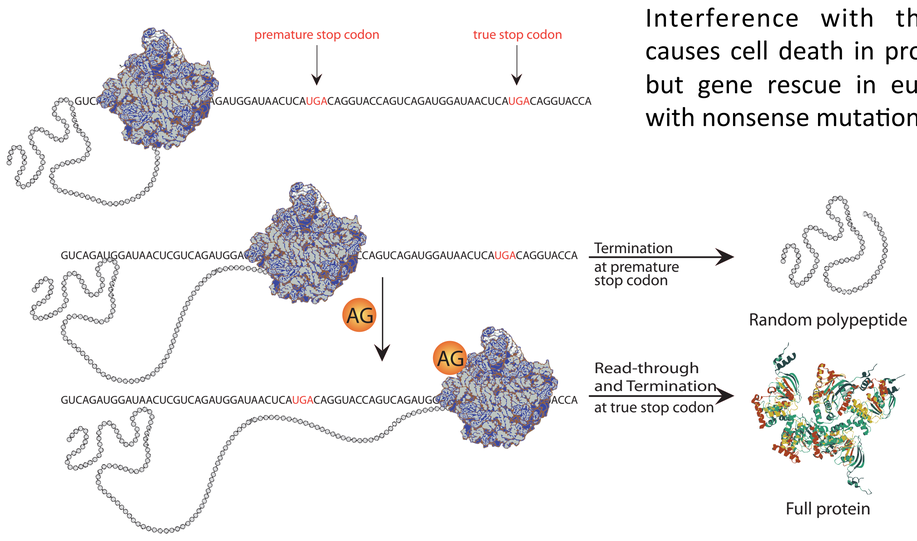


- Pseudomonas
- Proteus
- Serratia
- Staphylococcus



- Cystic Fibrosis
- Duchenne Muscular Dystrophy
- Rett Syndrome
- Usher's Syndrome

MECHANISM OF ACTION



Interference with the ribosome causes cell death in prokaryotic cells but gene rescue in eukaryotic cells with nonsense mutations.

ABSTRACT

Aminoglycosides: A tale of two therapies.
The aminoglycoside class of compounds has activity in bacterial cells as well as in human cells. Although their action within the two types of cells is identical, the result could not be more different…

In bacterial cells, aminoglycosides exhibit toxicity by binding to the small ribosomal subunit, causing a relaxation in mRNA proofreading and as a result, a large amount of errors in protein synthesis. The buildup of broken proteins eventually causes cell death, thus making aminoglycosides potent antibiotics.

In eukaryotic cells, again aminoglycosides bind to the small subunit of the ribosome, but the effect is much more subtle. In human cells, the binding of aminoglycosides causes the ribosome to ignore premature stop codons, genetic errors that occur in diseases like cystic fibrosis, Duchenne muscular dystrophy, Rett syndrome and a host of cancers. As a result, aminoglycosides can be seen as a small molecule gene repair agent, which has now been successfully verified in several clinical trials.

There is one setback in the widespread use of aminoglycosides: toxicity. Kidneys and audiosensory hair cells have membrane pumps that rapidly uptake aminoglycosides. The buildup in concentration causes toxicity and as a result, the major side effects of aminoglycoside treatment are kidney damage and deafness. Solving these problems entails 1: avoiding collection in these tissues and 2: making more selective aminoglycosides. The work presented discusses how nanoparticles can be used to improve the biodistribution of aminoglycosides and how palladium-catalyzed glycosylation can be used to generate less toxic aminoglycosides.

BIODISTRIBUTION

- **High positive charge** of aminoglycosides decreases membrane permeability
- Aminoglyclosides are trafficked into **kidneys** and **audiosensory hair cells**

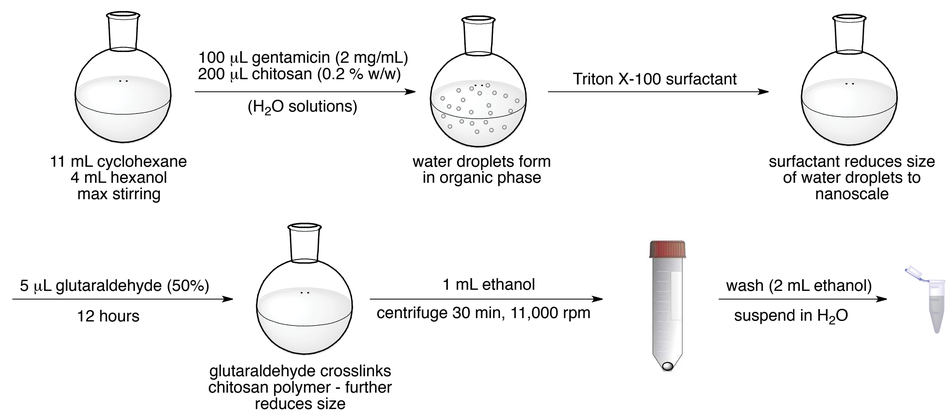
THE PROBLEM

- High concentrations of aminoglycosides are toxic to **any cell**
- Specific mechanism of toxicity is **unknown**

TOXICITY

NANOPARTICLE ENCAPSULATION

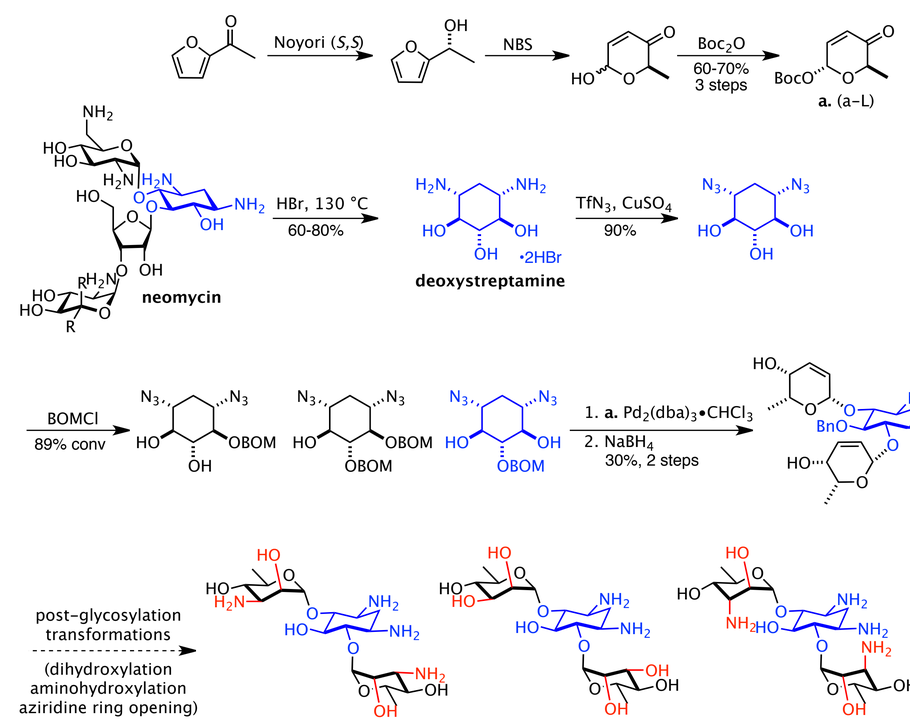
- Aminoglycosides are nanoencapsulated using a **Microemulsion** method
- **Gentamicin** has been encapsulated in **chitosan** nanoparticles of **26 ± 2nm** in diameter



THE SOLUTION

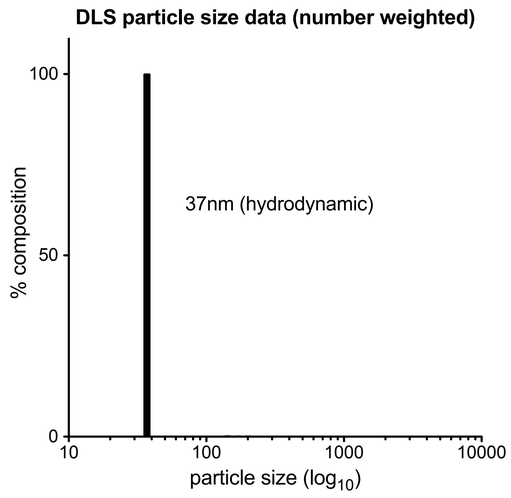
NOVEL AMINOGLYCOSIDES

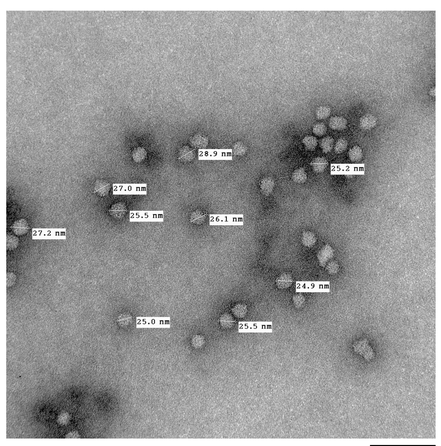
- **Deoxystreptamine** core is readily available from neomycin
- De novo asymmetric sugar synthesis generates **chiral** analogues from **achiral** starting materials
- **Bidirectional** route is tailored to medicinal chemistry
- Dozens of analogues available after **post-glycosylation transformation**



NANOPARTICLE EVALUATION

- Nanoparticles are sized with dynamic light scattering and transmission electron microscopy
- Determination of drug release and particle degradation by HPLC
- Tissue uptake determination using fluorescence microscopy with tagged components





BIO EVALUATION

- *e.* coli (natural and Gram positive mutant) for testing bacterial efficacy
- Protein rescue assays to test for read-through
- Mouse biodistribution model to determine effect of nanoparticle

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Presenter: Michael Cuccarese

IGERT
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