Ultrashort NSAID-conjugated Peptides as Bifunctional Nanomaterials


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Ultrashort NSAID-conjugated Peptides as Bifunctional Nanomaterials

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School of Pharmacy
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Outline

1. Ultrashort peptides
2. Self-assembling peptides
3. Ultrashort self-assembling antimicrobial peptides
4. NSAID-conjugated self-assembling peptides
What are Ultrashort Peptides?

- Ultrashort = 4-7 amino acids
- Cationic = net positive charge (+2)
- Cost effective → Upscale → Translational potential → Patient
- Numerous advantages including:
  - ↑ chemical versatility
  - ↓ immunogenicity
  - Tunable biocompatibility + biodegradability
  - Tailored self-assembly/pharmacological properties
  - Antimicrobial = innate immune response
  - Nanotechnology
Self-assembling Peptides

- Peptide Amphiphiles (Stupp)
- α-helices/Coiled coils (Woolfson/Tirrell)
- β-sheets (Agelli/Collier)
- β-haripins (Pochan/Schneider)
- Short Aromatics (Xu/Gazit/Ulijn)
Core Technology

Self-assembled Peptides

Stimuli
- pH
- Light
- Temperature
- Ionic Strength
- Specific enzymes

Assembly

Peptide Hydrogels

Short peptide sequences

External stimuli

Hydrophobic: Hydrophilic $\rightarrow$ Hydrogel (critical gelation concentration)
Biofunctional Nanomaterials Utilising the Building Blocks of Life!

- Infection and Medical Devices
- Wound healing
- Drug Delivery
- Stem Cells/Regenerative medicine
Planktonic vs. Biofilm Bacteria

- Planktonic form: Free floating in liquid
- Biofilm form: sessile, composed of aggregated microcolonies of cells surrounded by a protective extracellular polymeric matrix
- Mature biofilms can resist 10-1000 times the concentrations of standard antibiotic regimens that are required to kill genetically equivalent planktonic forms
Biofilms in the Environment and Medicine

Biofilm growth on rocks in a stream (USGS) and within a kitchen pipe (MSU Center for Biofilm Engineering).

SEM Pseudomonas aeruginosa, shown here attached to an implant surface, is one of many resistant microorganisms.

University of Illinois researchers tested a prototype of a new device that can see biofilms behind the eardrum to better diagnose and treat chronic ear infections.
Antimicrobial Resistance

• Healthcare associated infections
• Medical devices: reservoir for “superbugs”
• Chronic wounds
• Persistent burden on:
  • Patient morbidity & mortality
  • Family and carers
  • Healthcare budgets
What are the solutions?

Antimicrobial Activity of Short, Synthetic Cationic Lipopeptides

Garry Laverty, Martin McLaughlin, Christopher Shaw, Sean P. Gorman and Brendan F. Gilmore*

Biomaterials Research Group, School of Pharmacy, Queens University Belfast, Belfast BT7 1NN, Ireland

Pathogens 2014, 3, 791-821; doi:10.3390/pathogens3040791

Review

Evolution of Antimicrobial Peptides to Self-Assembled Peptides for Biomaterial Applications

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# Rational Design of Antimicrobial Peptide Motif vs Self-assembly

<table>
<thead>
<tr>
<th>Antimicrobial Activity</th>
<th>Propensity to Self-assemble</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophobic/Hydrophilic (Charge) ratio (more important with regard to antimicrobial activity than size)</td>
<td>Hydrophobic/Hydrophilic balance</td>
</tr>
<tr>
<td>Interactions with microbial extracellular membranes</td>
<td>Non Covalent intermolecular interactions (e.g. Van der Waal’s, π-π stacking)</td>
</tr>
<tr>
<td>Interaction with intracellular targets/processes (DNA, RNA, enzymes, protein synthesis)</td>
<td>Ability of peptide to form hydrogen bonds with each other and with water</td>
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Self-assembled Ultrashort Peptide Gels

- Successful library of ultrashort peptides: self-assembled at physiological pH
- \((X_1\text{-FF-}X_2)\)
- Hydrophobicity: naphthalene (Nap) grouping (at \(X_1\)) and varying quantity of phenylalanine (F) in primary structure
- Minimum of 2 charged units required for antimicrobial activity
- Primary amine group provides cationic charge
- Cationic amino acids vary by number of methylene units on R-group

Dual Antimicrobial Anti-inflammatory Nanomaterials

- Hydrophobicity provided by NSAID structure
- High in aromaticity
- Display self-assembly and gelation characteristics
- Potential applications in chronic infected wounds

Self-assemble to Hydrogel Networks

NpxFFKK 0.5 %

IbuFFKK 2 %

IndFFKK 1 %

NpxFFKK 2% (w/v)

IndFFKK 2% (w/v)
Confirmation of β-sheet Hydrogel Networks

Oscillatory rheology

FTIR

Log (Pa)

Frequency (rad/s)

Transmittance (%)

Wavenumber (cm⁻¹)
Percentage reduction of mature 24h biofilm treated with 2% w/v NSAID- conjugated hydrogels utilizing an alamarBlue assay.

Percent inhibition of COX 1 and 2 enzyme by NSAID self-assembled hydrogels and by the model COX inhibitor DuP-697 using a COX Fluorescent Inhibitor Screening Assay Kit.
Conclusion

- Developed a library of ultrashort self-assembling bifunctional peptides
- Vast potential for use against Biomaterial/Medical Device/Implant Infections
- Wound healing/surgical gel: Increased healing as mimics natural tissues
- Platforms/vehicles to deliver existing antimicrobials, extend spectrum of activity to Gram-negatives
- Translatable and economically friendly form of nanotechnology for patient benefit
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The Adams Lab, Department of Chemistry, University of Liverpool

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