Nexus of natural and engineered nanomaterial: Biofilm eradication using magnetic phage-nanocomposite conjugates

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Microbial problems of significance

Pathogens

~**1.8 million** people die each year due to waterborne infections.

Antimicrobial Resistance

ARM could cost the global economy **\$100** trillion by 2050.

Biocorrosion

> **\$ 7 billion** cost caused by biocorrosion and biofouling to infrastructure annually (US alone).

Biofouling

*“Achilles heel”
of membrane*

Conventional disinfectants **cannot** keep up with the new challenges

1. Non-selective

Functional bacteria
Problematic bacteria

2. Not effective to biofilm-protected microbe

3. Unintended consequences (e.g., disinfection byproducts)

Phage: abundant and versatile

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The broad impacts of the tiny phages

5

You can always make it better 😊

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How to obtain polyvalent phages?

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A small library of phages can target a wider range of problematic bacteria.

Phages production can be surrogated by a safer and faster-growing host.

Sequential multiple-host approach facilitated isolation of phage with broad host range

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Rational design of phage cocktails

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BIM= bacteriophage insensitive mutant

Phage	Phage Receptor
PER01	Surface Protein
PER02	Polysaccharide
MER01	Surface Protein
MER02	Polysaccharide

Phage resistance and fitness costs

1. Bacterial phage resistance ¹

2. Increased fitness costs

3. Loss of resistant plasmids

Polyvalence and fitness advantage in biofilm

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Phage-nano complex for biofilm removal

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Phage dilution

Phage barrier

From top to bottom

From bottom to top

Covalent linkage loaded more phages relative to physical adsorption

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Electrostatic interaction

CS-Fe₃O₄ = Chitosan coated Fe₃O₄ (rich in NH₂)

Surface amination contributed to right phage orientation (tails facing outward)

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Biofilm removal capability

(as % of plaque formed area in plate)

Nano-phage conjugates enhanced biofilm penetration and facilitated its removal

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Confirmation and quantification of surface-bound phages onto CNCs

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A1 CNCs (S)

A2 CNCs (M)

A3 CNCs (L)

B

C

Biofilm removal and phage propagation after free phage and PNCs treatments

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A

B

Numerical model construction & calibration

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Biofilm cross-section

$$P_{\alpha} = 1 - \exp \left(-\alpha N_0 \left(\frac{1 - \exp(-\delta \Delta t)}{\delta} \right) \right)$$

$$P_{\lambda} = 1 - \frac{e^{-\lambda_H \Delta t} + e^{-\lambda_V \Delta t}}{2}$$

$$P_{\delta} = 1 - \frac{e^{-\delta_H \Delta t} + e^{-\delta_V \Delta t}}{2}$$

$$\lambda_V = \lambda_H \times (1 + F_{\lambda})$$

$$\delta_V = \delta_H \times (1 - F_{\delta})$$

N_0 is initial phage number, α is infection rate coefficient, δ is degradation/trap rate coefficient, λ_H is horizontal diffusion rate coefficient, λ_V is vertical diffusion rate coefficient, δ_H is horizontal trapping rate coefficient, δ_V is vertical trapping rate coefficient, F_{λ} is facilitation coefficient for phage diffusion, F_{δ} is facilitation coefficient for phage trapping

Simulated phage infection patterns by free phages and different sized PNCs

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A (Free phages)

2h treatment

4h treatment

6h treatment

B (Small PNCs)

2h treatment

4h treatment

6h treatment

C (Middle PNCs)

2h treatment

4h treatment

6h treatment

D (Large PNCs)

2h treatment

4h treatment

6h treatment

Simulation and experimental results of biofilm removal after treatments

A (No phages)

B (Free phages)

C (LPNCs)

D (MPNCs)

E (SPNCs)

Bottom-up biofilm eradication by PNCs with magnetic field

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1. Mixed-species biofilm
2. Treated with free phage
3. Treated with large conjugates
4. Treated with small conjugates

Remained biofilm

- Control biofilm-protected pathogens and other problematic bacteria deteriorating water quality;
- Mitigate biofouling by target the bacterial species at biofilm bottom.

Conclusions

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- Polyvalent phages are more widespread than previously expected and can be readily isolated by using multiple sequential hosts.
- Polyvalent phages offer great potential for improved ARB control and ARG mitigation with simplified phage preparation process.
- The conjugation of polyvalent phages with nanomaterial can not only enhance the efficacy of phage treatment, but also extend the scope of phage application in environmental systems.

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