Synthetic Chemistry for the Chemical Modification of Polyfunctional Biopolymers as Antimicrobial Nanomaterials

2 November 2022, CSIR International Convention Centre

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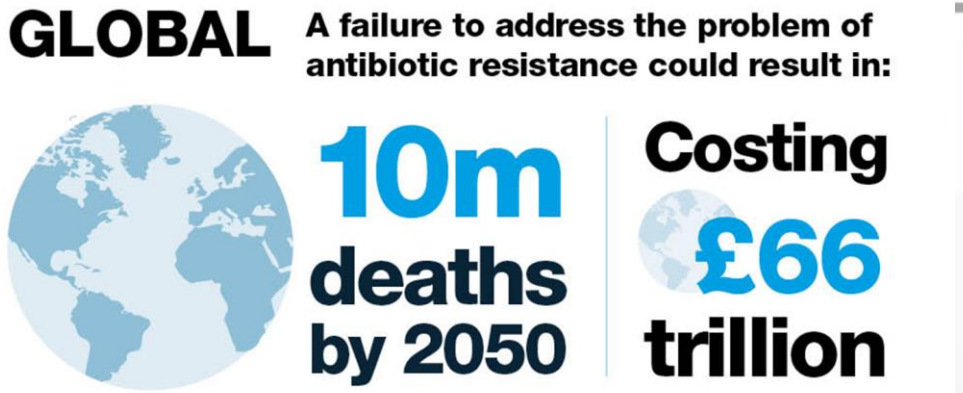
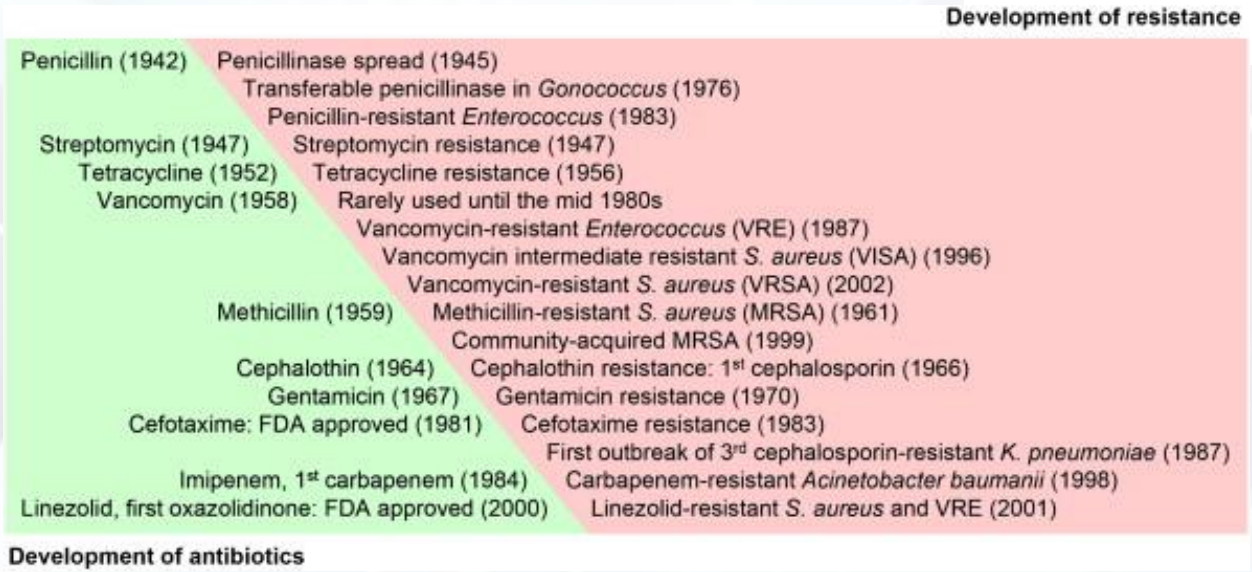
Why is there a crisis? Issues with small molecules

- We currently lack good “pipeline drugs” and designing novel or new antibiotics is increasingly more challenging.
- Research and development of new antibiotics can be risky and scientifically challenging
- Covid-19 Pandemic





SA hospitals face worrying rise in drug-resistant bacteria and ‘superbugs’

06 Jan 2022

Culled from The Lancet

1. Nanoantibiotics”: A New Paradigm for Treating Infectious Diseases using Nanomaterials in the Antibiotics Resistant Era. J. of Control. Release. 156, 128-145 (2011).
2. The Review on Antimicrobial Resistance Chaired by Jim O’Neill, **2016**

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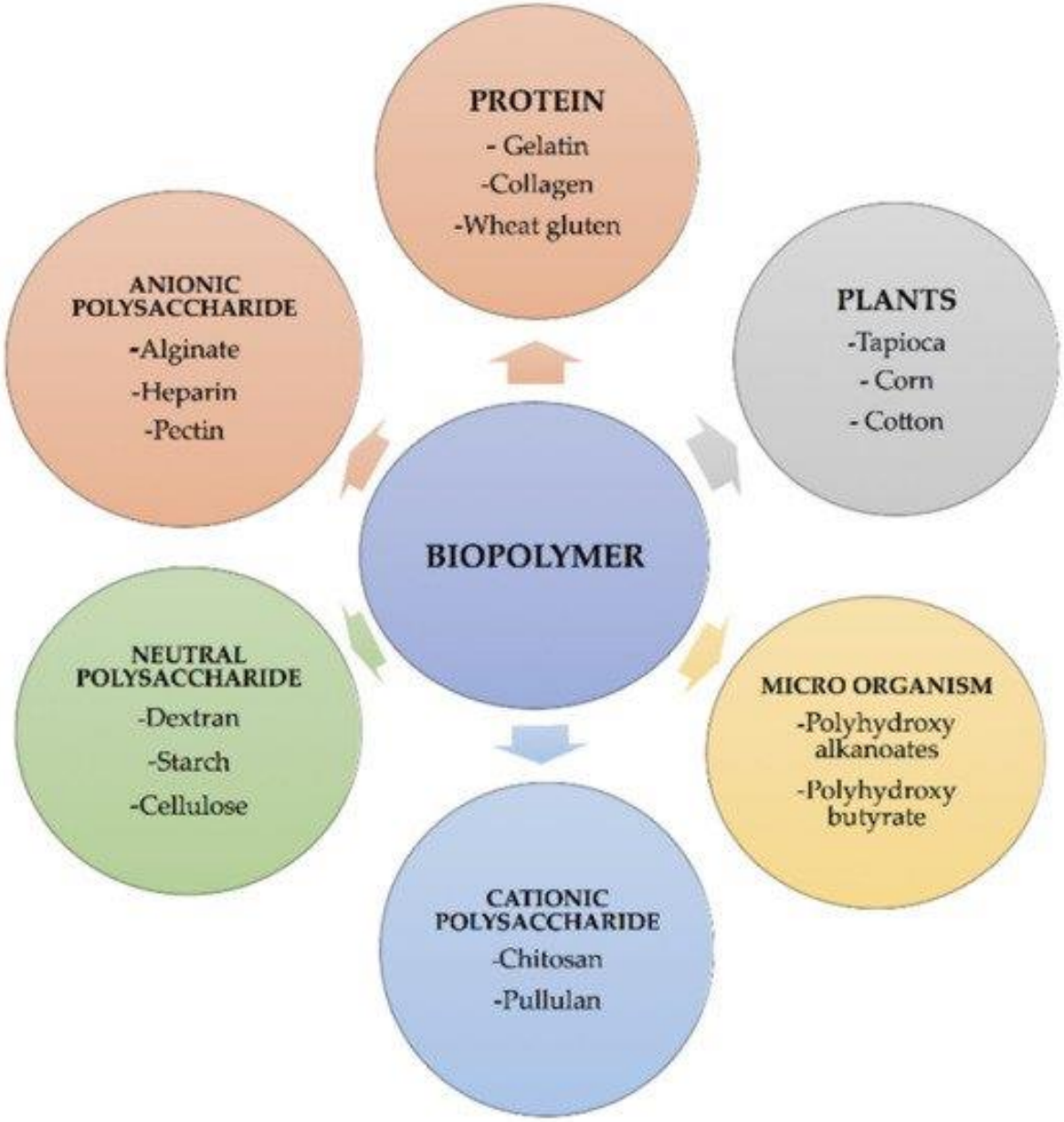
Biopolymers as alternatives to small molecules - Sources



Possible Applications

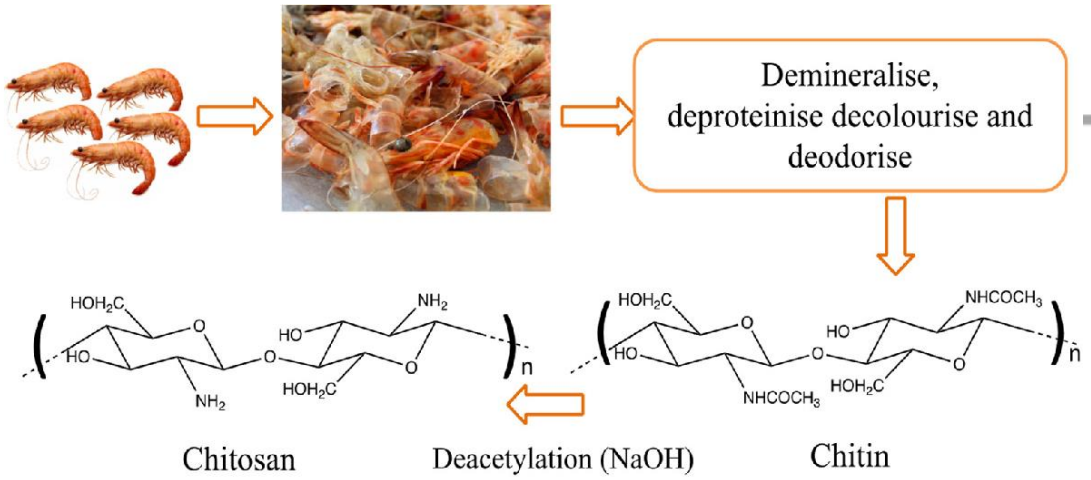
- Antiadhesion materials
- Binding materials
- Bone-setting materials
- Hemostatic materials
- Drug delivery system
- Synthetic skin
- Wound management
- Artificial tendon and ligament

Resistance :

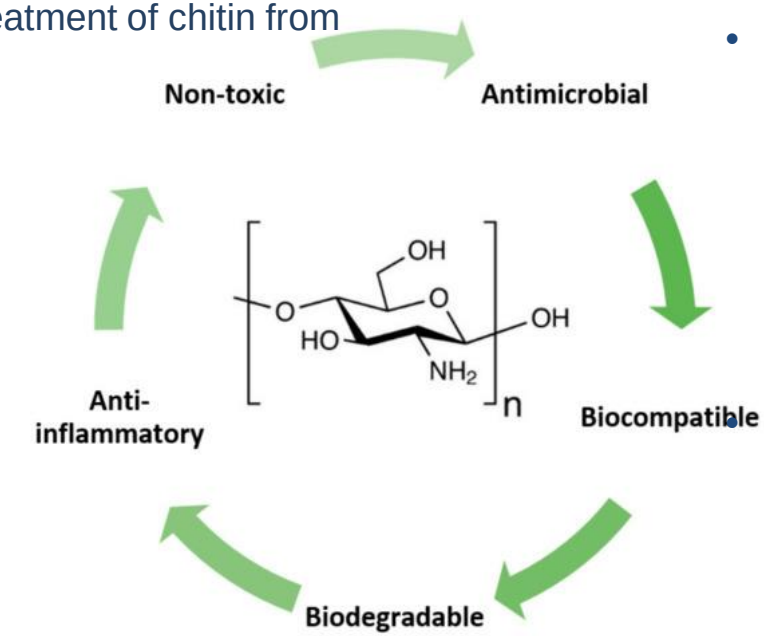
There are no reports of resistance to date. Lack of acquired resistance is likely due to multimodal antimicrobial.

Gibson *et al*. Antimicrobial Polymers: The Potential Replacement of Existing Antibiotics? Int J Mol Sci. **2019**; 20(11): 2747.

Chitosan – Properties and antimicrobial potential



Obtaining chitosan by the deacetylation alkaline treatment of chitin from shrimp shell wastes

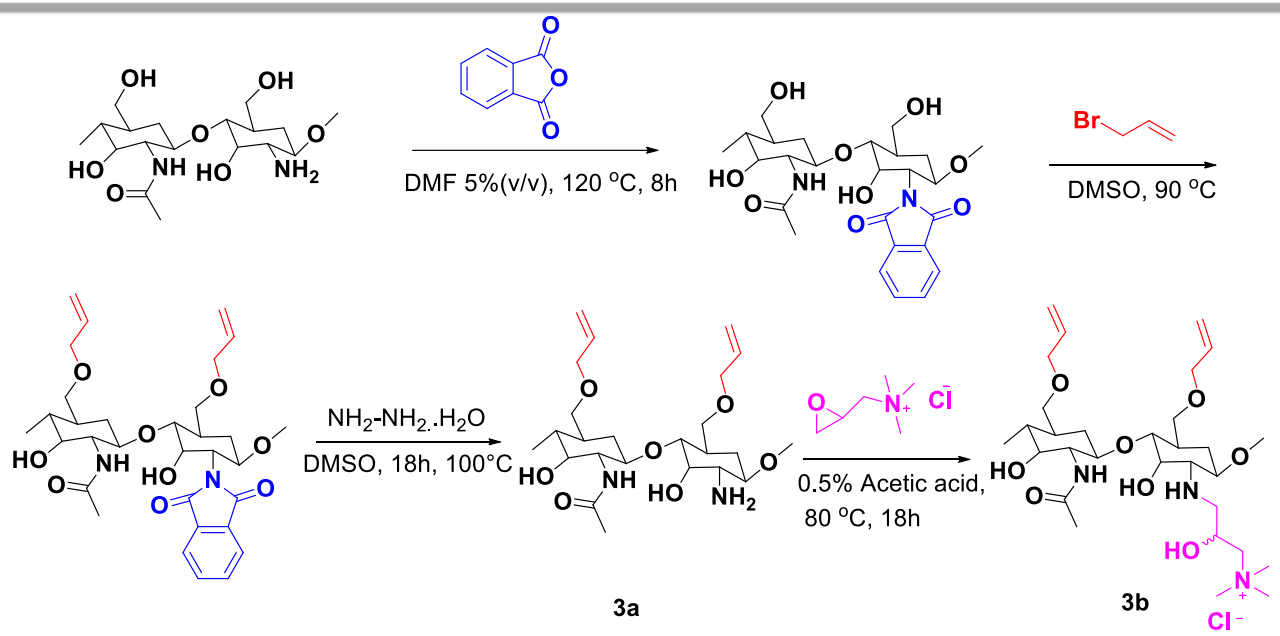


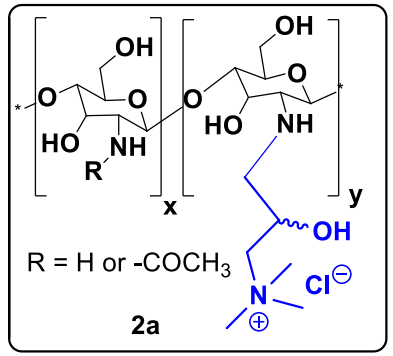
Properties affecting physicochemical characteristics of chitosan:

- Molecular weights (MWs) and MW distributions, chain lengths, degrees of deacetylation, charge densities and charge distributions, salt-forms, viscosities, and water retention values. Chitosan can also be modified to improve its properties.

Chitosan-Based (Nano)Materials for Novel Biomedical Applications. Molecules **2019**, 24(10), 1960-1982

Protection/Deprotection Chemistry - Synthesis and antimicrobial activity of O-Allyl quaternary chitosan



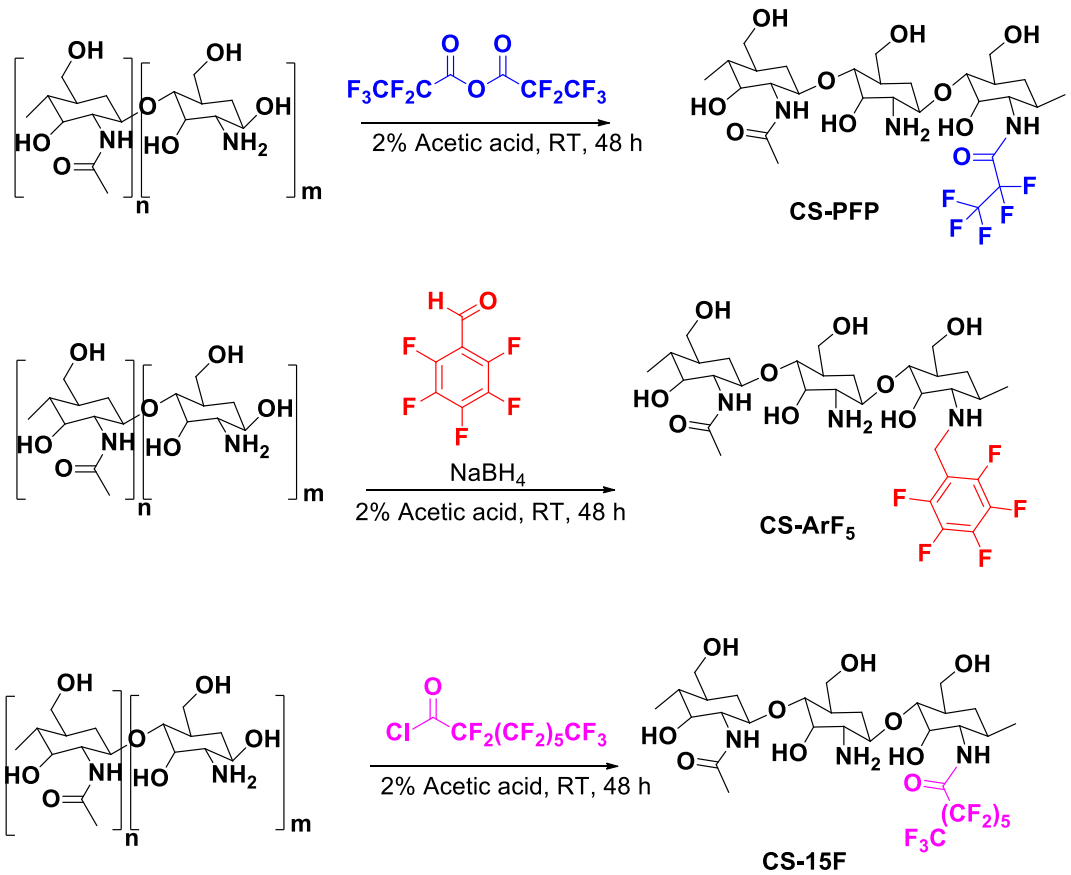


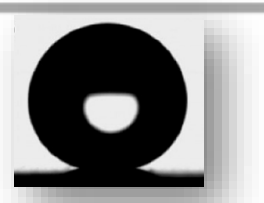
Size = 100 – 500 nm

	Bacteria	2a	3a	3b	Chitosan	Tetracycline	Ampicillin
1	*S. sanguinis ATCC 10556*	64	128	64	>512	<4	32
2	*S. aureus ATCC 29213*	64	>512	64	512	<4	<4
3	*S. epidermidis ATCC 12228*	64	512	64	>512	32	16
4	*Strep mutants ATCC25175*	>512	>512	>512	>512	32	<4
5	*L. rhamnosus ATCC 7469*	>512	>512	>512	>512	<4	<4

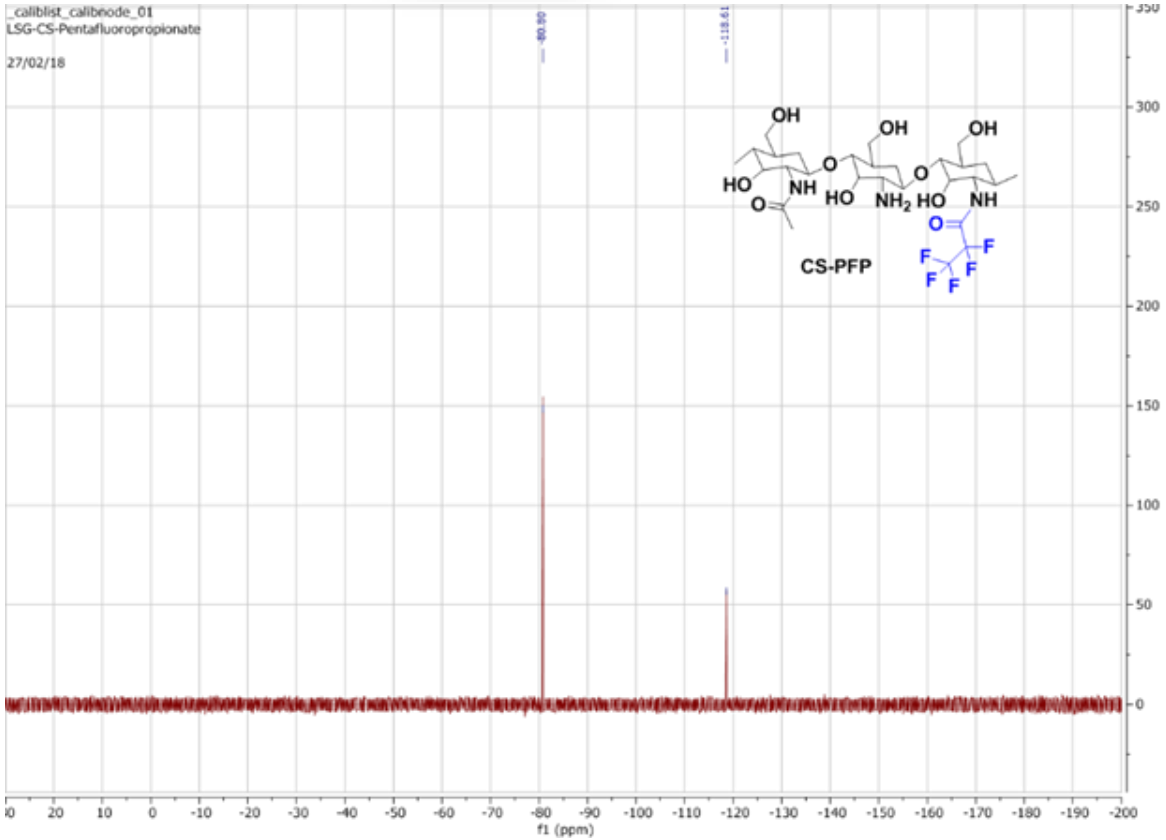
- The introduction of both cationic and hydrophobic moieties into the polymers improves the interaction with bacterial cells, leading to irreparable membrane damage and bacterial death.

Synthesis of fluorinated chitosan derivatives



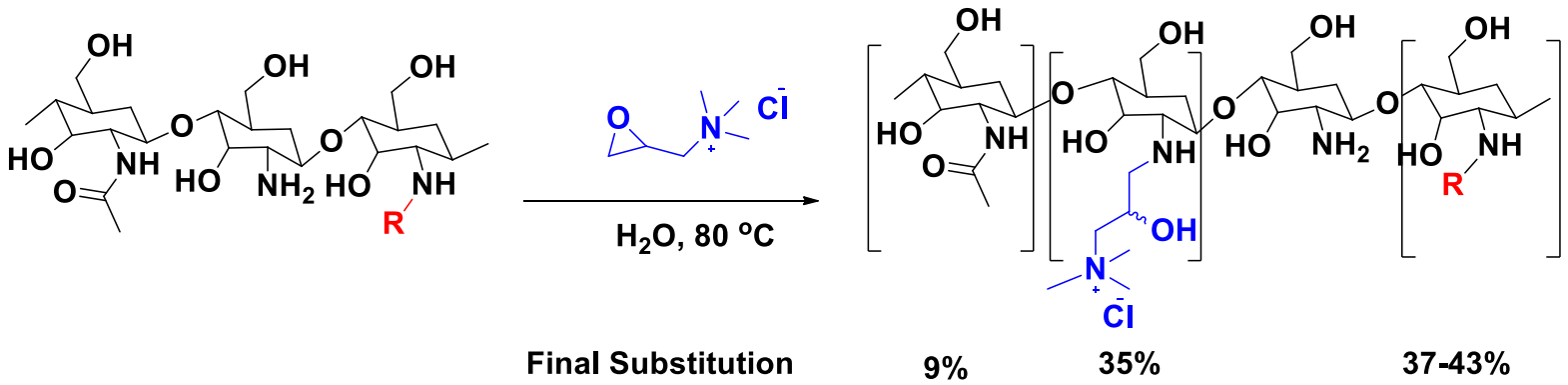


High contact angle droplet

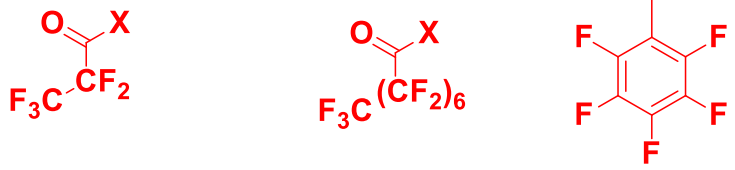


19F NMR Spectrum of Fluorinated Chitosan (41% Degree of Substitution)

Synthesis of fluorinated quaternary chitosan derivatives

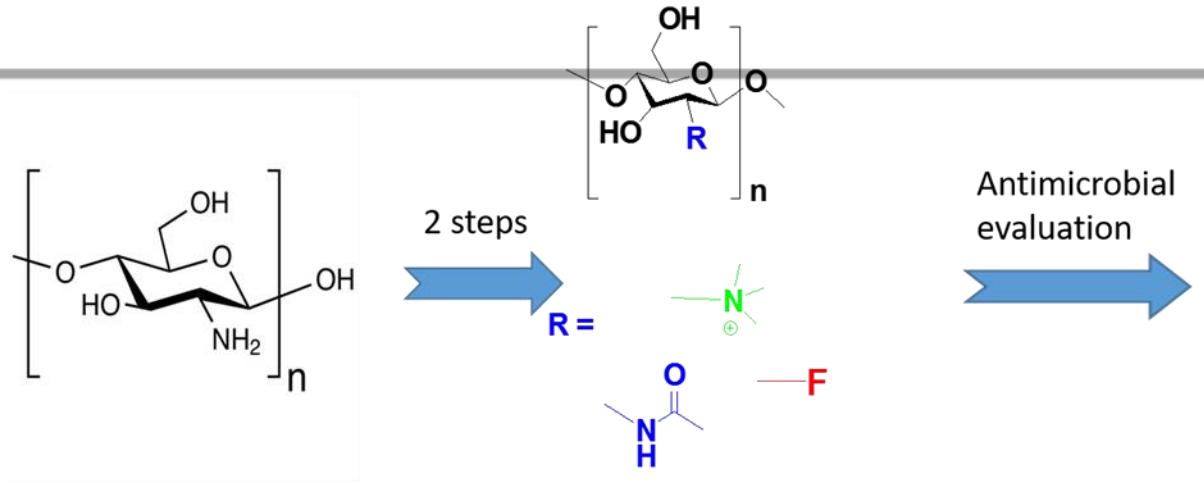


R =

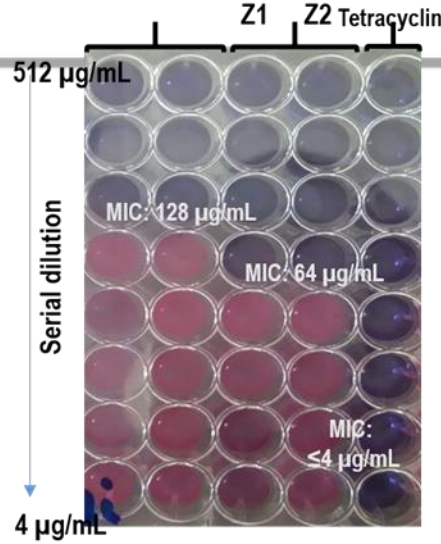


Degree of quaternization (DQ): Determined by using Mohr's titration

Antimicrobial assay



Chitosan derivatives containing fluorine and cationic moieties



ACS OMEGA

http://pubs.acs.org/journal/acsodf

Fluorinated Quaternary Chitosan Derivatives: Synthesis, Characterization, Antibacterial Activity, and Killing Kinetics

Zamani E.D. Cele, Anou M. Somboro, Daniel G. Amoako, Lindokuhle F. Ndlandla, and Mohammed O. Balogun*

Cite This: *ACS Omega* 2020, 5, 29657–29666

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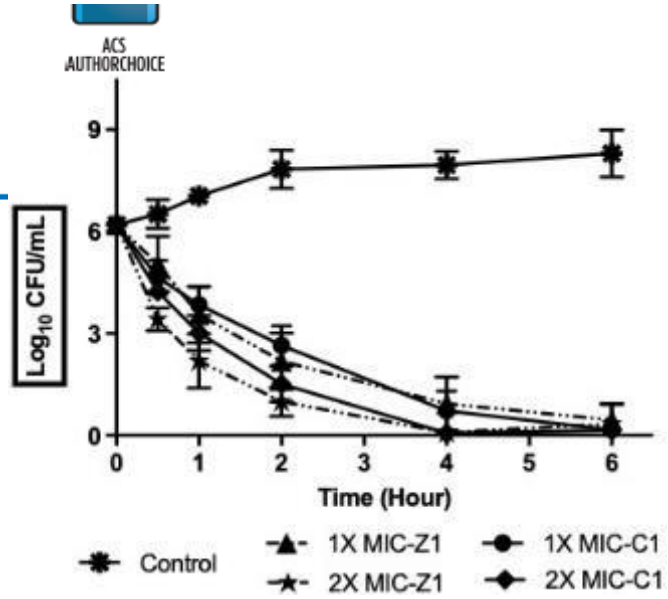
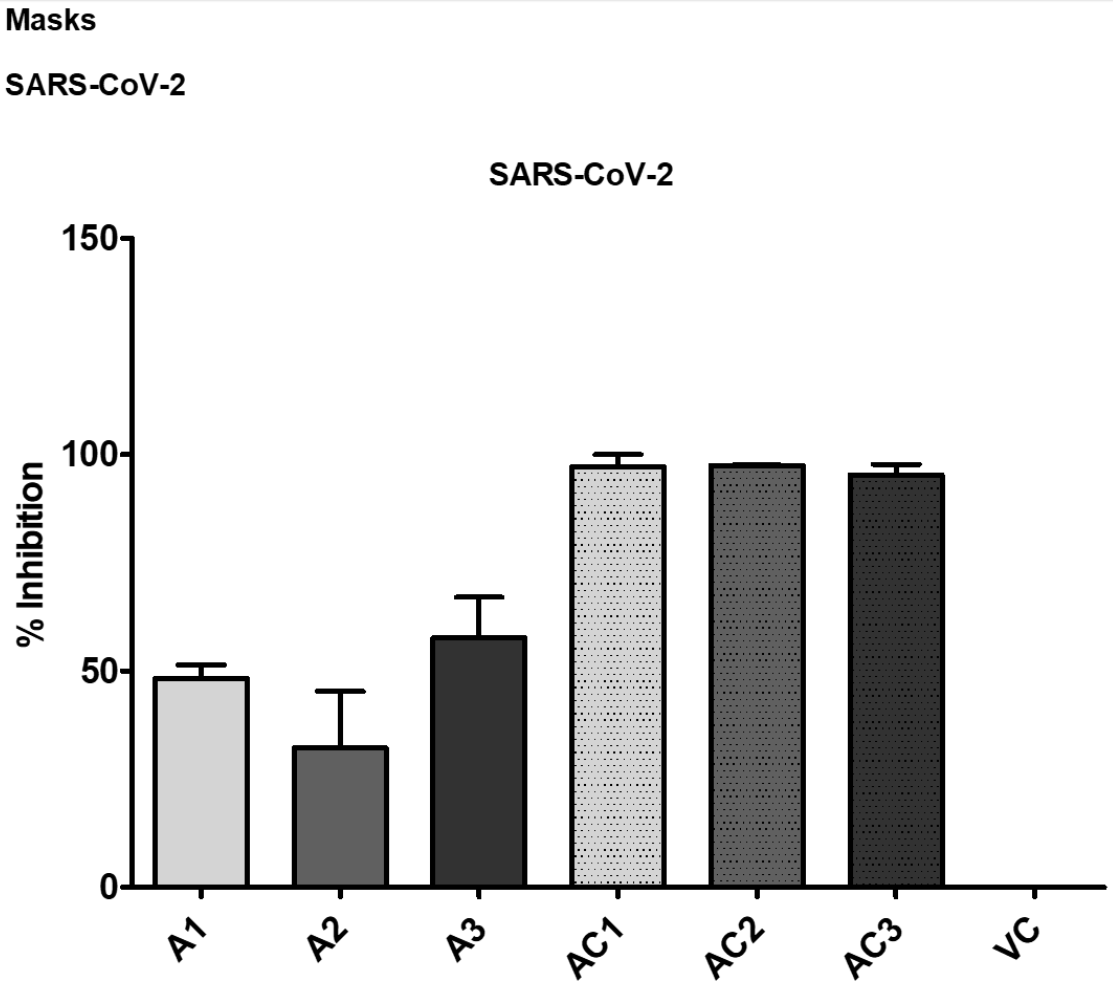
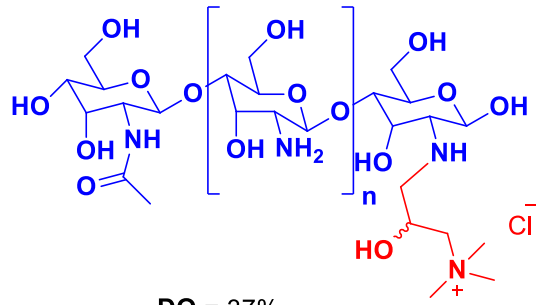


Quaternary chitosan antiviral inhibition against SARS-Cov-2

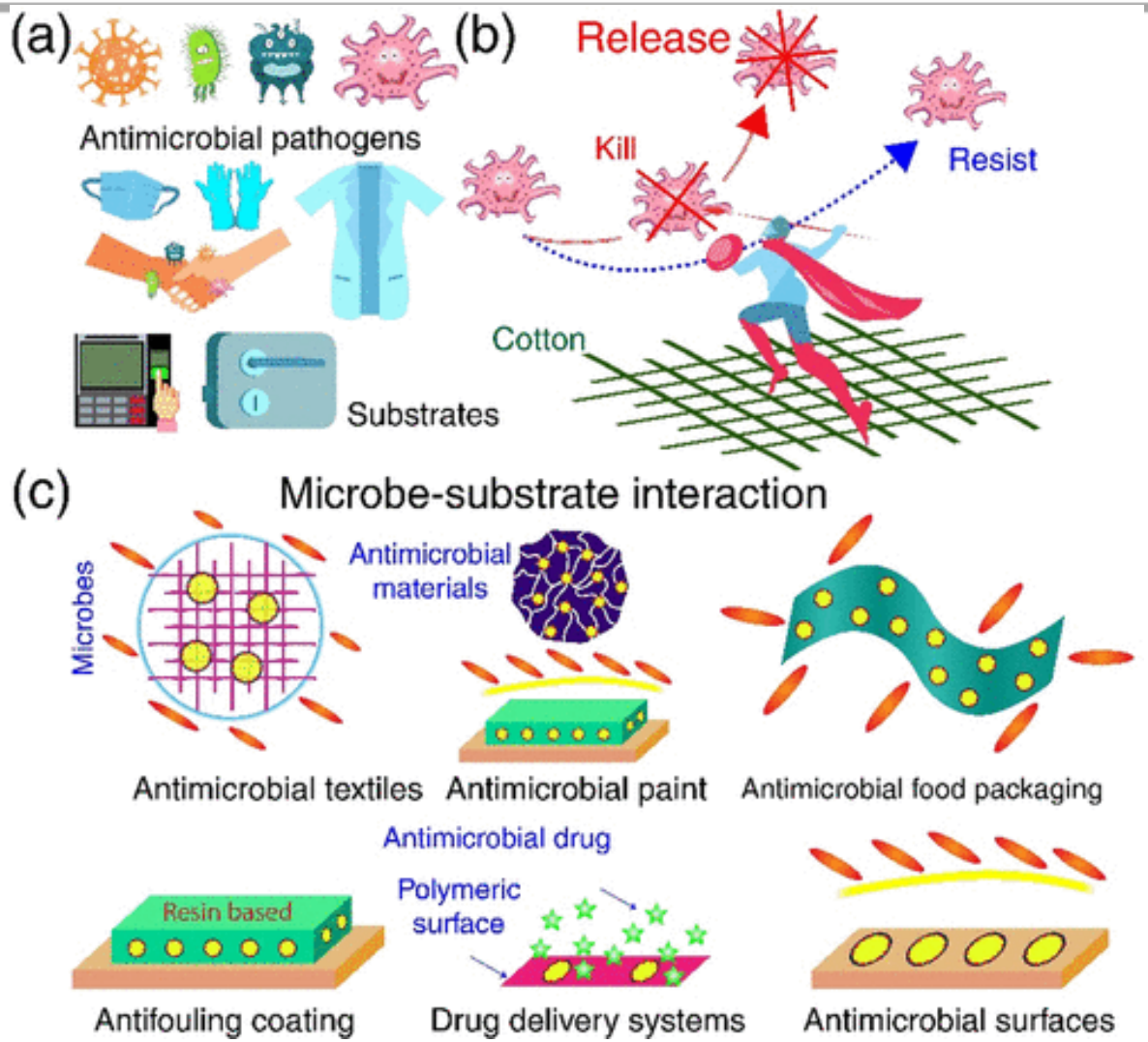




DQ = 37%

- Immobilizing polycations on various surfaces has been shown to convey antiviral properties for both enveloped and non-enveloped viruses.
- SARS-CoV-2 virus-capture onto uncoated (A1-3) and coated (AC1-3) masks.

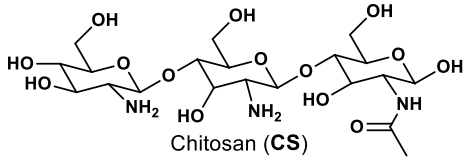
Applications of antimicrobial functional materials

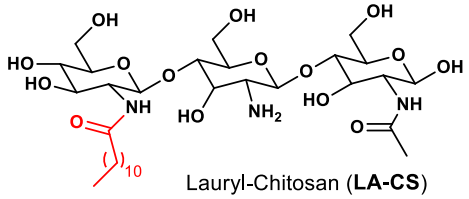


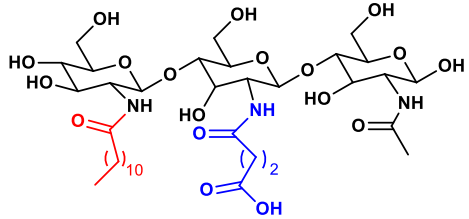
a) Emerging antimicrobial pathogens
b) Antimicrobial mechanism against the pathogens.
(c) Antimicrobial coatings for various applications

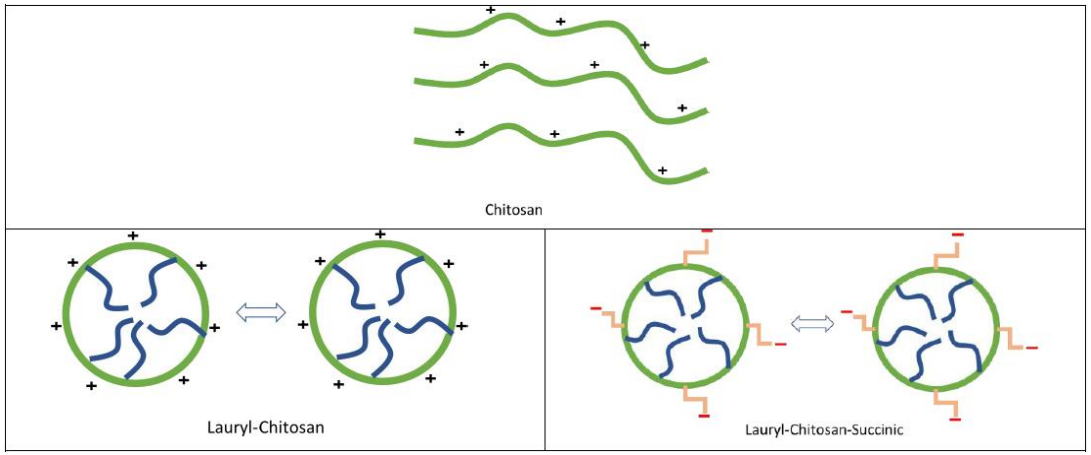
ACS Pharmacol. Transl. Sci. **2020**, https://doi.org/10.1021/acsptsci.0c00174

Chitosan-based nanomaterials as potential electrolytes









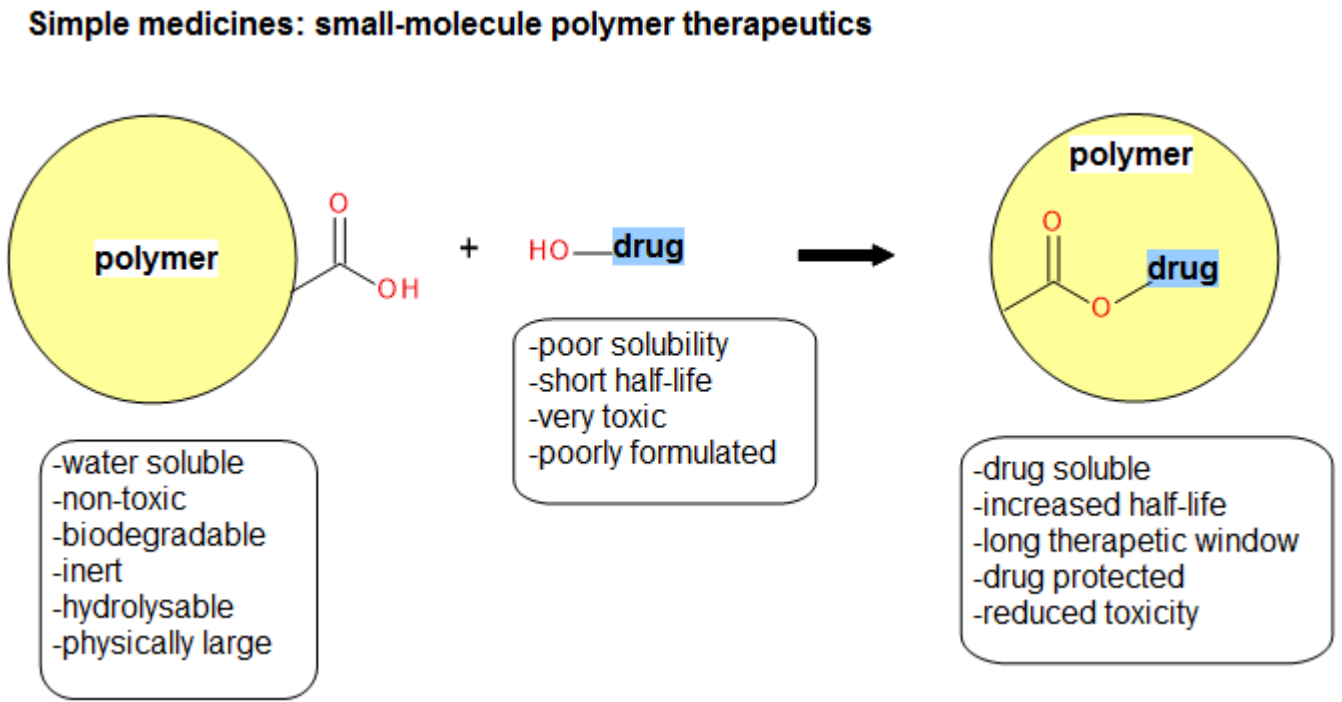
Particle size and surface charge of Chitosan derivatives in various aqueous diluents.

Material	Diluent	Particle size (nm)	Surface charge
LA-CS-Suc	dH2O	320	-20.77
LA-CS-Suc	PBS	216	-14.93
LA-CS-Suc	NaCl	257	-12.47
LA-CS	4% acetic acid	371	19.3
CS 10kDa	1% acetic acid	1078	26.93

These could find applications in health systems where charged delivery systems are required for tissue-specific delivery of bioactives.

Biopolymer-based materials in nanomedicine

- Combining small-molecule medicines with polymers could offer big rewards for pharmaceutical researchers.
- The theory is sound: you take a conventional small-molecule medicine and then attach it to a polymer and you get a new drug (a polymer-drug conjugate) that will have a longer *in vivo* plasma half-life than the drug alone.



Malaria

Global policies highlight the need to end malaria infections: Millennium Development Goals (MDG) and Sustainable Development Goals (SDG)

Sustainable Development Goals

•Target 3.3: "By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases."

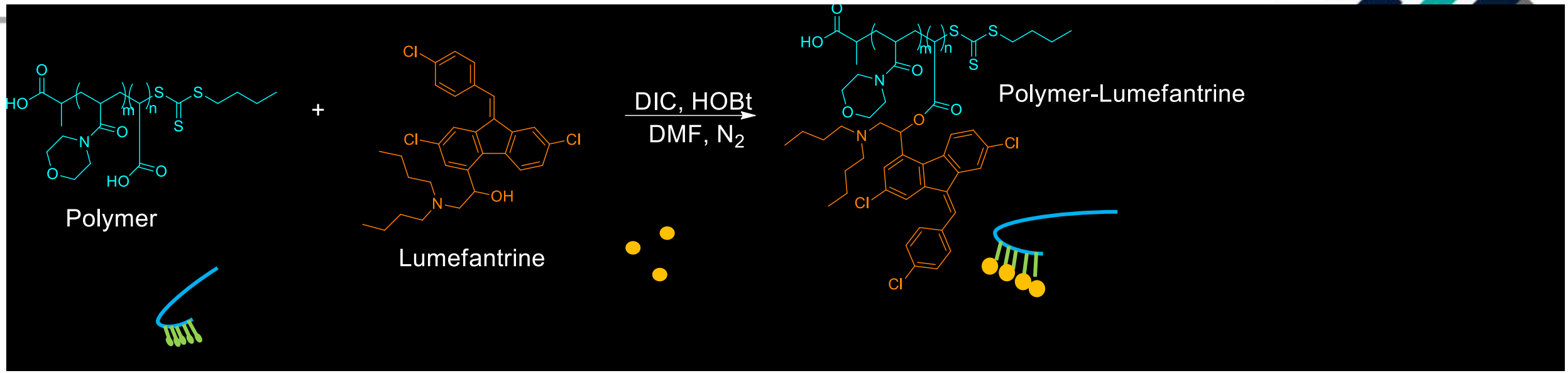
Our approach is to introduce modern therapeutic technologies – the parasite is a timeless master of adaptation.

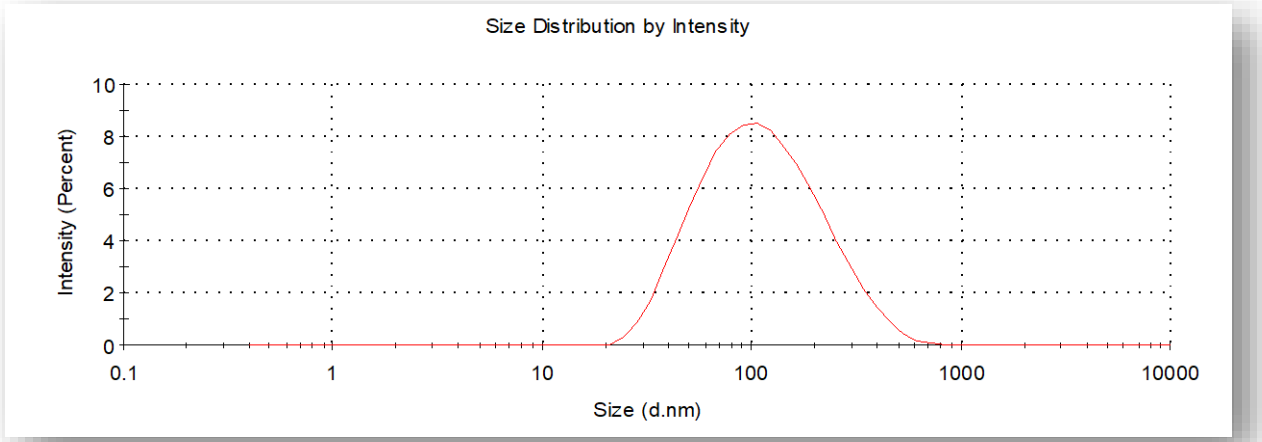
Malaria is an ancient disease still being treated with ancient drugs. *Quinine* (in use for over 4 centuries), the *artemisinins* (from Chinese folk medicine), *chloroquine* (>80 years); *primaquine* (>60 years).

Issues concerning drug solubility, biostability, toxicity, and uncontrolled pharmacokinetics can be overcome with adequately designed drug NCs based on liposomes, polymers or dendrimers. Furthermore, drug resistance evolves when one cannot deliver to the parasites a sufficiently high dose to kill them rapidly.

One major unmet clinical need in treatment: *No combination of drugs suitable for intravenous treatment of severe malaria currently exists*.

Conjugation of lumefantrine to a multi-valent polymer



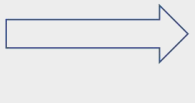


Size of polymer-drug conjugate = ~90 nm

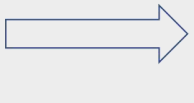
What have we achieved?

Development

Lumefantrine

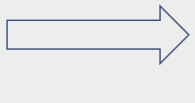


Add water



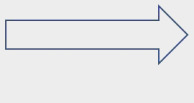
Centrifugation, 15 000 rpm, 1 h

Polymer-lumefantrine



Drugs

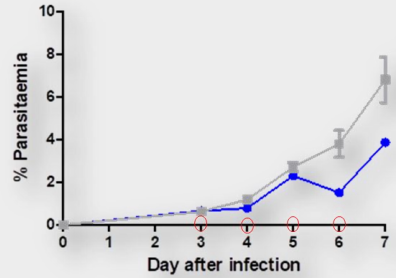
Aqueous Solutions



Supernatants

IV Formulation

PK/PD



Conclusions and future developments

- Modifications are often performed in order to improve the properties of biopolymers to suit them for different applications.
- It is important to understand the Mechanism of Action and Structure-Activity Relationship (SAR).
- We need to focus on studying the durability of biopolymers for numerous applications and discover novel processing techniques.

Acknowledgments

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THANK YOU