Preventing biofilm fouling of indwelling medical devices to reduce HAIs and AMR

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Summary

1. **Current drug development efforts to** combat HAIs are focused on free-living or planktonic cells -- acute infections.

2. However, **most HAIs are caused by biofilm** growth on medical devices, such as VAP.

3. Conventional antibiotics are **not effective against biofilms.**

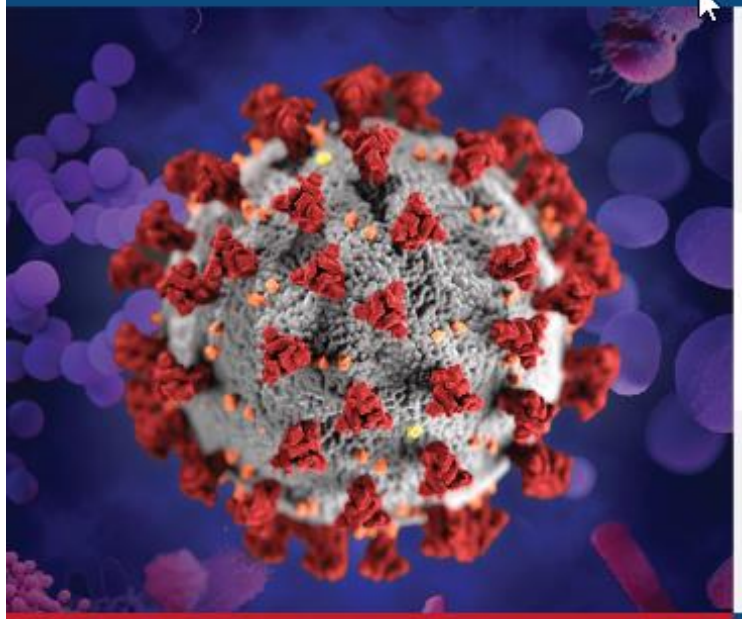
4. The only effective approach is to **PREVENT biofilm growth on medical devices.**

5. **New technology** has been developed that **can achieve this without inducing mutational resistance.**

6. Biofilm prevention is highly cost effective and **would significantly reduce the need for antibiotic therapy while saving billions.**

COVID-19 CREATED A PERFECT STORM

The U.S. lost progress combating antimicrobial resistance in 2020



↑15% Antimicrobial-resistant infections and deaths increased in hospitals in 2020.

~80% Patients hospitalized with COVID-19 who received an antibiotic March-October 2020.

Delayed or unavailable data, leading to resistant infections spreading undetected and untreated.

INVEST IN PREVENTION.

Setbacks to fighting antimicrobial resistance can and must be temporary.

Learn more: https://www.cdc.gov/drugresistance/covid19.html

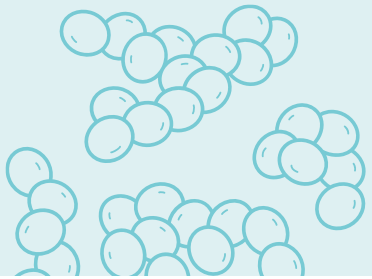
It is time to heed Dr. Bell's call for a paradigm shift

In 2001, Dr. Bell, Deputy Director of CDC's Division of Healthcare Quality Promotion, authored a seminal article "Biofilms: A Clinical Perspective" in which he said:

> *A fundamental shift* is needed in our approach to patient care and infectious diseases if we are to prevent device-associated infections, treatment failures, and undesired consequences (e.g. selection for antimicrobial-resistant bacterial strains)
>
> **due to biofilm-related infections.**

Source: Bell M. Biofilms: A Clinical Perspective. Curr Infect Dis Rep. 2001 Dec;3(6):483-486.

> **One factor** that is inextricably linked to, and exacerbates antibiotic resistance has been **consistently overlooked** to date; this **factor is biofilm**.



Biofilm fouling of medical devices account for approximately 65% of HAIs.

Source: Bowler P, Murphy C, Wolcott R. Biofilm exacerbates antibiotic resistance: Is this a current oversight in antimicrobial stewardship? Antimicrob Resist Infect Control. 2020 Oct 20;9(1):162.

FDA has also called for increased focus on prevention

> One thing the pandemic has done is to catapult anti-infectives & vaccines from sleepy and under-invested to **exciting and important…**
>
> Anti-microbial resistance and pandemic preparedness made it onto the G7 agenda.

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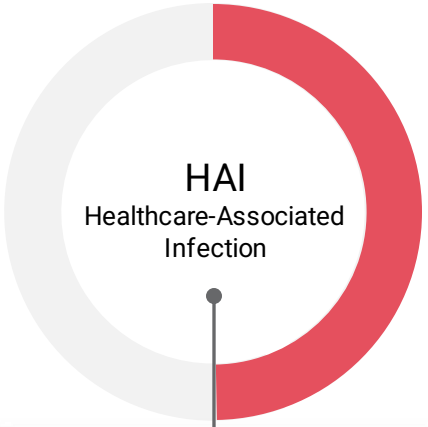
> The **best way** to prevent a resistant microbe from becoming resistant is to prevent patients from getting infection in the first place.
>
> *Former FDA commissioner Scott Gottlieb, Sept. 13, 2018*

N8 is pursuing a critical path to preventing HAIs

Preventing biofilm growth on medical devices would prevent 50% of all healthcare-associated infections

More than half of HAIs are **caused by medical devices**

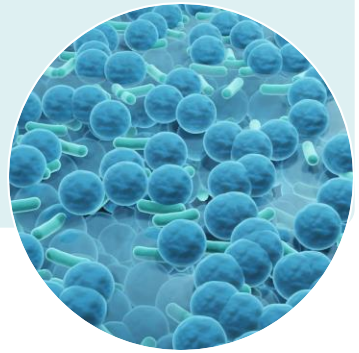


>50%
of HAIs are Medical Device Associated

6 million cases in US/EU
150,000 deaths
$28.4B US costs[1]

Medical devices promote biofilm growth on their surfaces

Acts as an antibiotic resistant reservoir of infections agents



PREVENTION IS SUPERIOR TO CURE

Source: 1. https://www.cdc.gov/policy/polaris/healthtopics/hai/index.htmlhttps://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143568.htm 2. Poster et al. 2018 Proc SPIE Int Soc Opt Eng. 2018 ; 10730:doi:10.1117/12.2500431

Dr. Rodney Donlan

Division of Healthcare Quality Promotion, CDC

Atlanta, GA, USA

> Another area of great importance from a public health perspective is **the role of biofilms in antimicrobial-drug resistance.**

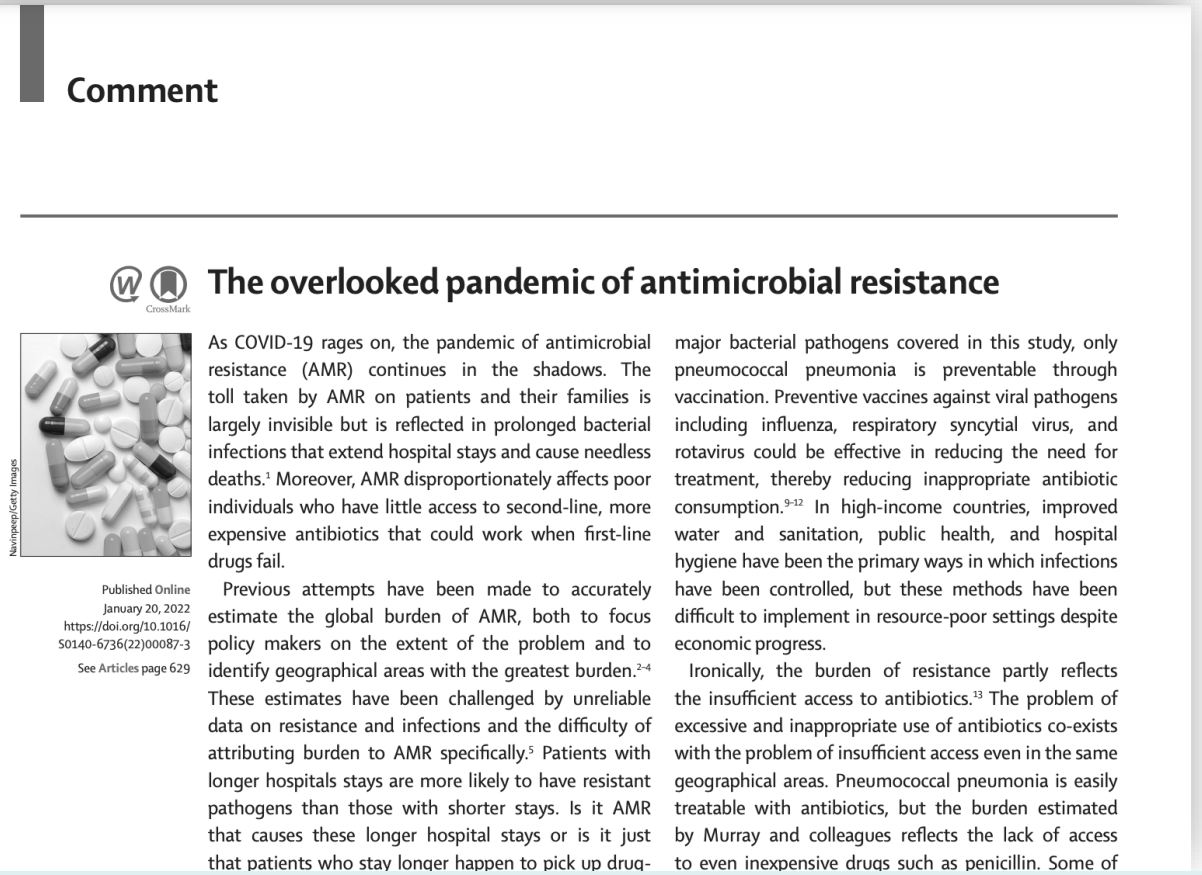
Bacteria within biofilms are intrinsically more resistant to antimicrobial agents than planktonic cells because of the diminished rates of mass transport of antimicrobial molecules to the biofilm associated cells or because biofilm cells differ physiologically from planktonic cells.

Antimicrobial concentrations sufficient to inactivate planktonic organisms are generally inadequate to inactivate biofilm organisms, especially those deep within the biofilm, potentially selecting for resistant subpopulations.

Donlan, Rodney M.. Role of Biofilms in Antimicrobial Resistance. ASAIO Journal: November 2000 - Volume 46 - Issue 6 - p S47-S52

“ Spending needs to be directed to **preventing infections in the first place**

The Lancet 2022



Comment

The overlooked pandemic of antimicrobial resistance

Navinpeep/Getty Images

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S0140-6736(22)00087-3

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As COVID-19 rages on, the pandemic of antimicrobial resistance (AMR) continues in the shadows. The toll taken by AMR on patients and their families is largely invisible but is reflected in prolonged bacterial infections that extend hospital stays and cause needless deaths.[1] Moreover, AMR disproportionately affects poor individuals who have little access to second-line, more expensive antibiotics that could work when first-line drugs fail.

Previous attempts have been made to accurately estimate the global burden of AMR, both to focus policy makers on the extent of the problem and to identify geographical areas with the greatest burden.[2–4] These estimates have been challenged by unreliable data on resistance and infections and the difficulty of attributing burden to AMR specifically.[5] Patients with longer hospitals stays are more likely to have resistant pathogens than those with shorter stays. Is it AMR that causes these longer hospital stays or is it just that patients who stay longer happen to pick up drug-

major bacterial pathogens covered in this study, only pneumococcal pneumonia is preventable through vaccination. Preventive vaccines against viral pathogens including influenza, respiratory syncytial virus, and rotavirus could be effective in reducing the need for treatment, thereby reducing inappropriate antibiotic consumption.[9–12] In high-income countries, improved water and sanitation, public health, and hospital hygiene have been the primary ways in which infections have been controlled, but these methods have been difficult to implement in resource-poor settings despite economic progress.

Ironically, the burden of resistance partly reflects the insufficient access to antibiotics.[13] The problem of excessive and inappropriate use of antibiotics co-exists with the problem of insufficient access even in the same geographical areas. Pneumococcal pneumonia is easily treatable with antibiotics, but the burden estimated by Murray and colleagues reflects the lack of access to even inexpensive drugs such as penicillin. Some of

Laxminarayan R. The overlooked pandemic of antimicrobial resistance. Lancet. 2022 Feb 12;399(10325):606-607

N8 BIOSCIENCES

Ventilator Associated Pneumonia (VAP) is the leading biofilm related medical device infection

Approximately **50%** of all **hospital antibiotic use** is for **patients in the ICU.**

A significant portion of that is for mechanically ventilated patients who develop Ventilator Associate Pneumonia (VAP) with **an estimated 200,000 cases per year.**

Patients with **mature biofilms on the inner lumen of their Endotracheal Tubes (ETTs)** are at **high risk for VAP.**

VAP adds 8 days of Mechanical Ventilation in the ICU with high doses of antibiotics accelerating development of MDRs. Estimated cost of $4k per day.

Total estimated costs of $6.4 billion annually which may be largely preventable if new technology can prevent biofilm growth on ETTs.

Source: Gil-Perotin S, Ramirez P, Marti V, Sahuquillo JM, Gonzalez E, Calleja I, Menendez R, Bonastre J. Implications of endotracheal tube biofilm in ventilator-associated pneumonia response: a state of concept. Crit Care. 2012 May 23;16(3)

New technology has been developed that can prevent biofilm growth on ETTs and other medical devices

Insights from innate immunology have led to the development of an ETT coated with a synthetic non-peptide mimic of an endogenous antimicrobial peptide found naturally in the lung (LL-37). Protects ETT from bacterial and fungal biofilms.

Active against all ESKAPE pathogens, fungi and lipid enveloped viruses such as **COVID** and **monkeypox**.

FDA has designated device as a "breakthrough device."
Already approved in Canada and Brazil. Working with **NCDC in Tbilisi Georgia** for upcoming VAP study in high risk patients.

In vitro and clinical testing has shown that the device significantly prevent bacterial and fungal (*C. auris*) biofilm growth on ETTs**, including polymicrobial challenges.**

C. auris study co-published with Dr. Shawn Lockhart of CDC's mycology division. CSA-131 tested against 100 *C auris* clinical isolates. MICs between 0.5 and 1.0 micrograms/ml. Active against all.

Hashemi MM, Rovig J, Bateman J, Holden BS, Modelzelewski T, Gueorguieva I, von Dyck M, Bracken R, Genberg C, Deng S, Savage PB. Preclinical testing of a broad-spectrum antimicrobial endotracheal tube coated with an innate immune synthetic mimic. J Antimicrob Chemother. 2018 Jan 1;73(1):143-150.

Prevention of VAP

May potentially save billions of dollars worldwide -- **no need for increased funding** for adoption or to fix the reimbursement scheme.

May potentially significantly reduce LOS in the ICU, need for more ICU beds, antibiotic use and attributable mortality.

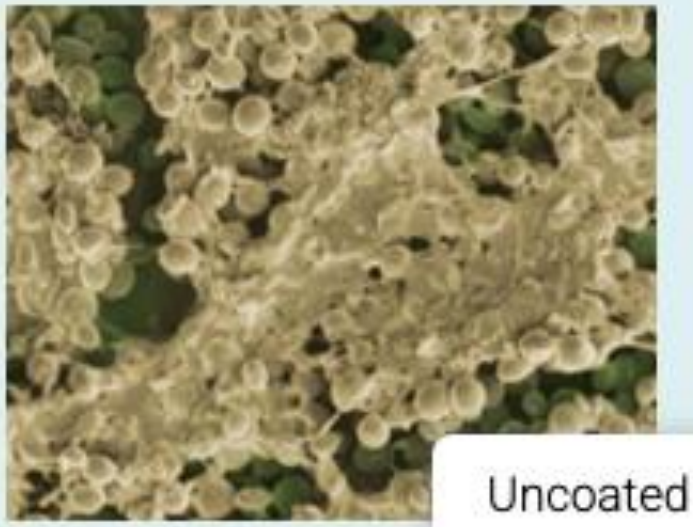
May be widely implemented internationally in the next few years, even in LMIC countries.

Cost of added case of **VAP in India** is **$6,000 USD.**

Money saved on treating VAP can be redirected to **develop and purchase expensive antibiotics** and to **address other critical healthcare concerns.**

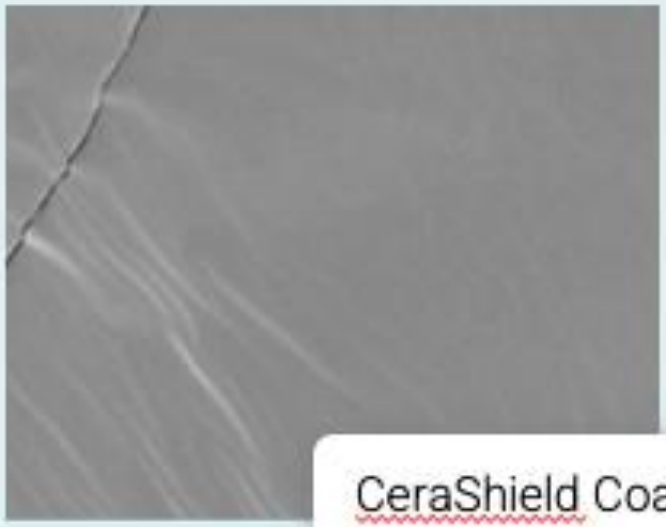
Scanning electron microscopy of ETTs challenged with PA01 and *C. auris*

SEM of ETT segments



Uncoated

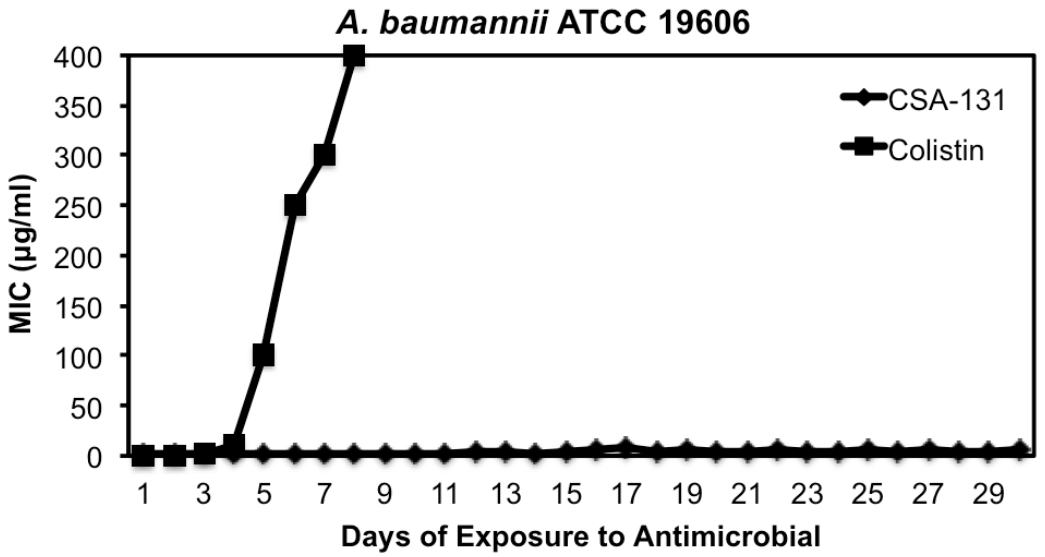
vs.

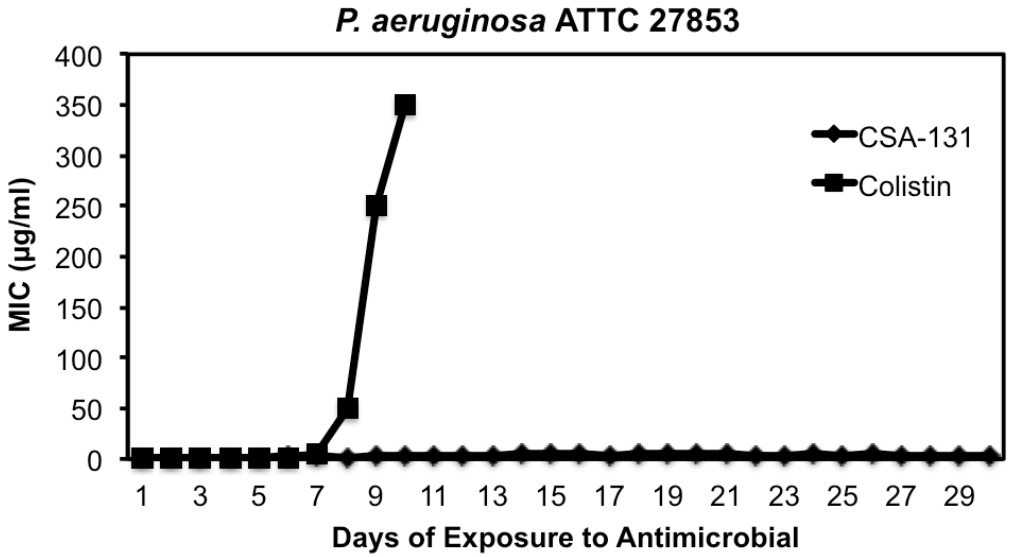


CeraShield Coated

Serial passaging study

Resistance generation to Colistin and CSA-131



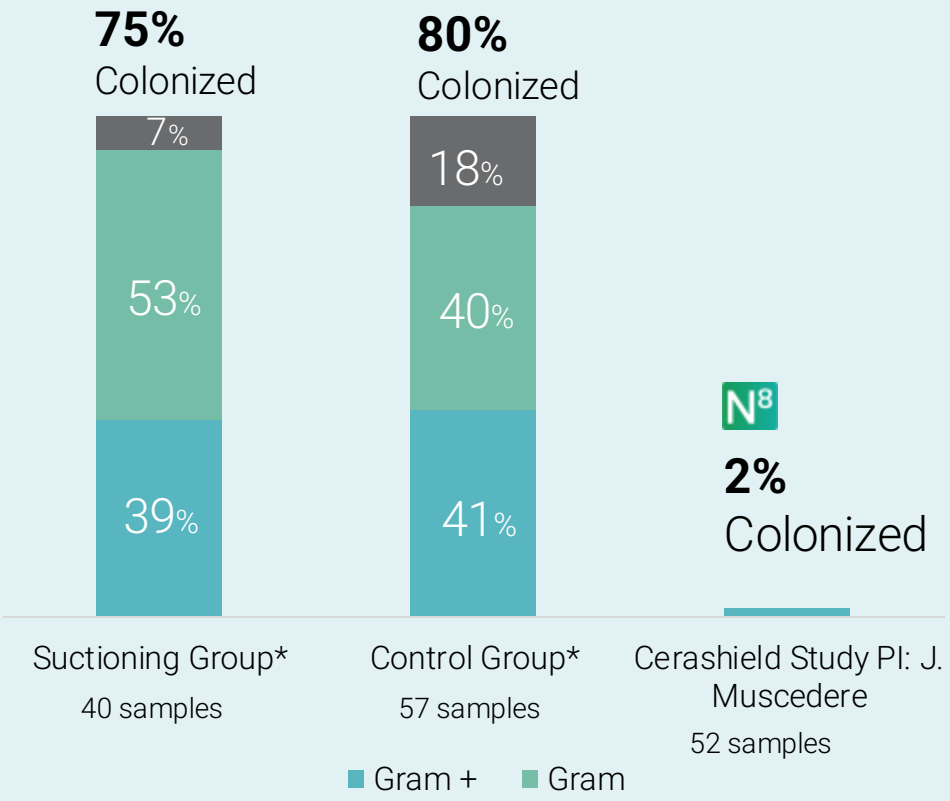


N8 ETT Canada Case Study: Reduces bacterial colonization by 97%*

ETTs surfaces are rapidly colonized with pathogenic bacteria and fungi that form antibiotic resistant biofilms

Biofilms secrete endotoxins that lead to inflammatory cytokine cascades and infection

By preventing biofilm, **we may significantly prevent VAP and other adverse outcomes**



* Girou, E., Buu-Hoi, A., Stephen, F. *et al.* Airway colonization in long-term mechanically ventilated patients. *Intensive Care Med* **30**, 225-233 (2004). https://doi.org/10.1007/s00134-003-2077-4

Ceragenin broad spectrum activity

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Active against all ESKAPE pathogens, MDR strains, fungal pathogens *(C. auris, Candida spp and Aspergillosis)* and lipid enveloped viruses -- COVID-19 and monkeypox.

Being developed as an inhaled drug for CF with support from the Cystic Fibrosis Therapeutics Foundation.

Able to **prevent and eradicate** biofilms.

Binds endotoxin and sequesters LPS superior **to Polymyxin B.**

Does not induce mutational resistance, similar to endogenous Antimicrobial Peptides (LL-37).

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Thank you

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