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Article

TiO_2 Nanostructures That Reduce the Infectivity of Human Respiratory Viruses Including SARS-CoV-2

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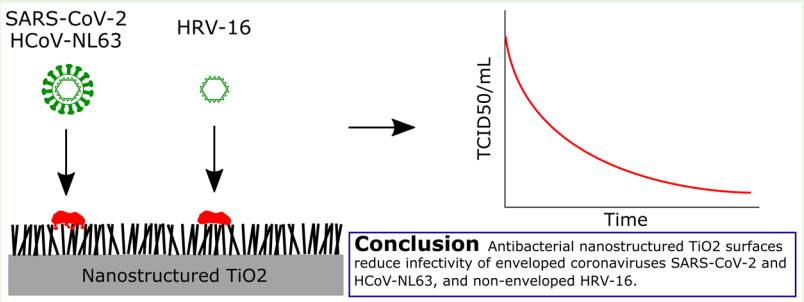

ABSTRACT: The rapid emergence and global spread of the COVID-19 causing Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and its subsequent mutated strains has caused unprecedented health, economic, and social devastation. Respiratory viruses such as SARS-CoV-2 can be transmitted through both direct and indirect channels, including aerosol respiratory droplets, contamination of inanimate surfaces (fomites), and direct person-to-person contact. Current methods of virus inactivation on surfaces include chemicals and biocides, and while effective, continuous and repetitive cleaning of all surfaces is not always viable. Recent work in the field of biomaterials engineering has established the antibacterial effects of hydrothermally synthesized TiO_2 nanostructured surfaces against both Gram-negative and -positive bacteria. The current study investigates the effectiveness of said TiO_2 nanostructured surfaces against two enveloped human coronaviruses, SARS-CoV-2 and HCoV-NL63, and nonenveloped HRV-16 for surface-based inactivation. Results show that structured surfaces reduced infectious viral loads of SARS-CoV-2 (5 log), HCoV-NL63 (3 log), and HRV-16 (4 log) after 5 h, compared to nonstructured and tissue culture plastic control surfaces. Interestingly, infectious virus remained present on control tissue culture plastic after 7 h exposure. These encouraging results establish the potential use of nanostructured surfaces to reduce the transmission and spread of both enveloped and nonenveloped respiratory viruses, by reducing their infectious period on a surface. The dual antiviral and antibacterial properties of these surfaces support their potential application in a wide variety of settings such as hospitals and healthcare environments, public transport and community hubs.

KEYWORDS: *SARS-CoV-2, human coronavirus, nanostructured surfaces, titanium dioxide, HCoV-NL63, HRV-16, antiviral surfaces, antibacterial surfaces*

1.0. INTRODUCTION

Coronaviruses are positive-stranded RNA viruses, with a genome consisting of major structural proteins in the 5′ to 3′ order, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins.[1,2] In contrast, human rhinovirus (HRV) is a nonenveloped virus with a single-stranded, positive sense RNA genome.[3] Seasonal coronaviruses (such as HCoV-NL63, HKU1, HCoV-229E, and OC43) and rhinoviruses frequently cause respiratory illnesses including the common cold.[2−5] In the last two decades, numerous pandemic coronaviruses have emerged including SARS-CoV in 2002 (10% mortality rate) and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 (37% mortality rate), causing widespread infection and death among children and adults.[6,7] The most recent of these emerging strains, SARS-CoV-2, has caused more infections and death than both SARS-CoV and MERS-CoV combined[3] since its first detection in 2019.

SARS-CoV-2 has caused global social, economic, tourism, and healthcare devastation since its initial detection.[8] To contain the spread of the virus, governments were moved to impose city- and nation-wide lockdowns, close both domestic

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and international borders, implement mask-wearing mandates, and enforce quarantine measures on both international and domestic arrivals. While multiple vaccines have been developed to minimize the risk of severe infection and hospitalization of COVID-19, there are currently no specific antiviral preventative or curative treatments for coronavirus infections.[7,9] Therefore, engineering surface and aerosol transmission controls remain an essential avenue for controlling infection spread. In addition, given the previous history of emerging SARS strains and subsequent mutations, it can be expected that new viruses will emerge with pandemic potential that will require rapid surface inactivation to control transmission.

Studies show that respiratory viruses, including SARS-CoV-2 are transmitted through a number of avenues[10] including direct contact between individuals, airborne transmission, and indirect contact with contaminated surfaces (fomites).[11] Surface transmission is caused when infected respiratory droplets (5−10 μm) and aerosols, generated when an infected person coughs or sneezes,[12−14] land on and contaminate a surface or inanimate object.[11,15,16] Subsequent users then contact this infected surface, transferring the virus to their hands, where transmission and infection can occur after touching their eyes, nose, or mouth. Studies suggest that transmission of SARS-CoV-2 and seasonal coronaviruses, such as HCoV-NL63, is due to their ability to survive and remain infectious on different surfaces for long periods of time at room temperature.[2,17,18] For example, SARS-CoV-2 can remain infectious on stainless steel for 3−4 days[19] and on smooth surfaces for 7 days.[20] SARS-CoV-2 RNA has been detected in hospital rooms, with viral loads most commonly detected on floors, electrical switches, chairs, toilet seats, and flush buttons.[21] Recommended disinfection methods for surfaces include ethanol sprays, bleach, and peroxide; however, these methods do not provide ongoing protection,[12] and given the rapid evaporation of alcohol-based solutions, surfaces can become reinfected within minutes. In addition, constant cleaning and disinfection can be expensive and time-consuming.

Recent advances in nanotechnology, namely, nanomaterials and nanoparticles, offer potential solutions for surface transmission. Some nanomaterials can be used to capture and inactivate or inhibit replication or entry of the virus into human cells, thus preventing infection.[6] Some antiviral agents such as copper, silver nanoparticles, nanocarbons, zinc, and polyethylenimine are used in personal protective equipment (PPE) such as face masks, immunodiagnostic assays, drug administration, and vaccines.[6,9,22−26]

This work investigates the antiviral properties of previously established antibacterial TiO_2 nanostructured surfaces[27−31] as a method of viral inactivation against enveloped human coronaviruses SARS-CoV-2 and HCoV-NL63, and non-enveloped HRV-16. This study aims to develop inherently antiviral surfaces which deactivate viral particles without the need for chemical disinfectants. This research is a step toward installation and implementation of these surfaces in high traffic environments or on highly touched surfaces to reduce transmission and infection of pathogens through communities.

2.0. MATERIALS AND METHODS

2.1. Nanostructure Fabrication. Commercially available Ti-6Al-4V (medical grade 5) was polished to a 0.04 μm surface roughness (mirror shine), sonicated in acetone for 10 min, and rinsed thoroughly with 18.2 MΩ H_2O. Samples were then placed in a custom-made PTFE holder with 60 mL 1 M NaOH in a 125 mL Parr acid digestion vessel at 180 °C for 2 h. After cooling to room temperature, samples were rinsed with 18.2 MΩ H_2O and dried using N_2 gas. Samples were then annealed in a furnace for 1 h at 300 °C and, once cool, submerged in 0.6 M HCl for 30 min for ion exchange. After rinsing with 18.2 MΩ H_2O, samples were calcined for 2 h at 600 °C.

2.2. Surface Characterization. Surfaces were characterized using JEOL 7001F scanning electron microscopy (SEM) to visualize nanostructure morphology at various magnifications. The SEM was operated using 15 eV and 8 mA probe current. Surfaces have previously been characterized using nanoindentation for mechanical properties, X-ray diffraction for chemical characterization, and contact angle for measuring wettability.[27−29]

2.3. Cell Culture. VERO E6 (ATCC, C1008, CRL-1586, Manassas, USA) and H1HeLa cells (ATCC CRL-1958), and Rhesus Monkey Kidney Epithelial (LLC-MK2) cells (ATCC, CCL-7) were cultured in Dulbecco's Modified Eagle Medium (DMEM) and Reduced-Serum Medium (Opti-MEM), respectively, supplemented with 2% Fetal Bovine Serum (FBS) and 1% Antibiotic/Antimycotic and incubated at 37 °C under 5% CO_2, until confluent.

2.4. Virus Testing. SARS-CoV-2 stock (strain QLD02/2020 GISAID accession number EPI ISL 407896, provided by Alyssa Pyke, Queensland Health) was propagated in VERO cells as previously described[32] in DMEM, supplemented with 1 μg/mL tosyl phenylalanyl chloromethyl ketone (TPCK)-treated trypsin (Worthington Biochemical). HCoV-NL63 (Amsterdam-1 strain, provided by Lia van den Hoek, University of Amsterdam) was propagated in LLC-MK2 cells as previously described.[33] HRV-16 (ATCC VR-283) was propagated using H1HeLa cells in DMEM with 5% FBS. Cell supernatant was harvested when the cytopathic effect was 75% and supernatant clarified by centrifugation at 10,000 rpm for 10 min at 4 °C. The titer of stock virus and the subsequent titer of virus postexposure to nanostructures were quantified using a standard $TCID_{50}$ assay.

Triplicate nanostructured TiO_2, polished Ti-6Al-4V, and tissue culture plastic surfaces were exposed to 10 μL of 1×10^6 $TCID_{50}$/mL virus suspension and incubated at room temperature for 2, 5, or 7 h. This volume of virus was chosen to replicate a real-life scenario, whereby an infected person either sneezes or coughs viral particles, contaminating a surface. At each time point, exposed surfaces were gently washed by pipetting 60 μL DMEM (SARS-CoV-2 and HRV-16) or Opti-MEM (HCoV-NL63) 10 times to retrieve live virus. Confluent cells (VERO E6 cells for SARS-CoV-2, LLC-MK2 cells for HCoV-NL63, and H1HeLa cells for HRV-16) were infected with 50 μL of the recovered virus at 10^{-1} to 10^{-4} dilutions in 96 well plates containing 100 μL of media and 0.1% TPCK-treated Trypsin. Cells were incubated at 37 °C under 5% CO_2 for 4−7 days, until a cytopathic effect was observed, after which the cells were stained using Crystal Violet dye. The viral titer was calculated using the Spearman-Karber algorithm for $TCID_{50}$/mL. Three independent exposure experiments were performed to confirm results.

2.5. Statistical Analysis. Statistical analysis for $TCID_{50}$ assay results was completed using two-way ANOVA Tukey's multiple comparison test in GraphPad Prism v8. Significant results are indicated in figures, where $*p < 0.1$, $**p < 0.01$, $***p < 0.001$, and $****p < 0.0001$.

3.0. RESULTS

Figure 1 shows SEM images of TiO_2 nanostructures formed via hydrothermal synthesis. General morphology of the surfaces shows that structures are random in nature, with no consistent orientation angle or uniform pattern. The average structure diameter was measured to be approximately 20 nm in diameter and 300 nm in height, using built-in JEOL software. Previously reported characterization of hydrothermally synthesized TiO_2 measured the surface's contact angle with water to be 14.3°, showing the surface to be hydrophilic in nature. Young's

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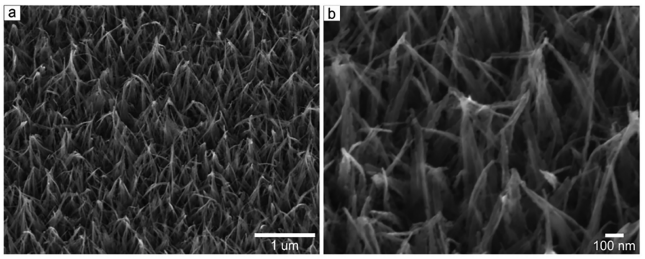

Figure 1. SEM images of hydrothermally synthesized nanostructured TiO_2 surface at various magnifications.

modulus and hardness were measured to be 12.2 GPa and 14.7 MPa, respectively.[28] In addition, it was found that structures remained mechanically stable, with no significant change in mechanical properties after 6 months.[29]

The results of the $TCID_{50}$ assays (Figure 2) show significant antiviral properties of nanostructured TiO_2 against all three viruses: SARS-CoV-2, HCoV-NL63, and RHV-16. Results show that nanostructured TiO_2 surfaces significantly reduced the infectious viral load of both enveloped and nonenveloped viruses at all time points, compared to control surfaces. Nanostructured TiO_2 surfaces reduced live infectious SARS-CoV-2 by 3 log from the initial viral titer (1×10^6 $TCID_{50}$/mL) after 2 h and 5 log after 5 and 7 h (Figure 2a). In contrast, polished Ti-4Al-6V control surfaces showed only a 1 and 2 log reduction after 2 and 5 h, respectively, with no significant reduction after 7 h. Similarly, virus exposed to tissue culture plastic showed 1 and 2 log reductions after 2 and 5 h of exposure, respectively, with no further significant reduction at 7 h. While viable virus was still detected in small amounts after 7 h exposure to nanostructured surfaces, this amount was significantly lower than both tissue culture plastic and polished Ti-6Al-4V controls.

HCoV-NL63 $TCID_{50}$ assay results (Figure 2b) show similar trends to SARS-CoV-2 test results (Figure 2a). Infectious HCoV-NL63 was significantly reduced by exposure to nanostructured TiO_2 for 2, 5, and 7 h (2, 3, and 3 log reductions, respectively), whereas both tissue culture plastic and polished Ti-6Al-4V produced a maximum of 1.6 log reduction over 7 h. Interestingly, the virucidal activity of TiO_2 was greater against SARS-CoV-2 than HCoV-NL63 and HRV-16 when compared to smooth Ti-6Al-4V surfaces, resulting in a larger reduction in live infectious virus at 7 h postexposure.

Nanostructured TiO_2 also caused significant viral load reductions of HRV-16 (Figure 2c) at all time points, resulting in 3 and 4 log reductions from the initial titer after 2 and 5 h exposure, respectively. The infectious dose continued to fall at 7 h of exposure to nanostructured surfaces. In contrast, exposure to tissue culture plastic and polished Ti-6Al-4V only produced a maximum of 2 log and 3 log reductions, respectively, over 7 h. While the viral infectious dose decreased on all surfaces after 7 h, nanostructured TiO_2 significantly accelerated this activity at all time points and for all viruses tested.

4.0. DISCUSSION

This study tested the antiviral properties of nanostructured TiO_2 surfaces against human respiratory viruses and reports encouraging results regarding a significant reduction in the recovery of live infectious coronaviruses SARS-CoV-2 and HCoV-NL63 and human rhinovirus HRV-16. We have

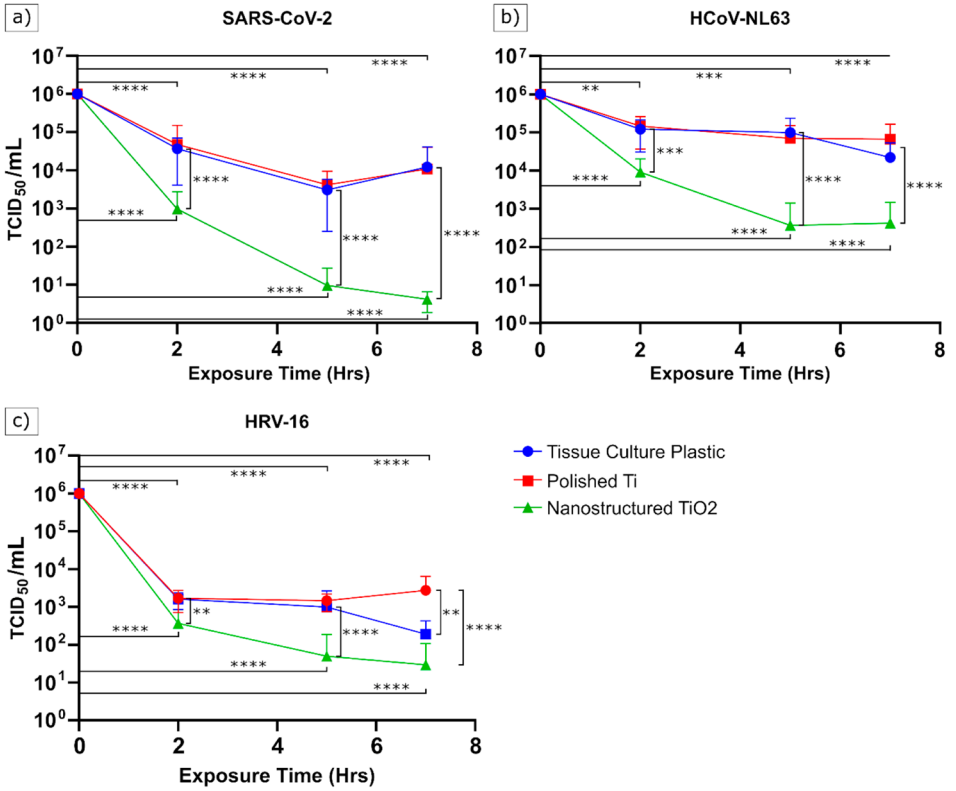

Figure 2. $TCID_{50}$/mL of (a) SARS-CoV-2 in VERO E6 cells, (b) HCoV-NL63 in LLC-MK2, and (c) HRV-16 in H1HeLa cells exposed to tissue culture plastic, polished Ti, and nanostructured TiO_2. Significant results are shown where $*p < 0.1$, $**p < 0.01$, $***p < 0.001$, and $****p < 0.0001$.

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previously reported that several viruses, including SARS-CoV-2, HRV, and respiratory syncytial virus (RSV), demonstrate reduced infectivity following exposure to aluminum surfaces treated with wet-etching.[34,35] However, the current study is a novel finding for nanostructured TiO_2 surfaces and adds critical evidence that etched nanostructures can be applied to various metallic substrates to produce antiviral and antibacterial surfaces that may reduce pathogenic transmission. Regarding self-cleaning antiviral surfaces to date, most of the research focus has been invested in studying silver, copper, and polymer-based nanomaterials.[6,9,22−26] However, the use of these materials is limited due to cost or suitability in applications that require mechanical durability. Therefore, a more generic method for generating antiviral surfaces on a range of metals may be more suitable.

The TiO_2 surfaces produced in this study are mechanically stable and have proved effective against Gram-positive *Staphylococcus aureus* and Gram-negative *Pseudomonas aeruginosa* bacteria, reducing bacterial viability within 3 h.[27−29] The exact mechanism by which nanostructures reduce infectivity of viruses is not known. However, a significant amount of research exists investigating mechanisms of action against bacteria.[36] One proposed mechanism of bacterial killing is via a biophysical model of interaction, in which the bacterial cell walls are stretched and disfigured in the regions suspended between two nanopillars, causing tearing of the cell wall and subsequent cell death.[37] This hypothesis has been recently challenged, with computational modeling finding that nanopillar tips create critical sites at the pillar apex, causing strains that lead to local rupture and penetration of the cells.[38] The mechanism of pathogenic deactivation via nanostructured surfaces remains an object of contention within the research community, and more research is needed to investigate the impact of nanostructure mechanical properties on this deactivation mechanism. However, it can be said that a certain degree of nanostructure rigidity is needed for either of the proposed mechanisms to be realized, whether it be tearing of the cell wall or strain-induced penetration.

Coronaviruses are enveloped viruses, and so it may be suggested that the mechanism of deactivation of enveloped viral particles by nanostructured surfaces may follow a similar theory to that of bacterial deactivation. It can be postulated that the viral envelope, which is a lipid bilayer derived from the host cell membrane, is disturbed, torn, or ruptured by the surface roughness of nanostructured surfaces. However, while similarities between bacterial and enveloped viral deactivation may exist, direct parallels cannot be drawn due to significant size and structural differences between bacterial cell and viral particle structure. In addition to having a lipid envelope with glycosylated surface attachment proteins, and no peptidoglycan cell wall like bacteria, coronavirus particles are 118−140 nm in size and rhinovirus is 30 nm in diameter, much smaller than bacterial cells.[39] In addition, this study shows a significant reduction in the infectious load of nonenveloped HRV-16 after exposure to nanostructured surfaces, indicating that the presence of a viral envelope does not significantly impact the antiviral performance of the nanostructured surface. We are currently investigating the nature of the viral deactivation mechanisms by nanostructured surfaces at a subcell level through coarse-grained molecular dynamic modeling methods. In addition, methods of visualizing viral attachment and morphology are being explored to further investigate deactivation mechanisms of nanostructured surfaces. One potential method of this is through immune-gold labeling, which may allow visualization of viral attachment by electron microscopy. This complex process is part of our ongoing research into in viral deactivation and will improve the understanding of the interaction between nanostructured surfaces and viral particles, and the significance of the viral envelope in this interaction.

Another possible mechanism of action for the reduced infectious dose of SARS-CoV-2, HCoV-NL63, and HRV-16 is that the highly rough and hydrophilic nature of the TiO_2 nanostructured surface (contact angle of 14.3°) cause viral particles to become trapped through irreversible adsorption onto the surface.[12] This phenomenon may result in less virus being recovered from the surface and therefore reduced infectivity of the recovered viral suspension as seen in this study for both enveloped and nonenveloped viruses. This theory suggests the idea that nanostructured surfaces may entrap virus particles instead of deactivating them through physical deformation. While this explanation indicates that the nanostructures themselves do not deactivate the virus particles, it does suggest that the presence of nanostructures reduces the amount of recovered infectious virus, thereby still reducing the potential for transmission.

Some studies suggest that nanostructure size and surface charge interact with spike proteins to block the initiation of viral infection[6] and disrupt infectivity,[9] thereby reducing the infectious dose as found in this study. Some studies also suggest that hydrophilic surfaces, such as the nanostructured TiO_2 surface tested here, may facilitate the inactivation of viruses due increased contact area between the surface and the infected droplet.[12,40,41] Interpretation of the data suggesting that nanostructures affect the infectivity of SARS-CoV-2 more than both HCoV-NL63 and HRV-16 needs to be carefully considered, as the $TCID_{50}$ assays for these viruses were performed using different cell lines, which may influence viral attachment and entry and thus the sensitivity of the assay.

Although the exact mechanism of action of nanostructures against viruses is yet to be elucidated, this study and others demonstrate the efficacy of this approach to the manufacture of antiviral surfaces. Most importantly, these nanostructures are effective against both enveloped and nonenveloped viruses. Therefore, nanostructure surfaces are an ideal strategy for inclusion in the arsenal required to protect humans from future emerging viruses for which vaccines and antiviral treatments may not be immediately available or completely protective. Despite excellent progress in the development of vaccines against SARS-CoV-2, it is apparent that public health measures and engineered transmission controls are still required to reduce the risk of exposure to the virus.[42] Thus, it is essential to continue studies such as this to develop effective antiviral surface treatments. Further investigation into the mechanism of deactivation of viral particles via nanostructured surfaces is currently being conducted; however, this study and the mechanisms suggested here provide a foundation with which to progress in this field.

Translation and upscaling of this technology is ongoing, with trials of large-scale nanostructured plates in hospital settings currently being conducted. Industrial-scale hydrothermal synthesis, wet-etching, and anodization are easily upscaled methods of nanofabrication, leading to translation of this technology onto surfaces with varying dimension and shape. By using methods such as these, nanostructures can be induced

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on many materials and products, creating wide-reaching impact.

5.0. CONCLUSIONS

We have shown that exposure to previously established antibacterial nanostructured TiO_2 surfaces significantly reduce the infectivity of human respiratory viruses SARS-CoV-2, HCoV-NL63, and HRV-16 within 2 h. These results provide evidence that nanostructured surfaces may reduce the transmission and spread of both enveloped and nonenveloped respiratory viruses. In addition, the proven antibacterial properties of these surfaces position nanostructured materials as a potential solution to wider pathogen transmission control. Adoption of these surfaces in various settings, particularly high-risk settings such as hospital and healthcare environments, transportation hubs, and community centers could reduce the spread of both viruses and bacteria through the community. While this study provides fundamental proof of concept for the antiviral properties of TiO_2 nanostructured surfaces, additional investigation into the deactivation mechanisms caused by the nanostructured surfaces is crucial. This ongoing work will allow for nanostructure optimization, working to reduce viral deactivation times and enhancing this antiviral effect, and will be fundamental to designing targeted surfaces for reducing the spread of viral infections.

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Author Contributions

AJ performed material fabrication, mechanical and viral testing with KS and AV, and wrote the manuscript. PKDVY and KS conceived the experiments, supervised and oversaw the whole work, and reviewed and approved the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

Data Availability: The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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