SurFACTS in Biomaterials

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From President Angela DiCiccio

Uncertainty was the only guarantee this year, and BioInterface 2020 was no exception. In the face of change we were challenged to reprioritize, refocus and make daring pivots—thank you to everyone who participated in, contributed to, and joined us for this dynamic opportunity. Within the foundation we tackled new open house and conference formats (including a change to our student participation), we challenged ourselves to evaluate how we are meeting membership needs, and we are prepared to make updates to each of these areas and several more in the next year. I am utmost impressed by the innovation and resilience of members of our Foundation who executed incredible innovations this year in response to changing unmet needs of our healthcare system and society. From reevaluating and accelerating the development and implementation of new technologies under EUAs, to completely reconstructing our approaches to education and communication, our organization collaborated to question convention and nimbly adapt to what "normal" is.

As we conclude our annual Surfaces in Biomaterials Foundation Conference and look toward next year, I want to take a moment to reflect and invite feedback from everyone who did (and perhaps did not) attend.

This year we pioneered a new app as a social platform for our annual conference. This effort coincided with our foundation's mission to promote communication, collaboration and networking. Ultimately the Foundation's mobile platform enabled constant communication with attendees and continual ability to watch our live recorded talks, something I found incredibly helpful when I wanted to review presentation content. Did anyone else rewatch a talk several times while cooking dinner because it was just that fascinating? I am eager to see if this technology continues to promote fruitful interactions as we carry it over into 2021 for our conference in Portland, Oregon, next September.

Congratulations and thank you to our student pitch pioneers, Scott Herting, Nicholas Fischer and

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Alyssa McCulloch, for embracing the opportunity to submit a pitch instead of a poster and seek mentors and feedback on performance and career opportunities. This transformation was in the works from the beginning of this year in an effort to provide unique growth opportunities to empower the voice of young professionals. It was an exciting test, but the board is challenged to question what else can we do to mature this new platform into a higher-valued exchange of student potential and matching with open opportunities. Have ideas? Reach out to join our early efforts to ripen this effort for next year!

Outside of changes and uncertainty, something that will never be derailed is the ability of visionary pioneers like Bob Langer, our Surfaces in Biomaterials Award winner, and Bob Ward, our keynote speaker. Without question, and regardless of how busy either were before the pandemic began, each dove in to develop and cater new technologies to the forefront of COVID treatments and relief, undoubtedly destined to impact numerous lives.

In one sense, this year established distinctly new definitions of silos and separation, unimaginable challenges for group work, and new universal norms. Yet, despite these seemingly "restrictive" trends, 2020 also brought with it an urgent need for focused problem solving, optimistic resilience in the face of unexpected pivots, and discoveries at a pace that may otherwise be missed. I am incredibly grateful, impressed, and honored to work with every member of our organizing committees, our board, our speakers and our participants.

Let's focus on making the seeds planted this year into the roots of a fruitful new era of nimble collaboration with new perspectives. We will continue to tune in to the voice of our membership and seek to shape our future from our learnings of the past, but to succeed we need your help in the form of feedback, outreach and participation. Thank you for reading, thank you for innovating, and thank you for pushing the frontiers of biomaterials as a thoughtful, brilliant group.

A Next Generation Antiinfective Foley Catheter With Implications for Other Infection-Susceptible Devices

David J. Vachon, Ph.D., Chief Executive Officer, Iasis Molecular Sciences Inc.

Healthcare-associated infections (HAIs) are infections that result in people that develop an infection as a result of their exposure to the hospital environment. Every year, nearly 100,000 people die as a result of HAIs. The annual (and recuring), non-reimbursable costs associated with HAIs are $30–40 billion/year. The rapidly evolving issues related to antimicrobial resistant infections is greatly complicating this problem. It is noteworthy that 65 percent of HAIs are medical device related, thus equating to annualized non-reimbursable costs of $19.5–26 billion. Given this paradigm, it is evident that effective preventative solutions are needed.

Some of the solutions aiming to prevent infection include: 1. Antimicrobial coatings (e.g. silver salts, silver nanoparticles, organic antiseptics, and antibiotics, 2. Inherently antimicrobial polymers (polyquats), 3. Materials modified by absorption, 4. First generation silver-based composites (Ag-zeolites), and 5. Passive (anti-adhesive) surfaces. To date, there are no clinically reliable prevention methods for devices. Generally, attempts to deliver antimicrobial agents from coatings have yielded unimpressive clinical outcomes. This is likely because the total coating volume, and hence total antimicrobial loading is small, typically on the order of microliters, and micrograms, respectively. As a consequence, sustained microbial inhibition and/or microbiocidal effects are unachievable. Importantly, and to this point, reducing a microbial insult by 3-logs may not be good enough on a medical device surface given that organism replication kinetics can allow for surfaces to be rapidly overrun with the initial formation of biofilm in a matter of hours.

Medical devices that are perhaps the most infection-susceptible tend to be tubular in nature. Examples include urological catheters (Foley's and stents), dialysis catheters, central venous catheters, endotracheal tubes, and wound drainage devices in certain cases.

At Iasis Molecular Sciences (IMS), our development focus is toward next generation urological catheters (Foleys and ureteral stents) with a goal of preventing some of the

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1 million catheter-associated urinary tract infections (CAUTIs) that occur in annually in U.S. hospitals and result in 13,000 deaths at a cost exceeding $500 million.

A significant causative factor of catheter-associated urinary tract infections (CAUTIs) is that the materials used to manufacture these devices allow bacteria to readily adhere to the surfaces thereby facilitating bacteriuria and/or infection.[1] It is accepted that the ideal urinary catheter biomaterial has yet to be developed.[2,3] At IMS we are addressing the problem by developing urological biomaterials that prevent or minimize the survival of adherent bacteria on surfaces.

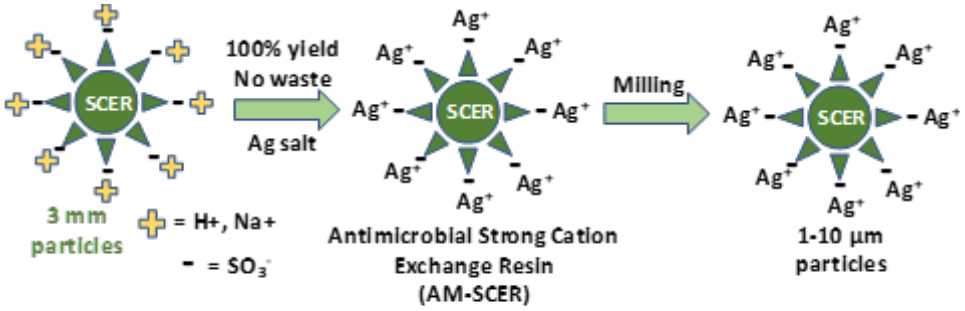

Figure 1. Synthesis of Silver-based (Antimicrobial) Strong Cation Exchange Resin (AM-SCER).

The biomaterials that are at the core of our product focus, include silicone rubber modified with a micronized silver-modified strong cation exchange resin (Ag-SCER, **Figure 1**). We have also demonstrated the efficacy of this additive in a number of other materials to include PVC, polyethylene, polyurethane and TPEs. Testing has proven these composites to be robust with a potential for broad medical device applications. The resins we employ are not nanoparticles. At 1-10 microns, they are easier and safer to work with. Because the chemistry relies on resins that are *structurally organic*, they interact strongly with the matrix materials of the planned composite to yield structurally stable materials. We note that uniform particle distribution in the polymer permits sustained delivery of the bound antiseptic for the planned life of the product.

Generally, a variety of species can be bound to the resin backbone(s) to produce antimicrobial ion exchange resins (AM-IERs). These species include various metal ions, quaternary ammonium ions, and small molecule antibiotics, inhibitors, and hydrophobes that can manipulate surface energy. AM-IERs are produced using single-step, water-based chemistry and yields are most often quantitative as dictated by resin exchange capacity. Subsequent filtration, drying and high-energy milling affords powders with uniform particle distributions in the single digit micron range, affording the preparation of compositions with good appearance (**Figure 2**). Because the material is inherently antimicrobial, inner and outer surfaces can provide protection, or coextrusion can be used to specify an active surface. Lubricious coatings over the active surfaces do not impede surface activity.

To test the limits of these surfaces to prevent bacterial survival and biofilm formation, samples were challenged with 108 CFUs of *Escherichia coli* for three hours (37oC in artificial urine, AU) and time-to-kill (TTK) evaluated. Bacterial counts for control silicone and the experimental material were determined at t0 to determine the number of adherent organisms. Test samples (and controls) were gently rinsed to remove non-adherent bacteria, transferred to fresh media, and incubated to 3, 8, 16, 24, and 32 hours and bacterial counts made. By 24 hours, all adherent bacteria had been killed with no trace of biofilm(s) noted. **Figure 3** is a graphical representation of the TTK log reduction following the 108 inoculation. These data are consistent with our observations of rapid and effective bacterial reductions observed in mechanical bladder (flow) systems using nutrient-modified artificial urine (**Figure 4**).

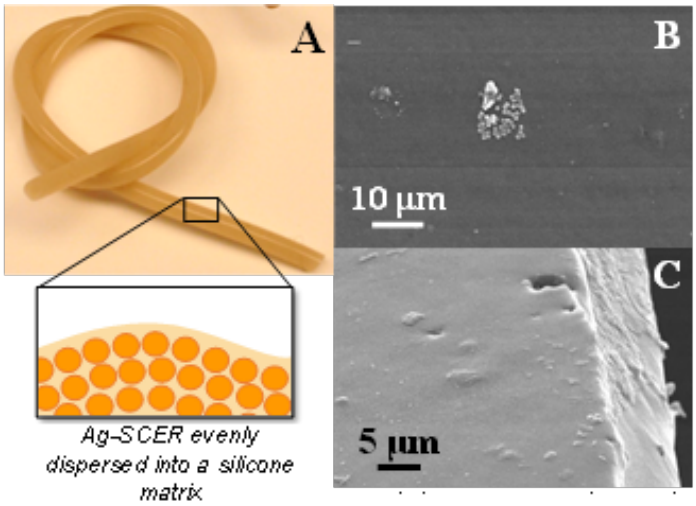

Figure 2. (A) Tubing compounded with 1.5 wt% Ag-SCER and SEM images of silicone surfaces following (B) with exposure to* S. aureus *and (C) after artificial urine extraction

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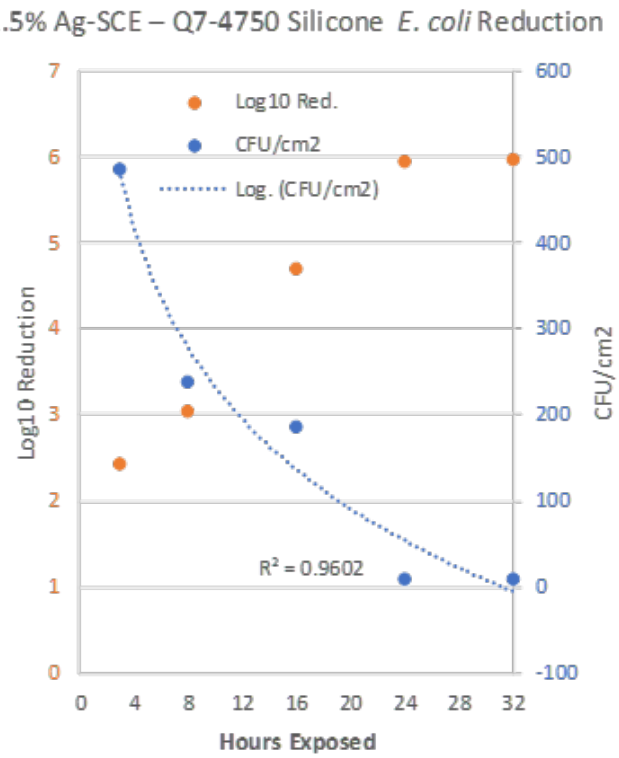

***Figure 3. Graphical representation of a time-to-kill assay following a three-hour exposure of 1x10⁸ CFU/mL of* E. coli.**

One key finding of our research is that Ag-SCER silicone composites appear to be robust enough to allow for the creation of inflatable retention balloons (cuffs) allowing us to manufacture fully antimicrobial devices that will possess greater levels of protection (**Figure 5**) whereas coating balloons is impractical as a consequence of the expanding surface area.

Importantly, these materials are non-toxic to kidney and bladder cell lines in culture, and 4- and 26-week ISO implant studies demonstrated the materials to be non-toxic and well tolerated.

We believe that this approach is a key step in the direction of designing safer, more effective urological catheters and we suggest that the potential of AM-IER composites to yield cost-effective antimicrobial solutions for medical devices is significant. Patents protecting these innovative materials are pending.

Screening of the AM-IE resin composites for their ability to kill bacteria has been carried out using the ASTM E2180 method.[4] **Table 1** provides an overview of some results obtained with 1.5 wt% silver-modified SCER (Ag-SCER) in Q7-4750 silicone against relevant uropathogens. Twenty-four hour and 28-day (with extraction) formats detail the surface efficacy with demonstrated 100 percent kills for each of three formidable uropathogens, even following artificial urine[5] (AU) extraction out to 28-days at 37oC. These experiments were supported by weekly ASTM E2180 evaluations in triplicate format. Urine is a challenging environment because the Na^+ content promotes Ag^+ exchange. These data support the idea that Ag-SCER composites can be more effective than Ag^+ coatings.[6,7]

Organism	24-hr. Log10 reduction (material as produced)	Log10 reduction after 28-days of extraction in artificial urine
Escherichia coli	5.77	5.79
MRSA	6.02	5.87
Proteus mirabilis	5.34	5.54

Table 1. ASTM E2180 results for Ag-SCER-silicone composite vs. 10e6 CFUs of uropathogens. Twenty-four hour results for materials as produced and with 28-day artificial urine extraction.

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In summary, the benefits of these antimicrobial composites are as follows: 1) Resin modification is scalable and reproducible; 2) Ion exchange release does not result in material porosity; 3) AM-IER-composites can deliver organic and metal antimicrobial cations; 4) Micronized AM-IERs incorporated into the bulk polymer yield uniform composites, adding < $1.00 to the cost of a Foley catheter. Further to this point, at a concentration of 1.25 wt% Ag-SCER in silicone, multi-log reductions of several uropathogens result even with 28-days of urine extraction.

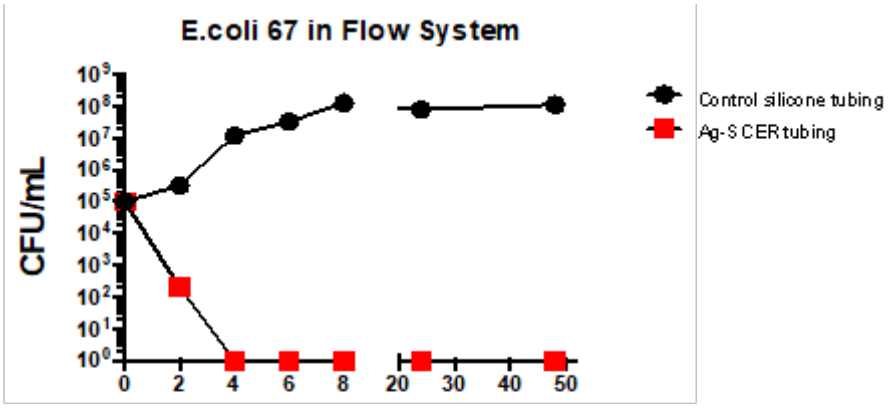

Figure 4. Ag-SCER silicone composite can kill* E. coli 67 *in a flow system: 1x10^5 CFUs* E. coli *in 300 mL of artificial urine was pumped through either test or control material for up to 48 hours. The test material completely kills a 1x10^5 inoculum of* E. coli *within four hours post inoculation. These data demonstrate the potency of the composition.

The approach described herein has proven to be robust. These results support the idea that Ag^+ can be effective at protecting urinary catheters, and other devices, beyond the token protection noted for silver-based catheter coatings.[6] The Foley catheter discussed here is the subject of a proposed multi-site, North American clinical study in a spinal cord injured population. The proposal is currently under review by the U.S. Army. We thank the agency for funding the original research aiding these discoveries (W81XWH-16-1-0697).

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Capture of Airborne Pathogen Protein On Air Filters & Personal Protective Equipment

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Introduction

Standard air filters, personal protective equipment (PPE) such as masks, medical and military grade protective apparels and a variety of similar products inadequately safeguard against harmful viruses, including COVID-19. They reduce exposure to airborne pathogens but, do not irreversibly capture and neutralize these infectious particles. Current PPEs become soiled with a range of pathogenic bacteria and viruses during typical use; they become one of the main sources of transmitting the same microorganisms in the air which can infect handling personnel.

HEPA (High-Efficiency Particulate Air) filters are considered gold standard and are highly effective in removing pathogens from the air. Due to the high cost of these filters however, they are typically used in more specialized settings such as hospitals and airlines; they are not broadly used in places of most public gatherings (schools, churches, hotel rooms, cruise line cabins, etc.) or in homes. The less expensive, non-HEPA filters typically found in homes and other public buildings do not effectively remove biological pathogens from the air. Given that most highly infectious viruses have a very low median infectious dose, even low levels of viral filter penetration represent a significant risk to human health (Review by Brian Heimbuch et al, 2009; Viral Penetration of HEPA Filters). Additionally, some viruses (including coronaviruses) remain infectious for up to three days on surfaces where they are inadequately trapped and yet remain highly infectious. For this reason, handling and disposing of used HEPA filters can also result in the redistribution of these pathogens back into the air.

We have embarked upon innovative and proprietary methodologies to combat the Coronavirus and any future airborne pathogens that may come to our shores. Our technology blends nano surface coating and novel bio-reactive chemistry to deliver uniform layers of this patent pending solution to completely immobilize pathogens via protein binding onto existing air filters and PPE's, including medical and military grade protective and defensive apparels. As shown below, viral and bacterial pathogens are encapsulated by a phospholipid layer that is densely populated with protein, enabling them to be efficiently captured, neutralized, and eradicated by this strategy. In other words, our invention will prevent any biological pathogens from passing through because they are entrapped and ultimately destroyed. The secondary benefit is enablement of safe handling of these contaminated products during replacement and disposal. This is because the nano-coated PPE's and air filters have captured the pathogens, preventing them from re-aerosolizing upon handling.

The novel coronavirus (SARS-CoV-2) causing COVID-19 disease, contains three proteins on the viral particle surface, all of which have been sequenced and characterized; the spike protein (involved in host cell infectivity), the membrane protein (facilitating the structural integrity of the viral particle), and the envelope protein (facilitating structural integrity of the viral coat). Each of these proteins provides unique opportunities for viral capture based on bio-reactive chemical properties.

Materials and Methods

Description of the chemistry and nano-coating methodologies.

Our lead chemistries are bifunctional silanes with organo-functional amino and/or epoxy groups that robustly bind protein and/or glycans. The silane forms a covalent attachment to the filtration medium and the protein/glycans of interest. They were identified using the protein binding assays described below. The nano-coating was applied by commercially available equipment (Model RPX-540) from Integrated Surface Technologies. The coating method uses a sub-atmospheric gas-phase flow-through reactor which is suitable for large batch processing.

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The specialized chemical precursors are vaporized into a temperature-controlled reaction vessel typically between 40 to 75oC. The partial pressure of the chemical vapors is metered to ensure no liquid condensation onto the PPE and other materials of interests. The reduced pressure reactor allows for the surface modification reactions to occur between 0.1 to 10 Torr which is controlled by a vacuum pump and usually takes less than 30 minutes to complete. To enhance the surface attachment of the chemical of interests, articles were pretreated using a low-pressure glow discharge with oxygen, water and alcohol.

Assays to determine the ability of coated material to capture virus.

Non-protein binding 96 well microtiter plates (Corning, catalogue # 3641) were nano-coated with various chemicals to determine their capacity for viral protein capture. High protein binding ELISA plates were used as a comparative control (Corning, catalogue # 9017). Purified SARS-CoV-2 spike protein was applied directly (in duplicate experiments) to non-protein binding plates that were either left un-coated or nano-coated with various bio-reactive chemistries. This was performed in serial dilutions of the viral protein, or at a fixed concentration for various time points prior to removal and washing to determine kinetics of protein capture. In some experiments, human IgG (R&D Systems, catalogue # 1-001-A) was used as a chemistry screening tool. Quantitation of viral protein or IgG capture was determined by using a standard ELISA (enzyme linked immunosorbent assay) format with an anti-spike protein-Fc reagent and a secondary antibody to Fc conjugated to horseradish peroxidase, and development with TMB (tetramethylbenzine) reagent that was detected with spectrophotometry (A450).

To determine viral protein capture to other Nano-coated materials, standard face masks (Machimpex, catalogue # 1005-544-988) were coated or not coated with the bio-reactive compounds. IgG was applied to the fabric and incubated for 30 minutes prior to washing in phosphate buffered saline. Detection of the captured protein after washing was performed by applying 200 µl Gel-Code protein staining dye (Thermo Fisher Scientific, catalogue # 24590) directly to the materials and incubating for one hour. Color change indicating protein capture was documented by photography. Binding of IgG and coronavirus spike protein was comparable in the more sensitive ELISA plate binding assay.

Results and Discussion

We have identified several bio-reactive compounds that when nano-coated onto non-protein binding plates enable the efficient capture of protein, including coronavirus glycoprotein. As an initial screen, we used IgG to identify chemistries capable of protein binding (data not shown), narrowing the scope of chemistries to be tested for capture of the novel coronavirus spike protein. Binding of the purified spike protein to non-coated or nano-coated plates is shown in Figure 1. Three lead chemistries were tested for binding to 96 well plates; NCT9021, NCT4502, and NCT1053, using serial dilutions of the spike protein from 3.3 to 100 ng/ml. Efficient capture of the spike glycoprotein was observed in each case. Additionally, glycoprotein capture was resistant to low pH washes (data not shown), suggesting some compounds have extremely high affinity, and potentially irreversible, binding.

To extend these observations to nano-coated materials other than 96 well plates, face masks were similarly nano-coated or not coated with the bio-reactive chemistries. IgG was used as a model for protein capture, as 1) it behaved similar to the full length coronavirus spike protein in the plate binding assay (data not shown), and 2) it was not feasible to purify sufficient amounts of the spike protein as is required in this assay. As demonstrated in Figure 2, both NCT1053 and NCT9021 efficiently captured the protein onto mask, relative to the non-coated mask. Visually, the NCT9021 compound appears to have captured more efficiently. These data lend support to the notion that multiple materials, including filters and other PPE, coated with these bio-reactive chemicals, will enable them to efficiently and rapidly capture biological pathogens from the air or contaminated surfaces.

These methodologies are unique and can be applied to all PPE and filters. We expect it to enhance these products without changing their characteristics including air flow, and to permanently immobilize and neutralize pathogens, such as the novel coronavirus. It adds a fractional cost to these components and is well-justified given the potential impact on viral spread.

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Conclusion

By using NCT selected chemistries and methodologies, we were able to nano-coat standard air filters and PPE with an array of chemicals and solutions that bestow upon them the ability to bind protein. These methodologies can be used to create specialized products for the military, health care, airlines, hospitalities, and many other industries. Our methodologies will greatly enhance air filters and PPE to permanently bind and prevent pathogen transmission. They will also prevent aerosolizing of pathogens and render the products safe for handling during replacement and disposal.

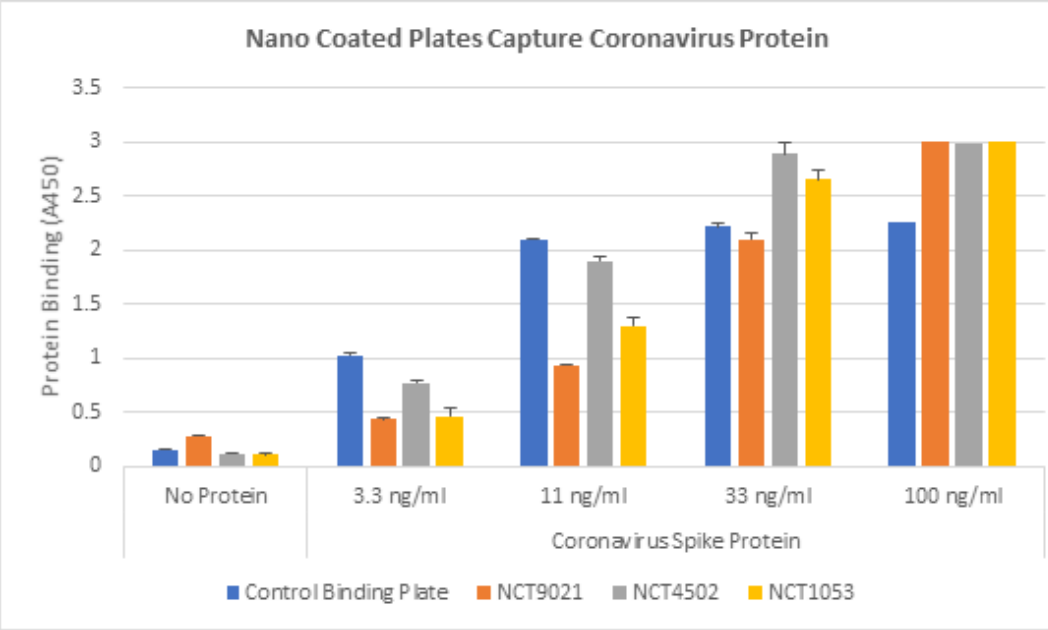

Figure 1. Efficient Capture of Coronavirus Spike Glycoprotein with Lead Nano-Particle Coating Chemistries. ***Binding to serial dilutions of the coronavirus full-length spike protein to plates coated with NCT chemistries. The standard high protein binding plate (Control Binding Plate, blue bars) was used as a positive control, and no protein added was used as a negative control. Protein binding is plotted on the y-axis.***

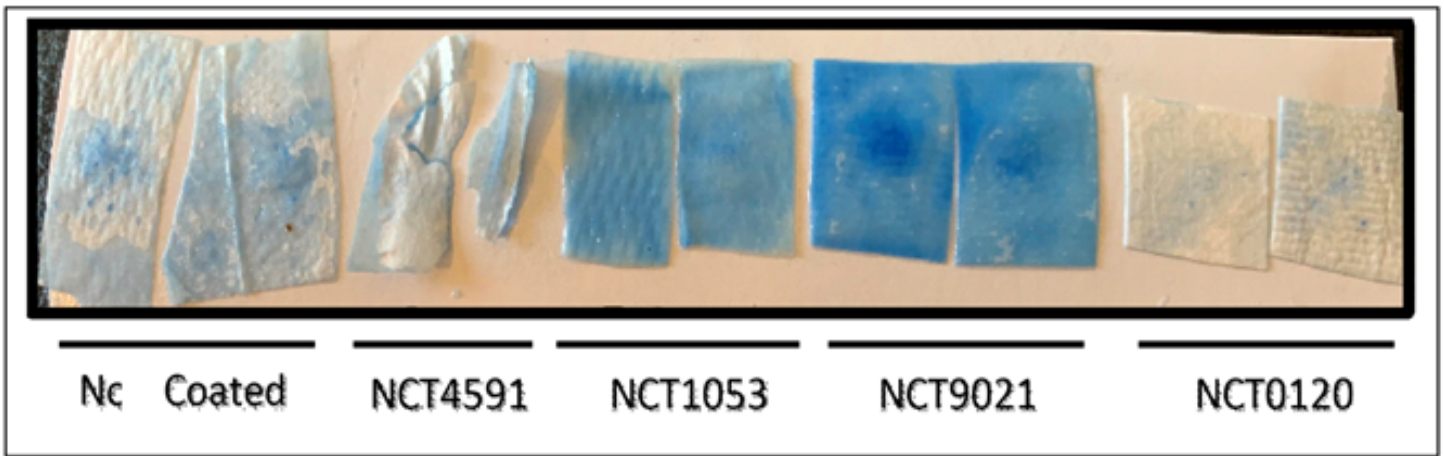

Figure 2. Nano-coated Face Masks Bind IgG. ***Protein binding to fabric from a standard face mask is shown following no coating (left), and nanoparticle coating with the indicated NCT chemistries. Protein binding following extensive washing was detected using coomassie blue protein stain. NCT0120 is a hydrophobic negative control coating that repels protein binding.***

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