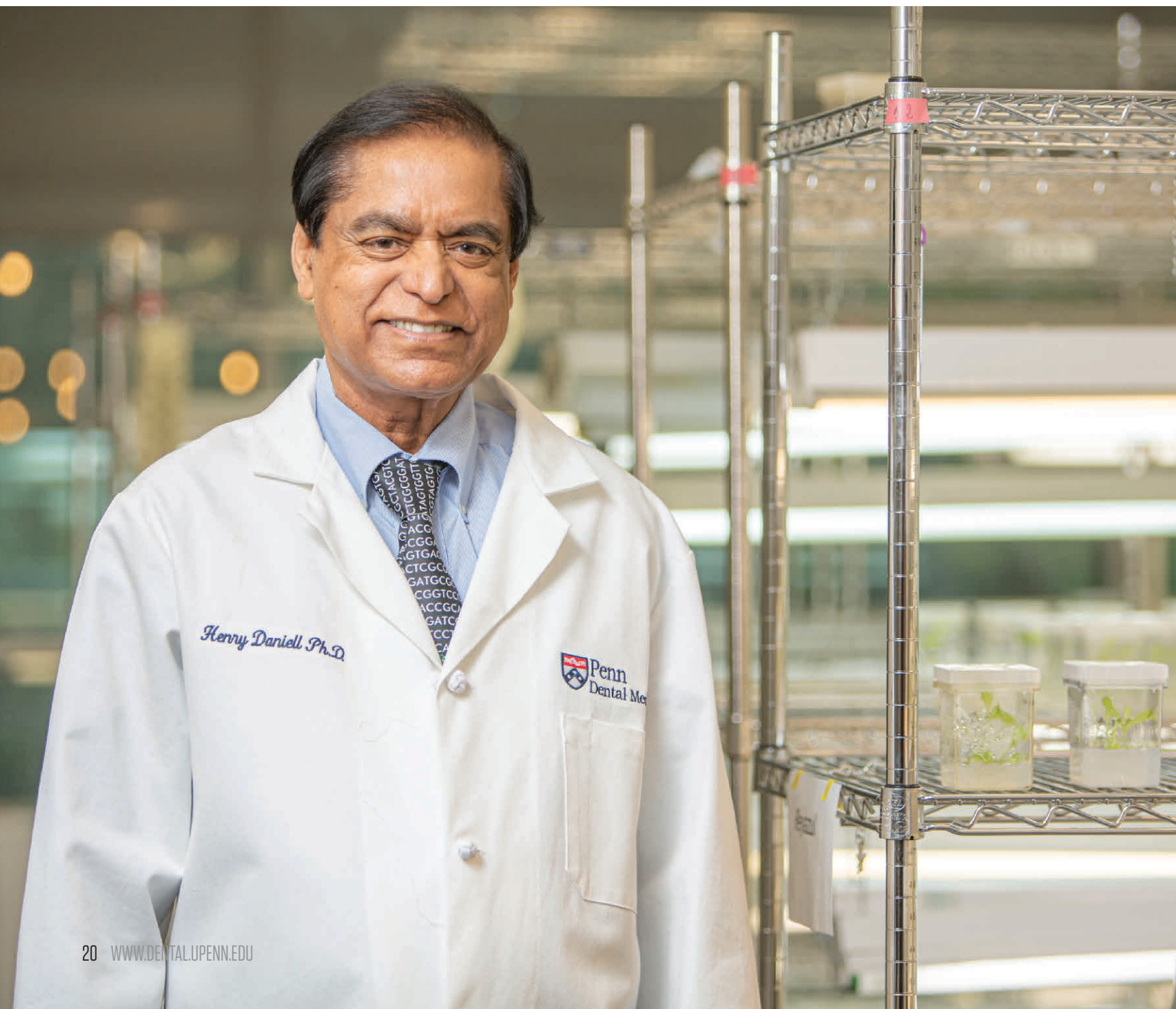


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# CHEWING TO CURB COVID-19

A CHEWING GUM DESIGNED TO TRAP SARS-COV-2 IN THE SALIVA USING DR. HENRY DANIELL'S PLANT-BASED PLATFORM BEGINS CLINICAL TRIAL



OPPOSITE: Dr. Henry Daniell, W. D. Miller Professor and Vice Chair of the Department of Basic and Translational Sciences.

TOP, ABOVE: The gum tablets containing ACE2, produced using Daniell's platform in which plant material is bombarded with the DNA of target proteins, coaxing the plant chloroplasts to take up the DNA and begin growing the proteins. The plant material is then freeze-dried and ground, and in this case, delivered by the chewing gum.

A RECENTLY LAUNCHED CLINICAL TRIAL AT PENN will evaluate a unique chewing gum designed by Penn Dental Medicine's Dr. Henry Daniell to trap SARS-CoV-2 in the saliva, potentially blocking transmission of COVID-19 from one person to another.

The trial will recruit participants from a pool of Penn Medicine employees whose responses to the PennOpen Pass screening system indicate that they may be battling a COVID-19 infection. Those who enroll in the clinical trial will be given a packet of a dozen experimental tablets of gum. Each morning, they will pop one in their mouth — and start to chew.

The cinnamon-flavored gum is designed to do far more than freshen breath. Thanks to innovations emerging from Daniell's lab, the gum contains plant-derived material genetically engineered to contain ACE2, a protein found naturally in human blood and saliva. The ACE2 receptor is found on human cells and is bound by SARS-CoV-2 virus during infection. In experimental models, chewing the gum released the embedded ACE2, blocking the interaction of the chewer's own ACE2 receptor and the viral spike protein.

In effect, the gum is designed to trap and neutralize SARS-CoV-2 in the saliva and, ideally, diminish the amount of virus left in the mouth. It is hoped that less virus would mean a lower likelihood of passing the infection on to others.

Daniell and colleagues are also working on another gum, containing a different protein, that could target a broader range of respiratory viruses, including influenza.

"I'm hoping that if this is effective and safe it will be the beginning of several other oral delivery drugs using this platform," says Daniell, W. D. Miller Professor and Vice Chair of the Department of Basic and Translational Sciences.

Findings from a preclinical study of the gum's efficacy in neutralizing SARS-CoV-2 and influenza virus in patient samples, published in the journal *Biomaterials* in July, showed it could reduce viral load to nearly





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— DR. MARK WOLFF

undetectable levels. The results supported an application to the U.S. Food and Drug Administration (FDA) for an Investigational New Drug, which went into effect in May and paved the way for the launch of the clinical trial.

The technology behind this experimental treatment has moved from the laboratory bench toward the beginning of clinical experimentation, all within Penn Dental Medicine, a first for the School. The partnership with colleagues from Penn Medicine enables the launch of the first-in-human clinical trial.

“This technology may have the ability to reduce the spread of COVID-19 and the flu as well as make it safer for dentists and other healthcare providers to provide care to patients who we know are infected,” says Dr. Mark Wolff, the Morton Amsterdam Dean of Penn Dental Medicine, who was also a coauthor on the *Biomaterials* study.

## A NOVEL CONCEPT FOR HALTING DISEASE TRANSMISSION

For years, Daniell has used his patented plant-based platform to generate a range of biomolecules with both therapeutic and commercial potential. By bombarding plant material (in this case lettuce) with the DNA of target proteins, they coax the plant chloroplasts to take up the DNA and begin growing the proteins. The plant material, freeze-dried and ground-up, could be used as a means of delivering the protein. Prior to the COVID-19 pandemic, one of the proteins his lab had explored was ACE2, originally with a view toward evaluating its impact on pulmonary hypertension.

As the pandemic began, ACE2 began receiving significant attention for a different reason: its receptor provides the docking station for the spike protein of SARS-CoV-2. Suddenly, Daniell’s work had found a new

potential application: as a trap for the virus that causes COVID-19.

Daniell had already been working on protein drug delivery via a chewing gum, and, given that the SARS-CoV-2 virus replicates in the salivary glands, delivering ACE2 to the mouth with a gum appeared to him to be a potentially powerful approach.

Another coincidence augmented the potential of the “viral trap” approach. During infection, not only does the SARS-CoV-2 spike protein bind to the host cell’s ACE2 receptor, but two other co-receptors on the virus, known as GM-1 receptors, facilitate the binding process. CTB, a protein that Daniell had already been evaluating in his ACE2 biotherapeutic, turns out to also bind GM-1, thus serving as an additional lure in the context of SARS-CoV-2 infection.

In a *Molecular Therapy* paper published in November 2021, Daniell and colleagues showed in preclinical studies that a chewing gum containing CTB and ACE2 could reduce SARS-CoV-2 viral loads in saliva obtained from COVID-19 patients under experimental conditions. The *Biomaterials* paper extended that work, using samples from the delta and omicron waves of the pandemic to demonstrate that the gum could neutralize these strains under these same in vitro conditions as well.

The latter publication also went beyond COVID to consider how such a gum might potentially block a broader cross-section of viruses, including those that do not rely on the ACE2 receptor to enter cells.

“I was very keen on developing this chewing gum delivery system to trap many different oral viruses,” says Daniell, “and was looking for a way to broaden the approach.”

To do so, Daniell and colleagues developed a gum containing a different protein, called FRIL, which is found naturally in the plant *Lablab purpureus*, also known as the Lablab or hyacinth bean. While the spike-ACE2 receptor interaction is specific to coronavirus, FRIL binds to molecules called complex-type N-glycans, which are found on a broader spectrum of viruses, including SARS-CoV-2 and influenza viruses.

The research team used two different assays to evaluate the in vitro performance

of the FRIL and CTB-ACE2 chewing gums; one, a microbubbling test developed by the Perelman School of Medicine's Dr. Ping Wang; the other, an electrochemical sensing test invented by Dr. Cesar de la Fuente of Penn Medicine and the School of Engineering and Applied Science. Both tests confirmed that the gum could significantly reduce viral levels in patient samples.

### PUTTING THE GUM THROUGH ITS PACES

Throughout the stages of evaluating the gum, Daniell and Penn Dental Medicine colleagues have worked in close collaboration with researchers from around Penn, particularly in the Perelman School of Medicine, enabling the work to take on special relevancy in the context of the evolving COVID pandemic. In addition to Wang and de la Fuente's testing platforms playing a role in evaluating the technology, Dr. Ronald Collman, a Professor of Medicine, helped collect COVID-positive samples with which to test the gum. Dr. Frederic Bushman, a Microbiology Professor, sequenced the viral samples to determine which strain of SARS-CoV-2 they represented. And Penn Medicine infectious disease specialists Dr. Pablo Tebas and Dr. William Short are the lead investigators for the phase 1/2 clinical trial with the Perelman School of Medicine serving as the regulatory sponsor.

The trial aims to enroll 40 participants. Each will receive gum tablets to chew and tubes for collecting saliva over the course of three days. The plant material for the trial is being produced and grown at Fraunhofer, a research and development organization, before being further processed at Penn Dental Medicine, using freeze-drying and grinding machines that meet FDA regulations to ready it for incorporating into gum tablets.

"Each day participants will chew four tablets of gum, and take eight samples of saliva, before and after chewing," says Daniell. "On the fourth day, they'll come to the clinic, chew a final tablet of gum, and get an examination, record their symptoms, and submit their samples."

The phase 1/2 trial will be used to ensure the gum is safe to use. Each of the participants' saliva samples will undergo multiple PCR tests to quantify the level of virus present.



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### A TOOL IN THE FIGHT AGAINST CONTAGION

With the gum, Daniell hopes to develop a tool that can complement others, such as vaccines and antivirals, to make a further dent in this pandemic — and perhaps future ones. He points out that the gum represents the first Investigational New Drug submission for a human therapeutic protein drug that does not require a cold chain or protein purification. Eliminating the protein purification step — made possible because of the protein being grown in plants — reduces costs dramatically. And being shelf-stable means the gum could more easily reach remote and less developed areas of the world without needing refrigeration or special handling.

To one day reach this scale, Daniell has partnered with Penn Center for Innovation (PCI) and its PCI Ventures to spin out this technology into a Penn startup company. PCI Ventures works directly with researchers to help form and launch new startups based

on Penn technologies. Michael Poisel, who manages PCI Ventures, says Daniell's desire for broad and global accessibility has been a primary motivation behind the development of the gum and other products — from their initial promise in the lab to the clinical trial ongoing today.

"One of the exciting things about the technology is the potential to help people in countries that don't have the resources to benefit as broadly from the current vaccines and other therapies," Poisel says. "Henry is really focused on making sure we can offer this in a cost-effective manner so the gum, once FDA approved, could be distributed as widely as possible and benefit as many people as possible." ■

— By Katherine Unger Baillie

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OPPOSITE, ABOVE: An FDA-approved freeze drier (opposite) and grinding machine (above) within the Daniell lab at Penn Dental Medicine ready the ACE2 plants for incorporating into the gum tablets.