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FEATURE STORY

Vaccine Revolution: Targeting Viruses in a New Way

PAGE 4

CROSSROADS WITH DR. RICHARD MERKIN

The Next Generation of Vaccine

PAGE 2

ANNOUNCEMENT

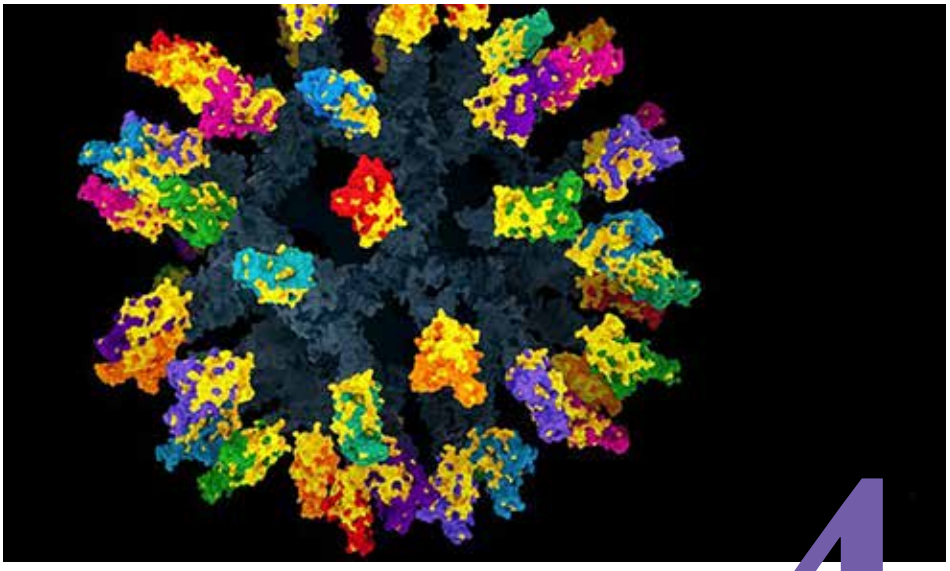
Nominations Open for the Merkin Prize in Biomedical Technology

PAGE 13

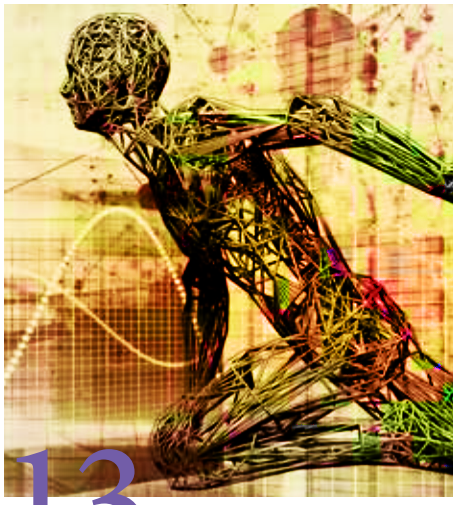
HERITAGE PROVIDER NETWORK | Winter 2022, Issue 47

Contents

FEATURE STORY



Vaccine Revolution: Caltech Vaccine Candidate Targets COVID-19 and SARS-Causing Viruses in a New Way 4



13

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Crossroads

With Dr. Richard Merkin

The unique perspective of Richard Merkin, M.D., as Innovation, Technology, Legislation and Care Delivery come together to impact the future of population health

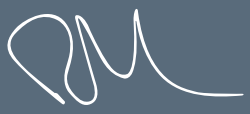
The Next Generation of Vaccine

Our knowledge about COVID-19 has continued to evolve as we are met with pandemic triumphs and setbacks. Now more than ever, the world's greatest minds are being put to the ultimate test of innovation against a novel and mutating virus.

Leaders in the field of science, healthcare and academia have collaborated across the globe to engineer brilliant and promising solutions, showing us that when the virus adapts, so do we.

In our feature story, a revolutionary new class of vaccine candidate emerges, spearheaded by David Baltimore Professor of Biology and Biological Engineering and Merkin Institute Professor Pamela Bjorkman, Ph.D., and her Caltech research lab. Now entering the human trial phase, this astonishing advancement in vaccine technology encourages the immune system to provide protection against SARS-CoV-2 and its known variants, variants it has not encountered and even variants that don't yet exist through a mosaic-8 nanoparticle mechanism.

As we continue confronting the challenge to outpace the pandemic, plugged into the forefront of discovery. I am proud and honored to support the efforts of my collaborators and colleagues who are changing the world with their willingness and ability to forge an unwalked path.

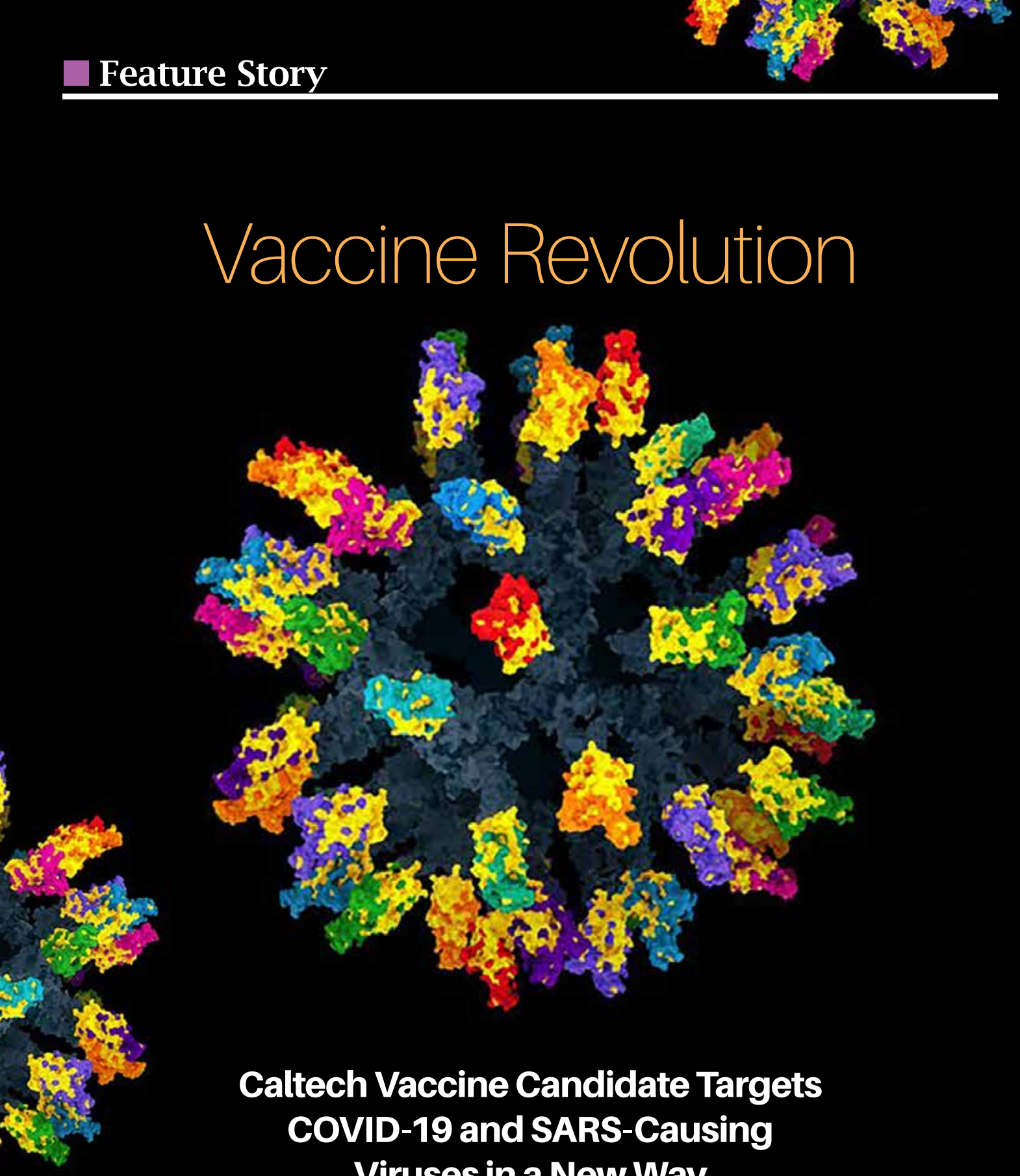


Richard Merkin, M.D.
President and CEO of Heritage Provider Network

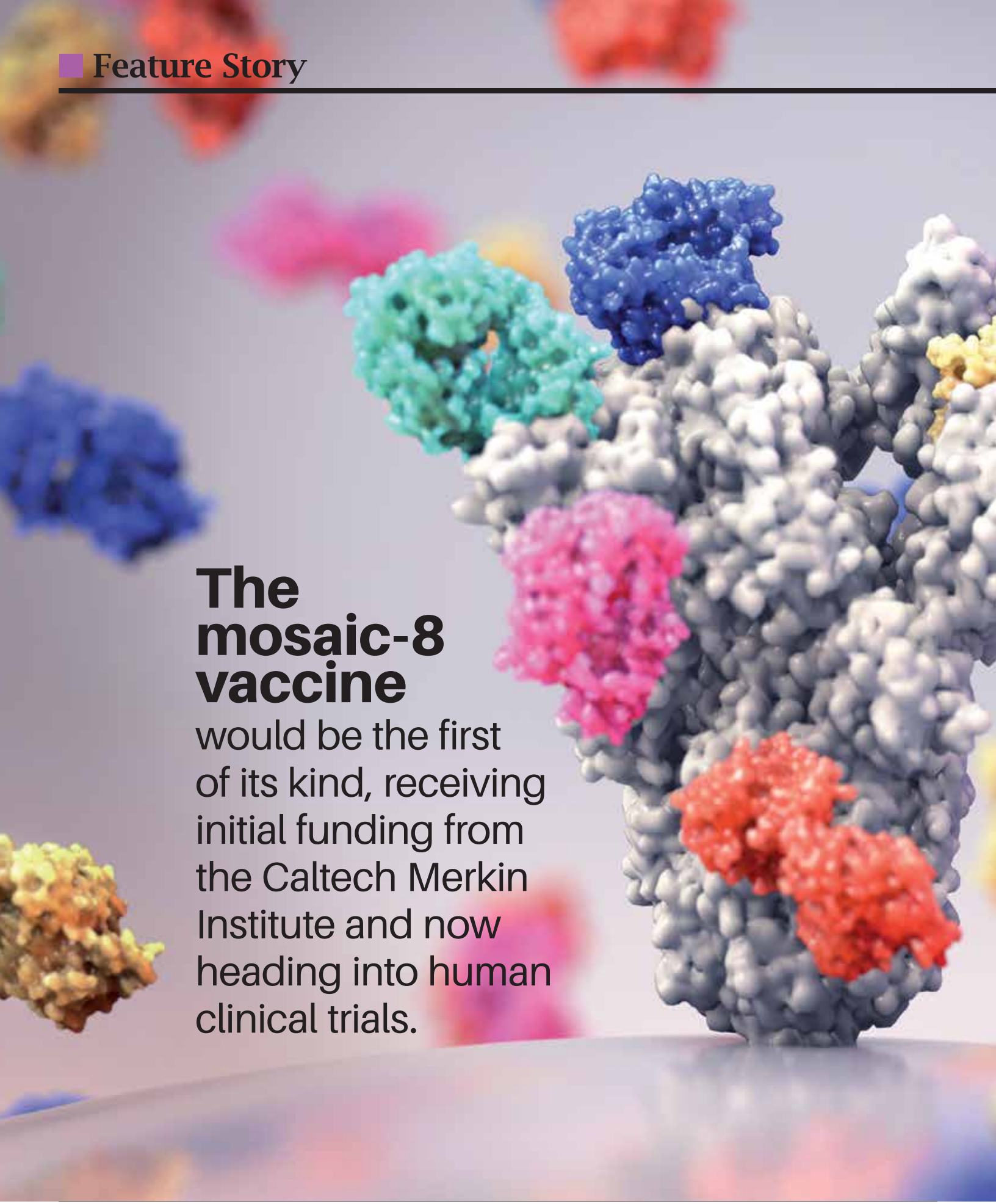
Richard Merkin, M.D.

Healthcare visionary Richard Merkin, M.D., has spent the last 40 years implementing a successful, workable business model to address the needs and challenges of affordable managed healthcare.

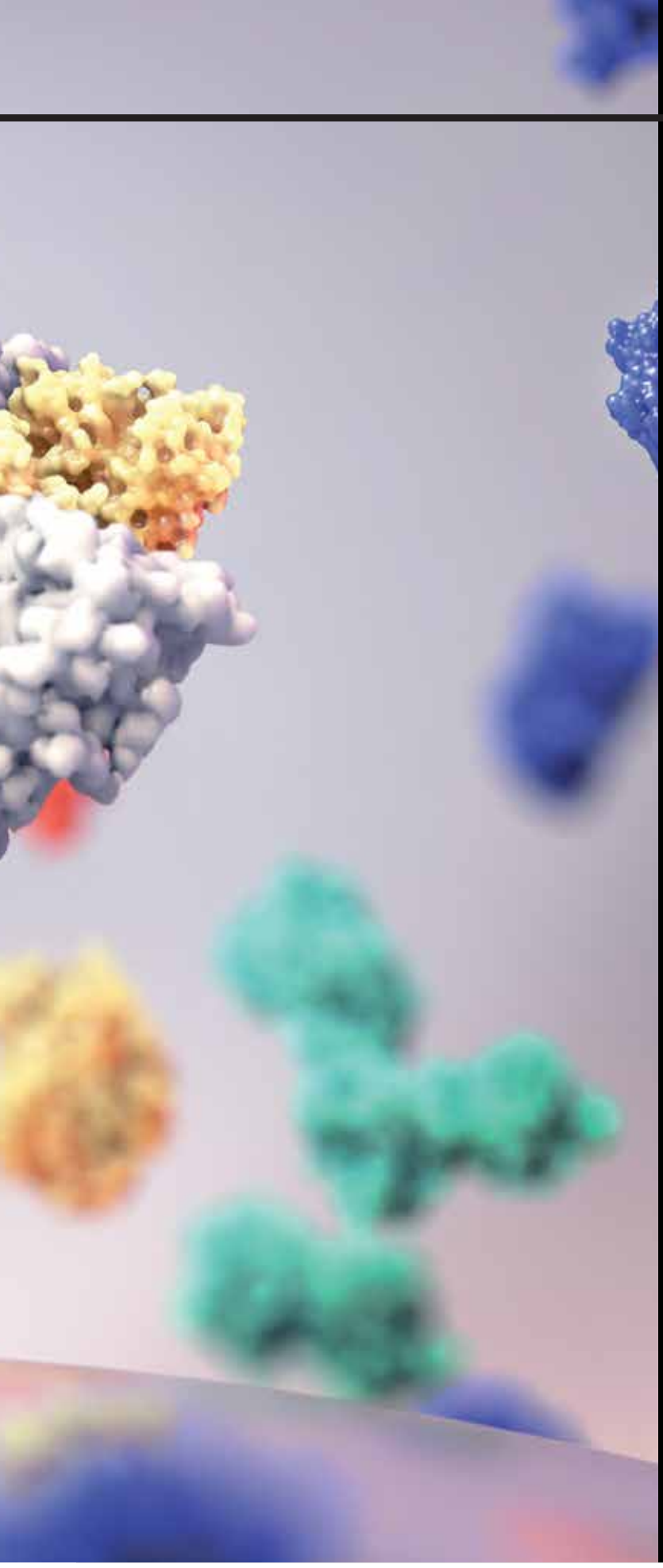
Vaccine Revolution



Caltech Vaccine Candidate Targets COVID-19 and SARS-Causing Viruses in a New Way

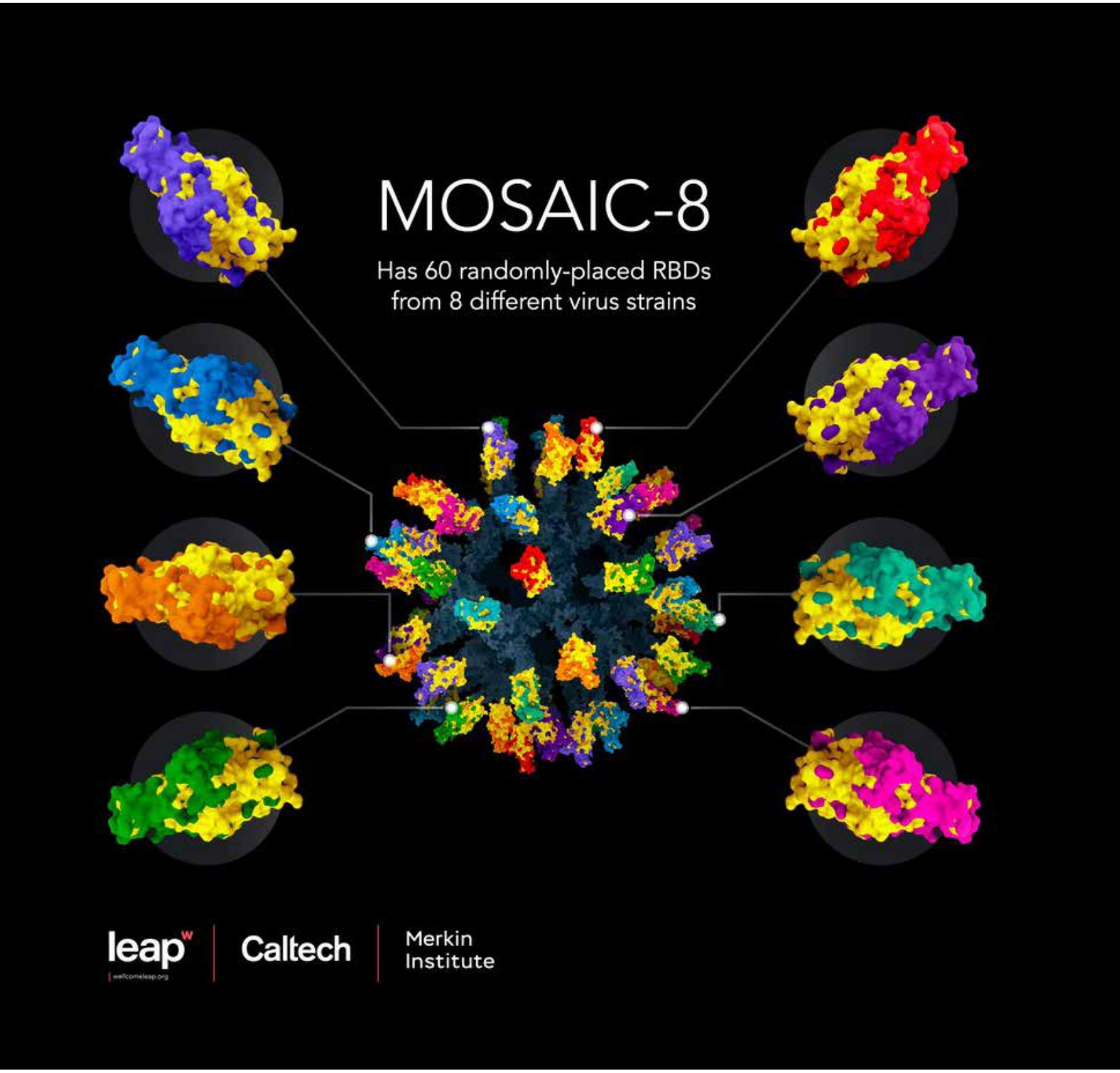


The mosaic-8 vaccine would be the first of its kind, receiving initial funding from the Caltech Merkin Institute and now heading into human clinical trials.



A driving force behind the COVID-19 pandemic is the virus's ability to rapidly mutate, causing currently available vaccines' protective responses to weaken against new variants. So what happens when a critical global need for effective vaccines is challenged by an evolving virus and development times that would typically exceed a decade?

Pamela Bjorkman, Ph.D., David Baltimore Professor of Biology and Biological Engineering and Merkin Institute Professor, and researchers at her Caltech lab decided to pursue a solution to that question. Her lab's vision was a new class of vaccine that would successfully protect against all known and future variants of SARS-CoV-2, as well as related coronaviruses that may eventually spread from animals to humans. "The fact that three betacoronaviruses — SARS-CoV, MERS-CoV and SARS-CoV-2 — have spilled over into humans from animal reservoirs in the last 20 years illustrates the need for making broadly protective vaccines. We can't predict which virus or viruses, among the vast numbers in animals, will evolve in the future to infect humans to cause another epidemic or pandemic," says Bjorkman. Thus far, her research has led to a so-called mosaic-8 nanoparticle vaccine candidate that, in mice and monkeys, has shown to provide protection against a variety of SARS-like betacoronaviruses, including SARS-CoV-2 variants.


MOSAIC-8
Has 60 randomly-placed RBDs
from 8 different virus strains
leap
wellcomeleap.org
Caltech
Merkin
Institute

Sarbecoviruses already seen in humans	Presented on Mosaic-8	Antibodies elicited	Confirmed in animal studies
SARS-CoV-2 Washington.1	✗	✓	
SARS-CoV-2 Beta	✓	✓	✓
SARS-CoV-2 Delta	✗	✓	✓
SARS-CoV-2 Omicron BA.1	✗	✓	
SARS-CoV-2 Omicron BA.2	✗	✓	
SARS-CoV-2 Omicron BA.2.12.1	✗	✓	
SARS-CoV-2 Omicron BA.4/BA.5	✗	✓	
SARS	✗	✓	✓

Animal sarbecoviruses with spillover potential	Presented on Mosaic-8	Antibodies elicited
RaTG13	✓	✓
SHC014	✓	✓
Rs4081	✓	✓
Pang17	✓	✓
RmYN02	✓	✓
Rf1	✓	✓
WIV1	✓	✓
LYRa3	✗	✓
Yun11	✗	✓
BM-4831	✗	✓
BtKY72	✗	✓
Khosta-2	✗	✓
RshSTT200	✗	✓

Before landing on an effective and safe vaccine candidate that could be presented for human trials, Bjorkman and her research group were met with a long road of scientific and engineering hurdles, and minimal time to overcome them. This required quickly organizing both their own work on the structure of the SARS-CoV-2 virus receptor and evolving data from the greater scientific community, combining it with their broad immune response theory, designing a detailed molecular model and prototype, then validating the design during animal trials.

Laying the groundwork

To initiate this enormously complex and challenging process, Bjorkman and her team collaborated with Dr. Richard Merkin and the Caltech Merkin Institute. With their support, Bjorkman's research lab was able to secure the funds to get the running start they needed. "The Caltech Merkin Institute supported the first experiments at a time when I was unable to find funding through other mechanisms that require a longer time to make funding decisions and distribute funds," says Bjorkman. "Overall, I think this project would not have gotten off the ground without Merkin's support — they provided the initial funds that allowed us to establish proof-of-concept and have continued to support efforts for our lab and others doing translational research."

"Professor Pamela Bjorkman's brilliant prior research ... demonstrated such promise for a broadly protective vaccine of its kind. This is research that I would not hesitate to support."

~ Dr. Richard Merkin, President and CEO of Heritage Provider Network

According to Dr. Merkin, "Professor Pamela Bjorkman's brilliant prior research leading up to the development of the mosaic-8 nanoparticle-based vaccine candidate demonstrated such promise for a broadly protective vaccine of its kind. This is research that I would not hesitate to support because this exploration can be world-changing."

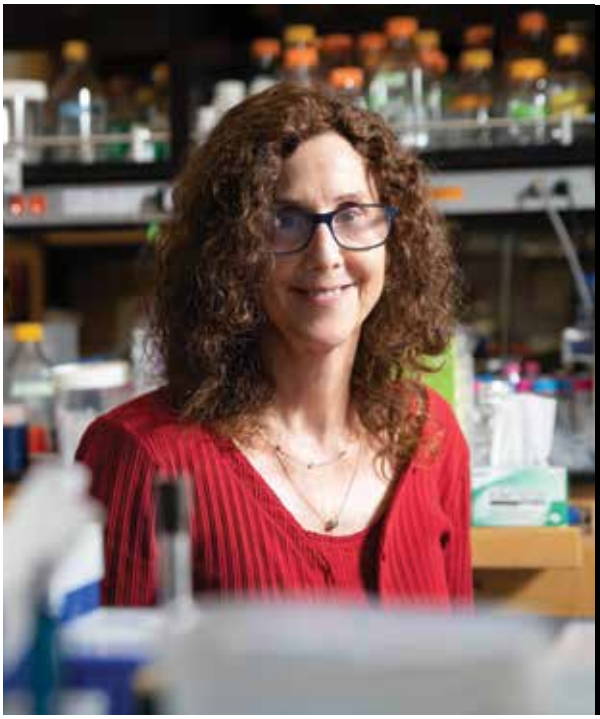
Bjorkman and her team have a long-standing interest in determining the structural correlates of broad and potent antibody neutralization of viruses, such as HIV-1 and Zika. Her prior lab work mapping the physical structures of receptor binding domains (RBDs) laid the groundwork for the vaccine candidate, combined with their knowledge of the way antibody-producing cells of the immune system can be stimulated by a vaccine. "When the COVID-19 pandemic started, we initiated similar structural studies of antibodies bound to coronavirus spike proteins to establish principles of which RBD epitopes were being targeted," she says. That led them to use a specific nanoparticle structure and to specify loading it with eight different RBDs rather than a smaller number.

How it works: the mosaic-8 nanoparticle vaccine

Bjorkman and then-graduate student Alex Cohen (PhD '21) decided to arrange specific pieces of eight different SARS-like betacoronaviruses on a protein nanoparticle structure. This included SARS-CoV-2, the virus responsible for the COVID-19 pandemic, plus seven related animal viruses that could potentially start a pandemic in humans. The viral protein piece they used is the RBD of the spike protein, which is critical for coronaviruses to enter human or animal cells. The RBD is also the part of the spike protein that most antibodies lock onto to block infection.

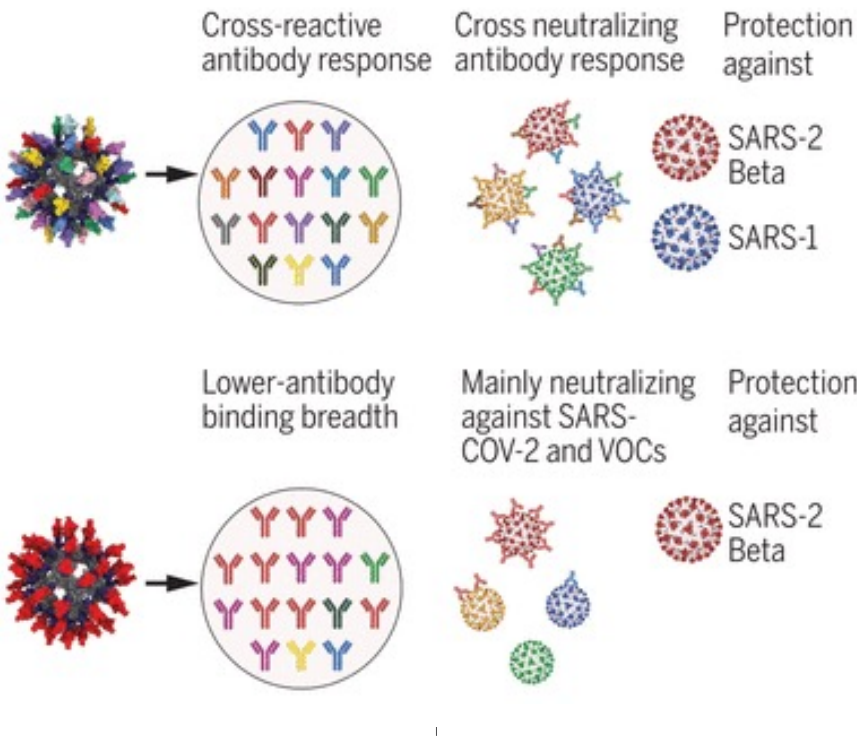
Some parts of the RBDs differ from one strain to another, and those same regions also accumulate new differences by mutation as the virus evolves. In comparison, SARS family RBDs also have regions that are similar from one virus to another, and they have developed few mutations during the pandemic. Bjorkman's vaccine candidate was designed to direct the immune system's focus to these shared regions and hopefully produce immunity to all sarbecoviruses and variants. This promising first study showed that this mosaic nanoparticle can generate antibodies effective against multiple viruses whose RBDs were not part of the vaccine, as well as those that were. Results of the first proof-of-concept experiments for mosaic-8 appeared in Cohen's Caltech PhD thesis and in the journal *Science*.

The vaccine technology to attach pieces of a virus to protein nanoparticles was originally developed at the University of Oxford. The foundation of the technology is a tiny cage-like structure (a "nanoparticle") made up of proteins engineered to have "sticky" appendages on its surface, upon which tagged viral proteins can be attached. These nanoparticles can be prepared to display pieces of one virus only ("homotypic" nanoparticles) or pieces of several different viruses ("mosaic" nanoparticles). When injected into an animal, the nanoparticle vaccine presents these viral fragments to the immune system. This prompts the production of antibodies and cellular immune responses involving T lymphocytes and innate immune cells.



Pamela J. Bjorkman, Ph.D.

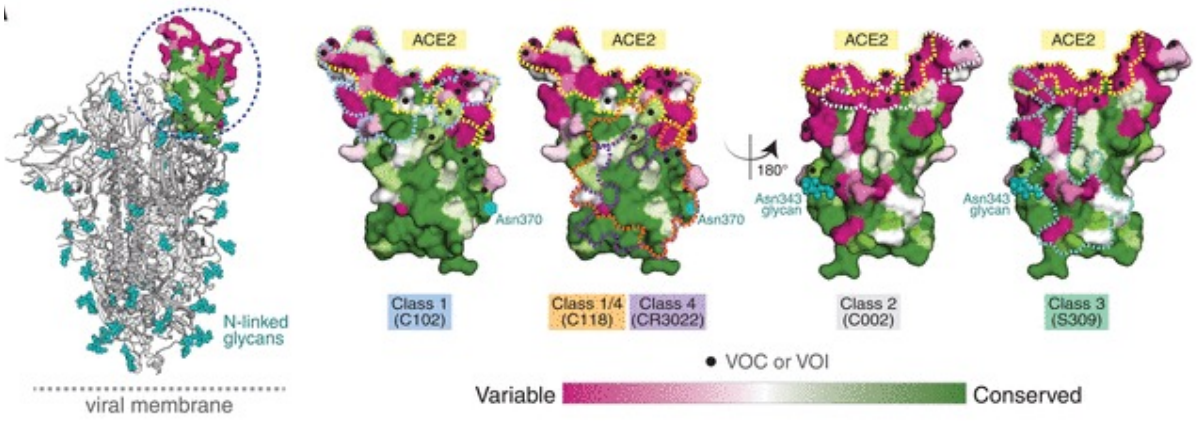
Pamela J. Bjorkman, Ph.D., is the David Baltimore Professor of Biology and Biological Engineering and a Merkin Institute Professor at Caltech. Her laboratory does basic and translational research to understand immune recognition of viral pathogens. They are particularly interested in understanding antibody responses against viruses in order to develop improved therapeutics and potential vaccines. Dr. Bjorkman is a member of the U.S. National Academy of Sciences, the American Academy of Arts and Sciences and the American Philosophical Society. She has received numerous recognitions and awards throughout her career, most recently the Ceppellini Award (European Federation for Immunogenetics) in 2019, being named a Citation Laureate in Physiology or Medicine (2020), and the Delphine Parrott award and the Pearl Meister Greengard prize in 2021.



Animal studies in mice

The animal studies conducted in mice built off of Bjorkman's lab's earlier research with mosaic 8 nanoparticles, and aimed to see if vaccination with the mosaic-8 vaccine could initiate production of protective antibodies in a live animal upon infection with SARS-CoV-2 or SARS-CoV.

The team conducted three sets of experiments in mice. In one, the control, they inoculated mice with just the bare nanoparticle cage structure without any virus fragments attached. A second group of mice were injected with a homotypic nanoparticle covered only in SARS-CoV-2 RBDs and a third group was injected with mosaic-8 nanoparticles. One experimental



Mosaic RBD nanoparticles protect against challenge by diverse sarbecoviruses in animal models, Volume: 377, Issue: 6606, DOI: (10.1126/science.abq0839)

goal was to see if vaccination with mosaic-8 would protect the animals against SARS-CoV-2 to the same degree as the homotypic SARS-CoV-2 immunized animals. A second goal was to evaluate protection from a "mismatched virus," one that was not represented by an RBD on the mosaic-8 nanoparticle. They chose SARS-CoV, the virus that caused the original SARS pandemic, to represent an unknown SARS-like betacoronavirus that could spill over into humans in the future and did not include it within the mosaic nanoparticle.

The mice used in the experiments were genetically engineered to express the human ACE2 receptor, which is the receptor on human cells that is used by SARS-CoV-2 and related viruses to gain entry into cells during infection. In this animal model, unvaccinated mice die if infected with a SARS-like betacoronavirus.

Results and primate studies

As expected, mice inoculated with the bare nanoparticle structure did die when infected with SARS-CoV or SARS-CoV-2. Mice that were inoculated with a homotypic nanoparticle only coated in SARS-CoV-2 RBDs were protected against SARS-CoV-2 infection but died upon exposure to SARS-CoV. These results suggest that current homotypic SARS-CoV-2 nanoparticle vaccine candidates being developed elsewhere would be effective against SARS-CoV-2 but may not protect broadly against other SARS-like betacoronaviruses coming from animals or against future SARS-CoV-2 variants.

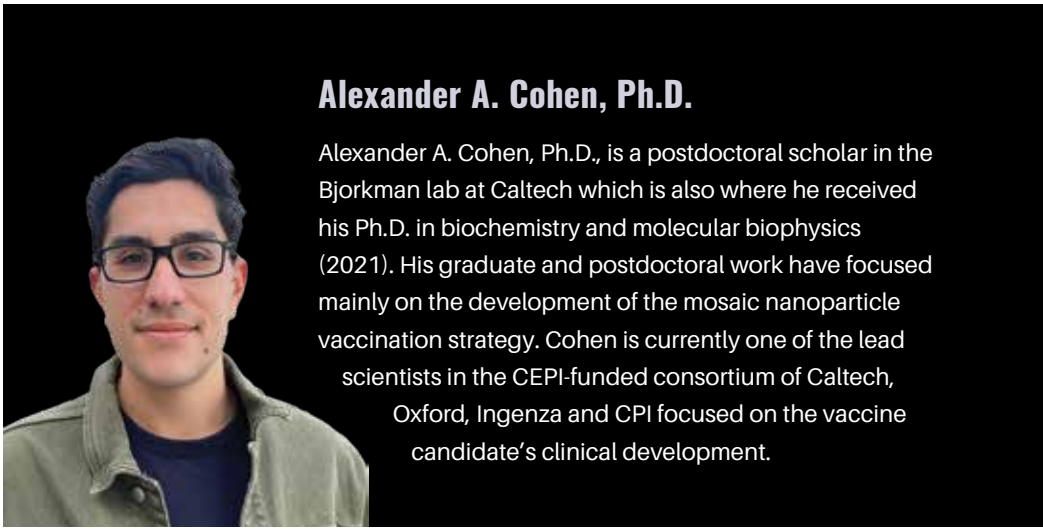
Jennifer R. Keeffe, Ph.D.

Jennifer R. Keeffe, Ph.D., is a senior research scientist in the Bjorkman lab at Caltech and the project manager for the mosaic RBD nanoparticle vaccine candidate. Keeffe received her Ph.D. in biochemistry and molecular biophysics in 2009 from Stephen Mayo's lab at Caltech, focusing on using design-based strategies to engineer antiviral proteins for increased potency and breadth. As a research scientist in the Bjorkman lab, she has worked on understanding the immune response to viral pathogens, including influenza, Zika, Dengue and HIV.

Remarkably, all of the mice inoculated with mosaic-8 nanoparticles survived both SARS-CoV-2 and SARS-CoV with no significant side effects.

The team then moved on to nonhuman primates, this time comparing the effects of mosaic-8 vaccination versus no vaccination in animal challenge studies. When vaccinated with mosaic-8, the animals showed little to no detectable infection when exposed to SARS-CoV-2 or SARS-CoV, again demonstrating the potential for the mosaic-8 vaccine candidate to be protective for current and future variants of the virus causing the COVID-19 pandemic, as well as against potential future SARS-like betacoronaviruses from animal hosts.

Importantly, the team found that antibodies elicited by mosaic-8 targeted the most common elements of the RBDs across a diverse set of other SARS-like betacoronaviruses. This provided evidence for the hypothesized mechanism by which the vaccine would be effective against new variants of SARS-CoV-2 or animal SARS-like betacoronaviruses. "The mosaic-8 vaccine encourages the immune system to target regions of SARS-CoV-2 RBDs that are relatively conserved between human and zoonotic (mostly bat) SARS-like betacoronaviruses (sarbecoviruses). These same regions are relatively conserved in the SARS-CoV-2 variants that have emerged," says Bjorkman. "We were surprised that the mosaic-8 RBD-nanoparticle immunizations worked as well as they have in animal models. Of course, we were hoping for that outcome, but it came as a pleasant surprise."



Alexander A. Cohen, Ph.D.

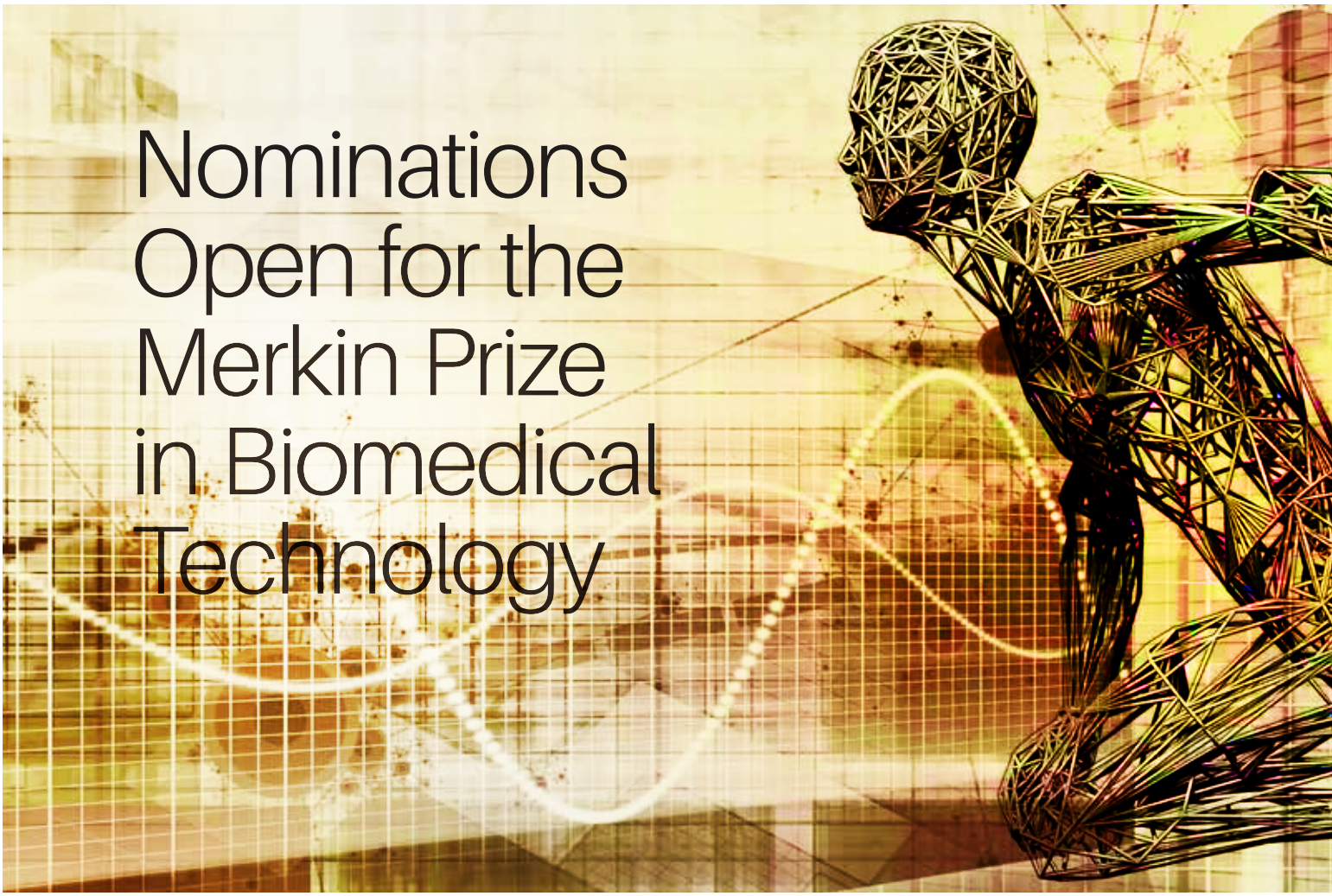
Alexander A. Cohen, Ph.D., is a postdoctoral scholar in the Bjorkman lab at Caltech which is also where he received his Ph.D. in biochemistry and molecular biophysics (2021). His graduate and postdoctoral work have focused mainly on the development of the mosaic nanoparticle vaccination strategy. Cohen is currently one of the lead scientists in the CEPI-funded consortium of Caltech, Oxford, Ingenza and CPI focused on the vaccine candidate's clinical development.

By contrast, homotypic SARS-CoV-2 nanoparticle injections elicited antibodies against mainly strain-specific RBD regions, suggesting these types of vaccines would likely protect against SARS-CoV-2, but not against newly arising variants or potential emerging animal viruses.

The future of human trials

The next step is for Bjorkman and colleagues to evaluate mosaic-8 nanoparticle immunizations in humans in a Phase 1 clinical trial supported by the Coalition for Epidemic Preparedness Initiative (CEPI). They are interested in seeing how immune responses from mosaic-8 vaccination are affected by prior exposure to SARS-CoV-2 infection and/or vaccination. To mimic the situation in which most humans have been either infected, vaccinated or both, they are studying immune responses in previously immunized animals. However, mice, non-human primates and other animal models are not people.

Bjorkman remains optimistic about the future of the vaccine: "If it works in humans as well as it does in animal challenge models, mosaic-8 RBD-nanoparticle immunization should protect against future SARS-CoV-2 variants, as well as future potential sarbecovirus spillovers into humans without the need for updating. Of course, there are a lot of immunological parameters that we need to verify through further studies before being able to say this for sure, but the results from preclinical animal studies look very promising so far."



Nominations Open for the Merkin Prize in Biomedical Technology

Nominations are now open for the first award of the Richard N. Merkin Prize in Biomedical Technology, which recognizes novel technologies that have improved human health.

Each year, the prize will celebrate a novel technology and recognize up to four key individuals and/or teams who contributed to the development of the technology, with a cash award to be shared among each year's recipients. The winning technology must have made a demonstrable real-world impact on human health by improving the treatment, diagnosis or prevention of disease.

The Merkin Prize is administered by the Broad Institute of MIT and Harvard, one of the world's leading biomedical research institutes.

"The Merkin Prize will highlight the inventors of an important medical technology and will demonstrate how their work is transforming healthcare," said Harold Varmus, M.D., chair of the selection committee. Varmus is the Lewis Thomas University Professor at Weill Cornell Medicine, a senior associate at the New York Genome Center and a recipient of the Nobel Prize in Physiology or Medicine for his work on the origins of cancer.

"Incentivizing outstanding researchers with prizes that recognize the importance of science and technology that continue to impact human health is a goal of mine, and I'm honored to acknowledge such critically important work," said Dr. Richard Merkin. "Additionally, I hope it will inspire younger researchers as they move forward with exciting opportunities to transform and improve our health and the quality of our lives."

Eligibility for receipt of the Merkin Prize extends to all living investigators from anywhere in the world, from any discipline in academia, the commercial sector or the government. Anyone may submit a nomination, but self-nominations are not permitted.

For further information, visit merkinprize.org.

> "Incentivizing outstanding researchers with prizes that recognize the importance of science and technology that continue to impact human health is a goal of mine, and I'm honored to acknowledge such critically important work."
>
> ~ Dr. Richard Merkin, President and CEO of Heritage Provider Network

About Broad Institute of MIT and Harvard

Broad Institute of MIT and Harvard was launched in 2004 to empower this generation of creative scientists to transform medicine. Founded by MIT, Harvard, Harvard-affiliated hospitals and the visionary Los Angeles philanthropists Eli and Edythe L. Broad, the Broad Institute includes faculty, professional staff and students from throughout the MIT and Harvard biomedical research communities and beyond, with collaborations spanning over a hundred private and public institutions in more than 40 countries worldwide.

America's Physician Groups Honors Heritage Provider Network With Highest Standards of Excellence

ALL MEDICAL GROUPS ACHIEVE ELITE STATUS

Heritage Provider Network (HPN), one of the nation's most experienced and innovative physician-led, value-based care organizations, and its family of medical groups, achieved the highest possible scores from America's Physician Groups (APG) annual Standards of Excellence™ survey. All medical groups in the HPN family earned Elite status, the top ranking in the nation.

"I'm so proud of all of our HPN team members in each medical group who have worked diligently throughout the pandemic to continue our quality, cost-effective care and achieve this highest honor," said Dr. Richard Merkin, president and CEO of HPN. "I'm delighted to share this with them."

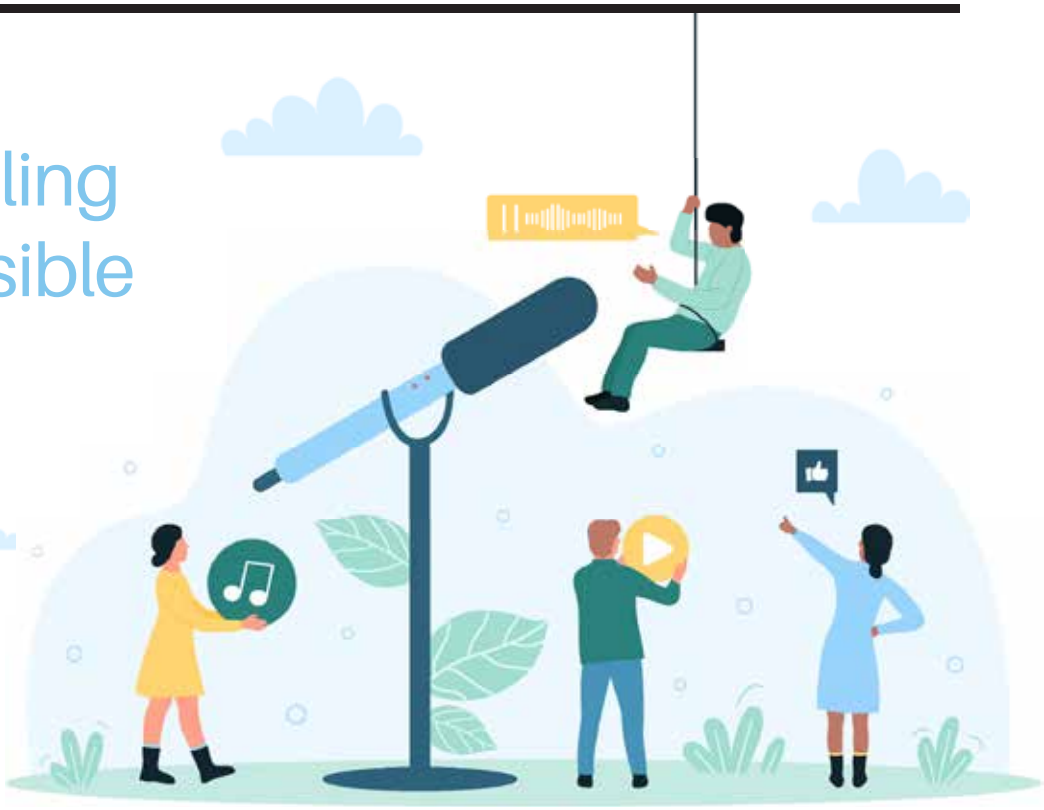
"Elite status signifies that these APG members are fully equipped with the necessary capabilities to thrive in value-based care models, and to take accountability and responsibility for the costs and quality of health care," said APG President and CEO Susan Dentzer, M.S.

The Elite five-star status is the highest possible honor awarded by the nation's leading association for physician organizations practicing coordinated care. Elite five-star status in all categories of the survey was achieved by all nine of HPN's family of medical groups, including:

- Regal Medical Group
- Lakeside Community Healthcare
- Affiliated Doctors of Orange County
- Heritage Sierra Medical Group
- Heritage Victor Valley Medical Group
- High Desert Medical Group
- Desert Oasis Healthcare
- Coastal Communities Physician Network
- Bakersfield Family Medical Center

APG is the country's leading organization representing physician groups practicing coordinated care. APG's Standard of Excellence™ Elite award for patient care includes five rigorous categories-care management practices, patient-centered care, information technology, group support of advanced primary care, and accountability and transparency.

Herencia: Fulfilling Gaps in Accessible Latinx Health Education



Heritage Sierra Medical Group redefines accessible Latinx health education for seniors in underserved communities.

An unanticipated impact of the COVID-19 pandemic was the closure of several Latinx media outlets providing local healthcare news in Spanish. Seeking to remedy the gap in health education, Heritage Sierra Medical Group first debuted its Spanish radio talk show, *La Hora de la Herencia,* or *The Heritage Hour,* in Fall 2020.

This year, Heritage Sierra Medical Group celebrates its third season of their radio talk show. Its successful viewership is linked to its distribution on a complimentary AM radio station — broadcasted locally within the Antelope Valley.

La Hora de la Herencia serves to connect Spanish-speaking senior audiences to educators, providers and featured healthcare guests. This allows the radio show to introduce complex topics in an informal conversational setting — making healthcare dialogue relatable, comfortable and entertaining. The show hosts a variety of diverse topics to encourage awareness of condition-specific information and available resources for support.

Featured topics include innovations in diabetic care where seniors may be eligible for insulin cost savings. Additional episodes cover changes to Medicare, overcoming taboos in mental health and state/federal savings programs to reduce healthcare costs amid inflation. More light-hearted segments include lifestyle practices, recipe guides and information on upcoming community-wide events.

One key indicator of *La Hora de la Herencia* is the continued participation from senior listeners — every Wednesday after the show concludes, Heritage Sierra Medical Group and its featured guests receive calls requesting additional information or recommendations on new episode topics for the following week. This enthusiasm from the community further supports Heritage Sierra Medical Group's mission to provide inclusive and accessible forums for health education.

Heritage Sierra Medical Group continues to invest in new channels that educate underserved communities to promote innovation in engaging health education.

High Desert Medical Group Senior Expo Returns for Thousands in Antelope Valley

One of the keystone events for health and wellness in the Antelope Valley, the Senior Expo hosted by High Desert Medical Group (HDMG), returned to its traditional location, welcoming thousands of people to the Antelope Valley Fairgrounds. The annual event, which was held online for two years during the height of the COVID-19 pandemic, opened on Oct. 20, 2022 in person to the public for the first time since 2019.

Dr. Richard Merkin welcomed seniors to the event. Dr. Merkin presided at the official HDMG "Senior of The Year" award ceremony, along with Don Parazo, M.D., HDMG's associate medical director. "Your service is an example to everyone who serves the senior community," Dr. Merkin said while presenting the awards to the 2022 winners, Shirley Hilger and Mary Sferrazza.

HDMG, part of Heritage Provider Network, has hosted Senior Expo for 32 years. At its founding, Dr. Merkin proposed the concept, asking "What is one great thing we could do for seniors in the Antelope Valley?"

A free, multiservice healthcare exposition resulted from the brainstorming. HDMG's Senior Expo provided free health services, as well as two open pavilions for healthcare vendors and providers. The day included continuous entertainment, along with free flu shots, health screenings and information about Medicare enrollment.

"We were thrilled about returning to the Antelope Valley Fairgrounds, which has been the locale for Senior Expo for many years," says Rafael Gonzalez, administrator at HDMG. "Our staff did a wonderful job throughout the day."

"It was so good to see all our friends in our senior community turn out for a day of resources, information and good times," says Charles Lim, M.D., medical director of HDMG. "It was a great success."

This year's Senior Expo featured celebrity entertainer Vicki Lawrence of *Mama's Family* and *The Carol Burnett Show* fame. Lawrence treated a packed pavilion audience to some of the best of her past skits with Carol Burnett and Harvey Korman.

The "Mama" character was the title role of the evergreen television situation comedy series *Mama's Family* from the 1980s and is still seen daily in syndication. "I think I have found that I agree with Mama more than I ever did. It's been fun to bring her into the 21st century and let her deal with everything that's going on," Lawrence says.

Additionally, HDMG partnered with Los Angeles County Supervisor Kathryn Barger in presenting its annual Veterans Community Service Award. This year's award went to the team that presents the Antelope Valley Mobile Vietnam Memorial, which is a half-scale tribute monument of the Vietnam Memorial in Washington, D.C. HDMG celebrates a job well done and looks forward to the 33rd Annual Senior Expo, which is scheduled for Oct. 19, 2023.

Heritage Provider Network Affiliated Medical Groups

THE LARGEST INTEGRATED PHYSICIAN-LED MEDICAL GROUP NATIONALLY

For more than 30 years, Heritage Provider Network (HPN) has provided quality, cost-effective healthcare to the communities we serve. Today, HPN and its affiliates manage the healthcare of more than 1 million individuals. Our network has thousands of primary care physicians and specialists and hundreds of hospitals.

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bfmc.com
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hcpipa.com
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hvvmg.com
Phone: (760) 245-4747
12370 Hesperia Road, Suite 6
Victorville, CA 92395
Counties Served: Los Angeles and San Bernardino

High Desert Medical Group
hdmg.net
Phone: (661) 945-5984
43839 N. 15th St. West
Lancaster, CA 93534
Counties Served: Kern and Los Angeles

Lakeside Community Healthcare
lakesidemed.com
Phone: (818) 637-2000
8510 Balboa Blvd., Suite 150
Northridge, CA 91325
Counties Served: Los Angeles, Riverside, San Bernardino and Ventura

Regal Medical Group
regalmed.com
Phone: (866) 654-3471
8510 Balboa Blvd., Suite 150
Northridge, CA 91325
Counties Served: Los Angeles, Orange, Riverside, San Bernardino, San Diego and Ventura

*touch*points

Heritage Provider Network
8510 Balboa Blvd., Suite 150
Northridge, CA 91325-5810

Our Awards

Recognition of Commitment and Excellence

The recognition we have received demonstrates our practices in excellence. We're proud to be awarded for our commitment to our members and our community.

- Wellness Excellence Award in Health Education — Southern California Foundation for Health Care
- Top 10 Physician Medical Networks in California by America's Physician Groups
- NCQA Certification for Utilization Management and Credentialing
- Elite Status of Excellence for the Standards of Medical Care by America's Physician Groups
- Recognized by the Integrated Healthcare Association for our diabetic registries

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