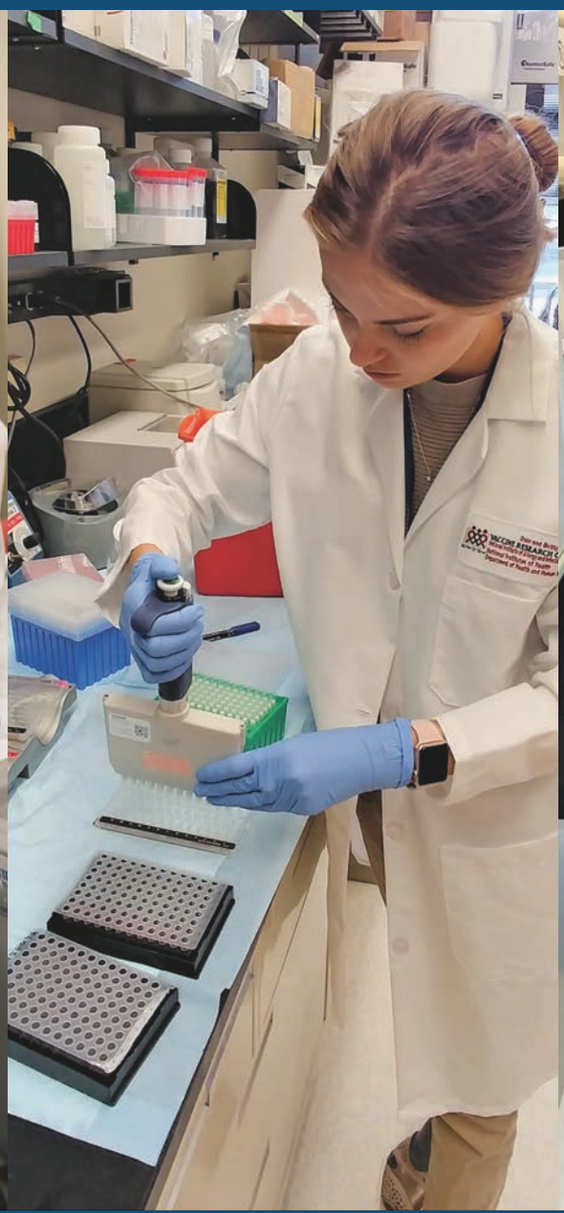
Vaccine Research Center

NIAID

National Institute of Allergy and Infectious Diseases

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health


Letter from John R. Mascola, M.D., NIAID Vaccine Research Center Director, and Anthony S. Fauci, M.D., NIAID Director

The Dale and Betty Bumpers Vaccine Research Center (VRC) was created by Presidential Executive Order in 1997 to accelerate the development of a vaccine directed against the devastating global pandemic caused by HIV. The VRC began its vital HIV work in 2000 and has since further expanded its scope and capabilities to combat other high-burden diseases such as influenza, respiratory syncytial virus (RSV), malaria, and tuberculosis, as well as biodefense threats and emerging infectious diseases, including Ebola, chikungunya, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), West Nile, and Zika.

As an intramural research arm of the National Institute of Allergy and Infectious Diseases (NIAID), part of the U.S. National Institutes of Health (NIH), the VRC is led by an integrated team of specialists in various disciplines, including immunology, virology, structural biology, and bioengineering. By encompassing these scientific disciplines under one roof, together with the capability to conduct human clinical trials, the VRC accelerates the process of scientific discovery leading to the design and development of prototype vaccines and biologics to protect against infectious diseases. The VRC operates as the closest analog at NIH to a private sector biotechnology entity, encompassing basic, translational, and clinical research programs along with all needed critical infrastructure to support these programs.

The VRC is a highly productive member of the NIAID/NIH intramural research community, producing and publishing many discoveries that have often been field-altering in scope, particularly in the areas of structural biology, immunological testing of new vaccine platforms, and rapid translation of basic scientific knowledge into vaccine or biologic products for clinical studies. To realize the public health potential of these new products, the VRC works closely with partners in government, academia, and industry to transition new vaccines and biologics into commercial use.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At the Core:
Goals and Capabilities for Turning Discovery Into Health

At the core of the VRC mission is the application of scientific and technological knowledge to design and develop vaccines and biologics against infectious diseases.

Accelerate biomedical discovery: Find answers and share solutions. High-quality basic research is the foundation upon which translational (applied) research is built. The VRC carries out pioneering research in the fields of microbiology, immunology, structural biology, and the natural history of disease. These discoveries expand our fundamental knowledge about infectious microbes and the human immune response, which are shared with the global scientific community and published in major scientific journals. This multi-disciplinary approach is the cornerstone of modern vaccinology, providing a framework for novel vaccine design strategies, including protein engineering, structure-based vaccine design, and gene-based vaccination, as well as novel methods of monitoring human immune responses.

Develop new technologies that enable the study of human infectious disease and the design of improved vaccines. The research efforts necessary to address the challenges of pathogens like HIV have created a foundational set of concepts, platforms, and innovative technologies that have been leveraged for the discovery and design of prototype vaccines and biologics to protect against other infectious diseases of high public health impact. For example, the VRC used DNA vaccine technology, a form of gene-based vaccination, to rapidly design and test a vaccine against the Zika virus. The technology to make virus-like particles (VLPs) has been applied to vaccine development for chikungunya virus, and knowledge of viral structure has been used to modify viral proteins—called structure-based vaccine design—leading to a vaccine candidate for RSV.

Facilitate the rapid advancement of new scientific discoveries into public health interventions. By designing new vaccine candidates and improved vaccine platforms for immunization, and by conducting Phase I proof-of-concept studies in humans, the VRC aims to attract potential industry partners and shorten the timeframe from discovery to licensure of effective public health tools, such as vaccines and biologics. Appropriate technology transfer agreements serve to protect publicly funded discoveries while also accelerating the time to commercial availability.

Shift resources quickly and efficiently within an integrated research program. The VRC's agile translational research and technology development capabilities allow it to apply advanced genetic sequencing and gene-based vaccine technology platforms to unexpected disease outbreaks and to shorten the time needed between the identification of a pathogen's genetic sequence and clinical testing of an experimental vaccine. For example, during the Zika outbreak that began in 2015, VRC manufacturing engineers delivered vaccine material and VRC clinicians initiated a Phase I clinical trial of a candidate Zika vaccine just 100 days after the vaccine was first designed in the laboratory. This same process had previously taken 4 months in the case of the 2009 H1N1 influenza outbreak, and 11 months in the case of the 2005 H5N1 outbreak.

Translational Research Infrastructure:
Advancing Toward Products That Improve Human Health

The iterative process of design and human testing allows VRC scientists to develop improved vaccines and related products rapidly and efficiently.

Vaccine development is a complex process, involving basic, translational, and clinical research. The VRC's integrated structure allows it to rapidly reprioritize basic, pre-clinical, manufacturing, and clinical development efforts based on the most urgent public health needs and government priorities. Furthermore, the organizational structure of the VRC emphasizes internal and external coordination and collaboration to expedite effective and timely responses to emerging and re-emerging diseases of public health importance, including design of new vaccines using state-of-the art technologies, outreach to national and international partners, and rapid advancement of these vaccines into first-in-human clinical testing.

VRC scientists and bioengineers design new vaccines and biologic products, such as antibodies, and develop methods to produce vaccine and antibody products for human testing. In addition, the VRC develops new vaccine platforms, such as genetic vaccination and nanoparticle display. Design and engineering are product driven and consist of (1) process development, which is an overarching term referring to processing methods (e.g., designing appropriate cell culture media), analytical tools (e.g., measuring product yields and purity), and formulation methods (e.g., ensuring stability in the vial for clinical products); and (2) the manufacture of pilot lot clinical materials.

Process development takes place at the VRC Vaccine Production Program in Gaithersburg, Maryland, and supports up to six VRC products per year.

Manufacture of pilot lot clinical materials, in compliance with FDA regulations under current good manufacturing practices (cGMP), takes place either at the VRC's Vaccine Clinical Materials Program in Frederick, Maryland—an approximately 130,000-square-foot facility with the capacity to manufacture two products concurrently—or at outside facilities under contract.

The primary mission of the VRC Clinical Trials Program is to facilitate and carry out clinical research, by conducting clinical trials at the NIH Clinical Center and providing a broad range of support for external trials conducted by the VRC and its collaborators and partners. These trials include evaluations of candidate vaccines and monoclonal antibodies targeting HIV, influenza, malaria, RSV, filoviruses, coronaviruses, flaviviruses, and alphaviruses. The VRC has developed and implemented numerous Phase I clinical trials, as well as advanced phase clinical studies, and has shown leadership in developing and coordinating international collaborations necessary for conducting complex, multi-site clinical studies. The VRC's Vaccine Immunology Program rapidly evaluates biological samples from early or advanced stage clinical trials to learn if they are producing the desired immune response.

Collaborations and Partnerships:
Getting Life-Saving Products to the People Who Need Them

The VRC seeks industry partners and collaborators who are interested in advancing products to commercial licensure.

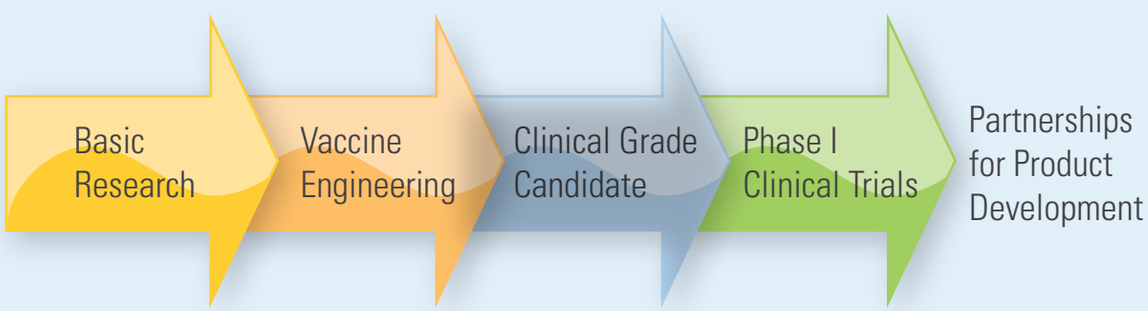
Vaccines can only protect public health if they are safe, effective, and commercially available. To translate scientific discovery into practical and available public health interventions, the VRC must partner with biotechnology or pharmaceutical companies interested in advancing products to commercial licensure.

The VRC conducts collaborative research and development of new products within the context of a cooperative research and development agreement (CRADA), and products can be licensed by industry partners for commercial development. The VRC carries out extensive internal strategic planning to identify ways to maximize intramural resources and identify barriers to achieving its product development objectives.

The VRC collaborates with NIH extramural networks (e.g., the HIV Vaccine Trials Network [HVTN], the HIV Prevention Trials Network [HPTN], the International Maternal Pediatric Adolescent AIDS Clinical Trials [IMPAACT] Network, the AIDS Clinical Trials Group [ACTG]) and with other U.S. government agencies such as the Military HIV Research Program (MHRP), the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), the Defense Advanced Research Projects Agency (DARPA), and the Biomedical Advanced Research and Development Authority (BARDA). The VRC also participates in the HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), which seeks to integrate vaccine research and development responses to emerging epidemic threats such as Ebola or Zika. The VRC provides scientific and operational expertise and resources to help accelerate responses to emerging and re-emerging infectious disease threats.

The Vaccine Development Pathway.

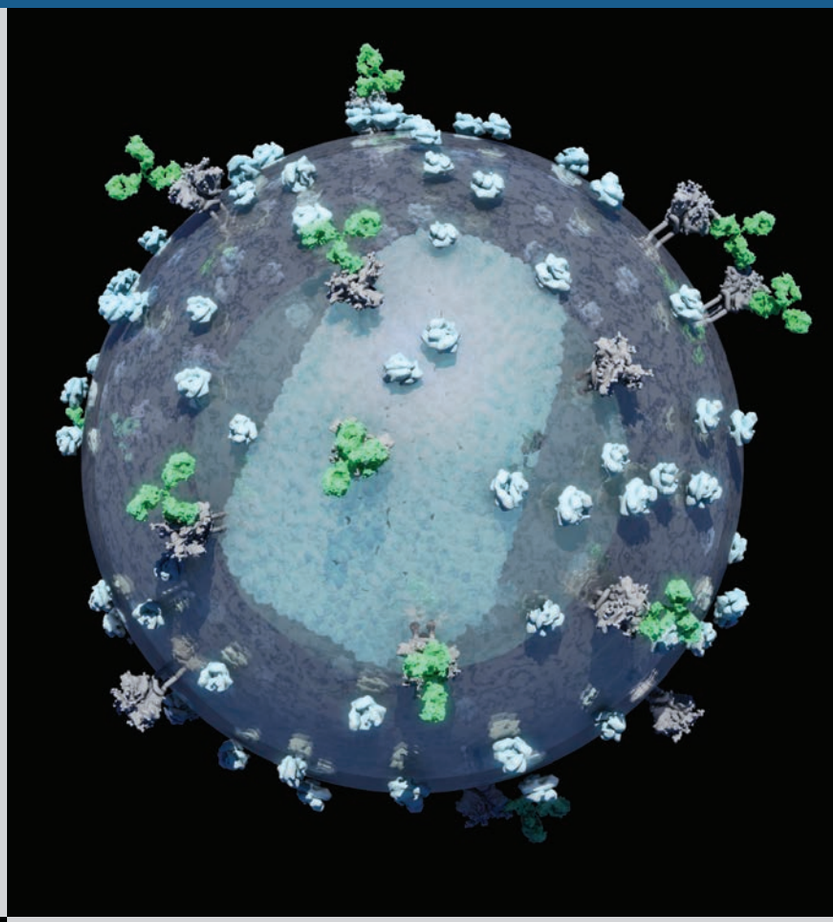
At the VRC, potential products discovered during basic research can move through design and engineering, manufacture of pilot lot clinical grade materials, and Phase I clinical trials, before being handed off to collaborators and partners for advancement to licensure.

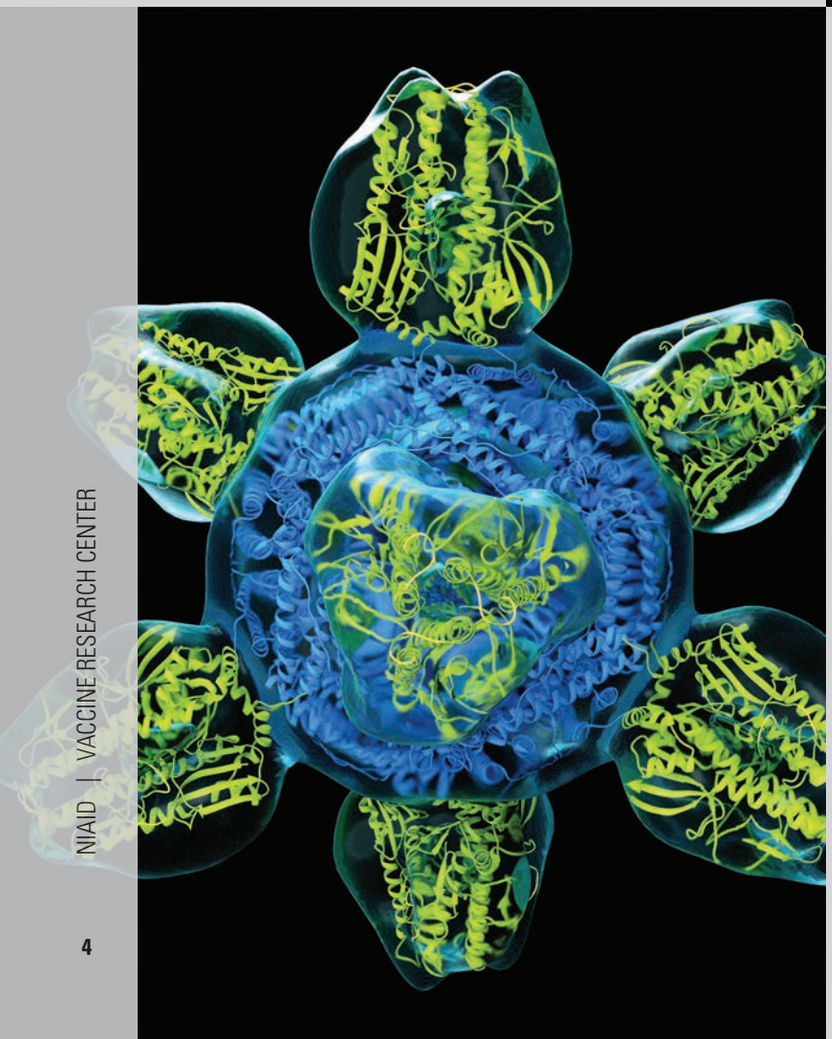


Research Program Areas of Focus

HIV

The major goal of the HIV program is prevention—that is, to develop a vaccine that protects against the acquisition of HIV infection. The design of an effective HIV vaccine remains a major scientific challenge, and VRC scientists have made key advances in understanding the viral structure of HIV, leading to the design of novel candidate vaccines that are entering clinical trials. In addition to vaccines, VRC scientists have isolated highly potent antibodies that can neutralize HIV (i.e., block viral infection of cells). These antibodies, derived from the cells of HIV-infected individuals, have been made into clinical products that are now in clinical testing for both prevention and treatment of HIV infection. The image to the right depicts one of these neutralizing antibodies (in green), called VRC01, binding to a specific protein on the surface of HIV, thus preventing HIV from attaching to and infecting human CD4 T-cells. Image created by and used with permission of Lisa Donohue, Fred Hutchinson Cancer Research Center.



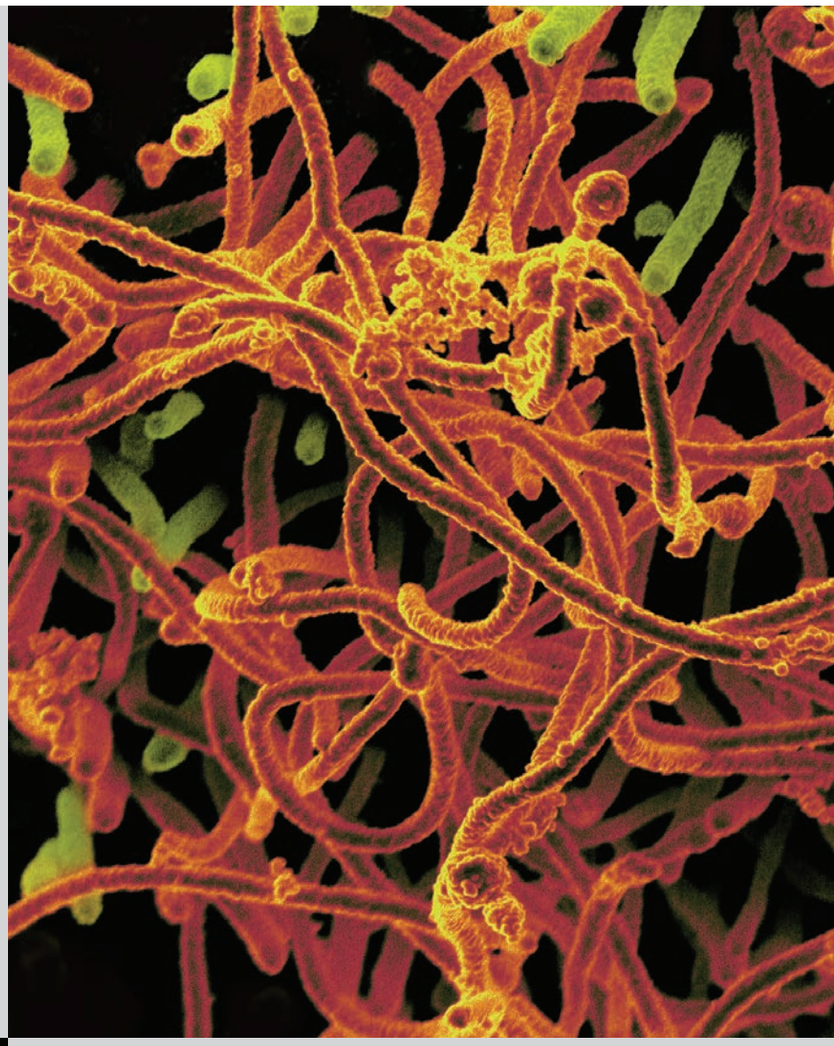


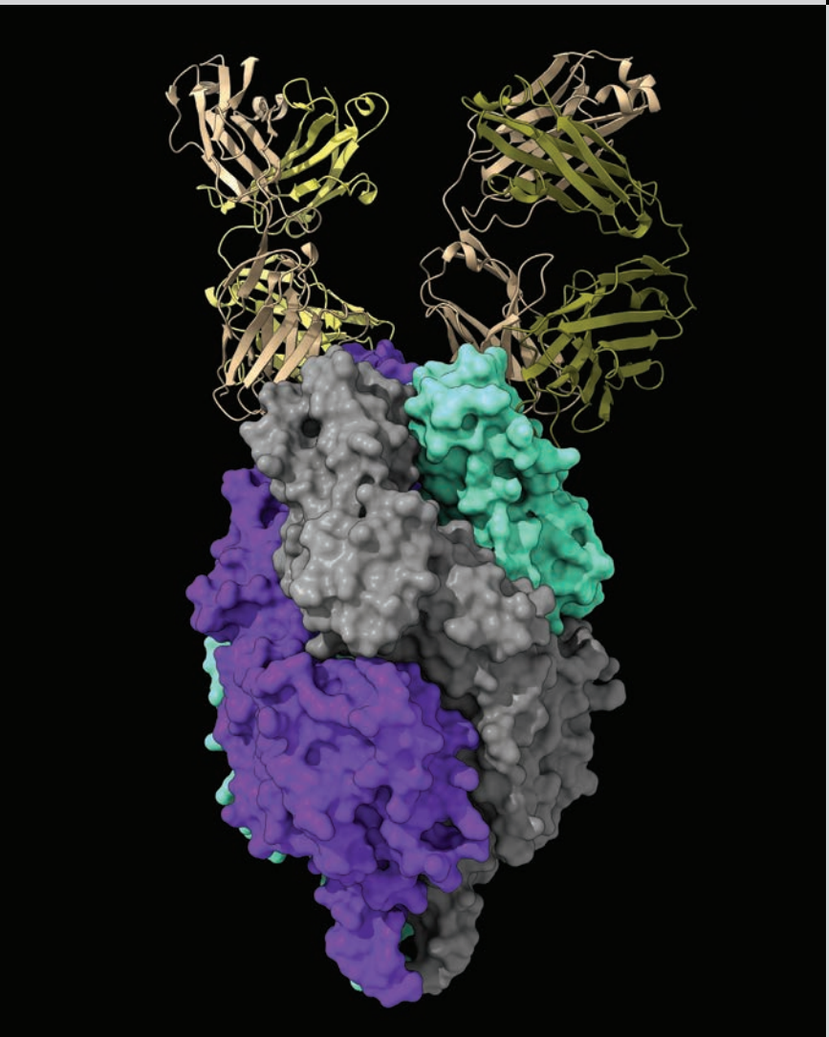
Influenza

The influenza vaccine program seeks to design a vaccine that can provide potent and long-lasting protection against all seasonal influenza strains as well as pandemic influenza. Guided by atomic-level details of protein structure, VRC scientists have engineered the hemagglutinin (HA) surface protein of influenza to direct the immune system to make antibodies targeting specific regions of HA, such as the head and stem components. In addition, the HA protein can be displayed on self-assembling nanoparticles, a platform technology shown to stimulate potent immunity to HA. Shown here is a colorized structure of a novel vaccine with eight copies of the stem portion of the HA protein (depicted in yellow-green) displayed on a ferritin nanoparticle base (in blue). The HA was specifically designed to display antibody binding sites common to many human influenza subtypes. The nanoparticle vaccine candidates developed by VRC scientists are being advanced into human clinical trials. 3D structure of the particle was determined by cryo-electron microscopy by John Gallagher and Audray Harris (NIAID Laboratory of Infectious Diseases).

Ebola and Marburg

Ebola and Marburg filoviruses cause sporadic but potentially fatal disease outbreaks. VRC scientists were among the first to demonstrate that vaccines could protect against fatal Ebola infection in animal studies. These vaccines, based on the insertion of Ebola or Marburg genes into safe viral vectors, have advanced into human testing with private sector partners. Ideally, such vaccines would be both fast acting (for acute protection) and durable (for long-term protection). In addition, VRC scientists have isolated and are clinically testing potent human antibodies against Ebola that have the potential to treat and cure people with Ebola infection. Shown here is Ebola virus isolated in November 2014 from patient blood samples obtained in Mali.



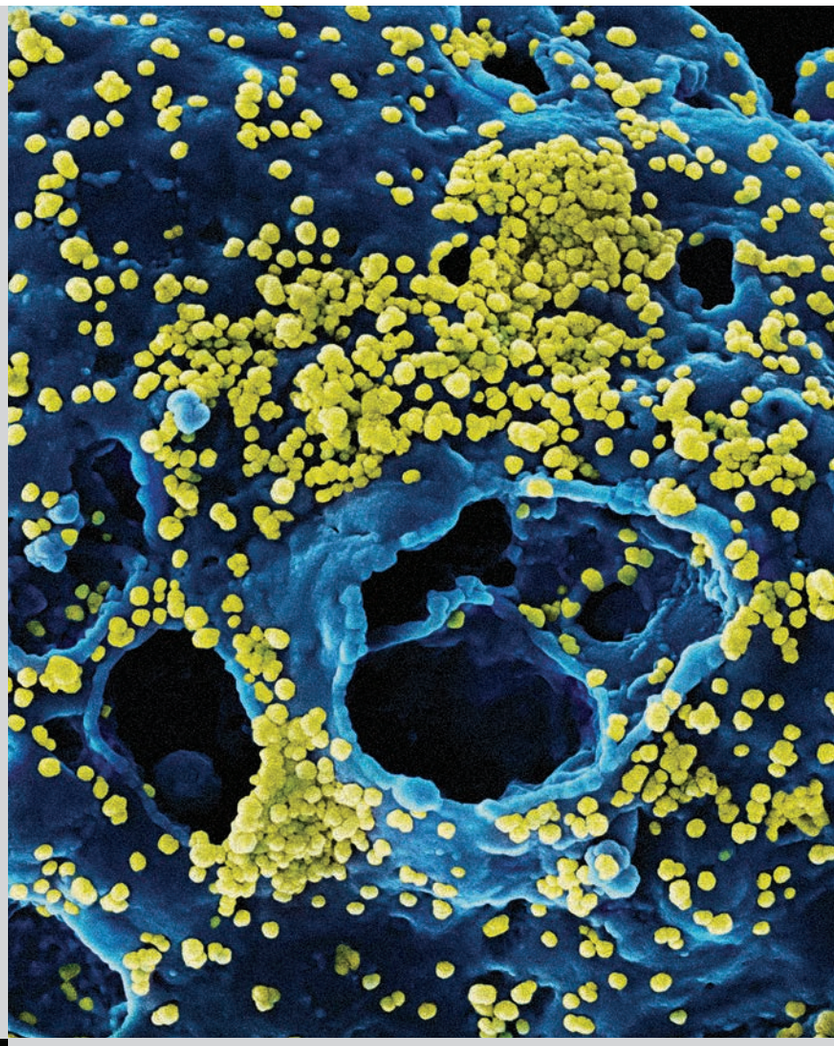


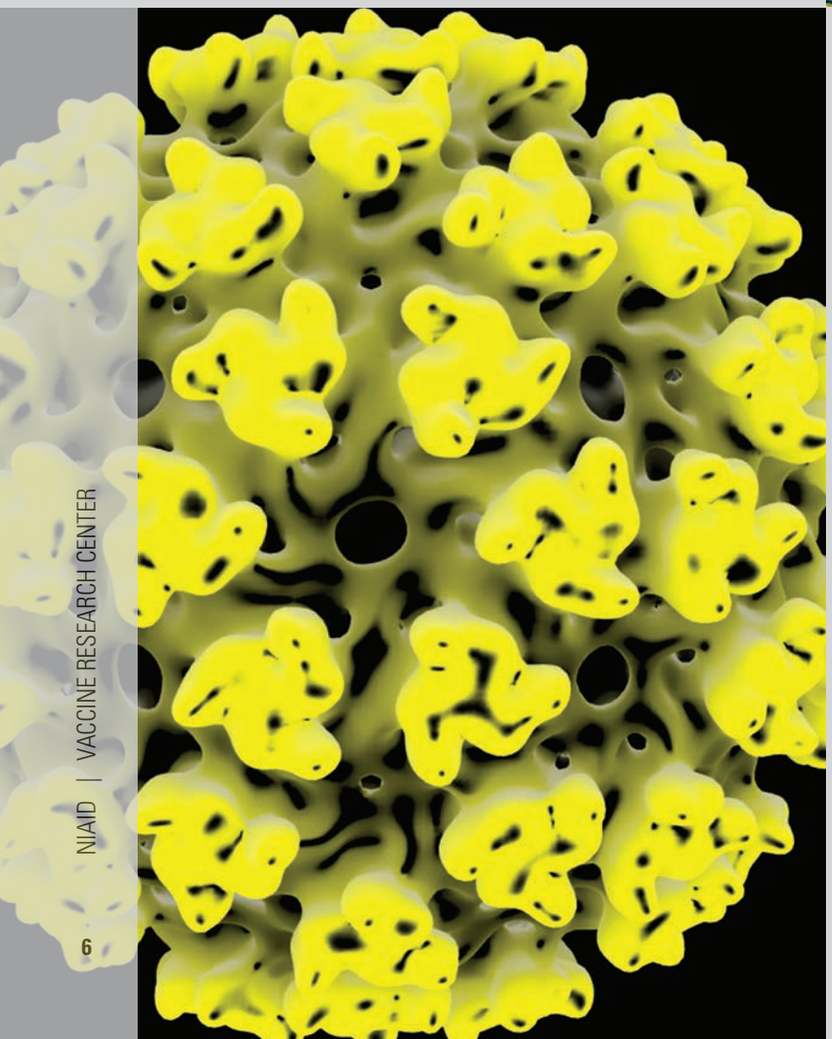
Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) causes upper and lower respiratory infections in children and adults of all ages and leads to significant morbidity and mortality in pediatric, immunocompromised, and geriatric populations. Worldwide, RSV is the leading cause of respiratory tract infections in children, and there is currently no licensed RSV vaccine. VRC scientists defined atomic-level details of the RSV F glycoprotein in its native state and used this structural information to design a vaccine candidate that has been evaluated in humans, establishing the first clinical proof-of-concept for structure-based vaccine design. This technology has been licensed to private sector partners for advanced development. As part of the vaccine development process, VRC researchers found that a highly potent neutralizing antibody (D25) (left, shown in ribbon structure) binds to a previously unknown antigenic site at the top of the prefusion F glycoprotein. Image created by Kaitlyn Morabito, VRC, NIAID, and Jason McClellan, University of Texas at Austin.

Coronaviruses (MERS/SARS)

When Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in 2012, VRC scientists mobilized quickly, using knowledge gained from the experience with severe acute respiratory syndrome coronavirus (SARS-CoV) vaccine development, as well as approaches informed by work on HIV and influenza to create MERS-CoV vaccine candidates. Following the paradigm established for the RSV vaccine, solving the atomic-level structure of coronavirus spike trimers is guiding the design of second-generation vaccine antigens for MERS-CoV, SARS-CoV, and other emerging coronaviruses. Depicted here is a color-enhanced scanning electron micrograph of Vero E6 cells infected with MERS-CoV.



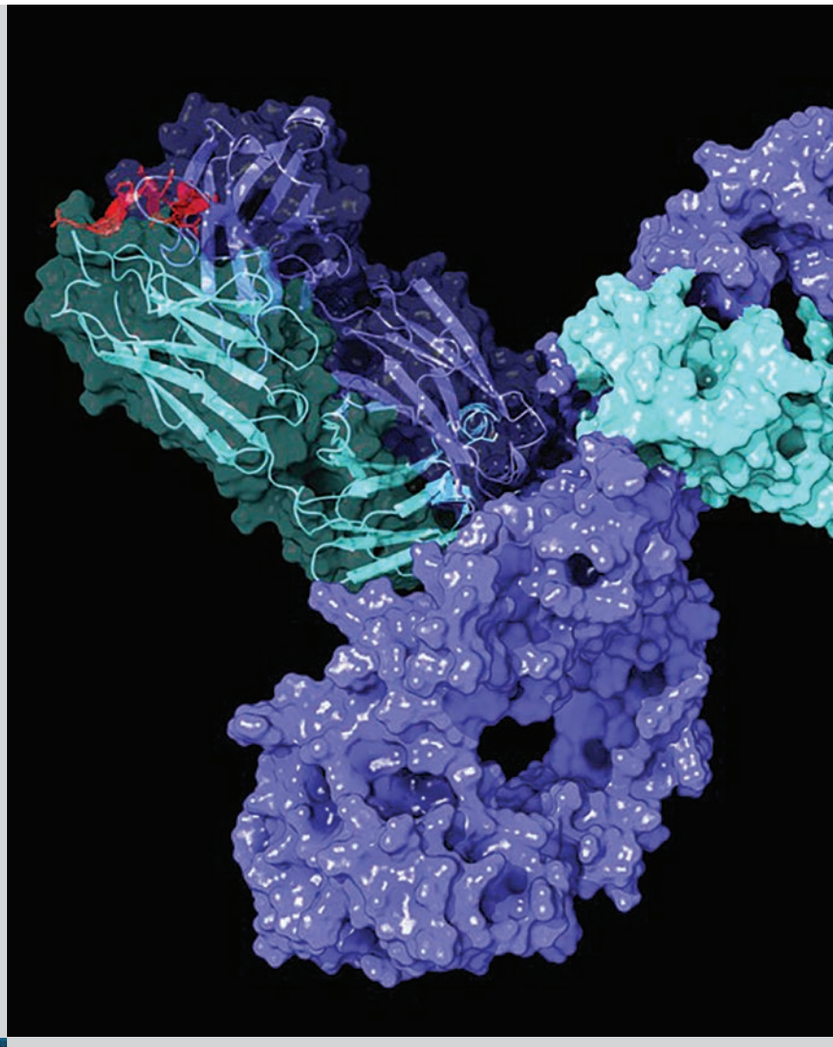


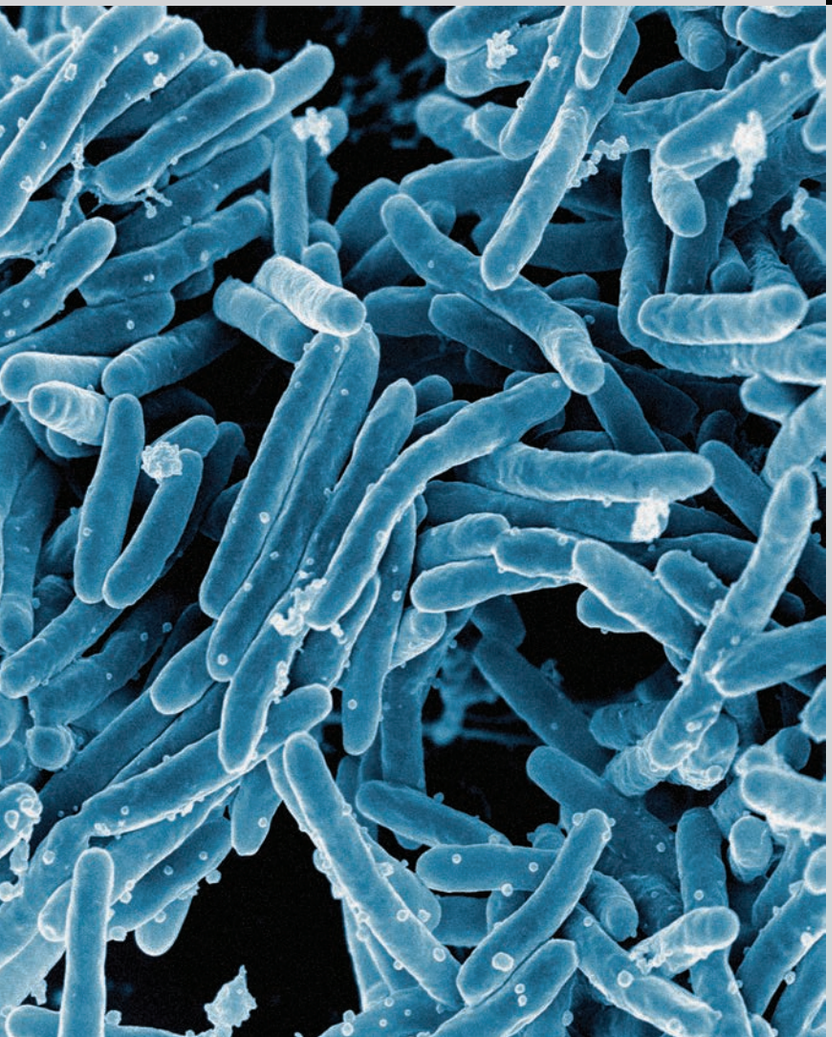
Alphaviruses

Developing vaccines for the prevention of mosquito-borne alphavirus diseases such as chikungunya, Western equine encephalitis, Eastern equine encephalitis, and Venezuelan equine encephalitis is a global public health research priority. In late 2013, chikungunya spread to the Americas, causing half a million reported cases in less than a year. The chikungunya VLP vaccine developed by the VRC has been clinically tested, has demonstrated safety and immunogenicity, and has been licensed to a pharmaceutical partner to advance the manufacturing and clinical evaluation of the vaccine. In addition to the chikungunya vaccine, the VRC is also developing equine encephalitis virus vaccines. Shown here is a 3D, colorized image of a VLP-based vaccine against Western equine encephalitis virus, which is similar in structure to chikungunya VLP. Image created by Sung-Youl Ko.

Malaria

VRC scientists have partnered with private sector and federal collaborators on a vaccine composed of irradiated sporozoites of the species *Plasmodium falciparum*. VRC investigators were first to demonstrate that intravenous immunization of this vaccine was safe and well tolerated and conferred high-level protection in malaria-naive adults in the United States. These studies provided the scientific and clinical basis for the development of improved malaria vaccines. VRC scientists are also focused on developing monoclonal antibodies to assess antibody-mediated protection that could be applied to seasonal prevention and elimination efforts. The image here depicts the CIS43 antibody, which binds to a specific portion of a highly conserved surface protein on the malaria parasite, *P. falciparum*. Image created by Katie Farney and Azza Idris.



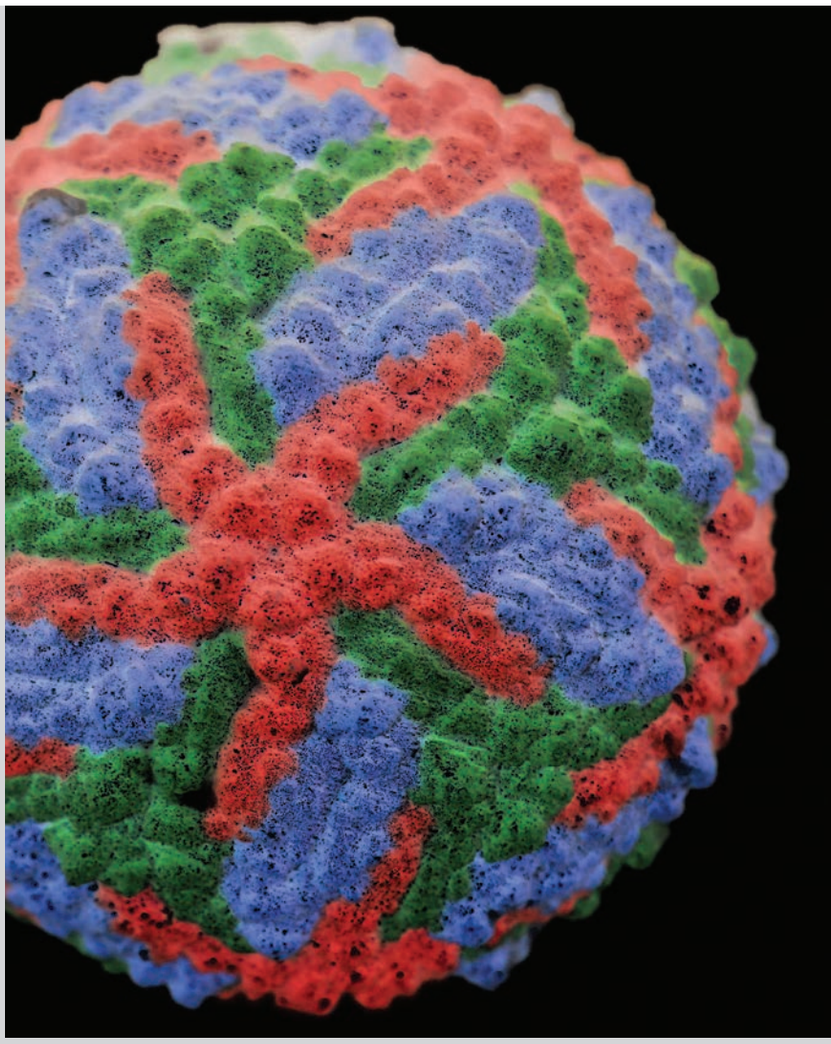


Tuberculosis

The currently available, intradermally administered bacille Calmette-Guérin (BCG) vaccine is effective against systemic tuberculosis (TB) in infants but has variable efficacy against pulmonary TB, which is the major cause of morbidity and mortality in adolescents and adults. Thus, there is an urgent need for new, safe, and effective approaches that protect pediatric and adult populations against pulmonary TB. Such approaches might involve combinations of new vaccines and routes of administration. The VRC is currently exploring alternative routes and doses of BCG vaccination in nonhuman primates to demonstrate high-level protective efficacy and define immune correlates and mechanisms of protection. Based on the findings of these studies, the VRC will advance vaccines into clinical trials. Shown here is a scanning electron micrograph of *Mycobacterium tuberculosis*.

Zika

Zika is a virus spread by mosquitoes and belongs to the *Flaviviridae* family, which also includes dengue virus, yellow fever virus, and West Nile virus. Since its discovery in Uganda in 1947, outbreaks of Zika have been reported in Africa, Southeast Asia, and the Pacific Islands. Zika emerged in Brazil in 2015 and then rapidly spread throughout the Americas. There is evidence that Zika virus infection during pregnancy can harm the fetus and cause microcephaly and other neurological disorders. There are currently no effective vaccines or therapies against Zika. The VRC led the rapid development of a safe and immunogenic DNA vaccine, while simultaneously partnering with collaborators to advance other vaccine approaches. The VRC continues to carry out basic and translational research to better understand Zika pathogenesis and immunological determinants of protection. This program established a precedent for moving from a genetic sequence selected for manufacturing to an international Phase II efficacy trial within one year. This image is a colorized, 3D representation of the Zika virus created by Kaitlyn Morabito and Jonathan Stuckey.



VRC Advances and Contributions

The resource, infrastructure, and biotechnology capabilities of the VRC uniquely position it to help advance novel vaccines and biologics and to help accelerate potential public health applications. The VRC's recognized track record of discovery and success in the field of vaccine research is illustrated by the following examples.

VRC scientists study the atomic level structure of key proteins on the surface of viruses because these proteins are necessary for viruses to infect human cells. If these proteins can be presented to the immune system in their natural form, the resulting immune system antibodies can block the virus and prevent disease. For example, VRC application of structure-based design has yielded success in creating a promising vaccine against RSV, which is a common cause of pneumonia and hospitalization in young children and the elderly. Using knowledge from the discovery that the RSV fusion protein (F) exists in multiple conformations on the cell surface, VRC scientists developed a method to stabilize the protein in its original native form, thereby preserving sites of vulnerability not present after protein rearrangement. This vaccine candidate, based on a single, structurally engineered protein, produces much stronger protective immunity than traditional approaches, which are based on a weakened or inactivated whole virus. This vaccine has been licensed for full clinical development.

VRC scientists have also applied structure-based vaccine design to HIV. Improving our understanding of the highly changeable HIV virus structure as it prepares to infect human cells is essential to developing an effective vaccine. Years of intensive VRC research have resulted in the identification and characterization of stable HIV protein structures (known as the prefusion closed conformation) that generate desirable immune responses, leading to the initiation of multiple clinical studies. To prevent HIV infection, VRC scientists have also developed antibodies that can block the vast majority of globally diverse strains of HIV. The antibodies are being developed clinically as a means to prevent HIV infection.

For influenza, VRC scientists created structure-based modifications of full-length hemagglutinin (HA), an influenza surface protein, to improve vaccine-induced immune responses. These modifications were based on the identification of key HA molecules that are vulnerable to antibody attack and conserved (i.e., less likely to mutate), making them useful targets for a broadly effective vaccine. VRC clinical studies are testing these new protein designs in unique combinations and displaying them on self-assembling nanoparticles to enhance the strength, durability, and breadth against multiple strains of the vaccine-elicited immune responses.

In the technology arena, VRC scientists can isolate, analyze, and sort individual immune system cells to study how each cell responds to infection and to assess how the immune system responds to vaccination. Using state-of-the-art flow cytometry and microfluidic tools

(e.g., high-throughput screening technologies that help identify physical, chemical, and immunological characteristics), each cell can be fluorescently tagged to describe its observable characteristics and to measure the immune proteins it produces, including antibodies that can attack microbes. VRC scientists also carry out full genetic sequencing of immune cells to understand the genetic basis of immunity. In total, this detailed immunological information is used to understand protective immunity and to optimize vaccine design. The VRC's use and refinement of advanced flow cytometric, x-ray crystallographic, and genomic technologies has advanced and accelerated the development of vaccines and antibodies against HIV, respiratory diseases (e.g., influenza and RSV), and zoonotic/vector-borne diseases (e.g., Ebola transmitted by animals such as bats or malaria transmitted by mosquitoes).

Clinical scientists at the VRC evaluate candidate vaccine and biological products for safety and to determine their optimal dose and route of administration. To this end, the VRC has developed a comprehensive clinical trial infrastructure and has implemented numerous first-in-human Phase I clinical trials at NIH and elsewhere, as well as multiple advanced phase clinical studies. The VRC has also demonstrated proven leadership in developing and coordinating the multinational collaborations and infrastructure necessary for conducting complex, multisite clinical studies.

Finally, the VRC promotes collaborations and partnerships to optimize scientific discovery, accelerate potential regulatory licensure, and hasten the introduction of VRC-developed products and technologies into commercial use. The VRC has successfully licensed many of its products and technologies and has created robust collaborations, partnerships, and technology transfer agreements with leading academic, government, private sector, and nongovernmental organizations around the world.

Credits

Cover: NIAID's Dale and Betty Bumpers Vaccine Research Center, NIH campus, Bethesda, MD. Credit: NIAID

pp. ii–iii: Montage of VRC staff at work in vaccine pilot lot production, research labs, and clinical trials. Credit: NIAID

p. iv: Robotic machinery at the Vaccine Production Program fills trays with vaccine production material. Credit: NIAID

p. 1: L, A quality control specialist inspects vaccine vials. R, Vaccine vials under quality control in the Vaccine Clinical Materials Program. Credit: NIAID

p. 2: L, Vaccine vial. R, Vaccine Clinical Materials Program staff in sterile gowning work in the fermentation suite. Credit: NIAID

p. 3: L, A Vaccine Production Program technician operates the robot. R, Pipetting. Credit: NIAID

p. 4: Top, Credit: Lisa Donohue, Fred Hutchinson Cancer Research Center. Bottom, Credit: NIAID

p. 5: Top, Credit: NIAID. Bottom, Credit: NIAID and Jason McClellan, University of Texas at Austin

p. 6: Top and Bottom, Credit: NIAID

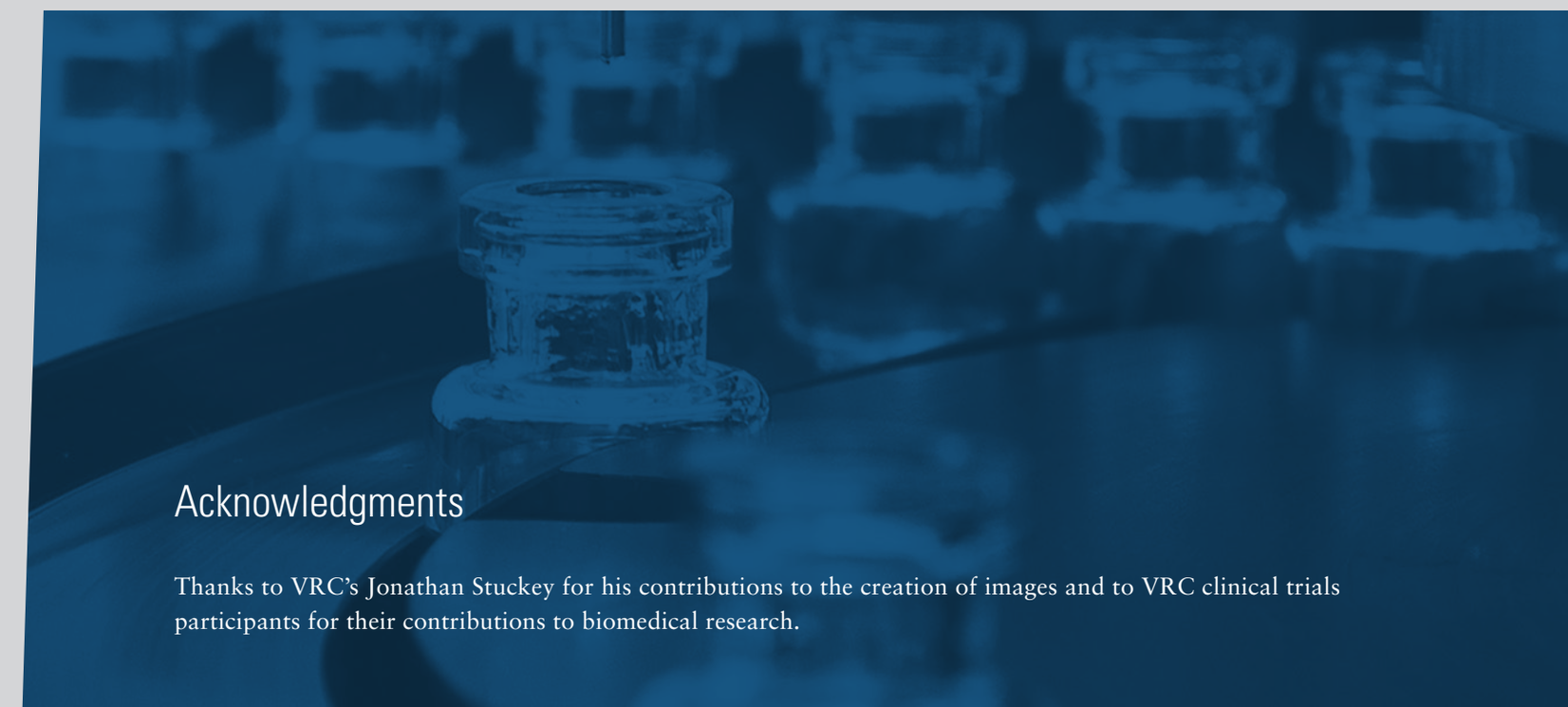
p. 7: Top and Bottom, Credit: NIAID

p. 8: Top, Credit: NIAID. Bottom, Vaccine Production Program staff prepare vaccine batches. Credit: NIAID

p. 9: L, Vials containing a candidate influenza vaccine are labeled and ready for distribution to clinical trial sites. R, A vial containing candidate vaccine receives closer inspection. Credit: NIAID

p. 10: A candidate vaccine is sorted in the Vaccine Clinical Materials Program filling room. Credit: NIAID

p. 11: Vaccine vial. Credit: NIAID



Acknowledgments

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