BY THE NUMBERS

19 Faculty
227 Staff

Awards
- Government: 45
- Universities: 9
- Foundations: 6
- Corporations: 23

Our Mission
To develop vaccines and therapeutics against diseases of global importance while training the next generation of scientists.

Our Vision
To support interdisciplinary efforts across Duke to develop vaccines and therapeutics against global infectious diseases.

Our Values
- Innovation through ingenuity and the pursuit of continuous improvement.
- Collaboration through embracing change and cultivating diversity to achieve synergy.
- Excellence through a commitment to respect, integrity and safety.

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ON THE COVER
HIV-1 neutralizing Fab-dimerized glycan binding antibody 2G12 bound to the SARS-CoV-2 spike. Cryo-EM structure at 3.2 Å resolution.
The Duke Human Vaccine Institute (DHVI) offers a highly collaborative environment in which its resources enable research teams to focus on complex scientific questions. Core laboratories house advanced equipment and greatly skilled technical teams to support projects in a manner that help to efficiently advance the science. Administrative management teams at the institute bring extensive financial and sponsored research management, project management and compliance support to faculty, students and staff engaged in our research endeavors. These have helped to develop best practices for the administration of large research programs.

These capacities have proven invaluable in enabling the DHVI to surmount unprecedented challenges in 2020. The institute's superb facility and safety management and operational platform ensured that DHVI's activities could continue apace amid the COVID-19 pandemic while protecting the health of its staff. DHVI's Diversity and Inclusion Committee also played a critical role to help address difficult but vitally important topics. We are immensely proud and grateful to all DHVI staff for pulling together as a community to support one another and continue fulfilling our mission.

The DHVI continues to leverage new innovative approaches to combat global public health threats as they emerge. One example is its current Good Manufacturing Practice (cGMP) program which enables DHVI to accelerate moving vaccines and therapeutics from basic science discovery to clinical trials. In 2019-20 the DHVI not only continued GMP production of critical HIV and influenza products but expanded its manufacturing capacity to include production of SARS-CoV-2 drug products.

In 2021, to accommodate a surge in sponsored research and rapidly expanding portfolio, the DHVI will expand into a 273,000 square foot facility in Research Triangle Park (RTP). The Alexandria Center for Life Science – Durham, also known as Duke@RTP, will be home to DHVI scientists from Duke School of Medicine's Departments of Surgery, Immunology, Pediatrics, and Medicine, as well as the Duke Collaborative Influenza Vaccine Innovation Centers.

We hope that you will enjoy reading this report and learning more about the institute and its programs.
AWARDS & HONORS

Munir Alam, PhD
Maria Blasia, PhD
Mattia Bonsignori, MD
Thomas Denny, MSc, MPhil
Barton Haynes, MD
Tony Moody, MD
Sallie Permar, MD, PhD
Wilton Williams, PhD

2019 Highly Cited Researchers, Cross-Field

Duke University School of Medicine Outstanding Leadership in Scientific Training at the Duke Center for HIV/AIDS Research

2019 Highly Cited Researchers, Cross-Field

Appointed Associate Dean of Duke RTP Campus

2019 Highly Cited Researchers, Microbiology, Immunology

Wilburt C. Davison Distinguished Professor of Pediatrics
E. Mead Johnson Award, Society for Pediatric Research
Duke University Research Mentoring Award for Translational Research
Duke University School of Medicine Outstanding Leadership in Scientific Training at the Duke Center for HIV/AIDS Research

HIGHLIGHTED PUBLICATIONS

Q Hahn, BF Haynes et al. (Cell)
Neonatal rhesus macaques have distinct immune cell transcriptional profiles following hiv envelope immunization.

KO Saunders, BF Haynes et al. (Science)
Targeted selection of HIV-specific antibody mutations by engineering B cell maturation.

M Blasi, M Klotman et al. (New England Journal of Medicine)
Detection of donor’s HIV strain in HIV-positive kidney transplant recipient.

CW Woods, EB Walter et al. (Vaccine)
An observer blinded, randomized, placebo-controlled, phase I dose escalation trial to evaluate the safety and immunogenicity of an inactivated West Nile virus Vaccine, HydroVax-001, in healthy adults.

R Goswami, SR Permar et al. (MBio)
Analytical treatment interruption after short-term antiretroviral therapy in a postnatally simian-human immunodeficiency virus-infected infant rhesus macaque model.

DHVI investigators authored more than 100 peer-reviewed publications in 2019-20. For a comprehensive list go to: dhvi.duke.edu/about-us/publications
TOP ACHIEVEMENTS

1. DHVI-led study reveals immune system can be coaxed into selecting key antibodies to fight HIV

2. DHVI completes GMP manufacturing and releases two HIV vaccine drug products for Phase I clinical trials

3. DHVI’s IVQAC plays integral role in Duke’s COVID-19 response by testing thousands of samples for SARS-CoV-2

4. DHVI study leads to the discovery of Fab-dimerized glycan-reactive antibodies that neutralize HIV and are prevalent in humans and rhesus macaques

5. DHVI publishes first study demonstrating structure-guided control of the SARS-CoV-2 spike protein for vaccine studies

6. DHVI receives Virology Quality Assurance Program contract to provide quality assurance and proficiency testing for virologic-based assays

7. DHVI builds mRNA vaccine and therapeutics platform and deploys for HIV, influenza and SARS-CoV-2 products

8. DHVI expands its vaccine production and live-virus capacity by building four additional GMP suites

9. DHVI selected to join the Collaborative Influenza Vaccine Innovation Centers (CIVICs) and serve as Manufacturing and Toxicology Core to improve the durability of seasonal influenza vaccines and develop a universal influenza vaccine
The DHVI is a highly collaborative research institute and a diverse community committed to the principles of excellence, fairness, and respect for all people. We believe that a diversity of perspectives will lead to the most innovative solutions for addressing the world’s public health problems. Visit the DHVI Diversity and Inclusion webpage for more information about current DHVI initiatives and upcoming events.

**DHVI Diversity & Inclusion Committee**

The DHVI Diversity and Inclusion committee is composed of faculty, staff, and students from the Research and Administration areas. The committee aims to promote and foster a diverse and inclusive environment that embraces individuality and acceptance, encourages openness and engagement, and leverages our collective differences to maximize the potential of the individuals and the institute. The goal of the committee is to raise awareness, diversify applicant recruitment and provide guidance, mentoring, and opportunities to all individuals within DHVI to foster the achievement of personal, professional, and Institutional goals.

In June 2020, the DHVI Diversity and Inclusion Committee launched the DHVI diversity and inclusion website. The website serves several purposes including but not limited to: celebrating the biomedical contributions of scientists and healthcare providers from diverse backgrounds, publicizing past and future DHVI Diversity and Inclusion events, and highlighting organizations and businesses that serve as resources for learning about different cultures.

In response to the recent tragic killings of Americans of color, the DHVI Diversity and Inclusion Committee created a series of virtual meetings called DHVI Perspectives. The DHVI Perspectives series provides a forum for DHVI employees to express questions, experiences, and reflections that bear on the racial and social injustices in our country. The goal is to build a sense of community within DHVI by trying to understand one another on a deeper level in order to create a more inclusive environment for everyone.

Discussion topics include:

- DHVI Employee Reflections on the George Floyd murder
- Interactions between the Community and Police
- Imposter Syndrome
- Past and present civil rights advocacy

The Diversity and Inclusion Committee hosted its first Diversity and Inclusion Summit in December 2020. The virtual half-day event included Keynote Speaker, Dr. Ada Gregory from the Kenan Institute for Ethics. The Summit covered topics such as implicit bias, organizational inclusiveness, allyship, and bystander interventions.
Dr. Kelly Soderberg supports DHVI leadership in managing administrative and scientific functions by advising the Director regarding key constituencies, providing context and background information on issues, and coordinating research projects and initiatives. Dr. Soderberg also oversees the grants program management team for DHVI and serves as the Associate Director for the Duke Consortium for HIV/AIDS Vaccine Development (CHAVD) program supporting Dr. Haynes.

Mr. Tom Denny oversees the daily operations of the DHVI and helps to develop long term strategic initiatives to assure that the DHVI remains scientifically competitive. He works with the leadership team to develop and implement best practices for each area of responsibility and to assure that the DHVI maintains the highest regulatory and financial compliance performance. Mr. Denny has been appointed Associate Dean of the Duke@RTP Facility.

Dr. Emmanuel Walter serves as the DHVI Chief Medical Officer and directs the Duke Vaccine and Trials Unit. He is the Principal Investigator of the NIH-funded Duke Clinical Core of the Collaborative Influenza Vaccine Innovations Centers (CIVICs). In these roles, Dr. Walter provides strategic and operational leadership for clinical research conducted at the institute. In addition, he provides oversight of regulatory compliance for DHVI clinical research activities.

Mr. Tom Denny oversees the daily operations of the DHVI and helps to develop long term strategic initiatives to assure that the DHVI remains scientifically competitive. He works with the leadership team to develop and implement best practices for each area of responsibility and to assure that the DHVI maintains the highest regulatory and financial compliance performance. Mr. Denny has been appointed Associate Dean of the Duke@RTP Facility.

Dr. Michelle Smith oversees all administrative and financial operations at DHVI. Dr. Smith works with leadership to ensure the appropriate infrastructure and processes are in place to support the DHVI’s research mission.

**WHY WE MAKE VACCINES**

Never have vaccines been more important than now. I work on vaccines because I have the opportunity to directly impact people’s well-being while solving some of the most fascinating problems in biology. It typically “takes a village” to develop vaccines, and through this work I have the opportunity to interact with brilliant scientist from other fields.

**Why do I make vaccines?**

Because vaccines save lives... and they do so by showing your immune system what to do when an undesired guest comes knocking at your door.

MARIA BLASI, PHD
Assistant Professor of Medicine
Vaccines can quickly and dramatically improve public health on a global scale. This has knock-on benefits for education, economic development and social equality.

ANDREW MACINTYRE, PHD
Assistant Professor of Medicine

In my early days of research training, an oft-uttered question in our group meeting was “what good will it do to mankind?” At that time, the translation of my basic research to applications in preventing human afflictions was not always a clear and direct path. After two decades of vaccine research, however, I take much satisfaction in saying “what better way to do good than to contribute towards developing vaccines that can prevent human suffering and death from infectious diseases.”

S. MUNIR ALAM, PHD
Professor of Medicine
The best defense against infectious diseases is to prevent them. As a medical student in Cameroon, I encountered patients with infectious diseases daily and realized that while as a physician I could help patients on a one on one basis, by contributing to the development of preventive measures such as vaccines, my work could have a global impact.

Growing up in India I witnessed first-hand the damage caused by infectious diseases, & the impact was much larger on the economically disadvantaged. By eliminating the threat of disease, vaccines not only protect health but are also tools for equality and justice.

Vaccines are training for the immune system, teaching the immune system how to deal with a problem before you get exposed. It’s like practicing self-defense. You hope you never need it, but when you do, it can really help.

I make vaccines because the most effective way to end the world’s most common and deadly diseases is to prevent them!

Jamaican sprinter Usain Bolt couldn’t have become the fastest man on earth without proper training. So too does the immune system, [it] needs to be trained by vaccines to generate lightning-fast responses to the myriad of pathogens we encounter in our environment.
HIV

DHVI Closes in on an HIV Vaccine

The Human Immunodeficiency Virus (HIV) has been a formidable foe, both in the body, where it escapes the immune system, and in the lab, where it has eluded efforts to create a vaccine.

Today, however, years of painstaking research and technological advancements are bearing fruit. More work remains to be done, but scientists at DHVI and their collaborators now have the tools, the know-how, and the plan to create a vaccine that will protect against HIV.

Leading the Charge for Decades

DHVI has been leading the HIV vaccine effort since 2005, when it received a $300 million dollar grant from the National Institute of Allergy and Infectious Diseases (NIAID), which is one of the National Institutes of Health (NIH).

The goal of the funding was to create the Center for HIV/AIDS Vaccine Immunology (CHAVI), which would tackle the vaccine challenge through team science. The center facilitated and prioritized collaboration and cooperation among a large group of people and institutions with complementary skills. Barton Haynes, MD, the Frederic M. Hanes Professor of Medicine and the director of DHVI, directed the center.

The CHAVI team went to Africa, the epicenter of the HIV epidemic, to study people who became infected, including the subset of people whose bodies eventually began making antibodies called broadly neutralizing antibodies, which are thought to be protective. In this first grant, the CHAVI team identified the roadblocks that had prevented the vaccine field from making a successful HIV vaccine despite 20 years of effort.

Since then, DHVI has received two more major grants from NIAID to continue the work on the HIV vaccine: the Center for HIV/AIDS Vaccine Immunology-Immunogen Discovery (CHAVI-ID) from 2012-2019, and the Consortium for HIV/AIDS Vaccine Development (CHAVD) from 2019-2026.

All together, the three grants total $639 million over 21 years and have funded investigators in Africa, Europe, and the United States.

With the second grant, CHAVI-ID, the team studied how the virus and antibodies evolved in HIV-infected individuals and mapped out how broadly neutralizing antibodies develop, thereby creating a blueprint for a vaccine design.

Now, with the third grant, CHAVD, the team is producing vaccine candidates for testing in human clinical trials. “The first grant was to figure out what the problem was, the second grant was to figure out what to do about it, and now, with the third grant, we’re implementing those solutions,” says Haynes.

Major funding has also come from the Bill and Melinda Gates Foundation. In 2005, the Gates Foundation supported DHVI with two grants to Haynes through the Collaboration for AIDS Vaccine Discovery and since has supported work by David Montefiori, PhD, professor of surgery; Georgia Tomaras, PhD, professor of surgery; and Sallie Permar, MD, PhD, professor of pediatrics, molecular genetics & microbiology, immunology, and pathology. In 2012, the Gates Foundation began supporting the DHVI Protein Production Facility led by James Peacock, PhD; Matthew Johnson, PhD; and Haynes. This facility makes HIV envelope proteins and antibodies for the Gates-funded investigators and also serves as a DHVI core facility.
New Vaccine Strategy Proves Promising

This past year, DHVI scientists offered proof-of-concept for a vaccine strategy that will guide the body’s immune system through the necessary steps to create antibodies that can neutralize multiple strains of the virus. The research, published in the journal Science in December 2019, shows that the strategy is feasible and lays out a path to success.

Some people infected with HIV are able to make neutralizing antibodies on their own, but it takes three to five years, by which time the virus has long since infiltrated cells and tissues. If these broadly neutralizing antibodies could be spurred to develop before exposure, they could prevent infection.

“The problem has been the body doesn’t want to make the kinds of antibodies that we need to fight off the virus,” Haynes says. “So we’re learning how to guide the immune system to go where we want it to go—in other words, we’re learning how to engineer the immune system.”

To engineer the immune system, first researchers had to discover the evolutionary pathway along which run-of-the-mill antibodies accrue mutations in order to transform into broadly neutralizing antibodies. But that’s only half the battle; they also have to figure out how to prod the immune system to take that pathway. DHVI researchers and collaborators have made great progress in these efforts and, in the December 2019 paper, showed how they could spur the first step along such a pathway in mice and non-human primates. To guide the immune system to take all the steps, in the right order, will likely require a series of vaccinations.

Kevin Saunders, PhD, assistant professor of surgery and DHVI director of research, says, “It gives us a clear path. When people ask when is the vaccine coming, we always say we don’t know the exact time but we know what we have to do to get there.”

Getting there will require the kind of team-based big science that has been a hallmark of DHVI and the HIV/AIDS consortium Haynes leads.

Team Science Makes it Work

The step-wise vaccine strategy has grown out of 15 years of immunological research. Dozens of labs, at DHVI and beyond, have built up this base of knowledge and continue to collaborate to push the field forward. The work is iterative, with each effort informing and improving the work of others.

Just as important has been the development of new technologies, including the ability to isolate antibodies from blood, build antibodies and other proteins in the lab, and visualize microscopic antibodies and virus particles.

Priyamvada Acharya, PhD, associate professor of surgery, uses a piece of equipment called the Titan Krios cryo-electron microscope to take incredibly detailed pictures of individual HIV proteins and antibodies. Seeing their structures at the atomic level allows her to understand their behavior and function. She can look at samples from a pre-clinical study to see how an antibody produced by an immunized mouse interacts with the outer part of HIV, called the envelope. “Our job is to get pictures of various stages of antibody development in complex with the HIV envelope,” she says. “We can say, ‘Guys, this is eliciting antibodies that we think will develop into good antibodies,’ or ‘This is bad, it’s binding to a site that is variable, so there is no way this will go on to become a super-potent antibody.’”

Researchers in her lab also use computational biology to reverse engineer the structure of various proteins, like antibodies or proteins on the HIV envelope, so that other labs can create these proteins and test their function.
Guiding the Immune System, Step by Step

Antibodies are manufactured by B cells. In order to respond to a novel pathogen, B cells in the lymph nodes and spleen engage in hyper-mutation. Most of the mutations will be useless, but some will create antibodies that are able to clear the pathogen from the body. This works well for the common cold, but HIV is devilishly tricky, so a long series of mutations, some quite rare, are needed to create B cells that can crank out HIV-neutralizing antibodies.

Kevin Wiehe, PhD, associate professor of medicine, helps elucidate that long series of mutations. Starting with genetic sequences from a group of effective antibodies, Wiehe uses computational methods to discover the genetic sequence of the likely common ancestor of those antibodies.

“We work backwards from what we can see to what we estimate is the starting point,” Wiehe explains. “We call it the reconstruction history of that B cell lineage. The question we’re asking is, ‘What does the original antibody sequence look like that has no mutations?’ If those starting points exist in people, we can make a vaccine that targets those starting points.”

In addition, Wiehe identifies milestone mutations along the evolutionary pathway. Combining this with studies of actual antibody development over time in infected individuals lays out the roadmap the immune system needs to follow.

Using Wiehe's genetic sequences, other researchers can make and test the antibodies. “Kevin Saunders is the protein wizard,” he says.

Saunders' lab, in addition to making antibodies, also makes immunogens, which are proteins that encourage antibodies to evolve in the desired direction. Saunders has designed an immunogen consisting of a naturally occurring nanoparticle covered in synthetic spikes that mimic a particular aspect of the HIV envelope. Gathering the spikes on a nanoparticle creates a “virus-like particle” that gets the attention of the immune system more effectively than solo spikes would.

This type of particle worked well in the proof-of-concept study, demonstrating its ability to selectively boost the production of antibodies with desired mutations.

“We’ve made one envelope that can select some of the early changes,” Saunders says. “Now we need to make two or three envelopes that can get the rest of the changes we need. That is our challenge.”

Helping Vaccines Work Better

In addition to designing and testing immunogens for the step-wise vaccine strategy, DHVI researchers are also investigating other aspects of immunity and vaccination. One of these areas is the study of adjuvants, which are compounds that can be added to vaccines to set the stage for a positive immune response.

This past year, DHVI researchers demonstrated in animal studies that a cancer drug called ipilimumab, which modulates the immune system, can support the work of B cells during vaccination.

The implication? “We can think about a vaccine where we can temporarily adjust or fine tune the immune system to give a little stronger response,” says Cain, who is studying lipid nanoparticles as adjuvants.
Probing the Secrets of the Child’s Immune System

Another major area of interest at DHVI is understanding—and harnessing—differences between the immune systems of children and adults.

Genevieve Fouda, MD, PhD, associate professor in pediatrics, studied samples from HIV-infected children and found that the children generated neutralizing antibodies more frequently than adults did, and faster. “That has very important implications for vaccination,” Fouda says, “because it could mean the early immune system presents advantages over starting a vaccine regimen later in life.”

Haynes and his lab recently led a study in non-human primates that also suggested early-life vaccination might be advantageous. The study describes differences in the behavior of many different kinds of immune cells in vaccinated infants compared to adults. Taken together, the differences create an immune landscape that encourages the production of the desired antibodies after vaccination.

Childhood vaccination could hold other advantages as well, according to Sallie Permar, MD, PhD, professor of pediatrics, molecular genetics & microbiology, immunology, and pathology. “Once children have finished breastfeeding, they aren’t at risk [of HIV exposure] until adolescence and sexual debut,” she says. “That gives us a window of time that we can use to train the immune system to make those protective broadly neutralizing antibodies.” Furthermore, children are much more likely than adults to actually receive vaccines, because most visit the doctor more often than adults and adhere to a standard immunization schedule.

Permar is involved in a study to further illuminate the differences between the immature and mature immune system. She and others will evaluate samples from a clinical trial in which infants born to mothers with HIV will receive a vaccine containing an immunogen developed at DHVI. The immunogen was previously used in a study with adults so the team will be able to compare the immune responses between the two age groups.

“We know that in the absence of any treatment, a high percentage of women don’t transmit the virus to their baby. It’s possible these women have some kind of mechanism through which the infants are protected.”

Permar and Fouda also study the mechanics of mother-child transmission, which can occur during pregnancy, delivery, or breastfeeding. Each year, more than 150,000 babies born to HIV-infected mothers become infected this way. Antiretroviral medicines can prevent mother-to-child transmission, but even in the absence of such medicine, only 30-40% of mothers pass the virus on to their babies. Understanding why transmission doesn’t always occur could help scientists devise strategies to protect babies.

Fouda says, “We know that in the absence of any treatment, a high percentage of women don’t transmit the virus to their baby. It’s possible these women have some kind of mechanism through which the infants are protected.” One factor may be maternal antibodies, only some of which cross the placenta to the fetus. Last year, Permar, Fouda, and colleagues discovered a mechanism that seems to determine which antibodies make the transfer. Being able to manipulate which antibodies get passed on—perhaps with a maternal vaccine—could help protect babies from HIV.

HIV Vaccine Evaluation

HIV is too wily to attack on only a single front, so multiple vaccine approaches are going forward simultaneously at DHVI and elsewhere. These various approaches are tested in clinical trials carried out at sites worldwide through the HIV Vaccine Trials Network (HVTN).

DHVI’s Georgia Tomaras, PhD; David Montefiori, PhD; and Guido Ferrari, MD, all in Duke’s Department of Surgery, have long-standing leadership roles in HVTN. In their respective labs, they do collaborative and complementary work to evaluate blood samples from HVTN clinical trials to look for the presence of neutralizing antibodies as well as other antibodies called binding antibodies. Their work helps identify the most promising vaccine candidates.

Wilton Williams, PhD, assistant professor of medicine is evaluating some HVTN trial samples in his lab to look for evidence of B cells that produce the antibodies the vaccines were intended to elicit.
“We are determining the capacity of candidate HIV vaccines to generate a response that we think leads to protection from future infection,” Williams says. “We know the antibody features that will likely confer protection so that gives us a blueprint result to look for.”

Some of the trials carried out by HVTN include vaccine candidates designed at DHVI, and in some cases produced in DHVI’s current Good Manufacturing Practice (cGMP) facility.

**DHVI Infrastructure Allows Responsiveness**

The GMP facility means that DHVI can manufacture clinical trial materials—from antibodies to immunogens to vaccines—quickly, facilitating laboratory research, pre-clinical trials, and Phase I human trials. The GMP team is led by Matthew Johnson, PhD; Amy Caparoni is the Director of GMP Operations.

Another major piece of infrastructure that underlies DHVI’s success is the Regional Biocontainment Laboratory (RBL) led by Greg Sempowski, PhD, professor of medicine and pathology. The RBL is an NIH-funded facility that can safely house research related to dangerous pathogens.

DHVI is also home to hundreds of thousands of samples of human blood and tissues, collected and stored over the years for research. The samples are used not just by researchers at Duke, but by institutions around the world. The collection spans many years and continues to grow, making it a valuable resource for research.

The repository is “fantastically important” says Tony Moody, MD, associate professor of pediatrics, who is head of accessioning and distribution. “The samples first collected in the CHAVI program [in the mid-2000s] are still important and maintaining them is an incredibly valuable resource,” he says. “We’re continuing to ask questions based on what was collected then.”

When Permar and Fouda discovered the mechanism that determines which antibodies are passed from mother to baby, they used samples from the repository collected as part of an NIH-funded study years ago, before the availability of the antiretroviral treatments that make transmission less common.

**A Sense of Promise. . . and Urgency**

After decades of research, it’s encouraging to see the results of that work starting to pay off in the promise of an effective vaccine. Yet much work remains to fully realize that promise, and scientists at DHVI and the HIV/AIDS consortium feel an urgency to complete that work.

Last year, 38 million people worldwide were living with HIV, and another 1.7 million became newly infected. These people are the motivation behind all of the HIV research at DHVI.

About 5,500 teenage girls and young women become infected each week. We can’t forget that. We’ve made tremendous progress in the last 15 years, but we’ve got to work hard and finish the job.

Barton Haynes, MD
DHVI Attacks COVID-19

When the novel coronavirus began to spread across China, DHVI researchers sprang into action and they haven't slowed down since. They are collaborating with each other and with other institutions to unlock the secrets of the virus that causes COVID-19 and to develop tests, vaccines, and treatments.

“We've done more work faster than we have ever done before, making real progress on antibodies, tests, and a vaccine,” says Barton Haynes, MD, the Frederic M. Hanes Professor of Medicine and the director of DHVI.

DHVI researchers are attacking the new virus by applying knowledge, experience, and technology gained from years of working with HIV, influenza, and other viruses.

“All the work we've done has allowed us to transition on a dime,” Haynes says. “All the vaccine constructs we've developed were immediately repurposed for COVID-19.”

And vaccine designs are only the tip of the iceberg. DHVI faculty are also developing and running assays and tests, accessioning and distributing blood and tissue samples for studies, and isolating antibodies from infected individuals. Using approaches from a number of different disciplines, they are beginning to put together a holistic picture of how the immune system and the novel coronavirus interact.

Two long-running programs at DHVI set the stage for the swift response. One is the HIV vaccine research program funded by the National Institute for Allergy and Infectious Disease (NIAID), a series of three grants that have provided continuous funding since 2005. The other is a pandemic preparedness program funded since 2017 by the Department of Defense's Advanced Research Projects Agency (DARPA).

The DARPA Pandemic Preparedness Platform (P3) seeks to develop strategies, technologies, supply chains, and expertise to make it possible to rapidly produce antibody-based treatments for any novel pathogen. These treatments, which can also be used for temporary prevention, are sometimes called passive vaccines or medical countermeasures.

Greg Sempowski, PhD, professor of medicine and pathology and leader of the P3 program, says, “I’m incredibly proud of how well our staff and scientists have stepped up. They have worked very long hours to quickly bring on all the systems needed to support this type of research. It’s not easy. Having really high-quality people who are committed is an enormous asset.”

DHVI's work on COVID-19 is being supported with emergency funding from the National Institutes of Health (NIH), supplements to existing grants, and $17 million dollars from the North Carolina legislature.

Antibodies as a Treatment and Preventative

Antibodies play a crucial role in the development of vaccines, antibody treatments, and even some kinds of COVID-19 tests, so the first order of business was discovering antibodies capable of neutralizing the new virus, SARS-CoV-2.

“Once we have the antibodies in hand, there are lots of different things we can do with them,” says Michael “Tony” Moody, MD, associate professor of pediatrics. “The key thing is getting the antibodies in hand.” Moody’s lab was one of several that collaborated to do just that.

DHVI researchers isolated more than 2,500 antibodies from individuals infected with COVID-19 in only ten weeks—a remarkable feat.
Kevin Saunders, PhD, assistant professor of surgery and director of research at DHVI, says, “The antibody isolation technique that we use was developed under our HIV grants over the last 15 years. We’ve really learned how to do that quickly and in depth. That’s why we could get to 2,500 antibodies in a matter of weeks.”

Of those antibodies, DHVI scientists have identified some with potent and complementary neutralizing powers against SARS-CoV-2. Together or individually, these antibodies could be a powerful treatment for people in the early stages of infection. They could also be used as a temporary preventative for people at high risk of exposure, such as healthcare workers.

One of these antibodies will be tested as a preventative in a Phase I trial in early 2021. Rather than manufacturing the antibodies, which is very time consuming, DHVI will manufacture mRNA molecules, the genetic blueprints that tell the body how to make the antibodies.

This effort is being supported by an additional $7.6 million grant from DARPA. Emmanuel “Chip” Walter, MD, MPH, professor of pediatrics, who directs the DHVI Clinical Trials Unit, will be running the trial. The manufacturing will happen onsite in DHVI’s current Good Manufacturing Practice (cGMP) facility, directed by Matthew Johnson, PhD.

These potent antibodies are also being used to create a test for COVID-19. Because they bind so well to the virus, the antibodies will attract SARS-CoV-2 like a magnet. This type of test could be faster and less expensive—and therefore more widely available—than polymerase chain reaction (PCR) tests.

**Active Vaccines**

A long-lasting vaccine, sometimes called an active vaccine to distinguish it from antibody treatments, is also a priority at DHVI.

An active vaccine spurs the body to create not only effective antibodies, but also “memory” cells that can churn out more of those antibodies in the future if needed.

Dozens of vaccine candidates are already being manufactured and tested around the world. This first wave of vaccines will doubtless slow down the spread of COVID-19, but it’s possible, even expected, that they will provide less than full protection.

DHVI is working on vaccines that will plug some of the holes. “We’re thinking about a second wave of vaccine with enhanced immunogenicity,” Saunders says. DHVI vaccines may be able to provide a boost to some of the front runners if they turn out to have a low potency or not to be effective in a particular population, such as older adults.

A multidisciplinary understanding of SARS-CoV-2 antibodies is crucial to this effort. “We really go deep,” Saunders says. “We’ve looked at a more global picture of antibody response.” That global picture is the necessary foundation for designing a highly effective vaccine.

“The power of the DHVI is that we have people who think about the problem in a different way, but we all come together and use our skill sets to make the biggest impact on the same problem,” Saunders says.
Kevin Wiehe, PhD, associate professor of medicine, studies the genetic sequences of antibodies using computational methods. He looks at how the antibody sequences from people with COVID-19 evolve as the infection progresses. “We normally do very deep sequencing so we can get hundreds of thousands of antibody sequences from an individual at any time point,” he says. “We can see the initial antibody response, which is potentially different than the [mature] antibody that occurs later.”

Other DHVI scientists are looking at the other side of the equation—the virus. SARS-CoV-2 is covered with spike proteins that allow the virus to infect cells. These spikes are where antibodies attach.

Rory Henderson, PhD, assistant professor of medicine, uses computer simulations to identify mutations in the spike protein that alter its shape, or conformation. In an actual infection, spike proteins change conformation frequently. But in a vaccine, some of these conformations will do a better job than others at spurring the immune system to produce effective antibodies. “It’s been remarkable how quickly we were able to go from not knowing anything about the coronavirus to having these designs,” Henderson says. “If one of the shapes is preferred, we already have that particle ready for a vaccine.”

“DHVI is pretty well positioned because of its experience with HIV, ranging from vaccine discovery to the ability to implement clinical trials. Shifting to COVID was challenging, but we had the resources to do it.”

Priyamvada Acharya, PhD, associate professor of surgery, puts it this way: “We have been studying a very difficult virus for a long time—HIV. So we have gained some superpowers.”

Acharya examines the engineered spike proteins at the atomic level in the Titan Krios cryo-electron microscope to make sure their shape is what was expected. Then the spikes can become ingredients in vaccines, either as mRNA or manufactured proteins. Indeed, some are already being evaluated in animal studies. Acharya uses the cryo-EM to take a look at samples from the studies to see if good antibodies are being produced and how they interact with the spike. So far, the results have been promising.

A Multidisciplinary Picture

While DHVI researchers are working on new-and-improved vaccine designs, they are also participating in the nationwide effort to get the first wave of vaccine candidates evaluated as quickly as possible by serving as a clinical trial site. Phase II and III clinical trials require tens of thousands of volunteers at multiple sites across the country. DHVI enrolled more than 80 volunteers for the Phase II/III trial of the Pfizer vaccine candidate, and is gearing up to participate in even larger trials later in the fall.

Walter, who is leading this effort as head of the DHVI Clinical Trials Unit, says, “DHVI is pretty well positioned because of its experience with HIV, ranging from vaccine discovery to the ability to implement clinical trials. Shifting to COVID was challenging, but we had the resources to do it.”

Walter also leads Duke’s participation in the nationwide series of trials to test treatments for patients hospitalized with COVID-19. The first trial studied remdesivir alone, and subsequent trials tested it in combination with other medicines. “The first study showed decreased time hospitalized for patients who got remdesivir, hence it became standard of care,” Walter says.
**Testing and Diagnostics**

Beyond vaccines, DHVI is also pursuing other avenues, including testing and diagnostics. Thomas Denny, DHVI chief operating officer, and his lab helped out with testing in the early days of the pandemic, when clinical labs were over-saturated. Denny and others at DHVI also designed and implemented the surveillance testing of students, staff, and faculty when students returned to campus in the fall.

Denny is also working on designing more sensitive assays that can determine not just whether the virus is present or not, but in what amounts. “With a lot of viral infections, like HIV, we’ve learned over the years that being able to quantify the viral amount has been useful as a signal with respect to disease prognosis or response to therapy,” he says. If the same is true for COVID-19, that information could be used to guide clinical decisions. Denny is analyzing samples from COVID-infected adults and children who are participating in observational studies at Duke. He will compare the results of his assays with notes on their clinical condition to look for correlations between viral load and disease progression.

Denny’s lab also developed assays to look for antibodies to SARS-CoV-2 in the blood, which could, among other things, be used in seroprevalence studies to show how many people have recovered from COVID-19.

**The Immune Response as Diagnosis**

Christopher Woods, MD, MPH, professor of medicine, and his team are coming at diagnostics from a different direction—looking at the immune response. The idea is that samples from an infected person will contain not only the pathogen, but also biochemical signals of the immune response. In fact, the immune signals may be easier to detect in early stages of infection than the pathogen, which is only just beginning to multiply. Woods has a track record in this area: he and his team have been able to distinguish viral from bacterial infections based on the immune response, and to identify infections 36 to 48 hours before the onset of symptoms.

“We have not had great success [in the past] being able to distinguish different types of viral respiratory infections,” he says. “Until COVID.” He and his team have found a unique signature in blood samples that indicates the immune system is mounting a response to SARS-CoV-2 infection. The samples used in that study were from people who were past the early stages of infection, but Woods is planning future studies to see if the signature is present in the pre-symptomatic phase of COVID-19. If so, a diagnostic test for that signal could help curb the spread of the disease and allow earlier treatment.

**The Immune Response to COVID-19 in Children**

Sallie Permar, MD, PhD, professor of pediatrics, molecular genetics & microbiology, immunology, and pathology, is working to understand the immune response to COVID-19 in children. Although children do get the disease, they are more likely to have no or few symptoms than adults. However, some children experience a severe inflammatory reaction to COVID-19, called Multisystem Inflammatory Syndrome in Children (MIS-C).

“Not only do we want to understand what about infant or pediatric infections leads to the lack of disease during the acute infection,” Permar says, “but also what are the factors that lead to post-infection inflammatory syndrome?”
To help answer some of these questions, Permar and Maria Blasi, PhD, assistant professor of medicine, are doing a study in non-human primates to track the immune response over the course of infection in adults and infants. They are also studying adult and infant lung cells in the lab to see how the cells respond to infection.

DHVI researchers are also studying children in several ongoing observational trials. These trials include infected children as well as children who are uninfected (at least initially) but living with someone who is. The children are being followed over time to learn more about immune activity and clinical symptoms during infection, recovery, and beyond. “We don’t yet know what a long-term response to the coronavirus is,” Permar says. “We’ll be studying them for at least a year.”

**A Vaccine for Future Coronavirus Pandemics?**

While the Haynes, Saunders, and Sempowski labs were isolating antibodies from COVID-infected individuals, they also looked at a sample from a person who had been infected with another pandemic-causing coronavirus—Severe Acute Respiratory Syndrome (SARS)—in 2003. They discovered that some of the SARS antibodies from that individual also neutralized SARS-CoV-2.

That raised a tantalizing question: Might it be possible to design a vaccine that elicits cross-protective antibodies? Such a vaccine—a pan-coronavirus vaccine—would protect against multiple coronaviruses, including Middle East Respiratory Syndrome (MERS), which emerged in 2012, as well as other as-yet-unknown coronaviruses.

“SARS-CoV-2 is not a one-off event,” Saunders says. “There seems to be a coronavirus pandemic every eight to ten years. We’re looking at the future pandemics and trying to predict what that will look like and to see if we can generate immunity for those types of viruses.”

DHVI has already begun working with scientists at UNC-Chapel Hill on a pan-coronavirus vaccine.

“It’s only a matter of time before the next coronavirus outbreak,” Haynes says, “and we will be ready for it.”
Preventing the Next Flu Pandemic

Even in the midst of the COVID-19 pandemic, DHVI researchers are preparing for the next influenza pandemic. “It’s not a matter of if, but when,” says DHVI director Barton Haynes, MD, the Frederic M. Hanes Professor of Medicine.

DHVI is part of an ambitious project to create a universal flu vaccine, which would protect against multiple familiar strains, as well as strains that we’ve yet to see.

The effort is backed by funding from the National Institute of Allergy and Infectious Diseases (NIAID), announced in September 2019, that could total up to $400 million for DHVI over the next seven years.

The funding is part of a larger NIAID effort called CIVICs (Collaborative Influenza Vaccine Innovation Centers), which also includes researchers at the University of Maryland School of Medicine in Baltimore, the Icahn School of Medicine at Mt. Sinai, the University of Georgia in Athens, and Digital Infuzion, Inc.

DHVI is receiving funding for three components of the work: vaccine discovery, vaccine manufacture, and clinical trials. Michael “Tony” Moody, MD, associate professor of pediatrics, is PI for vaccine discovery; Matthew Johnson, PhD, is PI for manufacturing; and Emmanuel “Chip” Walter, MD, MPH, professor of pediatrics, is PI for clinical trials.

Much of the research and clinical work will take place in the Research Triangle Park, at a 273,000-square-foot facility being leased by the School of Medicine to facilitate work on flu and HIV. Vaccine manufacturing will occur in five state-of-the-art manufacturing suites on Duke’s main campus.

Flu: An Ever-Changing Virus

Flu, which kills between 12,000 and 61,000 Americans each year, is a varied and changeable virus with many subtypes, all of which are prone to mutating. Eradicating flu is not likely because it flourishes in poultry and swine, with new strains periodically jumping to humans. Current flu vaccines prevent untold suffering and death each year, but there’s room for improvement. Protection wanes rapidly after a few months, unlike vaccines for diseases like measles and tetanus. That’s one reason flu shots are an annual affair. Another reason is that the combination of strains circulating varies over time. Scientists have to predict which three or four strains will be the most widespread during the coming year’s flu season, and, because of the lengthy manufacturing process, they have to make these predictions months in advance. If the prediction is off, the vaccine doesn’t work as well. Even when it’s a good match, the vaccine is less effective in older adults, who are particularly vulnerable to flu.
Perhaps most worrisome, current flu vaccines protect only against strains already in the human population, not against future pandemics. A pandemic begins when a new strain jumps from an animal to a human, and evolves to spread from human to human. Right now, there are several novel flu strains that are widespread in animals and have shown their ability to jump to humans. So far, none of these strains has become efficient at human-to-human transfer. But it's only a matter of time before that happens—with a known strain or a brand-new one.

**Right now, there are several novel flu strains that are widespread in animals and have shown their ability to jump to humans.**

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**Toward a Universal Vaccine**

The home run would be creating a vaccine that offers permanent or multi-year protection in all populations against multiple strains of influenza, including those yet to emerge. That might be possible if researchers can identify a vulnerable region on the covering of the virus that is the same in many or most flu strains. If a vaccine could spur the development of antibodies capable of targeting that vulnerable region, it would offer protection against every flu virus possessing that Achilles’ heel.

Another possibility is creating a “cocktail” of vaccine agents that would add up to broad immunity when taken together. Moody is pursuing both avenues with his team at DHVI and the rest of the CIVICs group.

Between here and the home run, however, are many smaller yet productive gains, including better protection in older adults, longer-lasting protection, and faster manufacturing processes, which would push back the deadline for predicting next season’s circulating strains.

“We don’t want to let the perfect be the enemy of the good,” Moody says. “Ultimately we want to make a universal vaccine, but we’re not going to give up better along the way just because we haven’t gotten to perfect.”

Animal studies are underway, and human studies aren’t far behind. One of the first will be a human trial testing ways of making the current vaccine more effective in older adults by increasing the dose and adding an immune-boosting adjuvant. “Even a small step in improving the seasonal flu vaccine can have a large effect,” Walter says.

As the head of clinical trials, Walter plans to make use of a challenge model in some studies, in which participants are vaccinated with either a vaccine candidate or a placebo and then purposefully exposed to the flu. “Challenge studies can be used to evaluate vaccine candidates in a more efficient manner than studies of tens of thousands of people,” Walter says. Large numbers of volunteers are needed for a statistically sound experiment when only a minority will encounter the pathogen, but far fewer are needed when all will be challenged with the virus.

Challenge studies require careful selection of a strain of flu strong enough to cause symptoms, but not severe enough to be dangerous. “We’re getting our challenge model straightened out now at the same time as [others are] developing vaccine candidates,” Walter says, “and then we can merge the two efforts.”

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“We’re always chasing our tail trying to predict what the next pandemic will be, and racing to try to test vaccines. The fix to that problem is a vaccine that’s more broadly protective, a more universal vaccine.”

Emmanuel “Chip” Walter, MD, MPH
Manufacturing Vaccines

Vaccines designed at DHVI can also be manufactured at DHVI, in the current Good Practice Manufacturing facility, run by Johnson. “If we didn’t have the GMP facility,” Johnson says, “it would add at least a year to the timeline of being able to take something out of the research world and get it manufactured for testing.”

The GMP facility, which has five manufacturing suites, is small compared to commercial plants, but it has the equipment and experienced personnel necessary to manufacture FDA-compliant products that can be used in small trials. “Our facility is nimble and flexible so we can follow the science,” Johnson says.

The flexibility of the GMP program is especially important because DHVI will be evaluating a variety of vaccine constructs. Current flu vaccines use proteins grown in mammalian cell culture or in chicken eggs, but some newer vaccine candidates are made of mRNA molecules, which are like genetic blueprints that tell the body how to build the proteins. “These vaccines are wildly different,” Johnson says, “but we can switch from one to another in under a month.” In a large commercial plant, retooling can take months or even years.

Manufacturing a vaccine is not just following a recipe, and Johnson says much of the team’s time is spent on development, which includes choosing equipment, creating procedures, and sourcing pure and traceable ingredients. The protocols are designed to be easily adapted to a larger scale should the products prove successful.

Being in close contact with Moody, Walter, and others who are designing the vaccines and clinical trials streamlines development because the work in each area informs the others.

“It’s unique that we have research, development, and manufacturing and the clinical teams all working together,” Johnson says. “In the first year of working on the program, it’s been tremendous in being able to get real-time feedback. It’s speeding up our timelines and making us more efficient.”

Protein Production Facility Director James Peacock and GMP Scientist George Barrett monitor the gas exchange in one of DHVI’s bioreactors
The DHVI Training and Mentoring Program (DTMP) was established to enable students, postdoctoral scholars & associates, clinical fellows, and early career faculty to develop into independent scientific professionals. The program offers training in a collaborative and nurturing environment for the next generation of biomedical researchers in vaccine immunology. The goal of this program is to expand each trainee’s knowledge base and confidence through the use of customized curricula and state-of-the-art technology and core facility resources available to trainees at the DHVI. The program provides mentoring, research seminars and lectures, journal clubs, training in research ethics, scientific writing and presentation to present individual research, and fosters community by providing opportunities for research collaboration. Additionally, the program seeks to create a safe environment where trainees can share any concern they might have.

Monthly meetings, where a variety of topics were discussed, including individual development plans, letters of support, career progression and transition, time management, ways to improve oral presentation skills, were well attended. To foster the trainee community, other social events were held. The DTMP trainees participated in a community service project where they packed and donated 68 hygiene kits for Urban Ministries of Durham.

The DTMP went virtual due to the pandemic, continuing with weekly Journal Clubs and hosting open discussions about science and policies and how to effectively communicate science to the general public. We hosted a DHVI Virtual Trainee Retreat in December 2020 for trainees to present their work.

In 2020-21, the DTMP looks forward to continuing with programming and mentoring that benefit and offer opportunities for trainees to connect and grow in their career paths. We will establish community outreach opportunities, participate in a community service project, and utilize resources and guest speakers inside and outside of the Duke community to educate and train members on a wide variety of topics. We are excited about the addition of new trainees in the coming year and to continue mentoring the scientists of tomorrow.

The goal of this program is to expand each trainee’s knowledge base and confidence through the use of customized curricula and state-of-the-art technology and core facility resources available to trainees at the DHVI.

In 2019-20, the DTMP had 37 members

- Female: 61%
- Male: 39%

undergraduate students: 8
graduate students: 12
MD/PhD students: 2
postdocs: 15

There are some common issues that we all face as scientists and by sharing experiences I faced as a trainee with others I hope to positively impact careers and quell any possible concerns those younger than me may have.

Dr. Maria Blasi
Co-Director, DTMP

49% presented at conferences and meetings
40% published (30% as first author)
The DTMP has been a beneficial experience for me because I have made connections with other trainees at various levels of study as well as faculty guests who come to meetings to share valuable information and tips for success in various aspects of science, including presentations, fellowship/grant applications, letters of support, etc.

Claire Otero
Graduate Student

Dr. Wilton Williams | Co-Director, DTMP

The DTMP has helped me build a sense of camaraderie both professionally and personally. Most of the programs are focused on ever challenging needs of a trainee and they do make me feel supported. Overall, it is a great program and provides beneficial support network for postdoctoral and graduate trainees alike.

Stella Berendam | Postdoctoral Associate

The DTMP provides a channel not only for the trainees to communicate with each other, it also bridges us to the senior immunologists and vaccinologists working in DHVI. This helps us gain insights about science and future career paths.

Jui-Lin Chen | Graduate Student

The DTMP has been a huge value for me as a postdoc. The DTMP has provided numerous professional development opportunities that have been an added value to my trainee experience. These include improving my presentation skills, learning more about various careers within the biomedical field and sharpening my critical thinking and experimental design skills. In addition, the DTMP provides the opportunity to connect with other DHVI trainees to share experiences with and ask questions to when I am needing support.

Stephanie Langel | Postdoctoral Associate

This program has helped me build more authentic professional relationships with near peer scientists, and those farther along in their career for mentorship. I feel more open in reaching out to other vaccinologists for valuable scientific and career guidance discussions. The DTMP has cultivated a community that allows me to more tangibly envision my next steps in my scientific training.

Tulika Singh
Graduate Student

The transition to a postdoc after earning my PhD was not easy and I experienced many challenges and frustrating moments. Until I joined the DTMP, I thought no one else was experiencing similar issues as me; now, being in a room of my peers and hearing they too have similar problems has been invigorating! The DTMP provides a safe space to discuss our concerns, ask questions, get advice, and get to know our colleagues better. Our meetings have been my therapy session and prescription for when an experiment didn't work. The DTMP meetings have been very influential in helping me narrow down my options and provide resources that I did not know existed.

Dr. Letitia Jones
Postdoctoral Scholar

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In July 2019 the DHVI launched the Duke Consortium for HIV/AIDS Vaccine Development (CHAVD) program. The Duke CHAVD is supported by the third in a series of seven-year NIAID/DAIDS programs awarded to the DHVI as a leader in HIV immunology and vaccine science. Under the direction of Barton Haynes, MD, the CHAVD program harnesses collaborating investigators from across intuitions to address key immunological roadblocks to HIV-1 vaccine development, and design, develop, and test novel HIV-1 immunogens and adjuvants.

To obtain an effective HIV vaccine, the CHAVD team is designing immunogens that, when administered through a series of vaccinations, prompt the human immune system to produce specific types of bnAbs that have been found highly effective in preventing HIV infection. Immunogens designed by the Duke CHAVD team are downselected for GMP manufacturing, then tested in small, iterative Phase I clinical trials in collaboration with the HIV Vaccine Trials Network (HVTN). These small and fast trials rapidly elucidate whether the desired immune response has been achieved, and further the design of additional immunogens required to mature HIV immunity.

In 2019-20, the Duke CHAVD was comprised of 17 investigators in Europe and the US, many of whom contributed to a seminal publication on the design of germline-targeting immunogens (Science 366: eaay7199, Dec. 6, 2019). During this period, DHVI's GMP unit also formally released two drug products (A244 gp120 and CH505 TF Trimer immunogens) for use in clinical trials and launch production for two additional immunogens.
In 2019, the DHVI was awarded a contract by the National Institutes of Allergy and Infectious Diseases to serve as one of two Collaborative Influenza Vaccine Innovation Centers (CIVICs) in the United States. The Duke CIVICs program aims to improve both the breadth of coverage and durability of the influenza vaccine through iterative vaccine design, pre-clinical animal studies, and early phase clinical trials. The Duke CIVICs program is comprised of the Duke CIVICs Vaccine Center (DCVC), the Duke Manufacturing and Toxicology Core, and the Duke Clinical Core.

**Duke CIVICs Vaccine Center**

The Duke CIVICs Vaccine Center (DCVC) is focused on developing both improved season and universal influenza vaccines. Current seasonal influenza vaccines are limited in durability and their ability to protect against all influenza types circulating in humans. The goal of the DCVC, led by Tony Moody, MD, is to improve seasonal influenza vaccines to provide better protection against infection and design influenza vaccines that protect for more than one influenza season and that are effective for all age groups.

In its first year the DCVC expanded its network to garner new vaccine ideas and designs. By mid-2020 it had progressed two vaccine candidates to GMP manufacturing, with a third to closely follow. In 2020-21 the DCVC will test new seasonal influenza vaccines in animal models to identify additional candidates to move forward. It will also test new technologies to provide faster, cheaper, and/or improved means of generating vaccines than the current egg-based season influenza vaccine production model.

**Duke Manufacturing and Toxicology Core**

The Duke Manufacturing and Toxicology core, led by Matthew Johnson, PhD, is housed within the DHVI manufacturing facility, which follows current good manufacturing practices (cGMP) to ensure patient safety and product quality. The Manufacturing and Toxicology Core's GMP Program is designed to meet the demand for fast, iterative, early-phase process development and clinical manufacturing as an enabler for research organizations.

The Core uses flexible, non-fixed equipment, to enable rapid layout configuration changes that keep pace with the shifting needs of the manufacturing facility. Additionally, the team uses single-use, closed system unit operations in manufacturing. The GMP team includes experts in the field with extensive experience in industry before joining the DHVI, works collaboratively with third party entities routinely for toxicology studies, and has its own regulatory staff who can prepare and submit Investigator's Brochures and Investigational New Drug applications.

The core has initiated the manufacturing pipeline for four novel flu vaccines since the contract was awarded in 2019. The team has also initiated work to develop a cell line in house to be used as a platform for manufacturing for current and future products. The team is working closely with additional vaccine centers to complete early manufacturability and feasibility studies to help new products enter the pipeline.
Immunology Virology Quality Assessment Center

The Immunology Virology Quality Assessment Center (IVQAC), led by Thomas Denny, MSc, MPhil, is a resource designed to help immunologists and virologist evaluate and enhance the integrity and comparability of laboratory determinations for multi-site viral studies. The IVQAC directs four programs funded by the National Institute of Allergy and Infectious Disease, as part of the National Institutes of Health: External Quality Assurance Program Oversight Laboratory (EQAPOL), the Immune Quality Assessment (IQA) Program, Virology Quality Assurance (VQA) Program and the Non-Human Primate Core Virology Laboratory (NHPCVL).

Duke Clinical Core

Emmanuel “Chip” Walter, MD, MPH
Principal Investigator, Duke Clinical Core

The Duke Clinical Core aims to design Phase I, Phase I/II, and controlled human infection trials for novel influenza vaccines. The Clinical Core, under the leadership of Emmanuel “Chip” Walter, MD, MPH, will serve as the primary biorepository for the CIVICs program and will oversee specimen management from all clinical trials conducted through CIVICs. The Clinical Core was funded as the lead site to oversee the development and implementation of a dose-ranging controlled infection study in adults with the University of Maryland. It will conduct primary and secondary endpoint assays for all clinical trials.

In 2020-21, the Duke CIVICs Clinical Core will implement several influenza vaccine and human challenge studies. In collaboration with the University of Maryland, Duke will enroll up to 150 subjects across two sites in a dose ranging challenge study to determine the safety and optimal infectious dose of a recombinant H3N2 influenza virus. The Clinical Core will also begin enrollment into a screening protocol for future influenza clinical trials. This protocol will establish a pipeline for continuous pre-screening of healthy individuals with low antibody titers against influenza challenge strains well in advance of future influenza challenge or vaccine trials. The Duke CIVICs Clinical Core will also partner with the University of Maryland on a dose-escalating study to assess the safety, tolerability, reactogenicity, and immunogenicity of the M2SR vaccine in children. Additionally, the Duke CIVICs Clinical Core will also establish numerous clinical trial protocols for novel influenza vaccine products anticipated from the Duke CIVICs pipeline.
Thomas Denny, MSc, MPhil, has led the Immunology Quality Assessment (IQA) program since 1999. The Program is designed to improve national and international standardization and overall performance of immunology laboratories participating in NIAD-sponsored clinical trials and research programs. The program develops new technology and laboratory assays used to monitor patients with HIV infection, evaluate potential HIV vaccines, and provide insight into the pathogenesis of disease progression.

The IQA program assists the NIAID-sponsored clinical trials network and collaborating study groups in a variety of capacities, including training sites for processing and freezing PBMCs from a leukapheresis. As part of the IQA program, three Proficiency Testing efforts are administered: Peripheral Blood Monoclonal Cell (PBMC) cryopreservation, CD4 and CD8 Immunophenotyping via flow cytometry, and Leukapheresis Real-Time external quality assurance Program.

The IQA proficiency testing programs serves over 200 sites worldwide helping to ensure quality and consistency in data generated from these sites. The PBMC cryopreservation program currently includes 86 domestic and international sites. The domestic Immunophenotyping program currently services 60 laboratories across the United States, Canada and Puerto Rico.

The IQA program also reviews the performance of and offers remediation to the international DAIDS laboratories participating in the United Kingdom National External Quality Assessment Service Immune Monitoring program. Currently, there are 63 laboratories from 18 countries participating in this international review and monitoring program for CD4 enumeration.

Since 2010, the External Quality Assurance Program Oversight Laboratory (EQAPOL) program has supported the development, implementation and oversight of external quality assurance programs monitoring laboratories engaged in HIV research around the world. In 2019-20 EQAPOL administered four External Quality Assurance programs with more than 90 sites to assess proficiency in interferon-gamma (IFN-y) and Enzyme-linked Immunosorbent Spot (ELISpot) assays, Intracellular Cytokine Staining by Flow Cytometry, Luminex bead-based assays, and HIV incidence assays. The EQAPOL’s Viral Diversity Program is establishing a panel of fully characterized viruses from acute, early and chronic HIV infections. These panels can be used to assess the impact of the viral genetic diversity on assay performance, develop and validate new assays, assist regulators in evaluating test kits, monitor resistance to HIV treatment, and inform HIV vaccine development.

In 2019-20, the EQAPOL program distributed proficiency testing for two limited antigen (LAg) HIV incidence assays, two ELISpot assays, and one Luminex Assay PT. Guido Ferrari, MD assumed leadership for the EQAPOL’s Flow Cytometry Proficiency Testing Program during the reporting period as well. He will be implementing new testing methods, proficiency grading criteria, and efforts to automate analysis. In early 2019, the EQAPOL began collaborating with Claude Tayou Tagny, MD of the University of Yaounde in Cameroon to collect samples of recent HIV infections detected among blood donors in African Francophone countries. In 2020-21, the EQAPOL team looks forward to continuing proficiency testing for the ELISpot, LAg Incidence Assay, Flow Cytomtery and Luminex programs and expanding its viral diversity panel.

The IQA program currently assists the AIDS Clinical Trials Group, Division of Microbiology and Infectious Diseases, National Institute for Research in Tuberculosis, the International Maternal Pediatric Adolescent AIDS Clinical Trials, the HIV Vaccine Trials Network, the HIV Prevention Trials Network, and the Microbicide Trials Network.
**Virology Quality Assurance Program**

The Virology Quality Assurance (VQA) Program was awarded to DHVI in 2019. The VQA program provides quality assurance and proficiency testing for virologic-based assays used in NIAID-funded clinical trials.

The VQA program promotes effective assay procedures and increased data integrity within multi-site clinical studies. The program works to ensure the validity and comparability of data obtained across sites by providing laboratories with proficiency testing and assay run controls. In 2019-20, the program administered nine proficiency tests for Quantitative HIV-1 RNA, Qualitative HIV-1 Nucleic Acid, and HIV-1 Drug Resistance Sequencing testing. Additionally, the VQA program began providing support to the ongoing NIAID funded SARS-CoV-2 studies.

In 2020-21, the VQA will continue providing quality control materials to laboratories participating in NIAID-funded clinical trials for HIV and explore the possibility of developing quality control material for SARS-CoV-2 assays.

**Non-Human Primate Core Virology Laboratory**

The Non-Human Primate Core Virology Laboratory (NHPCVL) was awarded to DHVI in December 2017. The NHPCVL supports the development and performance of simian immunodeficiency virus or simian human immunodeficiency virus viral load assays that are performed in support of HIV vaccine development efforts by research laboratories worldwide. With this contract, the IVQAC team will work to improve and develop assays that are used to detect and characterize viral RNA from samples obtained from non-human primates that are part of HIV/AIDS preclinical research studies.

The ultimate objective of the NHPCVL program is to provide accurate, precise and fast quantitative viral load results to investigators developing HIV vaccines. Detection of viral RNA is performed in specimens that include plasma, mucosal tissues or secretions, and lymphoid tissues from non-human primates that have been infected with SIV or SHIV. In order to improve RNA detection at the lowest levels, the IVQAC team works to improve the repeatability and limit of detection of VL in all sample types. The optimized SIV Viral Load assay has a limit of detection of 62 copies/mL using only 500 uL of plasma. In 2018-19, the NHPCVL performed 1,626 viral load assays for 15 studies.

In 2019, the IVQAC team traveled to the Oregon Health & Science University’s National Primate Research Center to train in situ hybridization to define and quantify SIV in tissue samples. Team members were trained by industry leader, Jacob Estes, on the next-generation RNAscope and DNAscope in situ hybridization platform for specific and sensitive detection of HIV/SIV RNA and DNA in tissue and brought back this technology to launch this service through the NHPCVL.

In 2020-21, the NHPCVL will expand its program to include a SARS-CoV-2 viral load assay. With additional support from NIAID, the NHPCVL will develop and perform quantitative RNA detection of the novel SARS-CoV-2 and make this assay available to sites developing vaccines against the novel coronavirus.
Biologic countermeasures, such as monoclonal antibodies (mAbs), are a rapid/effective means of controlling and containing outbreaks of emerging pathogens where no licensed therapeutic or vaccine is available. Funded in September 2017 by the US Department of Defense Advanced Research Projects Agency (DARPA), the Duke Pandemic Prevention Program (P3) combines expertise in virology, immunology and clinical manufacturing. Its goal is to develop first in human testing of innovative platform technologies that rapidly respond to pandemic viral outbreaks with gene-delivered monoclonal antibodies. The global pharmaceutical industry can produce billions of vaccine doses, but it lacks the capacity to manufacture monoclonal antibody protein at such a large scale. The DARPA P3 program was designed to innovate platform approaches for gene-delivered antibodies to overcome these challenges of production scale and speed to meet global pandemic needs.

The fully integrated platform is a major advancement in rapid pandemic countermeasure development and will address the significant global challenge pandemic outbreaks have on both civilian and military populations. Under the leadership of Gregory Sempowski, PhD, this platform combines expertise in virology, immunology and cGMP manufacturing to create a fully integrated platform capable of responding to a viral pandemic. For this program, we are focusing on three main areas of innovation to develop a platform that can be utilized in future pandemics:

1. Universal Virus Growth: Development of an on-demand universal platform to propagate known and unknown viral pathogens to high titer for us in downstream assays
2. Antibody Isolation: Identification and isolation of pathogen-neutralizing antibodies from convalescent PBMCs and transfer antibody sequence for production and delivery optimization/testing
3. Medical Countermeasures Delivery: Development of an mRNA-based antibody countermeasure with optimal potency, half-life and ease of use in the field

In 2019-2020, the Duke DARPA P3 program successfully completed the development phase of the P3 platform and a demonstration of platform operation using influenza virus. In response to the COVID-19 pandemic, the newly developed platform was implemented to isolate countermeasures to SARS-CoV-2.

At the end of July 2020, the Duke P3 platform was awarded an additional $7.6 million to move forward with cGMP manufacture and Phase I clinical trial of a SARS-CoV-2 antibody isolated and developed using the platform. Manufacturing will take place in late 2020 in the DHVI clinical Good Manufacturing Practice (cGMP) facility and a Phase I clinical trial with healthy volunteers is on target to start early 2021 in the Duke Vaccine and Treatment Unit.
The Duke Vaccine and Trials Unit (DVTU) is DHVI’s clinical trial arm led by Emmanuel “Chip” Walter, MD, MPH. The DVTU has nearly three decades of experience conducting clinical investigations related to the control and prevention of infectious diseases.

The DVTU seeks the further understanding of vaccine immune responses and correlates of protection from infection and to enhance vaccine safety. Its research activities have been funded by the National Institutes of Health, the Centers for Disease Control and Prevention, industry partners, and others. The DVTU includes a broad range of clinical investigators across multiple disciplines including pediatric and adult infectious diseases, obstetrics and gynecology, geriatrics, neurology, surgery, and family medicine and community health.

In 2019, the DVTU was awarded funding as one of two Clinical Cores for the National Institute of Allergy and Infectious Diseases’ Collaborative Influenza Vaccine Innovations Centers (CIVICs). As a CIVICs Clinical Core, the DVTU is evaluating promising next generation influenza vaccine candidates in human challenge studies and Phase I and II clinical trials. In 2019 the DVTU participated in the NIAID-led Human Influenza Challenge Study – the first of its kind conducted at Duke University. The DVTU also participated in the NIAID multicenter clinical trial demonstrating the safety and efficacy of remdesivir to treat COVID-19 in hospitalized patients.

In 2020-21 the DVTU will conduct numerous clinical trials assessing investigational and licensed vaccine products aimed at an array of pathogens including influenza. The unit also will continue intensively assessing novel treatments and vaccines for SARS-CoV-2, including enrolling 1,000 subjects into a Phase III COVID-19 vaccine efficacy trial. The unit will relocate to the Duke@RTP campus where it will co-exist with a number of DHVI programs including the Duke CIVICs Vaccine Center.

Emmanuel “Chip” Walter, MD, MPH
Director, DVTU

Duke Vaccine and Trials Unit team
DHVI Good Manufacturing Practice Program

The DHVI Good Manufacturing Practice (GMP) Program, led by Matthew Johnson, PhD, rapidly transitions candidate vaccines and therapeutic treatments from basic science into clinical research.

The team has expertise in every step of GMP, from cell line development, process development, and analytics to GMP production and quality control testing. It executes these steps under independent quality oversight to meet all International Council for Harmonization and regulatory body guidelines. The GMP Program manufactures products on widely diverse platforms, including mRNA; mammalian, bacterial, and insect cell culture-based processes; and live and inactivated viral-based processes. The net impact of the GMP is bringing therapies to clinical trials faster by working in close collaboration with innovator research laboratories.

The DHVI GMP team achieved significant milestones in 2019-20, including producing two NIAID-sponsored HIV candidate vaccines for Phase I clinical trials and establishing world-class manufacturing and analytics processes for mRNA-based products. In addition, the DHVI GMP Program was selected as the sole manufacturing center for the NIH’s Collaborative Influenza Vaccine Innovations Centers (CIVICs) initiative, which aims to develop and test a universal flu vaccine with broader coverage and more durable protection.

In 2020-21 the DHVI GMP Program will significantly expand its manufacturing capacity and equipment to meet DHVI’s expanding portfolio. It will manufacture more than five unique HIV and influenza vaccine candidates in anticipation of clinical trials. The DHVI GMP Program will also help fulfill DHVI’s mission to tackle human health challenges by manufacturing potential preventatives or treatments for SARS-CoV-2. The Program will see four new manufacturing suites come online in 2020-21. These will expand DHVI’s manufacturing platform for live and inactivated virus vaccines and its ability to produce multiple molecules concurrently.

Matthew Johnson, PhD
Director, GMP

2018
- IVQAC laboratory receives accreditation from College of American Pathologists

2019
- DHVI researchers find how natural killer cells regulate protective HIV antibodies, Cell
- Virology Quality Assurance Program awarded

2019
- DHVI-led study reveals immune system can be coaxed into selecting key antibodies to fight HIV, Science
- DHVI completes GMP manufacture and release two HIV vaccine drug products for Phase I clinical trials
- Collaborative Influenza Vaccine Innovation Centers awarded

2019
- DHVI expands its vaccine production and live-virus capacity by building four additional GMP suites

2019
- DHVI completes IVQAC laboratory
- DHVI researchers find how natural killer cells regulate protective HIV antibodies, Cell
The Division of Structural Biology, led by Priyamvada Acharya, PhD, harnesses diverse expertise to understand interactions between pathogens and the human immune system. The team uses X-ray crystallography, cryo-electron microscopy (cryo-EM), negative stain EM, small angle X-ray scattering, molecular dynamics, biophysics and biochemistry to investigate and characterizes the structure and function of viral proteins—especially the HIV-1 envelope—and the responses they elicit. Working in close collaboration with other DHVI groups, this division uses insights to inform vaccine design against HIV-1 and other viruses. The Division’s work is supported by NIH awards (CHAVD, R01 and R21) as well as the Translating Duke Health Initiative and Duke CFAR.

For high resolution structural determination, cryo-em and x-ray crystallography are the major techniques used. The Division of Structural Biology supports projects from design to structure and has frequent access to the Duke Titan Krios microscope and the SER-CAT beamline at Argonne National Labs. In addition, the Division offers a Negative Stain Electron Microscopy Center. Led by Dr. RJ Edwards and equipped with an in-house Philips EM420 microscope, this unit provides low-cost and fast-turnover quality control and low-resolution structural data on immunogens and antibodies of interest to DHVI vaccine programs. The Division also houses CHAVD’s Structural Biology Scientific Research Support Unit, which helps elucidate cryo-EM and crystallographic structures of newly-isolated broadly neutralizing Abs and NNAb from HIV-1 or SHIV-infected and Env-vaccinated humans and macaques, alone and in complex with Envs and immunogens.

In 2019-20 the Structural Biology Division solved and published the long-sought structures of the CH235 and DH270 unmutated common ancestors (CH235 UCA and DH270 UCA). With support from a Duke School of Medicine Interdisciplinary Colloquium Grant, the Division also played a central role in organizing the first Triangle Area Cryo-EM Symposium. The event enabled researchers from institutions across the region, including Duke, North Carolina State and Eastern Carolina Universities, the University of North Carolina at Chapel Hill, and the National Institute of Environmental Health Sciences to share scientific data and timely discoveries in the field of Cryo-EM technology. In 2020 the Division also rapidly translated knowledge and expertise gained from many years of research on the HIV-1 Env to create a high-resolution structural determination pipeline the SARS-CoV-2 spike protein. These efforts resulted in an NIH R01 Supplemental award and publication that, for the first time, demonstrated that the conformation of the SARS-CoV-2 spike can be controlled by rational design.
The National Institute of Allergy and Infectious Disease (NIAID) funds Integrated Preclinical/Clinical AIDS Vaccine Development Programs (IPCAVDS) to translate advanced, innovative and promising vaccine candidates into early clinical testing.

Programs funded by IPCAVD grants are charged with completing all steps necessary to bring an HIV vaccine candidate to clinical trial, from down-selecting vaccine candidates, to producing clinical-grade material under current Good Manufacturing Practice (cGMP) conditions and releasing the vaccine for use in clinical trials. Under Barton Haynes, MD as Principal Investigator, the DHVI was awarded its first IPCAVD program in 2017 and its second in 2018. DHVI’s first IPCAVD program is developing an HIV vaccine prime and boost that stimulate broadly neutralizing antibodies using an mRNA platform. Its second IPCAVD program focuses on a vaccine to elicit non-neutralizing antibodies.

In 2019-20, DHVI’s first IPCAVD program down-selected mRNA sequence candidates and developed the mRNA vaccine platform necessary to manufacture prime and boost vaccine components under cGMP conditions. The team produced mRNAs for multiple nanoparticle candidates, assessed the characteristics of the proteins produced from mRNA expression, selected top candidates, formulated them in lipid nanoparticles (LNPs), and conducted animal studies using those LNP mRNAs. In 2020, the Program selected the optimal modified mRNA sequence for the prime immunogen. In 2020-21 the program will complete upstream and downstream GMP process development and begin manufacturing the prime mRNA vaccine product under cGMP conditions. This product will be used in toxicity studies to ensure its safety before entering initial clinical trials. The program will also down-select for the boost immunogen and then proceed with GMP process development and manufacturing. Following these steps, both products will undergo rigorous analytical testing, quality release and finishing for use in an HIV Vaccine Trials Network (HVTN) clinical trial.

During 2019-20, the DHVI’s second IPCAVD program performed small animal studies to test potential candidates for antigenicity, down-selected to four sequences, used those sequences in modified nucleotide mRNA design, and produced four mRNAs for in vitro testing. The DHVI GMP team also developed the mRNA vaccine platform necessary to support both the IPCAVD 1 and 2 programs and additional mRNA products.
The National Institute of Allergy and Infectious Disease (NIAID) funds HIV Vaccine Research and Design (HIVRAD) Programs to address hypotheses crucial to the design of an efficacious HIV vaccine.

In 2019, Munir Alam, PhD received a HIVRAD P01 award entitled “Immunogen Design for Induction of HIV distal gp41 broadly neutralizing antibodies.” This program is designing immunogens to initiate and induce broadly neutralizing antibodies (bnAbs) that target a critical epitope on the HIV-1 Envelope membrane proximal external region (MPER). Inducing robust neutralizing antibodies against distal MPER is essential to an HIV vaccine but poses several hurdles including membrane masking of epitopes and immunological tolerance. The program uses structural-guided approaches to develop soluble and membrane-bound immunogens and relevant mouse models to evaluate immunogen constructs for immunogenicity.

In 2019-20, the program developed a lead germline-targeting prime immunogen in a multimeric form that binds to MPER bnAb-like human precursor antibodies and confirmed its immunogenicity in bnAb germline knock-in mice models. In 2020-21, the program will develop membrane-bound immunogens and continue developing mouse models with diverse precursors to test immunogens in a physiological setting. The program will also continue characterizing and determining bnAb development pathways for antibodies using next-generation sequencing and computational analysis methods such as ARMADILLO. These methods will be used to monitor maturation progress in further immunization studies and re-optimization of immunogen designs. Through this work, the program will continue tackling vaccine induction of disfavored antibody lineages in general and distal HIV-1 MPER bnAbs.

In 2019, Sallie Permar, MD, PhD and Kristina De Paris, PhD from University of North Carolina, Chapel Hill received a five-year renewal of their NIH/NIAID-sponsored HIVRAD P01 program, “Maternal and Infant Immunization to Eliminate Breast Milk Transmission of HIV-1”. The program aims to harness the unique qualities of the infant immune landscape to elicit vaccine-induced immune responses that can protect against HIV infection in high risk adolescents and young adults. Using two different vaccine strategies, the team will test to see if vaccination initiated in early life, combined with booster immunizations throughout childhood, is more effective at inducing protective immune responses to prevent HIV acquisition compared to a vaccine initiated in pre-adolescence.

In its first five years, the program established the long term persistence of HIV vaccine responses in infants, as well as vaccine strategies that are most immunogenic in infants. These findings yielded more than 16 peer-reviewed publications.
The Quantitative Research Division (QRD) is comprised of experts in the fields of Biostatistics and Computational Biology and supports the quantitative analysis needs of DHVI.

**Biostatistics Support**

The QRD supports DHVI investigators and their collaborators in study design, data collection and management, data analysis, and power calculations. Wes Rountree, MPH, leads the Biostatistics Support team in working with Principal Investigators and laboratories to create permanent datasets and systems databases. The QRD provides statistical support for clinical studies at DHVI where they manage statistical analyses and consult on study design and sample size/power calculations. The QRD collaborates with Principal Investigators to prepare individual and multi-investigator grants, as well as assists in preparing manuscripts for submission to a wide-range of peer-reviewed journals. The QRD biostatistics team has a wide variety of statistical expertise ranging from non-parametric and categorical analysis, epidemiologic methods, general and generalized linear models, structural equation models, and finite mixture models.

**Computational Biology Support**

The QRD supports the wide array of computational biology and bioinformatics needs of DHVI investigators. The team, led by Kevin Wiehe, PhD, is experienced in performing analysis with a multitude of state-of-the-art bioinformatics techniques and software and is fully-capable of delivering custom bioinformatics solutions including analysis pipeline building. The QRD is well-versed in applying computational genomics techniques with a particular strength in next-generation sequencing approaches for genomic sequencing and single-cell transcriptomics.

The QRD computational biology team offers computational structural biology services and helps DHVI investigators with molecular visualization, antibody structural modeling, antibody-antigen complex modeling, computational immunogen design, computational mutagenesis, in silico antibody affinity improvement, and molecular dynamics simulation.

In 2019-20 a computational tool called ARMADillo was developed by the QRD to identify rare antibody mutations that are critical to the development in broadly neutralizing HIV antibody lineages. In recent work published in Science, DHVI investigators showed that it’s possible to design a vaccine capable of eliciting these rare mutations in animal models, thus demonstrating a proof-of-concept that bottlenecks to inducing broadly neutralizing antibodies can be specifically targeted and overcome. The successful targeted selection of rare antibody mutations represents a breakthrough in our ability to precisely control the immune response through vaccination and has far-reaching implications for vaccine design not only for HIV, but for any pathogen where a specific type of antibody response is desired such as for influenza and betacoronaviruses.

The goals of the QRD for the coming year includes providing quantitative analysis support for DHVI investigators. The QRD is also looking forward to continuing the development of the computational methods and software, such as ARMADillo, to aid in the design of vaccine components that can effectively guide the immune system to successfully elicit broadly neutralizing HIV antibodies.
The DHVI's CAVD Protein Production Facility (PPF) was established to provide high-quality, research-grade recombinant proteins and antibodies to CAVD funding recipients. In July 2017, the PPF expanded into a DHVI Shared Resource Facility available to all Duke University researchers. It offers high-quality proteins and antibodies for in vitro assays for basic research as well as immune monitoring in clinical studies and helps facilitate immunogen discovery. The facility is equipped to produce and purify, at cost via subcontract, HIV-1 Env proteins and antibodies as standardized in vitro reagents for use in HIV vaccine research. These reagents are intended to optimize clinical trial immune monitoring and facilitate Env immunogen discovery; however, the proteins are not intended for use in humans or in clinical trials. The production of all proteins and antibodies is governed by a Quality Management plan with oversight by the Quality Assurance for Duke Vaccine Immunogenicity Program (QADVIP), Duke's Quality Assurance Unit. All proteins and antibodies are produced following Standard Operating Procedures (SOPs) and using Good Documentation Practices. Environmental monitoring of the laboratory space, freezers, refrigerators and incubators is maintained and recorded in compliance with PPF SOPs.

In 2019-20 the PPF generated a stable supply of germline-reverted forms of broadly neutralizing HIV antibodies (bnAbs) as reference reagents for quality control of bnAb precursor detection assays (e.g., antigen characterization, B-cell sorting, neutralization). These germline-reverted forms of bnAbs will be used as research reagents for basic vaccine discovery work.

Over the year, the PPF produced reagents supporting the following publications:

- **Induction of cross-reactive HIV-1 specific antibody responses by engineered V1V2 immunogens with reduced conformational plasticity.** Lai, J.I.; et al. *Vaccine*, 2020
- **Framework mutations of the 10-1074 bnAb increase conformational stability, manufacturability and stability while preserving full neutralization activity.** Kerwin, B.A.; et al. *Journal of Pharmaceutical Sciences*, 2020
- **Priming with a Potent HIV-1 DNA Vaccine Frames the Quality of Immune Responses prior to a Poxvirus and Protein Boost.** Asbach B; et al. *Journal of Virology*, 2019
- **Neutralization-guided design of HIV-1 envelope trimers with high affinity for unmutated common ancestor of the CH235 lineage of CD4 binding site broadly neutralizing antibodies.** LaBranche, C.C.; et al. *PLoS Pathogens*, 2019
- **Safety, pharmacokinetics, and immunogenicity of the combination of the broadly neutralizing anti-HIV-1 antibodies 3BNC117 and 10-1074 in healthy adults: a randomized, phase 1 study.** Cohen, Y.Z.; et al. *PLoS One*, 2019

In 2020-21 the PPF will continue providing quality proteins and antibodies in support of CAVD consortia members. The Facility also anticipates expressing a panel of antibodies to characterize ADCC responses of CD4-binding site targeting non-neutralizing antibodies generated by individuals in the US Military Research Program’s RV-305 trial. These antibodies will also be assessed for their ability to mimic CD4 and open the HIV-1 Env trimer.
Sallie Permar, MD, PhD  and Peter Barry, PhD, from University of California, Davis, received an NIAID P01 program, “Immunologic and Virologic Determinants of Congenital Cytomegalovirus Transmission and Disease in Rhesus Monkeys.”

This five year program brings together the three national primate centers (University of California, Davis, Tulane, and Oregon Health Sciences University) and scientists from across the globe to establish which vaccine targets are most critical for protection against congenital CMV transmission and disease.

In 2019-20, the program successfully generated a full length RhCMV and demonstrated wild type virus-like replication in seronegative NHP males. They completed studies which defined the requirements of a specific viral receptor, the pentameric complex, in crossing the placenta and infecting the fetus. Additionally, the program developed a mathematical modeling analysis plan to identify immune and viral correlates of CMV vertical transmission.

The program has successfully brought together experts from multiple areas of the CMV research community to advance congenital CMV vaccine research. Together, these experts aim to define the key immune responses and viral-host interactions that dictate primary fetal CMV transmission and disease in a highly relevant animal model.

Each June, Dr. Permar’s laboratory has joined the CMV Foundation in raising awareness of the cytomegalovirus by participating in the STOP CMV Hands Campaign. The team shares STOP CMV images and factual information relating to CMV on their social media channels to bring awareness of this common viral infection in the United States.
RESOURCES FOR SCIENTIFIC DISCOVERIES

The DHVI has assembled a group of state-of-the-art instruments, techniques and services to support basic and translational research in vaccine immunology, immune reconstruction, host-pathogen interactions, emerging infectious diseases and biodefense. These Core Facilities are available to the Duke community and their collaborators.

Not only are the DHVI Core laboratories a central repository of state-of-the-art instrumentation, we see these facilities, and more specifically their Directors/Managers, as institutional thought leaders in their respective areas (e.g., biocontainment, animal models, flow cytometry, immune monitoring etc.). The majority of our Core leadership has doctoral degrees in their respective field and provide mentorship to the next generation of scientists through hands-on user training opportunities and consultative services.

All DHVI Core facilities can be found in the CoreResearch@Duke system, a centrally supported, enterprise wide, efficient, booking to billing web portal to support the operation of all Duke University Shared Resources (https://coreresearch.duke.edu). For more information about individual core services, procedures for scheduling instrument time, requesting services and current pricing please go to https://shared-resources.dhvi.duke.edu/

The DHVI Core laboratories supported over 207 individual Principal Investigators at Duke and collaborating non-profit research institutions. Services were provided at cost to these investigators totaling $2.6M in fiscal year 2020. Investigators used over 455 unique grants, contracts and sponsored research awards to support their research efforts that accessed DHVI Core facilities.
DUKE REGIONAL BIOCONTAINMENT LABORATORY

Gregory D. Sempowski, PhD  |  Director
Heather E. Lynch, PhD  |  Associate Director for Program Management and Development
T. Scott Alderman, MS, CBSP  |  Associate Director of Safety and Operations

The Duke Regional Biocontainment Laboratory (RBL) supports basic research programs and has three collaborative core units that focus on Immunology, Virology, and Microbiology. These units are available to Duke faculty and their collaborators as fee-for-service shared resources. Through any of these units, users can receive safety/security training, animal model support and use of the containment environment. These units can be utilized separately or all together to provide comprehensive study support (regulatory compliance, study design, study execution and data analysis).

The Duke RBL supports sponsored research programs in safety and biopreparedness, vaccine and therapeutic development, host response and immune monitoring, and proficiency testing/quality assurance.

The RBL Immunology Unit provides access to specialized instrumentation for Real-Time PCR and Luminex-based multiplex assays. This unit assists investigators with design and implementation of molecular, protein, and cellular assays to quantify immune reconstitution or immune responses in vitro and in vivo.

The Virology Unit offers support for virus research requiring up to biosafety level (BSL) 3 containment. The unit offers quality-controlled virus stock propagation, viral load quantification, virus-specific serology assays, in vivo challenge models, and development of project-specific virology support assays.

The Microbiology Unit maintains secure inventories of approved BSL2, BSL3, and Select Agent bacterial pathogens for RBL projects and collaborating investigators. The unit aids collaborators with in vitro and in vivo study design and protocol optimization. Its service offerings include IVIS live animal imaging in ABSL2/3, aerosol-delivered infection, macrophage-mycobacterium infection, extraction of mycobacteria from human samples, and qRT-PCR.

The RBL has a comprehensive safety and operations program to provide state-of-the-art containment facilities for BSL2, enhanced BSL2, and BSL3 research, including small animal research. It consists of approximately 12,000 sq.ft. of BSL2/3 laboratory space, seven pathogen-specific BSL3 laboratories, two ABSL3 small animal holding and procedure suites (mice, rabbits, ferrets), and ABSL2/3 Aerobiology Exposure and small-animal IVIS imaging facilities.

In 2019-20, the RBL responded to the SARS-CoV-2 pandemic by rapidly developing BSL3 coronavirus virology assays to support multiple research programs both internal and external to Duke. The RBL also trained staff in BSL3 practices in order to expand Duke’s capacity to perform BSL3 laboratory assays.

In 2020-21 the RBL will support Duke investigators and non-Duke collaborators with assays and animal models for their infectious disease and immune response research. This includes support for the CIVICs program, coronavirus projects, and pathogen-specific antibody isolation programs.
Sequencing Core

The DHVI’s Sequencing Core provides sequencing and genomic technologies to serve the needs of the Duke Human Vaccine Institute, Duke Center for AIDS Research, Duke University and external collaborators. The Core offers small and large-scale Sanger DNA sequencing, automated amplicon purification and a suite of next-generation DNA/RNA sequencing technologies. It also performs state-of-the-art genome and transcriptome sequencing and high-throughput sequencing of antibody receptor and viral genes that help define host-virus events during natural HIV infection that lead to the induction of broadly neutralizing antibodies – information which is critical to vaccine development.

The DHVI Sequencing Core also offers single cell sequencing to understand the immune profile of antibody responses to various antigens and vaccine candidates. Additionally, the Core provides project consultation and preliminary analysis of sequence data. These services include primer design, multiple sequence alignments, construction of phylogenetic trees, determination of genetic distances and mutation rates, recombinant viral genome analysis, and detection of drug resistance mutations.

In 2019-20 the DHVI Sequencing Core established methods for high resolution studies of single B cells in rhesus macaques that can be translated into in-depth analyses of antibody responses to HIV infection and vaccination in the widely used macaque model. In 2020-21 the Core plans to test LIBRA seq and Multi-seq technologies that will help DHVI researchers in multiplexing while improving study throughputs in a cost effective manner.

Protein Production Facility

The mission of the DHVI Protein Production Facility (PPF) is to provide high-quality proteins and antibodies for in vitro assays for basic research and clinical study immune monitoring and to facilitate immunogen discovery. The facility is equipped to produce and purify, at cost via subcontract, HIV-1 Env proteins and antibodies as standardized in vitro reagents which can be used in HIV vaccine research. These reagents are intended to optimize clinical trial immune monitoring and facilitate Env immunogen discovery; however, the proteins are not intended for use in humans or in clinical trials. The production of all proteins and antibodies is governed by a Quality Management plan with oversight by the Quality Assurance for Duke Vaccine Immunogenicity Program (QADVIP), Duke’s Quality Assurance Unit. All proteins and antibodies are produced following Standard Operating Procedures (SOPs) and using Good Documentation Practices. Environmental monitoring of the laboratory space, freezers, refrigerators and incubators is maintained and recorded in compliance with PPF SOPs.

In 2019-20 the PPF supported many DHVI investigators and collaborators by expressing and purifying proteins and antibodies used in basic research as well as analytical development for the GMP QC team. Using a baculovirus expression system the PPF expressed hemagglutinin antigens in support of DHVI’s influenza research. Working with the Quality Assurance for Duke Vaccine Immunogenicity Programs, the PPF has streamlined our SOPs for laboratory operations, protein expression as well as protein purification.

In 2020-21 the PPF is looking forward to continued expression of hemagglutinin antigens as well as SARS-2 antigens and antibodies required to support the DHVI’s expanding portfolio of vaccine research and development towards a manufactured vaccine candidate.
The Clinical Support and Accessioning Unit Core is a shared resource that provides support for clinical and research studies that fall within DHVI’s mission of performing research against infectious diseases that impact global health. The Clinical Support team provides support for developing protocols and recruiting participants of all ages. The Accessioning Unit team processes, stores, and retrieves stored samples isolated from both human clinical studies and non-human primate research studies. The Accessioning Unit team also provides shipping for investigators at DHVI and training and consultation on sample processing and shipping.

In 2019-20, the Clinical Support and Accessioning Unit Core supported DHVI by:
• Processing a total of 2,500 samples including 25,000 aliquots,
• Providing 6,000 samples in response to 500 requests, and
• Shipping 400 packages and receiving 250 packages, including biological specimens and research materials requiring strict adherence to preservation and safety protocols.

In addition to continuing its essential support to programs across DHVI and Duke, in 2020-21 the Clinical Support and Accessioning Unit Core will:
• Provide processing and biorepository support for screening potential participants in the Duke CIVICs Influenza vaccine clinical trial,
• Continue supporting the Duke School of Medicine by processing samples from six clinical trials related to SARS-CoV-2, and
• Become an established CoVPN processing lab in support of a Phase III SARS-CoV-2 vaccine clinical trial.

Research Analyst Susan Stager processes blood specimens in the DHVI Accessioning Unit.
The DHVI Flow Cytometry and Cell Sorting Facility serves analytical and cell sorting needs of the DHVI and Duke Community. The Flow Facility offers state-of-the-art cytometric support to investigators in basic, developmental, and clinical research at BSL-2 and BSL-3 containment. The Facility currently operates four analytical cytometers and three sorting cytometers.

All facility staff are certified cytometrists. In addition to instrumentation, the facility provides:

- Training for independent use of analytical cytometers
- Tools for the design of instrument-specific antibody panels
- A repository of verified instrument-specific antibody panels
- Consultation services for advanced analysis of cytometry data, including viSNE, SPADE, FlowSOM, and Citrus
- Site licenses for Flowjo analysis software

In 2020-21 the Flow Cytometry and Cell Sorting Facility added 56 new users, for a total of 230 active users across the Duke research community. The Facility sorted over 1,300 antigen-specific B cells from SARS-CoV-2 patients. To accommodate this increased demand, an additional Flow Engineer was brought on board. The Facility will further expand its capacity and services in 2021 through a satellite facility planned to open at Duke@RTP.
The Biomolecular Interaction Analysis (BIA) Core provides specialized applications and support in Surface Plasmon Resonance (SPR) and Bio-layer Interferometry (BLI) based interaction analyses to basic and clinical researchers across the Duke Community. The facility offers state-of-the-art Biacore SPR and ForteBio BLI instruments for label-free, real-time detection of biomolecular interactions and measurement of binding specificity, kinetic association and dissociation rates, binding affinity, and active concentration. The sensitivity and sample compatibility of these platforms allows for complex interaction analyses including binding thermodynamics, epitope mapping, binding mechanism resolution, and immunogen-induced antibody avidity responses in clinical sera samples.


In 2020-21, the BIA Core will continue developing assays and training users and researchers across the Duke community. The BIA Core will also continue to provide critical analyses for the Duke CHAVD program, along with several ongoing R01 and P01 research programs, including “Antigen Recognition and Activation of B-Cell Receptors of HIV-1 Broadly Neutralizing Antibodies” and “Immunogen Design for Induction of HIV distal gp41 broadly neutralizing antibodies” (PI: Alam). In addition, the BIA Core will continue its analytical support to the DHVI’s GMP vaccine product development pipeline and provide assays essential to developing an effective SARS-CoV-2 vaccine.
The Immunology Virology Quality Assessment Center (IVQAC) Core Laboratory offers College of America Pathologist- and Clinical Laboratory Improvement Amendments-accredited immunologic and viral load assay platforms including flow cytometry acquisition time, CD4/CD8 Immunophenotyping, HIV-1 RNA Viral load, HIV-1,2+O EIA, HIV p24 (non-ICD) and Western Blot determinations.

Additionally, all IVQAC Core Laboratory procedures and assays are performed under Good Lab Practices (GLP), including core activities such as non-human primate SIV viral load, PBMC processing from Leukopaks and whole blood, Sterility testing for bacteria/ fungi, Mycoplasma testing, and Elutriation processing for cell separation.

In early March 2020, in light of the COVID-19 pandemic, new IVQAC core activities were added to the core to support not only cohort specimen processing but also testing.

As of July 2020, the IVQAC core has added new SARS-CoV-2 related testing:
- COVID19_SARS-CoV-2 ELISA IgG or IgA Antibody test (EuroImmun _EUA)
- COVID19_SARS-CoV-2 RT PCR Qualitative (Abbott m2000_RT PCT_EUA)
- COVID19_SARS-CoV-2 RT PCR Quantitative (LDT)

We aim to provide our IVQAC Shared Resources to the Duke community and their collaborators with GLP and efficient lab core activates and testing.

Thomas Denny, MSc, MPhil
Director, IVQAC

IVQAC Research Analysts Sarah Keinonen (top) and Marleney Campuzano and Linda Walker (bottom right) process SARS-CoV-2 samples for studies at Duke.
COVID-19 researchers are critical personnel in the fight against this virus... safe, urgent and collaborative work in the Duke Human Vaccine Institute with collaborators in and outside Duke to develop a countermeasure and vaccine...Thank you!

Mary E. Klotman, MD, Dean, Duke University School of Medicine
A primary goal for the immediate future is to acquire the resources that will allow us to continue to be an intellectual and financial resource as well as a research-training powerhouse for Duke University, while making major breakthroughs in the prevention of infectious diseases. With additional resources, DHVI can begin to export the DHVI model of success to other Duke groups.

Private philanthropy, from both individuals and foundations, is absolutely essential to our ability to conduct the kind of innovative exploration that leads to new cures, more effective therapies, and improved diagnosis against the most complex and devastating diseases of our time. Your gift to the DHVI will help us achieve our mission of developing innovative diagnostics, vaccines and therapeutics to prevent and treat diseases of global importance, while working to eliminate health disparities, and train the next generation of scientists.

If you would like information on the many ways you can help, please contact:

Ellen Medearis  
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Development & Alumni Affairs  
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919.812.4292

To achieve our goals, we have assembled a talented group of investigators and staff, each committed to teamwork and synergy to solve critical problems that stand in the way of difficult scientific problems. To learn more about DHVI and support our work, engage with us via social media and directly by email.

For media requests,  
general inquiries contact:  
caroline.cockrell@duke.edu

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The Duke Human Vaccine Institute continues to lead the scientific field with cutting edge vaccine research against infectious diseases that impact global health.