BioNEXUS

THE MAGAZINE OF THE INSTITUTE FOR BIOSCIENCE & BIOTECHNOLOGY RESEARCH ISSUE #2 / 2020

THE NEXT VACCINE

How Far We Have Come *and the* Hope *for* Tomorrow

ALSO INSIDE

THERAPEUTIC DEVELOPMENT AND DRUG DISCOVERY

BIOMOLECULAR MEASUREMENT SCIENCE AND TECHNOLOGIES

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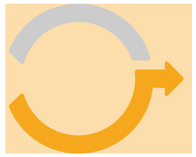

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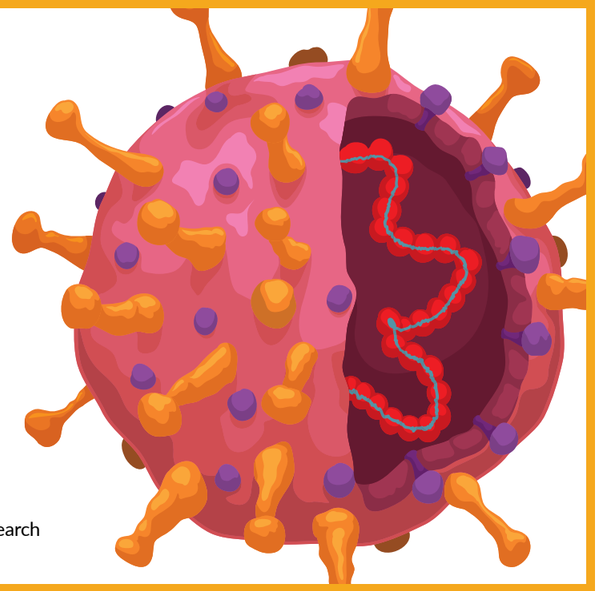

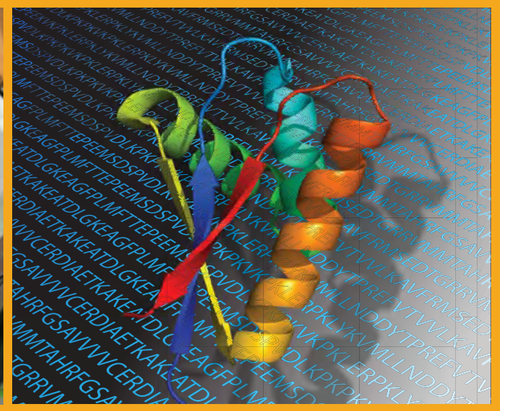

ON THE COVER
Visualization of the COVID-19 virus
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icons: circle: Mlap Studio/Adobe Stock; Freezer by Adrien Coquet/Noun Project
images: top: PenWin/iStock; bottom left: Daniel Nelson and Sara Linden photo by Dave Romero vibrantimage.com; bottom right: A ribbon representation of the three-dimensional structure (PDB 4YJX) of the candidate N-terminal Amino Acid Binder (NAAB) protein, Atu ClpS2. image by Jennifer Tullman

BACK COVER PHOTOS:
IBBR exterior photo by Nichelle Jefferson; *Circle images (clockwise):* Image 1 by John T. Consoli; Image 2 by Shunyuan Xiao lab; Image 3 by CDC; Image 4 by John T. Consoli; Image 5 by nopparit / iStock

FROM THE DIRECTOR

THIS YEAR has brought new and unexpected challenges given the COVID-19 pandemic. Through this, IBBR investigators have continued their commitment to addressing major bioscience, biotechnological and therapeutic issues. In response to current public health challenges related to COVID-19, several IBBR investigators have turned to new research areas to innovate and provide new insights into prevention and therapies for COVID-19.

Recognizing the public health issues today, this year's magazine's thematic feature is The Next Vaccine: How Far We Have Come and the Hope for Tomorrow. Investigators at IBBR are researching a breadth of infectious diseases, including COVID-19, Hepatitis C, HIV, Ebola, and Zika, to enhance understanding of immune responses and develop new vaccines.

In addition to vaccines, therapeutic discovery and development continue to be a significant research area among IBBR investigators. Within this issue, progress is described for using viral components to treat bacterial infections and approaches are outlined to identify new molecules and develop therapies for treating different forms of cancer.

IBBR's strengths in biomolecular measurements and the development of new technologies have led to advances toward protein sequencing, assessing the quality of vaccines and bio-manufactured products, and accessibility of SARS-CoV-2 structural data to the research community.

Looking back on the year in research, IBBR has moved forward structural approaches to addressing significant scientific and health issues, translation of discoveries into its application, training of early-career scientists, and partnerships to drive scientific innovation.

Since 2013, I have led the Institute to expand its robust research program, fostering advances in vaccine development, large and small molecule therapeutics discovery, antibody characterization, and development of new measurement tools and technologies. Recently, my responsibilities as Director were transitioned to Drs. David Weber and John Marino, who will now serve as Co-Directors. This transition will provide me with the new and innovative opportunity to advance research in vaccines and therapeutics and develop areas of commercial interest. As we move into the new year, we look forward to building upon the Institute's achievements to enhance research, training, collaboration, and enable discoveries to address critical biotechnology and health challenges.

Thomas R. Fuerst, PhD

Thomas R. Fuerst, PhD
Professor and Director (2013–2020)

INTERIM CO-DIRECTORS
(2020 - present)

David J. Weber, PhD
Professor, Department of Biochemistry & Molecular Biology, University of Maryland, Baltimore

John P. Marino, PhD
Leader, Biomolecular Structure and Function Group, National Institute of Standards and Technology

TOP AND BOTTOM PHOTOS BY JOHN T. CONSOLI, MIDDLE PHOTO BY UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE OFFICE OF PUBLIC AFFAIRS

About IBBR

IBBR is a joint research enterprise of the University of Maryland, College Park (UMCP), the University of Maryland, Baltimore (UMB), and the National Institute of Standards and Technology (NIST). IBBR is also financially supported in part by the University of Maryland Strategic Partnership: *MPowering the State*, an initiative designed to achieve innovation and impact through collaboration.

The Institute sits at the nexus of academic research and commercial application, bringing together critical elements necessary to inspire transformative discoveries in the field of biotechnology that provide innovative solutions to major scientific and engineering challenges important to society. IBBR researchers seek to advance the fields of disease pathways and biomolecular targets, biomolecular measurement sciences, and biomolecular engineering, including structure-based design of vaccines and therapeutics. The Institute also serves to expand the economic base of science and technology in the state of Maryland.

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CONTRIBUTORS

COMMUNICATIONS TEAM
Raegan O'Lone, PhD, *Assistant Director*
Viqar Aslam, *Director*, Business Development and Strategy
Nicole Tenly, *Event and Communications Coordinator*
Jennifer Paul Design
Catherine Gara, PhD, Writing SciSense
Photography: credits within magazine

We welcome your input: **communications@ibbr.umd.edu**
9600 Gudelsky Drive, Rockville, MD 20850
240-314-6000 / **www.ibbr.umd.edu**

The Next Vaccine:

How Far We Have Come *and the* Hope *for* Tomorrow

As a core preventative strategy against infectious diseases, vaccines are a critical component of a robust public health practice. The World Health Organization (WHO) estimates that they prevent approximately 2.5 million deaths per year, and drastically reduce illness and disease-related disability. Currently, vaccines are broadly used to prevent and control 25 vaccine-preventable infections, with a number of new vaccines in development. The recent COVID-19 pandemic has mobilized the research community worldwide to rapidly understand the causative virus, SARS-CoV-2, and develop a vaccine to reduce morbidity and mortality associated with the infection.

A First: Smallpox

Two hundred years of vaccine research have led to the incredible progress made in preventing diseases and significant impacts on human health today. The first vaccine was developed by Edward Jenner in 1796 against smallpox. For thousands of years, smallpox had been a significant health concern in many parts of the world due to high fatality rates and severe symptoms. Prior to Jenner's vaccine, doctors would transfer material from an individual infected with smallpox to an uninfected individual, a practice known as variolation. While variolation could result in protection from smallpox, it carried the risk of severe disease. Jenner's breakthrough came from his observation that milkmaids who had recovered from the milder disease cowpox were less likely to develop smallpox. So he developed a method for inoculating those unexposed to smallpox with material from people experiencing cowpox symptoms, resulting in protection from smallpox. Jenner referred to this new procedure as vaccination, taken from "vaccinia," the medical

1790 | 1800 | 1810 | 1820 | 1830 | 1840 | 1850 | 1860 | 1870 | 1880 | 1890 | 1900 | 1910 | 1920 | 1930 | 1940 | 1950 | 1960 | 1970 | 1980 | 1990 | 2000 | 2010 | 2020 | 2030

1796 Edward Jenner develops first vaccine for smallpox

1885
- Louis Pasteur develops rabies vaccine;
- Cholera vaccine developed

1892 Discovery of tobacco mosaic virus, the first virus identified

1896-1897 Typhoid and plague vaccines developed

1901 Discovery of first human virus: yellow fever

1914 Pertussis vaccine available

1926 Diphtheria vaccine available

1938 Tetanus vaccine available

1948 Combination DTP (diphtheria, tetanus, pertussis) vaccine developed

1955 Jonas Salk develops polio vaccine

1963 Measles vaccine developed

1964 U.S. ACIP[1] established

1967 Mumps vaccine developed

1969 Rubella vaccine developed

1971 Combination MMR (measles, mumps, rubella) vaccine available

1974 WHO established the Expanded Programme on Immunization (EPI)

1980 WHO declares smallpox eradicated

1981 Hepatitis B vaccine introduced

1985 Haemophilus influenzae type b vaccine available

1995 U.S. child/adolescent immunization schedule first approved and harmonized by ACIP[1], AAFP[2], and AAP[3]

1996 Varicella vaccine developed

1997 DTaP vaccine developed

1998 Rotavirus vaccine developed

2000 Hepatitis A vaccine developed

2001 Pneumococcal vaccine developed

2006 Human papillomavirus vaccine introduced

2011-2020 WHO Decade of Vaccines

2020
- Vaccines for 14 preventable diseases included on U.S. childhood immunization schedule;
- Phase 3 clinical trials conducted for mRNA vaccines for COVID-19; first COVID-19 vaccines available

[1] Advisory Committee on Immunization Practices, [2] American Academy of Family Physicians, [3] American Academy of Pediatrics

term for cowpox, which comes from vacca, the Latin word for cow. We now understand that exposure to the cowpox virus induced an immune response that was cross-protective against subsequent smallpox infection.

The Field Explodes

Although it took nearly a hundred years for scientists to develop the next vaccine (against rabies), the field has been growing continuously since then. New knowledge of infectious agents and the biological basis of disease, as well as significant advances in methods for manufacturing and disseminating vaccines, has allowed for broader implementation of vaccination and the expansion of vaccines to a range of other diseases.

By the 1940s, in addition to smallpox, vaccines for diphtheria, tetanus, and pertussis were recommended as public health measures. Advances in cell culture allowed for broader attenuation, or weakening, of live viruses by growing them in cells and identification of variants that had reduced virulence as pathogens. In 1955, a vaccine was licensed for polio, a spinal cord motor neuron disease that could result in paralysis or death, and became broadly implemented, dramatically reducing the annual number of polio cases in the United States. Further development and implementation of vaccines for a number of other diseases has also resulted in reduced incidence of those diseases.

While early vaccines involved live-attenuated virus, advances in the late 19th century showed that viruses could maintain their ability to elicit an immune response if inactivated by heat, chemicals, or radiation. The first successful inactivated virus vaccine was developed against influenza in the 1930s and others have followed.

Vaccination further evolved with the understanding of viral composition and infection and replication mechanisms. Subunit, polysaccharide, recombinant, and conjugate vaccines are all now available. In contrast to live-attenuated and inactivated vaccines that use complete viruses, these vaccines use only specific pieces of a virus, such as a protein, sugar, or other structural component. Due to the specificity of these pieces, they generally evoke a strong immune response.

Advancements in molecular and structural biology and bioengineering have led to additional approaches to vaccine development, like DNA, mRNA, and recombinant-vector vaccines. DNA vaccines introduce sequences of DNA, which code for a viral protein, into host cells. The host cells produce the viral protein and the immune system mounts a response. Recombinant-vector vaccines involve constructing a benign virus that contains a DNA or RNA sequence that codes for some piece of a virus. Like DNA vaccines, this approach relies on the generation of the viral protein by the host cell and a subsequent host immune response to generate immunity. These new approaches may have advantages in terms of vaccine stability, manufacturing at a large scale, specificity, and amplitude of the immune response.

IBBR's Contributions

Research by IBBR investigators on a breadth of viruses and their immune targets has led to critical insights into disease-causing viruses and bacteria as well as the immune components that interact with them. IBBR Fellows work across molecular biology, structural biology, virology, bioengineering, computational biology, and immunology to further elucidate key structures and functions. These discoveries can then be applied toward the development of new vaccines and new therapeutic approaches aimed at impacting human health through the prevention of infection.

Structure-Based Vaccine Design

Under the leadership of Thomas Fuerst and IBBR colleagues, the Institute has developed a structure-based vaccine design (SBVD) program, complemented with a novel immunoadjuvant and delivery (IAD) system, that is focused on controlling antigenicity at the atomic-level to create immunogens capable of eliciting robust neutralizing and protective immune responses. A fundamental aspect of this paradigm involves the study of immune responses in infected individuals and vaccinated subjects to define antigenic targets of both protective and non-protective antibodies. The ability to identify and isolate antibodies from infected individuals has advanced in recent years through use of single B-cell cloning technologies combined with next generation sequencing analyses that define the kinetics and maturation pathways of related antibody gene clusters.

Advanced structural biology tools can be utilized to define the conformations and key sites on proteins associated with pathogenic organisms. These sites can render them susceptible to protective immune responses, serve as immunodominant decoys for non-protective responses, and define structural signatures of their maturation pathways. These identified proteins can be engineered and formulated into vaccines in order to re-focus immune responses to key sites of protection, stabilize specific conformations deemed optimal for protection, silence non-protective epitopes, and guide maturation pathways of vaccine-elicited antibody responses in a structurally defined manner.

IBBR is using its core technology base and scientific expertise in SBVD and IAD to develop several

IMAGE BY BLUEBAY2014/ISTOCK

prophylactic vaccines of significant medical and public health importance. These include Hepatitis C Virus (HCV), the leading cause of liver cancer in the United States, Europe, and Japan known as the "silent epidemic" worldwide; Zika virus, a mosquito-borne disease that can pose serious developmental risks to fetuses such as microcephaly; Ebola virus and other filoviruses which can cause severe hemorrhagic fevers with high mortality rates; HIV, the causative agent of AIDS; and SARS-CoV-2, the virus responsible for our current COVID-19 pandemic. Several of these appear on the WHO's research and development blueprint prioritizing diseases and pathogens that pose the greatest public health risk. IBBR researchers are also investigating IAD systems to stabilize vaccine candidates and present these immunogens in multi-valent (many copies) form to enhance protective immune responses. The interdisciplinary research programs at IBBR are working to improve our understanding of infectious diseases and their interactions with the immune system, and to advance the development of vaccines to prevent infections.

Hepatitis C Research

Hepatitis C is a virus that infects over 70 million people worldwide. Underscoring its importance, three researchers who performed its discovery and initial characterization were awarded the 2020 Nobel Prize in Physiology or Medicine. Infection often leads to liver damage and can ultimately result in liver failure and cancer. There is currently no effective hepatitis C vaccine. Its development has been challenging due to the high rate of virus mutations and the levels to which hepatitis C virus antigens elicit immune responses. The SBVD program uses structural data to identify proteins that can be used in vaccines and to generate vaccine candidates.

The core program in HCV vaccine design, the team of which includes IBBR Fellows Thomas Fuerst, Brian Pierce, Alexander Andrianov, Roy Mariuzza, Gilad Ofek, Eric Toth, and Yuxing Li, in collaboration with Steven Foung of Stanford University, integrates structural biology, immunology, vaccinology, computational modeling, protein engineering and formulation chemistry to design antigens and evaluate their ability to produce broadly neutralizing antibodies and prevent HCV infection. To date, the group has collected a significant set of structural data regarding the virus' envelope protein (E2) and the binding of antibodies to it. The E2 protein is a structural protein, present on the envelope of the virus, which binds to a receptor on a human host cell and mediates virus entry into the cell, making it a promising target for vaccine development. The scientists are using the structural information they have garnered from their studies to design antigens that will elicit broadly neutralizing antibodies, which bind to a specific portion of the antigen across multiple strains of the virus and lead to inhibition of infection.

IBBR investigators are also developing a cutting-edge IAD-based adjuvant and delivery system, under the leadership of Alexander Andrianov, using HCV antigens as a model system. Adjuvants are molecules used in some vaccines to create a stronger immune response. Certain vaccines are composed of only portions of the virus and adjuvants help the body produce a stronger immune response and to provide better protection against the disease for which the vaccine is being administered.

In a recent collaboration among the IBBR Fellows and a nearby company Integrated BioTherapeutics, several adjuvants involving a polymer called polyphosphazene, the IAD platform technology, were studied for their ability to elicit an immune response to the HCV E2 protein. Polyphosphazenes are complex molecules made from smaller repeating units. They are well-suited to biological applications because of their degradable backbones, non-toxic degradation products, and their ability to self-assemble into complexes. The team designed and evaluated various polyphosphazenes, in combination with small molecule "Toll-Like Receptor" (TLR) agonists, specific stimulators of the immune system, as a combined IAD system to elicit potent immune responses. As a delivery system, polyphosphazenes have the remarkable ability to self-assemble with vaccine antigens, creating a complex of molecules (supramolecular assemblies) that present multiple copies of the antigen at once. These complexes are important for vaccine design and protective efficacy. Through this collaboration, polyphosphazene-based adjuvants showed remarkable potency in small animal model systems. These vaccine candidates are now being advanced into non-human primates.

Zika Research

Zika is an RNA virus that is transmitted primarily by bites from infected *Aedes* mosquitos. Following epidemics in Micronesia in 2007, the South Pacific in 2013-2014, and the Americas in 2014, the WHO declared Zika to be a Public Health Emergency of International Concern in 2016. Over eighty countries have evidence of mosquito-borne transmission of Zika virus. Many other countries with few or no reported cases of Zika disease have native *Aedes* mosquito populations that could be vectors, posing the risk of further spread of the disease. Zika virus infection is associated with serious risks to fetuses such as congenital Zika syndrome, fetal death, and preterm birth. Zika is

also associated with risk of Guillain-Barré syndrome, in which the body's immune system attacks the peripheral nervous system. There is currently no vaccine or specific treatment for Zika infection. Patients infected with Zika are treated for symptoms. Avoidance of mosquito bites is a prevention approach, but not uniformly feasible.

Yuxing Li, Alexander Andrianov, and Thomas Fuerst are working on a structure-based design approach to develop a Zika vaccine. The Zika surface E protein mediates viral entry into a host cell and is therefore a target for vaccine development. The team has been working to design a version of the E protein that avoids antibody-dependent enhancement (ADE). ADE occurs when a virus binds to a non-neutralizing antibody—one that doesn't disarm it. This binding actually enhances its entry into host cells and can lead to increased infectivity and virulence. Different species of flaviviruses, such as Zika and Dengue, co-circulate in certain regions and cross-reactive antibodies present the potential for ADE. Design of vaccines, therefore, must simultaneously address the potential for cross-reactivity and the creation of vaccine-induced antibodies that enhance the infectivity of other closely-related flaviviruses, while eliciting long-lasting antibodies specific to the virus to which the vaccine is developed. The research team has been designing a new version of the Zika E protein to identify protein variants that do not induce ADE, while still inducing an immune response to generate neutralizing antibodies to Zika virus. This approach could enhance the effectiveness and safety of a Zika virus vaccine.

Ebola Research

Ebola virus infection can cause internal hemorrhaging, which can be fatal. For many years, there were no proven treatments for Ebola virus disease and patients were treated for specific symptoms. The first treatment for Ebola virus disease, Inmazeb, a mixture of monoclonal antibodies which block attachment and entry of the virus, was recently approved in October 2020. The first vaccine, Ebvebo, was approved in 2019 for Zaire ebolavirus. These major advances would be augmented by development of additional vaccines providing protection against other strains of the virus, as well as more therapies that could be administered to potentially work in combination with the existing treatment or as alternatives in combatting this severe disease.

Yuxing Li's laboratory previously isolated an antibody, CA45, that recognizes and neutralizes four species of Ebola. The crystal structure of the CA45 antibody bound to the Ebola virus surface glycoprotein, which was subsequently determined by the Ofek laboratory at IBBR, helped define the structural basis for the breadth of CA45 recognition and neutralization of these viruses. Recent studies have shown

Yuxing Li

that CA45, as well as a second antibody, FVM04, bind to a wide range of variants of the Ebola virus glycoprotein, GP, which is critical for binding and entry to human cells. Given the existence of multiple species of Ebola virus, as well as mutations that can emerge, broadly binding to multiple variants is important for the effectiveness of a therapeutic. Li's and Ofek's research into the basis for broad neutralization, as well as exploring B cell responses to viral infection and vaccination, may inform the development of new therapeutics and vaccines.

HIV Research

The human immunodeficiency virus (HIV) attacks the body's immune cells, resulting in weakened immune response to infections. As of 2019, there were 38 million people living with HIV worldwide. There is currently no vaccine available, though researchers are working to develop one and there is a vaccine candidate in clinical trials. Patients diagnosed with HIV are currently treated with antiretroviral therapy to reduce the amount of virus in the blood and body fluids, though this treatment does not cure the disease. Yuxing Li's team, in collaboration with Brian Pierce, is working to better elicit broadly neutralizing antibodies to facilitate HIV vaccine development. (Broadly neutralizing antibodies are immune system proteins capable of rendering multiple genetic variants of a virus harmless.) Before HIV can enter a cell, its surface envelope (Env) protein binds to the cell's receptor protein CD4, which initiates a cascade of events leading to release of the viral genome into the cell. That makes the conserved CD4 binding site of HIV's Env protein a target of interest for vaccine development. In a recent study, Li's group designed a panel of novel immunogens (molecules that stimulate an immune response) by creating fusion proteins made of the HIV Env protein gp120 and the CD4 binding site. These fusion proteins had structural components selectively deleted to expose the CD4 binding site, eliciting a more focused antibody response. These findings will aid in developing vaccines and novel therapeutics to target HIV.

The design of HIV Env fusion protein vaccine candidate. Gray surface represents the HIV Env core molecule, with CD4 binding site highlighted in magenta; CD4i antibody moieties, highlighted in blue and orange are included in the fusion protein to focus immune response towards the CD4 binding site; flexible linkers in red are used to connect the functional moieties. (J Immunol. (2020). 204:1543-1561).

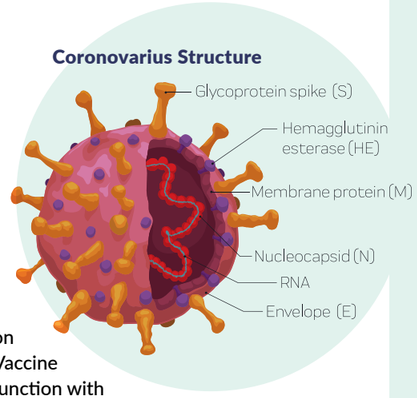
PHOTO BY JOHN T. CONSOLI; FIGURE: ANDREY GALKIN, INSTITUTE FOR BIOSCIENCE AND BIOTECHNOLOGY RESEARCH

CORONOVIRUS ILLUSTRATION BY PENWIN/ISTOCK, RSV FIGURE: J. CURTIS, NIST

COVID-19 Research

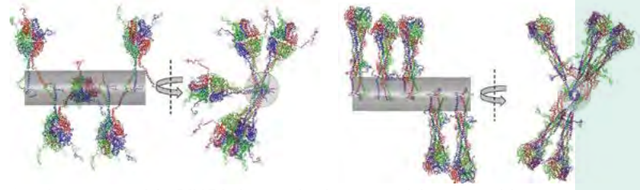
Vaccine candidates are urgently needed to fight the COVID-19 pandemic, caused by SARS-CoV-2, the most recently identified coronavirus. Coronaviruses are a large family of viruses, with several known to cause respiratory infections in humans. COVID-19 is currently affecting many countries globally and researchers around the world have been working to better understand the virus and its effects on the body, as well as developing novel treatments and vaccines to prevent infection.

Thomas Fuerst, Brian Pierce, Gilad Ofek, Eric Toth, Yuxing Li, and Alexander Andrianov, working in conjunction with University of Maryland School of Medicine faculty members Matthew Frieman and Nevil Singh, are working to generate novel vaccine candidates for SARS-CoV-2. The SARS-CoV-2 spike protein is a protein embedded in the viral envelope that mediates entry into host cells and is therefore a major target of SARS-CoV-2 vaccine and antibody-based therapeutics development. The team is applying computational design tools and high-resolution structural characterization to produce and optimize vaccine candidates based on the spike protein. Vaccine candidates, in conjunction with a polyphosphazene-based delivery system, will be tested for their ability to generate effective immune responses and stimulate long-lasting immunity. Findings from this study will inform the selection of a lead vaccine candidate for prospective clinical studies. Fuerst's laboratory group is further working in collaboration with several other laboratories to develop novel monoclonal antibodies to the SARS-CoV-2 spike protein that mimic the native virus.



SARS-CoV-2 and RSV Vaccine Research

Vaccines are generally delivered as complex formulations, including the active viral biomolecules, nanoparticle carriers, and adjuvants. Gathering information on the structure of these multi-component assemblies helps to optimize vaccine candidates for efficacy and better understand their mechanism of action. IBBR Fellow Alexander Grishaev and NIST researcher Tom Cleveland in collaboration with Novavax, Inc. and scientists at the NIST Center for Neutron Research are working to decipher the structure of several vaccine formulations, including those for Respiratory Syncytial Virus (RSV) and SARS-CoV-2. The research team is exploring how viral proteins that comprise the vaccine materials produced and provided by Novavax are presented in nanoparticle carrier material and how components are assembled. The team is also investigating the surface of the proteins in complex with the carrier that interact with host molecules that ultimately effect immunity and the conformation, or shape of the protein before and after it interacts with a host target. For such complex multi-component systems, applications of single experimental approaches are insufficient as they yield data on only portions of the complex. The team applies a combination of advanced structural techniques, including X-ray and neutron scattering, cryo-electron microscopy, and molecular modeling to generate ensembles of structural models for vaccine material at physiological conditions. For RSV, the vaccine research team has discovered presence of fusion proteins, viral



Arrangement of the RSV F fusion protein trimers around the nanoparticle carrier core in the vaccine material, as determined by solution X-ray and neutron scattering.

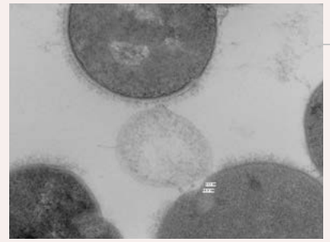
proteins that bind to host cells and mediate entry into the cell, in multiple conformations. These could either include previously characterized post- and pre-fusion states or correspond to yet unknown structural intermediates, which could impact interaction of the vaccine with the components of the human immune system. Such insights can inform understanding of vaccine activity and stability. The group is furthering this work to characterize the vaccine formulations for SARS-CoV-2 toward development of a new vaccine candidate, including the impact of mutations discovered with the progression of the pandemic.

Vaccines against viruses such as SARS-CoV-2 are also developed using fragments of viral ribonucleic acid (RNA) material. Structural characterization of the RNA assemblies is particularly challenging due to their flexibility and difficulties in applying techniques such as X-ray crystallography, or cryo-electron microscopy. IBBR Fellows Alexander Grishaev, Robert Brinson, and John Marino and collaborators at Duquesne University are applying solution X-ray scattering and NMR techniques to advance structural knowledge of the conformation of viral RNA in a number of virus strains. This type of information can aid in discovery and development of new vaccines and therapies.

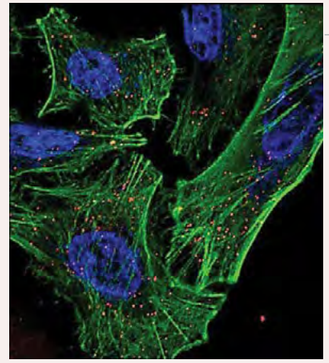
Therapeutic Development and Drug Discovery

Understanding of the structure and function of the molecules within cells and how they are altered in disease contributes to development of new therapies. IBBR investigators utilize new technologies and structural information to make discoveries to advance understanding of disease mechanisms and new drugs to treat diseases.

The 1.4 Angstrom crystal structure of PlyCB, the octameric cell wall binding domain of the PlyC endolysin.



Electron microscopy of a streptococcal cell undergoing endolysin-mediated lysis. The cell wall has been degraded and the extruding membrane is osmotically ruptured.



Confocal microscopy of intracellular PlyC endolysin (red) in lung epithelial cells. Actin cytoskeleton stained with phalloidin (green) and the nucleus is stained with Dapi (blue).

Ratcheting Up Virus-Made 'Dynamite' to Fight Disease

More and more disease-causing bacteria are acquiring mutations that allow them to escape death caused by administration of antibiotics. To address this growing problem, some scientists are working to make new antibiotics. IBBR Fellow Daniel Nelson is taking a different approach. He is conscripting enzymes made by viruses to break free from bacteria. By mixing and matching different components of the enzymes with previously existing technologies, he is adapting them to additional applications as well.

Each type of virus has evolved to infect a specific type of cell from a specific organism. Viruses that infect bacteria are called bacteriophages, or phages for short. After replicating within a bacterium, the phages use enzymes, called lysins, to clip molecular bonds within the bacterial cell wall, causing the bacterium to explode and release its viral load. Each phage produces lysins that target cell wall components specific to the type of bacteria they like to infect.

A naturally-occurring lysin is like a multifunctional tool that has different working ends for different jobs. On one side of the enzyme is a binding domain, whose job is to grab on tightly to the bacterial cell wall. At the other end is a "chewing domain," whose job is to dissolve the wall's cement.

Daniel Nelson

PHOTO BY DAVE ROMERO

Nelson's group has identified multiple lysins that target disease-causing bacteria, including *Staphylococcus aureus* and *Clostridium difficile*, which can cause deadly hospital-acquired infections, and *Bacillus anthracis*, which produces the deadly anthrax toxin. Using various bioengineering approaches, they have also generated novel lysins that act on bacteria from outside the cell, like one that has enhanced activity against *Streptococcus pneumoniae*, a cause of pneumonia. (Engineering efforts are now underway to create a nebulizer that would deliver the enzyme directly to infected lungs.)

Lysins are stable proteins amenable to a wide range of storage and application techniques and Nelson says they have several advantages over traditional antibiotics. Most importantly, he believes it will be much harder for bacteria to develop resistance to them because of their high specificity and robust ability to burst open bacteria. Lysins are like wrecking balls that destroy swiftly and completely, giving bacteria no chance to react.

Another boon for lysins is that they can penetrate biofilms, the physical equivalent of an energy shield erected around a population of bacteria to keep it safe from the body's defenses. Lysins also tend to work on a very narrow range of bacteria, leaving the body's cells and its helpful bacteria alone.

IMAGES BY DANIEL NELSON

Nelson's lab is also finding other uses for the lysin binding domain. For example, they have partnered with nearby Integrated Biotherapeutics on a project to develop enhanced antibodies. Antibodies act like flags within the body to mark foreign invaders for attack or clearance by immune cells. By replacing a lysin's chewing domain with an antibody so that the remaining binding domain acts like superglue, the invading bacteria can be covered in antibodies and increase the body's efficiency in clearing the pathogens. There is now a project to test one such altered antibody, against *B. anthracis* and its toxin, in preclinical models, and they're working on similar projects against *C. difficile* and pneumococcus.

Another application for altered lysins, says Nelson, is the development of field tests—as simple as a pregnancy test—to detect the presence of disease-causing bacteria. This time, a lysin's binding domain is attached to an enzyme that is activated upon binding to a bacterium. The enzyme's activity induces a color change on the dipstick, quickly alerting a veterinarian to an anthrax outbreak in livestock, for example.

Nelson is further extending this work on lysins to develop an approach to target *Cutibacterium acnes*, the bacterial species involved in acne. Acne affects the skin's oil glands and hair follicles and results in colonization of the skin by bacteria, which leads to inflammation. To develop a new kind of topical treatment, the laboratory will characterize lysins that are specific to *Cutibacterium acnes*, develop and test delivery formulas, and begin to assess safety and efficacy in model systems.

Nelson expects the field to start growing exponentially soon. "Research on lysins is currently a mile wide but only an inch or two deep. We've identified a lot of enzymes, gathered a lot of preclinical data, learned a lot about their structure and function. Now it's time to try to expand their specificity, increase their shelf-life and explore different delivery systems," he says.

Killing Two Cancers with One (Molecular) Stone

Prostate and pancreatic cancers are different diseases, but they might both be treatable with the drug galeterone, a multi-target small molecule developed by IBBR Fellow and University of Maryland School of Medicine Professor Vincent Njar and the late Angela Brodie of the University of Maryland School of Medicine. Njar and Brodie knew that molecules called androgens are key

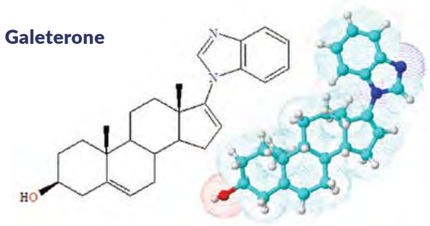
drivers of prostate cancer cell growth, so they worked to develop specific inhibitors of 17α-hydroxylase/17,20-lyase (CYP17), the key enzyme that catalyzes the biosynthesis of androgens. Galeterone exhibited multiple anti-cancer activities and has since gone through extensive pre-clinical studies. It has also been evaluated in a Phase 1 study assessing safety and dosage and a Phase 2 clinical trial for prostate cancer. It is now entering a Phase 2 trial for pancreatic cancer and a Phase 3 trial for prostate cancer to further evaluate its safety and efficacy.

Prostate Cancer

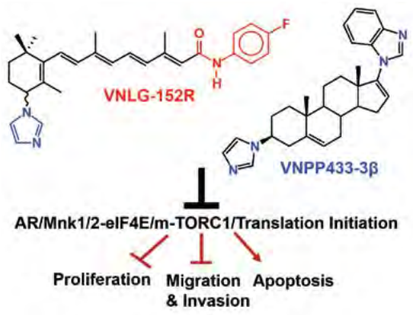
Prostate cancer is the most common solid organ cancer in men. It is often diagnosed at a stage when it is limited to the prostate gland and nearby tissues, and treatments such as prostate gland removal and radiotherapy are often successful in treating the disease. However, those treatments don't work for some men and the cancer can spread, or metastasize, to other organs. For cancer that has metastasized, resistance to first line-treatments, such as androgen deprivation therapy, often occurs, at which point the cancer is referred to as castration resistant prostate cancer (CRPC).

Njar's laboratory group has shown that galeterone—a steroid—targets and disrupts androgen receptors, which prostate cancers depend upon for growth and survival. Galeterone also interferes with the production of cancer-promoting proteins and induces the degradation of certain signaling molecules (mitogen-activated protein kinase-interacting kinases 1 and 2 (Mnkl/2)) implicated in cancer development, progression, and metastasis. Studies have shown that galeterone is effective against drug-naïve and drug-resistant prostate and pancreatic cancer cell lines and may inhibit cancer development and progression processes.

After the initial synthesis and characterization of galeterone by Njar and Brodie, the drug was licensed to Tokai Pharmaceuticals, which developed large-scale production processes and conducted Phase 1 and 2 clinical trials. In 2009, galeterone was designated an investigational new drug and evaluated in a Phase 1 clinical trial treating patients with CRPC. That same year, it received a Fast Track designation from the Food and Drug Administration for treatment of CRPC. Galeterone has also gone through a Phase 2 clinical trial and a prior Phase 3 trial was initiated to compare the effectiveness of galeterone versus another drug, enzalutamide, in patients with a specific genetic variation. Galeterone will now, under a license with Educational & Scientific, LLC, enter a multi-center Phase 3 clinical trial.



2-D and 3-D Structures of Androgen Receptor Modulator Clinical Agent Galeterone (VN/124-1 or TOK-001)



Schematic showing the structures of lead AR/AR-Vs and Mnk1/2 degraders (VNLG-152R & VNPP433-3β) and their impact in cancer cells

Pancreatic Cancer

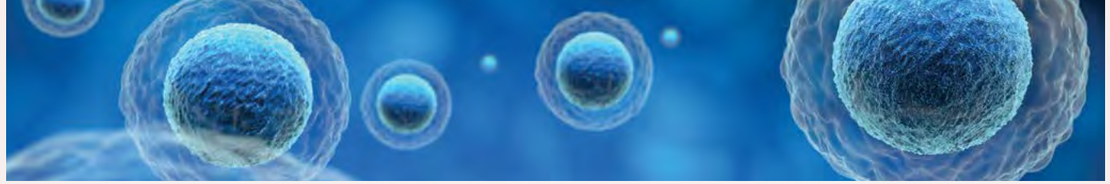
Pancreatic cancer is one of the leading causes of cancer-related deaths in the world. It can be difficult to detect due to the organ's position deep within the body, the lack of a specific screening test, and symptoms that may be nonspecific or absent until the cancer is well-developed. This late stage detection impacts prognosis, making it all the more critical to effectively target and treat the disease.

Galeterone acts as a potent inhibitor of pancreatic cell growth in cell culture and in preclinical models and it affects the cell's protein translational complex, which is responsible for building the cell's proteins from RNA codes. The translational complex is excessively abundant in pancreatic cancer and is involved in resistance mechanisms to a number of current therapies.

The safety and effectiveness of galeterone in treating metastatic pancreatic adenocarcinoma is now tested in a Phase 2 clinical trial at the University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center (UMGCCC). The trial is now under the direction of Dr. Yixing Jiang. Both galeterone alone and in combination with the chemotherapy agent gemcitabine will be evaluated. Gemcitabine is often administered as a treatment for patients with advanced or metastatic pancreatic cancer who have previously received chemotherapy. Njar's group has observed synergistic effects of galeterone and gemcitabine in laboratory models, suggesting promise for a combination treatment with enhanced efficacy for metastatic pancreatic cancer.

FIGURES: VINCENT NJAR

TOP IMAGE: CLAUDIOVENTRELLA/ISTOCK; FIGURE: ERIC TOTH; D. TRAVIS GALLAGHER; JOHN ORBAN; THOMAS FUERST; PHILIP BRYAN; GREGORY CUSTER (UMCP)



What's Next?

While the clinical trials take place, Njar and his group in the Center for Biomolecular Therapeutics (CBT) are developing next-generation analogs of galeterone. These molecules, structurally similar but not identical to galeterone, have been evaluated for therapeutic activity in cell cultures and preclinical models. Two compounds, VNPP433-3beta and VNPP414, have already demonstrated potent therapeutic effects in CRPC models and are under further investigation. Additionally, the Njar group is studying a class of compounds, known as novel retinamides, as potential therapies for prostate and triple negative breast cancers. Galeterone, next-generation analogs, and novel retinamides will be further investigated as potential therapies to treat diseases for which new and more effective cancer treatments are critical.

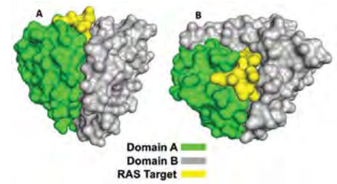
Structure-Based Discovery of Novel Therapeutics

IBBR investigators are working to integrate structural and mechanistic information about disease to develop small-molecule inhibitors as novel therapies. In a recent study, IBBR Fellows Alexander MacKerell, Kristen Varney, David Weber, and Wenbo Yu in collaboration with investigators from the National Institutes of Health and the University of California, San Francisco, applied new measurement methods to detect changes in the protein Ras, which plays a role in the progression of multiple types of cancer. Ras proteins are a family of small enzymes which are important in healthy cells for cell signaling, proliferation, and survival. Ras mutations are present in approximately one third of human cancers. KRas, a Ras subtype, is among the most frequently mutated proteins driving pancreatic, colon, and lung cancers, and cancers with mutations in KRas are often aggressive and resistant to chemotherapy. KRas would therefore be a promising target for new therapies. However, the KRas protein lacks deep binding pockets that can serve as points of interaction with other molecules, making it challenging to characterize its binding sites.

To better understand the dynamic changes in KRas protein shape and the molecules that could interact with and affect its binding regions, the team applied second harmonic generation (SHG), a method used to detect changes in protein conformation, or folded shape, in real time. In this method, light is applied to a protein sample, which is labeled with a dye, and a signal is generated. The signal changes based on the orientation of the sample in space and therefore information can be gathered on protein shape. If a ligand, a molecule that binds to another biomolecule, binds a protein and alters the shape of that protein, such changes can be detected based on changes in the signal.

Using SHG to screen ligands, the research team identified a protein fragment that binds to a form of KRas with a mutation common in many cancers. This study demonstrated the use of SHG as a screening method to identify molecules that bind proteins of therapeutic interest and which can augment other types of measurements, providing additional structural information. Varney further confirmed these findings using nuclear magnetic resonance (NMR). The study findings provide insights into changes in the shape of the KRas protein in response to binding of ligands and identification of molecular interactions that can aid in discovery and design of novel therapies to treat cancers such as pancreatic cancer where mutant KRas is considered a "driver" of the cancer.

IBBR researchers are further applying techniques to better characterize the structure of heterogeneous ribonucleoprotein A18 (hnRNP A18), which is involved in initiating protein synthesis and is upregulated in numerous cancers, including malignant melanoma. Specifically, the A18 protein promotes tumor growth by stabilizing the protein precursor RNA products of several pro-survival genes, which can lead to increased levels of those proteins in cancerous cells. MacKerell, Varney, Weber, and Yu are working with Dr. France Carrier, an oncologist at the University of Maryland School of Medicine, to identify small molecule inhibitors of hnRNP A18, which interfere with tumor progression in melanoma. The team gathered structural information to inform computational screening of compounds to identify molecules that bind hnRNP A18 and block the pro-survival function that the cancer cells



Two views of the domain structure for the RAS-specific protease (6UAO.pdb) with the RAS target sequence (yellow) bound. Binding of the correct target sequence along with a small molecule activator helps induce the RAS-specific protease to become highly active. We call this effect "chemical and conformational rescue" of protease activity. Panel B shows the view in A rotated 180 degrees around the vertical axis.

have hijacked to promote tumor progression. Promising compounds are then subject to further experiments to confirm binding as well as functional inhibition. Like the team's studies of KRas, this work uses structural information and screening approaches to identify compounds that could be further developed to treat cancers. These collaborative projects, using biophysical methods to better understand structural features of clinically relevant proteins, advance the identification of new inhibitors with therapeutic potential that could significantly impact human health.

Engineering SMART Molecular Machines to Fight Disease

Using structural and functional information about cellular molecules involved in disease initiation and progression, IBBR investigators are working to engineer new protein therapeutics, called SMART molecules, that have the ability to bind and act on molecular targets and respond dynamically to their environment—even to a patient's unique chemistry. This type of approach could result in more efficacious therapies with lower toxicity and fewer side effects.

Through a collaboration among IBBR Fellows Thomas Fuerst, D. Travis Gallagher, John Orban, Eric Toth, and David Weber, and Philip Bryan, Yingwei Chen and Biao Ruan of Potomac Affinity Proteins, researchers are designing an enzyme that targets and destroys the Ras protein. In cancer cells, the active Ras protein promotes uncontrolled cell growth and tumor formation. Designing a molecule that can target and inactivate the Ras protein could halt its tumor-promoting activity.

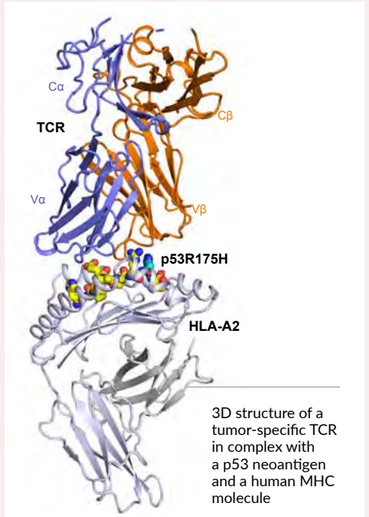
The team's work focuses on developing protein-based multiple-component molecular machines that can change in shape upon binding to a specific target, which then activates a specific response. The team has been working to develop SMART molecules to target the Ras isoforms HRas, KRas and NRas, that regulate cell division. When these Ras isoforms are stuck in the active conformation, they drive cancer progression of several different cancers. The research team recently reported their successful engineering of a protease—a protein that breaks down other proteins—that selectively targets active Ras, resulting in decreased Ras activity. Now they are testing how the protease affects Ras activity in cancer cell models. These design approaches, integrating structural biology, molecular biology, and bioengineering, could ultimately be adapted to other target proteins for the development of therapies for other diseases.

Insights into Immune System Recognition of Targets for Cancer Therapies

Adoptive T cell therapy (ACT) is a treatment for patients with several forms of cancer, and relies upon components of the immune system to recognize proteins produced by cancer cells. To better understand how proteins produced by tumor cells interact with the immune system and how these interactions impact therapeutic development, IBBR Fellows Roy Mariuzza, Brian Pierce, and D. Travis Gallagher are characterizing structures of tumor-specific proteins with immune system receptors.

The therapeutic effect of ACT is mediated by T cells through recognition of tumor neoantigens, which are proteins not previously recognized by the immune system. This recognition occurs through interactions with T cell receptors (TCRs), which are proteins on the surface of T cells.

The research team studied a neoantigen from the p53 protein, which is a tumor suppressor that is the most frequently mutated gene across all cancer types. Mutations in p53 are associated with progression of malignancies and are therefore candidates of interest as targets for ACT. The group determined the crystal structures of three tumor-specific TCRs in complex with a p53 neoantigen and a human MHC molecule. Since TCRs for ACT need to specifically recognize the neoantigen and not the non-mutated protein, this study, published in the journal *Nature Communications* in June 2020, sheds light on how different the neoantigen and the natural non-mutated protein need to be in order to evoke an immune response. The study of such differences can aid in structure-guided efforts to engineer therapeutic TCRs with improved potency toward enhancing treatments for patients.



3D structure of a tumor-specific TCR in complex with a p53 neoantigen and a human MHC molecule

FIGURE: ROY MARIUZZA

Biomolecular Measurement Science and Technologies

IBBR researchers gather information on molecular events and structure to understand complex biological systems. Using these discoveries, scientists at IBBR create new tools for analysis of biological molecules and apply engineering approaches to health challenges.

Katie Briggs (Postdoctoral Fellow, Yu Group) monitors data collection from the new Variable Temperature Benchtop NMR

PHOTO: MARC TARABAN, UNIVERSITY OF MARYLAND, BALTIMORE

Next-Generation Protein Sequencing

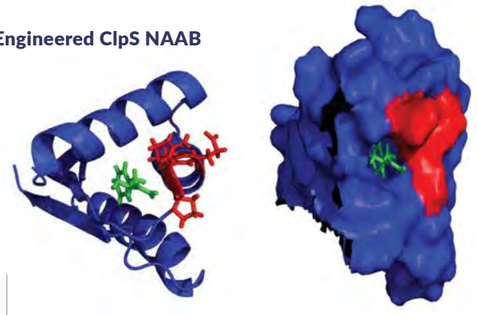
A research team led by IBBR Fellows Zvi Kelman and John Marino is developing new methods to sequence proteins. Sequencing determines the order of the building blocks of a molecule, such as a protein, RNA, or DNA. In recent decades, DNA and RNA sequencing technologies have created vast new opportunities to identify and quantify nucleic acids. The advent of "Next-Gen" DNA sequencing methods have allowed for large scale sequencing, including the complete sequencing of the human genome and many genome-scale studies that have provided insights into biological mechanisms and disease processes. High-throughput technologies now allow for the rapid interrogation of nucleic acid samples.

Similarly, Next-Gen protein sequencing techniques could drastically enhance the ability of researchers to collect information and understand how proteins contribute to cellular function and disease development and progression. Such sequencing technologies could one day assess the order of the amino acids that make up the proteins in biological samples, measure protein quantities, and detect single protein molecules. The availability of such information would enhance the characterization of the diversity and abundance of proteins in a cell and could contribute to the generation of novel diagnostics and treatments.

Current protein sequencing approaches involving mass spectrometry or antibodies binding to specific protein targets both require prior knowledge of the sample composition and protein of interest, which can limit the detection and discovery of novel proteins. Additionally, current methods can have trouble detecting proteins in low abundance. Development of a sequencing approach that would allow for characterization of any, and potentially all, proteins in a cell would allow for more rapid assessment and identification of previously uncharacterized proteins. Sequencing of single protein molecules would further allow for detection and characterization of proteins present even at very low levels in cells.

Sequencing of nucleic acids underlies many scientific discoveries in recent years and extending such an approach to proteins would add significant knowledge of cellular dynamics. However, protein sequencing technologies face specific technical challenges compared to nucleic acid sequencing. For example, DNA is composed of varied sequences of four nucleic acids. Proteins, however, are composed of varied sequences of 20 amino acids and therefore there are 20 possible options per position. Additionally, low abundance of DNA and RNA can be addressed by amplification techniques but these techniques do not exist for proteins.

Engineered ClpS NAAB



A representations of the three-dimensional structure of a candidate protein, Atu ClpS2 bound to a modified amino acid ligand, L-phenylalaninamide (PDB 4YJX), that has been used for N-terminal Amino Acid Binder (NAAB) reagent development. L-phenylalaninamide is shown in green and the amino acids of Clps S2 that have been changed to alter the natural protein binding specificity and affinity are shown in red.

The team led by Kelman and Marino is working to improve protein sequencing by developing new methods involving proteins that selectively bind to the amino acid at the beginning, or N-terminal, of a protein sequence. The proteins, called N-terminal amino acid binders (NAABs), can be fluorescently tagged so that the light they emit identifies the N-terminal amino acid. Then, the bond between the N-terminal and the second amino acid can be broken, revealing the next amino acid in the chain, which becomes the new N-terminal amino acid. By cycling between an N-terminal readout and a cleavage step, scientists can read a protein's sequence one amino acid at a time.

To develop NAABs for protein sequencing, the team is exploring proteins that are part of the protein degradation machinery present in bacteria. These naturally-occurring proteins are lacking some of the properties necessary to serve as components of Next-Gen sequencing reactions, so the team is engineering new versions of the proteins with properties like higher binding affinities, altered specificities, and enhanced stability. Development of new substances and methods to enhance protein sequencing will foster significant advances across scientific disciplines, allowing for a deeper understanding of cellular processes that can in turn contribute to bioengineering, drug discovery, and personalized medicine.

Rapid Detection for Vaccine and Biotherapeutic Quality

Millions of vaccines are administered worldwide each year. After manufacturing, many vaccines require refrigeration during distribution. Certain vaccines, including those with aluminum adjuvants, can be sensitive to freezing, which damages the vaccine. These vaccines must be carefully monitored using vial temperature gauges and high-tech cold boxes during storage and transport. Care providers are very careful to note storage temperature deviations and discard any vaccines that experience subzero temperatures for extended periods of time. Alternatively, analytical techniques can be used to evaluate the condition of vaccine formulations.

A team led by IBBR Fellow Bruce Yu has developed a rapid, non-invasive quality assurance method to detect freezing events of aluminum-adjuvanted liquid vaccines. Yu's assessment method measures the so-called "water proton transverse relaxation rate" by nuclear magnetic resonance (wNMR) relaxometry to quantitatively detect whether a vial has experienced a freeze-thaw cycle. wNMR relaxometry uses a magnetic field to detect relaxation of the resonance signal from water in a vaccine sample, which is sensitive to characteristics of other molecules/ingredients present in a vial.

A key advance of the technique is that it's fast and doesn't compromise the vial's integrity. Therefore, if a vial meets quality standards, it could still be used for vaccination. Additionally, with automation capabilities, all vials can potentially be assessed, rather than a random sample, providing enhanced data collection and the quality assurance of every vial. Given the need to distribute vaccines to billions of people worldwide within a short period of time due to the COVID-19 pandemic, this approach could be important for assuring the quality of large quantities of vaccines before they are administered to patients.

Yu's group is also investigating freezing and freezing variability detection for complex drugs, such as insulin, as well as process analytical techniques for vaccine manufacturing.

Microsensors for Rapid Assessment of Biomanufactured Products

Scientists and health authorities rely on a host of specialized tests to assure the quality of biomanufactured products. With the advent of biologics—drugs produced by living organisms—these evaluations have grown more complex. Chromatography and spectrometry-based methods are commonly employed for molecular analysis in biomanufacturing. These techniques are effective and well-characterized, but can be costly and involve extensive sample preparation. To help develop new analytical technologies, IBBR Fellows William Bentley and Gregory Payne, are working to improve the connection between electronic and biological systems. Their approach seeks to enable rapid, low cost, easily scalable measurements between labs, sites, and manufacturers, as well as to allow for comparative assessments between innovator products and products shown to be biosimilar to an approved product.

The researchers use a method called mediated electrochemical probing (MEP), developed by Bentley's and Payne's team, to assess samples. The system harnesses the chemical processes of reduction and oxidation (redox)—the gain and loss of electrons, respectively—to sense changes in the biochemical environment of a sample. The methodology relies on a microsensor that integrates microfluidics and microelectronics, as well as biological recognition elements that are sensitive to specific chemicals. Bentley's and Payne's team has already demonstrated that MEP can be used to detect the chemical imbalance known as oxidative stress, and to assess cell viability.

The team will use MEP to analyze cultures of cells that are most commonly used in biomanufacturing, that is, the use of live organisms to create products, like biologics, at an industrial scale. For this application, the microsensor will be used to measure glucose, glutamine, and glutamate—molecules that support cell growth and are therefore important to biomanufacturing using cell cultures. Metabolic byproducts will also be measured, including lactate as a marker of cytotoxicity, or cell death, allowing for an assessment of cellular health. Furthermore, MEP will be applied to measure the overall concentration of monoclonal antibodies (mAbs) in a sample. (mAbs can be developed as therapeutic molecules to treat cancers, autoimmune diseases, and other diseases.) Glycosylation, the addition of sugar molecules to proteins, will also be measured. Glycosylation of proteins, including that of therapeutic mAbs, is important to their structure and function, and knowledge of glycosylation patterns can inform the safety and efficacy of biotherapeutics.

The implementation of such microsensors by Bentley's and Payne's team would assist biomanufacturing by allowing rapid, inexpensive monitoring of essential molecules for cell growth, metabolites as indicators of cellular viability, and overall quantity and composition of therapeutic molecules. Their method could be integrated into production control processes to ensure the proper composition of the biologic product. Additionally, it could allow for site-to-site comparison of products and evaluation of innovator and biosimilar products, enhancing current product quality assessments.

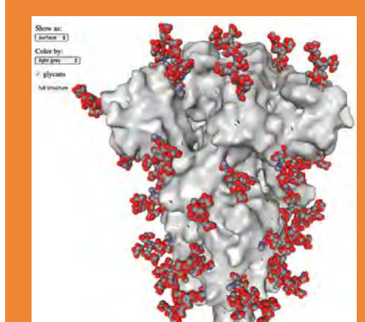
FIGURE: JOHN MARINO

FIGURES FROM COV3D: HTTPS://COV3D.IBBR.UMD.EDU; PHOTO BY JOHN T. CONSOLI

A Library for COVID Researchers

Brian Pierce

High resolution structures of coronavirus proteins are critical to understanding the SARS-CoV-2 virus and how it causes COVID-19, as well as how the immune system recognizes the virus. Together, this information can be used to design effective vaccines and antibody-based therapeutics. To this end, a team in Brian Pierce's laboratory has developed a simple database, CoV3D, as a library of protein structures from SARS-CoV-2 and other coronaviruses. CoV3D (https://cov3d.ibbr.umd.edu), available to all in the scientific community, updates weekly to include the latest experimentally-determined coronavirus protein structures as they are deposited by researchers around the world into the freely-accessible Protein Data Bank. Insights into how the viral proteins interact with the immune system and viral inhibitors are important for developing interventions, so the database also includes and annotates structures of coronavirus proteins in complex with antibodies, receptors, and small molecules. This database serves as a resource to the scientific community to facilitate understanding of coronavirus structures and further enable rational drug and vaccine design.



Left: SARS-CoV-2 spike structure with modeled surface glycosylation (shown as red/gray spheres) visualized on the CoV3D site.

Right: An interactive SARS-CoV-2 spike glycoprotein viewer on CoV3D, with regions of interest on the spike structure represented as different colors.

Translational Activities at IBBR

IBBR'S TRANSLATIONAL MANAGEMENT OFFICE facilitates collaborations between academia and industry and the translation of new biomedical and other life science discoveries to achieve industry relevant milestones.

Discovery
Assess and select commercially promising projects.

Project Management
Identify key components and create multidisciplinary teams leveraging internal and external collaborators.

Intellectual Property
Provide direction throughout discovery process regarding IP strategy to strengthen commercialization prospects.

De-risking, Implementation, and Funding
Seed projects to generate proof-of-concept data.

Commercialization
Identify market opportunites based on industry inputs; Maximize translational impact, notify potential partners, negotiate and finalize collaborations.

Seeding New Innovation at IBBR through MPower

The University of Maryland Strategic Partnership: MPowering the State (MPower) is a UMD initiative that promotes inter-campus collaboration between UMB and UMCP by funding interdisciplinary research. Through this funding, IBBR seeds projects evaluated by criteria such as the potential for translation, the ability to leverage external funding, and meeting an unmet medical need. Projects that complete commercially relevant milestones and produce proof-of-concept data move on to pursue follow-on funding from extramural sources (TEDCO, MII, NIH, and other foundations) to help them advance towards their milestone-driven research goals. Through its funding of IBBR's seed projects, MPower facilitates how IBBR bridges the funding gap to support UMCP/UMB interdisciplinary projects with high commercial value potential.

Viqar Aslam
Director, Business Development and Strategy

Yunus Abdul
IBBR Program and Project Manager

MPOWER FUNDED SEED PROJECTS

Crystallization and Receptor Studies of CD119, a Clostridium difficile Endolysin
(PIs: Daniel Nelson of UMCP and Edvin Pozharskiy of UMB)

Towards Engineering Anti-Haustorium Resistance in Plants
(PIs: Shunyuan Xiao of UMCP, Yuxing Li of UMB, and Illarion Turko of NIST)

Polyphosphazenes (PPZ) as Dental Restoration Materials
(PIs: Alexander Andrianov of UMCP and Michael Weir of UMB)

Structure-Based Design of Immunogens for a Malaria Vaccine
(PIs: Brian Pierce of UMCP and Eric Sundberg of UMB)

Structure-Based Design of a Zika Vaccine Candidate
(PIs: Yuxing Li of UMB and Yimeng Wang, Alexander Andrianov, and Tom Fuerst of UMCP)

INFOGRAPHIC: MLAP STUDIO/ADOBE STOCK; ICONS FROM THE NOUN PROJECT: LIGHT BY NUMERO UNO, KEY BY MAKARENKO ANDREY, NETWORK BY BUSINESSICONS13, VENTURE CAPITAL BY MICHAEL THOMPSONT, MEGAPHONE BY FAUZAN ADIIMA, LARGE INTESTINE BY BOMSYMBOLS, LEAF BY AISYAH, TOOTH BY LAYMIK, MOSQUITO BY ALISA ANDERSON, CA; PHOTOS BY JOHN T. CONSOLI

Green Initiatives

IBBR IS COMMITTED to enhancing sustainability through the reduction of energy consumption and carbon emissions. IBBR's Facilities and Laboratory Services team, led by Jim Johnson, has worked to develop and implement initiatives that work toward carbon neutrality. IBBR continues to evaluate opportunities to reduce waste, reduce energy use, and enhance efficiencies.

Past achievements:
Over the past 10 years, the University has reduced its carbon footprint by 27% with the goal of being carbon-neutral by 2050.

- A new, more efficient chiller and a chiller consolidation
- Facility-wide lighting upgrades
- New lab air-safety monitors
- Reduction of peak consumption during high energy demand days
- Significant water conservation measures
- HVAC office control and lab control upgrades
- Solar panel installations

Looking forward:
Measures to reduce energy consumption.

- New -80°C freezers
- Fume Hood *Shut the Sash* Program

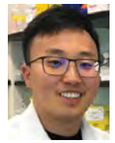
ICONS FROM THE NOUN PROJECT: LEAF BY YANTI, PORTABLE CHILLER BY VECTORS MARKET, FUME HOOD BY ANDREJS KIRMA, FREEZER BY ADRIEN COQUET, LIGHT BULB BY CREATIVE STALL, AIR QUALITY BY EMMA MITCHELL, VENTILATION BY VADIM SOLOMAKHIN, SOLAR PANEL BY ROCKICON, SOLOMON PHOTO BY TIMNA WYCKOFF, LEI AND KUNDU PHOTOS BY VICKI BUCKHOLZ

Training Highlight

IBBR offers a vibrant, multidisciplinary environment for postdoctoral and graduate training, as well as undergraduate and high school research internships.

Dissertation Defenses:

Tsega Solomon, November 1, 2019: "Protein fold switching: investigating the mechanism of αβ-plait to 3α fold interconversion," University of Maryland Biochemistry Graduate Program, in fulfillment of the requirements for the doctoral degree. *Dissertation Advisor: IBBR Fellow* John Orban



Lin Lei, March 20, 2020: "High-resolution analysis of HIV envelope-specific antibody responses to accelerate rational immunogen design," University of Maryland College of Computer, Mathematical, and Natural Sciences Graduate Program, in fulfillment of the requirements for the doctoral degree. *Dissertation Advisor: IBBR Fellow* Yuxing Li

Kunal Kundu, October 15, 2020: "Interpreting Genetic Variants for Discovering Disease Etiology and Mechanisms," University of Maryland Biological Sciences Graduate Program, in fulfillment of the requirements for the doctoral degree. *Dissertation Advisor: IBBR Fellow* John Moult

Kunal Kundu was also awarded an Outstanding Graduate Assistant Award from the UMCP Graduate School. Selection criteria for this award include making important contributions to a faculty member's research, mentoring other graduate assistants and students, showing future promise as a researcher, and having demonstrated scholarly achievement. Kundu's research focuses on new computational methods for identifying disease-causing genetic variants, the development of an online resource for describing and analyzing disease mechanisms, and the use of computational deep learning methods to model genetic disease.

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Exploring the structure and function of biomolecules

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