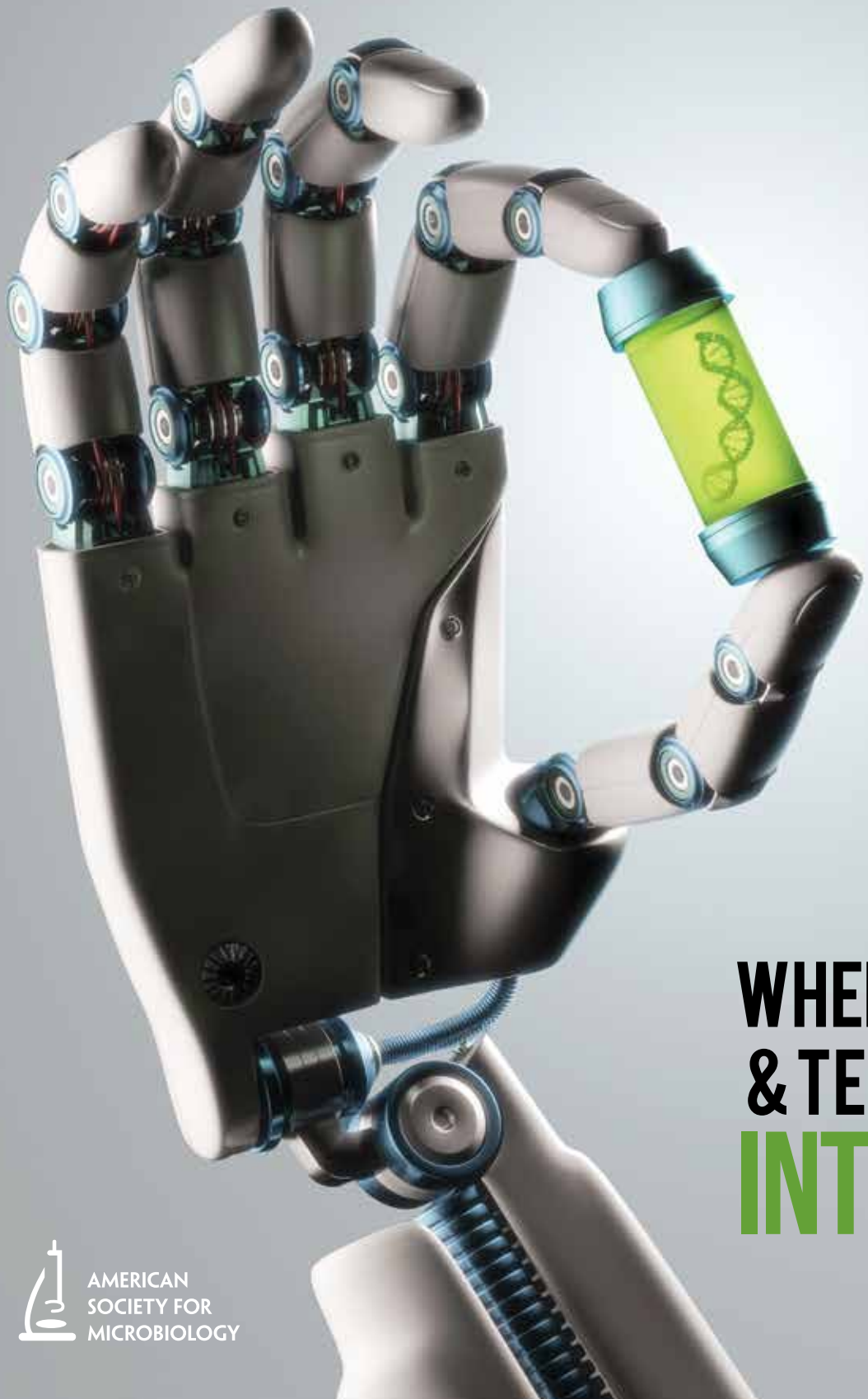
A publication of the American Society for Microbiology

Microcosm

Spring 2019



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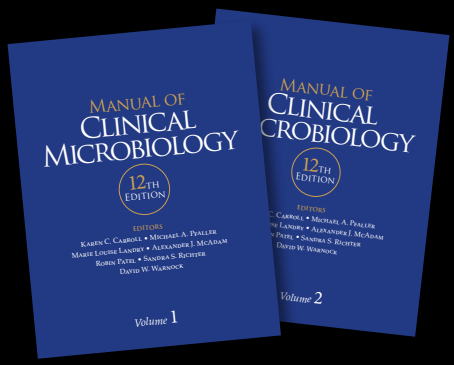

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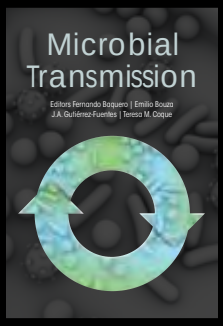

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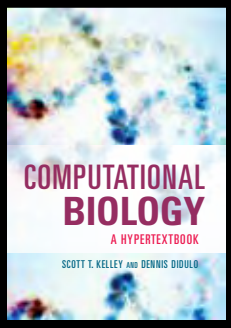

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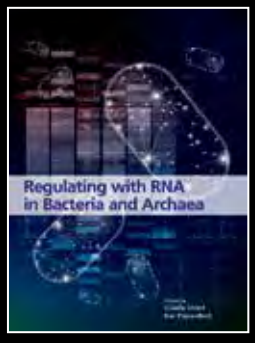

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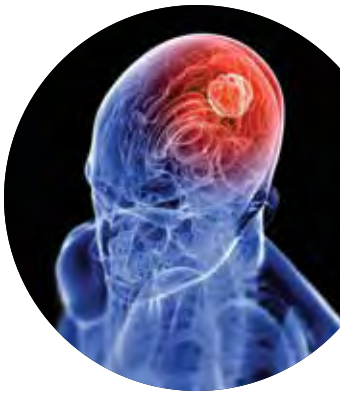

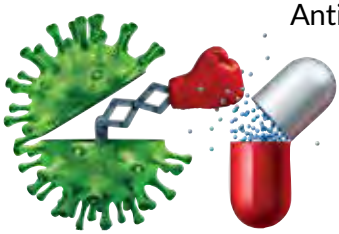

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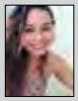

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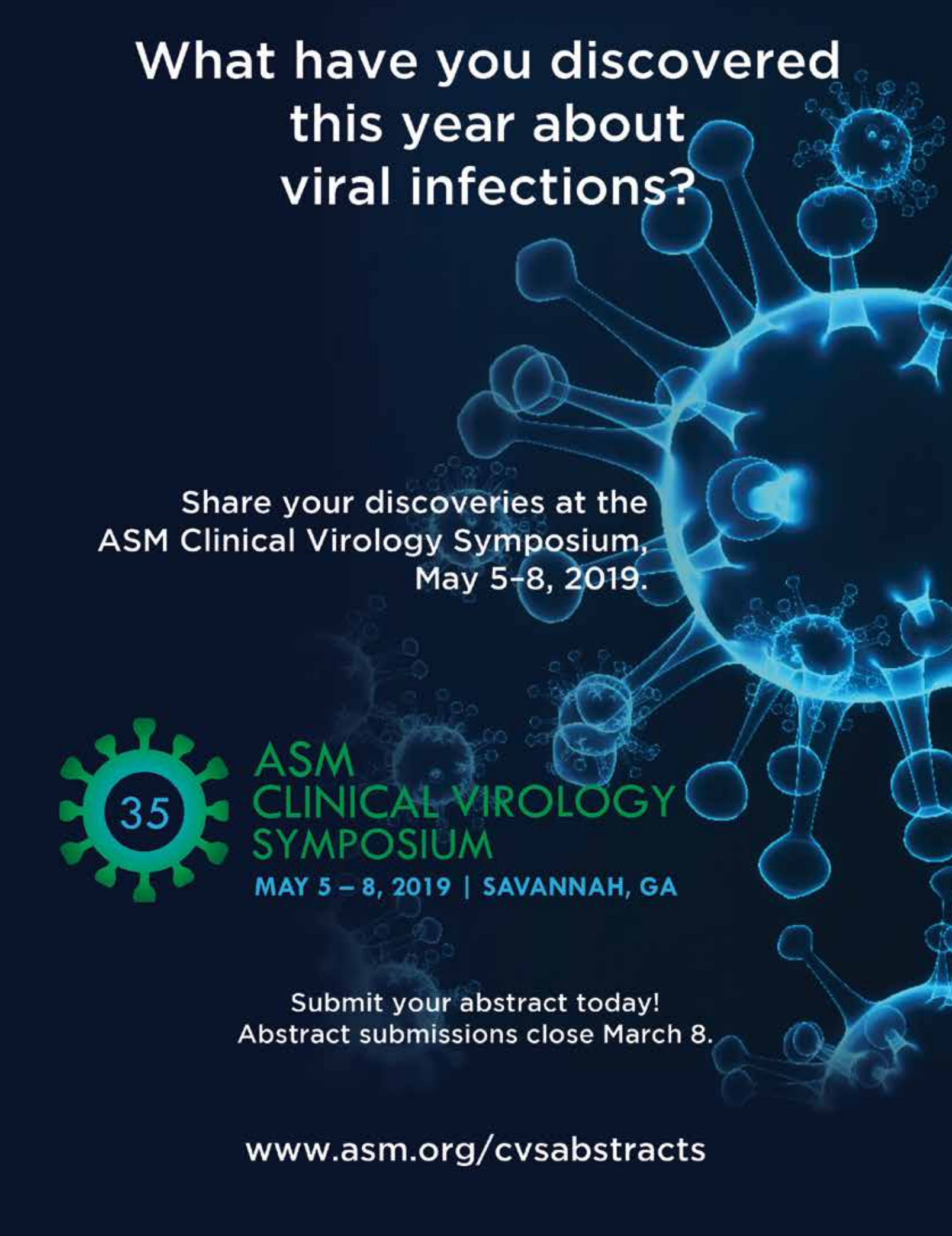
What have you discovered this year about viral infections?



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from the editor

What we now call the scientific method grew out of the observations and interactions with the world we experience in our daily lives. These experiences are limited by our own physical limitations. Technology, which can be defined as the practical application of knowledge, can extend these capabilities and allow us to learn more about and do more with our environment.

Our own field of microbiology grew out of the development of a technology from a completely different one. Developments in optics allowed Anton van Leeuwenhoek and Roger Hooke to see things others could not, demonstrating that we live in a world of microbes. New technologies developed in all disciplines of science have continued to expand the scope and capabilities of microbiology.

Now, the pace of technological development in the digital age has become blinding across all areas of life. By accelerating the rate that we can accumulate and analyze information, computational advances are driving transformations in all of the sciences. We now have the ability to break through boundaries and assess data in quantities and contexts that lead to insights that were previously inaccessible. We've certainly seen this in the explosion of 'omics—genomics, metagenomics, transcriptomics, proteomics, metabolomics and many more tools that allow the large-scale characterization of our ecosystem. These approaches have allowed us to study the microbiomes of humans, animals and plants from virtually every accessible environmental niche. These studies have allowed us to learn exquisite details about our world that we could not have inferred using earlier experimental tools.

In the first 2019 issue of *Microcosm*, we focus on some technological developments that build upon what we've learned about microbe-host interactions to promote favorable outcomes. Examples include using microbials to fight cancer, as highlighted in Rita Algorri's article on treatment of cancer with viruses. To treat diseases like phenylketonuria and Crohn's disease, we can not only alter our own gut microbiome, but also the metabolic capabilities of specific organisms in it, as described in the article by Monika Buczek. In addition to new approaches for treating disease, changes in diagnostic technology are transforming the clinical lab, providing results that are faster, more precise and cheaper, thereby setting the stage for a revolution in patient care.

This issue also marks the departure of Patrick Lacey as managing editor of *Microcosm*. Patrick has played a critical role in communicating science to members as editor of *ASM News* and *Microbe* prior to the evolution of *Microcosm*. He has provided innovative insights, perspicacious perspectives and careful editing that have made our society's magazines interesting, fun and readable. We will miss him greatly!

Stanley Maloy, Ph.D.
Editor-in-Chief

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BIOTECHNOLOGY AND DESIGNER MICROBES

A POTENTIAL LIVING CURE FOR PHENYLKETONURIA AND CROHN'S DISEASE

by Monica Buczek

Treating Disease from a New Angle

The composition of the human microbiome heavily influences host health, immunity and disease by contributing genes, proteins and metabolites to the human ecosystem. As scientists attempt to tease apart the contribution of microbes to various diseases, they have found that certain disorders, such as inflammatory and metabolic diseases, are a quagmire of human genetics, environmental stresses, microbe composition and both human and microbe metabolisms working in concert.

Instead of approaching disease from the human genetics angle, synthetic biologists ask whether they can engineer microbes to inform and treat disease. After all, microbes are essentially tiny single-celled factories that perform various enzymatic reactions within an exceptionally small volume. Could bacteria be re-engineered to perform specific tasks, such as sensing the environment or creating specific products, like drugs, to treat disease? That's exactly where the field of personalized medicine is going for two debilitating disorders that, as of yet, have no cures: the metabolic disorder, phenylketonuria (PKU), and the inflammatory bowel disorder, Crohn's disease.

Preventing Toxicity in Phenylketonuria

PKU is a genetic metabolic disease that causes the body to make insufficient amounts of an enzyme called phenylalanine hydroxylase, which breaks down phenylalanine (Phe) into the essential amino acid tyrosine (Tyr). People with PKU have abnormally high levels of Phe, causing problems by outcompeting with other amino acids essential for brain development from crossing the blood-brain barrier. PKU patients are also deficient in Tyr, necessary for the production of neurotransmitters epinephrine, norepinephrine, and dopamine. This combination of excess Phe and insufficient Tyr causes compounding neurological defects that lead to developmental delays, intellectual disability and microcephaly (small head size).

One of the ways PKU can be treated is with a strict diet that minimizes Phe consumption while increasing Tyr intake via supplements. Phe is an amino acid found most commonly in high-protein foods such as poultry, fish, nuts, egg whites, soybeans and some dairy products. However, there may be a microbial alternative to the PKU diet in the near future.

Scientists at Synlogic Inc., a biopharmaceutical company in Cambridge, Massachusetts, engineered a non-pathogenic strain of *Escherichia coli (E. coli)* to produce Phe-metabolizing enzymes in the mammalian gut. So far, results are promising. Activity of the engineered *E. coli* strain (SYNB1618) was tested by administration to mouse and primate disease models for PKU. After the animals consumed a high-protein, high-Phe diet, researchers tested the blood levels of Phe. Synlogic was able to show significant reduction of Phe in the blood serum of both species and that the ingested Phe was converted to a byproduct called trans-cinnamate. This molecule was then metabolized by the host to hippurate and was harmlessly excreted in the urine. Patients still need to supplement their diet with Tyr pills, but they can avoid the complexity and inconvenience of the PKU diet. Currently, SYNB1618 is undergoing clinical trials, and PKU patients can look forward to the results of phase I and II data in 2019.

But PKU patients shouldn't be the only ones celebrating this achievement. This research may be applied to other metabolic disorders by using *E. coli* engineered to produce enzymes important for normal human metabolic functions. One such genetic disorder is maple syrup urine disease (MSUD), a disorder in which the branched-chain

amino acids leucine, isoleucine and valine cannot be broken down by the body due to a mutation in one of four genes. Though MSUD is slightly more complex than the single-gene mutation of PKU, a combination of human genetic testing and bacterial synthesis of the missing gene product could be a promising therapy for this disease.

But what happens when a disease has hundreds of associated gene mutations instead of just one or four, as in the case of the inflammatory bowel disorder Crohn's disease?

Combatting Crohn's: Living Sensors Respond to and Rewire Our Gut

Crohn's disease, a disorder characterized under the umbrella of inflammatory bowel disorders (IBD), is a painful and debilitating disorder where the body's own immune system attacks the intestinal lumen. This leads to unpleasant symptoms such as abdominal pain and diarrhea, but can also cause more serious events such as malnutrition, ulcers, bowel obstructions and tears (fissures). Severe Crohn's disease cases can lead to the formation of unnatural openings (fistulas) that connect the intestine to other tissues or hollow organs.

Unlike PKU, which is a metabolic disorder stemming from a single characterized gene, inflammatory disorders like Crohn's disease are significantly more complex: not one single gene or pathogen has been identified as the sole cause. Over 170 regions on the human genome have been associated with an increased risk for IBD, and over 70 of those are associated specifically with Crohn's disease. But it's not all genetics either — several pieces of evidence suggest that microorganisms affect the pathogenesis of Crohn's. Some patients improve when put on extended courses of antibiotics, and germ-free animals almost never develop inflammatory bowel diseases. Furthermore, when the intestinal content of an afflicted mouse is transferred to a healthy mouse, inflammation often results.

How does one begin to attack a problem with a tangled web of hundreds and even thousands of possible causes? David McMillen, a synthetic biologist at the University of Toronto, believes that the answer lies in repairing damaged cells instead of wading through hundreds of underlying genetic and environmental causes.

McMillen is the leader of a Medicine by Design team dedicated to innovating regenerative medicine therapies for intestinal diseases. Based at the University of Toronto, the team is designing a molecule-sensing microbe that can sense inflammation in the gut, switch on drug-production, and regenerate damaged tissue all in one.

That seems like a tall order, but bacteria react and respond to their environments constantly, and McMillen's team is harnessing that natural cause-and-effect as a new therapeutic. When asked about his team's ideas of how to fight inflammatory disorders such as IBD and Crohn's, McMillen told reporters, "Our ideal outcome would be to be able to deliver a therapeutic into the gut with a programmable bacterium, which you could use for multiple diseases."

A reparative bacterial treatment would be a big improvement over current treatments for Crohn's disease, which address the disease cause, but with serious risks to patients. Often, treatment requires administration of steroids and other anti-inflammatory drugs that suppress the body's natural immune system. This puts patients in danger of acquiring potentially life-threatening infections (such as *Clostridioides difficile* (*C. diff*) and greatly reducing patient quality of life.

McMillen's team is taking advantage of the way that intestinal microbes quickly change their gene expression in response to inflammation. The goal is to identify the relevant gene expression changes and then transform them into inflammation sensors. Once the sensor is established, the team can work to engineer the appropriate response. That's where the work of McMillen's collaborator Dana Philpott comes in. Her team determined that intestinal bacteria secrete a molecule called muramyl dipeptide, which stimulates intestinal stem cells to proliferate and repair intestinal lumen by generating more intestinal cells. Theoretically, "it should be possible to stimulate the human receptor to the right level and promote healing of the cells that are hardest hit during Crohn's disease," Philpott explained.

The Sky is the Limit for Treating a Sick Gut

McMillen and Philpott's teams are working hard to connect the circuit of cause and effect within one bacterial cell, and they are hopeful not only for their own work but for the precedent this type of work sets for all sorts of diseases. (On a more lighthearted note, even hangovers can potentially be cured by probiotics thanks to an acetaldehyde-degrading *Bacillus* from Zbiotics.) Though much remains to be determined regarding safety and cost of these microbial drug factories, it is certainly an exciting time to be in the field of synthetic biology.

Monika Buczek holds M.Phil. and Ph.D. degrees in molecular, cellular and developmental biology from the City University of New York Graduate Center. She now works as a scientific program manager in translational cancer research. She is a writer for asm.org.

Game of Genomes:

Developing Biotech Tools for Microbiome Manipulation

UP CLOSE AND PERSONAL WITH

HARRIS WANG, PH.D.

by Karen Appold
based on an interview between
Dr. Julie Wolf and Dr. Wang

Columbia University Assistant Professor Harris Wang, Ph.D. is a scientist at the forefront of the intersection of science and technology. He conducts research in the Department of Systems Biology that focuses on key principles driving the formation, maintenance and evolution of genomes within and across microbial populations.

Regarding his broad research interests, Dr. Wang says, "I'm really excited about building technologies, especially those coming from synthetic biology, that we can apply toward understanding and engineering microbial communities. We use the gut microbiome as a model system; it has the right balance of complexity but also offers tractability and has important medical relevance."

Dr. Wang applies systems approaches married with a synthetic biology mindset to dissect complex interactions within microbial communities. "We look to tune and control [these interactions] in ways that might be useful in the context of microbiome engineering," he says. "We focus on understanding the parameters of governing principles associated with how microbial communities organize themselves, both in space and time as well as functionally. We also look at how those very complex interactions come together to increase a population's stability and maintain itself over long time periods and how they evolve over time as a result of these interactions. When armed with this knowledge, we hope scientists can start applying some of these understandings to ecological or microbial microbiome engineering. We're trying to develop technological capabilities as well increase our sophistication across those axes."

The Appeal of Microbiomes

Dr. Wang finds microbial communities a good ecosystem model because of their fast generation time and the high amount of inherent complexity in their many different strains and functions. "Many types of rich interactions can occur in terms of competition, cooperation, antagonism and cross feeding," he says. "We have some level of understanding of how each of those individual types of interactions might work in the context of a simple laboratory setting. We're trying to find out how we can scale that to understand how a community level functions, because it's a very dynamic process."

In his training at Harvard University with Dr. George Church, Dr. Wang and his colleagues developed early multiplex genome engineering platforms for microbes. "I spent a lot of time thinking about how to engineer a single microbe, such as *E. coli*, really well," he says.

A course in microbial diversity at the Marine Biological Laboratory in Woods Hole, Massachusetts, transformed Wang's focus from model microorganisms to model microbial ecosystems. "It helped me appreciate the complexity that exists in natural environments," he says. "I wanted to find out which missing technologies are necessary to bring the same type of genetic engineering into the context of a whole set of communities, whether it's engineering a specific strain that could interact with the rest of the community or engineering an entire community in a larger context."

One of the technologies that Wang's research centers on is horizontal gene transfer (HGT), the process by which microbes naturally share pieces of genetic data in the form of DNA. "Horizontal gene transfer is a natural process that has many engineering applications," he says. "It provides the ability to deliver new genetic functions into many different types of strains within a community." Programming HGT via synthetic biology applications allows researchers to determine which microbes share the DNA and what traits can be propagated among complex microbial communities.

"Horizontal gene transfer is a natural process that has many engineering applications. It provides the ability to deliver new genetic functions into many different types of strains within a community."

Ideally, Dr. Wang wants to build tools that enable everyone within the scientific

community to use them, regardless of application. He foresees these tools being used beyond their initial development by many other groups.

Mentoring Philosophies

Dr. Wang leads a research group that consists of nearly two dozen trainees and early-career scientists. He provides one-on-one face time in his laboratory to give each trainee the opportunity to develop skills at their own pace and hone the mentorship experience in a directed manner.

Conducting weekly individual meetings requires a significant time commitment on his part. "I meet individually with students; we brainstorm and talk about recent ideas, new data or the larger context of what we're trying to accomplish," he says. "I've seen this work well; it's very helpful to students."

Collaboration is also essential. "Almost all of our laboratory projects are driven by a few researchers who take key leadership roles," he says. "I encourage researchers to take ownership of their work, and I aim to instill a sense of passion and value for their work in them. It's important to have a hunger for knowledge and to absorb as much as you can, especially early on."

"I encourage researchers to take ownership of their work, and I aim to instill a sense of passion and value for their work in them."

"The more you're exposed to a variety of topics in different areas, the more your mind can think creatively because it has many different avenues to go down," Dr. Wang continues. "I advise early-career scientists to populate their fountain of knowledge of interests; it's important for trainees and scientists to be aware of research occurring beyond their laboratory. Many great advances have come from doing this."

Engaging With Non-scientists

Dr. Wang understands that science isn't done in a vacuum; it's done by people who are a part of a larger society. "We need to foster the growth of scientists and cultivate them so that they both have a sense of responsibility for their work and understand the impact of their efforts," he says. "Scientists should talk about their work with non-scientists and provide opportunities for [non-scientists] to discuss the enterprise of scientific knowledge acquisition."

Dr. Wang practices what he preaches. He seizes opportunities to speak about his work with the broader public at several local community biolabs, such as Genspace and Biotech Without Borders, both of which are based in New York City. "These have been some of the most exciting and interesting talks I've given: hearing people's reactions, questions and concerns about my work is quite exciting," he says.

Attendees come from all walks of life, such as high school students, artists and people who are interested in science but don't have previous experience. "There's a lot of hunger for science; even among people who aren't scientists," he says.

"Being able to share the unexpected joy of discovery with someone else—and having them envision how to use that knowledge toward building something even more fantastical in the future—that is what I think attracts people to science," Dr. Wang continues.

"Listeners enjoy getting a glimpse of the future," Dr. Wang says. "Scientists have the important role of portraying their work in a way that is both accurate, inspiring and responsible."

The Future of Microbiome Engineering

Looking ahead in the short-term, Dr. Wang foresees a new wave of engineered microbes emerging that could have medical applications. For example, "we might be able to build next-generation smart probiotics that could respond to a variety of diseases and ailments that implant or infiltrate a native community in a way that's both safe and effective," he says.

In the mid- to longer-term, researchers will focus on applications associated with ecological engineering like how to engineer entire biomes. "The future will involve looking at how to terraform and build biological systems that could alter or reverse problems associated with the effects of climate change, either here or on another planet," he says.

"Many of the challenges we face here have similar analogies in other parts of the world, such how do you build something on a planet where organic life doesn't exist or where there's a limited amount of resources," Dr. Wang says. "There are commonalities in terms of the engineering specifications regarding that, as well as the types of solutions."

Harris Wang, Ph.D., is an ASM member and the assistant professor in the Department of Systems Biology, Columbia University in New York, N.Y. Read more about the research going on in the lab at wanglab.c2b2.columbia.edu.

ONCOLYTIC VIRAL TECHNOLOGIES

OFFER A ONE-TWO PUNCH TO FIGHT CANCERS

by Rita Algorri

On August 25, 2018, Senator John McCain died after several months of battling glioblastoma, a particularly aggressive form of brain cancer, also known as glioblastoma multiforme (GBM). It's one of the deadliest and most common forms of brain cancer in adults, affecting two or three out of every 100,000 people. GBM has claimed the lives of several other well-known public figures including Senator Ted Kennedy, Joe Biden's son Beau Biden, composer George Gershwin and NASA astronaut Deke Slayton. Most patients survive less than 20 months following diagnosis.

Development of effective GBM therapies is complicated by the blood-brain barrier, a specialized membrane that evolved to prevent toxins and pathogens in the blood from reaching the brain. The protective function of this barrier also limits the ability of chemotherapy agents to reach GBM tumors. The alternative, radiation therapy, bypasses the blood-brain barrier, but poses its own challenges because it damages healthy brain cells in addition to tumor cells. Surgeries to resect the tumors can extend a patient's lifespan by several months but aren't curative, since glioma tumor cells migrate and embed deep within brain tissue in the majority of cases.

To address the lack of effective GBM treatment strategies, there are over 200 interventional clinical trials ongoing in the United States focused on innovating and/or optimizing therapies for managing GBM and improving survival, including creative engineering of infectious viruses to specifically attack tumor cells.

Oncolytic Virotherapy: New Designer Viruses Fight Glioblastomas from the Inside Out

One of the key tenets for advancing and improving cancer therapies is the pursuit of a therapy that kills or inhibits the growth of cancer cells, without affecting healthy cells.

Thus far, all attempts at developing immunotherapies for GBM have failed by not significantly improving patient survival compared to existing treatments. Many of these potential treatments rely on the patient's immune system to recognize cancer cells, but these therapies are often rendered ineffective by steroid treatments and the tumor's ability to evade immune detection.

Scientists looking for GBM therapies have thus turned to a type of microbe that can differentially affect different cell types: viruses. Viruses are an attractive method for targeting cancer cells because they have a variety of natural properties that can target cancer cells, such as a preference for replicating inside of cells with tumor-specific receptors, causing spontaneous lysis of cancer cells, and/or increasing tumor cell susceptibility to chemotherapy and radiation (Figure 1). Reoviruses, in particular, innately infect and kill cancer cells by preferentially replicating inside of cells containing activated cell growth signals known as Ras proteins, which are often present in rapidly-dividing cancer cells. Reoviruses more efficiently infect cells with activated Ras proteins because

Viruses are an attractive method for targeting cancer cells because they have a variety of natural properties that can target cancer cells

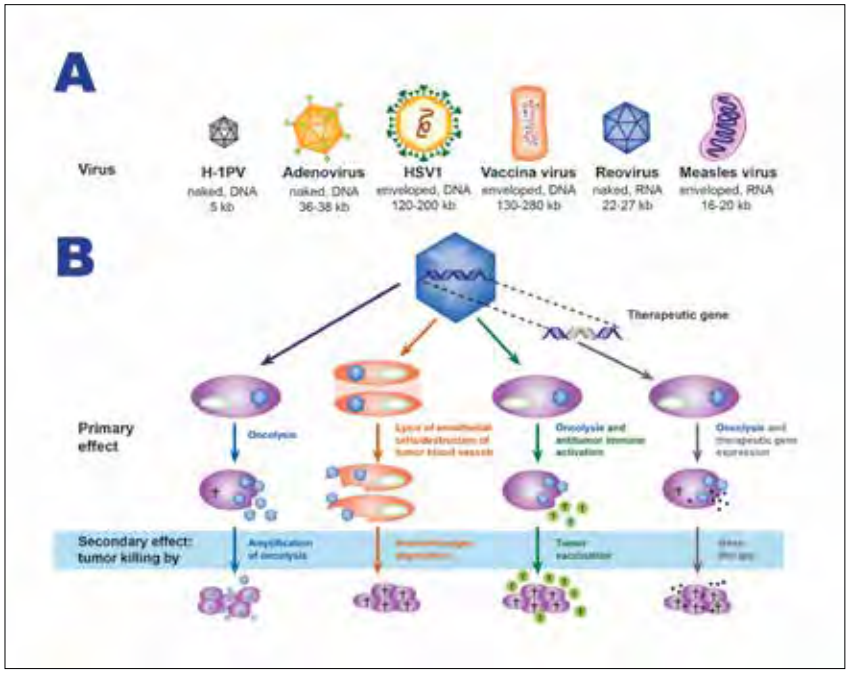

Figure 1: *A. Different families of viruses that can have oncolytic effects upon cancer cells. B. Varying mechanisms of action that viruses can employ to kill cancer cells.*

*Figure used with permissions. Originally printed in *Ungerechts, et al. Mol. Ther. Meth. & Clin. Dev.* 2016.

the virus can uncoat and disassemble more efficiently. When the virus uncoats, the immune system recognizes the viral nucleic acids that are released and launches an attack against the infected tumor cell, killing the cancer cells as a byproduct of eliminating the virus.

The concept of using viruses to fight cancer—also known as oncolytic virotherapy—is not new, and has been around since 1910, when a case of cervical cancer was successfully treated using the Pasteur-Rox live attenuated rabies vaccine. However, the advent of genetic engineering has put a new spin on an old trick, as scientists today have a powerful new tool for manipulating viral characteristics, such as receptors, target cells, replication and lytic cycles. While not all viruses have an innate preference for tumor cells, genetic engineering can help those viruses that are less able to discriminate between cancerous and healthy cells to target cancer cells.

PVSRIPO: A GBM-Targeting Poliovirus That Acts Through CD155

The promising results of a Duke University led phase I clinical trial (a trial with a small number of patients that tests the dosage, side effects and toxicity of a treatment) with a genetically modified poliovirus type 1 were recently published in the *New England Journal of Medicine*. Infectious poliovirus can infect neurons (causing paralytic poliomyelitis), but the modified virus, known as PVSRIPO, is a polio-rhinovirus chimera that is unable to infect healthy neurons due to replacement of a key poliovirus genomic sequence with a sequence from rhinovirus (best known for causing the common cold).

The PVSRIPO virus, like the unmodified poliovirus, targets GBM tumor cells through a cell surface receptor, CD155. CD155 is an immunoglobulin-like protein that is involved in immune-mediated killing and adhesion. It is expressed at low levels in healthy tissues, but is often overexpressed in solid tumors, including those present in GBM. Once the PVSRIPO virus detects CD155 on cancer cell surfaces, it initiates a two-pronged approach to eradicate the tumor cells.

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First, infection with PVSRIPO causes these cancer cells to lyse and die. Second, when the cells lyse, they release proteins that the immune system can recognize as a threat, causing production of interferons, which serve as "cancer alarms" for immune cells. Thus PVSRIPO both directly kills the cancer cells and alerts the immune system to the presence of tumor cells, which have many mechanisms to avoid immune detection (Figure 1). Conveniently, CD155 is also expressed on antigen-presenting cells (APCs), such as dendritic cells, which educate T cells on how to recognize potential pathogens and cancers. Unlike tumor cells, PVSRIPO does not cause APCs to lyse because the inserted rhinovirus genome sequence offers protection against cell lysis. PVSRIPO instead maintains a chronic infection inside the cell that keeps the immune system on the lookout for tumor cells.

During the clinical trial, 61 GBM patients received PVSRIPO delivered directly into the brain using a catheter. At 36 months following treatment, 21% of patients in the PVSRIPO group were still alive, versus 4% in a historical control group of patients with GBM. Some patients that received PVSRIPO lived for more than 5 years—a very atypical outcome for five GBM patients, and a positive sign for the continued success of PVSRIPO in future studies.

Henry Friedman, M.D., associate professor of medicine at Duke University, told *WRAL Tech Wire*, "The impressive results with PVSRIPO in this trial are the best we have seen to date in patients with recurrent glioblastoma and provide hope for these patients whose typical survival time is less than a year." He also added that there is potential to use PVSRIPO for treatment of other cancers as well, due to the prevalence of CD155 in solid tumors across cancer types.

DNX 2401: An Adenovirus That Seeks Out Cells With Irregular Growth Patterns

Another phase I study of oncolytic virotherapy led by Frederick F. Lang's group at the University of Texas MD Anderson Cancer Center demonstrated significant effects on GBM patient survival in a recent *Journal of Clinical Oncology* publication, using a modified adenovirus known as DNX 2401. DNX 2401 has been engineered to infect only cells that lack a functional retinoblastoma pathway, a pathway that controls cell growth and is disrupted in GBM. As a result, DNX 2401 cannot replicate in non-GBM tumor cells. The virus infects cells by binding integrins, proteins that help cells adhere to their environments and are highly expressed on tumor cells, including cancerous glioma stem cells.

Similar to the PVSRIPO viral therapy described above, DNX 2401 utilizes the same two-pronged model as PVSRIPO, including direct cell killing through cell lysis and indirect killing through the activation of immune cells with cancer-killing capabilities.

The clinical study of DNX2401 included 37 GBM patients, separated into two different treatment arms. All patients received intra-tumor injections of the viral therapy, but patients in Group A received single doses of different viral loads to determine which dose was most efficacious with the fewest side effects; patients in Group B received a fixed dose of DNX2401, followed by surgical intervention to remove GBM tumors, and a second dose of DNX2401.

Some patients experienced lengthy remission and long survival time, while other patients continued to progress, dying within 9.5 months. The median survival time in Group B was 13 months, with two patients surviving for two years. Findings from this study showed that not all patients were able to be infected. Infection inefficiency could account for the variabilities in patient outcomes

Dr. Lang told *Science Daily*, "Of those five long-term survivors, three had durable complete responses, which is impressive for a phase I clinical trial in glioblastoma. Many phase I trials might have one patient who does well, so our result is unusual, but we're always cautious in assessing results with this very difficult disease."

ZIKV-LAV: A Modified Zika Virus That Destroys Insidious GBM Progenitor Cells

Even after GBM-associated tumors are surgically removed from the brain, glioma stem cells can get left behind and embed deep within the brain. These stem cells can cause the cancer to grow. A new study from ASM's *mBio* showed that these GBM glioma stem cells can be targeted by a modified Zika virus, the virus that caused a global health crisis in 2016. The study, conducted by Pei-Yong Shi at University of Texas Medical Branch in Galveston, Jianghong Man of the National Center of Biomedical Analysis in Beijing, and Cheng-Feng Qin of the Chinese Academy of Military Medical Sciences, showed that Zika virus preferentially infects glioma stem cells, due to its natural proclivity to infect neural progenitor cells—a fact learned by scientists studying the mechanism by which Zika causes microcephaly in developing fetuses.

The investigators modified the live attenuated Zika virus (ZIKV-LAV) to reduce its virulence and increase its safety by deleting 10 amino acids in the three-foot untranslated region of the virus' genome. This deletion slows viral RNA replication and makes the virus more susceptible to inhibition by the immune system, thereby preventing the development of an uncontrolled Zika virus infection. Previously published studies of ZIKV-LAV suggest that the virus eliminates cancer cells by inducing apoptotic cell death. Like PSVRIPO and DNA 2401, ZIKV-LAV is potentially suitable as a GBM therapy because it preferentially selects for human glioma cells *in vitro,* unlike other flaviviruses, such as West Nile virus, which kills all cell types indiscriminately.

In mice, ZIKV-LAV appears to be safe when intracerebrally injected, as no neurovirulence, disease, or behavioral disturbances were observed in ZIKV-LAV treated mice, in comparison to healthy mice. The investigators also found that the modified Zika virus was unable to be spread to its usual vector, the Aedes mosquito, due to slow viral RNA replication and inhibition by interferons, alleviating concerns for the spread of ZIKV-LAV in the general

population.

In addition to its robust safety profile, ZIKV-LAV demonstrated effectiveness in controlling GBM in mice with implanted GBM tumors, as evidenced by increased survival, smaller tumor size, and, for some mice, complete elimination of visible tumors. As the previously discussed therapies do, ZIKV-LAV uses a two-pronged approach by causing direct oncolytic cell destruction and stimulating an immune response against infected tumor cells.

Looking Ahead: What is the Future of Tumor-Targeting Viruses?

While the results of these studies are promising, additional research is needed to understand and validate their efficacy and safety. The PVSRIPO study experienced several serious adverse events that may have been related to treatment, and both therapies involve invasive dosing procedures, which must be properly regulated and administered. As the National Brain Tumor Society told *CNET*, regarding PVSRIPO, "The evaluation of this treatment—and clinical trial process to ultimately determine if the treatment is safe and effective—is still in its very early phases, and there is a lot more data that needs to be seen."

The investigators who developed these viruses are now experimenting with combining viral therapies with chemotherapy agents and immunomodulators to enhance their efficacy.

The researchers testing PVSRIPO have begun recruiting for their phase II clinical trial, which involves more patients and the addition of a chemotherapy drug, lomustine. DNAtrix Therapeutics, the company now developing DNX 2401, is conducting phase II clinical trials of DNX 2401 in combination with the immunotherapy pemrolizumab. Similarly, Chen and colleagues, the ZIKA-LAV group, are working to further develop ZIKV-LAV for clinical testing in patients with GBM and have expressed interest in further modifying the virus to include an immunomodulatory component in the viral genome, which the virus would release to alert the immune system. If these current studies are successful, viruses may soon be accepted as integral components of GBM therapy.

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In addition to viruses that target GBM, viruses that target other types of cancer are currently in development. Notably, in a *Science Translational Medicine* article published in late January 2019, a modified adenovirus that targets the retinoblastoma pathway, much like DNX 2401, has recently demonstrated preliminary positive safety results in children with retinoblastoma. Retinoblastoma, while usually not fatal, is a pediatric cancer of the retina that can cause blindness. This type of cancer affects the immature retinal cells in children and treatment can require removal of the affected eye, in addition to exposing children to hearing-damaging chemotherapy agents, cisplatin and carboplatin. The novel adenoviral therapy, known as VCN-01, was shown to kill retinoblastoma cells isolated from 11 out of 12 patients, including chemotherapy-resistant cells, as well as mice implanted with patient retinoblastoma cells. Importantly, the virus did not cause systemic inflammation or spread outside of retinal tissues in two patients tested. The virus replicated only in tumor cells, indicating the virus' specificity for cancer-causing cells. The data collected thus far supports further development of VCN-01 as a potential treatment for retinoblastoma.

Rita Algorri is a Ph.D. candidate in clinical and experimental therapeutics and a master's student in regulatory science at the University of Southern California. Her doctoral research focuses on the immunomodulatory properties of antibiotics in the context of Staphylococcus aureus bacteremia *and* sepsis. *She is a writer for asm.*org.

What's New at ASM

ASM Weighs in on Congressional Vaccine Hearings

In March, health-focused committees in both the House and Senate held hearings focusing on recent measles outbreaks and highlighting the importance of vaccines to prevent the spread of infectious diseases.

ASM strongly supports the universal use of approved vaccines to prevent illness and death caused by infectious diseases. There is no doubt that the development and effective use of vaccines for a broad range of life-threatening illnesses has saved countless lives in our nation and around the world.

ASM applauds the committees on their work over the past year towards the reauthorization of the Pandemic and All-Hazards Preparedness Act.

February 27, 2019 *Energy and Commerce Subcommittee on Oversight and Investigations hearing on the measles outbreaks and response efforts in the United States.*

ASM is an Inaugural Member of the Societies Consortium on Sexual Harassment in STEMM

In an effort to promote an environment that allows free expression and exchange of scientific ideas, equal opportunities and respectful treatment for all, ASM is a proud inaugural member of the Societies Consortium on Sexual Harassment in STEMM (science, technology, engineering, mathematics, and medicine), along with 52 other leading academic and professional societies.

The consortium was organized during the AAAS Annual Meeting on February 15, 2019 to provide research- and evidence-based resources for addressing issues of sexual harassment to other professional organizations, including model policies and procedures for combating issues of harassment.

ASM Educates Families on the Microbial Sciences

ASM participated in the American Association for the Advancement of Science Family Science Days, Feb. 16 -17, 2019, in Washington, D.C. ASM members and staff guided an estimated 900 people through activities designed to showcase the breadth of the microbial world. Booth visitors got to see living household bacteria and fungi up close, find out which member of the human microbiome best matched their personality and see how health-related behaviors like not washing their hands affected their likelihood of getting the flu.

AAAS Family Science Days

Ambassador Profile

ASM Young Ambassadors are early-career leaders who represent ASM in their communities and strengthen science globally. In this issue we talk to Tatiana Pinto, Assistant Professor of Microbiology at Instituto de Microbiologia Paulo de Goes, Universidade Federal do Rio de Janeiro, Brazil. Pinto has been an ASM member since 2010 and has published in our journals, received travel grants and became a young ambassador to Brazil in 2017.

Tell us about your work.

My work is focused on better understanding virulence and antimicrobial resistance among *streptococcal* and *enterococcal* isolates recovered from different sources in Brazil.

What's your favorite event or activity you've run as an ASM Ambassador?

There have been many unforgettable moments:

- Bringing the Smithsonian's exhibit "Outbreak" to Copacabana beach in Rio de Janeiro, Brazil, and having the activity featured in Brazilian science magazines.
- Having the opportunity to speak at ASM Microbe 2018.
- My website, divulgamicro.com.br, disseminates online resources on science communication, a topic I'm passionate about. A paper on "DivulgaMicro" will be published in the spring issue of ASM's *Journal of Microbiology and Biology Education.*
- Implementing onsite workshops at six universities, with nearly 300 attendees.

What are your plans as an Ambassador for 2019?

To support the establishment of new ASM student chapters in Brazil. We already have two, at Universidade Federal do Rio de Janeiro and Universidade de São Paulo. I strongly believe that ASM student chapters are a great way to give power and voice to students and post docs, fostering the next generation of scientists.

If you are interested in volunteering as a young ambassador, visit www.asm.org/Articles/International/Become-a-Young-Ambassador.

Branch Spotlight:

The Eastern Pennsylvania Branch (EPAASM)

In 1912, a group of Philadelphians interested in bacteriology formed a "club" that met on a regular basis to discuss their common interests. Eight years later, David H. Bergey, a member of the existing bacteriology club, organized a committee that founded the ASM Branch, EPAASM, in March 1920. Dr. Bergey served as the first president. From 1920 to the present (almost 100 years!), the branch has maintained the tradition of meeting monthly. The 768th monthly meeting was just held in January. There are currently over 400 members, including emeritus members, on the EPAASM mailing list.

Members

The Branch membership reflects the diverse field of microbiology and related sciences being studied in Philadelphia, and includes academic educators and researchers, clinical microbiologists, public health microbiologists, immunologists and pharmaceutical and biotech research and development scientists.

Activities

The most popular activities are the Annual Branch Symposia and the annual Philadelphia Infection and Immunity Forum.

Sidney Pestka lecturer and sponsor representative with student officers from left to right: *Amanda Platt (Drexel University College of Medicine), Amanda Miller (Temple University Lewis Katz School of Medicine), Nawar Naseer (University of Pennsylvania Perelman School of Medicine). Dr. Thomas Wellems (NIAID), Natasha Lope Fischer (University of Pennsylvania Perelman School of Medicine), Jennifer Connors (Drexel University College of Medicine) and Dr. Thomas B. Lavoie (PBL Assay Science).*

In addition to the monthly meetings, the Branch Symposia and the Infection and Immunity Forum offer opportunities for Branch members to learn and share their passion for current important topics in microbiology. The 48th Annual Symposia on *"New Automated Methods and Molecular Diagnostics in Clinical Microbiology,"* held on November 8, 2018, drew attendees well beyond the branch region.

On December 7, 2018, the EPAASM student chapter hosted the 27th Annual Philadelphia Infection and Immunity Forum, a one-day event that brought together microbiologists, parasitologists, immunologists and virologists from the greater Philadelphia area to share their research, network among colleagues and hear outstanding scientists present their research. This year, over 140 scientists participated in the event. The 29th Annual Philadelphia Infection and Immunity Forum will be held on Friday, December 13, 2019.

Another active group of the EPAASM Branch is the Education Committee, which:

- supports microbiology educators with a focus on middle/high schools; undergraduate and graduate levels of microbiology education
- performs community outreach to share an understanding of microbiology in the community
- provides judges for local and regional science fairs, develops programs at local high schools and participates in STEM activities—all with the goal of sharing a passion for microbiology.

Student Chapter

The Branch has an active student chapter with members from Philadelphia graduate school programs including Drexel University, Thomas Jefferson University, the University of Pennsylvania and Temple University. The students organize one of the EPAASM monthly meetings each year, including student presentations and an invited speaker.

Keynote speakers and student officers from left to right: *Dr. Michael Abt (University of Pennsylvania Perelman School of Medicine), Amanda Miller (Temple University Lewis Katz School of Medicine), Natasha Lopes Fischer (University of Pennsylvania Perelman School of Medicine), Nawar Naseer (University of Pennsylvania Perelman School of Medicine), Dr. Stacy Horner (Duke University Medical Center), Amanda Platt (Drexel University College of Medicine) and Jennifer Connors (Drexel University College of Medicine).*

Website

www.epaasm.org/

Microcosm will be highlighting one ASM branch in each issue. If your branch would like to be featured, please send a high-resolution photo and information on your branch's history, members, activities, student chapter, and website to communications@asmusa.org.

New Opportunities to Get Members What They Need

by **VAUGHN COOPER** chair, Council on Microbial Sciences

In an effort to engage our members and help you advance, ASM's Council of Microbial Sciences (COMS) has launched several new programs to support our members at all career stages. The new initiatives are a reflection of the feedback we received from members, and we are excited that we were able to take your suggestions and start new programs. One of these offerings is the Conference Grant Program, a new benefit that empowers members to host in-person gatherings and events. In 2018, ASM awarded close to $60,000 to support 16 member-driven conferences and symposia. The Conference Grant Program supports both new and continuing conferences that cover the breadth of microbiology, spanning topics from antimalarial drug resistance to science communication. ASM members can apply for funding of up to $10,000 for organized conferences, workshops and symposia. The next deadlines to apply for conferences in 2020 are April 1 and October 1, 2019. COMS also initiated the Peggy Cotter Travel Award program, which provides funds for outstanding early career branch members to attend ASM Microbe. Named for ASM's past president, Dr. Peggy Cotter, these awards facilitate her commitment to mentoring by helping up to three early-career scientists per branch with awards of $1,650.

How did these new initiatives come about? And how does ASM gather feedback from members?

ASM's COMS does much of the behind-the-scenes work to anticipate trends in the microbial sciences, gather feedback from across ASM, and suggest actions that will advance our field. COMS doesn't do this alone; they are the "creative mind" of the society, continuously seeking input from membership, ASM's board of directors, and the American Academy of Microbiology. COMS is composed of 95 members of diverse scientific disciplines, ethnicities, cultures, and genders who are recognized for their scientific and professional achievements. COMS represents the society at-large including ASM's branches, divisions, committees, membership, and the microbial sub-disciplines. We are your representatives and we want to hear from you. Please reach out to your colleagues on COMS with your ideas or directly to me (see below).

Additionally, to better understand the needs of the scientific communities, in the last two years ASM has held four retreats for the following groups:

- Clinical and Public Health Microbiology: May 2017
- Ecology, Evolution, and Biodiversity: December 2017
- Host Microbe Biology: July 2018
- Molecular Biology and Physiology: December 2018

During these retreats, we defined the mission of each scientific community, identified ways to promote research within these communities, and discussed strategies to engage and support community members through ASM's journals, meetings, and other offerings.

Hopefully, most of you are familiar with COMS and the work that we do. If not, we hope this provides a glimpse of our role and what we have accomplished.

Vaughn Cooper, Ph.D., is the chair of the ASM Council on Microbial Sciences (COMS) and holds a Ph.D. in zoology/ecology and evolutionary biology from Michigan State University. His research focuses on the evolution, ecology and genome dynamics of experimental and clinical microbial populations.

What's Next?

In March 2019, the Professions of Microbiology (POM) community will meet for its retreat. To help accomplish the many goals established at the retreats, COMS is encouraging the assembly of executive teams for each community group to help implement the defining vision and priorities outlined at the retreats.

How Do I Get Involved?

If you have ideas you would like to share with us, please email us at **coms@asm.org.** We would love to hear your thoughts on how we can serve you better!

What's Hot in the Microbial Sciences

by Julie Wolf and Stanley Maloy

An Infectious Etiology of Alzheimer's Disease?

Does Alzheimer's disease (AD) have an infectious etiology? Research published in *Neurotherapeutics* found a retrospective association between herpes simplex virus (HSV) infection and a risk for developing dementia, which was mitigated by treatment with anti-herpetic medications. Shortly afterward, a study published in *Neuron* demonstrated that the amyloid-β protein, depositions of which are hallmarks of AD, have antimicrobial properties and that the protein oligomerizes on HSV surface glycoproteins, lending further support to a role for HSV brain infection in AD development. A study in *Science Advances* suggested an association between AD and an unrelated microbe, *Porphyromonas gingivalis*. This study demonstrated that inhibitors of *P. gingivalis gingipains*, a secreted cysteine protease virulence factor, blocked *P. gingivalis*-mediated amyloid-β protein production and neuroinflammation. Both studies suggest an underlying infectious agent may be the underlying cause of AD development and further research will reveal whether AD may ultimately be treatable with antimicrobial agents.

- *Tzeng N.S. et al. Anti-herpetic Medications and Reduced Risk of Dementia in Patients with Herpes Simplex Virus Infections: a Nationwide, Population-Based Cohort Study in Taiwan.* Neurotherapeutics. *February 27, 2018. https://link.springer.com/article/10.1007%2Fs13311-018-0611-x*
- *Eimer W.A. et al. Alzheimer's Disease-Associated Beta-Amyloid is Rapidly Seeded by Herpesviridae to Protect aagainst Brain Infection.* Neuron. *July 11, 2018. https://www.sciencedirect.com/science/article/pii/S0896627318305269*
- *Dominy S.S. et al. Porphyromonas gingivalis in Alzhemer's Disease Brains: Evidence for Disease Causation and Treatment with Small-Molecule Inhibitors.* Science Advances. *January 23, 2019. http://advances.sciencemag.org/content/5/1/eaau3333*

Adding Complexity to the Quorum Sensing Conversation

New aspects about who is listening during quorum sensing (QS) communications have been revealed in recent studies. Long considered a mechanism by which bacteria respond to a given population density, a scientific team published in *Cell Reports* that antibiotic treatment stimulated both quorum signaling molecule and biofilm production in the gram-positive *Streptococcus pneumoniae*. Antibiotic treatment induced long bacterial chain growth, which decreased the concentration of the QS signaling molecule required for QS- stimulated competence. Further complications came from a *Cell* report that demonstrated QS influences a Vibrio cholerae bacteriophage life cycle. The vibriophage VP882 encodes an antirepressor that binds QS molecules to determine its lysis-lysogeny life cycle. *Bacillus* phages also communicate to determine lysis-lysogeny decisions, but using the arbitrium communication system, and crystal structures of the B. subtilis phi3T phage arbitrium proteins published in *Molecular Cell* show surprising structural similarity to QS systems. The transcription factor AimR has shared structural features with the RRNPP QS family, and scientists determined that AimR activity is influenced by binding both its DNA operator and the signaling peptide AimP, which acts similar to a QS signal. Finally, a screen for inhibitors of QS pheromone degradation, published in *Journal of Biological Chemistry*, revealed a novel chemical that inhibits the Streptococcus endopeptidase PepO, prolonging QS and allowing researchers to tease out additional players in the system. Understanding the exact molecular communications within microbial consortia will ultimately allow human interference in this system.

- *Domenech A. et al. Antibiotic-Induced Cell Chaining Triggers Pneumococcal Competence by Reshaping Quorum Sensing to Autocrine-Like Signaling.* Cell Reports. *November 27, 2018. https://www.cell.com/cell-reports/fulltext/S2211-1247(18)31753-4*
- *Silpe J.E. et al. A Host-Produced Quorum-Sensing Autoinducer Controls a Phage Lysis-Lysogeny Decision.* Cell. *December 13, 2018. https://www.cell.com/cell/fulltext/S0092-8674(18)31458-2*
- *Gallego del Sol F., Penadés J.R. and Marina A. Deciphering the Molecular Mechanisms Underpinning Phage Arbitrium Communication Systems.* Molecular Cell. *February 7, 2019. https://www.cell.com/molecular-cell/fulltext/S1097-2765(19)30045-0*
- *Pérez Morales T.G. et al. A Novel Chemical Inducer of Streptococcus quorum sensing acts by inhibiting the pheromone-degrading endopeptidase PepO.* Journal of Biological Chemistry. *January 19, 2018. http://www.jbc.org/content/293/3/931*

Microbes in Space!

A number of recently published studies have resulted from research conducted on the International Space Station (ISS). A microbial survey published in *PeerJ* previously demonstrated that the ISS microbial community is more similar to home surfaces on earth than to human microbiome samples. Two characterization studies of fungi commonly isolated from the built environment, *Aspergillus niger* and *A. nidulans,* revealed expression of stress response genes and secondary metabolites in the ISS cultures, which will be important in planning for ISS crew exposure to these opportunistic pathogens. These studies were published in *Applied and Microbiology Biotechnology* and *mSystems*. The gram-positive bacterium *Bacillus subtilis* also increases its stress response when cultured on the ISS, including genes involved with biofilm formation and oxygen limitation, as published in *NPJ Microgravity,* and was observed during independent missions, confirming reproducibility of the microbial response. Finally, a recent *mBio* study demonstrated that exposure of *E. coli* cultured in ISS-mimicking conditions resulted in selection for persistent drug resistance. These studies will inform how to best prepare astronauts for long-term space missions, which can result in their immune suppression and increased susceptibility to infection.

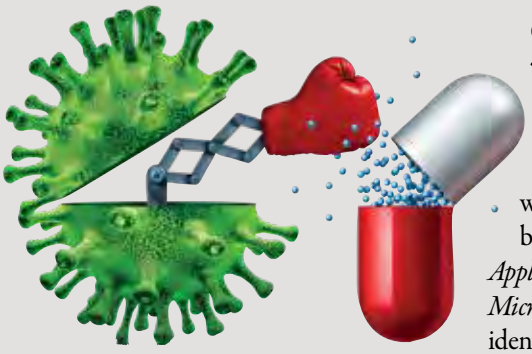
- *Lang J.M. et al. A Microbial Survey of the International Space Station (ISS). PeerJ. December 5, 2017. https://peerj.com/articles/4029/*
- *Romsdahl J. et al. International Space Station Conditions Alter Genomics, Proteomics, and Metabolomics in Aspergillus nidulans.* Applied and Microbiology Biotechnology. *December 12, 2018. https://link.springer.com/article/10.1007%2Fs00253-018-9525-0*
- *Romsdahl J. et al. Characterization of Aspergillus niger Isolated from the International Space Station.* mSystems. *September 18, 2018. https://msystems.asm.org/content/3/5/e00112-18*
- *Morrison M.D., Fajardo-Cavazos P., and Nicholson W.L. Comparison of Bacillus subtilis Transcriptome Profiles from Two Separate Missions to the International Space Station.* NPJ Microgravity. *January 7, 2019. https://www.nature.com/articles/s41526-018-0061-0*
- *Tirumalai M.R. et al. Evaluation of Acquired Antibiotic Resistance in Escherichia coli Exposed to Long-Term Low-Shear Modeled Microgravity and Background Antibiotic Exposure.* mBio. *January 15, 2019. https://mbio.asm.org/content/10/1/e02637-18*

Better Defining Beneficial Gut Microbes

Scientists are refining the list of which gut microbiome members promote health and how their growth can be promoted. Research published in *Nature* defined a microbial consortia of 11 strains that promoted clearance of the intracellular bacterial pathogen, *Listeria monocytogenes,* as well as improved response to cancer therapy, both in mouse models. Protection was mediated by increased recruitment and proliferation of IFNγ-producing CD8 T cells by the consortia strains, and was observed even when the consortia was added to germ-free mice in the context of additional mouse or human fecal microbiota. Meanwhile, a *Nature Microbiology* population-wide survey uncovered a correlation between buyrate-producing microbes and higher quality of life indicators. The authors further found a potential role of microbially-produced γ-aminobutyric acid (GABA), a neurotransmitter, in depression. A study in *mSphere* addressed dietary additives that can promote growth of health-promoting bacteria, particularly anaerobes that produce a number of short-chain fatty acids (SCFAs) that benefit the microbial ecosystem and host epithelial cells. The results demonstrate that wood-derived dietary prebiotics, acetylated galactoglucomannan (AcGGM) and acetylated arabinoglucuronoxylan (AcAGX) are selectively fermented by specific commensal bacteria to produce SCFAs. These findings will help scientists develop an encyclopedia of preventative dietary measures for optimal health.

- *Tanoue T. et al. A Defined Commensal Consortium Elicits CD8 T Cells and Anti-Cancer Immunity.* Nature. *January 23, 2019. https://www.nature.com/articles/s41586-019-0878-z*
- *Valles-Colomer M. et al. The Neuroactive Potential of the Human Gut Microbiota in Quality of Life and Depression.* Nature Microbiology. *February 4, 2019. https://www.nature.com/articles/s41564-018-0337-x*
- *Leanti La Rosa S. et al. Wood-Derived Dietary Fibers Promote Beneficial Human Gut Microbiota.* mSphere. *January 23, 2019. https://msphere.asm.org/content/4/1/e00554-18*

Antimicrobial Resistance Everywhere



Several studies have recently highlighted that sites considered pristine are in fact polluted with drug-resistant bacterial isolates. An *Applied and Environmental Microbiology* study identified antimicrobial-resistant *Escherichia coli (E. coli)* isolated from wild giraffes in the Ol Pejeta Conservancy wildlife reserve in Kenya. Resistant *E. coli* was most frequently detected in young giraffes and giraffes with frequent contact were more likely to share *E. coli* strains, suggesting transmission within the giraffe network. Antarctic soils were also found to harbor both gram-negative and gram-positive bacteria with a variety of antibiotic resistance genes, as published in *Microbiome*. Genes from 23 ARG families and representing all described mechanisms of resistance were found from this "antibiotic-naïve" location.

Surveillance of birdlife, including Antarctic penguins, revealed ARGs in birds from all tested locations, with birds feeding near wastewater treatment plants found to carry the highest ARG burden. This study, currently a *bioRxiv* preprint, suggests that human waste plays a major role in distributing ARGs.

- *Miller E.A. et al. Assessing Transmission of Antimicrobial-Resistant Escherichia coli in Wild Giraffe Contact Networks.* Applied and Environmental Microbiology. *December 13, 2018. https://aem.asm.org/content/85/1/e02136-18*
- *Van Goethem M.W. et al. A Reservoir of "Historical" Antibiotic Resistance Genes in Remote Pristine Antarctic Soils.* Microbiome. *February 23, 2018. https://microbiomejournal.biomedcentral.com/articles/10.1186/s40168-018-0424-5*
- *Marcelino V.R. et al. High Levels of Antibiotic Resistance Gene Expression among Birds Living in a Wastewater Treatment Plant.* bioRxiv. *November 5, 2018. https://www.biorxiv.org/content/10.1101/462366v1*

Evolution Driven by Shared DNA

Several recent studies have looked at the influence of both horizontal gene transfer of DNA and subsequent DNA incorporation on evolution. Transduction by bacteriophages can result in transfer of adjacent bacterial genomic DNA along with the phage genome, and the amount of host DNA incorporated is influenced by phage lifestyle. A recent *Science* article demonstrated that *Staphylococcus aureus prophage* DNA begin packaging into nascent phage heads while still incorporated in the *S. aureus* genome, and only when the phage head cannot fit more DNA does the prophage genome excise, bringing with it large sections of adjacent bacterial DNA spanning several hundred kilobases. This virtually ensures that phage infection brings host genes that are transmitted along with the virus, facilitating intraspecies evolution. Incorporation of foreign DNA by homologous recombination (HR) also influences evolution, and microbial lifestyle largely affects this ability, as reported in *mBio*. Analyzing HR machinery across a wide representation of microorganisms, the researchers found endosymbionts and obligate parasites less prone to undergo HR and identified genetic elements associated with higher rates of HR. Discerning how specific DNA sequences can be shared or incorporated will build a stronger understanding of the microbial web of life.

- *Chen J. et al. Genome Hypermobility by Lateral Transduction.* Science. *October 12, 2018. http://science.sciencemag.org/content/362/6411/207*
- *González-Torres P. et al. Impact of Homologous Recombination on the Evolution of Prokaryotic Core Genomes.* mBio. *January 22, 2019. https://mbio.asm.org/content/10/1/e02494-18*

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