APRIL 2020 - ISSUE 21

WAMJ

World Asian Medical Journal

Inspirational Asian Healthcare Leader

PATRICK SOON-SHIONG

Chairman and Chief Executive Officer, NantWorks

ENTREPRENEUR INTERVIEW
Stanley Kim, J.D.
Chief Executive Officer, WinSanTor

BIOPHARMA REPORT
Hidden Consequences of COVID-19: Why Small Biotechs Can't Just Wait This One Out

BIOPHARMA REPORT
Evofem's Amphora Requires 12-month Data to Convince Experts of Contraceptive Efficacy

OUR EDITORIAL BOARDS

World Asian Medical Journal is published bi-monthly by W Medical Strategy Group, 440 Sylvan Ave., Englewood Cliffs, NJ 07632. Tel. 201.402.1400, Email. wgroup@wmedical.org, Website www.wamj.org. Please send inquiries, subscription requests and address changes to the above address.

WAMJ
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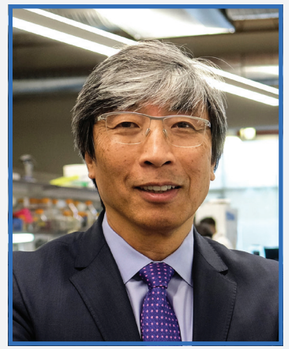

Cover Story

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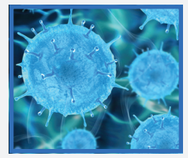
Biopharma Report



Hidden Consequences of
COVID-19: Why Small Biotechs
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Haste Plus Speed: The Need to
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Evofem's Amphora Requires 12-month Data to
Convince Experts of Contraceptive Efficacy

Melanoma Trials Using Antibiotic or Microbiome
Therapy Pretreatment Could Be Better Than Direct
Combination With Immunotherapy

From the Publisher

Unprecedented fight against the novel coronavirus is taking place in the United States and the world. Government leaders announced emergency executive orders to contain the spread of the virus. The U.S. government has also taken rapid measurements in therapeutic development for COVID-19, which included approval of decades-old malaria drug chloroquine in use for treating COVID-19.

Bayer, a global pharmaceutical company, responded by donating 3 million tablets to the U.S., and now Novartis, Mylan, and Teva are taking steps to deliver hundreds of millions of tablets to U.S. citizens to help them combat the disease. Multinational companies are showing their commitment and efforts to contribute to the well-being of their fellow citizens, and witnessing such contributions is truly inspirational.

Interviewing Dr. Patrick Soon-Shiong gave me a similar feeling of inspiration. The fundamental motivation for all of his accomplishments was affection toward people. His curiosity, research, and businesses all began from care and concern towards the people and their health. The impetus of his journey and reasoning of his work is saving peoples' lives from a terminal illness and threatening conditions. Furthermore, his philanthropic work reflects that he is an initiator who doesn't stop at his words, but puts his thoughts and words into action. In this sense, I see Dr. Soon-Shiong as a true teacher and role model to all of us in the life sciences industry.

We also had the chance to interview Stanley Kim, J.D., CEO of WinSanTor, for the entrepreneur interview. Mr. Kim mentioned that there are two principles that have driven his highly accomplished career. One was understanding the underlying mechanism of any problem, and the other was trying to solve problems with useful solutions. His principles of problem-solving led him to great success in repurposing drugs for patient needs.

In addition, this month's articles feature new trends and issues of the bio-health industry. In partnership with BioCentury and Biopharma Insight, we share significant and recent industry news with our readers.

Various writers and experts impart their knowledge and insights as co-authors in this edition of WAMJ. I sincerely hope that our readers will find these exciting selections of articles to be helpful and inspiring.

DoHyun Cho, PhD
Publisher
President & CEO of W Medical Strategy Group
Chairman of New York Health Forum

From the Editor-in-Chief

WAMJ is excited to offer in this issue an interview with Patrick Soon-Shiong, M.D., a true Renaissance man. Dr. Soon-Shiong was born in South Africa, where the lives of those of Chinese ancestry were not easy. At an early age, this son of a medicinal herbalist identified medicine as his career goal. The future surgeon was educated there, in Canada, and the U.S., and at academic medical centers achieved notable advances in transplantation surgery and the management of cancer and diabetes. Despite his clinical prowess, however, Dr. Soon-Shiong soon applied his formidable talents to a veritable smorgasbord of other fields, including pharmaceutical development, stem cell research, biotechnology, health information technology, supercomputers, augmented intelligence, journalism, philanthropy, and even, as a minority owner of the Los Angeles Lakers, professional sports. Perhaps somewhat less known than many of his other accomplishments was a stint at NASA, where, as part of the Shuttle program, he performed experiments to investigate the science of stem cells and nanotechnology. Today, Dr. Soon-Shiong and his colleagues, harnessing both innate killer cells and adaptive T cells, have made major progress towards the development of chemotherapy-free cancer memory vaccine, which has shown impressive efficacy against triple negative breast cancer and head and neck cancers.

Ordinarily, when WAMJ interviews prominent medical scientists, academics, and researchers, busy people all, we do our best to use their precious time efficiently. A time is set, and we tailor the interview to be sure it can be completed in the time allowed. It is telling, then, and a sure indication of the breadth and depth of Dr. Soon-Shiong's learning and contributions, that we had to complete his interview in two sessions. The first, you see, was interrupted by an urgent call from a highly-placed government official seeking advice on how best to manage the fight against COVID-19.

We also have the privilege to present an interview with serial entrepreneur Stanley Kim, J.D., CEO of WinSanTor, a biotechnology company focused on the development of treatments for peripheral neuropathies. Mr. Kim's company recycles compounds, in this case an existing API with nearly 40 years of use in the management of gastric ulcers. Using "repurposed" medicines, with their well-established safety profiles, minimizes risks associated with most drug development, particularly those related to safety and manufacturing. This approach reduces cost, time to development and concerns about potential side-effects.

Finally, this issue provides several Biopharma Reports, on a new approach to melanoma trials, Evofem's Amphora, COVID-19's implications for small biotechs, and the need to see that COVID-19 vaccines don't make infections worse.

We hope and trust you will enjoy Issue 21, especially Dr. Soon-Shiong's reminiscences and observations.

Joseph P. McMenamin, MD, JD, FCLM
Editor in Chief
EVP of W Medical Strategy Group

WAMJ Recap of the Last Issue

COVER STORY
David Ho, MD, Scientific Director and Chief Executive Officer of Aaron Diamond AIDS Research Center (ADARC)

Dr. David Ho is the scientific director of the Aaron Diamond AIDS Research Center, the world's largest private research center dedicated exclusively to fighting HIV/AIDS. After encountering one of the earliest cases of AIDS reported to the CDC in 1981, Dr. Ho has devoted his time to HIV/AIDS research, unraveling the dynamics of HIV in infected persons. Dr. Ho and his research team developed the antiretroviral therapy, also known as the "AIDS cocktail." This type of therapy durably controls HIV replication, no longer making AIDS a lethal disease. Also, Dr. Ho has worked hard to change the negative perception of the disease by educating the public that HIV/AIDS can only be transmitted by intimate contacts such as sex and sharing of needles and not by casual contact. The center's current goal is to develop new modalities such as vaccines, antibodies, and long-acting antiretroviral drugs to block HIV transmission or at least slowing it down. To learn more about Dr. Ho, please read issue 20 of WAMJ.

BIOPHARMACEUTICAL REPORT I
Novavax's NanoFlu Has Tepid Expert Market Forecasts in Influenza Versus Sanofi's Fluzone

Novavax's NanoFlu influenza vaccine has garnered lukewarm expert predictions for its market uptake, with experts noting it does not seem to be a major improvement upon Sanofi's Fluzone. Novavax's NanoFlu influenza vaccine is expecting positive Phase III results and subsequent FDA approval. Few highlights of the Nanoflu are its positive Phase II results showing superiority over Fluzone and its use of the SF9 insect cell baculovirus system instead of traditional chicken embryo use in its production. Despite high expectations, NanoFlu's similarity to Fluzone in terms of its components is a low bar for market advantage. NanoFlu's performance in the market will depend on other flu vaccines in the pipeline, with additional competition from the Fluzone. Also, even if NanoFlu were to demonstrate superiority over Fluzone in its Phase III, it would not automatically be a market leader, as Fluzone has been FDA approved since 1987. In fact, based on public information, it seems likely that NanoFlu will be more expensive than Fluzone to produce, thus leading to a higher sticker price. To learn more about expert views on Novavax's NanoFlu, please read issue 20 of WAMJ.

BIOPHARMACEUTICAL REPORT II
Bayer's Finerenone Use Will Face Off With SGLT2 Inhibitors

Bayer's Finerenone, a phase III mineralocorticoid receptor antagonist (MRS), is a diabetic kidney disease (DKD) treatment that has drawn the public's attention. While Finerenone will likely have an advantage over older drugs within its class, payers are likely to also scrutinize its value. The payers' doubts arise from the Sodium-glucose cotransporter-2 (SGLT2) inhibitors' growing prominence in DKD. The prevalent use of SGLT2 and the choice between the two in deciding a patient's regiment will become a factor of cost and payer coverage. The MRA class is a cornerstone of renal protection and physicians could likely accept Finerenone as the first choice between drugs of that class. However, the higher price of MRA may inhibit its use. While combination data is needed for finerenone/ SGLT2 inhibitor use, the expensewill be a significant factor. The challenge is that newer drugs like finerenone and the T2D therapies are expensive, and using the two classes together would be very expensive compared to using an older drug. To read more about Bayer's Finerenone, please refer to issue 20 of WAMJ.

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H A N A R O M E D I C A L F O U N D A T I O N

Dr. Soon-Shiong in NantWorks lab

Inspirational Asian Healthcare Leader

Patrick Soon-Shiong, M.D.

Chairman and Chief Executive Officer, NantWorks
Owner and Executive Chairman, Los Angeles Times and The San Diego Union-Tribune

COVER STORY

1. Dr. Patrick Soon-Shiong, as one of the leading scientists in our industry, you're a surgeon, CEO, professor, inventor, and philanthropist. Tell us about this remarkable journey, and why you chose surgery as your specialty.

- My father was a medicinal herbalist in China. After the Japanese invasion, my parents moved to South Africa, where my father still practiced. I think my father's work influenced what path I chose in life. I remember, as a child, seeing him treat members of our community and realizing the body could protect itself from disease and heal. I was 16 when I went to medical school. Choosing surgery was a difficult choice because I also wanted to be involved in pediatrics, to monitor and care for children suffering and dying of cancer. I soon realized that it was emotionally too difficult. I wanted to be in a specialty where I could immediately see and feel the outcome of my actions and treatment—so I became a surgeon.

Dr. Soon-Shiong being welcomed by Pope Francis at a Vatican conference on regenerative medicine in 2016

2. How have you been able to excel in so many different areas? What is your philosophy in life?

- I believe that everything is possible if you work hard and set your mind to it. I am both a scientist and biologist, actively translating science into medicine—as a physician and surgeon. My curiosity started at a young age. I had this belief that one day, society would be able to understand the human body at a level we've never seen before—at the genomic, proteomic level. That ability could enable us to figure out what makes this amazing biological system—the human body—work, and that's what drove the curiosity. To get into this chasm of three billion base pairs of human cells, we needed to create technology that didn't exist. That's what drove me to work at NASA in the very early stages of my career. It may not be well known, but I was a scientist at their Jet Propulsion Lab. I received a massive grant from NASA while I was also an academic surgeon, and another huge grant from the National Institute of Standards and Technology ("NIST") on nanotechnology. This was in the 80s, and we were way ahead of the curve in understanding not only the need for, but the potential of both nanotechnology and supercomputing. Because of my exposure to NASA, machine vision, and machine learning, I recognized that some of these technologies didn't exist. Therefore, I needed to not only understand them deeply but also build infrastructure, so that we could drive knowledge at the level necessary for us to translate that into medicine. From early on, I had exposure to NASA's Jet Propulsion Lab (JPL) while I was a surgeon at UCLA, and that's the beauty of Los Angeles. You have Cal Tech, JPL, and UCLA. Then together with Intel and BASF, I co-founded the California Nanosystems Institute at UCLA. This convergence allowed me, very early on in my career, to quickly build infrastructure that didn't exist. That was the underlying motivation to understand the biology of the human system. In doing so, we could create universal therapies for things like cancer and infectious diseases, which we are intimately involved with now.

Now, I look at nanotechnology as a mechanism for understanding human biology. How do you take a human cell down to a single base pair into a human body, and transfer that information into 7 billion people on the planet? That's exactly the challenge that drove me and still drives me today. The first question was understanding the proteins in the human cell and the human body, rather than understanding technology. I call this the "dance of proteins." However, it was like looking for God's particle on the Large Hadron Collider,* in real-time, in the human body. Therefore, very early on, I got involved with the National LambdaRail (NLR), the first transcontinental 10 Gigabit Ethernet network. This

* *World's largest and highest-energy particle collider/accelerator*

fiber-optic infrastructure connected Bern, Switzerland, with all the major medical academic centers and astrophysicists. I took over the NLR very early on, ran it for four years, and rebuilt it into a fiber infrastructure to integrate supercomputing across the network—which we now run, because it's like looking for God's particle in the human body for every single patient, every day. NantWorks has now accomplished that with the genomic DNA/RNA human immunotherapy, which just received FDA approval last December. The FDA approval was the result of about 25 years' worth of work: creating the fiber infrastructure; supercomputing; machine learning; taking normal samples of tumor tissue as well as infectious diseases like HIV, Zika, Ebola, and the Coronavirus, understanding their genetic makeup, and then figuring out how to create therapies at the biological level.

3. You've developed many firsts, in diabetes and cancer: the first whole-pancreas transplant at UCLA; the first encapsulated-human islet transplant for Type 1 diabetes; the first pig-to-man islet-cell transplant in diabetic patients; and the first human protein nanoparticle chemotherapeutic drug, Abraxane, approved for breast, lung, and pancreatic cancer. What was the impetus behind such innovative developments? Is there a common denominator, or was each uniquely motivated?

- The common denominator was the human biology of cells. About four years ago, my frustration was, "How do I explain to people, and how do I connect the dots?" So, I started a thing on Twitter called "Connect the Dots," to tell people that they could be strengthened by their cells. As a surgeon, one of the things that I treated was pancreatic cancer, and I performed the Whipple procedure (a challenging pancreatic cancer surgical operation). I also wanted to take on pancreatic transplants, so I did. Finally, I realized that it was just the Yin and the Yang: In transplant, I'm trying to help the body not to reject the organ, and in cancer, the cancer cells trick the body to believe that the cancer is normal and not to kill it. Thus, I quickly realized that the body has all the mechanisms within its cells to treat cancer appropriately. Moreover, when I became aware that stem cells could regenerate cancerous cells, I wanted to learn

> "A full understanding of this mechanism will lead to universal treatment for all tumor types in terms of cancer and in-progress infections–like the Coronavirus"

everything about stem cells—and I did. Then we did the world's first islet cell transplant from stem cells. I discovered that not only do stem cells require albumin to transport Zinc to make insulin, but also that cancer cells use albumin for transport intercellularly. I thought, *if albumin goes into every cell as a normal physiological mechanism to drive messages, why not make an albumin nanoparticle to trick a cancer cell?*—and that's Abraxane. Abraxane is now one of the ubiquitously used agents in immunotherapy.

Abraxane falls into what I call the tumor micro-environment; by developing Abraxane, I began to understand the mechanisms of the cancer cell's ability to hide from the immune system. Now, the focus of my entire career is looking at what turns the immune system on and off. That's why studies of the Coronavirus, HIV, influenza, and cancer are based on the same biological mechanisms—the Yin and Yang, the balance of the human body that can discern exactly what turns the balance on and off. The immune system has molecules to manipulate or modulate. A full understanding of this mechanism will lead to universal treatment for all tumor types in terms of cancer and in-progress infections—like the Coronavirus.

4. You established NantWorks, the integrated network of companies pursuing next-generation pharmaceutical development. The network includes NantHealth and NantKwest. What needs did you see in the industry that motivated you to create NantWorks? What made you expand from drug development to healthcare IT?

Dr. Soon-Shiong attending Los Angeles Lakers game at the Staples Center; he is a part-owner of Lakers

- Information technology, or cognition, is necessary to discern what's going on at the cellular level. Therefore, I refer to cancer as a knife fight, and the same goes for the Coronavirus. You need cell-to-cell combat unless you can understand the human body at the cellular *and* molecular level, which requires information technology. You'd have no wisdom as to what drugs might work and how to develop them. When I sold everything to the pharmaceutical world, my concern was that we were empirically developing drugs. One approach is to do an early trial to sort out what happened, and another approach is to understand the human body and create very deep *wisdom*, rather than knowledge. Unless you can go from knowledge to wisdom, it's like developing things in the dark. You can't go from knowledge to wisdom without information technology, machine learning, and machine vision; you also need supercomputing access and fiber optics technology, which we have now.

5. You have participated in businesses not only in healthcare but also in publishing, such as the LA Times. Why did you become interested in journalism?

- When I grew up as a kid in apartheid-era South Africa, my only access to knowledge was the newspaper. Unless you have access to valid news, as opposed to fake news, the infrastructure, democracy, and truthfulness will be lost.

In South Africa back then, Asians had no right to own property or to vote, and we even had segregated schools. Sometimes it was a little bit of a blessing because the Chinese community even hired teachers from Taiwan to educate the kids. When I was in medical school, there was a quota for how many Chinese could get in. I think

there were only 3 out of 200. I was the first Chinese doctor ever to be allowed to work in the white hospital—the "General Hospital." To hire me, they had to go to the Pretoria Government, which gave permission as long as I took 50% of the salary of my Caucasian peers. I was happy to do so for learning. My upbringing has formed everything I do here now; what we do as an organization of NantWorks, culturally, is figuring out a way to help the underserved and the underdogs. It has formed a lot of what we do, both businesswise and philanthropically.

6. As a philanthropist, you founded non-profit organizations such as the Chan Soon-Shiong Family Foundation, and the Chan Soong-Shiong Institute for Advanced Health. What are the foundations' goals, and what do you hope to achieve through such philanthropic activities? What made you decide to establish not one, but two charities?

- Chan is Herald Chan, my wife's father, who took me under his wing, and Soon-Shiong is my father, who died when I was still in medical school. So, the foundation's name came from my two fathers. The goals of my two non-profit organizations, namely the family foundation and the Institute of Advanced Health, are well-aligned. Our goal is that the family foundation, as well as NantWorks, address what we believe are critical issues that face humanity. We hope to help the underserved in many ways, whether it relates to healthcare or just basic fundamental services, like bringing energy, food, and education to underserved communities. The issues that face humanity and the underserved are universal, and healthcare was obviously my forte. That's why we supported the development of the Martin Luther King Community Hospital, which serves the disadvantaged community in downtown L.A. Before our support, this hospital had shut down because people were literally dying due to a shortage of budget.

I knew situations like this had to stop, so I worked with the L.A. county, specifically Mark Ridley Thomas, to build and open up a new hospital there. Then I turned my attention to major academic centers, several local community hospitals, and small Catholic hospitals, like Saint John's medical center in Los Angeles. After that, I looked to Windber, a community hospital for poor coal miners in Pennsylvania. Now, I am working with the Navajo and Apache Nations in Phoenix, AZ. These are truly some of the most underserved in the entire nation, and this is really the focus of healthcare. The Institute for Advanced Health strives to leapfrog these underserved communities—ones that struggle to receive even a chest x-ray—to the next generation treatment. The support would allow these communities to have machine learning or artificial intelligence, get next-generation care for infectious disease, make sure patients are cared for, and provide access to clinical trials. It can also help educate healthcare providers; my concern has always been that it takes almost 17 years for a medical breakthrough to integrate into the regular practice of medicine. These reasons are different but possess overlapping goals.

7. You and NantKwest are aiming to create the Cancer Memory Vaccine to achieve high-dose chemotherapy-free, biologically-driven immunotherapy for the prevention and early treatment of cancer. Could you please explain the idea behind the vaccine? How does this work affect our understanding and treatment of the Coronavirus?

LATEST UPDATE

In Response to Current Coronavirus Pandemic, the Chan Soon-Shiong Family Foundation Offers to Buy St. Vincent Medical Center

St. Vincent Medical Center

The Chan Soon-Shiong Family Foundation has offered to purchase the St. Vincent Medical Center in Los Angeles, which closed in bankruptcy, for $135 million to help California fight COVID-19. The foundation was approved as the lead bidder at the U.S. Bankruptcy Court to acquire St. Vincent from the hospital's bankrupt owner, Verity Health System of California Inc. If competing offers are not submitted and the purchase is approved by the bankruptcy court, the foundation would take over the state's lease obligations at St. Vincent. The foundation seeks to use the facility as a central command center to provide health-care services and facilitate research on the Coronavirus.

Source: Los Angeles Business Journal, The Wall Street Journal

- That's a complex question that I've grappled with for maybe 30 years of my career. Finally, in the year 2020, we have some clinical evidence for the hypothesis that cancer cells are quietly generating—and a thought experiment has come to light. The human body has evolved, not from a species, but from cells that have evolved over 500 million years to protect the human body. Until now, we did not realize this. Even worse, we did not realize that these highly protective cells—cells that create memory and protection against things like the Coronavirus, HIV, and cancer—are universal cells that we are born with and that we have inadvertently been wiping out with our treatment. That's a very frightening statement, and I was not prepared to make this statement public until I could prove it. Now, I am ready to do so, but it is complex.

We are born with multiple cell types in our blood that have different functions. Red blood cells form to provide oxygen, and if you don't have enough of those red blood cells, you get anemic. If you don't have enough white blood cells, you have a condition called neutropenia. You have three other cell types to protect you from diseases such as cancer, Coronavirus, and HIV; these are the natural killer cell, the T cell, and the dendritic cell. These three cells, which I call the "triple offense," are key to curing cancer and generating what I call a memory NK and T cell—a cancer vaccine.

For the past 40 years, the scientific and medical communities have gone down the assumption path that to kill cancer, we should bomb it with high dose chemo and radiation. Inadvertently, in doing so, we wiped out the "triple offense" which were there to protect us. While the industry has developed treatments to replenish red blood cells (Epogen) and anti-ineffective cells and to replenish cells to fight infection (neutrophils) in the form of Neupogen, nobody has addressed replenishing cells that protect us from cancer—the lymphocytes consisting of NK and memory T cells. In addition, nobody has addressed what happens when you wipe out these protective lymphocytes.

Enter the Nant cancer vaccine. We have developed techniques and biological mechanisms to awaken and rescue the lymphocytes, the triple killers (the natural killer cell, T cell, and the dendritic cell), the CD8, the memory cell, and the macrophage. Focusing on the cells that matter rather than cells we've wiped out is what we do in NantWorks, ImmunityBio, NantKwest, and NantHealth.

> "Our goal is that the family foundation, as well as NantWorks, address what we believe are critical issues that face humanity"

What is the Nant cancer vaccine? Well, the first cell that I am completely obsessed with is the natural killer cell, called the NK cell. It was born 500 million years ago to prevent us from getting bacterial and viral infections, and I think it will have a major role in combatting the Coronavirus. If you look at patients who died from this novel virus, the common denominator is lymphopenia, which is exactly what happens when a patient has high dose chemotherapy and radiation. Thus, we are now seeing complete responses in very late-stage cancers (triple-negative breast cancer, metastatic pancreatic cancer, and head and neck cancers). Ironically, we have done so by addressing the lymphopenia with the natural killer cells grown completely off the shelf with the engineered natural killer cells, or by introducing molecule IL-15, which stimulates the natural killer and T cells. We are in a registrational trial for lung cancer, pancreatic cancer, breast cancer, local cell carcinoma,


Dr. Soon-Shiong with a former LA Laker Kobe Bryant

Dr. Soon-Shiong at the LA Lakers game

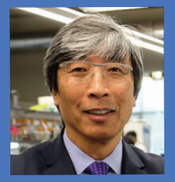
and bladder cancer. In fact, we've just filed a Phase 1 study with the FDA to use molecule IL-15 for the Coronavirus. We now have treated 700 patients safely; using thousands of doses with normal volunteers, we have shown that it activates the NK cell of the T cell, which is exactly the cell that could kill a Coronavirus-infected cell.

8. What is your biggest goal? What do you hope to see in the future as a result of following the path you pioneered?

- Well, I've got some big problems I'm trying to fix right now—cancer, HIV, and the Coronavirus. I have always been fearful of a pandemic such as this one, but I think we will have a universal treatment that can address it. We only have 8,000 doses of the drug that can mitigate the infection, which is still challenging. Thus, that's the big goal—trying to get that all done, together with the generating capability. The next goal is working on climate change. Today, we have a huge inflow of industrial heat that can change the way of generating electricity or create next-generation plastics that are completely renewable. Maybe we will be able to use hydrogen as a source of energy. These are the challenges I am very excited about. My colleagues and I have taken about three years into that development, and I want another two years for quiet work before sharing the results with the world.

9. Dr. Soon-Shiong, you have been a leader in many of the fields you are involved in. Many of our readers will find your path to be an inspiration. Could you please share a message for future entrepreneurs/ physicians that aspire to exceptional careers and accomplishments?

- Follow your passion. I think that's probably the most important statement I can make. Follow your passion, and also follow the science. I think you have to be realistic about the fundamentals of science. If you really have a scientific basis for a belief, a therapy or a treatment, and can demonstrate it scientifically, then you should pursue that belief with all your passion. The most important message I would like to share with the WAMJ readers is: *have perseverance and believe in yourself.*



Patrick Soon-Shiong, M.D.

Chairman and Chief Executive Officer, NantWorks
Owner and Executive Chairman, Los Angeles Times and The San Diego Union-Tribune

Patrick Soon-Shiong, M.D., is a physician, surgeon, professor, researcher, philanthropist, and a billionaire entrepreneur. He is the Chairman and CEO of NantWorks, the umbrella organization for an ecosystem of companies aiming to create transformative global health information and next-generation Pharma development network. Dr. Soon-Shiong invented and developed the revolutionary blockbuster drug Abraxane, which is known for its efficacy against lung, breast, and pancreatic cancer. Over the span of his career, he has also pioneered novel therapies for both diabetes and cancer, published over 100 scientific papers, and issued over 230 patents worldwide for groundbreaking advancements spanning myriad fields of technology and medicine. As a surgeon, he performed the world's first encapsulated human islet transplant, the first engineered islet cell transplant and the first pig-to-man islet cell transplant in diabetic patients. With the mission to erase disparities in access to healthcare and education, he founded two non-profit organizations, the Chan Soon-Shiong Foundation and the Chan Soon-Shiong Institute for Advanced Health. Dr. Soon-Shiong's visionary leadership and commitment to advancing medical and scientific research and bringing new treatment options to cancer patients was recognized by many international and national awards, including the Franklin Institute Award in 2016. In addition to his businesses in the healthcare arena, he is also the owner of the Los Angeles Times, The San Diego Union-Tribune, and part-owner of LA Lakers.

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Entrepreneur Interview

Stanley Kim, J.D.,
Chief Executive Officer, WinSanTor

1. WinSanTor is a biotechnology company focused on the development of treatments for peripheral neuropathies (PN). Could you please explain to our readers about WinSanTor and its leading compound?

Peripheral neuropathy is a neurodegenerative condition that affects several hundred million people globally. It is the nerve damage caused by many major diseases and injuries, including diabetes, cancer/chemo, HIV, etc. Today, there is no treatment for this nerve damage, only pain treatments. The leading scientists were brought together to solve this problem. Degeneration of nerve fibers due to peripheral neuropathy has been linked to mitochondrial dysfunction. They discovered a novel pathway via AMPK, and more importantly, discovered anticholinergics that regulate nerve regrowth through mitochondrial reactivation. They've shown both reversal and prevention in animals and humans showing nerve growth, reduction of symptoms including pain, and improvement of quality of life. A recent study (double-blinded, controlled) presented early evidence that these drugs are efficacious in significantly improving structural and functional measures of small fiber function (IENF density, improvement in neuropathy scores, pain questionnaires) and quality of life (Norfolk QOL DN survey) in T2DM subjects. No improvements were seen in the placebo group. WinSanTor was established to advance this science with its lead drug, WST-057, now in phase 2.

With strong academic roots, WinSanTor's primary objective is to ensure the development of high impact drugs for patients with the greatest likelihood of success. We have an experienced drug development team, use the leading CROs, work with the leading clinicians in the space with strong academic credentials, and try to use the science, not the business, to guide the development. We reduce significant risk by reusing as many resources and processes as possible. WST-057 is a topical drug recycling a previously approved API (approved in most major countries but not in the U.S.) with strong safety and manufacturing history—it was originally approved in a pill for gastric ulcers. WST-057 is now in Phase 2 in several sites in Canada, with plans to begin phase 2b/3 in many of those countries where it was previously approved. We are using the data from the scientist's previous studies in both animals and humans to guide the protocols, as well as the collective experience of nearly every clinician in the space. The goal is to see drug approval by 2022 or 2023.

2. What are the major philosophies, missions, and future goals of WinSanTor?

There has been a lack of basic scientific understanding of peripheral neuropathy, and past clinical studies to treat the disease have all failed (Feldman EL. et al. New Horizons in Diabetic Neuropathy: Mechanisms, Bioenergetics, and Pain. Neuron. 2017 Mar 22; 93(6): 1296–1313.) The leading researchers in diabetic peripheral neuropathy, Dr. Paul Fernyhough and Nigel Calcutt, were gathered to collectively address this growing unmet need. This expanded to recruiting the leading academic clinicians to guide the clinical development of the discoveries of these researchers. WinSanTor is merely the commercial manifestation of this collective endeavor to address this problem, which is one reason the company and its scientific works received significant funding from government stakeholders.

The company, WinSanTor, goes beyond science. By reutilizing an existing API with nearly 40 years of use as a pill for stomach ulcers, the company minimizes risks associated with most drug development, particularly as it relates to safety and manufacturing. This reduces overall cost, time to development and anxiety of potential use. Reformulating the API into a topical solution targets the API to the affected areas, minimizes systemic effect, increases safety, and makes the drug more usable. It also creates commercial value to encourage and sustain the development of the product.

The concept study in humans, the proof of mechanism, established significant evidence that the class of drugs being developed by WinSanTor can provide patients some semblance of their previous "normal" lives. This is magnified by the hundreds of millions that are affected globally including over 50% of the nearly 500 million diabetics, approximately a third of ALL cancer patients and HIV patients, and many others. WinSanTor and its team strive to impact the lives of all these patients, globally. This patient-oriented development strategy drives the company as it seeks approval of potentially the only disease-modifying treatment for peripheral neuropathy.

3. Along with your role as the CEO of WinSanTor, you have had various accomplishments in different fields, including biotechnology/pharmaceutical, medical device, and software. How did you shift from law school to software development, then to the biotech industry? What values led you through your career?

There are two principles that have driven my career: understanding the underlying mechanism of any problem and trying to solve the problem with useful solutions. Although I started my career as an attorney, my educational background is in life sciences, specifically genetics. The combination of the two, as well as my desire to start companies, began at The Salk Institute, where I managed the intellectual property for the Institute. The Salk Institute is one of the top 5 biological research institutes in the world. One of these areas of research is in the field of computational neuroscience—modeling neuroscience digitally. My first two companies were in this space, which were machine learning for signal separation/processing for telecommunication/software applications, later medical devices, and computer vision software applications. Thus, most of my experiences to date are in the life sciences.

Very few times in life will anyone have an opportunity to work on something that may have the potential to impact the lives of so many people. With my previous companies, SoftMax and Emotient (a.k.a. MPT), the impact was with the caliber of the people I was working with and their potential. The technologies that were built from this group are now on every cell phone. Unfortunately, we never maximized their potential at the companies – they were sold very early. In WinSanTor, we hope we can maximize the potential for Drs. Fernyhough's and Calcutt's work.

Development of technology in biotechnology is in many ways similar to every other field, and arguably easier as there is a formula for drug development (preclinical, phase 1, phase 2, and phase 3). The difficult part of drug development was easy in my case. My scientific colleagues were responsible for validating the science, both in animals and in humans. The API, in this case, is an established API with nearly 40 years of history. We have a strong development team, strong clinical support through leading CROs (service providers) and

Stanley Kim with his colleagues at WinSanTor

have the support and guidance of the leading clinicians in the space. The difficulty in the biotechnology industry is aligning drug development with the interests of the pharmaceutical industry, which I've now discovered is not in alignment with the discovery of impactful drugs.

Fortunately, I've surrounded myself with strong personalities, including the scientists at the Salk, my colleagues, Patrick Soon-Shiong, Seth Neiman, our advisors, and others. If you are a problem solver, you learn directly and indirectly from all interactions and experiences and having iconic advisors, you learn from their experiences, both positive and negative. Following trends is not in their DNA.

4. As the CEO of WinSanTor, what are some significant changes or trends you have noticed in the biotechnology industry? How do you forecast the global biotechnology industry will be like in the next five to ten years?

Not coming from a biotechnology background, I observe trends differently than others within the industry. I see an over-reliance in the industry of acquisitions. It is understandable. Drug development is expensive and few people, especially investors, like to take risks particularly with new science. Therefore, companies are created to be acquired before phase 3, during which it is much riskier and very expensive, in therapeutic areas that acquirers want. With only a handful of acquirers—your starting technology, your team, your intellectual property, your strategy—everything is exclusively centered around being acquired long before the technology is validated. This is one reason that there is so much focus on certain therapeutic areas (nearly 90% of overall spend is three therapeutic areas, 60% of this just in cancer). It is also made much more difficult as drugs are not made today for the international market, but for the U.S. market (nearly 50% of ALL revenues are generated from the United States).

This may be an overgeneralization, but too many companies are created to be acquired, developing similar technologies for the U.S. market without true accountability. This is one reason I believe too many international companies developing technologies for their own market are finding it difficult, especially following this formula. This is also one of the main reasons why true innovations, at least from my perspective, have such a difficult time.

I hope there is a change in the next 5-10 years. As with most things, globalization forces industries to think internationally, both in development and commercialization. When costs (development and commercialization) are insulated, whether through subsidies or protections, it creates isolated industries reliant on the status quo. There is a strong disincentive for true innovations. The U.S. market is reliant on subsidies and patients insulated from the true cost and efficacy of the products they use. This is shifting. Insurance companies are forcing patients to absorb the cost of the drugs they use, and outside forces are looking at ways to remove the "middleman." Pricing and affordability will be a part of every equation of developing drugs, and the ability to adapt and rely on markets outside the market will bring new industry leaders.

WinSanTor is developing a high-impact product for the international market. We are not relying on acquisition but preparing to evolve to be part of this evolution/revolution in the healthcare market, particularly the U.S.

5. In the past, you founded software startups, SoftMax and Emotient, that were acquired by Qualcomm and Apple, respectively. Many startups aim to achieve innovation and results with an optimal return, as you have accomplished with your innovative technologies that now reside on many of the current smartphones. Could you please share the background of these accomplishments? Also, do you have any words of advice for startups and entrepreneurs that have the same goals?

I wish I could take credit for these accomplishments. It is only that I associated myself with individuals of such high caliber, and that I saw the potential for the technologies they were developing. Most of the credit for working with such individuals has to do with the caliber of people that are in San Diego, including The Salk Institute. It is easy to find strong science and technology in communities where talent concentrates. Knowing what is valuable or potentially valuable is more difficult. Extracting the value from where the value is not evident is even more difficult.

With the first two companies, we did not seek to be acquired. With the first two companies, my co-founders were pioneers in their respective spaces. We were trying to make the companies the leaders in their field and at some point, we realized there would be a wall to truly maximize the value of the people and the technology. The true value of the technologies that were extracted could only have come forth with large platform technology companies like Qualcomm and Apple who have the resources to exploit the technologies.

WinSanTor is arguably different. The true value of the technology is not in alignment with large pharma—who are focusing on lower-volume and higher-cost drugs. We know that we can make significant revenues by doing good for a larger population, particularly by partnering with regional pharmaceutical companies who do not have the luxury of reimbursement of subsidized high-priced drugs.

For other startups and entrepreneurs, I always start with the people and their expectations and be as specific as possible. Making money alone is not an expectation. When, how, where, etc. are all things that should be discussed. If these are aligned, then you build on all the other parts that are necessary to achieve their expectations, and you bring in others with the same expectations. Once you have imbalance, then that is usually when problems occur. Bringing in the best person is not always the best thing to do especially when that person is not in alignment with the vision of the company.

I hope that one day, we reach our expectations. but at least we seem to be on track. W

Stanley Kim, J.D.

Chief Executive Officer, WinSanTor

Stanley Kim, J.D., CEO of WinSanTor, is a seasoned entrepreneur and the founder of companies in diverse industries, including pharmaceutical/biotechnology, medical device and software. WinSanTor, his current affiliation, is a clinical-stage biotechnology company focused on the discovery and development of treatments for peripheral neuropathies. WinSanTor's mission is to simple-develop a drug that works and to impact the lives of millions of patients heavily burdened by peripheral neuropathy. His first company, SoftMax, was acquired by Qualcomm and his second company, Emotient, was acquired by Apple. Both technologies now reside on most of the smartphones.

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Biopharma Report

BIOPHARMACEUTICAL REPORT I

BIOPHARMACEUTICAL REPORT I
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CORONAVIRUS

Hidden consequences of COVID-19: Why small biotechs can't just wait this one out

BY C. SIMONE FISHBURN, EDITOR IN CHIEF

It's still anyone's guess as to how long the COVID-19 outbreak will take to peak, let alone wane after that. But small biotechs could see knock-on effects that play out over a longer time frame than the course of the virus' spread. Anticipating those, and acting pre-emptively, might be the difference between emerging unscathed and spending years making up for lost time.

The pressing question is what is the tipping point at which the disruptions to daily business turn into long-term problems.

The point isn't that there's zero chance of an all clear within the next few weeks, so that's the time frame to worry about. It's that there's a fair chance this could carry on through year-end.

The escalating clampdown on travel, and the fallout from that, is going to disrupt small companies, even if they don't have supply chain concerns or product revenues on the line.

Delays in clinical trials, a by-product of the restrictions on travel as well as transport of APIs, would jeopardize milestones that not only serve as catalysts for public investors, but trigger deal payments that companies have been banking on. That would affect balance sheets, with implications for FTE counts and future operations.

Other effects are more intangible, but no less consequential.

The strictures on travel will mean a loss of face-to-face meetings. Partnering deals, M&A and investments all come about through long-term relationship-building that is often seeded at conferences and in-person meetings -- the reason executives spend much of their time on the road.

Arguably, pharmas and big biotechs will take less of a long-term hit. Supply chains will be hurt. Sales will likely suffer, and the market downturn and delayed regulatory submissions will throw off their projections. But they have large teams that drive relationship-building, and less hangs on any single lost opportunity. None of this will impose any existential risk.

For the thousands of companies with small pipelines, though, how long they can ride this out depends on where they are in the development cycle, how much cash they have and how they manage it, and what alternatives they can find to keep building while hunkered down.

We're all consumed and concerned by the spread of cases and the human cost of this crisis. The public health impact and progress of countermeasures, rightly, are front of mind (see "Coronavirus Analysis").

Companies are, or at least should be, attending to the first orders of business: the ability to contribute to the global effort, the health of their employees, and their financial stability through the uncertainty.

But that's not enough -- there's no room for a "this too shall pass" approach. The success stories will come from companies with contingency plans, rather than those who cross their fingers and hope.

Clinical outcomes

Biotechs with 2020 trial readouts or starts will need to plan for clinical delays that could affect regulatory submissions, as well as the milestone payments and investor activity that the readouts bring.

All of this will affect the P&L. Companies cannot continue to burn cash with stalled programs. Fund-raising should be a priority, even if the coffers seem full enough now.

patients. One U.S.-based biopharma executive told BioCentury he is keeping a keen eye on Europe, where his company has many study subjects. Restrictive isolation measures such as those in China would mean study sites couldn't be opened, and monitors couldn't go in to verify data.

Some workarounds are in play. Remote monitoring of patients offers relief in some trials and means staff don't have to travel to hospitals -- an option being introduced in some Chinese trial sites. While that might not be in the plans for many small companies, it's an avenue to explore that could pay off regardless of this outbreak.

No travel, no money

It's hard to predict the precise impact of curtailed travel, but China has already seen a drop in venture fund-raising in the first two months of the year.

Chinese biotechs raised $268 million in January and February, a 72% decrease from the nearly $1 billion raised in the same period in 2019. The number of companies raising money fell from 15 to seven (see "COVID-19 Stalling Venture Financings").

Europe and the U.S. have not yet seen a drop, but the numbers are a lagging indicator.

BEING FAR FROM AN OUTBREAK CENTER OFFERS LITTLE INSULATION FROM THE RISK.

Being far from an outbreak center offers little insulation from the risk.

China is a major producer of APIs -- together with India accounting for 18% of worldwide FDA-certified manufacturing sites, and, according to Sanofi (Euronext:SAN; NASDAQ:SNY), about 60% of worldwide API production. Exports from China and India are already at risk, which will affect clinical trials broadly, regardless of company size (see "India Restricting API Exports").

The impact could be even bigger, given the virus' spread to Italy and Japan, which have the largest number of API manufacturing sites after the U.S., China and India (see "COVID-19: API Sites on the Line").

Moreover, Italy and South Korea, two of the top three countries hit hardest by the outbreak outside of China, are key areas for industry-sponsored clinical trials, with 1,942 ongoing in Italy, and 1,376 in South Korea, according to ClinicalTrials.gov. China has 1,466 ongoing trials in ClinicalTrials.gov, and likely many more not recorded in the database. (The third country is Iran).

Clampdowns on movement in affected areas will hit clinical operations, with trial patients and staff not being able to get to trial sites, not to mention hospital resources being diverted to concentrate on COVID-19

VCs tell BioCentury over and over again that the make-up of management teams is critical to investment decisions. Building trust, especially for newcos and first-time investments, requires meeting the teams, usually many times.

Likewise, IPOs don't happen without roadshows. Companies that have already done the legwork can still make good. Passage Bio Inc. (NASDAQ:PASG) priced an upsized IPO on Feb. 27, during a week in which major indexes fell 10-11% (see "Passage Prices Upsized IPO").

But the flood of IPOs that companies planned for the first half, to get ahead of potential election doldrums, may turn into a trickle. Market jitters are only part of the problem. Sending slide decks is a poor substitute for in-person meetings.

That means ramping up meetings while there's still a window. Beyond deploying executives, it means creatively figuring out how to deploy other stakeholders, like board and SAB members, who may be able to keep the conversation alive with local investors and stop the trail from going cold.

Lack of congress

Conference cancellations are growing daily and almost all major conferences are on the watch list.

The next inflection points could be BIO-Europe Spring in Paris, scheduled for March 23-25, and the AACR meeting in San Diego, in April. The latter was canceled at the last moment during the 2003 SARS crisis.

For BIO, its annual slate of conferences brings in 44% of its revenue, according to spokesperson Rich Masters. For AACR, meetings and workshops represent about one quarter of the revenue, but the annual meeting is a flagship event, and has grown from an important research conference to a major item on biotech's oncology calendar, arguably matching ASCO.

Beyond the losses for the organizers, the meetings are places where deals are started, research is presented, and panel discussions inform audiences about state-of-the-art thinking on hot topics.

But the open truth is that attending conferences is as much about building a network as about achieving any specific business goal.

Hallway conversations, meetings over drinks and chance introductions will fall by the wayside. Those are the places where deals are spawned, and there are few ways to make up for that lost ground.

BioCentury will publish the results of a survey in the next few days documenting how biotechs and VCs are responding to the crisis.

There's no recipe for all the contingency plans companies should make. But necessity is the mother of invention, and this could be a good test of how far video-conferencing services can be leveraged, or what other ways technology can be deployed to solve the problem.

Because while the hope is that the outbreak will crest sooner than the worst fears predict, the certainty is that this crisis won't be the last.

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NEWSROOM:
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SAN CARLOS, CA:
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BioCentury Inc.
BioCentury International Inc.

MAIN OFFICES
1235 Radio Road, Ste. 100
Redwood City, CA 94065-1217
+1 650-595-5333; Fax: +1 650-595-5589

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"THERE IS A HUGE DIFFERENCE BETWEEN THE POSSIBILITY THAT A VACCINE WILL SENSITIZE A SUSCEPTIBLE, SERONEGATIVE RECIPIENT TO AN ANTIBODY-ENHANCED DISEASE AND THE REALITY THAT IT ACTUALLY DOES."

SCOTT HALSTEAD, USUHS

CORONAVIRUS

Haste plus speed: the need to ensure COVID-19 vaccines don't make infections worse

BY SANDI WONG, ASSISTANT EDITOR

The rush to make a vaccine for COVID-19 has raised concern that some candidate treatments could make infections worse. The main risk is the chance of inducing antibody-dependent enhancement, a process known to complicate vaccine development in Dengue and several other diseases.

The topic drew attention at a global online forum sponsored last month by WuXi Apptec Co. Ltd. (Shanghai:603259; HKEX:2359) (see "Plotting a Scientific Path to Counter COVID-19").

ADE is usually triggered by non-neutralizing antibodies or sub-neutralizing levels of antibodies.

Two papers published in *Cell* and the Journal of Virology in February showed it can happen with neutralizing antibodies as well.

While it's too early to know if COVID-19 carries a risk of ADE, other coronaviruses, including SARS-CoV and MERS-CoV, have been associated with the phenomenon, Scott Halstead, who introduced the ADE concept 40 years ago, told BioCentury.

This does not make ADE a foregone conclusion with COVID-19, Halstead noted. "There is a huge difference between the possibility that a vaccine will sensitize a susceptible (seronegative) recipient to an antibody-enhanced disease and the reality that it actually does." Halstead is an adjunct professor at the Uniformed Services University of the Health Sciences.

For SARS and MERS, antibodies against the viruses -- elicited either by infection or vaccination -- have been shown to cause ADE in animal models, including non-human primates. In cell cultures, they have been shown to potentiate infection of primary human macrophages.

There's also evidence that feline infectious peritonitis virus, a coronavirus that infects domestic cats, is enhanced both by maternal antibodies transferred to kittens and by vaccination, resulting in severe and fatal feline disease.

Halstead is unaware of any "evidence that severe or fatal SARS or MERS result from antibody-mediated infections."

Vaccine developers "must be aware of and look for" the possibility of ADE caused by COVID-19 vaccines, he cautioned.

In Dengue, the phenomenon has held up vaccine development for several drug developers (see "Dengvaxia's Warning").

Johan Van Hoof, global therapeutic area head for infectious diseases and vaccines at Janssen unit of Johnson & Johnson (NYSE:JNJ), told BioCentury that ADE is linked to an imbalance of responses of two types of T cell, Th2 vs Th1, favoring the former.

Van Hoof thinks companies could use this fact during Phase I testing to demonstrate a low risk of ADE by showing their candidate induces a Th1-driven immune profile. Showing a vaccine candidate elicits neutralizing antibodies will also be important, he said.

Designing out ADE

A variety of vaccine design approaches have been proposed to help lower risk for ADE.

Most companies developing COVID-19 vaccines have not said whether they are using these or other approaches.

Kizzmekia Corbett, scientific lead of the coronavirus team at NIH's vaccine research center, previously told BioCentury that the candidate from Moderna Inc. (NASDAQ:MRNA), mRNA-1273, which encodes the

Antibody-dependent enhancement and strategies to avoid it

Preclinical studies in MERS-CoV and SARS-CoV, as well as research on cat coronaviruses, have raised the possibility that COVID-19 vaccines might cause antibody-dependent enhancement (ADE) of subsequent infection, making the disease more instead of less severe.

The majority of COVID-19 vaccines in development aim to elicit neutralizing antibodies against the spike protein that prevent the virus from binding ACE2 on lung cells and entering via endocytosis.

However, some antibodies, especially non-neutralizing antibodies, can enhance disease by binding to the virus and Fc receptors on monocytes, macrophages and other immune cells, enabling viral uptake by cells that don't express ACE2. The result is additional viral replication, and a skew toward Th2 rather than Th1 immune responses.

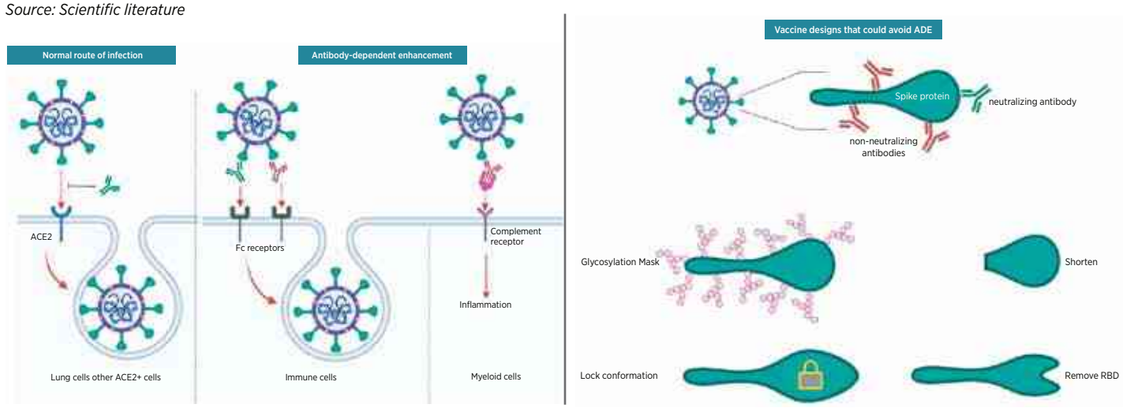
Antibodies against another coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV), have been shown to cause ADE in animals by an additional mechanism: complement activation, which further increases pulmonary inflammation and immune cell recruitment.

At least four vaccine design approaches that could avoid ADE have been proposed in the literature (bottom).

A *Journal of Virology* study in February noted that some anti-spike neutralizing mAbs bind epitopes outside the protein's receptor-binding domain (RBD), and suggested designing subunit vaccines without the domain as a way to focus the immune response on other neutralization epitopes.

Immunofocusing constitutes one of the main methods proposed to prevent ADE and skew adaptive immunity toward protective responses. Other immunofocusing strategies include masking undesired antibody epitopes with glycosyl groups; truncating the spike protein; and locking the antigen into conformations that display epitopes for neutralizing antibodies.

Source: Scientific literature



virus' spike protein, incorporates mutations that stabilize the spike in a prefusion conformation to ensure it induces the right kind of antibodies to confer protection.

Peter Hotez, co-director of Texas Children's Hospital Center for Vaccine Development at Baylor College of Medicine, told BioCentury his team's strategy involves "reducing the size of the subunit vaccine" to focus the immune response on the receptor-binding domain of the spike protein.

CureVac AG spokesperson Thorsten Schüller told BioCentury the company took into account preclinical and animal data regarding coronavirus-associated ADE "for the design of our vaccine candidates for SARS-CoV-2 by carefully selecting the target protein." He declined to disclose the details.

Janssen spokesperson Paul Graves told BioCentury the company is exploring approaches that "target all or some parts of the protein" for its vaccine and "will select which targets to pursue based on the results of our early research."

Moderna's mRNA-1273, partnered with NIH, will be among the first preventative vaccines to enter the clinic; it is scheduled to start Phase I testing Friday. The first clinical batch of mRNA-1273 was delivered 42 days after the genome of the virus that causes COVID-19 was released; design and manufacturing took 25 days.

CureVac hopes to have an mRNA vaccine in the clinic by June or July, and Janssen plans to take a candidate from its recombinant adenovirus (rAdV) vector platform into the clinic within a year.

More than three dozen companies and academic groups have announced COVID-19 vaccine programs (see "A Growing List of Vaccines" and "U.S. Testing of Coronavirus Vaccine, Therapeutic Begin").

BIOCENTURY

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NEWSROOM:
pressreleases@biocentury.com

SAN CARLOS, CA:
+1 650-595-5333

CHICAGO:
+1 312-755-0798

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+1 202-462-9582

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+44 (0)1865-512184

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BioCentury Inc.
BioCentury International Inc.

MAIN OFFICES
1235 Radio Road, Ste. 100
Redwood City, CA 94065-1217
+1 650-595-5333; Fax: +1 650-595-5589

CORPORATE

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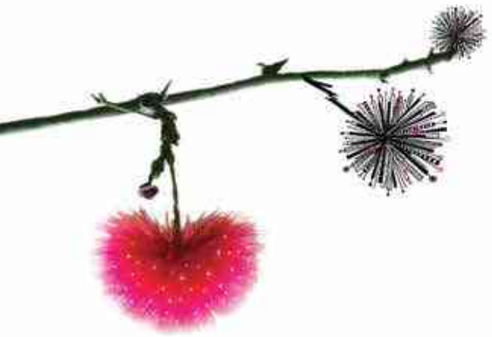


Happy smile and hope after pain

D.K. Lee has related to It's A Wig that she will promote to cancer patients about the beauty classes and healing programs she attended. The beauty classes are held at Kyung Hee Medical Center and it is for cancer patients to help them feel more womanly during their hard times. She would like to thank all the people who gave her hope. "Thank you for giving me a second chance to live as a woman. With the hopes and gifts that I have received, it encourages me to work harder to volunteer my time for the people who are fighting against cancer."

Kyung Hee Medical Center patient
D. K. Lee

Cancer-free D.K. Lee

D.K. Lee attending
beauty classes while chemotherapy treatment

Evofem's Amphora Requires 12-month Data to Convince Experts of Contraceptive Efficacy

Evofem's (NASDAQ:EVFM) contraceptive gel Amphora leaves experts needing detailed 12-month efficacy data despite available Phase III seven-cycle data, along with participant demographics, to determine usability if it is FDA approved.

Amphora is under FDA review for approval with a 25 May PDUFA date, as per a December 2019 press release. While some experts found the Phase III AMPOWER trial (NCT03243305) results comparable with other FDA-approved barrier contraceptive methods, others found AMPOWER's pregnancy rates high in general and as such its use is likely to be limited as a secondary contraceptive option.

In terms of approval, an analyst report stated an advisory committee is unlikely, since Evofem worked closely with the FDA. Interviewed experts, however, were reluctant to estimate Amphora's approval chances or even degree of use if approved, citing the lack of 12-month efficacy data, considered standard in the contraceptive field.

Nonetheless, experts said the need for more nonhormonal contraceptive alternatives was strong, as noted in a second analyst report, which underscored the lack of solutions for women who want hormone-free birth control. There will be some women who would prefer using a gel like Amphora instead of condoms, intrauterine devices (IUDs) or other barrier methods, interviewed experts added. However, they noted, use should ideally be accompanied by counselling based on reproductive goals, health and socioeconomic background.

Data from a separate Phase IIb/III (NCT03107377) trial indicating Amphora's protective efficacy against certain sexually transmitted infections (STIs) provided an additional incentive for use, especially for those who would not use condoms, experts said. However, they cautioned against considering Amphora a fail-safe method for STI prevention until there is data with more patients and against other STIs, particularly since Phase IIb/III was limited to chlamydia and gonorrhea. Amphora sales are estimated to reach USD 275m in 2027 following a 2020 launch, according to the first analyst. Evofem's market cap is USD 223.7m.

Evofem declined to comment but referred this news service to its press releases.

Data comparable with on-demand options but 12-month data critical

The 13.7% pregnancy rate observed in AMPOWER is high for a contraceptive option, said Dr John Guillebaud, emeritus professor, Family Planning and Reproductive Health, University College, London. Among 1,130 women who used at least one Amphora application in AMPOWER, the cumulative pregnancy rate was 13.7% as per an ASRM 2019 poster (p-497). The trial's primary endpoint was contraceptive efficacy over seven cycles of use.

The pregnancy rate is especially high compared with an IUD, said Dr Oskari Heikinheimo, professor, Department of Obstetrics & Gynecology, University of Helsinki, which has a failure rate of less than 1%. Many women cannot tolerate IUDs since they can lead to device expulsion or heavier and longer menstrual cycles, or they don't want it, Dr Nicole Economou, clinical instructor, Obstetrics/Gynecology & Reproductive Sciences, University of California, San Diego, explained. In AMPOWER, vaginal burning sensation and vaginal itching were reported in 20% and 11.2% participants, respectively, but less than 2% discontinued due to adverse events in the single-arm trial.

> "It is important to look at the pregnancy rate in terms of an entire year in the first year of use to understand the actual failure rate"

The most effective method may not always be the best method, said Dr David Eisenberg, associate professor, Department of Obstetrics and Gynecology, St. Louis, Missouri, emphasizing the need to find a contraceptive method that works best for an individual woman. It is more appropriate to compare Amphora to male or female condoms, since they are also on-demand approaches versus an implanted, long-term IUD, said Eisenberg. Amphora can be used with an applicator up to one hour before sexual intimacy. Nonhormonal methods like male or female condoms, or the diaphragm, have a 12–24% failure rate and so Amphora's efficacy data is comparable, said Eisenberg and Economou.

However, three experts emphasized the lack of 12-month data made interpreting Amphora's efficacy challenging for real-world relevance. It is important to look at the pregnancy risk in terms of an entire year in the first year of use to understand the actual failure rate, said Guillebaud. Economou and Guillebaud both referred to the Pearl Index as the gold standard for determining contraceptive efficacy and safety and the need for Amphora data as per this metric. The Pearl Index is used to indicate the number of pregnancies with respect to the number of months or cycles of exposure to a contraceptive in a trial. Even compliance rates need to be studied over a year, Heikinheimo added.

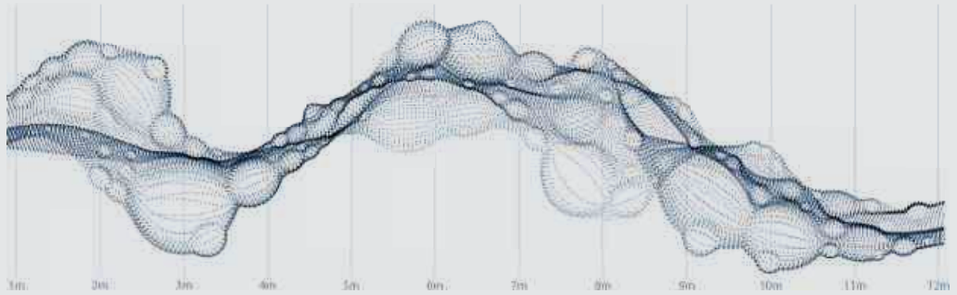
AMPOWER's reported 13.7% pregnancy risk was recorded for seven cycles only, so if the trial had continued for a further five months to complete one year, the projected contraceptive failure rate could probably be more than 20%, said Guillebaud. In AMPOWER, where efficacy is measured over seven cycles, one cycle spans 21–32 days. Post-marketing trials that follow patients in a real-world setting are key to understanding Amphora's efficacy, said Eisenberg and Heikinheimo.

Trial patient profile needed to find ideal users

Full data, particularly participant characteristics, would be important to judge its FDA approval chances, added Economou. It is important to understand the demographics of AMPOWER participants in terms of race, education and number of children, to make it more relevant to a larger population and not just a subset of women that may be on a trial, she added.

Women on clinical trials are highly motivated to use any product and are comparatively more compliant and less diverse than those in the real world, said Heikinheimo, but this is true for most contraceptive trials. Study participants choose to enroll on a trial and hence may be different from the general population, said Economou.

Assuming 12-month efficacy also reports a 13.7% failure rate, acceptance would depend on the individual, said Economou. Daily oral contraceptives have a 9% failure rate, which some women don't find acceptable and hence



use a second method, she added. Hence, Amphora's use as a standalone method would also depend on their individual reproductive goals, she noted. Amphora's failure rate may be high enough for couples to want to use another method as well, said Guillebaud. AMPOWER participants had to be willing to use Amphora as the only method of contraception to be recruited.

Women are looking for a choice, and a patient-centric approach is to analyze the acceptability of each method, said Economou. The contraceptive failure rate needs to be communicated very clearly, added Heikinheimo.

Amphora's STI protection data limited

It is biologically plausible that Amphora's pH regulator mechanism can decrease bacterial transmission rate, said Economou. In the Phase IIb/III study, the infection rate for chlamydia was 4.9% for women who used Amphora compared with 9.8% for placebo (p=0.024), while the rate for gonorrhea was 0.7% with Amphora versus 3.2% on placebo (p=0.03), as per a 2 December press release.

Since Phase IIb/III did not cover other STIs like HIV and syphilis, barrier methods like condoms should still be used with Amphora, said Economou. The low pH maintained in the vaginal environment can affect the bacterial flora and thereby prevent certain STIs, but that still leaves the risk for other STIs open, said Heikinheimo. However, it is important to understand how it can reduce STIs or potentially affect the acquisition of others, before any STI protection conclusions are made, noted Eisenberg.

Using a dual method of contraception is an important approach, but Amphora's compatibility with latex and nitrile—the most common materials used for male and female condoms, respectively—is not yet known, said Eisenberg. There can be some situations where a woman cannot persuade a man to use a condom, and based on Amphora's Phase IIb/III STI data it would provide better STI protection than nothing at all, noted Guillebaud. W

Manasi Vaidya
Reporter, New York

Manasi Vaidya joined as a reporter in New York in February 2015 and has covered the drug development space across a number of therapeutic areas, and built an expertise in writing about oncology. While focusing on analysis pieces about ongoing clinical trials, her coverage has also branched out to regulatory issues, pricing and reimbursement and patent litigation. She has covered practice-changing developments from high profile conferences like ASCO and SABC, in addition to FDA regulatory meetings. She previously covered the Asian biotechnology industry for BioSpectrum, a monthly magazine in India, for two years. She has a Masters degree in Science, Health and Environmental Reporting from New York University, and a Masters degree in Biotechnology from Dr. D. Y. Patil University. Her work has appeared in Nature Medicine, Nautilus and Technology Review India.

FOLLOW THE JOURNEY OF VIREAD

COMPLETE RESPONSE RESULTS AT YEAR 1...

#1 **Prescribed oral antiviral** according to US prescription data for treatment of CHB[1a]

AT YEAR 1
The primary endpoint—complete response*—was evaluated in Studies 102 and 103[2]

THROUGH YEAR 8
Resistance was evaluated as a secondary endpoint[2,3]

In Study 102 (HBeAg–, n=375) and Study 103 (HBeAg+, n=266), a combined total of 641 adult patients with chronic hepatitis B (CHB) and compensated liver disease who were primarily nucleoside treatment naïve entered a 48-week, randomized, double-blind, active-controlled treatment period comparing VIREAD 300 mg to adefovir dipivoxil 10 mg. Subjects who completed double-blind treatment at Week 48 were eligible to roll over with no interruption in treatment to open-label VIREAD. Of 641 patients enrolled in the initial trials, 412 (64%) completed 384 weeks of treatment.[2]

***The primary endpoint in Studies 102 and 103 was complete response to treatment at 48 weeks as defined by HBV DNA <400 copies/mL (69 IU/mL) + histological response (Knodell necroinflammatory score improvement of ≥2 points without worsening in Knodell fibrosis score). Annual evaluation of resistance was a prespecified secondary endpoint. Cumulative VIREAD genotypic resistance was evaluated annually for up to 384 weeks in Studies 102, 103, 106, 108, and 121.[2,3]**

71% of HBeAg– VIREAD patients vs **49%** of adefovir dipivoxil patients.[2-4]
67% of HBeAg+ VIREAD patients vs **12%** of adefovir dipivoxil patients.[2,3,5]

INDICATION AND USAGE

VIREAD® (tenofovir disoproxil fumarate) is indicated for the treatment of chronic hepatitis B in adults and pediatric patients 12 years of age and older.

The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:

- The indication in adults is based on data from treatment of subjects who were nucleoside–treatment-naïve and treatment-experienced with documented resistance to lamivudine. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease
- VIREAD was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease
- The numbers of subjects in clinical trials who had adefovir resistance-associated substitutions at baseline were too small to reach conclusions of efficacy

IMPORTANT SAFETY INFORMATION

BOXED WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals**
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted**

[a]Healthcare Analytics Monthly data, August 2014-June 2015.

Please see Brief Summary of full Prescribing Information including **BOXED WARNING** on the following pages.

GILEAD IS COMMITTED TO THE EDUCATION AND TREATMENT OF CHRONIC HEPATITIS B.

Viread® 300 mg tablets
tenofovir disoproxil fumarate

Not an actual patient, but is representative of a real patient type. Models are used for illustrative purposes only.

...AT 8 YEARS: NO RESISTANCE WAS

Annual evaluation of resistance was a prespecified secondary endpoint for Studies 102 and 103 in HBeAg- and HBeAg+ chronic hepatitis B patients[3]; no evidence of resistance was found. Cumulative VIREAD genotypic resistance was evaluated annually for up to 384 weeks in Studies 102, 103, 106, 108, and 121.[2,4,5]

- In the nucleotide-naïve population from Studies 102 and 103, HBeAg+ subjects had a higher baseline viral load than HBeAg– subjects and a significantly higher proportion of the subjects remained viremic at their last time point on VIREAD monotherapy (15% vs 5%, respectively)[2]
- HBV isolates from these subjects who remained viremic showed treatment-emergent substitutions; however, no specific substitutions occurred at a sufficient frequency to be associated with resistance to VIREAD (genotypic and phenotypic analyses)[2]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

- **New onset or worsening renal impairment:** Cases of acute renal failure and Fanconi syndrome have been reported with the use of VIREAD. In all patients, assess estimated creatinine clearance (CrCl) prior to initiating and during therapy. In patients at risk for renal dysfunction, including those who previously experienced renal events while receiving adefovir dipivoxil, additionally monitor serum phosphorus, urine glucose, and urine protein. In patients with CrCl <50 mL/min, adjust dosing interval and closely monitor renal function. Avoid concurrent or recent use with a nephrotoxic agent. Cases of acute renal failure, some requiring hospitalization and renal replacement therapy, have been reported after initiation of high dose or multiple NSAIDs in HIV-infected patients with risk factors for renal dysfunction; consider alternatives to NSAIDs in these patients. Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function
- **Coadministration with other products:**
  – Do not use in combination with other products containing tenofovir disoproxil fumarate
  – Do not administer in combination with adefovir dipivoxil
- **Patients coinfected with HIV-1 and HBV:** Due to the risk of development of HIV-1 resistance, VIREAD should only be used in HIV-1 and HBV coinfected patients as part of an appropriate antiretroviral combination regimen. HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD
- **Bone effects:** Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia, have been seen in patients treated with VIREAD. Consider assessment of BMD in adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for bone loss. In a clinical trial conducted in pediatric subjects 12 to <18 years of age with chronic hepatitis B, total body BMD gain was less in VIREAD-treated subjects as compared to the control group. In patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms, hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered

ADVERSE REACTIONS

- **In HBV-infected subjects with compensated liver disease:** Most common adverse reaction (all grades) was nausea (9%). Other treatment-emergent adverse reactions reported in >5% of patients treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash
- **In HBV-infected subjects with decompensated liver disease:** Most common adverse reactions (all grades) reported in ≥10% of patients treated with VIREAD were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%)

DRUG INTERACTIONS

- **Didanosine:** Coadministration increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy). Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. In patients weighing >60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered with VIREAD and in patients weighing <60kg, the didanosine dose should be reduced to 200 mg once daily when coadministered with VIREAD

DETECTED AT YEAR 1 THROUGH YEAR 8

NO HBV RESISTANCE DEVELOPED YEAR 1 through YEAR 8

in clinical trials (Studies 102 and 103)[2,3]*

*Data for Years 2 through 8 are from the open-label phase.[6]

- There was a 64% (412/641) retention rate at Year 8: 266/426 patients given VIREAD→VIREAD; 146/215 patients given adefovir dipivoxil→VIREAD[2,6]

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS (cont'd)

- **HIV-1 protease inhibitors:** Coadministration decreases atazanavir concentrations and increases tenofovir concentrations; use atazanavir given with ritonavir. Coadministration of VIREAD with atazanavir and ritonavir, darunavir and ritonavir, or lopinavir/ritonavir increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity
- **Drugs affecting renal function:** Coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir

DOSAGE AND ADMINISTRATION

- Recommended dose, in adults and pediatric patients ≥12 years of age (≥35 kg), for the treatment of chronic hepatitis B: one 300 mg tablet, once daily, taken orally, without regard to food
- In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown
- Safety and efficacy in pediatric patients <12 years of age or weighing <35kg with chronic hepatitis B have not been established
- The dosing interval of VIREAD should be adjusted (using recommendations in the table below) and renal function closely monitored in patients with baseline creatinine clearance <50 mL/min

DOSAGE ADJUSTMENT FOR PATIENTS WITH ALTERED CREATININE CLEARANCE

	Creatinine clearance (mL/min)[a]			Hemodialysis patients
	≥50	30-49	10-29	
Recommended 300 mg dosing interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis[b]

[a]Calculated using ideal (lean) body weight.

[b]Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD should be administered following completion of dialysis.

- The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients
- No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50-80 mL/min). Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be performed in these patients
- No data are available to make dose recommendations in pediatric patients with renal impairment

Please see Brief Summary of full Prescribing Information including **BOXED WARNING** on the following pages.

References: 1. Data on file, Gilead Sciences, Inc. Healthcare Analytics. **2.** VIREAD [package insert]. Foster City, CA: Gilead Sciences, Inc.; May 2015. **3.** Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med.* 2008;359(23):2442-2455. **4.** Data on file, Gilead Sciences, Inc. Study 102 CSR. **5.** Data on file, Gilead Sciences, Inc. Study 103 CSR. **6.** Marcellin P, Gane EJ, Flisiak R, et al. Long term treatment with tenofovir disoproxil fumarate for chronic hepatitis B infection is safe and well tolerated and associated with durable virologic response with no detectable resistance: 8 year results from two phase 3 trials [AASLD abstract 229]. *Hepatology.* 2014;60(4)(suppl):313A-314A.

For more information, visit www.viread.com/hcp

300 mg tablets
Viread®
tenofovir disoproxil fumarate

VIREAD® (tenofovir disoproxil fumarate) tablets

Brief summary of full Prescribing Information. Please see full Prescribing Information including Boxed WARNING. Rx only

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals *(See Warnings and Precautions)***
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted *(See Warnings and Precautions)***

INDICATIONS AND USAGE: VIREAD is indicated for the treatment of chronic hepatitis B in adults and pediatric patients 12 years of age and older.

The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:

- The indication in adults is based on safety and efficacy data from treatment of subjects who were nucleoside-treatment-naïve and subjects who were treatment-experienced with documented resistance to lamivudine. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease *(See Adverse Reactions)*
- VIREAD was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease *(See Adverse Reactions)*
- The numbers of subjects in clinical trials who had adefovir resistance-associated substitutions at baseline were too small to reach conclusions of efficacy

DOSAGE AND ADMINISTRATION: For the treatment of chronic hepatitis B the recommended dose, in adults and pediatric patients ≥12 years of age (≥35 kg), is one 300 mg tablet, once daily, taken orally, without regard to food. In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. Safety and efficacy in pediatric patients <12 years of age with chronic hepatitis B weighing <35 kg have not been established. **Dose Adjustment for Renal Impairment in Adults:** Significantly increased drug exposures occurred when VIREAD was administered to subjects with moderate to severe renal impairment. Therefore, the dosing interval of VIREAD tablets 300 mg should be adjusted in patients with baseline creatinine clearance <50 mL/min using the recommendations in Table 1. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease (ESRD) requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients *(See Warnings and Precautions)*. No dose adjustment of VIREAD tablets 300 mg is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of calculated creatinine clearance, serum phosphorus, urine glucose and urine protein should be performed in patients with mild renal impairment *(See Warnings and Precautions)*.

Dosage Adjustment for Adult Patients with Altered Creatinine Clearance

	Creatinine clearance (mL/min)[a]			Hemodialysis patients
	≥50	30-49	10-29	
Recommended 300 mg dosing interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis[b]

a. Calculated using ideal (lean) body weight.

b. Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD should be administered following completion of dialysis.

The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients. No data are available to make dose recommendations in pediatric patients with renal impairment.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS: Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with VIREAD should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). **Exacerbation of Hepatitis after Discontinuation of Treatment:** Discontinuation of anti-HBV therapy, including VIREAD, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue VIREAD should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. **New Onset or Worsening Renal Impairment:** Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of VIREAD *(See Adverse Reactions)*. It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with VIREAD. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of VIREAD, and periodically during VIREAD therapy. Dosing interval adjustment of VIREAD and close monitoring of renal function are recommended in all patients with creatinine clearance <50 mL/min *(See Dosage and Administration)*. No safety or efficacy data are available in patients with renal impairment who received VIREAD using these dosing guidelines, so the potential benefit of VIREAD therapy should be assessed against the potential risk of renal toxicity. VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)) *(See Drug Interactions)*. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir DF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction. Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients. **Coadministration with Other Products:** VIREAD should not be used in combination with the fixed-dose combination products ATRIPLA®, COMPLERA®, STRIBILD® or TRUVADA® since tenofovir disoproxil fumarate is a component of these products. VIREAD should not be administered in combination with adefovir dipivoxil *(See Drug Interactions)*. **Patients Coinfected with HIV-1 and HBV:** Due to the risk of development of HIV-1 resistance, VIREAD should only be used in HIV-1 and HBV coinfected patients as part of an appropriate antiretroviral combination regimen. HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with VIREAD.

Bone Effects

Bone Mineral Density: In clinical trials in HIV-1 infected adults, VIREAD was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving VIREAD *(See Adverse Reactions)*.

Clinical trials evaluating VIREAD in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the VIREAD-treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected *(See Adverse Reactions)*.

The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adults and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Mineralization Defects: Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of VIREAD *(See Adverse Reactions)*. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and

Brief Summary (Cont'd)

osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF *(See Warnings and Precautions)*.

ADVERSE REACTIONS: Clinical Trials in Adult Subjects with Chronic Hepatitis B and Compensated Liver Disease: *Treatment-Emergent Adverse Reactions:* In controlled clinical trials in subjects with chronic hepatitis B (0102 and 0103), more subjects treated with VIREAD during the 48-week double-blind period experienced nausea: 9% with VIREAD versus 2% with adefovir dipivoxil. Other treatment-emergent adverse reactions reported in >5% of subjects treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash. No significant change in the tolerability profile was observed with continued treatment with VIREAD for up to 384 weeks.

Laboratory Abnormalities: in Studies 0102 and 0103 (0–48 Weeks) laboratory abnormalities (Grades 3–4) reported in ≥1% of subjects treated with Viread (n=426) and adefovir dipivoxil (n=215), respectively, were: any ≥Grade 3 laboratory abnormality (19%, 13%); creatine kinase (M: >990 U/L; F: >845 U/L) (2%, 3%); serum amylase (>175 U/L) (4%, 1%); glycosuria (≥3+) (3%, <1%); AST (M: >180 U/L; F: >170 U/L) (4%, 4%); and ALT (M: >215 U/L; F: >170 U/L) (10%, 6%). Laboratory abnormalities (Grades 3–4) were similar in subjects continuing VIREAD treatment for up to 384 weeks in these trials.

The overall incidence of on-treatment ALT flares (defined as serum ALT >2 × baseline and >10 × ULN, with or without associated symptoms) was similar between VIREAD (2.6%) and adefovir dipivoxil (2%). ALT flares generally occurred within the first 4-8 weeks of treatment and were accompanied by decreases in HBV DNA levels. No subject had evidence of decompensation. ALT flares typically resolved within 4-8 weeks without changes in study medication. The adverse reactions observed in subjects with chronic hepatitis B and lamivudine resistance who received treatment with VIREAD were consistent with those observed in other hepatitis B clinical trials in adults. *Clinical Trial in Adult Subjects with Chronic Hepatitis B and Decompensated Liver Disease:* In a small randomized, double-blind, active-controlled trial (0108), subjects with CHB and decompensated liver disease received treatment with VIREAD or other antiviral drugs for up to 48 weeks. Among the 45 subjects receiving VIREAD, the most frequently reported treatment-emergent adverse reactions of any severity were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%). Two of 45 (4%) subjects died through Week 48 of the trial due to progression of liver disease. Three of 45 (7%) subjects discontinued treatment due to an adverse event. Four of 45 (9%) subjects experienced a confirmed increase in serum creatinine of 0.5 mg/dL (1 subject also had a confirmed serum phosphorus <2 mg/dL through Week 48). Three of these subjects (each of whom had a Child-Pugh score ≥10 and MELD score ≥14 at entry) developed renal failure. Because both VIREAD and decompensated liver disease may have an impact on renal function, the contribution of VIREAD to renal impairment in this population is difficult to ascertain. One of 45 subjects experienced an on-treatment hepatic flare during the 48 week trial.

Clinical Trials in Pediatric Subjects 12 Years of Age and Older with Chronic Hepatitis B: Assessment of adverse reactions is based on one randomized study (0115) in 106 pediatric subjects (12 to less than 18 years of age) infected with chronic hepatitis B receiving treatment with VIREAD (N = 52) or placebo (N = 54) for 72 weeks. The adverse reactions observed in pediatric subjects who received treatment with VIREAD were consistent with those observed in clinical trials of VIREAD in adults. In this study, both the VIREAD and placebo treatment arms experienced an overall increase in mean lumbar spine BMD over 72 weeks, as expected for an adolescent population. The BMD gains from baseline to Week 72 in lumbar spine and total body BMD in VIREAD-treated subjects (+5% and +3%, respectively) were less than the BMD gains observed in placebo-treated subjects (+8% and +5%, respectively). Three subjects in the VIREAD group and two subjects in the placebo group had significant (greater than 4%) lumbar spine BMD loss at Week 72. At baseline, mean BMD Z-scores in subjects randomized to VIREAD were −0.43 for lumbar spine and −0.20 for total body, and mean BMD Z-scores in subjects randomized to placebo were −0.28 for lumbar spine and −0.26 for total body. In subjects receiving VIREAD for 72 weeks, the mean change in BMD Z-score was −0.05 for lumbar spine and −0.15 for total body compared to +0.07 and +0.06, respectively, in subjects receiving placebo. As observed in pediatric studies of HIV-infected patients, skeletal growth (height) appeared to be unaffected *(See Warnings and Precautions)*.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of VIREAD. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: allergic reaction, including angioedema, lactic acidosis, hypokalemia, hypophosphatemia, dyspnea, pancreatitis, increased amylase, abdominal pain, hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT), rash, rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy, acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria, asthenia. The following adverse reactions listed above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

DRUG INTERACTIONS: Didanosine: Coadministration of VIREAD and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. When administered with VIREAD, C_{max} and AUC of didanosine increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of $CD4^+$ cell counts has been observed in patients receiving VIREAD with didanosine 400 mg daily. In patients weighing >60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered with VIREAD. In patients weighing <60 kg, the didanosine dose should be reduced to 200 mg once daily when it is coadministered with VIREAD. When coadministered, VIREAD and didanosine EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). For additional information on coadministration of VIREAD and didanosine, please refer to the full Prescribing Information for didanosine. **HIV-1 Protease Inhibitors:** VIREAD decreases the AUC and C_{min} of atazanavir. Viread should not be coadministered with atazanavir without ritonavir. Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations. Tenofovir disoproxil fumarate is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir disoproxil fumarate is coadministered with an inhibitor of these transporters, an increase in absorption may be observed. Patients receiving VIREAD concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir should be monitored for VIREAD-associated adverse reactions. VIREAD should be discontinued in patients who develop VIREAD-associated adverse reactions. **Drugs Affecting Renal Function:** Since tenofovir is primarily eliminated by the kidneys, coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *(See Warnings and Precautions)*. In the treatment of chronic hepatitis B, VIREAD should not be administered in combination with adefovir dipivoxil.

USE IN SPECIFIC POPULATIONS: Pregnancy: *Pregnancy Category B:* There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VIREAD should be used during pregnancy only if clearly needed. *Antiretroviral Pregnancy Registry:* To monitor fetal outcomes of pregnant women exposed to VIREAD, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263. *Animal Data:* Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. **Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1.** Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is secreted in human milk. The impact of this exposure in breastfed infants is unknown. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving VIREAD. Geriatric Use:** Clinical studies of VIREAD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Patients with Impaired Renal Function:** It is recommended that the dosing interval for VIREAD be modified in patients with estimated creatinine clearance <50 mL/min or in patients with ESRD who require dialysis *(See Dosage and Administration)*.

For detailed information, please see full Prescribing Information. To learn more call 1-800-GILEAD-5 (1-800-445-3235) or visit www.VIREAD.com.

Melanoma Trials Using Antibiotic or Microbiome Therapy Pretreatment Could Be Better Than Direct Combination With Immunotherapy

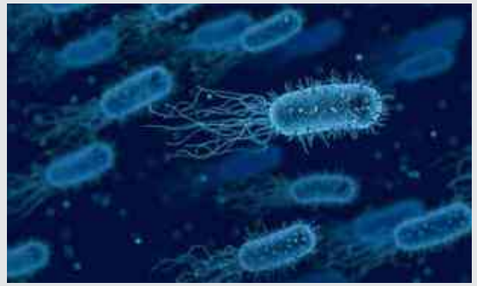
Early-phase melanoma trials testing microbiome approaches that leverage a broad-spectrum antibiotic or microbiome monotherapy before coupling with a checkpoint inhibitor have some advantages over a straight combination approach, experts said. Nevertheless, it is not fully clear which approach will have the edge, with patient diversity likely the ultimate obstacle in demonstrating clinical value, they added.

Several companies have ongoing trials in melanoma with microbiome-focused therapeutics designed to enhance checkpoint inhibitor efficacy. While giving the microbiome therapy and immunotherapy at the same time would make efficacy evaluation cleaner, the approach to either use an antibiotic or the microbiome treatment first are designed to boost proliferation of the introduced bacteria, which may be needed for efficacy, experts explained.

While preclinical data provide theoretical rationale for manipulating gut flora to systemically help the immune system recognise tumours, gut flora differences make it challenging to prove that in a clinical trial setting, experts said. It can be different among patients owing to regional variations and even within each person's gut, they noted.

Some of the microbiome therapeutics being tested introduce one bacteria type versus a combination of bacterial strains. While the first approach may make it easier to pinpoint what caused any efficacy signals, the combination and ratios of multiple bacterial types may be more critical for efficacy, experts added.

The Phase II (NCT03595683) data on **Evelo Biosciences**' (NASDAQ:EVLO) EDP1503 are expected in 2H20, while Phase Ib (NCT03817125) results for **Seres Therapeutics** (NASDAQ:MCRB) SER-401 are anticipated in 2H20 and Cambridge, Massachusetts-based **Vedanta Biosciences'** Phase I/II (NCT04208958) in 2021. **4D Pharma's** (LON:DDDD) Phase I/II trial (NCT03637803) is ongoing and timelines have yet to be disclosed.



Seres' SER-401 is the only therapeutic under clinical investigation in melanoma only, while the other trials are solid tumour basket studies. It is unclear if melanoma is most susceptible to a microbiome approach, owing to other indications sharing the same neoantigen features that make melanoma ideal for checkpoint inhibition, an expert noted.

Time to allow for bacteria proliferation could be crucial

There is no precedence regarding how microbiome approaches should be administered to improve checkpoint inhibitor efficacy, experts said. One strategy—employed by Seres and Vedanta—involves using an antibiotic prior to treatment with the experimental microbiome therapy combined with an approved checkpoint inhibitor.

Administering vancomycin before the microbiome therapeutic may be necessary, as the antibiotic acts as a reset button in the gut, said Dr Diwakar Davar, medical oncologist, University of Pittsburgh Medical Center, Pennsylvania. The investigator-led Phase Ib trial studying Seres' SER-401 includes a four-day vancomycin pretreatment before SER-401 and **Bristol-Myers Squibb's** (NYSE:BMY) anti-PD1 Opdivo (nivolumab). Vedanta's basket Phase I/II trial has a five-day vancomycin pretreatment before VE800/Opdivo.

> "Administering vancomycin before the microbiome therapeutic may be necessary, as the antibiotic acts as a reset button in the gut"

Antibiotic use could make way for the introduced bacterial strains in the microbiome therapeutic to proliferate, added Meenhard Herlyn, director, The Wistar Institute Melanoma Research Center, Philadelphia, Pennsylvania. Without the antibiotic pretreatment, it could be hard to repopulate the gut, noted Steven Fiering, PhD, professor of microbiology and immunology, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire.

The strategy in the investigator-led Phase II trial of Evelo's EDP1503 to skip antibiotic pretreatment but administer EDP1503 for two weeks before combining it with **Merck's** (NYSE:MRK) anti-PD1 Keytruda (pembrolizumab) may also work, noted Claudia Gravekamp, PhD, associate professor, Department of Microbiology and Immunology, Albert Einstein College of Medicine, New York. This would allow time for bacterial engraftment such that the immune system is triggered systemically before immunotherapy is administered, she said.

4D Pharma's basket Phase I/II trial administers MRx0518 on the same day as Keytruda. This approach would make it easier to link any observed efficacy to the two therapies, Gravekamp noted. If the microbiome therapy is administered earlier, there is the risk the introduced bacteria would be overpowered by existing gut microbiome, she explained. But administering the microbiome therapy beforehand could allow for stool sample checks to see if the introduced bacteria are successfully proliferating before administering the checkpoint inhibitor, Fiering noted.

A 4D Pharma spokesperson said while stool samples are collected during the trial, MRx0518 is not intended to recolonise the gut microbiome but to directly stimulate the innate immune system and so pretreatment may not be critical. He also pointed to initial six-patient data from the 12-patient part A cohort, which showed two had partial response with evidence of tumour shrinkage and a third had stable disease. The three other companies did not respond to comment request.

4D's trial also includes renal cell carcinoma, bladder and non-small cell lung cancer (NSCLC). In the part A cohort, two other patients reportedly withdrew due to progressive disease and the sixth withdrew due to a disease-related adverse event.

The 4D study is recruiting anti-PD1 failure patients, and Davar said in such melanoma patients, even a 10–20% overall response rate (ORR) is significant. Yet, ORR would only confirm mechanism rather than lay a foundation for efficacy profiles, he explained. Anti-PD1-refractory patients are also recruited in the Phase II cohort 2 studying Evelo's therapy. The Vedanta VE800 study limits accrual to patients who have received no more than three lines of prior systemic therapy.

On the other hand, the Phase II cohort 1 studying EDP1503 is recruiting anti-PD1-naïve patients, as is the Phase Ib Seres trial. All four studies have safety and tolerability primary endpoints and ORR as a secondary endpoint, except for the Phase II EDP1503 trial, which has it as a coprimary endpoint.

Gut flora approach has many blind spots

Nevertheless, it is still unclear which microbiome approach is better—boosting a specific bacterial strain's frequency versus introducing a broad variety of bacteria, Davar said. MRx0518's *Enterococcus gallinarum* was selected for its in vitro immunostimulatory profile, with the bacteria's flagellin shown to be a potent agonist of toll-like receptor 5 (TLR5), the 4D spokesperson said. Evelo's EDP1503 is derived from a single clone of the *Bifidobacterium* bacteria. In contrast, Vedanta's VE800 employs 11 bacterial strains, and Seres' SER-401 features a variety of gut bacteria derived from melanoma immunotherapy responders.

The upside of introducing a specific bacterial strain is that it sidesteps the risk of unknown bacteria to proliferate, Davar said, adding that the cause of any potential efficacy signal would be clear. However, which specific bacterial strain should be introduced is still up for debate, Fiering noted.

While preclinical data show immunotherapy responders harbour specific bacteria, overall gut flora composition may be more critical than individual strains, Gravekamp said. Preclinical data show a variety of bacteria could cause a cytokine boost, making the immune system better at recognising the tumour, she added. Faecal microbiota transplantation from cancer patients into mice models show this procedure ameliorated antitumour effect of anti-PD1 blockade (Routy, B, et. al, Science. 2018 Jan 5;359(6371):91-97).

But it is challenging to identify the ideal bacterial ratio or gut bacterial composition that each patient should have for efficacy due to the immense variety of bacteria involved, noted Herlyn.

Yet, a wealth of preclinical data show gut bacteria ratio and composition can impact the immune system in a variety of ways, supporting these trials' exploratory rationale, added Fiering. SER-401 preclinical research demonstrates that response to anti-PD1 is restored in mice with the introduction of bacteria chosen based on in vivo and microbiome signatures, an April 2019 media release states.

There are no severe toxicity concerns with gut flora manipulation based on experience, Fiering added. No therapeutic-related serious adverse events were reported in the first six patients in the Phase I/II MRx0518 trial. Still, gut inflammation, stomach upset or increased inflammatory cytokines in the blood should be monitored, Fiering added.

However, since gut flora is different among patients, each could react differently to the same approach, Gravekamp said. Patient diversity makes it hard to study these therapy options in a controlled environment like clinical trials, Herlyn added. The four aforementioned trials are all US-based. But Herlyn noted there could be regional US gut flora diversity. MRx0518's mechanism targeting TLR5 may mean that its efficacy may be independent of background microbiota, the 4D spokesperson said.

Another point that needs to be understood further is the bacterial diversity in a patient's gut, Fiering said. For example, bacteria can reside closer to the gut wall or in the lumen, and the former may be more therapeutically important, he explained.

It is unclear if melanoma would be more susceptible to the microbiome/checkpoint inhibitor approach compared with other solid tumours, Gravekamp said. While melanoma is an ideal target for checkpoint inhibition as such tumours express their own neoantigens, the same could be said for NSCLC and renal cell carcinoma, she added. Seres' SER-401 is the only therapeutic under clinical investigation in melanoma only.

Seres has a USD 254.8m market cap, while Evelo's and 4D Pharma's are USD 137.7m and GBP 55.7m (USD 72.3m), respectively. W

Reynald Castaneda

Reporter, London

Reynald Castaneda, prior to moving to London, was a journalist for healthcare newspaper New Zealand Doctor, covering primary care health politics and medical research. He has a BSc in Biological Sciences from the University of Auckland and a postgraduate diploma in journalism from AUT University. Prior to venturing into journalism, Reynald worked as a laboratory technician for Massey University's Institute of Molecular Biosciences.

Conference Alerts

North America

American Society of Clinical Oncology 2020 Annual Meeting (ASCO 2020)

May 29-June 2, 2020 | Chicago, Illinois, USA

Website: https://am.asco.org
Contact: customerservice@asco.org

The ASCO 2020 Annual Meeting brings together more than 25,000 oncology professionals, patient advocates, industry representatives, and major media outlets worldwide. The meeting makes an excellent venue for exploring the theme of the meeting – "Unite and Conquer: Accelerating Progress Together."

2020 BIO International Convention

June 8-11, 2020 | San Diego, California, USA

Website: https://www.bio.org/events/bio-international-convention/
Contact: info@bio.org

Hosted by the Biotechnology Innovation Organization (BIO), The BIO International Convention will gather more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products.

2020 AACC Annual Scientific Meeting & Clinical Lab Expo

July 26-30, 2020 | Chicago, Illinois, USA

Website: https://meeting.aacc.org/
Contact: custserv@aacc.org

With more than 800 companies exhibiting, the 2020 American Association for Clinical Chemistry Annual Scientific Meeting & Clinical Lab Expo is the world's largest exposition for clinical laboratory products and services. As the place to learn about the breakthrough innovations shaping the future of clinical testing and patient care, AACC's Clinical Lab Expo gives attendees the opportunity to browse exhibitors in person for the solutions to the lab related needs.

Europe

Healthcare Summit 2020

June 15-16, 2020 | Barcelona, Spain

Website: https://europe.healthconferences.org
Contact: healthcare@brainstormingmeetings.com

Healthcare Summit, the 16th World Congress on Healthcare and Technologies, aims to bring together in all the areas of healthcare and technologies. The conference focuses on the theme "Promoting Human Healthy by the Method of Healthcare and Its Aspects" through the topics, engage participants in debate, and facilitate mutual understanding. The goal of the event is to provide a place for academicians and professionals with the interests related to healthcare, advanced healthcare and primary care to meet and interact with members inside and outside their own particular methods.

DIA Europe 2020

June 30-July 3, 2020 | Brussels, Belgium

Website: https://www.diaglobal.org/Flagship/DIA-Europe-2020
Contact: https://www.diaglobal.org/en/contact-us

DIA Europe 2020 is Europe's largest and most forward-looking neutral healthcare conference. The DIA provides a global, neutral forum allowing stakeholders to exchange knowledge, information and insights. This annual event spans DIA's strategic initiatives across a range of Thought Leadership streams – Clinical Development & Operations, Regulatory Science & Operations, Value and Across, Medical Affairs and many more.

2020 European Society of Cardiology (ESC) Congress

August 29-September 2, 2020 | Amsterdam, Netherlands

Website: https://www.escardio.org/Congresses-&-Events/ESC-Congress
Contact: https://www.escardio.org/Contact

European Society of Cardiology Congress brings more than 33,000 dedicated colleagues to share, challenge, and learn. The theme for ESC Congress 2020 is "The Cutting Edge of Cardiology," featuring specific sessions on the latest technology in clinical cardiology available today and on the horizon including: the use of advanced therapies, wearable technology to reshape the delivery of medical care, and robotics to introduce remote care.

Asia

Singapore Hepatology Conference 2020

June 5-6, 2020 | Singapore, Singapore

Website: https://www.shc-sg.com/
Contact: info@shc-sg.com

The scientific program of Singapore Hepatology Conference (SHC) is the premier liver meeting for all clinicians in the region. The meeting dedicates to clinical management of chronic Hepatitis B and C and includes a multi-disciplinary approach to the assessment, diagnosis and treatment strategies to eradicate HBV, HCV, HCC, and NASH. The 7th Singapore Hepatology Conference 2020 will continue to provide focused updates, advances in the prevention, treatment and management of liver diseases.

BIO Asia-Taiwan 2020 Conference & Exhibition

July 22-26, 2020 | Taipei, Taiwan

Website: https://bioasiataiwan.com/
Contact: register@taiwanbio.org.tw

The BIO Asia-Taiwan 2020 Conference and Exhibition will bring together biotechnology and pharmaceutical executives and investors from America, Europe, and Asia to meet and explore business opportunities with biotech sector. The conference and exhibition is one of the largest gatherings and attracts more than 2,000 attendees from 30+ countries representing the full spectrum of biomedical disciplines and industries.

LATEST HEALTHCARE INDUSTRY NEWS

JAN – APR 2020

1. Boehringer Ingelheim, Enleofen Ink $1B-Per-Product Anti-IL-11 Partnership Focused on NASH, Lung Disorders

Boehringer Ingelheim announced that it has acquired exclusive global rights to Enleofen Bio's preclinical interleukin-11 (IL-11) platform to develop new therapies for non-alcoholic steatohepatitis (NASH), interstitial lung diseases (ILDs), and multiple other fibrotic human disorders, in a deal that could generate more than $1 billion per product developed. Through their new collaboration, Boehringer Ingelheim agreed to advance Enleofen's platform into clinical development by working with AMC researchers, with an initial focus on NASH and ILDs—two core disease focus areas for Boehringer Ingelheim. The companies said they could expand their partnership into additional fibro-inflammatory conditions based on IL-11's central role in disease.

https://www.genengnews.com/news/boehringer-ingelheim-enleofen-ink-1b-per-product-anti-il-11-partnership-focused-on-vnash-lung-disorders/

2. Rise in R&D Efforts to Push Rare Neurological Disease Treatment Market

According to TMR Research, the global market for rare neurological disease treatment will be driven by the rise in the number of initiatives and incentive policies by government organizations in the field of rare neurological disease treatment. Increased interest among new pharmaceutical companies and several well-established market players and a vast rise in R&D activities in the field has been observed in the recent years. The market is expected to expand at a promising pace over the next few years owing to these factors. Governments across the globe are also putting more focus on the provision of suitable treatment options for rare neurological diseases and guidelines to affected families. Increased efforts into the improvement of diagnostic procedures for a number of rare neurological conditions could also drive the market.

https://www.biospace.com/article/rise-in-r-and-d-efforts-to-push-rare-neurological-disease-treatment-market/

3. AbbVie, Allergan Merger May Face Regulatory Delay Due to COVID-19 Despite Drug Sell-off: Report

AbbVie and Allergan are looking for a quick close for their $63 billion merger after agreeing to sell off three drugs to help clear antitrust hurdles. AbbVie and Allergan signed a "consent decree" with the FTC to divest late-stage gastrointestinal candidate brazikumab and two pancreatic replacement enzymes. Earlier in March, the pair closed that sale in the EU for the merger's approval. But despite AbbVie's high hopes of closing the merger in two short months, regulators are warning that the continuing novel coronavirus pandemic could knock that plan off the rails. The FTC said it may consider requesting extensions if companies are not able to produce documents and employees in a timely manner for a review.

https://www.fiercepharma.com/pharma/abbvie-allergan-merger-may-face-regulatory-delay-due-to-covid-19-report

4. Amid a Pandemic, Roche Bets $190M on Arrakis and Drugging RNA

Roche will pay privately held Arrakis Therapeutics $190 million in a wide-ranging deal to co-develop small molecule drugs that target RNA molecules. Cambridge, Massachusetts-based Arrakis will handle the early drug development work, after which Roche can license those that show promise and take the lead on clinical testing. The deal includes a variety of conditional payments that could ultimately exceed "several billion dollars," though that cash is tied to milestones and may never materialize. Arrakis is one of several emerging companies aiming to target shifty RNA molecules with chemical drugs. Their approach offers the potential to reach drug targets inside cells that are difficult to get at through other methods.

https://www.biopharmadive.com/news/arrakis-roche-deal-drugging-rna/575695/

5. Coronavirus Prompts Hospitals to Fast-Track Telemedicine Projects

Hospital chief information officers are putting in place new systems and workflows to get ahead of a growing coronavirus epidemic that threatens to tax limited resources and staff. Some health systems are fast-tracking planned technology projects such as telemedicine, aimed at screening patients without requiring them to visit a hospital. To support the new telemedicine effort, the health system also is speeding up software upgrades to Microsoft Corp.'s Windows 10 and Office 365 on PCs at about 60 locations. Doctors will use Microsoft Teams as a collaboration tool for videoconferencing with patients and, if necessary, with other specialists.

https://www.wsj.com/articles/coronavirus-prompts-hospitals-to-fast-track-telemedicine-projects-11583876313?mod=searchresults&page=1&pos=15

6. Digital Molecule Designer Schrödinger Taps Google Cloud for Parallel Computing

Schrödinger aims to upload its digital drug discovery efforts to Google's cloud network with plans to employ thousands of processors to simulate billions of potential compounds per week. The three-year collaboration with Google Cloud is designed to substantially increase the speed and capacity of its physics-based molecule modeling platform, with supercomputer-level power being distributed among nationwide centers. "This partnership is expected to allow us to expand the use of our physics-based computational platform to continue to rapidly explore very large swaths of chemical space," Brauner said in a statement. The agreement comes on the heels of Schrödinger's Nasdaq IPO last month—which went on to raise about $232 million—to help boost its own early pipeline of internally developed drugs.

https://www.fiercebiotech.com/me dtech/digital-molecule-designer-schrodinger-taps-google-cloud-for-parallel-computing

7. Takeda's Small Celiac Disease Bet Turns into Acquisition

Takeda has exercised its option to buy U.S.-based PvP Biologics after seeing Phase 1 data from its only candidate, a celiac disease drug called KumaMax that was invented by a University of Washington undergraduate team. The deal will be worth up to $330 million for PvP's owners, based on development and regulatory milestones for KumaMax, which will now be called TAK-062. Takeda signed PvP to an option deal in 2017, which provided $35 million to cover research costs and allowed the company to bypass traditional venture capital funding. In Takeda's pipeline, TAK-062 will join TAK-101, in-licensed from COUR Pharmaceutical in 2019, in clinical trials for celiac disease.

https://www.biopharmadive.com/news/takeda-pvp-celiac-disease-330-million-deal/573034/

8. Be Careful With Biosimilars Marketing, FDA and FTC Say. We're Watching

The FDA and the Federal Trade Commission (FTC) recently reinforced a commitment to address misleading promotions and anti-competitive practices. The two agencies released a joint statement detailing their promise to police promotional messaging as well as review patent agreements to prevent antitrust collations, share best practices and collaborate on public outreach. In the issued statement, the FDA also announced new draft guidance which notes that companies should be careful when using a reference product and a biosimilar product and should avoid suggesting that a biosimilar product is not highly similar to a reference product or that there are clinically meaningful differences.

https://www.fiercepharma.com/marketing/fda-and-ftc-issue-joint-notice-be-careful-biologic-and-biosimilar-marketing-we-re

9. Bristol-Myers Launches Biotech Targeting Fibrosis, Inflammation

Bristol-Myers Squibb and partner BioMotiv, a biopharma accelerator, launched a new company focused on creating inflammation and fibrosis medicines. The company, Anteros Pharmaceuticals, is investigating a new class of drugs with intellectual property developed at Yale University and in-licensed by Bristol-Myers. In addition to the IP, Bristol-Myers is contributing data and reagents for a series of small molecules that work on an undisclosed mechanism. Anteros' initial targets are liver and lung fibrosis, with one specific disease being IPF, or idiopathic pulmonary fibrosis. Per deal terms, BioMotiv will monitor the early stages of research and development. If or when Anteros nominates a pre-clinical candidate, Bristol-Myers Squibb has the right to acquire the company.

https://www.biopharmadive.com/news/bristol-myers-biomotive-launch-anteros-biotech/571650/

10. Lilly Announces Agreement to Acquire Dermira for $1.1B

Eli Lilly and Company and Dermira, Inc have announced a definitive agreement for Lilly to acquire Dermira for $18.75 per share, or approximately $1.1 billion, in an all-cash transaction. This acquisition expands Lilly's immunology pipeline with the addition of lebrikizumab, a novel, investigational, monoclonal antibody for the treatment of moderate-to-severe atopic dermatitis in adolescent and adult patients, aged 12 years and older. The acquisition agreement also expands Lilly's portfolio of marketed dermatology medicines with the addition of QBREXZA, a medicated cloth approved by the US Food and Drug Administration for the topical treatment of primary axillary hyperhidrosis (uncontrolled excessive underarm sweating). Under the terms of the agreement, Lilly will commence a tender offer to acquire all outstanding shares of Dermira, Inc.

https://www.europeanpharmaceuticalreview.com/news/113660/lilly-announces-agreement-to-acquire-dermira-for-1-1bn/

11. Biogen Finds $75M Home for Pfizer Alzheimer's Drug

In an unusual deal between large drugmakers, Biogen will pay Pfizer $75 million to acquire an experimental drug designed to address sleep-related symptoms of Alzheimer's and Parkinson's disease. Pfizer has completed early-stage safety studies for the drug, but in 2018 decided to step back from neuroscience research, offloading some of its investigational therapies into a spin-off called Cerevel Therapeutics. For Biogen, the deal adds another Alzheimer's asset to its pipeline of five therapies aimed at the neurodegenerative condition. That line-up includes the controversial aducanumab, which the Cambridge, Massachusetts-based biotech plans to submit for U.S. approval this year.

https://www.biopharmadive.com/news/trump-administration-sue-gilead-prep-hiv-patents-truvada/566834/

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