September 2016 - ISSUE 11

WKMJ

World Korean Medical Journal

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Biopharmaceutical Report
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Democratizing Antibodies

NY-ESO-1 Therapy Renewed Enthusiasm Underscored By New Checkpoint Inhibitors

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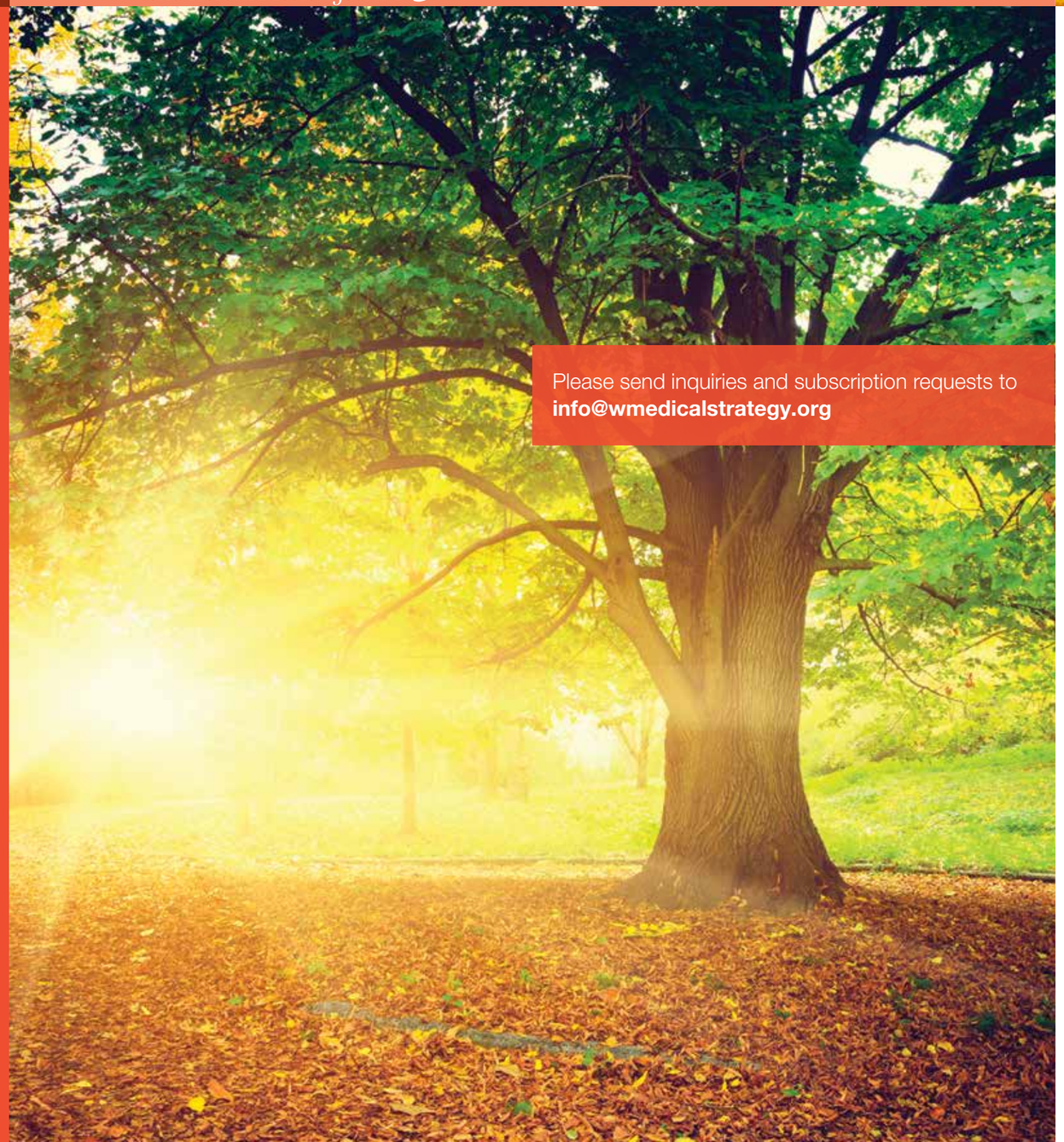

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FROM THE PUBLISHER

Dear Colleagues,

I hope everyone had a great summer as the fall is just beginning. Serving as the president of the World Korean Medical Organization, this summer was very meaningful for me in that it held a forum in the Halls of US Congress. The meeting was featured in the past WKMJ issue on Global Health Disparities because of its innovativeness. Also in this summer, some Korean physicians met with Korean congress over the issue of limiting SSRI for depression by non-psychiatrist to 60 days and they sought out international opinion. We were able to help in that arena with Dr. Tai Yoo who organized Korean Mental Forum on prior WKMO meeting. Next year, we hope to hold a forum in Korea on various health issues.

In this 11th issue, WKMJ features a prominent Korean American physician Dr. Augustine Choi, who spoke at the World Korean Medical Organization meeting in New York a few years ago with many international Korean medical students. He specifically encouraged the students to find their passions and to pursue them. Dr. Choi is a Chairman and Professor of Cornell Medical Center Department of Internal Medicine. He is also a Physician in Chief of Weill Cornell Medical Center. He was recently appointed interim Dean and interim Provost of Weill Cornell Medical School of Cornell University. His interview highlights the triple threat of an academic physician as educator, researcher and clinician. Dr. Choi embodies all that but also the highest medical leadership that Deans and Provost hold in the University.

The entrepreneurial physician interview is with Dr. Leon Reyfman who is the CEO of Advanced Clinical Laboratory Solutions (ACLS). Laboratory testing is such an important facet of modern medical care and the need for rapid and cost effective testing is an area that he saw there was a need. ACLS has special expertise in drug testing and toxicology that has grown to be an epidemic problem and hopefully these tests will help practitioners and patients navigate appropriate drug use and avoid abuse. ACLS is also focusing on pharmacogenomics testing which is truly in the path of providing optimized individualized care.

In closing, this year's Presidential election process in America is a historic one for many reasons, including Dr. Ben Carson entering the fray and hopefully he will inspire other physicians to politics.

David Y. Ko, MD
Publisher
President of WKMO
Keck School of Medicine of USC

FROM THE EDITOR-IN-CHIEF

After Eli Lilly announced their Open Innovation Drug Discovery (OIDD) platform several years ago, many multinational companies have adopted the idea of open innovation. Ideas, policies, strategies, and behaviors sometimes behave just like outbreaks of infectious disease. Malcolm Gladwell once wrote "they are social epidemics." Couple of days ago, Allergen's CEO Brent Saunders has stepped forward to issue the "Saunders Manifesto" on his Allergan CEO blog. Titled as "Our Social Contract with Patients", Saunders's commitments include fair pricing of drugs and enhancing accessibilities to medicines. If other companies follow Allergan's lead, pharmaceutical industry can start to clean up its reputation and earn some respect from the world. Social epidemics and outbreaks in pharma world can be started following Saunders's lead on transparency, accessibility, and innovation.

Through the edition 11 of WKMJ, we have interviewed another leader in therapeutic world, who has brought positive changes and synergistic model of science leadership. Dr. Augustine Choi, who is the Chairman of the Weill Cornell Medicine, Physician-in-Chief for New York-Presbyterian Hospital/Weill Cornell Medical Center, and dean for Cornell School of Medicine, showed us three major sectors in medicine - research, medical education, and clinical care - can be harmonized by well-orchestrated leadership. Dr. Choi shared his story and insight with our readers, and anticipated bright future by saying, "I am optimistic about the future of medicine as we work together with fellow researchers and physicians around the globe, so we may move forward, expand our horizon, and push our limits in caring for our communities."

For the Entrepreneur Interview, we featured Dr. Leon Reyfman, CEO of Advanced Clinical Laboratory Solutions, Inc. who shared significant importance of toxicology testing to physicians and patients.

Addition to these two major articles, we have rich selection of articles which will bring amusement to our readers. Hoping to see more leadership like Saunders' and Choi's in the therapeutic world in near future.

Thank you.

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

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Cover Story
Inspirational Korean Healthcare Leader "Dr. Kyung Sun, Chairman of Osong Medical Innovation Foundation"

Dr. Sun is currently Chief Director of Osong Medical Innovation Foundation since 2015. In the past, he served as a director of Korea Artificial Organ Center, a president of Korean Society of Medical and Biologic Engineering, and a chair of Board in Korean Society for Thoracic and Cardiovascular Surgery. Dr. Sun received an award for Health Industry Technology from Ministry of Health and Welfare in 2008 and National Medal for Presentation Order from Korean Government in 2013. Dr. Sun is a cardiovascular surgeon also serving as a professor at Korea University. To read more about Dr. Sun's successful physician story, please read issue 10.

Special Report
Korea Rise: New Strategies Transforming Korean Biopharma Landscape

The Korean biopharma industry is mainly known for biosimilar and me-too products. But, as the Korean government investment and partnering money have begun to flow into the sector, a virtuous circle has been set in motion in which Korean biotechs are deploying a larger proportion of their revenues to R&D. That in turn is expected to lead to innovative products that could attract more multinationals to the partnering tables. VCs are also coming on board. In 2015 alone, venture investors poured $270-$260 million into Korean life sciences, compared to $197 million in 2014 and $166 million in 2013 according to Citi Asia Healthcare. To find out more about current Korean biopharma, please refer to issue 10.

Biopharmaceutical Report I
South Korea Trials Drive Further Opportunities for Global Pharma and CROs

South Korea's foreign sponsor and CRO attraction over the last decade has scope to increase if it can improve capabilities in early-phase and complex trials, experts said. Clinical trial registration in South Korea shot up from 17 multination-sponsored trials in 2002 to 296 in 2015, according to figures from Korea's Ministry of Food and Drug Safety (MFDS). The US National Institutes of Health clinical trials database indicates 293 trials registered in Korea so far in 2016, and ranks South Korea first in Asia by number of protocols. Read issue 10 for more detailed report about current South Korea pharmaceutical trials.

Biopharmaceutical Report II
PCSK9 Inhibitor Competition: Amgen, Sanofi, and Regeneron Show Equally Decent CVOT Outlooks

Amgen's (NASDAQ:AMGN) Repatha (evolocumab) and Sanofi (EPA: SAN)/Regeneron Pharmaceuticals' (NASDAQ:REGN) Praluent (alirocumab) are expected to produce positive cardiovascular (CV) event outcomes in their respective CV outcomes trials (CVOTs), experts agreed. Previous post-hoc major cardiovascular event (MACE) analysis data and low-density lipoprotein-cholesterol (LDL-C) lowering outcomes inspires continued positive signal optimism for the PCSK9 inhibitors. Please read Issue 10 to find out more.

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INSPIRATIONAL KOREAN HEALTHCARE LEADER

Weill Cornell Medical College Chairman of Medicine Augustine M.K. Choi, MD

Dr. Augustine M.K. Choi (center) with research fellows (left) Drs. Ilias Siempos and Mitsuru Imamura. Photo credit: John Abbott

1. What was your reason for attending medical school? Why did you want to become a physician?

- I was attracted to the field of Medicine because I wanted to help bring about positive impacts on the lives of people, especially concerning the quality of healthcare. My father, a brilliant physician as well as a great role model, was certainly the biggest influence in my decision to pursue medicine. Over the years, I watched my father serving the community through his medical practice, taking care of patients and people suffering from illnesses. I wanted to touch other's life in the same way he did. I never felt pressured to follow his paths; rather, my parents wanted us to find our own passion. My two siblings found their passion in their own field of choice, and I eventually found medicine as my life's work after considering a few different paths.

COVER STORY

2. As a physician, you may have gone through various obstacles; can you share some of the most difficult moments during your career?

- Attending the medical school and training to become a physician requires commitment and dedication. It's not different from other professions that demand years of learning. It takes discipline, hard work and perseverance to be the best doctor one can be. During the four years of medical school, I rigorously absorbed and mastered many different skills and knowledge, after which, I was ready to interact with patients. During the medical residency, I realized that finding compassion and ways to truly care for a patient are not something you learn overnight. It is a life-long process; it does not stop after medical school.

Dr. Augstine Choi and the Department of Medicine Celebrates its Voluntary Physicians at Griffis Faculty Club. From Left Drs. Arthur Radin (Hematology & Medical Oncology), Augustine M.K. Choi (Chairman, Department of Medicine), David S. Blumenthal (Cardiology) and Bruce Gordon (Rogosin Institute)

3. You've been appointed as the Chairman of the Weill Cornell Medicine and Physician-in-Chief for New York-Presbyterian Hospital/Weill Cornell Medical Center. What are your responsibilities and principles of leading one of the most comprehensive academic and clinical departments in the country where physicians and research scientists focused on clinical care, research and medical education?

> **"One of my most important duties is shaping research landscape of the department. The Weill Cornell medicine is a hub for innovative biomedical research and clinical care, and it has a longstanding tradition of excellence."**

- The department of medicine is usually the largest unit in a medical school. Cornell is no exception. Weill Cornell Medicine is comprised of 16 divisions and more than 1,700 faculty members, physicians and research scientists focused on clinical care, research and medical education. Ever since I took the position as a chairman and physician–in-chief, I have directed and supervised clinical activities performed by each division. The Weill Cornell medicine covers wide variety of clinical services, including cardiology, clinical epidemiology, clinical pharmacology, emergency medicine, internal medicine and many more. It is also a home to more than 200 residents and fellows. It is also my responsibility to oversee medical education of the next generation of phisicians and researchers. Speaking of research, one of my most important duties is shaping research landscape of the department. The Weill Cornell medicine is a hub for innovative biomedical research and clinical care, and it has a longstanding tradition of excellence. Though I am kept very busy due to various tasks at hand, it has been more than rewarding to participate in many successes the Weill Cornell medicine yielded over the years.

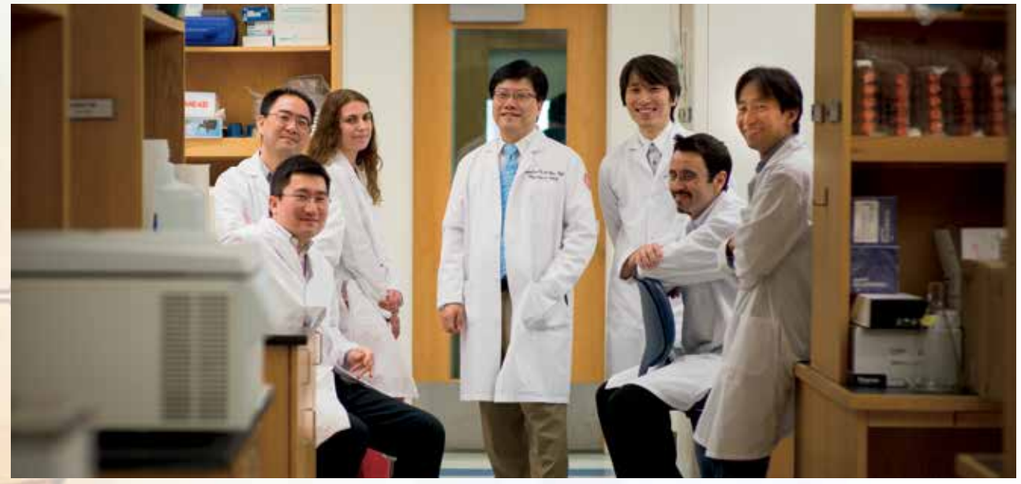
4. What are some of the major performances and outcomes you have accomplished under your leadership? What are the long-term goals and visions you hope to see the Weill Cornell Medicine to achieve?

- The Weill Cornell Medicine has three major missions: clinical care, medical education and research. For clinical care, I am proud to say that we are fortunate to host some of the best physicians in the world. What we offer doesn't stop with innovative and top of the line clinical techniques; it also includes intimate and compassionate care for our patients who need as much emotional support as clinical treatment. In medical education, we continue to train our medical students, residents and fellows to reach their full potential as doctors or researchers. In research, we have enriched our research portfolio and increased grant funding on many different areas including cancer, cardio vascular diseases, pulmonary diseases and herpetology at the Weill Cornell medicine. Personally, as a pulmonologists, I study chronic obstructive pulmonary disease (COPD). COPD is third leading cause of death in the United States following cancer and cardio vascular diseases. Despite the common perception, COPD does not develop from smoking in every case, non-smokers also develop COPD. There is no ultimate cure at this point, and current treatments have much room for improvement and continuing optimization. My research is to better understand the mechanism of COPD and to develop molecular targets for both diagnostics and therapeutics.

A ribbon-cutting ceremony officially opens the Jill Roberts Institute for Research in Inflammatory Bowel Disease's permanent laboratories at Weill Cornell Medicine. From left: Dr. Ellen Scherl, Jill Roberts, Dr. Augustine Choi, Jessica Bibliowicz and Dr. David Artis. Photo credit: Studio Brooke

5. In the biomedical research, what are some significant changes or trends you have noticed in biomedical industry? What do you forecast the industry will be like in the next five years?

- In the foreseeable future, biomedical research will empathize on translational research. The field will explore to find innovative methods of diagnostics and therapeutics. The objective is to utilize available technology to diagnose as early as possible in diseases process. It will allow doctors to intervene and treat patients in the earlier stages of diseases, which can increase effectively the success rate of the treatment. Secondly, National Institute of Health (NIH) funding has been decreasing throughout last decade. From 2003 to 2015, NIH lost 22% of its capacity to fund research due to budget cuts, sequestration, and inflationary losses. It means that biomedical research will not be able to rely solely on federal government funding. Importance of private sector funding will be inevitably amplified as result.



Dr. Augustine M.K. Choi (center) with his laboratory team. Photo credit: Roger Tully

6. What would be your advice or comments for current medical students as well as those who aspire to become a doctor?

- The field of medicine can be a fulfilling career path for anyone because of its versatility. There are three major sectors in medicine: research, medical education, and clinical care. These three pillars of medical science cannot exist without the other. Regardless of one's choice to focus more on one over the others, the knowledge and experience one gain from any of these medical fields can be enormously helpful as you learn and practice medicine anywhere in the world. There are an infinite number of career paths to choose from; and in that search, the idea is to find and pursue what fits best your personality and aptitude. Medicine is definitely a rewarding and noble career for young people to explore given it has a wide and significant impact on the lives of many people, locally as well as globally. From an orthodontist to a heart surgeon, different professions of medicine all require different sets of skills and talents.

7. WKMJ has readers from more than 10 countries globally. Please share your words or thoughts with our readers.

- We are at the most exciting era of biomedical research. New discoveries are rapidly being made in both diagnostics and therapeutics. New approaches such as stem cell research and Nano-technology are opening new doors righto possibilities of treatments previously thought otherwise. I'm optimistic about the future of medicine as we work together with fellow researchers and physicians around the globe, so we may move forward, expand our horizon and push our limits in caring for our communities.

Dr. Augustine Choi and his wife Dr. Mary E. Choi at W Medical Strategy Group event in Yale Club

Augustine M.K. Choi, MD

Chairman, Department of Medicine at Weill Cornell Medical College

Physician-in-Chief, New York Presbyterian/Weill Cornell Medical Center

Dr. Augustine M. K. Choi has been appointed chairman of the Department of Medicine at Weill Cornell Medical College and physician-in-chief at New York Presbyterian Hospital/Weill Cornell Medical Center. Dr. Choi is the Parker B. Francis Professor of Medicine at Harvard Medical School and chief of pulmonary and critical care medicine at Brigham and Women's Hospital in Boston. Dr. Augustine M.K. Choi is a clinician-scientist with expertise in the pathology and biology of lung disease. After receiving his medical degree from University of Louisville, Dr. Choi served as an intern, resident and assistant chief resident in internal medicine at Duke University Medical Center. He then completed a fellowship in pulmonary and critical care medicine at Johns Hopkins University. Prior to joining Harvard and Brigham and Women's Hospital as chief of the Division of Pulmonary and Critical Care Medicine in 2007, Dr. Choi served on the faculty and medical staff of Johns Hopkins, Yale University and University of Pittsburgh, where he served as chief of pulmonary, allergy and critical care medicine. Dr. Choi has authored more than 235 peer-reviewed manuscripts and serves as the Associate Editor of the American Journal of Respiratory Cellular and Molecular Biology. He is a member of the American Society of Clinical Investigation and the Association of American Physicians.

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Entrepreneur Interview

Entrepreneurial Physician Leads Fight Against Drug Epidemic
Q&A with Leon Reyfman, M.D., CEO, Advanced Clinical Laboratory Solutions, Inc.

1. We understand that Advanced Clinical Laboratory Solutions, Inc. (ACLS) is a rapidly growing laboratory testing company offering toxicology and pharmacogenetics testing services. What are the major business philosophies or strategies of ACLS?

I began my career as a pharmacist, learning about drug dispensing and the challenges patients encountered with drug interactions, adverse events and drugs that simply did not work for certain people. In 2011, I set out to build the best laboratory services in the country. Today, ASCL is a state-of-the-art lab that reflects my mission to provide the highest quality of testing, expedient delivery of results, and superior customer service to clients throughout the United States. Our business philosophy is to stay ahead of innovations in toxicology and pharmacogenomics as the future of medicine.

We remain focused on turning around tests quickly and accurately, while being affordable and accessible to everyone, physicians and patients alike.
My passion for this business continues to grow – reinforced by such headlines as the recent story about 33 people who died from overdosing on synthetic marijuana in Brooklyn, my home territory. This rash of drug overdoses and spotlight on opioid abuse has underscored our driving strategy to give communities and individuals greater access to toxicology testing.

2. How will you be positioned to compete with the large, high-profile lab companies?

Independent clinical laboratories specializing in clinical toxicology and pharmacogenetics, like ACLS, are the best option for accessing convenient, high-quality testing services and accurate, timely test results. In fact, smaller labs are more responsive, and feature improved scheduling opportunities, faster turnaround of test results, accurate reporting and more competitive pricing.
This could make a vital difference for individuals in the U.S. and around the world who need addiction treatment.

Laboratory drug testing is critical for supporting clinicians, but with insurance costs on the rise, many of those suffering from addiction are unable to get full coverage for lab testing. Given the persistent and evolving introduction of new and highly dangerous drugs in communities, this kind of rapid drug testing as a primary prevention, diagnostic and monitoring tool can identify the presence or absence of drugs of abuse or therapeutic agents in multiple settings. Making lab testing more affordable and available across communities is essential for preventing drug abuse – and saving lives – especially among teens and young adults.

3. Why is toxicology testing becoming so important for both physicians and their patients?

The staggering statistics tell the story. Deaths from drug overdoses have risen in nearly every county across the United States, driven by an epidemic of addiction to prescription painkillers and heroin. The number of these deaths reached 47,055, a new peak, in 2014. In fact, the death rate from drug overdoses is climbing much more quickly than other causes of death.
One report found that much of the increase in opioid dependence occurred since 2011. Patients ages 19 to 35 were most likely to be diagnosed as opioid-dependent compared to other age groups.

As for physicians, accessible, reliable, and rapid testing enables them to get the information necessary to achieve the highest quality care and outcomes.

4. We see that you have recently launched a healthcare advisory board. What was the motivation or inspiration behind this?

ACLS formed a Business Advisory Board composed of healthcare luminaries and thought leaders as part of our commitment to providing convenient, high-quality testing services. These leaders and influencers share our passion for ending the country's heroin and opioid addiction crisis, and will help fuel our ongoing efforts.
Addiction to opioids and the use of street drugs, such as the K2, a synthetic marijuana, pose serious community issues that impact public health and social welfare, but clearly it is also a severe economic issue that affects everyone.

The primary diagnosis of opioid generates a number of medical services, including office visits, lab tests and other related treatments. In fact, the number of such services went from about 217,000 in 2007 to about seven million in 2014.

The Business Advisory Board will help spread this message among payers, healthcare providers and policymakers, who are well-advised to focus on insurance coverage that would enable these tests to be performed at smaller laboratory testing services.

5. As an entrepreneur, what would you say are the top three priority assets or skill sets needed to be successful in the global healthcare industry?

First of all, stay focused on innovation. Personalized medicine will be critical. This means being committed to finding the most optimal treatment regimen for each particular patient just by pinpointing the right drug at the right dose, for the right patient.

This ties into putting the patient first – the second important factor for success in the healthcare industry. This is essential across every area of healthcare. For example, our goal is to find the most effective and individualized balance at which a patient experiences maximum desirable analgesic relief and minimal undesirable adverse effects.

By initiating ongoing innovations for toxicology testing, labs like ACLS and others can implement more effective outreach, engagement, treatment, and coordination with the health and mental health systems and social supports.

Third, focus on the highest possible standards. For instance, ACLS is committed to medical research, quality and expedient testing that exceeds current standards of clinical toxicology because we want to do more than the bare minimum. We want to provide clients with the highest toxicology and clinical testing in the industry, including drug testing of urine and oral fluids, and pharmacogenetics for personalized prescribing. What we do matters. How we do it matters even more.

6. WKMJ has readers from over 10 countries globally. Please share your final words or thoughts with our readers.

I'd like to emphasize the value of pharmacogenomics testing-- identifying how genes affect a patient's response to medication. Genomic differences influence the efficacy of medication and can be the source of serious drug side-effects and increase the risk of drug-to-drug interactions. Pharmacogenetic testing is the alternative to one-size-fits-all drug prescribing, which can lead to potentially serious side effects, treatment failure and poor patient compliance.

Pharmacogenetic testing can also indicate which patients will be likely to experience adverse events with particular drugs — another application of particular interest to seniors, who often take multiple medications. Pharmacogenetic test results show how each particular medication is metabolized in the liver, providing each referring physician with a laboratory analysis of many of the patient's liver enzymes.

Along with the analysis, ACLS offers a detailed pharmacist's report that analyzes the patient's medication list and notes how it could be altered, based on information provided by the genomic test. People with certain genotypes have increased risk of life-threatening bleeds when introduced to the blood thinner warfarin or when dosages are changed. A dosing algorithm based on the patient's genotype can potentially thwart this risk.

Research has shown that maintaining steady levels of opioids contributes to pain relief, but patients metabolize pain medications at different rates. Slow metabolizers of opioids may sustain dangerously high levels of opioids in the body, resulting in adverse events. Personalized knowledge of a patient's metabolism patterns may assist in dosing.

Furthermore, pharmacogenetic test results may assist pain physicians in demonstrating that a particular patient requires a higher medication dose to experience pain relief. For example, for an ultra-rapid metabolizer, typical doses may not control pain for high metabolizers, who run the risk of being labeled abusers. W

Leon Reyfman, M.D., FIPP, RpH

Chief Executive Officer, ACLS

Dr. Reyfman, chief executive officer, ACLS, is board-certified in Anesthesiology and Pain Management. He serves as director in Interventional Pain Medicine at Long Island College Hospital, and is assistant clinical professor of Anesthesiology at SUNY Downstate Medical School. Dr. Reyfman is a member of American Society of Interventional Pain Physicians, as well as the International Spine Intervention Society. He is actively involved in pain medicine research and teaching, has given multiple lectures in the areas of neuropathic pain, cancer pain, approach to diagnosis and treatment of lower back pain, and has extensive clinical experience and training in invasive and noninvasive pain management.

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BIOPHARMACEUTICAL REPORT I

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Biopharmaceutical Report I

FDA Review Policies for PD-1/ PD-L1 Inhibitors Spark Expert Debate

The potential for changes to FDA oncology drug application review and approval policies has drawn contrasting expert opinions following comments by a high-ranking agency official bemoaning copious PD-1/PD-L1 inhibitors in development.

Comments made by Dr Richard Pazdur, Head of the FDA Office of Oncology, likely just reflect a personal desire for better company investment in other drug targets, several experts said. However, others said the agency could require larger studies and longer-term monitoring to discourage a crowded development space, as well as place me-too products on a lower review priority. Companies entering the space late still could leverage novel applications for PD-1/PD-L1 inhibitors in new combinations or using them in unexplored populations, one expert noted.

At last month's ASCO conference in Chicago, Pazdur was quoted in a Reuters article questioning the industry's current approach asking: "would we be better off spending those resources into looking at more novel drugs?" when discussing PD-1/PD-L1 inhibitors. He also noted that "the number of similar drugs in development at the same time is a first in the oncology field and latecomers to the PD-1 market will likely be relegated to 'niche' indications."

Bristol-Myers Squibb's (NYSE:BMY) Opdivo (nivolumab) and Merck's (NYSE:MRK) Keytruda (pembrolizumab) are examples of PD-1 inhibitors that have been approved for non-small-cell lung cancer (NSCLC) and melanoma. The former is additionally indicated for renal cell carcinoma and Hodgkin's lymphoma. AstraZeneca's (LON:AZN) durvalumab and Roche's (VTX:ROG) Tecentriq (atezolizumab) are both PD-L1 inhibitors under investigation for the treatment of lung cancer. Tecentriq was recently approved in locally advanced or metastatic urothelial carcinoma.

The FDA did not respond in time for comment.

Possible policy changes debated

Pazdur's comments will not signal any change in FDA policy such as accepting only innovative therapies beyond PD-1 and PD-L1 inhibitors or reviewing additional PD-1 therapies negatively, said Matthew Weinberg, CEO of consultancy The Weinberg Group, Washington, DC. The FDA has been aggressive in approving new oncology drugs in a timely way and this is unlikely to change, agreed Wayne Pines, president, Health Care, APCO Worldwide, Washington, DC. It's likely that Pazdur's intentions were just to encourage innovation in the space over policy change, said Dr David Lim, president and principal consultant, Regulatory Doctor, Roanoke, Virginia.

The FDA may choose to become more critical on reviews and require larger studies for approval, or require longerterm monitoring and stronger label warnings

The comments indicate Pazdur's personal views appealing for more breakthrough therapies with new targets rather than me-too/follow-on therapies, Weinberg and Pines said. The comments likely do not apply to all cancer immunotherapy, rather just the PD-1/PD-L1 inhibitors, Dr Grant Williams, president, Williams Cancer Drug Consulting, Philadelphia, Pennsylvania.

However, the FDA could potentially increase the bar for approval concerning PD-1/PD-L1 inhibitors as more is learned about their safety profiles, Lim explained. The FDA may choose to become more critical on reviews and require larger studies for approval, or require longerterm monitoring and stronger label warnings, he added.

Yet, the comments could still signal a change in FDA policy, said Nigel Smart, vice president, Smart Consulting Group, West Chester, Pennsylvania, with the agency giving greater priority to reviewing drugs with improved therapeutic value as opposed to me-too drugs.

Whilst the FDA won't change its overall policy, it's possible me-too PD-1/PD-L1 inhibitors may no longer qualify for the FDA's breakthrough designation or for accelerated approval, said Williams. Breakthrough designation allows more access to agency advice and communication, and the accelerated approval path allows early approval based on surrogate endpoints, he noted. Both are available when there is an advantage over available therapy, he said. Thus, PD-1/PD-L1 inhibitors may have to go through the full development pathway of showing clinical benefit in a large randomized study before approval is granted, he said.

Niche market options

Whilst Pazdur mentioned that latercomers would be relegated only to the "niche markets", one unnamed oncologist countered that this was unlikely. Companies developing novel PD-1/PD-L1 antibodies are often doing so for the purpose of new combinations, said the oncologist and Williams. Whilst a PD-1/PD-L1 inhibitor might offer nothing new in non-niche indications such as lung cancer, where there are approved PD-1 inhibitors, combining them with a novel therapy could provide patient value as it could boost response rates, explained the oncologist. This is especially important given the heterogeneity in response rates and the need for combinations to boost responses in certain individuals, he said.

For example, Tesaro (NASDAQ:TSRO) has its own PD-1 inhibitor yet to enter clinical trials, said the oncologist. However, the company intends to use it primarily in novel immunotherapy combinations, such as with anti-LAG-3 or anti-TIM-3 antibodies, as opposed to monotherapy trials in solid tumours, the oncologist explained. Other companies are looking at combining their own PD-1/PD-L1 inhibitors with other immunotherapy targets such as Ox40, GITR, 4-1BB amongst others, he added. This news service reported on 5 July that Pfizer has planned a Phase I trial for its PD-L1 inhibitor in combination with a 4-1BB agonist and an Ox40 agonist.

The unnamed oncologist noted that companies developing PD-1 inhibitors are now focusing on

niche areas that have not received much attention, such as mesothelioma, so breakthrough approval could still be attainable for PD-1/PD-L1 drugs in these cases. Williams agreed, noting breakthrough therapy is not dependent upon mechanism of action, but rather, upon the patient population being treated and whether an unmet medical need is being addressed. Even some of the bigger players entering the race later are targeting more niche populations with unmet needs, said the unnamed oncologist and Williams.

For example, Pfizer (NYSE:PFE) and Merck KGaA (ETR:MRK) are collaborating to develop their PD-L1 inhibitor, avelumab, in smaller patient populations such as Merkel cell carcinoma, said the unnamed oncologist. Some companies are selecting patients using genetic subgroups where PD-1/PD-L1 inhibitors may work best in unserved populations and leverage FDA opinion, said Williams.

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Reporter, London

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Biopharmaceutical Report II

Democratizing Antibodies

> "Will it be mammalian cells forever? Or is there an opportunity to get even better and to get to the next step change in productivity?"
>
> Jorg Thommes, Biogen Inc.

TOOLS & TECHNIQUES

DEMOCRATIZING ANTIBODIES

By Michael Leviten, Senior Writer

With the goal of expanding access to antibody-based drugs worldwide, the Bill & Melinda Gates Foundation is turning to industry to innovate its methods of manufacturing the proteins. In the last two months, the organization signed deals with Biogen Inc. and Just Biotherapeutics Inc., fostering programs to reduce costs and increase yields that benefit both the for-profit and not-for-profit enterprises.

On Aug. 8, the Gates Foundation and Biogen announced a project to improve antibody production and manufacturing techniques, using eight undisclosed expression systems that include yeast, fungi and algae. The idea is to search for alternatives to Chinese hamster ovary (CHO) cells, which have served as the workhorse of antibody manufacturing for 25 years. Biogen will conduct the research over an 18-month period, and the results will be made publicly available.

Financial details were not disclosed but the organizations are contributing roughly equal amounts, according to Stephen Hadley, senior program officer for vaccine development at the Gates Foundation. Hadley said Biogen is also contributing an antibody to use as a benchmark and some of the analytics.

The partnership comes two weeks after the Gates Foundation invested $8 million in a series A2 round for Just Biotherapeutics, a start-up focused on streamlining antibody production. A further $6 million was invested by existing investors Merck & Co. Inc., Lilly Asia Ventures and Arch Venture Partners. Last year, the foundation awarded the company $24 million in grants over five years to develop low-cost HIV antibodies and technology platforms for low-cost biologics.

Despite the success of CHO cells for supporting antibody production, the yield has hit a ceiling after years of optimization; however higher yields and more streamlined manufacturing are needed to reduce costs for emerging and third world markets.

But according to Tim Moore, EVP of technical operations at Kite Pharma Inc., since the 1990s when a platform based on CHO cells was established, there has been little motivation in industry to innovate or switch expression systems. Moore was previously SVP and global head of Pharmaceutical Technical Operations Biologics at Roche's Genentech Inc. unit.

"There were hardly any players in that space, so it made a lot of sense just to build upon [the early methods] and then come up with different ways to get higher titers," he said.

Hadley told BioCentury that was the first challenge he faced when he joined the organization three years ago and was tasked with exploring mAbs for infectious diseases at production costs that could be practical in focus regions such as sub-Saharan Africa and South Asia.

"Most of the antibodies and biologics developed for the world marketplace enjoy extremely nice margins, so for cost of goods there has never been a pressure driver on the industry to figure out how to lower costs," he said.

Hadley said there was little interest among most of the biotechs he spoke to about developing better methods. "Frankly, people are pretty set with their processes and installed capacity."

However, the Gates Foundation's approach was to make "catalytic investments" that will get the field to move in a new direction, said Hadley, and to find industry partners that see a commercial benefit to improving the technology that complements rather than competes with the organization's interests. "We don't have any alignments on products; this is all around technology. Their portfolio of products is different than our interests."

Whereas the funding for Just Biotherapeutics supports lower-cost methodology for CHO-based manufacturing, the Biogen project is looking beyond CHO cells, and is using an open model that hopes to engage other companies that might see the upside of creating a next-generation, low-cost platform.

Jorg Thommes, SVP of technical development at Biogen, told BioCentury the field has reached an inflection point. "We're now at this point of saying 'OK what's next?' Will it be mammalian cells forever? Or is there an opportunity to get even better and to get to the next step change in productivity?" he said.

WHOLESALE CHANGES

According to Thommes, the ongoing adherence to CHO cells has not been for want of trying to find alternatives. The problem has been that there's been no coherent or coordinated strategy to replace the cells.

"People have been trying out alternate expression systems for a long time," he said. "And they've been executed sporadically with different focus. And there has never been a real head-to-head comparison of many alternate expression systems with the current high-productivity mammalian cells."

Overall, the efficiency of antibody production from CHO cells has increased by a factor of nearly a thousand in the last 25 years, with common yields approaching 3-6 grams per liter of CHO cells, due largely to a greater understanding of CHO cell biology, said Thommes. "We've gotten much, much better at understanding what these cells need to grow and thrive so we can maximize their number in a reaction system and the time that we can keep them alive and happy."

But those improvements also capped progress. "Mammalian cells make proteins that are very well tolerated by humans, and are fully functional. So there was no need to look outside of that mammalian cell box because we got so much better at it," Thommes said.

However, the main drawback is the long growth cycle, he said. Mammalian cells are typically cultured for 10-14 days during a production run, compared with 2-3 days for yeast or bacteria. Microbes are used at large scale to produce biologics like insulin and human growth hormone, which are made in yeast and bacteria, respectively.

Thommes said that the main advances have been in the "upstream" part of antibody manufacturing, which involves protein production, where using lower-cost media and achieving higher titers has improved productivity and reduced costs. But the principal need is in the "downstream" part of the process which involves protein purification, where costs have remained stagnant.

> "Most of the antibodies and biologics developed for the world marketplace enjoy extremely nice margins, so for cost of goods there has never been a pressure driver on the industry to figure out how to lower costs."
>
> Stephen Hadley, Bill & Melinda Gates Foundation

"Alternate expression systems with increased productivity will most likely present a different, possibly leaner, background to isolate antibodies from. This could open up intriguing opportunities for disruptive downstream processing technologies," said Thommes. In particular, he thinks replacing traditional chromatography methods with other unit operations might be interesting, and the current focus on virus inactivation and removal steps for mammalian cell expression might be reduced with alternate hosts.

Hadley believes that the results of the Biogen project can seed bigger advances once opened up to the research community. "I think the trajectory would be similar to what happened with CHO. Eventually organizations, when they landed on CHO, they brought their own CHO cell lines and vector technologies into their own organizations, optimized them, and controlled the IP around that."

JUST SAYIN'

By contrast, the investment in Just Biotherapeutics is meant to help the start-up double down on CHO cells, using protein engineering and infrastructure improvements to reduce costs.

"It's the extreme opposite of the very large-scale stainless steel model that's been very successful, but there's a production cost floor that it's difficult to figure out how to break through," said Hadley.

The company was started by a team of Amgen Inc. veterans, who aim to introduce changes throughout the process, from molecule design to facility layout, to lower costs tenfold and bring cheaper antibodies to developing markets.

> "You have to look at it from everything from molecular design for manufacturability all the way through the plant and how well the plant is designed. So we can optimize in both directions."
>
> Jim Thomas, Just Biotherapeutics

"You have to look at it holistically. You have to look everything from molecular design for manufacturability all the way through the plant and how well the plant is designed. So we can optimize in both directions," said Just CEO Jim Thomas.

Hadley said the Gates Foundation is solely interested in infectious disease antibodies in the project, which it wants to expand to third world nations, following the model of Synagis palivizumab, a humanized mAb against respiratory syncytial virus (RSV) from AstraZeneca plc's MedImmune LLC unit.

For the HIV project, the target product profile calls for a subcutaneous product dosed quarterly. The aim is to use protein engineering to enable low-viscosity formulations at about 150 mg/mL, and modifications to the Fc region to extend the half-life.

Hadley said the Gates Foundation grant covers HIV antibodies from four different academic groups funded by the Collaboration for AIDS Vaccine Discovery (CAVD). The antibodies include eCD4-Ig from The Scripps Research Institute and 3BNC117 and 10-1074, which are in Phase I trials, from The Rockefeller University.

COMPANIES AND INSTITUTIONS MENTIONED

Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Bill and Melinda Gates Foundation, Seattle, Wash.
Biogen Inc. (NASDAQ:BIIB), Cambridge, Mass.
Genentech Inc., South San Francisco, Calif.
Just Biotherapeutics Inc., Seattle, Wash.
Kite Pharma Inc. (NASDAQ:KITE), Los Angeles, Calif.
MedImmune LLC, Gaithersburg, Md.
Merck & Co. Inc. (NYSE:MRK), Kenilworth, N.J.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
The Rockefeller University, New York, N.Y.
The Scripps Research Institute, La Jolla, Calif.

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Biopharmaceutical Report III

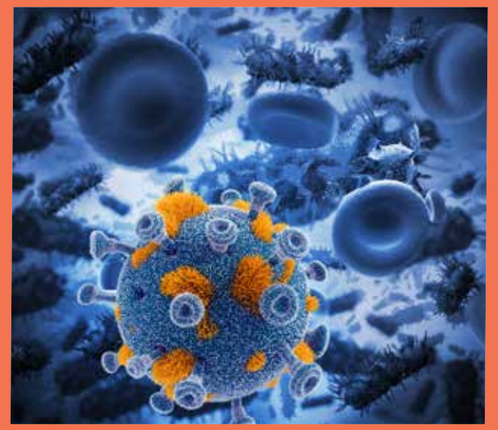
NY-ESO-1 therapy renewed enthusiasm underscored by new checkpoint inhibitors

NY-ESO-1 targeting immunotherapies are seeing renewed clinical development interest as the antigen is widely expressed in certain solid tumors and sarcomas, experts said. They noted recent checkpoint inhibitor approvals and modified T cell receptor (TCR) research underscore the enthusiasm, experts said.

Combinations with checkpoint inhibitors and other immune modulators have the potential to increase response rates seen with existing NY-ESO-1 directed vaccines, and TCR approaches offer newer strategies to exploit the NY-ESO-1 antigen over-expression in cancers. There is some caution on how well the approaches will pan out. Furthermore, experts expressed the need to target multiple additional antigens besides NY-ESO-1 to induce significant immune responses.

While Adaptimmune (NASDAQ:ADAP) and Immune Design (NASDAQ:IMDZ) are using a modified TCR approach with a Phase I/II NY-ESO TCR, and Phase I LV305 with CMB305, respectively, for multiple cancers, Celldex (NASDAQ:CLDX) is exploring a vaccine approach in different cancers with the Phase II CDX-1401, an NY-ESO-1-targeting vaccine. Early trials at academic centers like Memorial Sloan Kettering, New York and Roswell Park Cancer Institute are also underway.

Adaptimmune, Immune Design, Celldex did not respond to a request for comment.



NY-ESO-1 antigen expression

NY-ESO-1 expression in normal tissues is relatively narrow and from an antigen standpoint, it is a wonderful antigen to start research with, said Dr Paul Sabbatini, deputy physician-in-chief for clinical research, Memorial Sloan Kettering Cancer Center, New York.

The NY-ESO-1 antigen is widely expressed in synovial sarcoma (SS), myxoid round-cell liposarcoma (LPS), melanoma, ovarian cancer, glioblastoma (GBM) and other tumors, but it has the most potential in sarcomas and melanoma due to their being immunogenic in nature, experts said.

NY-ESO-1 is expressed highly in SS and myxoid round-cell LPS in about 60-70% of tumors, said Dr Sant Chawla, director, Sarcoma Oncology Center, Santa Monica, California. NY-ESO-1-targeting seem to especially benefit SS, and there have been remissions observed in these patients, said Dr Sebastian Bauer, professor of medicine, West German Cancer Center, Germany.

Among 24 patients in a Phase I study of Immune Design's LV305 in sarcomas, one had a partial response, and 13 had stable disease (SD), with a median progression-free survival (PFS) of 4.6 months, according to data presented at the ASCO annual meeting. Among 14 patients receiving CMB305, 10 had SD, with a median 5.5-month PFS.

NY-ESO-1 expression in ovarian cancer is said to be in the range of 42- 60%, said Sabbatini and Dr Oliver Dorigo, associate professor, obstetrics and gynecology, Stanford University Medical Center, Palo Alto, California. The NY-ESO-1 antigen has been of particular interest in ovarian cancer since as patients have had their ovaries removed, NY-ESO-1 expression in normal ovarian tissue is not a clinical issue, added Dorigo.

However, it's not necessarily the expression of the antigen, but also the tumor immunogenicity that's important, said Dr Brent Hanks, assistant professor of medicine, Duke University School of Medicine, Durham, North Carolina. Melanomas are just more responsive to immunotherapies than gastric or colon cancer, he added. NY-ESO-1 expression in melanoma can range from 25-50+%, depending on which research study is considered, he added.

Though melanomas do overexpress the antigen, it is unknown if that is enough to drive T cell responses, cautioned Dr Jason Luke, assistant professor of medicine, University of Chicago. Therapies that target NY-ESO-1 have been around for many years, he and Dr Anthony Olszanski, co-director, cutaneous oncology and melanoma, Fox Chase Cancer Center, Philadelphia agreed. Luke noted most researchers would find it unlikely that targeted NY-ESO-1 would be a particularly efficacious way to move forward. Previous studies have not shown any significant response rate in melanoma, Olszanski added. However, now with the introduction of PD-1 inhibitors, the hope is that a combination approach can capitalize on the antigen recognition and improve the efficacy of these therapies, he said.

Ultimately, future research will focus on combination approach in the form of a vaccine with the checkpoint inhibitor

Across indications, it still needs to be explored if the ideal patient population would be one in remission with a lower disease burden, or those with active disease and a higher antigenic load, said Sabbatini.

Promising combinations

NY-ESO-1 vaccinations have induced mild immune responses in a disease like ovarian cancer, but the question is always on how to enhance those responses across all tumor types, said Sabbatini. If the focus is on just one antigen and the induced immune response is not potent enough to generate T-cell responses to other antigens, then the tumor can simply downregulate the expression or processing of those antigens, agreed Hanks and Dorigo. NY-ESO-1 expression in ovarian cancer is more heterogeneous and patchy than in others, and it might be necessary to target a second or third antigen or add another other antitumor treatment for a clinical response, Dorigo explained.

New co-stimulatory molecules and checkpoint inhibitors could modulate these immune responses, said Sabbatini. Ultimately, future research will focus on combination approach in the form of a vaccine with the checkpoint inhibitor, agreed Hanks. Other agents that have been designed to reverse immune suppression or reverse immune invasion by the cancer could be combined as well, he added. The next generation of therapies is looking at the addition of these immune molecules to elicit a robust immune response, said Sabbatini.

Immune Design is studying (NCT02609984) CMB305, a dendritic cell-targeting vector that expressed NY-ESO-1 and a NY-ESO-1 recombinant protein in combination with Roche's (VTX:ROG) Tecentriq (atezolizumab). An investigator sponsored Phase I trial (NCT02737787) at MSKCC will explore Bristol-Myers Squibb's (NYSE:BMY) Opdivo (nivolumab) in combination with a dual NY-ESO-1 and WT1-directed vaccine. Celldex is also evaluating CDX-1401 in a Phase I/II (NCT02413827) study in Stage III/IV melanoma patients in combination with its anti-CD27 antibody, varlilumab, and BMS' anti-CTLA4 antibody Yervoy (ipilimumab).

However, it is not clear if there's a role for NY-ESO-1-based vaccines and combination with checkpoint inhibitors have not proven to be particularly efficacious, differed Luke.

TCRs or vaccines

The best way to target the antigen may depend on the host immune response, said Liau, adding that TCRs or vaccines could be potential strategies to use NY-ESO-1. For patients who are able to mount an active immune response, a vaccine may be optimal, while adoptive immunotherapy with engineered T cells may be preferable for those who cannot, she added.

By tailoring the antigen-targeting treatment to each patient, researchers can look at individual tumor presentation and customize T cell directed therapy, said Dorigo. One reason for the recent focus on TCRs is that chimeric antigen receptor T-cells (CAR-Ts) haven't been shown to be effective in solid tumors yet, said Dorigo, though they could be in the future. Adaptimmune is running multiple clinical trials where a patient's T cells are extracted and modified to identify NY-ESO-1 in ovarian cancer and certain sarcomas. However, with a TCR approach, the impact of induced myelosuppression on heavily pretreated ovarian cancer patients is not yet known, said Dorigo.

Modifying T cells is a newer approach than vaccines, but vaccines have not been studied in combination with immune-modulating agents before, said Sabbatini. It is still too early to determine which approach would work best or how effective it would be, said Dorigo.

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Reporter, New York

Alaric DeArment covers cancer drug development for BioPharm Insight. He served as associate editor of Drug Store News from 2008 to 2014, covering branded and generic drugs from development to distribution, retail and specialty pharmacy and regulatory affairs. In 2011-2012, he edited the book Contestation and Adaption: The Politics of National Identity in China. A native of Seattle, he graduated with honors with a bachelor degree in journalism from Ball State University and also lived in China from 2001-2004. Follow Alaric on Twitter @AlaricD_BPI

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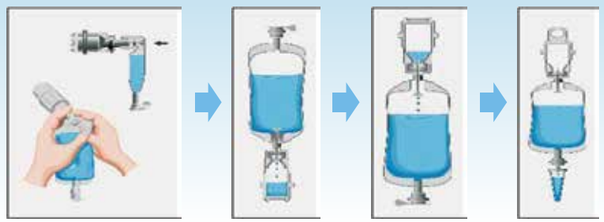

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#1 **Prescribed oral antiviral** according to US prescription data for treatment of CHB[1a]

FOLLOW THE JOURNEY OF VIREAD

COMPLETE RESPONSE RESULTS AT YEAR 1...

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® 300mg 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 DETECTED AT YEAR 1 THROUGH YEAR 8

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]

0%

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)

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

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.

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 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)*.

Brief Summary (Cont'd)

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.

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Natural Products Expo East
September 21-24, 2016/ Baltimore, MD, USA

Website: http://www.expoeast.com/ee16/public/enter.aspx
Contact: tradeshows@newhope.com

Attended by 24,000 industry professionals and featuring thousands of exhibits, Natural Products Expo East is the largest natural, organic, and healthy products trade show on the East Coast. With the newest and best-selling products and branded ingredients available, this show features the best in organics, offers an extensive retailer training program and provides an advocacy platform through a strategic partnership with Natural Products Association East. Natural Products Expo East is ranked as one of the top 200 tradeshows in the US.

6th New York Health Forum
September 27, 2016/ New York, New York, USA

Website: www.newyorkhealthforum.net
Contact: (201)402-1400

6th New York Health Forum's title is "Korea Rise: New Strategies Transforming Korean Biopharma and Unparalleled Opportunities for Collaboration." This forum will provide the setting for stimulating and informative discussions on the investment trends, landscapes, risks, and more. Investors, biopharma and medtech representatives, and healthcare professionals will all come together to connect, learn, and share.

15th Annual Trans-Pacific Health Sciences Dialogue
September 21-24, 2016/ Baltimore, MD, USA

Website: http://transpacifichsd.com/
Contact: conferences@demy-colton.com

The 15th Annual Trans-Pacific Health Sciences Dialogue is a meeting for biopharmaceutical industry executives and business development executives who want to accelerate, explore and develop collaborations and partnerships with their counterparts in the most important Trans-Pacific health care markets including Japan, China, South Korea and North America.

SupplySide West
Oct 4-8, 2016/ Las Vegas, Nevada, USA

Website: http://west.supplysideshow.com/
Contact: SupplySideWest@experient-inc.com

For 20 years, CPG manufacturers, marketers and formulators have relied on SupplySide West when searching for their next innovative ingredient. SupplySide West will have thousand exhibitors and 120 hours of education programming bringing together companies in the global dietary supplement, functional food and beverage, personal care, and sports nutrition industries.

The 58th American Society of Hematology (ASH) Annual Meeting & Exposition
December 3-6, 2016/San Diego, California, USA

Website: http://www.hematology.org/Annual-Meeting/
Contact: (888)273-5704

The American Society of Hematology (ASH) Annual Meeting is the world's premier event in malignant and non-malignant hematology. The meeting provides an invaluable educational experience and an opportunity to review thousands of scientific abstracts highlighting updates in the hottest topics in hematology. This meeting will allow networking with top minds in the field, as well as a global community of more than 20,000 hematology professionals from every subspecialty.

28th Annual National Forum on Quality Improvement in Health Care
December 4-7, 2016/Orlando, Florida, USA

Website: http://www.ihi.org/education/Conferences/Forum2016/Pages/default.aspx
Contact: info@ihi.org

IHI's Annual National Forum on Quality Improvement in Health Care is more than a chance to network with nearly 6,000 health care professionals and gain actionable ideas for your organization. It's also an opportunity to play a part in effecting real change in health care quality and safety.

Keystone Symposia: Cellular Stress Responses and Infectious Agents
December 4-8, 2016/Santa Fe, New Mexico, USA

Website: http://www.keystonesymposia.org/17S4
Contact: info@keystonesymposia.org

The conference will bring together cell biologists studying various cellular stress responses and researchers interested in how various infectious agents activate and manipulate host cellular stress responses. This conference focuses on the study of interactions between infectious agents and these pathways providing new insights about cellular stress responses and identifying new targets for the development of novel therapies for the treatment of infectious diseases.

The 2017 HIMSS Annual Conference & Exhibition
February 19-23, 2017/Orlando, Florida, USA

Website: http://www.himssconference.org
Contact: himss@compusystems.com

The 2017 HIMSS Annual Conference & Exhibition brings together 40,000+ health IT professionals, clinicians, executives and vendors from around the world. Exceptional education, world-class speakers, cutting-edge health IT products and powerful networking are hallmarks of this industry-leading conference. More than 300 education programs feature keynotes, thought leader sessions, roundtable discussions and workshops, plus a full day of preconference symposia.

17th Annual Minimally Invasive Surgery Symposium 2017
February 28-March 3, 2017/Las Vegas, Nevada, USA

Website: http://www.miss-cme.org/site/Default.aspx
Contact: klally@hqtrs.com

The 17th Annual Minimally Invasive Surgery Symposium (MISS) will offer compelling lectures, surgical video presentations, and lively discussions and debates by world-renowned experts on advanced laparoscopic techniques for managing metabolic disorders, hernia, foregut and diseases of the colon.

Europe

CPhi Worldwide
October 4-6, 2016/ Barcelona, Spain

Website: http://www.cphi.com/europe
Contact: customerservice@ubm.com

CPhI Worldwide, together with co-located events ICSE, InnoPack, P-MEC and FDF, hosts more than 36,000 visiting pharma professionals over three days. 2,500+ exhibitors from 150+ countries gather at the event to network and take advantage of more than 100 free industry seminars. It will be a great opportunity to establish new business relationships, meet with global partners and stay updated on the latest industry trends. The exhibition showcases cover the whole spectrum of pharmaceutical manufacturing and ingredients sourcing, offering products and services that cover the entire supply chain.

17th International Conference on Lung Cancer
December 4-7, 2016/Vienna, Autria

Website: http://wclc2016.iaslc.org
Contact: wclc2016-registration@icsevents.com

The 17th World Conference on Lung Cancer of the International Association for the Study of Lung Cancer (IASLC) focuses on the science of lung cancer, which is advancing very rapidly. The Conference motto "WCLC 2016 Together against Lung Cancer" captures the collaborative spirit of the Conference which will be a scientific and educational event covering three major topics: Active Prevention, Accurate Diagnosis, and Advanced Care. Medical doctors, scientists, nurses, health professionals, government officials, partners from the industry, health advocacy groups and patients will come together in order to obtain and exchange information.

8th European Multidisciplinary Colorectal Cancer Congress
December 11-13, 2016, Amsterdam, Netherlands

Website: http://www.emccc2016.org/en/Home_10_6_12.html
Contact: info@congresscare.com

The European Multidisciplinary Colorectal Cancer Congress (EMCCC) is the European conference that truly provides a platform for in-depth multidisciplinary interaction among the various research areas. The conference will have separate workshops on surgery, medical oncology, radiotherapy, pathology, imaging, gastroenterology, and genetics, but all other sessions are plenary in order to have optimal interaction between all disciplines.

31st International Papillomavirus Conference
February 28-March 4,2017, Cape Town, South Africa

Website: http://hpv2017.org
Contact: reg_hpv17@kenes.com

Through workshops, invited lectures, and oral and poster sessions presenting the latest research results, the conference will cover papillomavirus (PV)-related topics from basic science to global health impact. The conference themes will include the epidemiology and molecular biology of PVs; animal models for the study of papillomaviral disease; impact of the microbiome on HPV; basic immunology and pathogenesis of PVs; therapeutic and prophylactic vaccines; prevention of cervical cancer and other PV-associated diseases, and promotion of the spread of the scientific knowledge to benefit the whole community.

2017 Pharma CI Europe Conference & Exhibition
February 21-22, 2017, Prague, Czech Republic

Website: http://europe.pharmaciconference.com/
Contact: info@pharmaciconference.com

This is the event featuring a world-class line up of speakers and panelists offering their unique insights and expertise on the topics you care about the most. The Pharma CI Conference & Exhibition is the industry's gold standard for senior level pharma, biotech, and device professionals seeking the latest news and the rare chance to network with all the industry's luminaries.

The 13th International Conference on Alzheimer's & Parkinson's Diseases
March 29-April2, 2017/ Vienna, Austria

Website: http://adpd2017.kenes.com
Contact: reg_adpd17@kenes.com

The series of Alzheimer's and Parkinson's Diseases Conferences attract international medical and scientific professionals worldwide. The Conference is at the forefront of unraveling the mechanisms and improving the treatment of Alzheimer's, Parkinson's and other related neurodegenerative diseases. AD/PDTM Conferences uniquely combine distinct neurodegenerative diseases in one setting and examine their similarities and differences; a strong focus is mechanisms of disease, prevention and therapy.

Asia

7th Emirates Otorhinolaryngology Audiology and Communication Disorders Congress
January 18-20, 2017/Dubai, United Arab Emirates

Website: http://www.emiratesrhinologyandotology.ae/
Contact: eroc@mic-group.com

The 2017 congress will provide a platform to share experiences and discuss breakthroughs in various specialist fields, a necessary prerequisite to successfully assess and expand practices. The congress includes keynote lectures, round table discussions, instructional courses, video sessions, and abstract sessions covering a wide array of topics and introduces latest technologies and techniques in the field. There will also be several live surgical pre-congress workshops on state of the art anatomical specimens.

12th Congress of Asia & Oceania Thyroid Association 2017
March 16-19, 2017/Busan, South Korea

Website: http://www.aota2017.com
Contact: office@aota2017.com

The congress will feature the latest advances in thyroidology as well as an update on the day to day practice of clinical thyroidology by renowned experts from the region. Since it had been established in 1975, Asia & Oceania Thyroid Association (AOTA) has grown rapidly and now it is one of the leading medical societies in Asia. At this congress, a number of thyroid experts from different Asian countries will bring together to exchange their scientific knowledge and build a strong networking with each other. These experts will highlight the peculiar nature of thyroid diseases in our region.

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August~September

1. Pfizer to Buy Cancer Drug Maker in $14 Billion Deal

Pfizer has acquired Medivation, which makes the big-selling drug Xtandi to treat prostate cancer, with a $14 billion agreement, representing $81.50 a share in cash. Pfizer, just as all the other pharmaceutical companies, is making a big push into oncology. The main big reason is that cancer drugs can sell for well over $100,000 a year and so far have been more resistant to cost-cutting efforts by insurers than drugs for some other diseases. Xtandi has generated $2.2 billion in global sales in the last four quarters and analysts see sales eventually reaching $4 billion or more annually. Ian Read, chairman and chief executive of Pfizer, expects that proposed acquisition of Medivation will immediately accelerate revenue growth and drive overall earnings growth potential for Pfizer.

http://www.nytimes.com/2016/08/23/business/dealbook/medivation-pfizer-14-billion-deal.html?rref=collection%252Ftimestopic%252FPfizerInc.&action=click&contentCollection=business&region=stream&module=stream_unit&version=latest&contentPlacement=5&pgtype=collection&mtrref=www.nytimes.com&_r=0

2. Why a Chinese Billionaire is Now the Biggest Investor in CHS

Turnover among top shareholders of distressed Community Health Systems has happened so dramatically over the past eight months that management could be excused if they need an introduction to the newcomers. The new largest shareholder of CHS is Tianquiao Chen, a Chinese billionaire, and he has announced that he had accumulated about 11.4 million shares of CHS, or 10% of common shares. During the time Chen and Wellington, second largest shareholder, were buying big into CHS this year, the company's stock was trading for less than $20 a share whereas it was traded for $60 a share a year ago. Neither Chen nor Wellington likely intend to be activist investors and demand board seats to foist operational changes on management.

http://www.modernhealthcare.com/article/20160820/MAGAZINE/308209967/why-a-chinese-billionaire-is-now-the-biggest-investor-in-chs

3. U.S. Funding for Fighting Zika Virus is Nearly Spent, C.D.C. Says

The director of the Centers for Disease Control and Prevention warned that federal funds to fight the Zika virus were nearly exhausted, and that if Congress did not replenish them soon, there would be no money to fight a new outbreak. The C.D.C. had spent $194 million of the $222 million it was allocated to fight the virus. The issue of funding is urgent because the Gulf Coast, where the Zika mosquito mostly lives, is only about halfway through peak mosquito season and the chances that the virus could start circulating in Houston or New Orleans are relatively high. There is currently a record of 16 infants born in the US with Zika-related microcephaly.

http://www.nytimes.com/2016/08/31/health/us-funding-for-fighting-zika-virus-is-nearly-spent-cdc-says.html?rref=collection%2Fsectioncollection%2Fhealth&action=click&contentCollection=health&region=stream&module=stream_unit&version=latest&contentPlacement=39&pgtype=sectionfront

4. HCA Pouring $2.7 Billion into Hub Hospitals and Markets

HCA Holdings plans to spend $2.7 billion this year to expand patient access in its hub markets. HCA, the nation's largest investor-owned hospital chain, is developing more than a dozen free-standing emergency rooms in its markets through 2017 to go along with the 57 already open. HCA is also adding ambulatory surgery centers, urgent-care centers, diagnostic centers, and new hospital wings to provide convenience and the right setting for the severity of illnesses and injuries. Healthcare demand has been up 4% and more across the country. But that is likely to taper to a more traditional 2% rate and HCA wants to be ready to capture those patients at any point in the continuum by having the facilities in place when patients come.

http://www.modernhealthcare.com/article/20160908/NEWS/160909906/hca-pouring-2-7-billion-into-hub-hospitals-and-markets

5. EpiPen Price Rises Could Mean More Riches for Mylan Executives

Mylan, the pharmaceutical giant, has been vilified for price increases on its EpiPen allergy treatment. Although Nina Devlin, a spokesperson stated that Mylan's big price increases were not intended to help propel its performance toward the earnings and stock price targets, Brian Foley, an independent compensation consultant argued it is impossible to separate the company's business decisions from its pay practice. Under the grant, Mylan executives will be rewarded if the company's earnings and stock price meet certain goals by the end of 2018. Given that EpiPen accounted for $1 billion of Mylan's $9.4 billion in revenue in its most recent year, the allergy treatment's price increases seem integral to meeting those targets and generating a big payday.

http://www.nytimes.com/2016/09/04/business/at-mylan-lets-pretend-is-more-than-a-game.html?rref=collection%2Fsectioncollection%2Fhealth&action=click&contentCollection=health&region=stream&module=stream_unit&version=latest&contentPlacement=28&pgtype=sectionfront

6. Obamacare Premiums Set to Rise, Even for Savvy Shoppers

In the last few years, even though premiums in the Affordable Care Act's health insurance marketplaces were rising, most customers could avoid a big price rise by shopping for a cheaper plan. Next year, according to a preliminary analysis, that is going to be a lot harder. There is expected to be an average premium increase of 11%. The plans that were least expensive this year in the popular "silver" category are no longer price leaders in most markets. People who want to stay in their current plan could face much larger increases.

http://www.nytimes.com/2016/09/01/upshot/obamacare-premiums-set-to-rise-even-for-savvy-shoppers.html?rref=collection%2Fsectioncollection%2Fhealth&action=click&contentCollection=health&region=stream&module=stream_unit&version=latest&contentPlacement=32&pgtype=sectionfront

7. A Push to Lower Drug Prices That Hit Insurers and Employers the Hardest

Insurers and employers say that a big financial shock has come from a largely overlooked source: expensive anti-inflammatory medications like Humira and Enbrel, drugs taken by millions of people for conditions like rheumatoid arthritis. In recent years, the prices of these medications have doubled, making them the costliest drug class in the country. Express Scripts, the nation's largest drug benefits manager, changed its recommendations to insurers and employers saying they should cover fewer drugs for many inflammatory conditions. The idea is that the new limits will force drug companies to lower their prices, saving insurers and employers money.

http://www.nytimes.com/2016/09/09/business/express-scripts-urges-narrower-coverage-of-anti-inflammatory-drugs.html?rref=collection%2Fsectioncollection%2Fhealth&action=click&contentCollection=health&region=stream&module=stream_unit&version=latest&contentPlacement=6&pgtype=sectionfront

8. Pfizer Snaps Up Gene Therapy Group Bamboo for $645m

Pfizer has snapped up the remaining stake in privately-held, US gene therapy group Bamboo Therapeutics in a deal that could be worth as much $645 million. The US drug giant already owned around 22% of the firm's fully diluted equity, and has now acquired the remainder for an upfront payment of $150 million. Under the deal, Bamboo's selling shareholders will also be eligible for potential milestone payments of up to $495 million contingent upon the progression of key assets through development, regulatory approval and commercialization. The move significantly ramps up Pfizer's expertise in gene therapy.

http://www.pharmatimes.com/news/pfizer_snaps_up_gene_therapy_group_bamboo_for_$645m_1087970

9. Pharma Industry Should Self-Police Drug Prices, Allergan CEO Says

Recently, a pharmaceutical company, which makes products such as Botox, pledged to limit annual increases on prescription drugs and Brent Saunders, Allergan CEO believes others can and should do the same. He says that government intervention isn't the answer to keeping drug prices in line. Saunders announced that Allergan would self-police their prices and raise prices no more than once a year. Allergan is getting a positive feedback from the drug industry.

http://www.cnbc.com/2016/09/08/pharma-industry-should-self-police-drug-prices-allergan-ceo-says.html

10. Why You've Probably Never Heard of the Mysterious Scientist Behind One of the Greatest Advances in Neuroscience

The new lab technique, called optogenetics, is one of the biggest breakthroughs in neuroscience in decades and it has the potential to cure blindness, treat Parkinson's disease, and relieve chronic pain. Two American inventors, Karl Deisseroth at Stanford University and Ed Boyden at the MIT have collected tens of millions in grants and won millions in prize money in recent years for their breakthrough invention. However, it turns out that it may be Zhuo-Hua Pan who invented optogenetics first. Pan is a vision scientist at Wayne State University who was driven by a desire to cure blindness and came up with the germ of the idea of optogenics in the early 2000s. Boyden et al. and Pan worked on channelrhodopsin during similar time frame. However, Pan wasn't able to receive much attention only because the editor at Nature Neuroscience published Boyden's paper first.

http://www.businessinsider.com/zhuo-hua-pan-optogenetics-2016-9?from=singlemessage&isappinstalled=0

11. Health Care Providers Scramble to Meet New Disaster Readiness Rule

An estimated 72,315 American health care providers and suppliers will have a little over a year to meet federal disaster preparedness requirements completed early September by the Centers for Medicare and Medicaid Services. The new rule is aimed at preventing the severe breakdown in patient care that follows natural disasters while also strengthening the ability to provide services during other types of emergencies, such as pandemics and terrorist attacks. The rule is unusual in that it has provisions for 17 different provider types, including outpatient surgery site, physical therapy offices and home health agencies. While the vast majority of organizations have had to adhere to at least some emergency preparedness requirements for accreditation, others were not subject to any and it is expected to have a big impact on those facilities.

http://www.nytimes.com/2016/09/10/us/medicare-requirements-disaster-readiness.html

12. Don't Worry about Orphan Drug Costs, Study Says. The Years of Fast Growth are Over

Researchers at IMS Health and Celgene state that a years-long upswell in orphan drug spending should slow down. The IMS Health and Celgene authors found that – when limited to rare disease indications – orphan drug spending grew to $30 billion in 2013 from $15 billion in 2007. However, the authors expect that growth to slow down for the 2014-2018 period.

http://www.fiercepharma.com/pharma/rising-orphan-drug-costs-aren-t-a-cause-for-concern-study-contends

13. St. Jude Sues Short-Seller Over Heart Device Allegations

St. Jude Medical Inc sued short-selling firm Muddy Waters and cybersecurity company MedSec Holdings Ltd, saying they intentionally disseminated false information about its heart devices to manipulate its stock. Muddy waters, run by Carson Block, said in late August that St. Jude's pacemakers and defibrillators, which are used to regulate heart rhythm and treat cardiac arrest, had cybersecurity flaws that enabled them to be hacked and manipulated, with potentially fatal consequences. These accusations based on research from start-up cybersecurity company MedSec, knocked St. Jude's shares back 10% on Aug.25. In the lawsuit, St. Jude stated that Block's statements were defamatory and false.

http://www.reuters.com/article/us-st-jude-medical-cyber-idUSKCN11D1FR

14. Congressman Wants a Hearing on Cosmetics Safety

Politicians are putting pressure on the FDA to review and potentially revise existing regulations that govern the cosmetic industry to make sure products are safe. Rep. Frank Pallone Jr noted that there haven't been substantial changes to policies regarding cosmetics since 1938, when the FDA was first charged with overseeing cosmetic safety. He says that the committee with jurisdiction over cosmetic regulation should examine the existing framework and determine that improvements are necessary. With the cosmetic industry raking in hundreds of billions of dollars per year, projected to reach $675 billion in revenue by 2020, it's an important time for a review to ensure consumer safety.

https://www.yahoo.com/beauty/congressman-wants-a-hearing-on-cosmetics-safety-232444488.html

15. FDA Warns Ovarian Cancer Tests Not Reliable

The U.S. Food and Drug Administration warned that screening tests for ovarian cancer are not reliable and should not be used. Despite extensive research and published studies, currently there are no accurate screening tests for ovarian cancer. However, numbers of companies have marketed tests that claim to screen for and detect ovarian cancer. But these tests may lead to delays in effective preventive treatments for high-risk women who have no symptoms, or result in unnecessary medical tests and/or surgery for those who do not have the disease.

http://www.webmd.com/ovarian-cancer/news/20160909/fda-warns-ovarian-cancer-tests-not-reliable

IT WAS HARD TO TELL THE McCARTHY TWINS APART. THEY EVEN HAD THE SAME CANCER.

Fortunately, they also had the same hospital: the University of Chicago Medicine. Kelly McCarthy was eight months pregnant when she was diagnosed with stage IIB breast cancer. After her son was born, she underwent chemotherapy, radiation, and surgery to remove her right breast. Just four months later, her identical twin Kristen was diagnosed with stage 0 breast cancer, requiring a double mastectomy followed by reconstructive surgery. Later, when Kelly underwent a second mastectomy and also required reconstruction, **Dr. David Song** transplanted some of Kristen's skin and tissue to create one of Kelly's new breasts. Which is why these twins will tell you the same thing: There's no other medical center like the University of Chicago Medicine. For more information, contact James Bae, Regional Manager of International Programs at youngjoo.bae@uchospitals.edu or call +1-224-315-3948.

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