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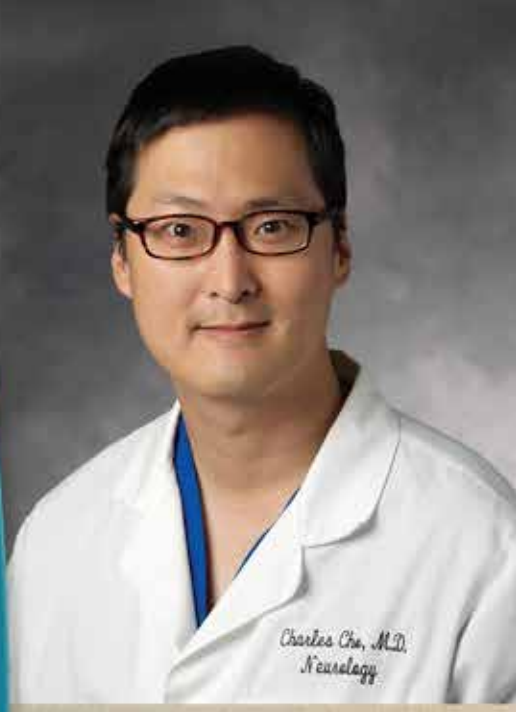
WKMJ

World Korean Medical Journal



Cover Story

A NEW DIRECTION: PHYSICIANS BEYOND CLINICAL MEDICINE

Charles Cho, MD
Han Choi, MD, LLM
Doug Yoon, MD, PhD, MPH, MBA

Expert Interview

Joseph P. McMenamin, MD, JD, FCLM

Special Report

Key Trends in U.S. Biopharma/Medtech Investing

Biopharmaceutical Report

Samsung RA Biosimilar EU Uptake Tied To Perceived Cost Despite Physician Concerns

Early CAR-T Multiple Myeloma Data Promising, Though Efficacy, Safety Remain Unclear

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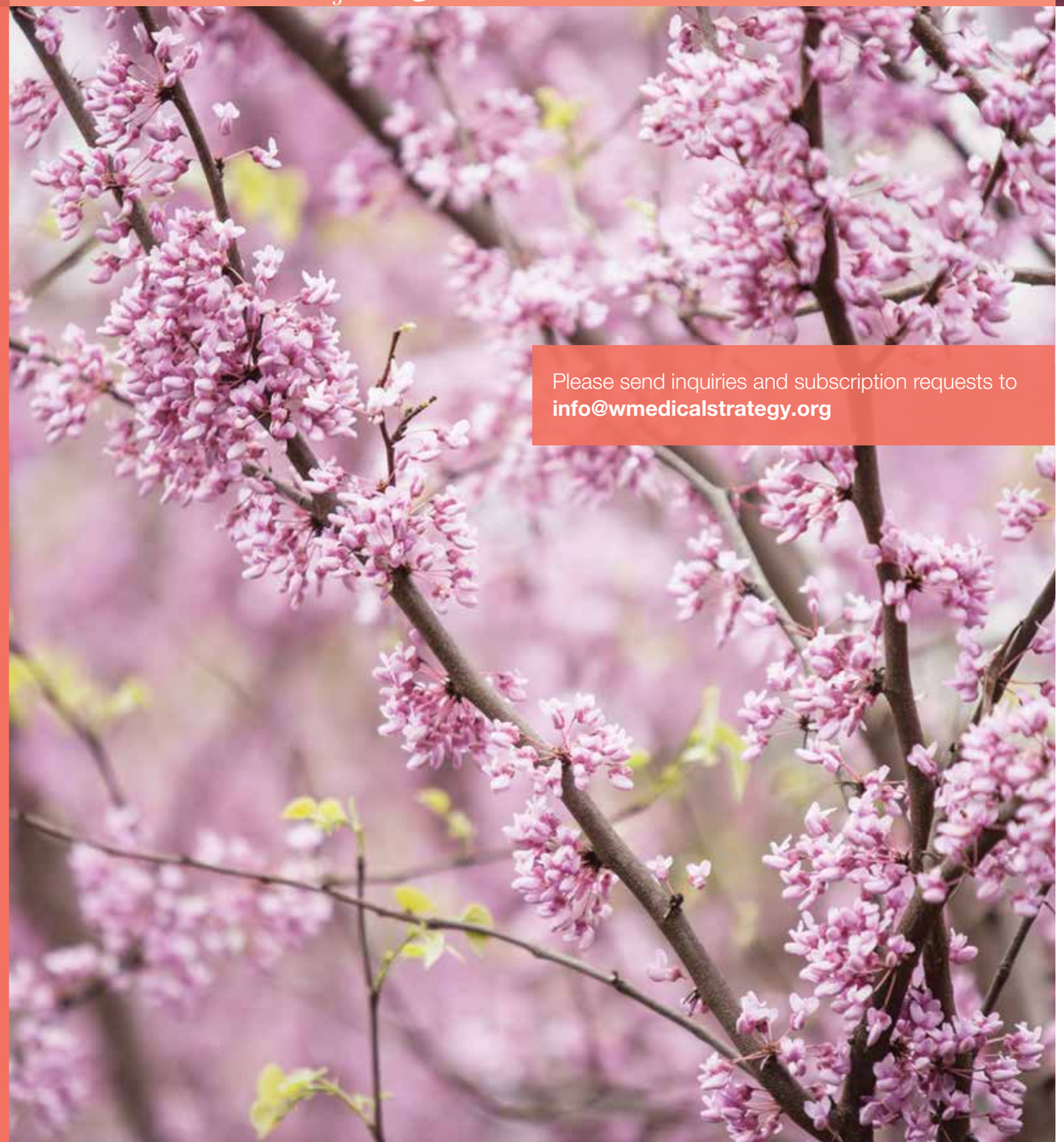

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FROM THE PUBLISHER

Dear Colleagues,

Hope your spring is going well. In this issue, we feature a round table interview of three physicians who have significant non-traditional interest in medicine. Medicine is part of the medical industrial complex that has surpassed the military industrial complex in terms of the GDP in the post-Cold War era. It is a significant development and great news to know that an increased amount of resources and funds are being put into health and medicine instead of war.

A physician can have career opportunities in the many facets of medicine. We feature 3 Korean-American physicians who have roles beyond the practice of medicine. Drs. Cho, Choi, and Yoon are highly successful, leveraging good physician traits of rigorous study and analysis on regulatory, legal and investment opportunities in medicine. For example, a physician has insight that a straightforward investor can never have, which gives the business of medicine a human touch and not just a ROI perspective. The opportunities in the business side of medicine are huge and translational not only scientifically but also financially. The investment in research and development for new or better therapies is commercially driven and thus there are great risks and rewards, but in the end the advances benefit all mankind.

The expert interview is of Dr. Joseph McMenamin, who like Dr. Choi, pursued a law degree and has had a long and distinguished career combining two very complex fields—the medical and legal field. Dr. McMenamin works the complex interface of medicine, business and government. Navigating the medical corporate legal environment takes special expertise and passion. This field is becoming even more complex with the international presence of medical companies as many Korean medical companies are expanding globally.

In February, a WKMO regional forum was held in Seoul that focused on health care in North Korea. Join us at the Annual Convention in Washington DC on June 9 -10 as we will have the historic opportunity to take part in the meeting of the Halls of US Congress (more information can be found on www.WKMOnet.org). Also at the convention, WKMO will honor the first Korean American physician graduate of George Washington University. I look forward to seeing you in D.C.

Yours,

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

FROM THE EDITOR-IN-CHIEF

If you are a fan of Korean dramas, you most likely have heard of the television series “Descendants of the Sun” which has been sweeping the hearts of viewers all over Korea and receiving immense popularity across Asia. The 16-episode series stars Korea’s top stars such as Song Joong-ki, Song Hye-kyo, Kim Ji-won and Jin Goo. The plot is essentially a love story that develops between a surgeon and a special forces officer as they serve together in a fictional war zone. In the series, the character Yoon Myeong-Joo (portrayed by actress Kim Ji-Won) serves as an army doctor in the war zone. Many viewers are captivated by her skill sets as a physician and disciplined and strong character as a lieutenant.

Just as the character Yoon Myeong Joo is a physician who practices in the army, there are several physicians who extend their range of services and expertise beyond clinical practices. Though medicine requires a lot of time and dedication, perhaps over a decade of studying and training, there are multiple physician trained professionals who are involved beyond direct patient care.

For this edition’s Cover Story, the World Korean Medical Journal explored and interviewed three significant physicians who are actively engaged beyond clinical medicine. Dr. Charles Cho and Dr. Han Choi are investment experts and Dr. Doug Yoon is a science consultant. Their insight and experience will prompt readers to question their assumptions about physicians. Most doctors choose to dedicate their professional skills to the clinical fields while others deploy their talents in other ways that also contribute to the society. This edition’s cover story exhibits examples of alternative professions that require knowledge and experience pertaining to the medicine.

Also featured in this issue’s biopharmaceutical reports are the new trends and issues of the bio-health industry. The article from BioCentury examines the culture of publication in the bio-pharma research world. In particular, it emphasizes the ‘reproducibility’ of research publication. In another article, it discusses the price aspects of Samsung’s newly developing biosimilar products. The last article focuses on the Chimeric Antigen Receptor T-cell studies presented at the ASH meeting in Orlando.

Lastly, this edition’s journal contains two Special Reports. For the first report, our staff interviewed Joe McMenamin, MD, JD, who is a physician trained lawyer. The second report summarizes the events that occurred at the 5th New York Health Forum and the topics discussed.

Various writers and experts have shared their knowledge and insights as co-authors in this edition. I hope that our readers will find these exciting selections of articles to be helpful and inspiring. Enjoy the read!

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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WKMJ RECAP OF THE LAST ISSUE

Cover Story
Inspirational Korean Healthcare Leader "Dr. David H. Song, the President of the American Society of Plastic Surgeons"

Dr. David H. Song is an internationally recognized expert in plastic surgery with additional training in reconstructive microsurgery. He specializes in breast reconstruction and oncoplastic surgery. He is the Cynthia Chow Professor of Surgery, Vice-Chairman of the Department of Surgery, Chief of Plastic Surgery and Residency program director at the University of Chicago Medical Center. Currently, Dr. Song serves as president for the American Society of Plastic Surgeons (ASPS). To read more about Dr. Song and his great contributions to medicine, check out WKMJ Issue No. 8.

Entrepreneur Interview
Paula Wilson, President and Chief Executive Officer of Joint Commission Resources and Joint Commission International

Paula Wilson is the President and Chief Executive Officer of Joint Commission Resources (JCR) and its international division, Joint Commission International (JCI). JCR and JCI are non-profit organizations working to improve health care quality and patient safety in nearly 90 countries around the world. Ms. Wilson has more than 30 years of experience in the health care industry. To learn more about Paula Wilson and her work, read WKMJ Issue No. 8.

Special Report I
Korea's Enzychem Lifesciences Launches New Global Initiative

Korea's leading biopharmaceutical company Enzychem Lifesciences has launched its major global initiative in the United States. The initiative will help facilitate licensing, strategic partnerships and investment opportunities for the self-developed global new drug candidate EC-18's development and commercialization in the USA market. Please refer to Issue No. 8 to find out more.

Biopharmaceutical Report I
No Differentiation Expected Among PARP Inhibitors

PARP inhibitors like Tesaro's niraparib, Clovis Oncology's rucaparib, and AstraZeneca's approved Lynparza (Olaparib) will find it challenging to differentiate from one another according to expert reports. The side-effect profiles may have a role in differentiating one PARP from another. However, the side-effect profiles are not showing much separation. For more detailed information about PARP inhibitors, please refer to Issue No. 8.

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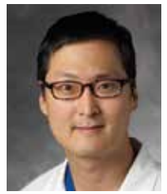
A NEW DIRECTION: PHYSICIANS BEYOND CLINICAL MEDICINE

This edition's cover story details the career paths of three physicians, Dr. Charles Cho, Dr. Han Choi, and Dr. Doug Yoon, and their thoughts on the evolving relationship between and beyond their clinical roles.



Charles Cho, MD

Managing Director, Palo Alto Investors
Clinical Professor, Neurology & Neurological Sciences, Stanford Medicine

Charles Cho, MD, joined Palo Alto Investors in 2008 and specializes in the healthcare sector. Dr. Cho is a practicing board certified neuromuscular specialist and serves on the faculty at the Stanford Medical Center where he is the Director of the Amyotrophic Lateral Sclerosis Clinic. Previously, Dr. Cho was a Clinical Instructor at the Harvard Medical School. Dr. Cho received his bachelor of science from Brown University and his doctor of medicine from Georgetown University School of Medicine. He completed his residency at Stanford and did a post-graduate fellowship at Massachusetts General Hospital.

Han Choi, MD, LLM

Principal, Oracle Investment Management

Han Choi, MD, LLM is currently a Principal at Oracle Investment Management, a healthcare hedge fund based in Greenwich, Connecticut. Prior to joining Oracle, he held positions of increasing responsibility in licensing and business development at Pharmacia Corporation and Bristol Myers-Squibb Company. Dr. Choi received his M.D. from the Mount Sinai School of Medicine and trained in General Surgery at New York University Medical Center. He also holds law degrees from Oxford University and Harvard Law School and is admitted to the New York State Bar, Third Judicial Department.

Doug Yoon, MD, PhD, MPH, MBA

Chief Scientist, Washington Scientific

Doug Yoon, MD, PhD, MPH, MBA is the Chief Scientist of Washington Scientific, a health science consulting firm based in the Washington metropolitan area. Dr. Yoon specializes in the application of scientific principles and evidence-based risk management strategies to medical, environmental health, and pharmaceutical issues. Dr. Yoon is a strong advocate for humanitarian actions. He worked as the United Nations Peace Keeping Officer in 1997. He has participated and led medical relief actions responding to various disasters including the 2005 tsunami and the 2006 earthquake. In November 2014, the Korean government selected Dr. Yoon as a physician member of the Korean Disaster Response Team (KDRT) to fight against the Ebola outbreak in West Africa.

"A "physician" or "medical doctor" is a professional who practices medicine, which is concerned with promoting, maintaining, or restoring human health. Nonetheless, there are a growing number of physicians who are leveraging their clinical backgrounds to roles beyond direct patient care. As the Cover Story of the April edition, WKMJ interviewed three such physicians who are actively engaged beyond clinical medicine."

Dr. Choi caught in action during a meeting.

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

[HAN] As with many other Korean families, my parents played a big role in my going to medical school. My mother was one of the first women to have a faculty position at a major teaching hospital in Korea in the 1950s right after the Korean War. She was very dedicated to her academic practice, even putting off starting a family until she was in her mid-forties. Her influence was so strong that she convinced me to do a six-year accelerated B.S.-M.D. program, which led to my becoming a doctor when I was 22 years old. My age ended up being a problem when I started my general surgery residency because patients would take one look at me and say, "you're just a kid, there's no way you're operating on me." So after getting my medical license, I decided to take some time off from my residency and became a public health officer at the U.S. Centers for Disease Control and Prevention. While at CDC, I ran public health and health policy programs both in the U.S. and in Africa, which is where I first developed an interest in the non-clinical side of healthcare. From there, I decided to go back to school and became an attorney with the intention of doing health policy work at the federal or international level afterwards. However, I ended up joining and eventually leading the licensing and business development functions for two multi-national pharmaceutical companies where my medical and legal backgrounds were useful in structuring and negotiating licensing deals and company acquisitions. Then 13 years ago, I was recruited by a hedge fund to manage their pharmaceutical and biotechnology investments, which is where I am today.

[CHARLIE] As a young child (a very long time ago), I enjoyed the excitement of looking for then discovering something interesting and seeking new experiences. This manifested in many ways during my young life, but also over my educational and career choices. I studied and majored in History, Geology, and Literature during my undergraduate education; then, went on to seek a more basic science post-graduate schooling. After starting a career in Investment Banking, I applied to and attended Medical School, Residency, and Fellowship subspecializing in increasingly more specific desperate diseases. With each differentiating step, there was a growing awareness of need, not just medical care delivery, but also for diagnostic and therapeutic solutions for diseases without adequate cures. Each patient was a mystery needing a solution, and these investigations led to diagnosis and cures.

[DOUG] I lost my ability to walk due to a rare bone disease when I attended elementary school as a second grader. My mother had to carry me on her back to and from the school every day for three years. It was a difficult situation for anybody. One bright aspect of it was, however, that it forced the young boy in a small fishing village to think about the future path relatively early. One day, when I was left alone in the classroom during a physical education class while other friends were playing outside, I gave up the idea of becoming a fisherman because I was not sure that I could walk again. Instead, I made up my mind - "I will do something to fix this kind of embarrassing disease." I guess that was the beginning of processes that led me to a medical school eventually.

2. Please introduce your current profession in the clinical and/or non-clinical setting. What experiences have motivated you to pursue your current profession? What are the long-range career goals with your profession?

[HAN] I am currently a Principal at Oracle Investment Management, which was the first sector-specific healthcare hedge fund in the U.S. Although we invest across all subsectors of healthcare, my primary responsibility is to manage our investments in pharmaceutical and biotechnology companies. The last few years have been a great time to be a biotech investor. The pace of clinical research has been staggering, and I consider myself fortunate to have seen many small research-focused companies we invested in mature and grow to become very profitable multi-billion dollar commercial-stage companies. What is even more encouraging is that I am seeing more and more Korean biotech companies attract interest from both the big multi-national pharmaceutical companies as well as from U.S. and European institutional investors. There is a lot of cutting-edge research being done by Korean universities and companies that I think will lead to tremendous growth of the Korean biotech sector in the coming years.

Dr. Yoon pictured while attending a CDC Ebola training in 2014

[CHARLIE] As a clinician, I am a Professor at the Stanford University School of Medicine Department of Neurology. As a Neuromuscular specialist and Director of the ALS Clinic, I see a focus of patients with truly devastating and life-threatening diseases. I used to also run large multi-center clinical trials to seek curative therapies for these diseases, but have stopped this part of my practice a decade ago, primarily due to my desire to seek more creative solutions and invest in a broader range, and hopefully have a bigger impact in healthcare.

My other professional focus is as a portfolio manager at a Hedge Fund, investing our collective funds into promising healthcare companies in the US, EU, and Korea. The areas of interest include drugs, biologics, devices, and diagnostics. Over the last 9 years, we have deployed over $3 billion into public companies in these three regions. This mission is similar to my clinical activities in that they both are investigating the basic and clinical science technology and seeking treatments and cures to extremely serious diseases.

[DOUG] I currently work as the Chief Scientist at Washington Scientific, a health science consulting firm that I established in the Washington metropolitan area after working for five years at a large NASDAQ-listed science consulting company. Washington Scientific works on the intersection of medicine and epidemiologic principles. We often are involved in controversial issues such as unwanted effects of drugs or chemical compounds, association vs. causation, and cancer cluster claims.

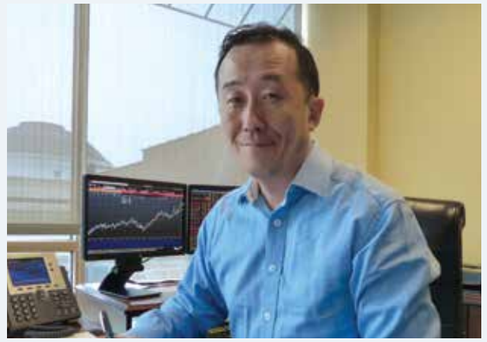
Before working in the non-clinical setting, I practiced medicine for 18 years in a large academic hospital system in Korea. Evaluation of the epidemiologic evidence behind the clinical decisions was one of the tasks during that era. That's when I developed further interests on systemic reviews and evidence-based medicine. I decided to earn a degree in public health focused on those areas during my sabbatical year. When I finished my degree in epidemiology, I decided to take a job that might present more opportunities in which I could utilize both of my clinical and epidemiologic training.

As a founder of Washington Scientific, I want to see my company grow from a mere consulting firm into a think tank that helps society navigate into the future. As a society, we are facing many issues currently overarching scientific principles and clinical practices. Health insurance system issues, discrepancies between scientific evidence and real-world clinical practice, and misuse of societal assets in healthcare areas are just a few of them. I dream that Washington Scientific will provide critical guides to the society in overcoming those issues.

3. Especially for your non-clinical career experience, have you identified any advantages and/or disadvantages of being a physician?

[HAN] Being a physician is an advantage anywhere within the healthcare industry because doctors will always make the majority of diagnostic and treatment decisions for their patients. That said, there are an increasing number of dual-disciplined physicians these days including M.D., Ph.D.s, M.D., M.B.A.s, and M.D., J.D.s., including on Wall Street. In the investment management field, being a physician is an advantage because a significant part of our due diligence on companies involves speaking with thought leaders across all specialties about ongoing clinical trials, practice trends, and reimbursement models. Being able to engage thought leaders as peers is often useful in these discussions and having first-hand clinical experience is also helpful in determining whether a healthcare company's business model is sound or flawed.

[CHARLIE] It is during times of extreme change and distress that the measure of someone's true character becomes apparent. Personally, I've witnessed dramatic changes for the worse sweep over my field of Neurology over my 20 year medical career. For example, programs in Alzheimer's disease taking a decade to develop continue to fail, not even in curing, but in even slightly helping memory and function. Dozens of studies in ALS fail, leaving absolutely no curative treatment for this fatal disease. Not to mention hundreds of Neurological diseases in children and adults that also remain untreatable despite advances in science. Then, there are the logistic changes in medicine that are unfunded mandates of reimbursement hurdles, litigation risk, documentation requirements, service practice laws, etc. As a physician, we live these tectonic shifts to the field of medicine that an average (or even extraordinary) investor may not be able to appreciate, let alone understand in any detail. My most recent appreciation of the medical background in the investing world was during FDA discussions about a cancer drug's potential black-box warning. There are nuances to the story, but basically, Wall Street discounted the drug's possible approval or eventual adoption into doctor's treatment algorithm due to the potential black-box. My understanding of the existing treatments, and the exceedingly dire need of the patient's with this type of cancer suggested that a black-box would have no bearing on patients or doctors' decision to use the drug. This is a classic mismatch of non-medical investors and doctors. Eventually, my thesis proved true and the drug was both approved and became the standard of care with widespread use throughout the world.


Dr. Choi photographed in his office


Dr. Cho photographed in his office

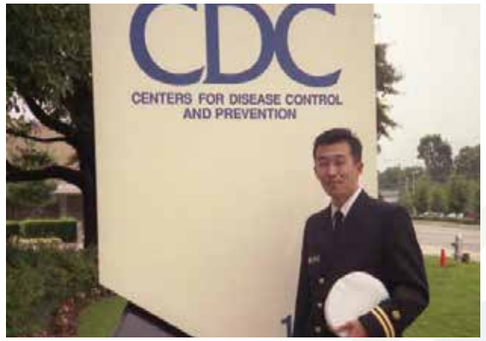
[DOUG] Understanding science behind the disease and hands-on experience in clinical settings are critical assets in my work. People often overlook scientific evidence and epidemiologic principles behind the clinical practice. Being a physician with extensive clinical experience provides a unique perspective when you examine the situations overarching scientific principles and society, especially on controversial and sensitive issues.

4. Currently, many doctors are demonstrating their knowledge and skills around the world beyond clinical fields. Do you think this can evolve into a trend? How do you foresee the landscape of the healthcare professions in the future?

[HAN] Healthcare is very different from all other industries because there are so many stakeholders involved. In most industries, supply is generated by a provider of a good or service and demand is generated by the consumer of that good or service. In the healthcare industry, although the patient is the one receiving the good or service, they are not empowered to decide when and which good or service they will get, which is decided by their doctor. Furthermore, that good or service is usually paid for by an insurance company or a government program whose incentives are often misaligned with the patient as well as the doctor. On top of all this, healthcare is a highly regulated industry because it involves public safety. With so many different stakeholders involved, there are multiple segments of the healthcare industry that go beyond direct patient care. I think more physicians will continue to become leaders in these non-clinical segments, which is a positive trend that will benefit both physicians and their patients.

Dr. Yoon and fellow healthcare workers at a CDC Ebola training in 2014

[CHARLIE] Medicine requires a lot of time and dedication, perhaps 10+ years after college to just finish training, then more time and effort to acquire experience and domain knowledge to become a great doctor. Some would argue it is a lifelong pursuit of a singular skill. For these and other personal intangible reasons, most doctors choose to dedicate their professional skills to the clinical fields. However, with these shifts in external factors that affect medicine, such as reimbursement and litigation risks, our skill sets may allow more individuals (rather than huge trends) to deploy their skills in other ways that also contribute to society. This article's other featured doctors and myself are just a few examples of alternative professions that benefit from the medical background, but there are certainly many other possibilities.



Dr. Choi served as a lieutenant of the U.S. Public Health Service at CDC in 1993

[DOUG] I think that more and more doctors will work on the issues beyond the clinical area. This is a trend that is only getting stronger regardless of the region.

Two trends are evident in the healthcare system. First, the modern healthcare system is getting more complex. Working in the healthcare system now requires more skill sets and broad understanding of the healthcare system than ever before. Some people say that artificial intelligence will replace doctors fairly soon. The people who think such thoughts don't understand the complex processes and interpersonal skills that doctors are using in a seemingly simple patient encounter. The doctor's role in the healthcare system and outside of clinical practice will increase and be more diverse.

Second, there is a growing trend of seeking efficiency as the modern health insurance system expands. That, in turn, often poses restrictions on clinicians. Insurance companies love efficiency and directing patients to the cheapest facility available. That means healthcare will be more fragmented and less humanistic unless we, as a society, step in. Finding a right balance between efficiency and humanistic medical care will be a new trend. In that trend, doctors will have more roles in leading society than merely seeing patients.

5. Do you have any comments or advice for current medical students as well as those who aspire to become a doctor?

[HAN] I think becoming a doctor involves such a substantial commitment of time, resources, and effort that it only makes sense for those who want to treat patients. That said, many physicians split their time between seeing patients and other administrative or executive roles usually in some business-related aspect of healthcare. The one constant in the rapidly evolving healthcare industry is that physicians will never be rendered obsolete in the clinical setting so the opportunities in adjacent segments can only grow.

[CHARLIE] These are very exciting times for young doctors and doctors-in-training. Science and technology are evolving at an accelerated pace and we may witness amazing new treatment options for our patients. Future doctors will have the great honor of treating the terrible diseases that is not possible today, eradicate cancers, reverse dementia, cure aging. In addition, there will be so many options for clinician-scientists and entrepreneurial endeavors to start companies, join industries and assist in healthcare legal activities including patent law, healthcare IT, services, regulatory sciences, sales/marketing. Also, the investment side that I participate will always be available, either at the earlier venture stage or later public stages.

[DOUG] Congratulations. You are among the selected group of people or those about to be selected. However, do not stop thinking about the future and your potential. Only you can set your full potential.

Dr. Yoon served as a military doctor for the United Nations in 1997

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

[HAN] The other unique aspect of healthcare is that although basic human anatomy and physiology are universal, the delivery of healthcare services varies tremendously between counties and sometimes within different parts of the same country. There is no one country who has the best healthcare system, and I have always found it fascinating to see how differently healthcare works across the globe. As physicians around the world continue to share advances in cutting edge research for the benefit of their patients, I think it's also incumbent on physicians to share best practices for the non-clinical aspects of healthcare as well to improve the overall delivery of healthcare in each country.

Dr. Choi pictured with his wife and two daughters

Dr. Cho pictured with his father, one of the founders of Korean Air/Hanjin Group and his son

[CHARLIE] My focus has been the translation of basic science to important clinical therapies, hopefully in diseases that currently have no other treatment, or perhaps diseases that only have symptomatic medicines. This focus was both through the practice of medicine but also by investing and providing capital to companies that I felt would have the highest impact and chance of succeeding. This approach carries many scientific, trial, regulatory, and marketing risks. Instead, for many other countries, a medical background may be better focused on transfer of existing technologies/drugs, and perhaps either generics or biosimilar therapies that lower costs to society. There will always be alternative career choices with a medical background, but the specific opportunities may not be the same from country-to-country. I believe by treating patients, teaching (leveraging your knowledge by spreading it to the next generation), investing (multiplying the leverage by using knowledge to potentially treat thousands-millions of patients) scientists and doctors can contribute to society and make a huge difference to the future of healthcare.

Dr. Cho photographed with his two sons

[DOUG] Regardless of the region in the world, the healthcare system is a big issue that everybody has something to say. Whatever the issue, in the end, I believe the scientific principles and humanity should prevail. I encourage the readers to look beyond the issue you are looking at. W

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Special Report

SPECIAL REPORT I

EXPERT INTERVIEW

JOSEPH P. MCMENAMIN, MD, JD, FCLM

SPECIAL REPORT II

KEY TRENDS IN U.S. BIOPHARMA / MEDTECH INVESTING

Expert Interview

As the range of nonclinical roles in healthcare expands, more physicians are entering alternative career paths beyond clinical medicine. Dr. Joseph P. McMenamin, MD, JD, FCLM, shares his experiences working in the non-clinical setting.

Dr. Joseph P. McMenamim at the opening celebration of W Medical Strategy Group

1. Please introduce your current profession in the clinical and/or non-clinical setting. What experiences have motivated you to pursue your current profession?

I have two businesses: a law practice, and a consultancy. Both focus on medicolegal topics.
I became a doctor because human life is my highest value, and in no other profession is it so directly served.

I became a lawyer for three main reasons. First, even in med school, and certainly in residency, I became concerned about the profession's non-clinical burdens. Even then, doctors had to devote considerable time and energy to reimbursement, tort claim risk, and other innervating but necessary matters. I anticipated that the trend would continue, and probably accelerate. Unfortunately, this prediction proved to be accurate. Second, I developed a still-growing intellectual interest in questions arising where the fields overlap. Medicolegal issues are complex, but for me, endlessly fascinating. Third, and perhaps most important, I felt I could more effectively utilize whatever talents I might have through the practice of law, especially those branches pertaining to healthcare, than I could through the practice of medicine.

What I decided on would not be for everyone, but thirty years on I am glad I pursued the law.

2. What are the pros and cons of being a physician trained lawyer?

Pros: I am bilingual in law and medicine. A lot of what I do is akin to translation: helping physicians understand the law, and helping lawyers understand medicine. I empathize with providers, even those trained in fields I never entered, because the similarities among the disciplines, especially their shared philosophies, outweigh the distinctions. And, without exposing patients to risk, I get the chance to learn about developments in almost every branch of medicine.

Cons: Clients sometimes assume I do not need their help to learn about their diagnostic and therapeutic methods. My training was confined to internal medicine, so in most medical disciplines, of course, I have no specialty training at all. Even in medicine, I am thirty years removed from clinical care. Whatever branch of healthcare a particular matter implicates, I still need instruction and insight from those who care for patents, and those who develop medicines and devices.

3. You are collaborating with W Medical Strategy Group as an executive and an expert. We recognized that you've received the 2016 WMSG Contribution Award as well. What is your current and past relationship with W Medical Strategy Group and other Korean healthcare communities and/or organizations?

I am privileged to serve as counsel to WMSG and as its EVP. As a result, I have had the good fortune to meet, work with, and learn from some outstanding Korean healthcare leaders, both here and, on three occasions now, in Seoul. Among them have been academicians, private practitioners and medical scientists, including entrepreneurs fairly bursting with energy and ideas. Exposure to so many bright and highly-trained individuals has been enlightening.

I also serve the World Korean Medical Organization, representing physicians throughout the Korean diaspora in virtually every specialty. Founded by Dr. Chul Hyun, and currently under the leadership of Dr. David Ko, WKMO provides a forum for scientific and cultural exchange, and a platform for advancing public health goals, such as hepatitis control.

Most recently I have had the great honor to counsel a Korean pharmaceutical company with respect to the U.S. clinical trials law, helping to manage the associated risks.

4. Since you have represented multiple healthcare companies, what would you say are the top three priority assets or skill sets needed to be a successful company in the healthcare industry?

First, an emphasis on quality. A company that demands of its personnel their best efforts, and that insists that its products meet or exceed marketplace expectations, will not only improve patient health, but will achieve its business objectives as well. A good reputation earned in this way will also provide better insulation from unfairly broad criticisms recently leveled at the industry's commercial practices.

Second, an ability to adapt. For more than a century, change has been a given in the life sciences. What is exceptional about today, however, is the rate of change. Technological achievements nearly unimaginable a generation ago become obsolete in a matter of years now, and are replaced by still newer technologies that at times seem like science fiction. Companies have to be exceedingly agile and adroit to spot changes early, assess their significance, and pivot as needed to adapt to new challenges.

Third, a focus on the big picture. Too often, companies concentrate on hitting their numbers for the present quarter, or the one to come, rather than thinking about the company's position 5 and 50 years hence. Investor pressures make this understandable, but long-term value depends on long-term scientific progress and fiscal health.

5. The healthcare industry is one of the most unique fields where collaboration among multiple entities is a 'must'. What would be your advice to companies in maintaining effective and long lasting relationships with partners including consultants and other service providers?

To make the most of the skills and knowledge of service providers, a company should require them to develop a deep, broad understanding of its culture, personnel, goals, and challenges. An on-site visit, or perhaps several, especially with large, complex organizations, is ideal. Interviews with the leadership team and with employees whose roles are most directly pertinent to the project will help the consultant to understand the company better, which should in turn result in better "diagnoses" and "treatments" for the issue(s) to be addressed. Within reason, service providers ought to be willing to take the time to achieve this improved understanding at no or reduced fees, to build a collaborative foundation, to improve the quality of the consultant's services, and in anticipation that this investment of time and energy will bring mutual benefit. Experience, expertise, and a sound work ethic are invaluable as well, but nothing can replace a thorough grasp of the client's business for enhancing the likelihood that engaging with a service provider will yield abundant fruit.

Dr. Joseph P. McMenamin paneling at the New York Health Forum

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

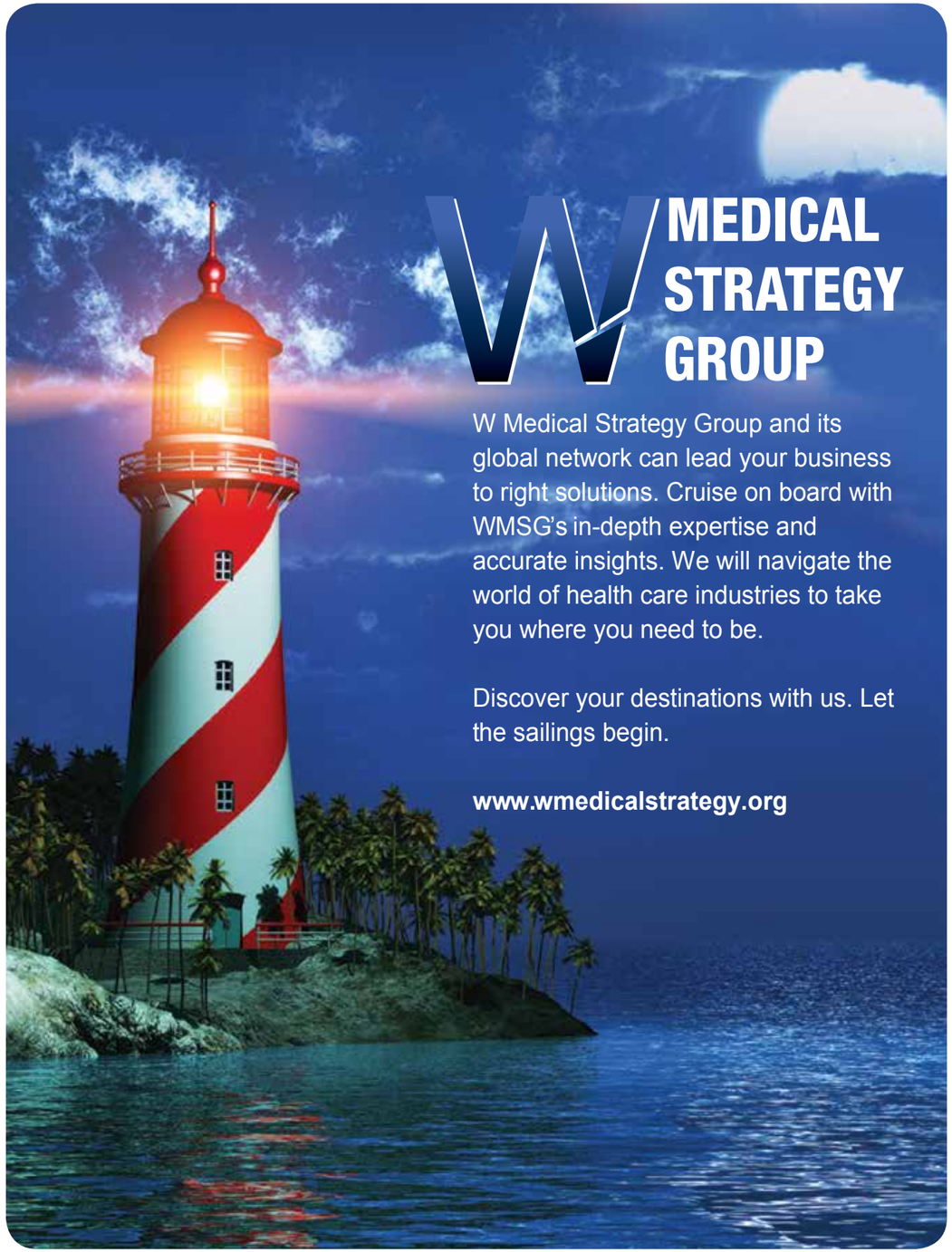
By no means am I am a scholar of Korean history. I am highly conscious, however, of its struggles in the 20th Century. Korea was occupied and dominated by a foreign power for decades before and during WWII. At its end, the peninsula was divided to forestall Soviet occupation of its entire land mass. Only a few years after V-J Day, war erupted in the country, causing yet more death and destruction. After such prolonged trauma, the prognosis for peace and prosperity must have seemed meager. Yet in fields such as shipbuilding, car manufacturing, and electronics, the Koreans have achieved astonishing success over a comparatively short time, all while building a stable democracy. The country has now set its sights on the life sciences, and I am confident it will achieve comparable results there as well.

Joseph P. McMenamin, MD, JD, FCLM

EVP, W Medical Strategy Group

Principal, McMenamin Law Office

Joe McMenamin is General Counsel and EVP at W Medical Strategy Group, as well as the Principal at McMenamin Law Offices. Before starting his own firm, Joe was a litigation partner at McGuireWoods LLP. He earned his MD at the University of Pennsylvania School Of Medicine and trained in internal medicine at Emory University. He earned his law degree at the University of Pennsylvania School Of Law and is admitted in Virginia. Joe is a Fellow of the College of Legal Medicine and an Associate Professor in the Department of Legal Medicine at Virginia Commonwealth University



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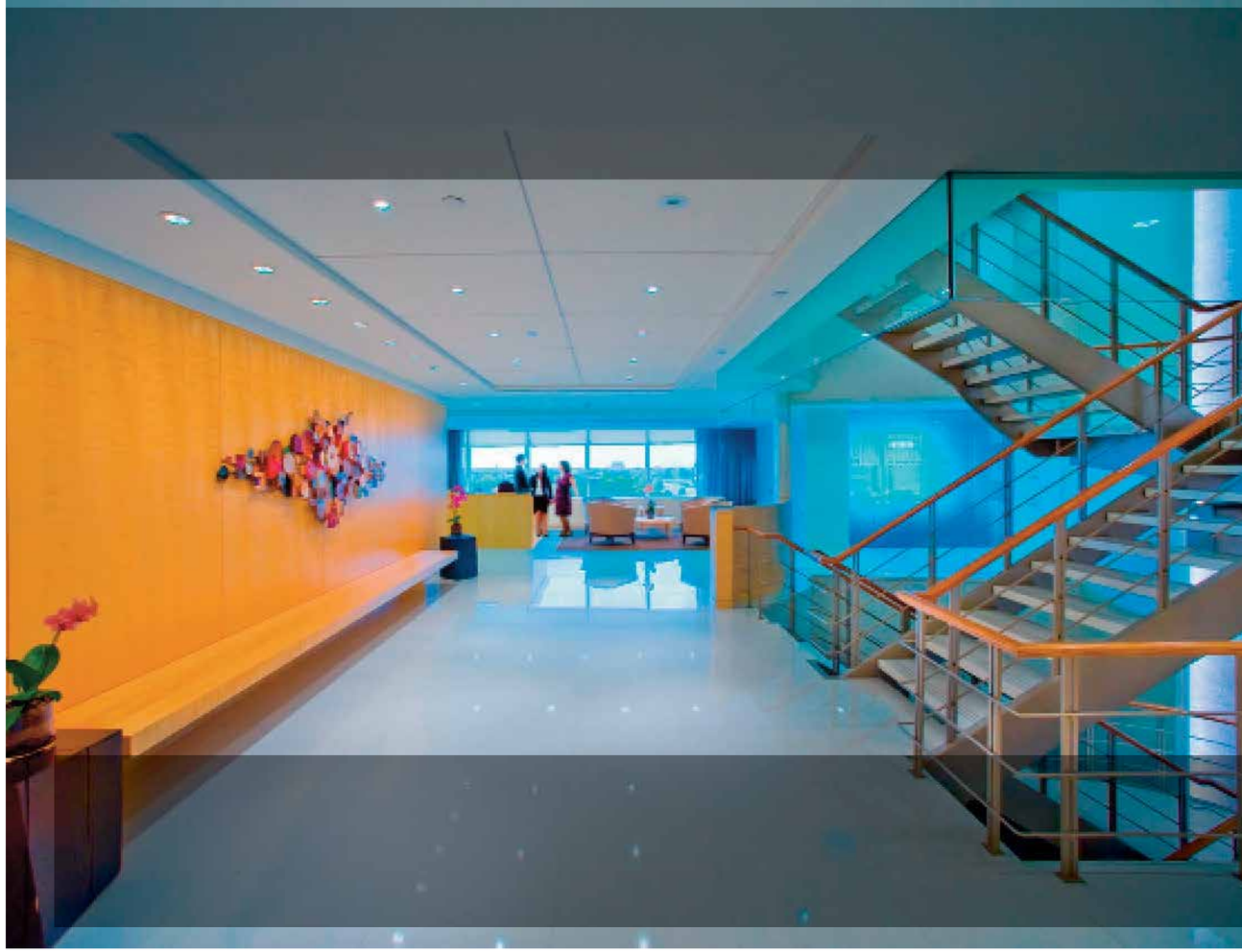

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Key Trends in U.S. Biopharma/Medtech Investing

The 5th New York Health Forum

Date: March 31st, 2016 | Venue: The Yale Club of New York City | Time: 1 pm to 5 pm

Opening Remarks: DoHyun Cho, PhD CEO and President, W Medical Strategy Group / Chairman, New York Health Forum

Networking Break

The 5th New York Health Forum was held at the Yale Club of New York City on Thursday, March 31st of 2016. It provided a setting for stimulating informative discussions on topics such as investment trends, landscapes, and risks in the current healthcare industry. The central theme for this forum was "Key Trends in US Biopharma/Medtech Investing". Over 70 guests including investors, biopharma and medtech representatives, and healthcare professionals attended the forum to provide opportunities, share information, and discuss ideas.

The program began with a luncheon and an opportunity for the attendees to associate and connect with one another. Following this was an opening remark delivered by DoHyun Cho, PhD, CEO and President of W Medical Strategy Group and the Chairman of the NYHF. A total of three active sessions were held followed by a Q&A session, creating a moment for the audience to engage with the panelists and voice their opinions as well.

The first session titled "Biopharma/ Medtech Funding Trends and Investment Landscape" was moderated by Joseph P. McMenamin MD, JD and FCLM and paneled by Sean Drake, the Managing Director at Stony Lonesome Group LLC, and Katya Hancock, the Director of Strategic Partnerships at StartUp Health. During this session, the panelists examined the current state of biopharma/medtech financing and the factors that have led to the current financing environment.

Special Report II

The second session titled "The Key Factors to Raising Capital: What Will Attract Investors?" was moderated by Kimberly Ha and paneled by Norman Yun, Managing Director at H. C. Wainwright & Co., and Vincent Liu, PhD, Senior Advisor for Shanghai Fosun pharmaceutical group. At this session, discussion took place on the trends and dynamics of current biopharma/ medtech industry investment.

The final session was moderated by Tony Chen, CEO of PrimeVax Immuno-Oncology Inc. and titled "New Breed of Contributors: Alternative Biopharma/Medtech Financing". Panelists included Frank Borchetta, CEO & Co-Founder of Repairogen Corporation, Imran Babar, PhD, Senior Associate at OrbiMed LLC, and Karen Carr, Regional Development Officer at Gateway for Cancer Research. The panelists discussed the new trends and matrices of alternative health care finance and shared how disease foundations, private donors, and nonprofit organizations became huge contributors for the development of new therapies.

Session 1: Biopharma / Medtech Funding Trends and Investment Landscape (From Left to Right) Joseph P. McMenamin, MD, JD, FCLM (Executive Vice President of WMSG) moderated the first session, along with panelists Sean Drake (Managing Director, Stony Lonesome Group LLC), and Katya Hancock (Director of Strategic Partnerships, Startup Health)

The forum was hosted by W Medical Strategy Group and sponsored by It's a Wig, FTI Consulting, and Green Alley. The next New York Health Forum will be held in June. For further information about the NYHF and for more photos, please visit www.newyorkhealthforum.net

Session 2: The Key Factors to Raising Capital: What Will Attract Investors? (From Left to Right) Kimberly Ha (Senior Director, FTI Consulting) moderated the session along with panelists Vincent Liu, PhD (Senior Advisor, Fosun Pharma) and Norman Yun (Managing Director, H.C. Wainwright & Co.)

Session 3: New Breed of Contributors: Alternative Biopharma/Medtech Financing (From Left to Right) Tony Chen (CEO, PrimeVax Immuno-Oncology Inc) moderated the last session along with panelists Karen Carr (Regional Development Officer, Gateway for Cancer Research), Frank Borchetta (CEO & Co-Founder, Repairogen Corporation), and Imran Babar, PhD (Senior Associate, OrbiMed LLC)

Rachel Hong, RN
Agenda Coordinator
New York Health Forum

Rachel is editorial staff of WKMJ and agenda coordinator of New York Health Forum.
She is associate of Business Operations at W Medical Strategy Group.

Yisun Yuk
Manager, Business Operations
W Medical Strategy Group

Yisun is manager of Business Operations at W Medical Strategy Group.
She also is an editorial staff of WKMJ and organizing executive of New York Health Forum.

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Health Forum

6th Forum | June 30th, 2016 1:00 PM - 4:00 PM

"Key Trends in US Biopharma/Medtech Investing"
| *5th Forum | March 31, 2016* |

"Furthering Global Biopharma: Opportunities for Development with East Asia"
| *4th Forum | November 12, 2015* |

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Samsung RA biosimilar EU uptake tied to perceived cost despite physician concerns

- Reference companies may lower drug prices too
- Payers may mandate biosimilar use in tender markets
- Immunogenicity reactions give pause for switching

Samsung Bioepis' three rheumatoid arthritis (RA) biosimilar candidates - SB4, SB2 and SB5 - will lead to pricing wars in the cost-conscious EU once approved, experts said. Anticipated drug costs in turn will impact market uptake but rheumatologists expressed concern they may be shut out of the decision-making process.

Several said they preferred to have patients, especially well-controlled ones, stick with standard of care for fear of immune reactions.

Samsung Bioepis is a joint venture between Samsung Biologics and Biogen (NASDAQ:BIIB).

Benepali, formerly known as SB4, is a biosimilar to Amgen (NASDAQ:AMGN) and Pfizer's (NYSE:PFE) Enbrel (etanercept). It received a positive opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP), according to a 23 November 2015 press release. The company awaits a CHMP opinion on SB2, its biosimilar to Johnson & Johnson's (NYSE:JNJ) Remicade (infliximab). The company will submit an MAA for SB5, its biosimilar to AbbVie's (NYSE:ABBV) Humira (adalimumab), in 2016, according to company information.

This news service reported on 11 December that all three biosimilars are likely to be approved in the EU based on equivalence data.

Samsung did not respond to a request for comment.

Total global sales of Enbrel for all indications peaked in 2015 at USD 8.5bn, according to BioPharm Insight data. Total global sales of Remicade for all approved indications also peaked in 2015 at USD 8.5bn. Total global sales of Humira for all indications are expected to peak in 2018 at USD 17.1bn, according to BioPharm Insight data.

Pricing wars to ensure

The EU is aggressive about trying to save costs so biosimilars - with their anticipated lower sticker prices to originator drugs - are keenly eyed, said Dr Lee Simon, rheumatologist, former division director of analgesic, anti-inflammatory and ophthalmologic drug products, FDA, Cambridge, Massachusetts. If these drugs are priced correctly - and there will be aggressive negotiations - they will get market uptake, he said.

Considering the European introduction already of other biosimilar monoclonal antibodies to Remicade like Pfizer/Hospira's Inflectra and Celltrion's (KOSDAQ:068270) Remsima, a pricing war is inevitable, agreed Steven Bradshaw, managing director & head of European Office, Market Access Solutions, London, UK.

A price decline of 69% for a Remicade biosimilar by Finnish company Orion Oyj in Norway may set the stage for volatile biosimilar pricing negotiations in some countries, said Bradshaw and Tim Riley, CEO, The Wellstate Group, London, UK. These could affect decisions on whether innovators or biosimilars will get the lion share of the market. However, it's unlikely that in the UK, France or Germany there will be such price declines, Bradshaw said, noting that may be unsustainable for biosimilar makers in the long-term. Inflectra/Remsima are about 15-30% lower than Remicade in the aforementioned countries, he added.

As biosimilars come to market, reference product companies lower the price of their drugs, diluting the financial advantage of biosimilars, explained Bradshaw and Dr Rene Westhovens, professor, University of Leuven, Leuven, Belgium. When the competition is gone, the reference companies can raise their prices again, he said.

Innovator companies can also play into brand loyalty for market wars, Bradshaw said. They may make the case there can be assurance of product supply continuity as opposed to manufacturing uncertainty with these newer biosimilar developers, he said. Innovators may also try to steer the market by offering value-added services like at-home devices making administration easier or employ scare-mongering about biosimilar safety or quality, he said.

As biosimilars come to market, reference product companies lower the price of their drugs

Treatment decisions

In a new patient there is no reason not to prescribe a biosimilar, Westhovens said. For many physicians and patients, they prefer to use a drug that's been on the market longer, even if two drugs are considered to be equivalent, Dr Gilberto Castaneda Hernandez, investigator, department of pharmacology, Research Center, Mexico City, Mexico differed.

Physicians want the opportunity to decide how to treat their treatment-naive patients, Westhovens explained. However, eventually some government authorities or hospitals may force rheumatologists to switch patients to biosimilars, he said. Lee added physicians will have little say on biosimilar uptake.

In tender-based markets, payers mandate physicians switch to the lowest-cost products but in others the ultimate choice remains with the physician, Bradshaw said. In the UK, physicians opting for more expensive innovative biologics have to provide compelling justification versus a less expensive alternative, Riley said.

The uptake of biosimilar from country to country will also vary based on patent expiration which differs across countries in the EU, said Dr Jiri Vencofsky, professor of medicine, Charles University, Prague, Czech Republic. In Denmark, Norway, Ireland, the UK and France, biosimilars are recommended to be used first, he added.

In a patient that is well-controlled on Remicade, physicians would prefer not to be obligated to switch to a biosimilar because of the chance of immunological reactions, Westhovens said.

Switching from Enbrel to a biosimilar has less of a chance of negative reaction than Remicade to biosimilar, because Remicade is a chimeric which creates higher immunogenicity, said an investigator at the recent American College of Rheumatology (ACR) conference.

Payers are not so concerned about tolerability issues unless they are particularly egregious, Bradshaw said.

In some cases, uptake may favor the biosimilar, as with Benepali, Hernandez noted. At 52 weeks, there were 52 injection site reactions with Enbrel versus 11 with Benepali, which is typically due to the vehicle and injection device, he explained. It appears Benepali is manufactured with an improved pharmaceutical technology compared to innovator product, therefore patients might prefer Benepali, he said. To actually show preference, a specific study addressing this would be required, however, he added.

Additionally, rheumatologists are excited about the prospect of another option for patients if immunogenicity does become an issue in the originator anti-TNF, said Dr Jean Satish, lecturer, molecular and clinical pharmacology, University of Liverpool, UK.

Rheumatologists also worry that in addition to being forced to switch patients, biosimilars might be approved across indications, or extended to the other indications for which the originator is approved, explained Dr Nathan Wei, rheumatologist, Arthritis Treatment Center, Frederick, Maryland. Just because biosimilars are shown to be equivalent in one indication does not necessarily mean that equivalence can be extrapolated across indications which makes rheumatologists nervous if they perceive payers determine treatment, he explained.

Jennifer C. Smith-Parker

Journalist, London

Jennifer is an award-winning biopharmaceutical industry journalist. Prior to joining BioPharm Insight Jennifer was Associate News Editor at FDA Week, covering FDA regulatory policy for all FDA-regulated product areas. She also worked at The Monitor, where she covered health, environment and science issues and conducted a year-long project on indigent healthcare services. She was awarded the Texas Medical Association's Anson Jones journalism award for an article on breast cancer. Jennifer graduated from New York University with a Bachelor's with Honors in History and Journalism. Follow her on Twitter @JsmithParker

Alissa Fleck

Journalist, New York

Alissa is a former freelance editor and journalist who has been a regular contributor for Bankrate, the Huffington Post, Truthout, Global Post and three Straus News publications in Manhattan. She has written medical and health copy for websites including SF Gate (the San Francisco Chronicle online) and Livestrong as well as for private clients.

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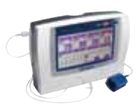
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Biopharmaceutical Report II

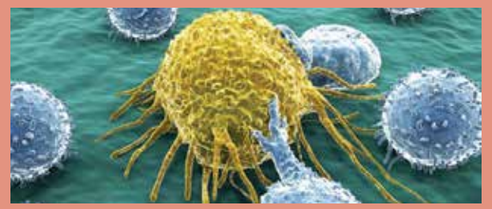
Early CAR-T multiple myeloma data promising, though efficacy, safety remain unclear

- Source of anti-CD19 CAR-Ts' benefit obscure
- Targeting multiple antigens may be necessary, says expert
- Cytokine release syndrome remains a challenge

Chimeric antigen receptor T-cell (CAR-T) therapies for multiple myeloma (MM) drew some cautious expert optimism at the recent meeting of the American Society of Hematology (ASH). However, they also expressed uncertainty about their long-term efficacy, antigen targets and tolerability.

Data from several MM CAR-T studies was presented at the ASH meeting in Orlando, Florida, including clinical data from a National Cancer Institute (NCI) study and preclinical data from Cellectis (EPA:ALCLS), bluebird bio (NASDAQ:BLUE) and academic centers in Germany, Japan and the Netherlands.

Cellectis and bluebird bio did not respond to requests for comment. Novartis (VTX:NOVN), which is also developing its CTL019 for MM but did not present data from its Phase I study (NCT02135406), declined to comment.



Cautious optimism at ASH

CAR-Ts are in very early days, and while they could have a place in myeloma, so far they have not shown as much efficacy as in acute lymphoblastic leukemia, a Massachusetts expert and Dr Yutaka Okuno, associate professor, Department of Hematology, Kumamoto University of Medicine, Japan said. Dr Tomer Mark, associate director, Multiple Myeloma Center, Weill Cornell Medical College, New York, however, expressed optimism about CAR-Ts as potential treatment options for myeloma, saying they could yield long-term remissions.

In Novartis' Phase I study, a patient with refractory MM received CTL019 after myeloablative therapy with the chemotherapy drug melphalan and autologous stem-cell transplantation, leading to a complete response (CR) with no evidence 12 months after treatment of progression or measurable serum or protein associated with the disease in the urine. The CD19-targeting CAR-T's efficacy came despite absence of CD19 expression on virtually 100% of the patient's cells (N Engl J Med 2015; 373:1040-1047).

However, given that patients in the study got stem-cell transplants before CAR-T, it is uncertain whether the efficacy benefit comes from the transplant or the CAR-T, said Dr Rajshekhar Chakraborty, hospitalist, Essentia Health, Brainerd, Minnesota, who is also a research collaborator with the Mayo Clinic in Rochester, Minnesota. Autologous stem-cell transplant is a common treatment used for MM.

In Novartis' Phase I study, a patient with refractory MM received CTL019 after myeloablative therapy with the chemotherapy drug melphalan and autologous stem-cell transplantation

A BCMA-targeted CAR-T developed by the NCI resulted in one of six patients treated at the lowest dose level having a transient partial remission (PR), while the other five had stable disease (SD), according to Phase I (NCT02215967) data presented at ASH (abstract no. LBA-1). At higher dose levels, two patients had SD, while one had a very good PR (VGPR). Of the two patients treated at the highest dose, one experienced a stringent complete remission (CR), while the other did not have detectable bone marrow plasma cells four weeks after infusion.

The reasons for CD19-targeting CAR-Ts' efficacy in myeloma despite the disease not expressing the antigen are unclear, said Okuno and Dr Saad Usmani, director, Plasma Cell Disorders Program, Levine Cancer Institute/ Carolinas Healthcare System, Charlotte, North Carolina. It is possible that myeloma cells pick up some CD19 expression post-transplant, Okuno said. Usmani said it probably has to do with immune modulation and some effects in the bone marrow. Melphalan possibly has some role to play in some of the cytoreduction, but perhaps during immune reconstitution the CAR-T cells are taking immunomodulatory actions where they are causing a much more robust plasma cell cytoreduction, Usmani added.

Many antigens are being explored, Mark noted, and there may need to be different antigens targeted for different patients.

In addition to Novartis' CD19-targeting CAR-T and the NCI's anti-BCMA therapy, Cellectis presented preclinical data on a CS1-targeting CAR-T for myeloma (abstract no. 116); researchers from Japan's Hiroshima University and Miyazaki University presented preclinical data on an anti-CD38 CAR-T (abstract no. 591); and researchers from Würzburg University in Germany presented data on a preclinical CAR-T targeting SLAMF7 (abstract no. 115). bluebird bio's CAR-T also targets BCMA.

Genmab (CPH:GEN) and Johnson & Johnson's (NYSE:JNJ) multiple myeloma drug Darzalex (daratumumab) targets, while Bristol-Myers Squibb (NYSE:BMS) and AbbVie's (NYSE:ABBV) Empliciti (elotuzumab) targets SLAMF7.

A major challenge with CAR-Ts in general is dealing with cytokine release syndrome (CRS), a potentially fatal toxicity, said Usmani. While the current CAR-Ts will suit patients who aren't too sick, tolerability will make them a challenge for the general myeloma population, he said.

Three patients experienced CRS in the aforementioned NCI study.

While CRS has been an ongoing concern with CAR-Ts, it is likely that such kinks will be worked out as later generations of the therapies appear, said Mark.

Cellectis' market cap is EUR 910.7m. bluebird bio's is USD 2.3bn. Novartis' is CHF 219.8bn (EUR 203.4bn).

Alaric DeArment

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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Changing the Channel

Overcoming Crisis : Reproducibility Initiatives

STRATEGY

CHANGING THE CHANNEL

By Mark Zipkin, Staff Writer

Having helped expose the reproducibility crisis about five years ago, Amgen Inc. is staying at the forefront of the issue with its support of *F1000Research*, an open-science platform to let researchers check each other's data. But as the field wrestles with causes and solutions, some academics are starting to bristle at the intrusion.

The issue was sparked by a pair of papers in 2011 and 2012 from Bayer AG and Amgen, respectively, that showed each company could only reproduce a small percentage of published data when the experiments were tried in-house.

Although many companies routinely rerun published experiments to verify them, they rarely go the distance of publishing their findings.

Alexander Kamb, SVP of discovery research at Amgen, told BioCentury there has long been a "culture of publication" at the company that has included publishing negative data, but the environment in the scientific community is changing to make that rarer.

"The nature of the process is more challenging and tends to favor new findings as opposed to reconsideration of something," said Kamb. He added that in the current climate, "more prosaic, disconfirming results aren't so easily published."

Now, Amgen has put its weight behind the efforts of life science publisher Faculty of 1000 (F1000) to address the problem with the launch of the Preclinical Reproducibility and Robustness channel on the publisher's *F1000Research* platform.

On Feb. 4, to mark the channel's launch, Kamb published a joint editorial with Bruce Alberts, former editor in chief of *Science* and an *F1000Research* advisory board member, outlining the goal of the channel as an effort "aimed at strengthening the self-correcting nature of science through the widespread, rapid publication of the failures (as well as the successes) of attempts to reproduce published scientific findings."

The same day, Amgen posted the channel's first three papers in which the biotech documented experimental details of internal studies that refute published findings from four different groups, including one paper from its own scientists.

NAMING NAMES

The channel was the brainchild of Kamb and Alberts. According to Michael Markie, associate publisher at *F1000Research*, the increasing unease in the scientific community about the reproducibility crisis prompted the duo to create an alternative publishing outlet to traditional journals, which routinely prioritize the impact of a study over its rigor.

According to Markie, publishing in the *F1000Research* channel differs from publishing in a journal in several key ways.

> **"It was kind of known in the genomics world that a certain study was quite difficult to believe. It was like the whispers of the conference hall."**
>
> Michael Markie,F1000Research

First is speed to publication: submissions are posted after editorial checks — covering ethical standards, methodology and open access to the data — are performed, but before any peer review.

In addition, publication does not hinge on the potential impact on the field.

Reviewers are solicited once a prepublished study is posted to the channel's site, where readers can also post comments. *F1000Research* authors choose their referees, although the publisher screens the choices to prevent conflicts of interest.

Once three referees approve a paper, *F1000Research* indexes it widely on search engines such as PubMed.

Markie said that although there's still a certain stigma attached to openly contesting published findings, the platform is designed for transparency and dialogue.

The idea that the preclinical research community could go beyond the stigma came from a dispute around results from the Mouse ENCODE Consortium.

In 2014, two papers by the consortium's scientists published in *Nature* and the *Proceedings of the National Academy of Sciences* presented controversial findings on comparative gene regulation data, claiming that the patterns of gene expression data tended to cluster more by species than tissue. The studies contradicted common beliefs in the field.

"It was kind of known in the genomics world that a certain study was quite difficult to believe. It was like the whispers of the conference hall," said Markie.

In 2015, two researchers from the University of Chicago refuted the findings in the Genomics, Computational & Systems Biology subject area of *F1000Research*. After the negative data were posted, four referees — with names attached — approved it, although one approved it with reservations.

According to Markie, the widespread attention prompted a healthy discussion.

"What happened there was a big lively debate with a lot of the key stakeholders in that area of science who all chipped in, in a constructive way," he said, adding that even the original authors contributed to the conversation. "Everything was quite civil."

NEGATIVE FINDINGS

The studies Amgen posted on the new channel address the roles of specific pathways in obesity, neurodegeneration and Alzheimer's disease (AD). All three are still awaiting peer review.

The first challenged a pair of 2012 publications concerning GPR21 in obesity.

A paper in *Biochemical and Biophysical Research Communications* by Amgen researchers reported that GPR21-knockout mice were resistant to diet-induced obesity, and one in *The Journal of Clinical Investigation* from the University of California San

REPRODUCIBILITY INITIATIVES

The low reproducibility of published preclinical research — often dubbed the "reproducibility crisis" — has sparked several initiatives from publicly funded organizations to tackle the underlying causes. The table lists select initiatives launched since 2012. Most highlight training, materials or transparency as keys to increasing rigor in research. *Source: BioCentury Archives; organization websites*

YEAR	INITIATIVE	ORGANIZATION	TYPE	PURPOSE
2016	Preclinical Reproducibility and Robustness channel	**F1000Research**	Online channel	Offer prepublication and peer review for academic and industry researchers seeking an avenue to publish studies confirming or disconfirming earlier data.
2016	Reproducibility2020	**Global Biological Standards Institute** (GBSI)	Action plan	Improve reproducibility by 2020 by promoting improved reagent validation and standardization, improved training, and sharing of data and protocols.
2016	Enhancing Research Reproducibility	**Federation of American Societies for Experimental Biology** (FASEB)	Guidance document	Recommendations to meet new NIH grant guidelines by standardizing definitions, improving reporting of experimental detail and conducting additional training in labs, with a detailed focus on use of mouse models and antibodies.
2015	Enhancing Reproducibility through Rigor and Transparency	**National Institutes of Health** (NIH)	Revised policy on NIH grant applications	Enact more rigorous criteria for grant applicants such as consideration of sex as a biological variable, authentication of key biological and chemical resources, and additional detail on the rigor of planned experiments.
2015	Antibody validation	**Structural Genomics Consortium** (SGC)	Published protocol	Produce a standardized method for assessing and validating antibody quality.
2014	Enhancing Reproducibility through Rigor and Transparency	NIH	Training modules	Grants for development of training modules and video training tools, and funding for intramural workshops, focused on experimental design, appropriate use of techniques, data analysis and interpretation.
2013	The case for standards in life sciences research: Seizing opportunities at a time of critical need.	GBSI	White paper	Address quality of research methodologies, identify areas of concern and recommend the use of standards to improve the reproducibility of preclinical research.
2012	The Reproducibility Initiative	**Science Exchange Inc.**; **Public Library of Science** (PLoS); **figshare**	Virtual organization	Facilitate third-party validation for researchers by finding appropriate academic lab or CRO that can reproduce experiments.

> "There is work that might be defined 'reproducible' in a very narrow sense, but what we're trying to do here is find mechanisms and hypotheses that are robust enough to really make it in the clinic."
>
> Alexander Kamb, Amgen

Diego and Pfizer Inc. showed GPR21 knockout improved insulin sensitivity.

But in Amgen's *F1000Research* findings, new GPR21-knockout mice were generated that did not replicate either of the earlier studies. Instead, the paper suggested the metabolic phenotypes of the original GPR21 knockout mice were due to unintentional changes in expression of a nearby gene, RABGAP1, caused during generation of the knockouts.

Because mouse GPR21 is encoded within a RABGAP1 intron, the *F1000Research* paper's authors thought the neomycin cassette insertion used to generate the original knockout mice might have altered RABGAP1 expression. In the new knockout mice — which were generated via a 29-base pair deletion in GPR21 using transcription activator-like effector nucleases (TALENs) — RABGAP1 expression was unaffected, and the mice showed no improvements in glucose and insulin metabolism compared with wild-type littermates.

The second paper contested a 2010 *Nature* report from a group at Harvard Medical School that suggested USP14 slows the degradation of proteasome substrates such as tau and TDP-43, which play an important role in neurodegenerative diseases.

Whereas the Harvard group's evidence showed a catalytically inactive form of USP14 decreased tau and TDP-43 levels in HEK293 cells compared with functional USP14 — supporting the idea that functional USP14 prevents their degradation — the Amgen team found no difference between the two. In addition, siRNA knockdown of USP14 by the Amgen team did not affect endogenous tau expression in a different cell line.

The Amgen team indicated in its paper that differences in the method, such as the expression vector used, could underlie the discrepancy, and noted that follow-up studies by the Harvard group had failed to show the USP14 effect occurred *in vivo*.

At least one company has been targeting USP14. In 2013, Proteostasis Therapeutics Inc. received a grant from The Michael J. Fox Foundation for Parkinson's Research to develop a USP14 inhibitor to promote clearance of α-synuclein to treat Parkinson's disease (PD), aiming for the clinic in 2015.

In December 2013, Proteostasis announced a partnership with Biogen Inc. to continue development, and in 2014 it received milestone payments from Biogen. Biogen did not respond to requests for comment.

The third paper was the only one to receive a response so far — which highlighted how some in the community are viewing the initiative.

The study centered on results from a 2012 *Science* paper from an academic group headed by Gary Landreth at Case Western Reserve University School of Medicine. Landreth's study used a mouse model of AD, and showed the RXR agonist Targretin bexarotene produced more than 50% reduction of β-amyloid plaque area within 72 hours, reversed cognitive and social behavior deficits, and improved neural circuit function. Landreth is a professor of neurosciences and neurology, and director of the Alzheimer Research Laboratory at Case Western.

The Amgen group treated wild-type Sprague-Dawley rats with Targretin, but detected no significant change in β-amyloid levels after three days or seven days. It did not perform behavioral assays or examine neural circuit function.

In a response posted on *F1000Research*, Landreth argued that the reason for the difference is that the Amgen researchers used "the wrong formulation." In the 2012 study, his group used the clinically approved formulation of Targretin, which is a microcrystalline form of the drug. Amgen's group used a soluble form of the molecule, which Landreth stated would have a different PK profile that would affect its activity.

He added in his response that the importance of the formulation had been well documented in the literature and the FDA filing, and was detailed in a response to four comments on his study published in 2013 in *Science*. He also noted the use of different species in the Amgen study.

> "We don't want it to turn into this 'pharma can't do it' channel."
>
> Michael Markie, *F1000Research*

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> "The pharma/biotech industry doesn't do its own basic research anymore. It relies on research that's paid for by NIH, and yet it screams 'bloody murder' when things go wrong."
>
> Judith Kimble, University of Wisconsin-Madison

"The Amgen scientists (and others) clearly did not make an effort to understand and replicate the original study design," he wrote in his rebuttal on *F1000Research*.

Landreth concluded by stating a "logical flaw" in the Amgen paper undermines its conclusion. "I think this study is emblematic of the problems associated with reporting 'failure to replicate' findings in studies that do not genuinely reproduce the published work," he wrote.

According to Landreth, ReXceptor Inc. licensed options from Case Western on the use of bexarotene in the treatment of AD. ReXceptor did not respond to requests for comment.

At least one other company is developing an RXR agonist: Io Therapeutics Inc. has IRX4204 in Phase I testing for AD and PD.

WHOSE CRISIS?

Since the problem was brought to light by Amgen and Bayer, the academic community has responded with several initiatives to address reproducibility (see "Reproducibility Initiatives").

According to Kamb, to define what constitutes "reproducible," it's important to think about what the data need to support.

"The key thing is that the clinical hypothesis applies robustly in the maelstrom of the clinic," he said. "So there is work that might be defined 'reproducible' in a very narrow sense, but what we're trying to do here is find mechanisms and hypotheses that are robust enough to really make it in the clinic."

At the Global Biological Standards Institute (GBSI)'s annual summit on Feb. 9, keynote speaker Judith Kimble said the two papers kicking off the reproducibility crisis were "a bomb" for biomedical researchers. However, she added, "The first question is, is it true? And I think we don't really know whether or not it's true yet."

Kimble is a professor of biochemistry at the University of Wisconsin-Madison and an investigator at Howard Hughes Medical Institute (HHMI).

Kimble questioned the accuracy of one of the leading points of the summit: a GBSI-backed study published in a June 2015 Perspective in *PLoS Biology* which calculated the costs of irreproducible clinical research at $28 billion.

"Trying to define what is reproducible and what is not — what is a reproducible paper, what is a reproducible panel — is a science in and of itself," said Kimble. But regardless of the exact number, she added, "There are clearly problems."

During her talk, Kimble pointed to a number of well-known causes of irreproducibility, covering inadequate training, problematic stocks, lack of transparency and occasional fraud or misconduct. But Kimble characterized these as symptoms, adding: "The elephant in the room is hypercompetition."

Hypercompetition, she said, has resulted from ratcheting up the healthy competitive pressures of the field to "the point where something starts to break."

"I would say that the system is at that point," she added.

One culprit is the push from scientific publishers, the job market and industry to see that results and publications are clinically relevant, she said. Another driver is the increase in the number of researchers while overall financial funding has decreased, with NIH funding down 30% in constant dollars since 2003.

Although NIH received a budget increase of 3%, bringing its total for FY16 to $31 billion, Kimble said it would require 5% annual increases for the next five years just to get back to 2003 levels, meaning it is unrealistic to expect the public sector alone to solve the hypercompetition issue.

"This bomb that came in 2012 came from the pharma/biotech industry," said Kimble. She added: "The pharma/biotech

industry doesn't do its own basic research anymore. It relies on research that's paid for by NIH, and yet it screams 'bloody murder' when things go wrong."

F1000Research expects more companies besides Amgen will get involved in the channel as it has actively solicited research from industry, and Markie expects several pharmaceutical companies will jointly publish a paper on the channel in the coming weeks. Still, he said, "We don't want it to turn into this 'pharma can't do it' channel."

"Obviously Amgen have taken the leadership position here like they did with the Bayer article a few years ago," said Markie. But he hopes the channel will grow to see 50-100 publications annually, from both industry scientists and academics, "when someone else apart from Amgen has done it."

COMPANIES AND INSTITUTIONS MENTIONED

Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Bayer AG (Xetra:BAYN), Leverkusen, Germany
Biogen Inc. (NASDAQ:BIIB), Cambridge, Mass.
Case Western Reserve University, Cleveland, Ohio
Faculty of 1000 (F1000), London, U.K.
Global Biological Standards Institute (GBSI), Washington, D.C.
Harvard Medical School, Boston, Mass.
Howard Hughes Medical Institute, Chevy Chase, Md.
Io Therapeutics Inc., Santa Ana, Calif.
The Michael J. Fox Foundation for Parkinson's Research, New York, N.Y.
Mouse ENCODE Consortium, Stanford, Calif.
National Institutes of Health (NIH), Bethesda, Md.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Proteostasis Therapeutics Inc. (NASDAQ:PTI), Cambridge, Mass.
ReXceptor Inc., Cleveland, Ohio
University of California San Diego, La Jolla, Calif.
University of Chicago, Chicago, Ill.
University of Wisconsin-Madison, Madison, Wis.

TARGETS AND COMPOUNDS

GPR21 - G protein-coupled receptor 21
RABGAP1 - RAB GTPase activating protein 1
RXR - Retinoid X receptor
SNCA - α-synuclein
tau (MAPT; FTDP-17) - Microtubule-associated protein τ
TDP-43 (TARDBP) - TAR DNA binding protein 43
USP14 (TGT) - Ubiquitin specific peptidase 14 tRNA-guanine transglycosylase

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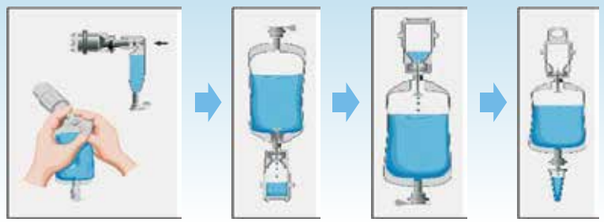

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FOLLOW THE JOURNEY OF VIREAD

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.

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...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.

Conference Alerts

North America

The Society for Healthcare Epidemiology of America (SHEA) Spring Conference 2016—Science Guiding Prevention

May 18-21, 2016 | Atlanta, Georgia USA

Website: http://sheaspring.org/attendees/registration/

Contact: info@shea-online.org

The SHEA 2016 Planning Committee combines the expertise of SHEA members who have served on SHEA meeting planning committees for many years and active leaders from the SHEA Education Committee. The conference includes broad subject matter expertise in healthcare epidemiology, long-term care, research methods, clinical microbiology, patient safety and quality, implementation science, and networking and communication.

5th Antiviral Drugs Research & Development Conference

June 1-2, 2016 | San Diego, California USA

Website: https://www.gtcbio.com/conferences/antiviral-drugs-research-development-overview

Contact: infogtcbio@gtcbio.com

This conference will bring together an exciting balance of industry and academia, where drug and vaccine designs in HIV, RSV, Hepatitis B/C, Influenza, etc. will be discussed. Top researchers will share their experiences with new inhibitory mechanisms, longer acting drugs, and strategies en route for cures. Delegates have the unique opportunity to network with colleagues from different sectors and gain fresh perspective on the research in antiviral drugs.

14th Vaccines Research & Development: All Things Considered

June 2-3, 2016 | San Diego, California USA

Website: https://www.gtcbio.com/conferences/vaccines-research-development-overview

Contact: infogtcbio@gtcbio.com

Newly emerging infections have opened up dialogue about the need for novel treatments and government response to such infections. There are a number of exciting new developments including traditional vaccines and application of vaccines to new diseases, such as cancer vaccines. We will also discuss innovative efficacy trials and how to accelerate vaccine development. This conference will discuss newly licensed vaccines, new vaccine technologies, RNA-based vaccines, and adjuvant discovery.

2016 ASCO Annual Meeting | Collective Wisdom: The Future of Patient-Centered Care and Research

June 3-7, 2016 | Chicago, Illinois USA

Website: http://am.asco.org/

Contact: customerservice@asco.org

The goal of the 2016 ASCO Annual Meeting is to foster communication among oncology-related subspecialties and the exchange of a wide range of ideas related to cancer. ASCO's objectives are to advance the education of physicians and other professionals caring for patients with cancer, to support the development of clinical cancer researchers, and to facilitate the delivery of high-quality healthcare to patients with cancer.

2016 BIO International Convention

June 6-9, 2016 | San Francisco, California USA

Website: http://convention.bio.org/

Contact: convention@bio.org

The BIO International Convention (BIO) attracts over 15,000 biotechnology and pharma leaders who come together for one week of intensive networking to discover new opportunities and promising partnerships. This event covers a wide spectrum of life science and application areas including drug discovery, biomanufacturing, genomics, biofuels, nanotechnology and cell therapy.

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: (202)776-0544 MD

The ASH Annual Meeting provides an invaluable educational experience and an opportunity to review thousands of scientific abstracts highlighting updates in the hottest topics in hematology. Network with top minds in the field, as well as a global community of more than 20,000 hematology professionals from every subspecialty.

Europe

Understanding the Function of Human Genome Variation

May 31-June 4, 2016 | Uppsala, Sweden

Website: http://www.keystonesymposia.org/16K1

Contact: info@keystonesymposia.org

The goal of this meeting is to bring together experts that may address important questions such as the function of noncoding variation, the connection between selection and disease, the diverse action of variants in different physiological and pathological scenarios, who develop and apply novel tools to connect genotype and phenotype both in disease and in an evolutionary context.

Translational Vaccinology for Global Health

October 26-30, 2016 | London, United Kingdom

Website: http://www.keystonesymposia.org/16S1

Contact: info@keystonesymposia.org

This conference aims to bring together those pioneering novel, creative solutions to problems of global vaccine discovery and development across the academic/biotech/product development partner/pharma spectrum.

Asia

The 36th Annual Meeting of the Korean Society of Nephrology

June 2-5, 2016 | Seoul, Republic of Korea

Website: http://www.ksn2016.kr/eng/

Contact: ksn2016@ksn2016.kr

The KSN2016 will provide a four-day program replete with various topics of nephrology. The topics will range from basic research, clinical nephrology to advanced technology of dialysis. Parallel sessions will be open for pediatric nephrologists, dialysis nurses and technicians.

The 33rd World Congress of Internal Medicine

August 22-25, 2016 | Bali, Indonesia

Website: http://www.wcimbali2016.org/index.php

Contact: wcim2016ser@pharma-pro.com

The International Society of Internal Medicine (ISIM) was founded in 1948 in Basel, Switzerland. Its purpose is to promote scientific knowledge and unity in Internal Medicine, to further the education of young internists and to encourage friendship between physicians in all over the world. The conference is organized biennially and it focuses on subjects like medical, internal medicine, chemical biology and health care.

ISPOR 7th Asia-Pacific Conference

September 3-6, 2016 | Suntec City, Singapore

Website: http://www.ispor.org/event/index/2016singapore

Contact: info@ispor.org

The ISPOR Asia-Pacific Congress features 3 thought-provoking plenary sessions and more than 600 presentations in the form of workshops, issue panels and podium presentations plus posters on innovative research methods, health policy development using outcomes research, patient preferences, real world data, clinical, economic, and patient-reported outcomes.

International Continence Society 46th Annual Meeting (ICS 2016)

September 13-16, 2016 | Tokyo, Japan

Website: http://www.ics.org/2016

Contact: reg_ics16@kenes.com

The meeting is an international event on continence medicine and care. It is unique in bringing together multidisciplinary professionals including urologists, gynecologists, neurologists, physiotherapists, nurses, physiologists and scientists. The topics discussed will be issues on pathophysiology, diagnosis and management of incontinence. The scope of the meeting will widely range from basic laboratory/animal experiments to surgical, physical and medical treatments to psychosocial aspects of elimination problems.

The 9th Asia Pacific Heart Rhythm Society Scientific Session

October 12-15, 2016 | Seoul, Republic of Korea

Website: http://www.aphrs2016.com/start.asp

Contact: aphrs2016-info@intercom.co.kr

APHRS 2016 will bring together over 3,000 attendees including professionals and experts from the Asia Pacific region to keep up-to-date on the latest clinical trials and studies in the sphere of arrhythmia, share their experience, ideas and strategies, and to discuss the current issues facing those involved in this field.

March - April

1. F.D.A. Toughens Warning Labels for Some Opioid Painkillers

The Food and Drug Administration is now requiring new warning labels for certain types of opioid painkillers. The agency said the changes would mostly apply to immediate-release opioids—usually intended for use every four to six hours—and would include new boxed warnings, the agency's strongest type, about the risks of abuse and death. Back in 2013, the agency toughened labeling requirements for extended-release opioids, which are often seen as a bigger addiction risk because of their potency. All the changes announced by the FDA would apply to 87 brand-name drugs and 141 generics. The new labeling requires that drugs should be reserved for pain severe enough to require opioid treatment and for which alternative treatment options are inadequate or not tolerated. The new labels also include "clearer instructions" for directions like initial drug dose and dose changes during therapy. But officials said there were no dose thresholds given, or maximum amounts, which some addiction specialists had been calling for.

http://www.nytimes.com/2016/03/23/health/fda-toughens-warning-labels-for-some-opioid-painkillers.html?_r=1

2. Report Shows Theranos Testing Plagued by Problems

According to an inspection report released by federal regulators, medical testing done by the medical start-up Theranos was plagued by quality control problems that could have led to inaccurate results for patients. Among other findings in the report, the company used unqualified or inadequately trained personnel and stored samples in freezers that were not at the proper temperature. It also failed to ensure that the quality control for an important blood-clotting test was acceptable before reporting results for patients. The report is from an inspection last fall of Theranos's laboratory in Newark, Calif., by the Centers for Medicare and Medicaid services, which regulates clinical laboratories.

http://www.nytimes.com/2016/04/01/business/report-shows-theranos-testing-plagued-by-problems.html

3. Pfizer Confirms Termination of Proposed $160 Billion Allergan Merger

Pfizer Inc. and Allergan Plc terminated their $160 billion merger after the U.S. government proposed regulations to crack down on corporate tax inversions. Both companies blamed the U.S. Treasury Department proposal for ending the deal, and Pfizer said in a statement that it will pay Allergan $150 million in reimbursement for expenses associated with the failed transaction. The termination represents a victory for the Obama administration, who proposed tougher-than-expected new rules aimed at making inversions like the Pfizer-Allergan deal harder to achieve. In an inversion, a U.S. company shifts its tax address overseas, often through a merger. Allergan, which is run from New Jersey but has a legal domicile in Dublin, agreed last year to merge with Pfizer in a deal that would have given the U.S.-based company an Irish address and a lower tax rate. By combining with Ireland-based Allergan, Pfizer could also get access to the billions of dollars in revenue it was keeping overseas in order to avoid paying U.S. taxes on top of the taxes it had already paid in foreign countries.

http://www.bloomberg.com/news/articles/2016-04-06/pfizer-allergan-end-160-billion-merger-amid-new-tax-rules

4. Allergan signs $3.3bn deal with Heptares

Allergan has signed a $3.3-billion deal with Heptares for access to the UK-based group's portfolio of experimental neurological therapies. The Dublin, Ireland-headquartered firm has bought global rights to a portfolio of novel subtype-selective muscarinic receptor agonists in development for the treatment of major neurological disorders, including Alzheimer's disease. Under the deal, Heptares, a wholly-owned subsidiary of Sosei, will bank an upfront payment of $125 million from Allergan, and also stands to receive contingent milestone payments of up to around $665 million linked with clinical development and launch of the first three licensed compounds for multiple indications, as well as $2.5 billion on achieving certain annual sales thresholds.

http://www.pharmatimes.com/Article/16-04-10/Allergan_signs_3_3bn_deal_with_Heptares.aspx

5. FDA Panel Votes Against Approving Clovis's Cancer Drug on Current Data

An independent panel of experts advising the U.S. Food and Drug Administration recommended that Clovis Oncology Inc.'s lung cancer drug not be approved based on existing trial data. The panel voted 12 to 1 against giving the drug an accelerated approval, and recommended the FDA wait for the results from an ongoing late-stage trial that compares the drug's effect to that of chemotherapy. An accelerated approval would allow Clovis to conditionally market the drug, Rociletinib, based on early evidence of its clinical benefit. Rociletinib is designed to treat a subset of patients with advanced non-small cell lung cancer whose condition has worsened despite treatment. It targets patients with a genetic mutation known as T790M that helps tumors evade current lung cancer pills. The panel said existing data on Rociletinib did not adequately characterize its benefit-risk profile over current treatment and also expressed uncertainty about the proposed dose. The FDA is expected to announce its final decision on the drug by June 28.

http://www.reuters.com/article/us-clovis-oncology-fda-idUSKCN0X920A

6. Sean Parker Donates $250 Million to Launch Cancer Immunotherapy Institute

Silicon Valley billionaire Sean Parker will donate $250 million to launch the Parker Institute for Cancer Immunotherapy, which aims to develop more effective cancer treatments by fostering collaboration among leading researchers in the field. The new institute will focus on the emerging field of cancer immunotherapy, which harnesses the body's immune system to fight cancer cells. It will include over 40 laboratories and more than 300 researchers from six key cancer centers across the United States including New York's Memorial Sloan Kettering and Stanford Medicine.

http://www.nbcnews.com/health/cancer/sean-parker-donates-250-million-launch-cancer-immunotherapy-institute-n555196

7. U.S. Drug Spending Climbs

In 2015, the total spending on prescription drugs in the U.S. rose 12.2% to nearly $425 billion, continuing a steep climb fueled by the introduction in recent years of expensive new drugs for cancer and infections, as well as price hikes for older drugs. The spending growth rate decelerated from the 14.2% rise in 2014, partly because of patient expirations for certain drugs, but the growth was still well above the average for the past decade, according to a research arm of IMS Health that produces the annual report on spending. IMS estimated that after rebates and other price breaks, manufacturers received $309.5 billion for U.S. prescription drugs last year, up 8.5% from 2014. The higher total spending figure—$425 billion—is based on the list prices that pharmacies and hospital customers pay drug-wholesale distributors. And while the average list price for patent-protected brands rose 12.4% last year, the net price growth after discounts was 2.8%. Politicians, health-care payers, doctors and patients have increasingly criticized drug pricing in the past year, saying medicines are out of reach for many patients and are straining health-care budgets.

http://www.wsj.com/articles/u-s-drug-spending-climbs-1460606462

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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