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Marking Milestones in Therapeutic Agents for AMD and Stargardt Disease

Ever since he began researching a therapeutic agent to retard the course of dry-form age-related macular degeneration (AMD) and Stargardt disease, **Konstantin Petrukhin, PhD**, has surpassed expectations. He identified not one but several lead compounds with drug development potential. He singled out two of the most promising compounds, one of which will soon be produced for clinical trials. And, he isolated a serum biomarker that demonstrates compound activity in animal models and therefore suggests effectiveness in humans. Moreover, he achieved these milestones faster than anyone would have imagined.



Ophthalmoscope image of macular degeneration shows numerous yellow drusen spots on the retina.

Since 2011, Dr. Petrukhin has belonged to the National Institutes of Health's (NIH) Blueprint Neurotherapeutics Network, a five-year program that supports investigators in their efforts to develop new drugs. In addition to funding his research, the Blueprint Network has been providing Dr. Petrukhin with millions of dollars in services typically earmarked for pharmaceutical companies. These services include the assistance of pharmaceutical and biotechnology industry consultants throughout the drug development process, from chemical optimization, to biological testing, to early-stage clinical trials.

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Identifying Concerns over Dosage Variations in Widely Used Eye Drug

Research by investigators at NewYork-Presbyterian/Weill Cornell Medical Center have found that custom-made versions of a widely prescribed, low-cost drug used to prevent a leading cause of blindness in the elderly vary widely in their dosages. While they saw no evidence of impurities or contamination, they did find that many of the samples, which were prepared by pharmacists through compounding, contained less medication than doses of the drug obtained directly from the manufacturer. The research, published in the *JAMA Ophthalmology*, is likely to increase scrutiny of compounding pharmacies, which tailor-mix drugs for individual patients, and to question whether eye care specialists should continue to prescribe the cancer drug Avastin® for age-related macular degeneration (AMD).

"Our evaluation showed significant differences in doses of compounded Avastin, as well as lower drug levels overall compared to Avastin that came from the manufacturer. This is troubling because

"The wide variations in the Avastin doses in the various samples suggest that, in clinical practice, some patients who are 'nonresponders' may simply have been underdosed, and other patients may have received higher doses than recommended. Clearly, greater precision is needed to provide the best care for our patients."

— Dr. Donald J. D'Amico

the prescribed dosing regimen potentially won't produce the desired therapeutic response, or may put a patient's health at risk," says lead author **Szilárd Kiss, MD**, an ophthalmologist at NewYork-Presbyterian/Weill Cornell whose primary focus is the surgical and medical management of adult and pediatric vitreoretinal disorders.

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Marking Milestones in Therapeutic Agents for AMD and Stargardt Disease (continued from page 1)

Under the terms of his funding agreement, and to maintain access to Blueprint resources, Dr. Petrukhin and his co-investigators must meet a new research milestone every six months. They have done more than that. As **George A. (Jack) Cioffi, MD**, Chairman of the Department of Ophthalmology, NewYork-Presbyterian/Columbia University Medical Center, notes, “They have met or exceeded every milestone every step of the way.”

Dr. Petrukhin, an Associate Professor of Ophthalmology, acknowledged that these six-month milestones are very unusual, but meeting them is the only way to make sure taxpayers’ money is being spent the right way. The NIH Steering Committee that oversees the project can terminate funding at any time during the grant period if the milestone objectives are not met.

Dry-form AMD and Stargardt disease occur when photoreceptor cells in the eye degenerate. This deterioration is believed to stem partly from the toxicity produced by derivatives of retinol, which is needed for vision. Dr. Petrukhin and his team are studying compounds that would reduce the levels of toxic retinoids in the eye.

They began their research by optimizing a single compound: transforming its chemical structure into a drug that they tested *in vitro* and *in vivo*. One of their first milestones was to identify the compound’s absorption, distribution, metabolic, and excretion properties. The milestone also involved establishing a “clean off-target” profile to make sure the compound would not react with other proteins. “Over a period of three years, more than 400 analogs of the compound were synthesized and characterized in *in vitro* and *in vivo* efficacy assays,” Dr. Petrukhin explains. From these analogs, he identified a handful of advanced lead compounds belonging to different structural classes that he will continue studying as potential therapies for dry-form AMD and Stargardt disease.

Another major early milestone was the validation of serum retinol-binding protein 4, RBP4, a serum biomarker that can prove compound activity in animal models and help determine an effective

dose in human clinical trials. RBP4 concentration is easily measured in patients’ blood samples. Biomarkers are very important in drug trials because they allow clinicians to determine if the drug is working in advance of changes in the eye. Administration of test compounds identified in the Blueprint project should reduce the concentration of serum RBP4 which, in turn, correlates with inhibition of atrophic lesion growth in a patient’s retina. Researchers administered their advanced lead compounds in rats, mice, and monkeys, and demonstrated remarkable reduction of RBP4 levels in the animals’ blood. The reduction of RBP4 in a mouse model of Stargardt disease correlated with the profound inhibition of the accumulation of cytotoxic retinoid derivatives in the retina.



Dr. Konstantin Petrukhin

Dr. Petrukhin notes that the availability of this easily measurable serum biomarker will be important for future clinical development. “In the absence of a biomarker, you have to wait for results of Phase II clinical trials before you see evidence of drug activity,” he says. “In our case, a simple blood test will tell us from day one of a Phase I clinical trial whether the drug is working as expected.”

To meet their most recent milestone, Dr. Petrukhin and his co-researchers had to characterize advanced lead compounds

and then nominate a single pre-clinical candidate for Investigational New Drug-enabling studies. From the more than 400 analogs comprising five novel structural classes, they identified two advanced lead compounds with exceptional *in vivo* and *in vitro* properties.

Biomarkers are very important in drug trials because they allow clinicians to determine if the drug is working in advance of changes in the eye.

“The two compounds are so potent, interesting, and good-looking that the NIH Steering Committee agreed to support parallel preclinical characterizations of two advanced leads for a very short time, so compound prioritization can be done after additional toxicology studies,” Dr. Petrukhin says. “Because the two compounds are so perfect, it’s impossible to decide at this point which one will be produced for clinical trials.” Once a single compound is chosen, the researchers will produce kilogram quantities of a drug candidate with which to conduct the required additional preclinical development studies and begin Phase I clinical trials. Trials are expected to begin one year from now.

While Dr. Petrukhin’s main goals are to find therapies for dry-form AMD and Stargardt disease, the benefits of his research extend beyond drug development. He says, “My research is important for gaining new basic knowledge about retinoid metabolism in the eye and for defining the role of RBP4 in the pathogenesis of other disorders, such as diabetes and obesity, where it may play an important role.”

[Article by Andrea Kott reprinted with permission from Spring/Summer 2014 issue of *Viewpoint*, Department of Ophthalmology, NewYork-Presbyterian/Columbia University Medical Center]

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Identifying Concerns over Dosage Variations in Widely Used Eye Drug (continued from page 1)

“Although there were no signs of contamination, these findings raise legitimate concerns about the quality practices of compounding pharmacies.”

Pharmacy compounding is the practice of creating customized, prescription medications to meet individual patients’ needs. At the request of a physician or other healthcare provider who is authorized to write prescriptions, a licensed pharmacist alters ingredients in drugs, such as removing allergy-causing dyes or preservatives or preparing an alternative dosage form to make it easier for patients to take their medications. An estimated 3,000 compounding pharmacies fill more than 30 million prescriptions a year in the United States.

Many ophthalmologists use Avastin, which is only approved by the U.S. Food and Drug Administration to treat cancer, as an off-label treatment for AMD, retinal vein occlusion (RVO), diabetic macular edema (DME), and other similar eye conditions. Compounding pharmacists divide the drug, which for cancer patients is typically injected into a vein, into multiple smaller doses that are then injected into the eye. Doctors and patients have no other way of obtaining Avastin for off-label use to treat these eye diseases other than through compounding pharmacies.

When injected into the eye, Avastin (bevacizumab) stops blood vessels from leaking and growing. Two similar medicines, Lucentis® (ranibizumab) and Eylea® (aflibercept), are FDA-approved for this serious, sight-threatening “wet” form of AMD, but cost approximately 40 times more per dose than Avastin. Many doctors prescribe Avastin for AMD, RVO, and DME because of the significant, potential cost savings to patients and insurers. But in recent years, several compounding pharmacies have sold tainted drugs, including Avastin, which have blinded and sickened hundreds of patients.

In the study, researchers obtained three Avastin samples prepared in syringes from 11 compounding pharmacies from around the United States. Two samples from each pharmacy were tested for protein concentration (to measure the average amount of drug in the syringe), while the remaining 11 samples were tested for contaminants. The researchers compared individual doses of compounded Avastin to samples obtained directly from the drug manufacturer, Genentech – formulations identical to those compounding pharmacies buy from the company to make eye injections. They found 17 samples with significantly less drug than the respective Genentech doses (and less than what was stated on the compounding pharmacy label), as well as one syringe that was completely empty, containing absolutely no medication at all.

The researchers also compared protein concentrations of the two samples from each pharmacy. They observed significantly different drug levels between the samples in three of 10 facilities.



Dr. Szilárd Kiss

None of the samples tested positive for bacteria or other impurities.

“The study sharpens our understanding of the complexities of selecting the appropriate treatment for patients suffering from AMD or other diseases that affect blood vessels in the eye,” says co-author **Donald J. D’Amico, MD**, Ophthalmologist-in-Chief at NewYork-Presbyterian/Weill Cornell, and an internationally recognized leader in the field of vitreoretinal surgery. “It adds a new and critical element to the national debate regarding the efficacy, costs, and safety of off-label Avastin compared to similar, on-label medications – namely, a careful analysis of what is actually in the Avastin syringe obtained from a compounding pharmacy.

“Although, reassuringly, all of the syringes in our study were contaminant-free, the wide variations in the Avastin doses in the various samples suggest

that, in clinical practice, some patients who are ‘nonresponders’ may simply have been underdosed, and other patients may have received higher doses than recommended. Clearly, greater precision is needed to provide the best care for our patients,” adds Dr. D’Amico.

Dr. Kiss is encouraged that the federal government is actively addressing deficiencies in the pharmacy-compounding industry through tighter controls and regulations, such as new manufacturing rules, routine inspections of facilities, and self-reporting of adverse side effects. Compounders are licensed and regulated by their respective state boards of pharmacy, but a law passed in 2013 – the Drug Quality and Security Act – enforces new quality control guidelines and increased federal supervision to guard against unsafe and sometimes illegal compounding practices. To help reduce treatment costs, scientists also have proposed further research exploring whether fewer injections of the more expensive AMD drugs work as well as Avastin.

“I’m hopeful the legislation will maintain patient access to needed compounded drugs while ensuring the predictability and reliability of these medications. This should raise the level of confidence among pharmacies, providers, and their patients,” says Dr. Kiss.

Reference Article

Yannuzzi NA, Klufas MA, Quach L, Beatty LM, Kaminsky SM, Crystal RG, D’Amico DJ, Kiss S. Evaluation of compounded bevacizumab prepared for intravitreal injection. *JAMA Ophthalmology*. 2014 Sep 18. [Epub ahead of print]

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Prominent Glaucoma Specialist Joins Columbia Ophthalmology

In January 2015, **Jeffrey M. Liebmann, MD**, joined the Department of Ophthalmology at NewYork-Presbyterian/Columbia University Medical Center as Vice Chair of Ophthalmology and Director of Glaucoma Services. A leading clinician and researcher in glaucoma for nearly three decades, Dr. Liebmann currently maintains one of the busiest tertiary care glaucoma practices in the country. At NewYork-Presbyterian/Columbia, he will expand the clinical, research, and teaching programs in glaucoma.

“Dr. Liebmann’s recruitment signifies our commitment to further develop excellence in every subspecialty within ophthalmology and is a game changer for our institutions,” says G.A. Cioffi, MD, Chair of Ophthalmology and Ophthalmologist-in-Chief, NewYork-Presbyterian/Columbia.



Dr. Liebmann most recently served as Director of Glaucoma Services at Manhattan Eye, Ear, and Throat Hospital and NYU Langone Medical Center. In addition to his clinical expertise, Dr. Liebmann brings to NewYork-Presbyterian/Columbia a robust research program that includes studies on the causes and risks of glaucoma, rate of progression,

glaucoma surgery, ocular imaging, and neuroprotection. He is currently a principal investigator for two multicenter National Eye Institute Clinical Trials sponsored by the National Institutes of Health evaluating the relationships between changes in the structure and function of the optic nerve and the genetics of glaucoma progression leading to vision loss. Dr. Liebmann will continue this work at Columbia.

“The physicians and scientists at Columbia excel in the care they provide and the research they pursue to prevent unnecessary loss of vision from this disease,” says Dr. Liebmann. “I look forward to integrating their scientific and clinical acumen with my current research programs, which will provide a significant opportunity to rapidly advance our understanding of glaucoma and revolutionize the way it is detected and treated.”

Dr. Liebmann currently serves as President of the World Glaucoma Association, Secretary/Treasurer of the New York Glaucoma Society, and co-editor of the *Journal of Glaucoma*. He is a Past President of the American Glaucoma Society and currently a member of the Board of Governors of the World Glaucoma Association and Boards of Directors of The Glaucoma Foundation and the American Glaucoma Society Foundation.

Dr. Liebmann completed his ophthalmology residency at the State University of New York/Downstate Medical Center, and glaucoma fellowship training at The New York Eye and Ear Infirmary. He has authored or co-authored more than 1,000 scientific publications and abstracts, and lectures extensively in the United States and abroad on glaucoma diagnosis, management, and research.

“Two to three percent of our population has glaucoma, and a larger proportion is at risk,” says Dr. Liebmann. “With longer life expectancy, the risk of visual impairment and blindness due to this disease is greatly increasing. Through our research, we hope to better understand glaucoma’s rate of progression and innovate ways to mitigate the loss of vision. The field of ophthalmology is going to experience many changes over the next few years, with a focus on using genetic information, risk factor assessment, and personalized medicine to target and treat individuals at the greatest risk. These are some of the ‘big picture’ topics that we really want to tackle.”