

Ocular Drug Delivery Via Micro- and Nanoparticles

A proprietary noninflammatory particle platform may unlock the potential to deliver large- and small-molecule therapeutics.

AN INTERVIEW WITH MICHAEL O'ROURKE AND JUSTIN HANES, PhD

The delivery of ocular therapeutics via microparticles or nanoparticles offers a unique opportunity to encapsulate drug within polymer particles that degrade over time and slowly release drug close to the point of pathology inside the eye. Much of the work on candidate products in this sphere has centered on the use of poly(lactic-co-glycolic acid) PLGA, a copolymer used in a number of drugs and devices approved by the US Food and Drug Administration, including an injectable ocular implant already on the US market. However, PLGA particles can induce an inflammatory response in the eye, thus limiting their use to treat ocular diseases.

One company, GrayBug, says it has “solved the problem of inflammation associated with PLGA particles” through development of a patented proprietary bio-erodible particle formulation, according to the company’s president and CEO Michael O’Rourke. This has facilitated the creation of a drug delivery platform potentially capable of delivering small- and large-molecule drugs, including proteins, safely and effectively to the back of the eye in a minimally invasive fashion that would also extend the duration of the drug’s effect while reducing the need for retreatment. Yet, GrayBug’s strength may lie in the fact that the company is simultaneously developing promising candidate drugs for the treatment of various ocular diseases that can be packaged within this unique delivery mechanism.

Retina Today recently interviewed Mr. O’Rourke and Justin Hanes, PhD, founder and chief scientific officer of

GrayBug, to learn about the company, its technologies, the rationale for nano- and microparticle drug delivery, and GrayBug’s plans for development.

MICHAEL O’ROURKE

Retina Today: Could you share a little bit about how GrayBug was formed and what the company’s business objective is?

Michael O’Rourke: GrayBug was formed in September 2011 by Justin Hanes, PhD, who is the director of the Center for Nanomedicine and the Lewis J. Ort Professor of Ophthalmology at the Wilmer Eye Institute of Johns Hopkins and an expert in extended release drug delivery, including small to large molecules, along with Peter J. McDonnell, MD, who is the Director and William Holland Wilmer Professor of Ophthalmology at the Wilmer Eye Institute at Johns Hopkins, and Peter Campochiaro, MD, the George S. & Dolores Doré Eccles Professor of Ophthalmology and Neuroscience at Johns Hopkins. It was started as an ophthalmic pharmaceutical company focused on developing breakthrough therapeutics and propriety injectable drug-delivery platforms.

The strategy behind GrayBug is to develop 2 major business initiatives: To provide drug delivery platforms that enable longer intervals between intraocular injections commonly used for eye diseases, and to develop new therapeutics using our drug delivery platforms. This is a different business model from conventional drug delivery companies who may concentrate on the tech-

nology and then try to partner with a drug company somewhere.

The real catalyst behind GrayBug is a proprietary particle formulation that can be used with various polymers, including PLGA, in the creation of microparticles and nanoparticles that are far less inflammatory to the ocular tissues than other conventional particle formulations.

RT: In what ocular disease states is GrayBug currently doing active research and what is the market opportunity? What is the unmet need that GrayBug is attempting to address?

Mr. O'Rourke: Significant unmet needs exist in the treatment of wet age-related macular degeneration (AMD), diabetic retinopathy, and glaucoma. If you look at intraocular drug delivery devices, only 4 products have been approved to date. Vitrasert (ganciclovir; recently discontinued), Retisert (fluocinolone acetonide; Bausch + Lomb), and Ozurdex (dexamethasone; Allergan); a fourth product, Iluvien (fluocinolone acetonide; Alimera Sciences) is approved in Europe. But none of these implants is used to treat wet AMD.

The second big opportunity is that even with 2 approved products on the market for wet AMD, Lucentis (ranibizumab; Genentech) and Eylea (aflibercept; Regeneron), which have been extremely successful, they are still not ideal because they do not have extended drug delivery capability. This opens up a whole new category of potential products that need to be long acting—lasting 4 to 6 months or longer—with potential to treat a broad range of diseases, while not causing inflammation in the eye.

The long-standing problem with intraocular injections to treat serious eye diseases is the frequency of injections. In most cases, injections must be done every 4 to 8 weeks. Past attempts at prolonging the interval between injections have failed. GrayBug has developed a technology to solve this problem, providing the potential of injections every 4 to 6 months, dramatically improving compliance and reducing risks associated with repeated intraocular injections. In addition, GrayBug is applying its novel technology to a best-in-class compound that blocks 2 key pathways of neovascularization in wet AMD, VEGF and PDGF. This product has the potential to replace the combination therapies being developed today, as well as reduce the frequency of injections to twice per year. With the capital raised from a planned Series B, GrayBug will validate its technology and first product in clinical trials in patients with wet AMD.

Another totally untapped market potential is in

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—Michael O'Rourke

glaucoma. The vast majority of glaucoma patients are treated with multiple eye drops, and there are no extended release products for treating glaucoma. Although the primary focus of GrayBug at the moment is wet AMD, there is potential with our technology to look at glaucoma, in particular neuroprotection, where GrayBug's proof of concept has been demonstrated with several drug candidates.

RT: Other than the proprietary technology being developed, how is the GrayBug approach different from other companies developing products in this sphere?

Mr. O'Rourke: We think that we have found an elite compound that is going to completely separate GrayBug from the competition, and we have a world-class team behind us.

GrayBug really presented its case by developing its proof of concept in 5 different animal models across wet AMD, open-angle glaucoma, and corneal graft rejection. From this, we know that GrayBug's technology works, and it works well with various types of drugs. That includes steroids, intraocular pressure-lowering drugs, neuroprotection drugs, and antiangiogenic drugs, like the combination anti-VEGF and anti-PDGF compound we are developing for use in wet AMD. We have tested all these drugs in our drug delivery platforms, and so far in animal models they have produced excellent results. In addition, we have shown that inflammation associated with our particles is the same as saline.

A real distinguishing factor for GrayBug, in my opinion, is the team of scientific experts we have in house and those we collaborate with. Our team has over 100 peer-reviewed publications on the delivery of large molecules, including proteins and other biologics. That is a huge asset for a small company to have.

Our capabilities actually lend us some flexibility to partner with external sources as well. If a major pharma company wanted to consider a partnership

with GrayBug, they could say “we have a drug, let’s see if it works in your technology.” We could be open to that. It really means that we have our own proprietary products with the GrayBug technology with our own drugs, but there are also business development opportunities in which we are open to discussions about collaborations.

RT: Can you talk a little bit about GrayBug’s ophthalmic pipeline? Where are your various assets at the current time in terms of development?

Mr. O’Rourke: Our lead product for wet AMD is called GB-102, a compound that is both anti-VEGF and anti-PDGF that we are targeting to last up to 6 months in humans. Our projection is an Investigational New Drug application in late 2015. GB-102 could also be used to treat diabetic eye diseases. We are in the preclinical stage in which we are doing animal work with many of our compounds. A second priority for GrayBug is GB-202, a long-lasting glaucoma treatment, as well as GB-203 and GB-204, which also have potential in glaucoma. GrayBug also has a product in development for corneal transplant, GB-301.

RT: Other than ocular pathologies, in what other disease states is GrayBug actively pursuing development?

Mr. O’Rourke: We have published data on a long-lasting and potent HIF1 inhibitor, and we have shown that it works well in wet AMD, but there may actually be a bigger opportunity in oncology. There are not any extended-release preparations on the market that could enhance the treatment of cancer by effectively suppressing tumor neovascularization. If one combines GrayBug technology with an HIF1 inhibitor like doxorubicin and delivers it into the tumor in a sustained fashion, it could lead to great antitumor efficacy.

JUSTIN HANES, PhD

RT: How is drug delivered to the retina via microparticles and/or nanoparticles? How does this concept work?

Justin Hanes, PhD: The way that we are doing that is not much different from a standard injection such as ranibizumab (Lucentis, Genentech) or aflibercept (Eylea, Regeneron). However, in our case, the drug is packaged within biodegradable particles that slowly meter it out over months. The GrayBug technology helps the particles stay right at the injection site so they do not cloud the field of vision, and they slowly release drug that then diffuses throughout the vitreous and the rest of the eye, including the retina.

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—Justin Hanes, PhD

RT: What advantages does microparticle or nanoparticle delivery of ophthalmic drugs have over other proposed mechanisms for extended or sustained drug delivery?

Dr. Hanes: One thing is that you can inject these small particles through fairly small gauge needles compared to implants. Implants can be injected through relatively large needles: 25 gauge for Iluvien or 22 gauge for Ozurdex. The GrayBug platforms are injected through a 27-gauge needle or smaller. So that is 1 advantage.

Another advantage is that more mass can be injected than is typical with 1 of the current implants, which means that more drug can be delivered over time. We make our system completely out of biodegradable polymers, so they are designed to dissipate completely after the drug is gone.

As you go up in molecular weight with proteins, you can usually get longer half-life. But the increase in duration with larger molecular weight appears to max out somewhere around 100 kD at about 2 months. With the GrayBug delivery system, we can make things last a lot longer.

Finally, GrayBug’s biggest advantage compared to other companies is our drug delivery technology. Our drug delivery technology has a patented ability to reduce inflammation that is caused by the injection of PLGA particles.

RT: What is PLGA and why is it used in drug delivery technologies?

Dr. Hanes: PLGA is a material that has been used for decades in biodegradable sutures in humans. In the drug delivery field, it is the most commonly used polymer. The problem has been that when you inject it into the eye, the polymer causes inflammation. If you are delivering a steroid, the steroid can counteract that, so the PLGA

systems that have been approved for the eye all deliver a steroid. But if you are getting away from steroids, then you need a technology that can eliminate the inflammation caused by that polymer. That's what GrayBug's technology does, and that is a real differentiating factor between us and other drug delivery companies focused on the eye.

RT: What are the benefits of reducing inflammation associated with PLGA?

Dr. Hanes: The major benefit is that it may be the difference between success and failure in human clinical trials.

RT: Can you explain a little bit about GrayBug's lead candidate product GB-102? What is the science behind this approach?

Dr. Hanes: It is a single molecule that potently inhibits the action of VEGF and PDGF. That is important because those are the 2 pathways that have been validated in humans to be important for efficacy in wet AMD. We know that inhibiting both of these pathways provides better efficacy than that achieved by inhibiting either 1 alone.

Right now, if the only anti-PDGF agent in phase 3 clinical trials (Fovista; Ophthotech) gets approved, then there is going to be requirement for 2 injections: injection of an anti-VEGF agent and the anti-PDGF protein. So it could be more expensive and require an additional injection. Also, it may still require injections every month or so. With GB-102, we are aiming to inhibit the action of both VEGF and PDGF with a single agent that we hope could be injected every 6 months, and that would greatly improve the convenience for patients and their family members who bring them to their visit. ■

More information on GrayBug may be found at www.graybug.com.

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