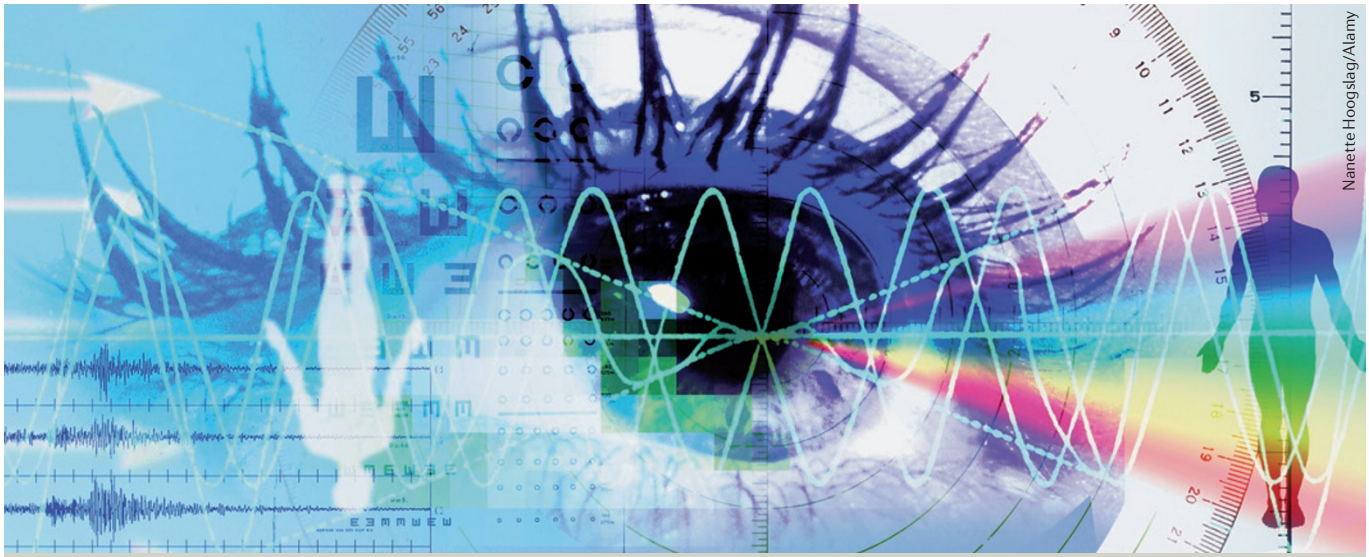

DEAL WATCH

Novartis eyes vision-enhancing therapy for macular degeneration

Novartis has acquired the non-US rights to Ophthotech's Fovista, an aptamer-based therapy for wet age-related macular degeneration (AMD), in a deal potentially worth more than US$1billion, including $200 million upfront. Fovista is currently in Phase III trials as an adjuvant to ranibizumab (Lucentis; marketed by Novartis outside the United States), aflibercept (Eylea; Regeneron) or bevacizumab (Avastin; Genentech), which are the standard-of-care therapies for wet AMD.

Wet AMD requires acute intervention as it can quickly lead to central vision loss. It is associated with increased vascularization in the macular area of the retina, a process in which vascular endothelial growth factor (VEGF) has a key role.

"The treatment for wet AMD has improved substantially in the past decade," says Tien Wong, a professor and senior consultant ophthalmologist at the Singapore National Eye Centre; three protein therapeutics targeting VEGF have been introduced during that period (ranibizumab, bevacizumab and aflibercept). These agents can prevent vision loss in 90–95% of patients with wet AMD, and have been so effective that "preventing vision loss is not a goalpost anymore", says Wong. "We now want to have improvements in vision." Current anti-VEGF agents can increase vision in only 30–40% of patients when used alone, so additional gains remain possible.

In a Phase IIb trial, the combination of Fovista and ranibizumab was superior to ranibizumab monotherapy, as measured by the prespecified primary end point of a change in visual acuity over 6 months.

Fovista is an aptamer that is designed to bind to and inhibit platelet-derived growth factor (PDGF). "We believe Fovista works through a dual mechanism of action," explains David Guyer, Ophthotech's CEO. "First, it strips off the pericytes. This allows the abnormal vascular endothelial cells to be more vulnerable to an anti-VEGF attack." The second potential mechanism is the inhibition of fibrosis — a process in which PDGF has previously been shown to have a role. In a retrospective analysis of data from their Phase IIb trials, a decrease in subretinal fibrosis was noted in patients treated with Fovista plus ranibizumab, which could have also contributed to improvements in vision.

Aptamers have been touted as the nucleic acid equivalent of antibodies, as they are custom-made macromolecules that bind to specific targets. "The main challenge for the field is that many groups have tried to make them to compete with antibodies," says Bruce Sullenger, a professor at Duke University Medical Center. Aptamers have a very short half-life in the blood, so Sullenger thinks they are most likely to be useful in situations where they are injected into a compartment that is isolated from the circulation (such as the vitreous cavity), or for indications (such as blood coagulation) where the short half-life is an important feature.

> "preventing vision loss is not a goalpost anymore … We now want to have improvements in vision"

The only currently approved aptamer therapeutic — pegaptanib sodium (Macugen; Valeant) — targets VEGF, and was actually the first such agent to be approved for treating wet AMD. "It was supplanted, really, in the market by the [anti-VEGF] antibodies, and the feeling in the field is that it's because that particular aptamer is too specific," and might therefore inhibit fewer isoforms than the antibodies do, explains Sullenger. Two other PDGF inhibitors, one small molecule (X-82; TyrogeneX) and an antibody (REGN-2176; Regeneron), are also in clinical development for the treatment of wet AMD, but neither has entered Phase III.

Wong is cautiously optimistic, and highlights the need for data from the Phase III trial. "This is the first time that a combination therapy has had such promising results," he says. "This is a very exciting era."

Megan Cully