Adenovector Pigment Epithelium–Derived Factor (AdPEDF) Delivery for Wet Age-Related Macular Degeneration

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Wet age-related macular degeneration (AMD) is the initial target indication in GenVec's adenovector (Ad) pigment epithelium–derived factor (PEDF) ocular program. If the studies go well, we intend to expand into other retinal degenerative disorders.

Our drug development strategy at GenVec is to identify medical areas of high importance, to try to understand the biology of diseases in the areas, and then identify compelling, relevant, biologic activities suitable for treatment interventions. In the case of AMD, this is PEDF. We test the identified substance for efficacy in preclinical models and for safety in preclinical toxicology studies. In parallel, we try to identify whether there is a commercial pathway that would be profitable.

We sought to identify a protein with therapeutic properties for wet AMD that would 1) protect and/or rescue retinal cells, 2) reverse and prevent abnormal blood vessel development, and 3) stop blood vessel leakage. Ideally, the protein would be delivered directly. However, because proteins are generally unstable and have a very rapid half-life, an indirect model that uses or leverages the protein's gene is used.

We have focused on PEDF, because of its potential to provide a multifaceted approach to stopping vision loss. Pigment epithelium–derived factor was first identified in 1989 as a neurotrophic and neuroprotective factor[1,2] and later shown to promote regression of preexisting abnormal blood vasculature.[3] The latter feature was key to us, because abnormal neovascularization characterizes wet AMD. GenVec and others have shown that PEDF is a very potent antiangiogenic factor. It can prevent choroidal and retinal neovascularization.

It is interesting that PEDF opposes several angiogenic stimuli, including vascular endothelial growth factor (VEGF), fibroblast growth factor, platelet-derived growth factor, and interleukin-8. Most recently, it has also been shown to be an antipermeability factor. Several laboratory groups have found low PEDF levels in vitreous samples of patients with wet AMD compared with patients with nonneovascular disease.

In a rat model of light-induced photoreceptor degeneration, PEDF prevents photoreceptor death and protects retinal function, as determined by electroretinogram analysis.[4] In a VEGF transgenic mouse model with increased retinal neovascularization, PEDF diminishes the neovascularization and prevents further blood vessel growth.[3]

Our delivery approach is to use a second-generation adenovector to produce PEDF protein locally. This adenovector is multiply deleted in three of the key viral genes and, thus, no longer able to replicate. Because PEDF had not been used previously in humans, we also deemed it prudent to use a transit-expressing vector.

Our criteria for translation from preclinical to clinical studies are as follows:

1. The molecule must show strong efficacy in preclinical models.
2. It must demonstrate good safety in preclinical toxicology models.
3. We must be able to manufacture good manufacturing practice material.
4. We must identify a feasible clinical and regulatory plan.
5. We must secure intellectual property protection.

The Phase I clinical trial design for wet AMD using AdPEDF, carried out by GenVec, found AdPEDF to be well tolerated in all of the doses, even up to $1 \times 10^{9.5}$ pu. We saw no dose-limiting toxicities, no drug-related serious adverse effects, no endophthalmitis, and no significant ocular inflammation. Some patients showed some transient anterior chamber flare and cells. Some patients had intraocular pressure increases, unrelated to dose, that were transient and responsive to standard care.

Our AdPEDF program, similar to several of our other programs, shows that GenVec has the capability to take our vector designs and translate them into clinical leads. Internally, we have the ability to manufacture Phase I, II, and III materials. We also have

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Quality Assurance and Quality Control departments. We have submitted several investigational new drug applications in the field of cancer, cardiology, vaccines, and ophthalmology. We now have a biologic master file for our vaccine program, and we have moved forward with several clinical indications for oncology, cardiology, and vaccine programs. We have internal expertise for securing intellectual property rights.

Our next step in the AdPEDF program is to advance to clinical testing in wet AMD patients with less impaired vision. We intend to extend into other ocular indications.

References

1. Tombran-Tink J, Johnson L. Neuronal differentiation of retinoblastoma cells induced by medium conditioned by human RPE cells. Invest Ophthalmol Vis Sci 1989;30:1700–1707.
2. Chader GJ. PEDF: Raising both hopes and questions in controlling angiogenesis. Proc Natl Acad Sci U S A 2001;98: 2122–2124.
3. Mori K, Gehlbach P, Ando A, et al. Regression of ocular neovascularization in response to increased expression of pigment epithelium–derived factor. Invest Ophthalmol Vis Sci 2002;43:2428–2434.
4. Imai D, Yoneya S, Gehlbach PL, et al. Intraocular gene transfer of pigment epithelium–derived factor rescues photoreceptors from light-induced cell death. J Cell Physiol 2005;202: 570–578.