Glaucoma is a group of diseases that can damage the eye’s optic nerve and result in vision loss and blindness. According to the World Health Organization, glaucoma, including open-angle glaucoma and angle-closure glaucoma, is the second leading cause of blindness in the world. In the United States, 2.2 million Americans age forty and older are affected by open-angle glaucoma. In addition, another 2 million do not know they have the disease. Intraocular pressure (IOP) is the most important risk factor. As of today, it still remains the only risk factor that can be treated to prevent the disease’s progression.

Various classes of antiglaucoma agents have been developed to lower IOP (preferably below 12 mm Hg), including beta blockers (e.g., timolol), prostaglandin analogues (e.g., latanoprost), alpha-adrenergic agonists (e.g., brimonidine), and carbonic anhydrase inhibitors (e.g., dorzolamide).

The safe and effective treatment of glaucoma, like that of most ophthalmic diseases or disorders, relies heavily on topical application of drugs to the eye. Because of ease of use and low-cost production, conventional dosage forms (including aqueous solutions, suspensions, and ointments) dominate the global market of ocular drug delivery, accounting for nearly 90 percent of marketed formulations. These efforts have focused on increasing the ocular-residence time of drugs and drug adsorption, which are essential for increasing the duration of drug activity. Nonconventional delivery systems and formulations for topical application of antiglaucoma drugs are also under rapid development, and this has been a research focus for interdisciplinary collaborators at the School of Engineering, and the School of Medicine. Recently, Dr. Hu Yang, assistant professor, Department of Biomedical Engineering and his clinical collaborators including Dr. Christopher Leffler, assistant professor of ophthalmology at VCU, and Dr. Uday Kompella, professor of pharmaceutical sciences at University of Colorado Denver, have developed a novel, highly adaptable and multifunctional polyamidoamine (PAMAM) dendrimer hydrogel platform with potential for ocular drug delivery.

The dendrimer hydrogel network consists of PAMAM dendrimer nanoparticles crossed linked with polyethylene glycol (PEG). The novelty of dendrimer hydrogel (DH) is that it possesses many unique structural characteristics and desirable properties for ocular drug delivery as follows. First, PAMAM dendrimers are highly branched nanoparticles with a number of surface groups and charges. The dendrimer hydrogel network allows for simultaneous delivery of both hydrophobic and hydrophilic drugs as needed. In particular, the interior hydrophobic core of the dendrimer can encapsulate hydrophobic compounds, thus increasing their water solubility and loading amounts, while the cross-linked PEG network can load hydrophilic drugs. Second, DH solutions are light sensitive and are able to become viscous solutions or form gel in situ upon light exposure. Third, DH exhibits pH-dependent degradation responsiveness, controllable release kinetics, and swelling behavior. Fourth, DH has demonstrated good mucoadhesive-ness, making possible sustained drug release, and it has favorable biological properties, such as non-toxicity. Further, this new platform integrates the structural characteristics and properties of in situ gelling, mucoadhesive, and nanoparticle delivery systems, representing a new generation of ocular drug delivery platform.

Developing long-acting antiglaucoma drug dosage formulations represents an unmet clinical need of improving long-term patient compliance. With support from the Wallace H. Coulter Foundation through a translational research award granted to Yang, Leffler, and Kompella, the current focus is to prove the feasibility of developing a new dosage formulation based on this novel dendrimer hydrogel platform to enhance the bioavailability and prolong the therapeutic efficacy of antiglaucoma drugs in the hope of reducing the dosing frequency to improve long-term patient compliance. Each member of the research group makes a significant contribution to the project. Leffler is currently working on the association of beta-adrenergic receptor polymorphisms with response to glaucoma medications and has determined optimal methods to evaluate glaucoma drug effect in clinical practice. The variation observed in intraocular pressure control has played a part in convincing him of the need for long-acting glaucoma therapeutics. Prototype products will be validated in animal studies in collaboration with Kompella. Dr. Stephen Hutcherson, president and CEO at Visionary Therapeutics Corporation, serves as consultant to this project, providing advice on product commercialization. Yang works closely with the VCU technology transfer office for patent application, licensing and commercialization of this technology. Before receiving the Coulter award, Yang was awarded the VCU Technology Validation Fund in 2008 for pilot study of this technology. The versatility of this novel ocular drug delivery platform ensures that products are capable of rapid evolution and transition as new formulations are discovered. The validation of DH for antiglaucoma drug delivery will open up opportunities for developing DH formulations for delivery of other ocular drugs because of DH’s high structural adaptability and its favorable properties.

Figure 1. A highly adaptable and multifunctional PAMAM dendrimer hydrogel platform for ocular drug delivery.