# *Editorial*

# Is Pharmacologic Vitreolysis Brewing?

In the 4 years since this page was last dedicated to the subject of pharmacologic vitreolysis,[1] there has been considerable interest in further developing this approach to treat vitreoretinal pathology. Effective liquefaction of gel vitreous and safe separation of vitreous from retina pharmacologically require thorough understanding of the molecular organization of vitreous and the vitreoretinal interface.

Vitreous is a viscoelastic extracellular matrix that is 98% water and normally exists in a gel state as a result of the intricate organization of its macromolecular components. Hyaluronan imparts viscoelasticity whereas the structural *frame* is provided by collagen, primarily type II but also type IX, and a hybrid of types V/XI (Figure 1).[2] As the type IX collagen is situated on the surface of the fibril, it likely mediates vitreous collagen fibril interaction with other molecules and may thereby play an important role in maintaining the gel state. Various proteoglycans, glycoproteins, and other molecules such as fibrillins, opticin, and vit1 may also play a role in organizing the two major structural macromolecules into a three-dimensional network[3,4] that achieves the physiologic functions of media clarity and shock absorption. The peripheral vitreous cortex consists of densely packed collagen fibrils and has a high concentration of hyaluronan. In youth, the posterior vitreous cortex firmly adheres to the internal limiting lamina of the retina. The internal limiting lamina, actually the basal lamina of retinal Müller cells, is composed of type IV collagen closely associated with glycoproteins. At the rim of the optic disk, the retinal internal limiting lamina ceases, although a basal lamina exists known as the "inner limiting membrane of Elschnig."

Although the exact nature of vitreoretinal adhesion is not known, it most probably results from the biophysical properties of the extracellular matrix molecules found at this interface. During aging, this adhesion weakens,[5] probably because of the effects of free radicals generated by incident light and cell metabolism in the tissues surrounding vitreous, in addition to changes typical of basement membrane aging throughout the body. Liquefaction of the gel may also be caused by light[6] as well as the action of proteolytic enzymes[7] and endogenous metalloproteinases.[8] Concurrent weakening of the vitreoretinal interface and gel liquefaction results in posterior vitreous detachment (PVD). Liquefaction without concurrent vitreoretinal dehiscence results in anomalous PVD, with traction exerted on the retina. This final common pathway in the pathogenesis of many vitreoretinopathies causes different pathologies depending on where traction is exerted. In the periphery, retinal tears and detachments result, whereas at the macula, vitreo-

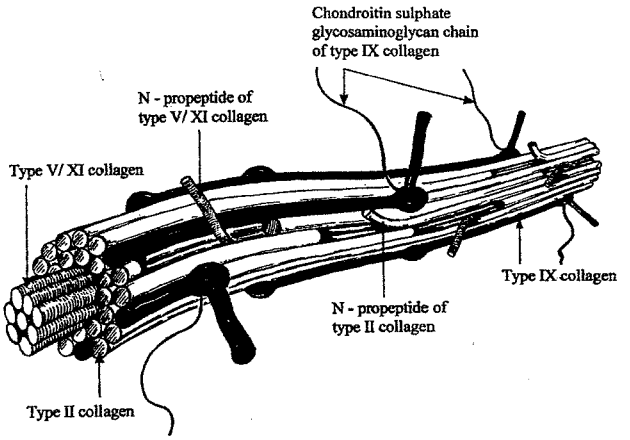


**Fig. 1.** Schematic diagram of the molecular composition and organization of the major heterotypic collagen fibril in vitreous (reprinted from reference 2 with permission). The central core is a hybrid of types V and XI, with type II, the most prominent type in vitreous, surrounding the central core. Type IX collagen is situated on the surface and may be important in mediating interactions between this molecule and other extracellular matrix molecules in vitreous. Reprinted from Bishop.[2]

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macular traction syndrome, macular holes, or premacular membranes with pucker may result.

The ideal approach to crafting pharmacologic means to manipulate the gel state of vitreous and its attachment to the retina would be to first definitively characterize the molecular nature of these phenomena and to then design precise methods to alter these states. Vitreoretinal dehiscence should be induced first, followed by liquefaction, otherwise one could actually cause anomalous PVD. Alas, the nature of the quest for scientific progress is often far less deliberate and planned than this ideal. Thus, a variety of approaches have been attempted to date. Hyaluronidase was employed as early as 1949[9] and collagenase in 1973.[10] A purified preparation of the former agent is now in Phase III of the Food and Drug Administration's clinical trials of its efficacy to clear vitreous hemorrhage without vitrectomy. Whereas this agent is also proposed to induce PVD, there is little theoretical basis for this approach, because hyaluronidase alone will not likely degrade the molecules responsible for vitreoretinal adhesion. Indeed, experimental trials of hyaluronidase in rabbits failed to achieve PVD.[11] However, combining hyaluronidase with $C_3F_8$ has purportedly induced PVD in the rabbit,[12] a finding also reported for plasmin combined with sulfur hexafluride.[13] It is plausible that the expanding gas and not the enzyme is responsible for these effects; many years ago Lincoff et al[14] and Thresher et al[15] reported similar effects with expanding gas alone.

Early observations of the effects of blood on vitreous laid the groundwork for approaches based on extracting active agents from blood for pharmacologic vitreolysis. Autologous plasmin induced PVD in rabbits[16] and has since been used intraoperatively to facilitate pediatric[17] and adult[18] vitreoretinal surgery. Chondroitinase has been shown[19] to disinsert vitreous from retina and facilitate surgical removal of premacular membranes. Because of the important role played by sulfated chondroitins in maintaining gel vitreous as well as mediating vitreoretinal adhesion, chondroitinases hold great promise for pharmacologic vitreolysis. Regrettably, no recent studies are devoted to developing collagenase for pharmacologic vitreolysis. If a highly specific form of collagenase, in particular a type IX collagenase, were employed, it is conceivable that the mediating role of this molecule in promoting the gel state would be attenuated and liquefaction would be induced without acting on other collagen types, thereby obviating potential untoward side-effects.

In a recent issue of *Retina*, Oliveira et al[20] used Dispase to facilitate posterior vitreous separation during vitrectomy in young pigs. Because Dispase has proteolytic activity against type IV collagen and fibronectin, it would seem well suited as an agent to induce vitreoretinal dehiscence, but would not likely liquefy vitreous. Indeed, previous studies[21] found that Dispase disrupted collagen fibrils within the lamina rara externa of the internal limiting lamina of the retina, with lesser effects upon the lamina densa. Those investigators concluded that these effects should not be deleterious to retinal function, because the footplates of Müller cells were intact. Their predictions were correct, as McCuen's group found no abnormalities on electroretinography or any of the histologic and ultrastructural investigations that were undertaken after using Dispase during vitrectomy in young pigs. It is important to note that in these two studies, there was no evidence of vitreous liquefaction. This underscores the concept that no single agent can achieve both of the desired components of pharmacologic vitreolysis, i.e., liquefaction of the gel and vitreoretinal dehiscence. Dispase causes dehiscence but not liquefaction. Hyaluronidase liquefies vitreous gel[22] but without gas probably does not induce PVD. Chondroitinase may do both, but the depolymerization of hyaluronan and chondroitin sulfate results only in reduced vitreous gel wet weight and not gel destruction.[23] Collagenases would probably be needed to achieve such effects. Indeed, vitreous molecular morphology is so complex and there are so many different changes that occur with aging and various diseases that brew masters may be required to successfully address the problem of concocting future pharmacologic vitreolysis regimens.

In conclusion, a better understanding of vitreous molecular morphology and the structure of the vitreoretinal interface would enable the development of more precise and effective agents for pharmacologic vitreolysis. No single agent is likely to achieve all that is required to remedy the pathophysiology seen in most vitreoretinal conditions. Rather, the future will most likely see the use of a mixed brew of agents whose relative concentrations will be adjusted depending on the patient's age and disease and the desired effect. Ideally, this would begin by inducing vitreoretinal dehiscence, followed by liquefaction of the gel vitreous.

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