BIOCHEMISTRY SEMINAR

Shomoita Sayed

Graduate student | Low Group | Purdue University

"Development of a folate conjugated ASO for the treatment of wet AMD (Age related Macular Degeneration)"

Age related Macular Degeneration (AMD) is an irreversible vision disorder that affects millions of individuals over the age of 40. In the advanced stage of the disease, known as 'Wet or Neovascular AMD', patients lose their central vision due to the growth of abnormal blood vessels disrupting the retinal cell layers. Overexpression of Vascular Endothelial Growth Factor (VEGF) secreted from Retinal Pigmented Epithelial (RPE) cells is the main cause of wet AMD. To slow down the disease progression, VEGF neutralizing antibodies are directly injected into the eye. This invasive drug administration is a major limitation in ocular drug development field. To address this limitation, we developed a folate linked Antisense Oligonucleotide (ASO) drug that can be targeted to the RPE cells via systemic routes. We showed that the ASO drug reduces the VEGF mRNA levels in the mouse RPE-retina. The folate-ASO drug also reduced the abnormal vascular spots in the VLDLR (-/-) mice, a model of abnormal vascularization. We tested whether ASO drug causes any changes to the normal vasculature of healthy tissues. Our data showed that frequent dosing for over three months didn't cause vascular regression or tissue death in the healthy tissues. These findings support the hypothesis that targeted delivery of a folate conjugated drug to the RPE can address the limitations of invasive intravitreal injections without causing systemic toxicity.

BIOCHEMISTRY SEMINAR

Sazzadul Bari

Graduate student | Low Group | Purdue University

"Development of fibroblast activation protein-targeted anti-fibrotic drug conjugates for the treatment of fibrotic diseases"

Fibrosis originates from the excessive or aberrant activation and proliferation of fibroblasts at sites of tissue injury. While fibroblasts are indispensable in the wound-healing process, pathological fibrosis can lead to tissue damage and progressive loss of organ function. Consequently, the development of effective treatment options for fibrotic conditions remains a global priority. The selective expression of fibroblast activation protein (FAP) in activated myofibroblasts provides an opportunity to devise targeted drug delivery strategies specifically within fibrotic tissue. Both phosphatidylinositol 3-kinase (PI3K) inhibitors and transforming growth factor-beta (TGF-β) inhibitors have been explored as potent anti-fibrotic agents; however, their use has been limited by extensive systemic toxicities. The lack of tissue specificity of these drugs has also curtailed their accumulation within fibrotic regions, often necessitating higher dosing regimens to achieve therapeutic efficacy. In our approach, conjugating a highly potent FAP-binding ligand with either a PI3K inhibitor or a TGF-β inhibitor via cleavable linkers enables the localized delivery of these inhibitors within fibrotic tissues, thereby substantially reducing associated toxicities and required doses. We have designed and evaluated the anti-fibrotic potential of such conjugates in a folic acid-induced renal fibrosis model. Treatment of fibrotic mice with FAP-ligand-conjugated PI3K and TGF-β inhibitors resulted in diminished collagen deposition and reduced genetic expression of collagen and other pro-fibrotic markers compared with those of untreated fibrotic controls. Histopathological staining and Western blot analysis further confirmed the decrease in collagen levels in treated mice relative to untreated counterparts. These findings demonstrate the therapeutic efficacy of FAP-targeted PI3K and TGF-β inhibitors in a murine model of renal fibrosis and underscore the potential of these conjugates for broader application in the treatment of other fibrotic diseases in vivo.