

**DEPARTMENT OF COMMUNITY AND PREVENTIVE MEDICINE
RESEARCH PROPOSAL**

**Synthetic Triterpenoids Inhibit Myofibroblast Differentiation *In Vitro*:
A Potential Novel Therapy for Corneal Scarring**

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Corneal scarring is the second most common cause of worldwide blindness. Despite its high prevalence, there is no safe and efficacious treatment for this vision-threatening disease process. Ocular inflammation, as seen with ocular infections, trauma, chemical burns, and surgeries, can cause corneal scarring. The underlying pathology of corneal scarring is the differentiation of corneal fibroblasts (also called keratocytes) to myofibroblasts. Myofibroblasts are light-reflective and produce extracellular matrix molecules, which result in the corneal opacities and shape changes associated with corneal scarring. Myofibroblast differentiation is caused by the cytokine, transforming growth factor beta-1 (TGF β 1), which is released by immune cells in the cornea under inflammatory conditions.

Pharmaceutical agents that inhibit TGF β 1-induced myofibroblast differentiation could be potential therapies for corneal scarring. Certain members of the peroxisome proliferator-activated receptor gamma (PPAR γ) agonist family of drugs have been shown to be effective inhibitors of TGF β 1-induced myofibroblast differentiation. We hypothesize that a PPAR γ ligand and synthetic triterpenoid, cyano-3,12-dioxolean-1,9-dien-28-oic acid (CDDO), will inhibit corneal fibroblast to myofibroblast differentiation *in vitro*. The primary objective of this study is to assess the ability of CDDO to prevent corneal fibroblast to myofibroblast differentiation. The secondary objectives are to compare the ability of CDDO and other PPAR γ ligands to prevent myofibroblast differentiation, investigate the mechanism by which CDDO prevents corneal fibroblast to myofibroblast differentiation, and assess the ability of CDDO to reverse corneal fibroblast to myofibroblast differentiation.

In this study we will use laboratory techniques to assess the ability of CDDO to inhibit TGF β 1-induced myofibroblast differentiation by comparing the expression of myofibroblast proteins and messenger RNA in human corneal fibroblasts treated with TGF β 1 with or without CDDO co-treatment. Similarly, to compare the ability of CDDO and other PPAR γ ligands to inhibit myofibroblast differentiation, we will assess the expression of myofibroblast proteins in corneal fibroblasts treated with TGF β 1 with or without CDDO or other PPAR γ ligands co-treatment. We will also investigate the mechanism through which CDDO inhibits TGF β 1-induced myofibroblast differentiation by comparing the protein expression of molecules involved in TGF β 1 signaling in corneal fibroblasts treated with TGF β 1 with or without CDDO. To study the ability of CDDO to reverse myofibroblast differentiation, we will examine myofibroblast protein expression after treatment of corneal fibroblasts with TGF β 1 for several days, followed by treatment with or without CDDO. Results from this study may establish CDDO or other small molecules as potential novel therapies for corneal scarring that warrants further study *in vivo* using animal models of corneal scarring.

Committee Chair:

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12:30PM – 1:00 PM

Helen Wood Hall, Room 4W301

EVERYONE IS WELCOME