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OSMOTIC RIBOFLAVIN AND TRANSEPITHELIAL CXL

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Riboflavin and the eye

- Riboflavin plays an important role in a number of important ocular functions including the functioning of the retinal photoreceptors and protection against nuclear cataract[1,2].
- Also, high levels of riboflavin were measured in the cornea relative to other ocular tissues according to a study by Batey et al.[3]

1 Miyamoto et al. Proc Natl Acad Sci USA. 1998;95:6097–6102
2 Cumming et al. Ophthalmology. 2000;107:450–456
3 Invest Ophthalmol Vis Sci 1991; 32:1981–1985

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Transepithelial, Fact or Fiction?

- Despite the critical role played by riboflavin in the cornea and other ocular tissues, the molecular mechanism and regulation of *riboflavin translocation is poorly understood*.
- It was generally believed that molecules traverse the corneal epithelium simply by passive diffusion through a transcellular/paracellular route.
- If that is the case, then epithelium removal would be essential for riboflavin to enter the stroma, as the tight junctions would make the cornea an impermeable wall for the riboflavin, hence *transepithelial* CXL would be *Fiction*!

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Transepithelial, Fact or Fiction?

- **However**, a number of membrane transporters were identified to be involved in the translocation of various nutrients and substances across the epithelium and endothelium.
- Ocular transporters include carriers for peptides, amino acids, glucose, lactate, and nucleosides/nucleobases and are primarily localized on the corneal epithelium and endothelium.

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Transepithelial, Fact or Fiction?

- As demonstrated by Hariharan et al.*, we believe that *riboflavin* transport is *carrier mediated*, and this correlates to the clinical results we obtained.
- In the light of this information, we know that ***transepithelial*** CXL is a ***FACT***!
- Corneal epithelium is ***permeable membrane!***

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- Current Eye Research 2006; 31:811-824
- "Keratoconus Surgery & Cross Linking" – 2009; Jaypees

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Osmotic Transepithelial CXL

Preliminary Laboratory Results

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What is microcarriers CXL?

- This is transepithelial CXL facilitated by a management of microcarriers.
- Microcarriers are used as a *penetration enhancers* by changing the ionic resistance of the cornea.
- Therefore they can be used **in very low concentration** to *enhance* the *transepithelial riboflavin transport* for CXL.

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ParaCel™: Osmotic Riboflavin

ParaCel™:

- 0,25% Riboflavin
- Methyl Cellulose
- Hypotonic NaCl
- Benzalklonium Chloride
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ORIGINAL ARTICLE

Riboflavin Osmolar Modification for Transepithelial Corneal Cross-Linking

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ABSTRACT

Purpose: To investigate the influence of osmolarity on the transepithelial permeability of riboflavin solutions in a cross-linking procedure.

Methods: Several riboflavin 0.1% solutions that contained different NaCl and benzalkonium chloride (BAC) concentrations were applied to 36 rabbit eyes for 30 min. To serve as a control, the epithelium was removed in group A (standard protocol). The groups then received the following solutions: (A) riboflavin 0.1% in NaCl 0.9% solution; (B) riboflavin 0.1% in NaCl 0.44% solution with BAC 0.02%; (C) riboflavin 0.1% in NaCl 0.44% solution with BAC 0.01%; (D) riboflavin 0.1% in NaCl 0.44% solution without BAC; (E) riboflavin 0.1% in NaCl 0.9% solution with BAC 0.02%; and (F) riboflavin 0.1% in NaCl 0.9% solution without BAC. Six eyes in each group were treated. The absorption coefficients of the corneas were measured to characterize the riboflavin penetration into the cornea.

Results: There is a large difference in the transepithelial riboflavin penetration of riboflavin 0.1% + BAC 0.02% solutions that contain different NaCl concentrations (NaCl 0.9% versus NaCl 0.44%). The absorption coefficients differed by more than a factor of two ($P = 0.004$). No statistically significant difference was found between riboflavin 0.1% in NaCl 0.44% solution containing BAC 0.02% and BAC 0.01%. Compared to the standard protocol, these solutions resulted in an absorption coefficient of 37% (BAC 0.02%) and 33% (BAC 0.01%) of the standard epithelium-off procedure.

Conclusion: The transepithelial riboflavin solution should contain no dextran, but it should include 0.01% BAC and 0.44% NaCl to promote the permeability of riboflavin through the epithelium, resulting in a sufficient concentration of riboflavin in the corneal stroma.

Keywords: Cross-Linking, Keratoconus, Riboflavin, Transepithelial CXL, Epithelial permeability, Benzalkonium chloride

CONCLUSION

The results of our experimental study may contribute to the mechanism of the transepithelial CXL and its influencing factors. The transepithelial riboflavin solution in the CXL procedure should not contain dextran, but it should include 0.01% BAC and 0.44% NaCl to increase the permeability of the epithelium, which will allow for the riboflavin to reach probably sufficient concentration in the corneal stroma. Further investigations regarding the biomechanical effects and toxicity are necessary to detect a real clinical effect and possible endothelial damage prior to introduction of this modified CXL treatment into the broad clinical practice.

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Osmotic Transepithelial CXL

First Laboratory Report

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Laboratory results

- Rabbit corneas were cross-linked in vivo without removal of the epithelium, using ParaCel™ solution.
- The corneas were then examined by light and electron microscope for evidence of collagen cross-linking;
- Non treated eyes were compared with treated ones.

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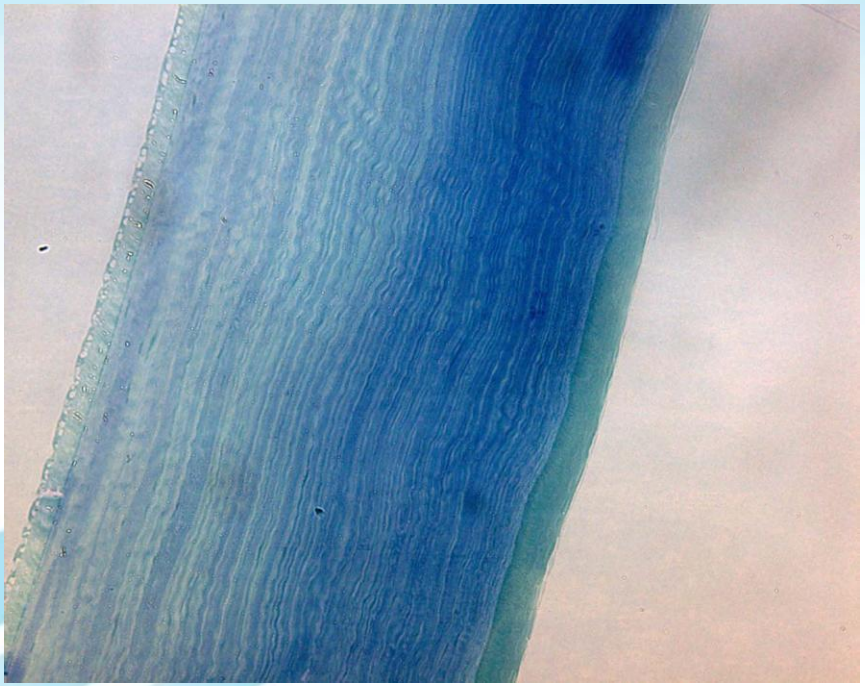
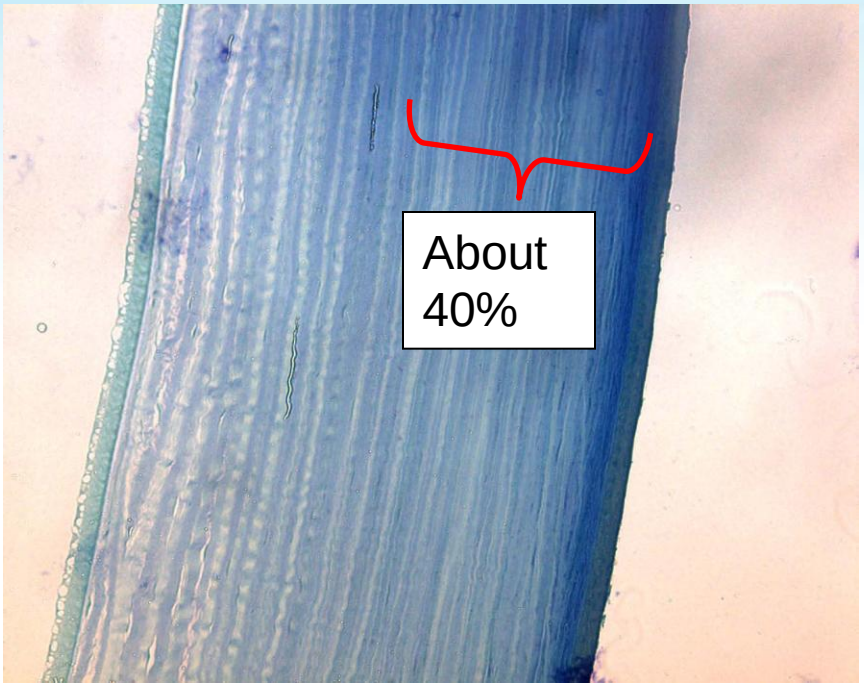
Light Microscope 20X

According to Kohlhaas and Spoerl et al.* CXL stiffens the anterior 200 µm of the cornea only.

- Control



- OTCXL



*J Cataract Refract Surg 2006; 32:279-283.

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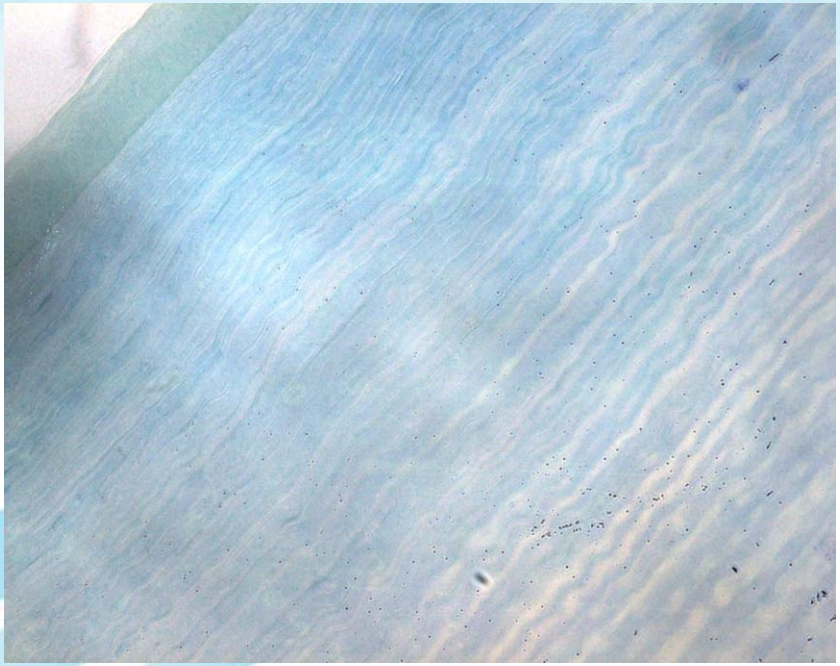
Light Microscope 40X

According to Kohlhaas and Spoerl et al.* CXL stiffens the anterior 200 µm of the cornea only.

- Control



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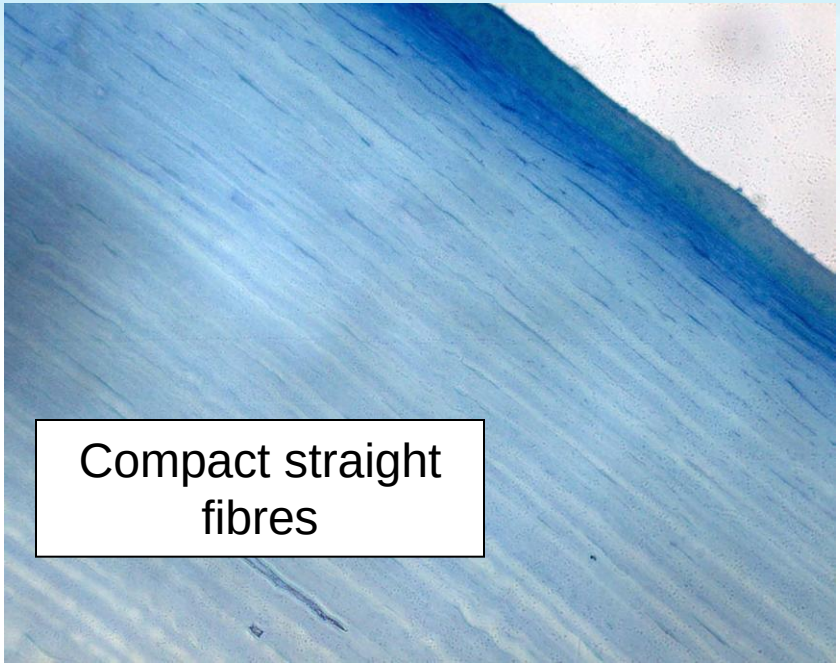

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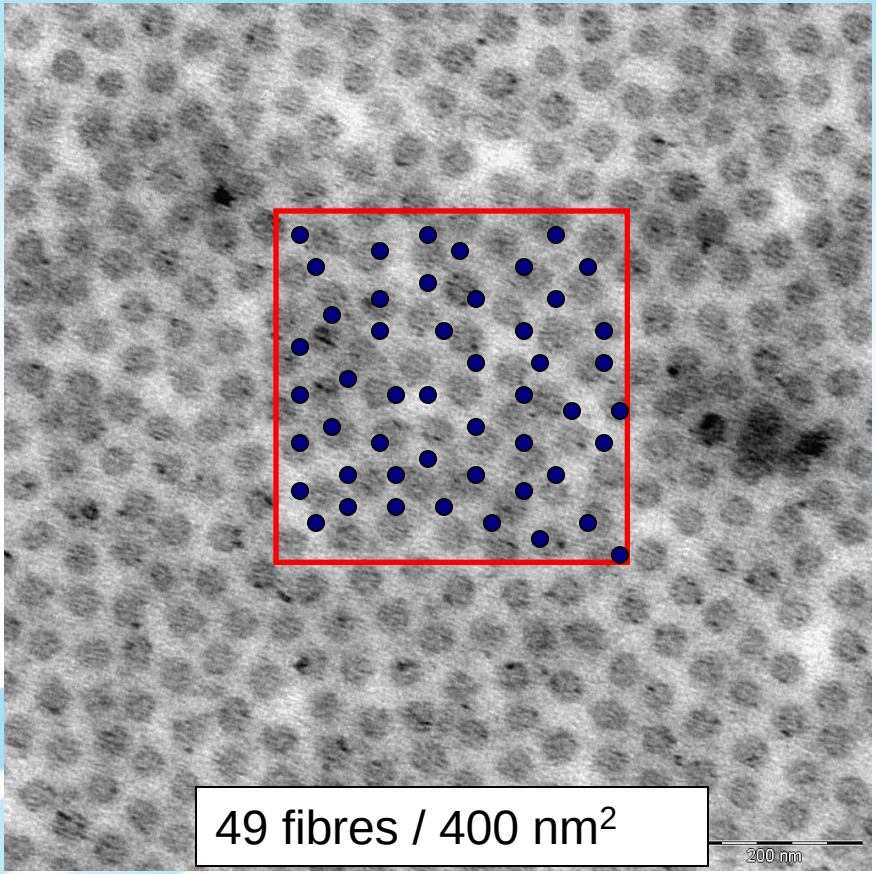
Electron Microscope 16000X (upper 200 µm)

- Control



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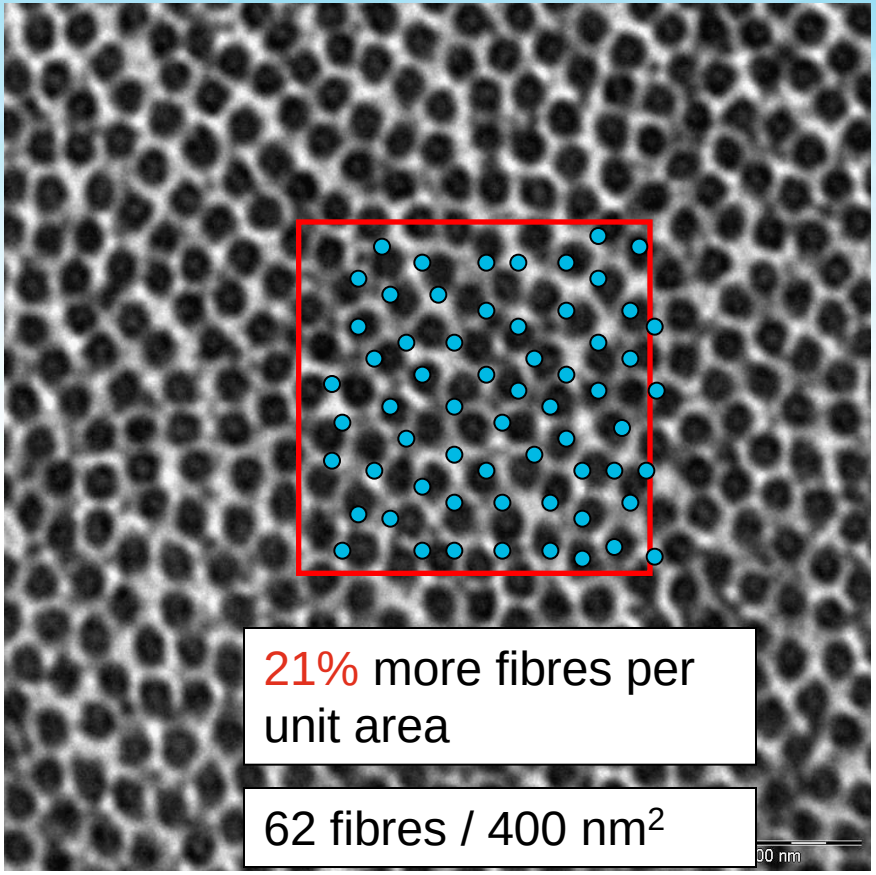

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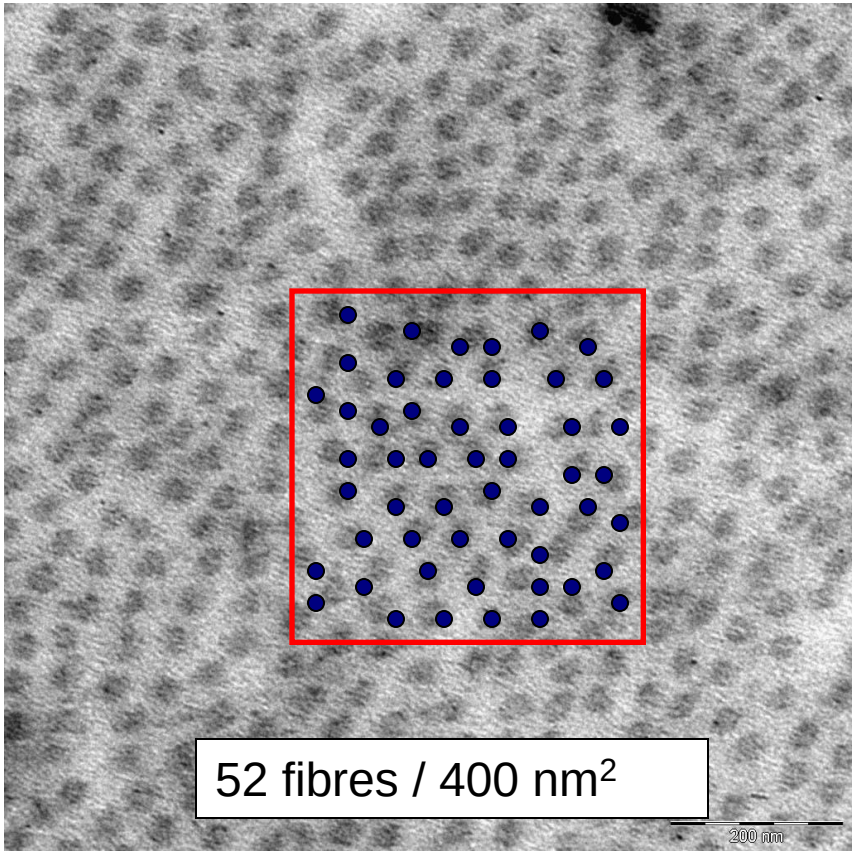
Electron Microscope 16000X (upper 100 µm)

- Control



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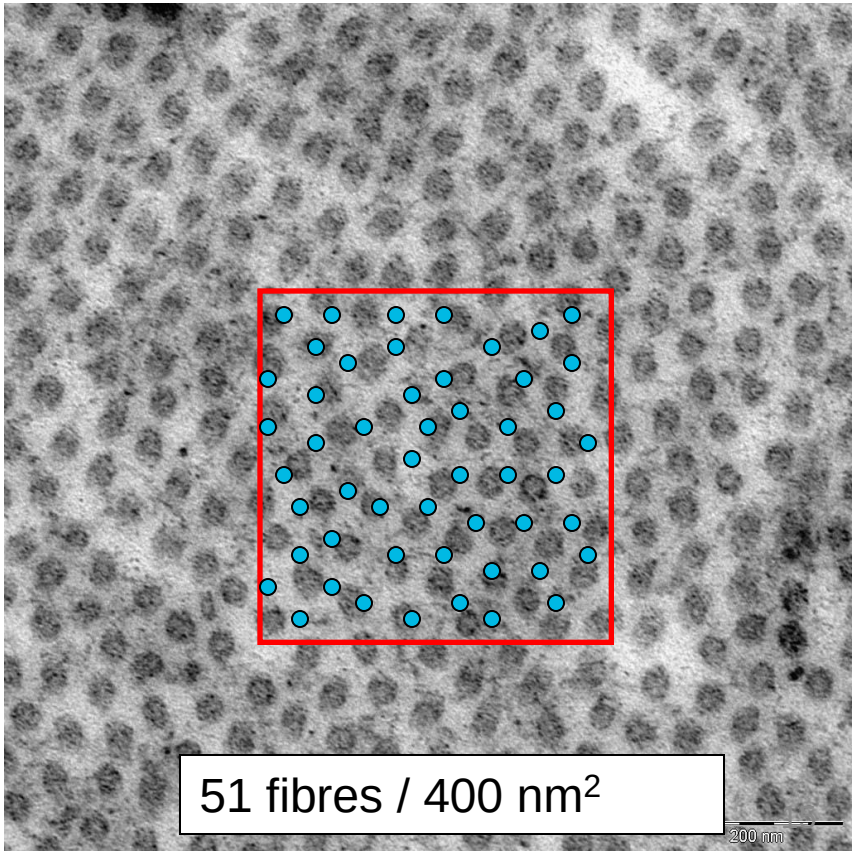

TAKE HOME MESSAGE

- Microwave technology;
- Fast CXL (3 minutes);
- LASIK Xtra and …PRK Xtra?
- ParaCel™:
  transepithelial riboflavin osmotically efficient

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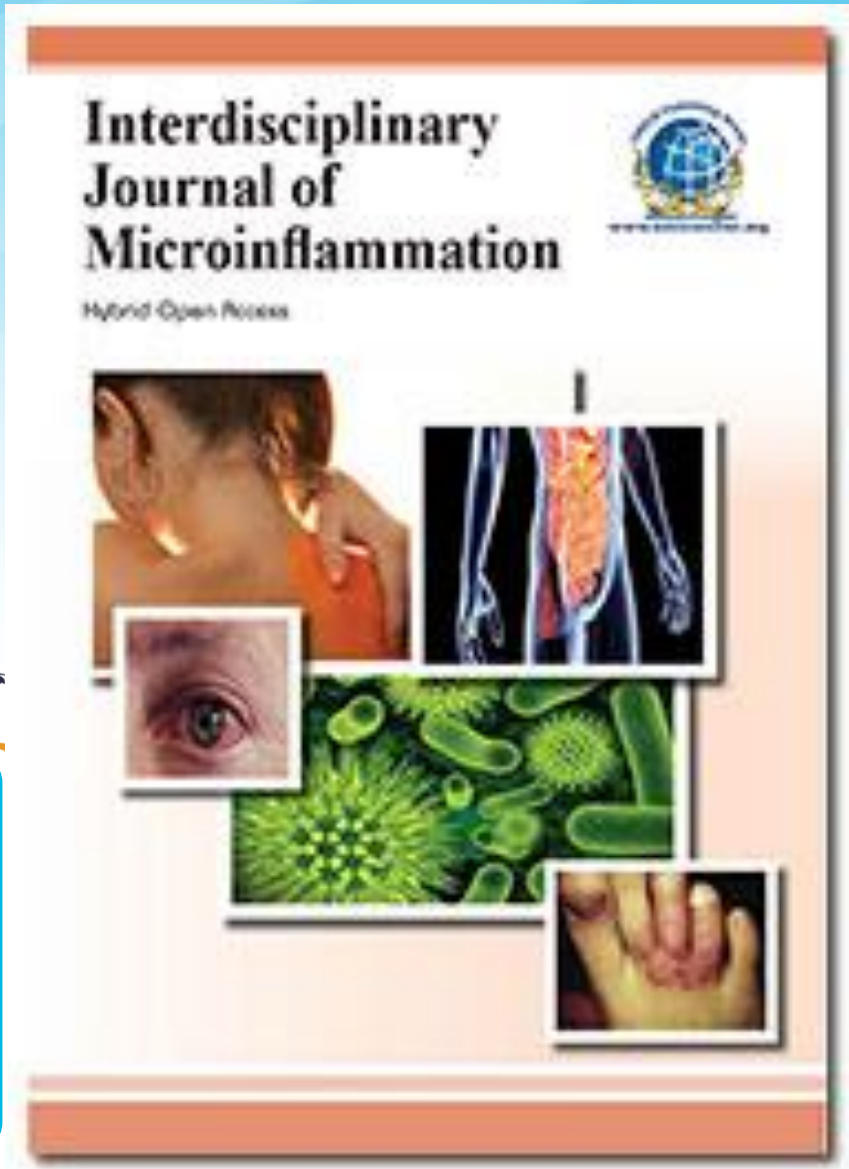

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