Targeting CYP51 in the Treatment of Acanthamoeba Keratitis

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Background

- *Acanthamoeba castellanii* is a free-living amoeba capable of causing opportunistic infections, including encephalitis and keratitis. (**Fig. 1**)[1-4]
- The first Acanthamoeba keratitis (AK) cases were reported in 1974.[2]
- Acanthamoeba poses a significant risk to contact wearers with improper hygiene and exposure to contaminated water. (**Fig. 2**)

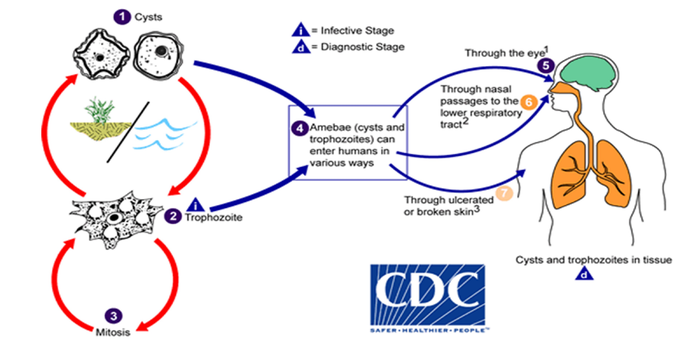

Figure 1. Biology and infection of *Acanthamoeba castellanii*. Adapted from Ref. 1.

Clinical Manifestation and Epidemiology

- Significant risks that expose an individual to AK include corneal trauma, exposure to contaminated water, and the use of homemade solutions for contact lens storage and cleaning.[2-4]
- Most common symptoms of an AK include pain (84.2%), decreased vision (73.6%), ocular infiltrates (73.6%), redness (68.4%), photophobia (52.6%), and oedema (50%).[5]
- This rare infection is often diagnosed late and overlooked by physicians, leading to a poor prognosis of permanent vision loss.[2,3]
- Early patient presentation include pseudodendrites with a grey-white epithelial infiltrate. (**Fig. 3**) These early signs can progress to deep stromal infiltrates, corneal perforation, and anterior uveitis.[2-4]

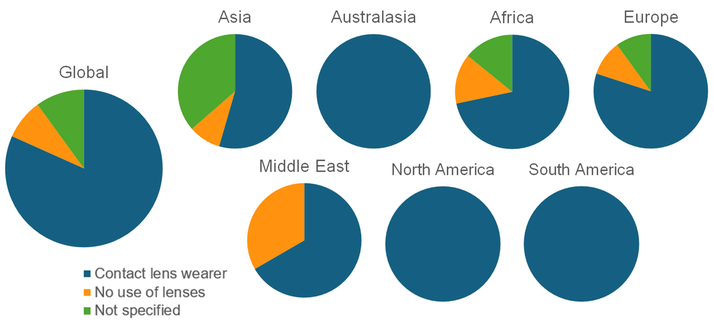

Figure 2. Risk factors of AK. Frequencies contact lens usage in AK cases as reported by Ref 5.

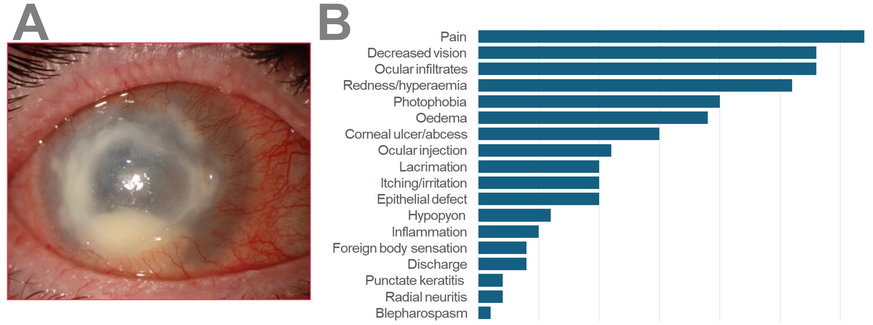

Figure 3. Clinical manifestations of AK. (A) Ocular presentation, Ref. 4. (B) Frequencies of symptoms in AK cases as reported by Ref. 5.

Diagnosis and Management

- Gold standard diagnostics involve culturing corneal scrapings and contact lenses/cases. PCR and direct smear-stain have been used for confirmatory evidence.[3]
- AK is typically treated with a biguanide in combination with a diamidine; however, there are numerous reports of Acanthamoeba developing resistance to diamidines.[6]
- Steroids remain controversial due to Acanthamoeba's ability to adapt rapidly and switch to resistant cyst forms.[2]
- Keratoplasty is often the next treatment option after pharmacological therapy has failed.[3]
- It's imperative to discover new treatments due to lengthy treatment time and increasing drug resistance.[2]

CYP51-Targeting Therapies

- Ergosterol is a critical lipid in both fungi and protozoa contributing to cell membrane fluidity.[7] (**Fig. 4**)
- *A. castellanii* produces ergosterol and other phytosterols in abundance during its metabolic trophozoite stage, aiding in its replication.[8]
- Antifungal azoles, such as fluconazole and voriconazole, target sterol 14α-demethylase (CYP51) in the ergosterol biosynthesis pathway, and have potential in AK management.[7,8]
- Due to the importance of phytosterols in *A. castellanii*, azoles show promise as monotherapies or in combination with antiamoebals.

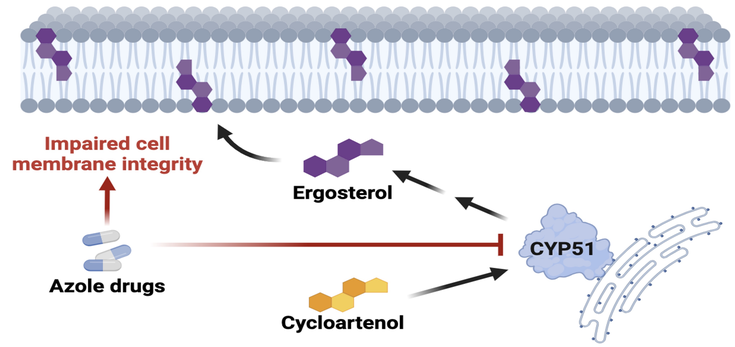

Figure 4. Cell membrane role of ergosterol and phytosterols and CYP51 inhibition by azole drugs. Created with BioRender.com.

Methods and Preliminary Results

- This scoping protocol follows JBI Methodology and follows PCC framework.
- The strategy includes a string for Acanthamoeba keratitis and a string for azole drugs. (**Fig. 5**)
- Inclusion criteria is clinical cases with monotherapies or combinations. Animal or laboratory studies will be excluded.
- Preliminary search on PubMed included 5,365 results.
- Preliminary search retrieved systematic reviews on Acanthamoeba keratitis and on CYP51 inhibitors exclusively but none on the combined topic.

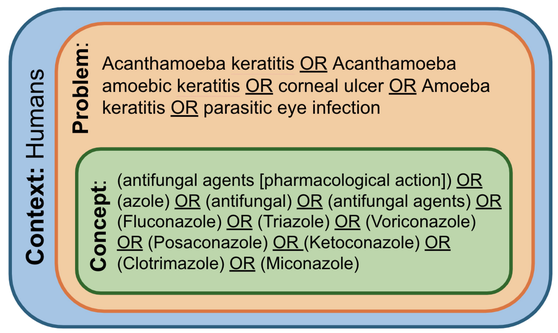

Figure 5. Search strategy.

Next Steps

- Scoping review protocol will be registered with Open Science Framework.
- Review protocol will be submitted to JBI Evidence Synthesis for peer-review.
- After the protocol is finalized:
  - We will be adapting the MEDLINE (PubMed) strategy for other information resources.
  - We will commence title/abstract screening and full-text article screening.

References

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Acknowledgment

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