Theranostics in the management of *Acanthamoeba* infections

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Text

The morbidity and/or mortality associated with *Acanthamoeba* infections has remained significant despite modern developments in healthcare and antimicrobial chemotherapy. Lack of awareness and/or delayed diagnosis and a lack of effective drugs are major hurdles to overcome these challenges. Nanomaterials have emerged as vital tools for concurrent diagnosis and therapy, which, in combination are referred to as “theranostics”. Nanomaterials offer highly sensitive diagnostic systems and possess viable therapeutic effects as a single modality. There has been good progress to develop nanomaterials-based efficient theranostic systems against various tumours, but this field is yet immature in the context of infectious diseases, and almost neglected against parasitic infections (Bauckneht et al., 2024; Jiang et al., 2024). For example, a radioactive molecule employed to image tumours can also deliver therapeutic radiation to the tumour in real time (Dash et al., 2015; Strosberg et al., 2020). Herein, we propose the potential value of theranostics against *Acanthamoeba* keratitis. *Acanthamoeba* keratitis is a sight-threatening infection, often associated with the improper use of contact lenses (Marciano-Cabral and Cabral, 2003; Visvesvara et al., 2007; Dart et al., 2009; Panjwani 2010; Niederkorn 2021). In most cases, patients suffer from redness, blurred vision, photophobia, tearing and pain. Due to the opportunistic nature of the parasites and rarity of the infection, topical application of antibiotics is the first course of action that often leads to a delay in correct diagnosis. The presence of antibacterials results in cellular transformation of active amoebae (vegetative trophozoites) into dormant cysts, further complicating treatment. Cysts have minimal metabolic activity enabling them to resist anti-amoebic drugs (Lloyd 2014). This is not surprising as drugs often target the function of the parasite, not its structure. Even with correct diagnosis, treatment can last up to six months indicating seriousness of the infection and the economic burden on the

affected patient, their family and the community (Robaei et al., 2015). This is puzzling as there are over 140 million contact lens users with over 40 million contact lens users in the USA alone (Swanson, 2012). The use of contact lens for vision-correction and/or cosmetics is on the rise and it is worth over 15 billion USD. Hence, there should be significant interest and investment by the pharmaceutical industry to manage this blinding infection. Theranostics offer an excellent opportunity in the management of *Acanthamoeba* keratitis. Given the diagnosis of *Acanthamoeba* keratitis through visual inspection and/or microscopy, and the topical application of drugs for treatment, it is sensible to develop theranostics in the management of *Acanthamoeba* keratitis. Utilizing nanoparticles as carriers, diagnostic and therapeutic agents in a combined manner, will ensure targeted delivery of drugs and diagnostic agents.

The biochemistry of *Acanthamoeba* trophozoites and cysts has provided useful leads in the development of biomarkers in the specific diagnosis of the parasites. For example, mannose-binding protein (MBP) expressed on the surface of *Acanthamoeba* trophozoites (Garate et al., 2002), can be exploited using fluorescein isothiocyanate (FITC)-linked anti-MBP antibodies and/or simply the use of exogenous mannose linked with FITC to target amoebae. Similarly, the presence of cellulose in the cyst walls of amoebae is a useful target. Such FITC-linked imaging biomarkers together with anti-amoebic drugs such as miltefosine/ Polyhexamethylene biguanide (PHMB)/chlorhexidine can be combined using nanoparticles as carriers and these can be explored to both diagnose and potentially treat *Acanthamoeba* keratitis through targeted therapeutic interventions.

The ability to precisely target the parasite while limiting the impact on host tissue is a primary benefit of theranostics (Bauckneht et al., 2024; Jiang et al., 2024). In addition, combination of diagnostics and therapeutics as a single procedure will provide simplicity, time-

and cost effectiveness, thus improving the overall patient outcome. Furthermore, these studies will stimulate research in the development of theranostics against other parasitic infections. Nonetheless, the development of "theranostics" approaches against *Acanthamoeba* keratitis will require rigorous regulatory review to ensure safety and efficacy, as well as these agents ought to be validated using *in vivo* models before they can be widely used in clinical practice (Jiang et al., 2024). Despite these challenges, "a theranostic approach" presents a timely and promising way forward in the effective management of *Acanthamoeba* keratitis to improve patient outcome.

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