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Commentary

A new angle on myopia therapeutics: Not just a fishing expedition

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Myopia (short- or near-sightedness) is a widespread and costly eye disorder, affecting as many as 80–90% of young adults in some Asian cities [1,2]. It is a condition in which vision at a distance is blurred, so that myopic individuals (myopes) have to bring objects closer to see them clearly. Myopic vision can be corrected with prescription lenses or corneal refractive surgery, making vision clear at any distance; but this does not correct the underlying problem, excessive elongation of the eye along the visual axis, which increases the risk of more severe consequences including retinal detachment and visual impairment. Simple, safe, and effective therapies are needed, to prevent the onset and progression of unrestrained axial elongation [1,2].

Such therapies are available – as eye drops containing the drug atropine [3], multifocal contact lenses [4], and overnight orthokeratology [5] – but none of them is completely satisfactory. Drugs might seem to be the treatment of choice, because of convenience for administering, and low risk of ocular infection or trauma. Low-dose atropine (0.01–0.05%) [3] is available and used rather widely; but for myopia treatment it is strictly off-label, it is not 100% effective, and it produces undesirable side-effects. These side effects are due mainly to atropine's well-known and generally assumed action as antagonist at muscarinic cholinergic receptors; they might be eliminated by switching to non-muscarinic agents such as alpha-adrenergic agonists [6]. However, discovery of such an alternative by the usual methods of drug development has largely failed.

Ideally, one could select candidate drugs by testing those that are expected to target the underlying pathogenetic mechanisms. Mechanisms responsible for myopia have been investigated in animal models: form-deprivation myopia (FDM), in which viewing through a translucent diffuser causes blurred vision, and lens-induced myopia (LIM), in which defocus by a negative lens causes hyperopic defocus and compensatory axial elongation [7]. Studies using these models in laboratory animals, ranging from hatchling chickens to mammals including non-human primates (NHPs), has contributed much to understanding what causes myopia [7]; but still, after decades of such studies, that understanding remains imperfect. Research on NHPs is most informative, but it remains slow, cumbersome, expensive, and limited by ethical considerations. Research on chicks is more rapid, economical and productive, but the eyes of chicks and mammals are sufficiently different to limit direct translation of suggested therapies to human myopia.

It follows, then, that a novel experimental animal model is needed, which offers low cost, high throughput testing of candidate drugs – and thus accelerated discovery of promising candidates for myopia treatment, involving limited follow-up studies in NHPs. In this issue of *EBioMedicine*, Lin et al. [8] report a new model for screening anti-myopia drugs. A gene-silencing agent (morpholino) was used to null expression of the gene (*zlum*) encoding an extracellular matrix protein, lumican, in zebrafish embryos; this causes rapid and excessive enlargement of the sclera (outer coat of the eye). A library of miscellaneous drugs approved by the US FDA was then screened for ability to prevent scleral enlargement; atropine and several matrix metalloproteinase (MMP)-inhibitors were found to be effective for *zlum*-null myopia, and testing in mice and hamsters demonstrated that they also inhibited FDM in mammals.

The zebrafish *zlum*-silencing model focuses attention on myopia mechanisms and therapeutic targets in the sclera [9], where lumican is an important component of the scleral extracellular matrix. Whether lumican is expressed in the retina or choroid – through which visual control of scleral expansion is exercised – is unknown, but unlikely. The outcome of the zebrafish trials suggests that the sclera, rather than its retina-choroid input, is a direct target for anti-myopia actions of atropine and the other effective agents. This is particularly interesting, because the site of atropine's anti-myopia action has been subject to debate [10].

In summary: This work is proof of principle, establishing the zebrafish as a model system for rapid and inexpensive high-throughput screening of candidate anti-myopia drugs. By identifying targets for myopia-inhibiting therapy in the sclera, the findings encourage new therapeutic developments that are independent of functions in the retina-RPE-choroid relay system – and which, unlike atropine, might have minimal effects on visual processing in the retina. Finally, the *zlum*-null model introduced here, based on disruption of the scleral extracellular matrix, might be modified to target structures and functions in other ocular tissues. The identification of specific cell types and neural circuits in the retina, plus the roles and mechanisms

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of retinal pigment epithelium (RPE), and choroid, would greatly expand its scope and power and likely yield new insights into the biological mechanisms responsible for human myopia, ultimately making possible rational therapies directed at those targets.

Author contribution

WKS is the sole author.

Declaration of Competing Interest

The author has no conflicts of interest to disclose.

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