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## The First Histologic Evidence of a Paravascular Pathway Within the Optic Nerve

We read with great interest the article by Mathieu et al.<sup>1</sup> entitled "Evidence for Cerebrospinal Fluid Entry Into the Optic Nerve via a Glymphatic Pathway," published recently in *Investigative Ophthalmology & Visual Science*.

First, we congratulate the authors for their excellent work and for their efforts to identify a "glymphatic pathway" within the optic nerve of mice. Elucidation of a paravascular transport system in the eye and optic nerve may help explain many of the puzzling features not of only glaucoma but also of common ocular diseases, such as age-related macular degeneration, which have been proposed to share a common glymphatic background<sup>2-5</sup> and exhibit substantial overlaps as well as co-occurrence with Alzheimer's disease.

As nicely reported by the authors, cerebrospinal fluid (CSF) enters the optic nerve via spaces surrounding blood vessels, bordered by astrocytic endfeet.<sup>1</sup> The authors cited one of our recent full papers,<sup>5</sup> providing, to the best of our knowledge, the first histologic evidence for a paravascular pathway within the optic nerve. Evidence supporting the existence of a paravascular pathway in the human optic nerve came from our postmortem study in which we examined cross-sections of human optic nerves by light microscopy after injecting India ink into the subarachnoid space (SAS) of the optic nerve.<sup>5,6</sup> In fact, this evidence was first reported in our Letter to the Editor published in 2016 in *Investigative Ophthalmology & Visual Science*.<sup>6</sup> We acknowledge the inherent limitations of our postmortem study, including the fact that we could not rule out artifacts due to changes in optic nerve sheath pressure resulting from injecting India ink into the SAS of the optic nerve, the fact that it was not possible to determine whether a complete glymphatic transport system was present in the optic nerve, and the fact that our observations were based upon a small sample size (only two cases) and thus relied upon anecdotal evidence. However, our study was carried out with human tissue and not with animals. Furthermore, the fact that no tracer was found in the surrounding axons<sup>5,6</sup> strongly supports that this finding demonstrates a well-defined anatomical structure, such as a paravascular pathway. Interestingly, Singh and Dass<sup>7</sup> performed an extensive study of the central artery of the retina and described "a space around the artery" in their histologic work. They, however, did not apply a tracer and the space they described could also have been an artifact resulting from shrinking tissue. We were therefore delighted to read the study by Mathieu et al.<sup>1</sup> providing new support for the existence of a paravascular pathway in the optic nerve and providing the first evidence of CSF entry via these paravascular spaces into the orbital optic nerve. Their study adds support to the notion that a glymphatic system is present in the optic nerve, and we believe that the next years will see a rapid expansion of the field of ocular glymphatic research, with great

potential for the development of novel diagnostic and therapeutic strategies for many ocular diseases.

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