Beyond inhibiting proangiogenic cytokines (in whichever form or in whatever combination) to reverse neovascular AMD, a current pipeline of translational endeavours are focussed on the role of inflammation, with the emphasis on redressing complement dysregulation or via inhibiting the assumed negative impact of chronic low-grade inflammation such as inflammasome activation. However, and not ignoring the complexity and as yet ill-defined underlying immunobiology, there is compelling contrary evidence that altered immune responses (increasing with age) provide an ability to maintain and preserve tissue function.1 This current work of Doyle et al.2 extends their pivotal observation, albeit still controversial in some circles, promulgating the relevance and impact of the authors’ previous work.3 That is, the activation of the inflammasome has a protective effect in this case through IL-18 production, protecting RPE, and preventing angiogenesis.4 The therapeutic adjuvant effect, therefore of IL-18 could be construed as augmenting the pathophysiological effect that is consequential to the inherent inflammasome activation that occurs during AMD and resultantly attenuates pathology and maintains the health of the RPE. This notion is supported by data in other systems as well so not surprisingly their current translational preclinical work delivers compelling data to show suppression of VEGF and VEGR2 expression, maintenance of vascular health, and suppression of spontaneous choroidal and retinal angiogenesis in rodents and ultimately demonstrating safety and efficacy in a Bayesian designed analysis of the study of intravitreal administration of human recumbent IL-18 to cynomologus monkeys. The data displays elegantly and optimizes the data from small numbers of nonhuman primates an iterative progression from their original observations, further countering any opposing data and hopefully takes us more rapidly toward adjuvant therapy modulating multiple pathways and in this case through augmenting aspects of inflammatory responses to protect the tissue.

References