

Author Response: The Role of IL-18 in the Treatment of AMD

We thank Zhang¹ for his interest in our work and for asking some questions pertaining to the use of IL-18 immunotherapy for AMD, which we will address. With regard to the mechanism of IL-18 and its antiangiogenic role in the eye, we concur that the distinct mechanism(s) is(are) yet to be fully resolved; however, we do know with certainty that IL-18 can potently downregulate VEGFR2 transcript and protein levels, which can effectively impact on the VEGF signaling axis. We are also currently examining the intricate pathways upon which IL-18 acts; suffice to say that it is almost certain that it is signaling through its cognate receptor (IL18R1) and its adaptor protein MyD88. We hope to publish these data in the near future.

We respectfully disagree with Zhang's statement that "IL-18 could not be used as a major agent to treat choroidal neovascularization (CNV)." As all in the research community will appreciate, the primate model of laser-induced CNV is not wet AMD and only recapitulates certain stages of CNV development in humans. As with laser-induction of lesions in other species, it is essentially an injury model, which yields high levels of VEGF in response. The CNVs are rate-limiting and are generally assessed using fundus fluorescein angiography (FFA) 15, 22, and 29 days post induction. This is a relatively short time to determine efficacy, and given the model is highly VEGF-dependent, it is no surprise that Lucentis (with an intraocular half life of 9 days; Genetech, San Francisco, CA, USA) is so efficacious. It does not, however, mean that IL-18 could not have utility in treating CNV secondary to wet AMD in human subjects. This can only be determined after well-controlled interventional medical studies have been conducted. As we outlined in our recent study, the use of IL-18 as an adjunct to current anti-VEGF approaches is favorable in the first instance; however, if efficacy dictates, it could represent a standalone intervention for some patients.

Zhang is correct in stating that we have previously shown IL-18 and anti-VEGF agents to work more effectively together, but this was in murine models, and as outlined above, the nonhuman primate model is very different and the effect of Lucentis would likely negate any further observable benefit. It is in fact the case, and is exemplified further in our paper, that intravitreal application of marketed anti-VEGF therapeutics are almost 100% effective in suppressing the emergence of grade IV lesions in this model, and consequently the model is not able to discriminate the potential of additional efficacy of other therapeutic approaches. In postulating on future experiments with this model, however, it would be very interesting to establish a titration curve for various doses of Lucentis in combination with varying doses of IL-18. This paradigm could be used to establish synergy or additivity with the two different therapeutic approaches.

With regard to systemic administration of human IL-18 in nonhuman primates, we would point out that IL-18 is already clinically enabled as a systemic agent in humans, and has been injected repeatedly at doses of up to 1000 µg/kg in subjects with an excellent safety profile.² Its use as a systemic agent in cynomolgous monkeys, however, is not as straightforward as human IL-18 is strongly immunogenic in monkeys, and repeated injections similar to those we carried out in previous studies in mice are problematic due to the generation of anti-drug antibodies. Zhang does, however, raise an exciting point with regard to systemic administration of IL-18 in humans for CNV treatment, and given its proven safety in human clinical

trials to date, we are fully aware of its potential use in the noninvasive management of CNV in human subjects.

Zhang is incorrect in stating that we have only assessed IL-18 in CNV induced by laser burn. We have extensively examined the effect of murine IL-18 in a spontaneous model of CNV and retinal angiomatous proliferation (RAP), the JR5558 mice (see fig. 1 in our recent paper).³

In relation to the use of IL-18 for other neovascular ocular diseases, we would highlight that IL-18 has previously been shown to have efficacy in preventing corneal neovascularization in addition to inner retinal neovascularization in murine models.⁴⁻⁶ Pertinently, however, the clinical studies cited by Zhang relating to IL-18 and VEGF suggest that IL-18 has a clear role in neovascularization in the eye. The paper by Song et al.⁷ was a pilot study that simply examined IL-18 and VEGF levels in vitreous of proliferative diabetic retinopathy (PDR) patients undergoing vitrectomy, and found high levels of both components in PDR patients compared to control subjects (macular hole); this does not allow for a statement of cause/effect relationship to be established, as a huge range of other cytokines are also increased in vitreous of PDR patients. However, the study by Shen and colleagues⁶ actually showed a dynamic and reciprocal relationship between levels of IL-18 and VEGF in patients with macular edema secondary to retinal vein occlusion. In this study, the authors examined levels of IL-18 in the aqueous of patients prior to a 3-month course of Lucentis injections. Individuals displaying high levels of IL-18 at baseline had significantly improved visual acuity after treatment with Lucentis. Rather than being a discrepancy, these studies actually bolster our own data in the nonhuman primate, suggesting that IL-18 will likely have therapeutic efficacy in treating neovascularization in human subjects.

Ultimately, however, the real value of IL-18 for neovascular AMD treatment will only be realized in full during controlled experimental clinical studies. Immunotherapeutic- and adjuvant-based approaches to treating AMD are a rapidly expanding field, and we thank Zhang for his interest and intellectual input in our project. Forums such as this can only benefit the entire vision research community.

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