Author Response: Comments on Enrichment of Macular Pigment Enhances Contrast Sensitivity in Subjects Free of Retinal Disease: CREST - Report 1

We note the letter from Professors Richard Bone and John Landrum[1] in response to our recently published clinical trial entitled "Enrichment of Macular Pigment Enhances Contrast Sensitivity in Subjects Free of Retinal Disease: Central Retinal Enrichment Supplementation Trials – Report 1"[2] and we thank our colleagues for their positive comments on our study. We acknowledge also their concerns about our Figure 1, which was prepared and included in our manuscript to help with the description of what we know about the distribution of lutein, zeaxanthin, and meso-zeaxanthin at the macula, and, more importantly, what we have learned from interventional trials using the macular carotenoids.[3] In other words, we believe our figure reflects the totality of available evidence. For example, we know that, in subjects with central dips (i.e., at 0.25° eccentricity) in their macular pigment, supplementation with a formulation containing meso-zeaxanthin (and not lutein) is required to rebuild their central macular pigment,[3] and this observation is important because it indicates that meso-zeaxanthin is the candidate composite of central macular pigment.

It is important to point out that Figure 1 in our manuscript does not claim to quantify the carotenoids at the macula, but rather showcase what we have learned regarding the relative distribution of the macular carotenoids. Also, and in reply to the main concern raised by Bone and Landrum in their letter, we do not feel that our figure presents "L as an annular ring around the fovea." Review of Figure 1 and the accompanying legend suggests that lutein is also present in the central macula but is distributed further into the periphery, where meso-zeaxanthin is not. The high concentration of meso-zeaxanthin presented centrally in our figure, and only centrally, may influence the interpretation of this figure, so it is important that it is clarified here, as per the explanation above. However, we do not doubt that there is room for improvement in our illustrative attempt, and we will take on board Bone and Landrum's comments in any further refinements of the Figure in question.

Of course, the pioneering work by Bone and Landrum must also be acknowledged, as it informed all those working on macular pigment with respect to the distribution of the carotenoids at the macula.[4,5] However, it is our view that additional work is needed, and across differing populations (e.g., healthy control eyes, eyes with AMD, eyes with Macular Telangiectasia) using the now sensitive and further developed HPLC methods available, to further understand the distribution of the carotenoids at the macula. This is particularly important because (unlike in 1997) we now know from the literature that the distribution of macular pigment is not as simple as originally proposed (i.e., it cannot just be described as a first-order exponential decline with increasing retinal eccentricity) (Delori FC, et al. *IOVS* 2004;45:ARVO E-Abstract 1288).[6–9] Also, careful review of the papers cited by Professors Bone and Landrum, show that we are still lacking HPLC carotenoid distribution analysis information for central macular pigment. For example, there is no information in their papers about the distribution of the carotenoids at 0.25° or 0.5° eccentricity, and very little information at 1.0° of eccentricity (i.e., the 0.25-mm radius = circa 1° eccentricity). We still do not know what how the carotenoids are distributed at the very center, and therefore we can only draw conclusions from the carotenoid interventional trials in tandem with the information we can take from the HPLC studies by Bone and Landrum. It would be very useful if Bone and Landrum were able to report their data in millimeters from the degree data they reported in their papers.

In summary, we welcome this correspondence from Bone and Landrum, and are pleased that this important scientific discussion continues. Additional studies will help further our understanding of the distribution of the carotenoids at the macula and this needs to be performed for different populations.

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References

1. Bone RA, Landrum JT. Comment on enrichment of macular pigment enhances contrast sensitivity in subjects free of retinal disease: CREST - Report 1. *Invest Ophthalmol Vis Sci*. 2016;57:5415.
2. Nolan JM, Power R, Stringham J, et al. Enrichment of macular pigment enhances contrast sensitivity in subjects free of retinal disease: Central Retinal Enrichment Supplementation Trials - Report 1. *Invest Ophthalmol Vis Sci*. 2016;57:3429–3439.
3. Nolan JM, Akkali MC, Loughman J, Howard AN, Beatty S. Macular carotenoid supplementation in subjects with atypical spatial profiles of macular pigment. *Exp Eye Res*. 2012;101:9–15.
4. Bone RA, Landrum JT, Fernandez L, Tarsis SL. Analysis of the macular pigment by HPLC: Retinal Distribution and Age Study. *Invest Ophthalmol Vis Sci*. 1988;29:843–849.
5. Bone RA, Landrum JT, Friedes LM, et al. Distribution of lutein and zeaxanthin stereoisomers in the human retina. *Exp Eye Res*. 1997;64:211–218.
6. Bone RA, Brener B, Gibert JC. Macular pigment, photopigments, and melanin: distributions in young subjects determined by four-wavelength reflectometry. *Vision Res*. 2007;47:3259–3268.
7. Dietzel M, Zeimer M, Heimes B, Pauleikhoff D, Hense HW. The ringlike structure of macular pigment in age-related maculopathy: results from the Muenster Aging and Retina Study (MARS). *Invest Ophthalmol Vis Sci*. 2011;52:8016–8024.
8. Kirby ML, Beatty S, Loane E, et al. A central dip in the macular pigment spatial profile is associated with age and smoking. *Invest Ophthalmol Vis Sci*. 2010;51:6722–6728.
9. Berendschot TT, van Norren D. Macular pigment shows ringlike structures. *Invest Ophthalmol Vis Sci*. 2006;47:709–714.

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