E Anitua[1,2,3], R Prado[1,2,3], F Muruzabal[1,2,3] and G Orive[1,2,3]

[1]Foundation Eduardo Anitua, Vitoria, Spain
[2]Biotechnology Institute (BTI), Vitoria, Spain
[3]University Institute for Regenerative Medicine and Oral Implantology - UIRMI (UPV/EHU-Fundación Eduardo Anitua), Vitoria, Spain
E-mail: gorka.orive@ehu.eus

Eye (2018) **32,** 472–473; doi:10.1038/eye.2017.182; published online 8 September 2017

Sir,
Reply to Anitua *et al*: Searching for the best blood-derived eye drops

We thank Anitua *et al.* for their stimulating comments and welcome further discussion.[1]

We note most of their comments are based on the effect of growth factors on epithelial defects, whereas our study[2] was on treating chronic dry eyes.

We agree that the growth factor concentration in platelet-rich plasma (PRP) is likely greater than in plasma of fresh whole blood. Despite this, our preliminary results suggest fingerprick autologous blood (FAB) efficacy is comparable to that of autologous serum.[3] We propose two possible explanations for this. Firstly, platelet activation may occur in the process of FAB draw and application, and the authors are correct that quantitative characterisation of the degree and reliability to which this occurs requires further study. Additionally, fresh platelets may be able to adhere to areas of the inflamed dry eye anterior surface, allowing for a targeted activation and release of growth factors, as opposed to simply coating the eye momentarily with growth factors from PRP. Secondly, we propose that FAB efficacy might relate to other factors in whole blood, such as fibronectin, vitamins, and other chemicals at physiological level, and their interaction than just growth factors alone. We also note that although Anitua *et al* recommend from their experience higher concentrations of growth factors than blood for optimal therapeutic effect, long-term safety data are lacking. Higher concentrations may induce harmful effects such as corneal neovascularisation from greater epidermal growth factor[4] or impaired epithelial wound healing from high concentrations of transforming growth factor beta.[5] Anitua *et al* rightly mention that non-activated PRP was less effective than its activated counterpart;[6] however, this was a laboratory study only looking at corneal wound healing on rabbit eyes and therefore cannot be directly extrapolated to real-life conditions of human severe dry eye patients. As mentioned in our paper discussion, there may also be release of growth factors by red blood cells,[7] providing an additional source of and possibly different growth factors than just platelet activation. Only fresh blood has the potential to offer an orchestrated response with its additional adaptive cellular composition to the ever-changing ocular surface environment, particularly in dry eyes. The exact mechanisms will need to be elucidated. Speculation on superior efficacy and putative mechanisms of different blood-derived products is limited by a lack of mechanistic studies and direct comparisons between them. We encourage such studies and suggest FAB be included in these comparisons.

The potential variability in cellular composition from drop to drop has been considered by the authors and again further work is suggested to evaluate this.

Anitua *et al* propose an interesting approach of 'inactivation protocol for the immune component of the eye drops' for diseases such as Sjogren's. We agree, but this might affect the antimicrobial properties and any unknown beneficial effect of these inactivated components. The increased use of allogenic serum in Sjogren's patients may give us a better understanding in this area.

The authors note the valid concern regarding viability of long-term compliance in light of repeated fingerpricks during treatment. The subjective improvement noted by these patients has resulted in all continuing treatment after study conclusion (the longest for over 3 years). This would suggest that the discomfort of regular fingerpricks is outweighed by the improvement in quality of life provided by relief from severe dry eye syndrome. We feel a major advantage that FAB presents is not being impeded by many of the barriers experienced by other blood-derived therapies such as cost, repeat venesections, and storage.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We thank the NIHR Moorfields Biomedical Research Centre for their infrastructural support.

References

1 Anitua E, Prado R, Muruzabal F, Orive G. Searching for the best blood-derived eye drops. *Eye (Lond)* 2018; **32**: 472–473.
2 Than J, Balal S, Wawrzynski J, Nesaratnam N, Saleh GM, Moore J *et al.* Fingerprick autologous blood: a novel treatment for dry eye syndrome. *Eye (Lond)* 2017; **31**: 1655–1663.
3 Nesaratnam N, Shah S, Kumar B, Wawrzynski J, Than J, Sharma A. Fingerprick autologous blood is a feasible alternative to autologous serum in the treatment of dry eye secondary to Sjögren's syndrome. In: *ARVO 2016*: Seattle, USA. Program Number: 5688. Poster Board Number: A0034, 2016.
4 Gospodarowicz D, Bialecki H, Thakral TK. The angiogenic activity of the fibroblast and epidermal growth factor. *Exp Eye Res* 1979; **28**(5): 501–514.
5 Tsubota K, Goto E, Fujita H, Ono M, Inoue H, Saito I, Shimmura S. Treatment of dry eye by autologous serum application in Sjögren's syndrome. *Br J Ophthalmol* 1999; **83**(4): 390–395.
6 Freire V, Andollo N, Etxebarria J, Hernáez-Moya R, Durán JA, Morales MC. Corneal wound healing promoted by 3 blood derivatives: an in vitro and in vivo comparative study. *Cornea* 2014; **33**(6): 614–620.
7 Antunes RF, Brandão C, Maia M, Arosa FA. Red blood cells release factors with growth and survival bioactivities for

normal and leukemic T cells. *Immunol Cell Biol* 2011; **89**(1): 111–121.

S Balal[1], J Than[1], N Nesaratnam[1], BAR Sharma[1], J Enson[2] and A Sharma[1]

[1]Moorfields Eye Centre at Bedford Hospital, Bedford, UK
[2]Imperial College School of Medicine, Kensington, London, UK
E-mail: anant.sharma@bedfordhospital.nhs.uk

Eye (2018) **32,** 473–474; doi:10.1038/eye.2017.183; published online 15 September 2017

Sir,
A novel use of ultrasound biomicroscopy

Ultrasonic biomicroscopy (UBM) is an imaging technique that utilizes 50 MHz high-frequency sound waves to produce a high-resolution image. It has multiple applications in ophthalmology to evaluate both anterior segment structures and peripheral posterior segment anatomy. When used with a ClearScan cover, it can image anterior segment angles, angle tumours, peripheral choroidal tumours, ciliochoroidal detachments, and pars planitis, as well as identify intraocular foreign bodies.[1–5] ClearScan is a sterile, single-use, water-filled bag that covers the end of the UBM probe. A securing collar with a flexible inner ring at the base of the bag creates a watertight seal around the UBM probe. It allows examination of the cornea and structures 10 mm distal. We report the first use of ClearScan and UBM to evaluate periocular structures such as the eyelid and adjacent fleshy areas. We present a novel use of UBM to identify and remove periocular metallic foreign bodies that were prohibiting a patient from undergoing magnetic resonance imaging needed for cavernous sinus mass evaluation.

Our patient is a 56-year-old man who presented with diplopia. On examination he was found to have progressive ophthalmoplegia involving multiple cranial nerves. A computed tomography scan was obtained, which showed multiple small periorbital metallic foreign bodies along the lateral and superior orbital rim, but did not show a cavernous lesion. Radiology recommended further evaluation with MRI for better evaluation of the cavernous sinus. Upon further questioning, the patient, who is a welder, recalled having met with an accident at work involving a piece of metal striking his face. He did not seek medical attention after the accident. Upon discussion with the patient, he elected to undergo foreign body removal and MRI testing. We elected to try the novel use of ultrasound guidance for intraoperative localization to maximize surgical success.

Prior to removing the foreign bodies, an intraoperative Quantel Aviso 50 MHz UBM in combination with a ClearScan cover were used to locate the foreign bodies. UBM images showed multiple high signal spikes/bright 'dots' underneath the skin, and the incisions were made over those areas (Figure 1). Dense fibrotic, reflectile material was extracted from these areas. Subsequent X-rays did not show foreign bodies, and the patient was then able to safely undergo an MRI.

We present this case to the reader to highlight the ease, efficacy, instant feedback, and lower cost of using UBM/ClearScan cover intraoperatively to assist in the excision of periocular foreign bodies. We suggest that the use of UBM/ClearScan cover can further be extended to superficial foreign body removal from any area of the body.

Conflict of interest

Dr Thomas Prager is a paid consultant for ESI, manufacturer of the ClearScan. The remaining authors declare no conflict of interest.

References

1 Deramo VA, Shah GK, Baumal CR, Fineman MS, Corrêa ZM, Benson WE *et al.* Ultrasound biomicroscopy as a tool for detecting and localizing occult foreign bodies after ocular trauma. *Ophthalmology* 1999; **106**: 301–305.
2 Janssens K, Mertens M, Lauwers N, de Keizer RJ, Mathysen DG, De Groot V. To study and determine the role of anterior segment optical coherence tomography and ultrasound biomicroscopy in corneal and conjunctival tumors. *J Ophthalmol* 2016; **2016**: 1048760.
3 Ozdal MP, Mansour M, Deschenes J. Ultrasound biomicroscopic evaluation of the traumatized eyes. *Eye (Lond)* 2003; **17**: 467–472.
4 Raina UK, Kumar V, Kumar V, Sud R, Goel N, Ghosh B. Metallic intraocular foreign body retained for four years–an unusual presentation. *Cont Lens Anterior Eye* 2010; **33**: 202–204.
5 Mannino G, Abdolrahimzadeh B, Calafiore S, Anselmi G, Mannino C, Lambiase A. A review of the role of ultrasound biomicroscopy in glaucoma associated with rare diseases of the anterior segment. *Clin Ophthalmol* 2016; **10**: 1453–1459.

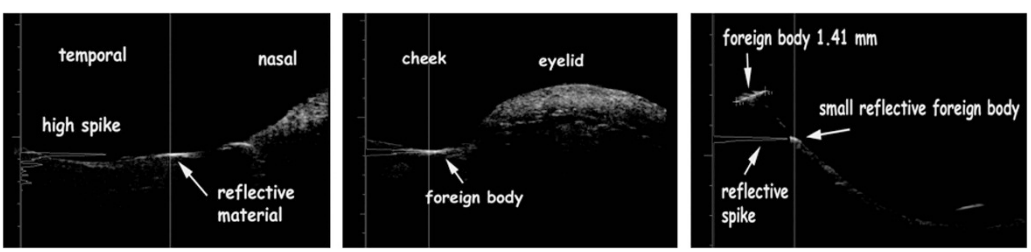

Figure 1 UBM images showing multiple high signal spikes/bright 'dots' underneath the skin corresponding to the foreign bodies.