An In Vitro Evaluation of the Anew Zephyr Open-Bag IOL in the Prevention of Posterior Capsule Opacification Using a Human Capsular Bag Model

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Purpose. During cataract surgery an IOL is placed within the capsular bag. Clinical studies show that IOLs with a square edge profile and complete contact between the IOL and the anterior capsule (AC) are currently the best way to prevent posterior capsule opacification (PCO). This has been challenged by recent clinical and experimental observations, which suggest that if the capsular bag is kept open with separation of contact between the AC and posterior capsule (PC) by an "open-bag device" PCO is dramatically reduced. Therefore, the current study set out to evaluate the putative merits of an open-bag IOL (Anew Zephyr) in a human capsular bag model.

Methods. An in vitro organ culture model using the bag–zonular–ciliary body complex isolated from fellow human donor eyes was prepared. A capsulorhexis and lens extraction were performed, and an Alcon Acrysof IOL or Anew Zephyr IOL implanted. Preparations were secured by pinning the ciliary body to a silicone ring and maintained in 6 mL Eagle's minimum essential medium (EMEM) or EMEM supplemented with 2% vol/vol human serum (HS) and 10 ng/mL TGF-β2 for 28 days. Cell growth and capsular modifications were monitored with phase-contrast and modified dark-field microscopy.

Results. In serum-free EMEM culture conditions, cells were observed growing onto the PC of preparations implanted with an Anew Zephyr IOL, but this was retarded relative to observations in match-paired capsular bags implanted with an Alcon Acrysof IOL. In the case of cultures maintained in 2% HS-EMEM plus TGF-β2, the movement on to the PC was again delayed with the presence of an Anew Zephyr IOL. Differences in the degree of growth on the PC and matrix modifications were apparent with the different donors, but in each case the match-paired Alcon Acrysof implanted bag exhibited significantly greater coverage and modification of the capsule.

Conclusions. The Anew Zephyr open-bag IOL performs consistently better than the Alcon Acrysof IOL in the human capsular bag model. We propose that the benefits observed with the Anew Zephyr result from a reduction in growth factor levels available within the capsular bag and a barrier function imposed by the ring haptic.

Keywords: intraocular lens, posterior capsule opacification, cataract, human, in vitro, model

Cataract is a consequence of the ageing of the lens and is the major priority in the global initiative to eliminate avoidable blindness by the year 2020.[1] At present, the only means of treating cataract is by surgery, which initially restores high-quality vision and this is currently the most performed operation in developed countries. Unfortunately, posterior capsule opacification (PCO), the most common complication of cataract surgery develops in a significant proportion of patients to such an extent that secondary visual loss occurs.[2]

A modern cataract operation generates a capsular bag (the basement membrane of the lens), which comprises a proportion of the anterior and the entire PC.[2] The bag remains in situ and partitions the aqueous and vitreous humors, and usually houses the IOL. Following surgery, light can pass freely along the visual axis through the transparent IOL and thin acellular PC. However, lens epithelial cells (LECs) remain at the time of surgery and recolonize denuded regions of the anterior capsule (AC), and most importantly colonize the previously cell-free PC.[2] Subsequent changes to the matrix and cell organization result in light scatter. If these changes are sufficiently severe, vision can become seriously impaired and corrective neodymium-doped yttrium aluminium garnet (Nd:YAG) laser surgery is required to remove the opacified PC,[2] which is both expensive, logistically difficult with elderly patients, and not without medical risk.[3]

There are a number of factors that can increase the incidence of PCO, for example, young age, intraocular inflammation, and surgical factors.[2] However, studies have shown that PCO rates can be diminished by improved IOL design,[4,5] especially a square edge profile, which produces a barrier to LEC migration. However, in spite of these improvements approximately 10% of patients still require a Nd:YAG laser capsulotomy within 2 years of surgery, which places a strain on healthcare resources, medical time, and the quality of

TABLE. Relevant Information Associated With Donors Used in This Study

Donor Age	Sex	Cause of Death	Culture Conditions
79	Male	Cerebrovascular accident	SF EMEM
56	Female	Pneumonia	SF EMEM
61	Male	Prostate cancer	SF EMEM
84	Male	Unknown	2% HS + 10 ng/mL TGF-β
53	Male	Unknown	2% HS + 10 ng/mL TGF-β
63	Male	Bowel cancer	2% HS + 10 ng/mL TGF-β

SF, serum-free.

a patient's life.[6] These problems are exacerbated in pediatric patients, when cataract surgery is performed on patients with ocular inflammation or following insertion of multifocal IOLs that have a reduced barrier function. Therefore, PCO impact is a socioeconomic, geographic, and ageing problem, and novel approaches in PCO prevention need to be developed.

At present, it is widely considered that an IOL with a square edge profile and a capsulorhexis completely in contact with the anterior surface offers the best PCO prevention, but this has been challenged by clinical and experimental observations in rabbit and monkey eyes, which demonstrate that if the AC and PC components are kept apart there is a profound reduction in PCO.[7–9] Similar results in rabbit eyes have been shown with a novel disc design of IOL, which keeps the bag open.[10] This animal work has been corroborated by clinical observations with the Synchrony dual optic IOL (Abott Medical Optics, Santa Ana, CA, USA), which was developed as an accommodating IOL and consists of two linked IOLs implanted in the capsular bag which, by coincidence, keep the capsule open; an impressive observation has been that these eyes have extremely low PCO rates. Further support in human eyes comes from a recent Japanese study using a ring device to separate the capsules showing a consistent reduction in PCO with up to 7 years post surgery.[11] In summary, there is now a substantial body of evidence, which shows that various devices that keep the capsular bag open, limit PCO. Anew Optics (Bristol, TN, USA) has developed a novel disc design of IOL, which keeps the bag open and using rabbits as a test system, this has proven to be successful in reducing PCO formation.[10,12] it is now important to understand the relationship between the IOL and human lens capsule and its associated cells. Therefore, in the current study, we used an in vitro human capsular bag system to evaluate the ability of the Anew Optics Zephyr IOL in the prevention of PCO.

METHODS

All reagents were from Sigma (Poole, Dorset, UK) unless otherwise stated.

Capsular Bag Preparation

Cataract surgery generates a clear capsular bag, and it is this procedure that has been transferred from the operating theater to the laboratory. The model previously described by Liu et al.[13] and developed by Cleary et al.[14] was employed. Pairs of donor eyes (corneas previously removed for eye banking; Table) were obtained within 48-hours post mortem with national research ethics committee approval and used in accordance with the tenets of the Declaration of Helsinki. The procedure involves washing the lens briefly with Eagle's minimum essential medium (EMEM) before creating a small rhexis and removing the central lens mass from donor globes to leave a capsular bag for implantation of the IOL. The capsular bag containing the IOL was removed from the eye following careful separation from the ciliary body and transferred to a tissue-culture dish. The ciliary body was secured to a silicone ring using entomologic pins. Using this method, the lens capsule remains intact and the capsular bag physiologically suspended from zonules. As a control IOL we tested an Alcon Acrysof single piece IOL, which is recognized to have excellent performance in suppressing PCO and is often regarded as a gold standard[2] (Fig. 1A). The test IOL used was the Anew Zephyr open-bag design. This is an IOL with a circular fenestrated 360° ring haptic connected by spokes to the optic. The design of the ring haptic separates and prevents adhesion of the ACs and PCs and allows aqueous to percolate into the equatorial bag[10,12] (Fig. 1B). Capsular bag preparations were maintained in nonsupplemented (serum-free; SF) EMEM or EMEM supplemented with 2% human serum (HS), 10 ng/mL TGF-β2 and 50 μg/mL gentamicin for a 28-day period. Ongoing

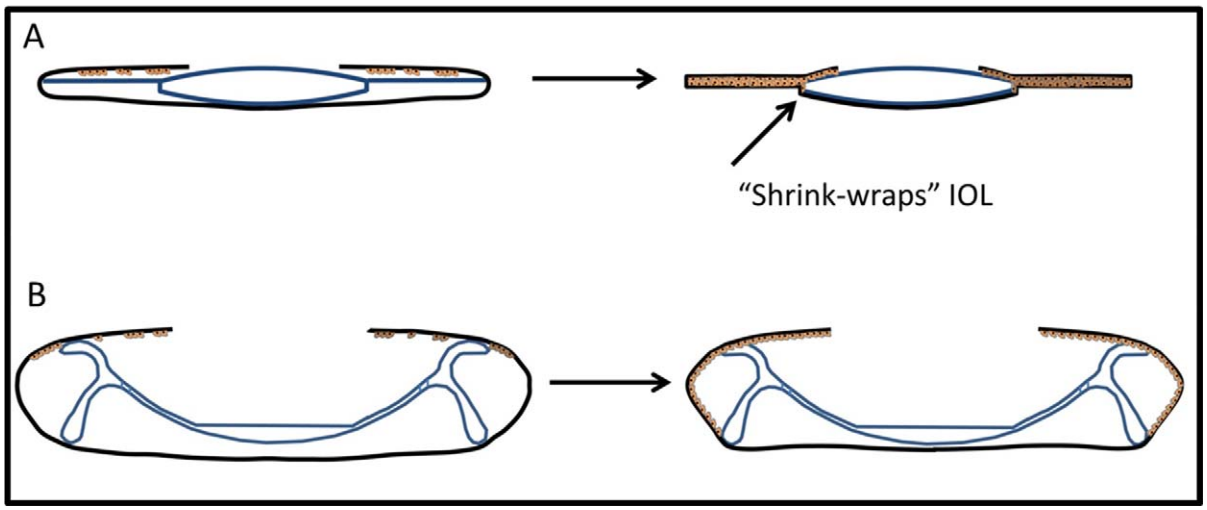

FIGURE 1. A schematic diagram illustrating the position of (**A**) a conventional square edge IOL and (**B**) the open-bag Anew Zephyr IOL within the capsular bag and how their physical properties could provide a barrier to cell movement.

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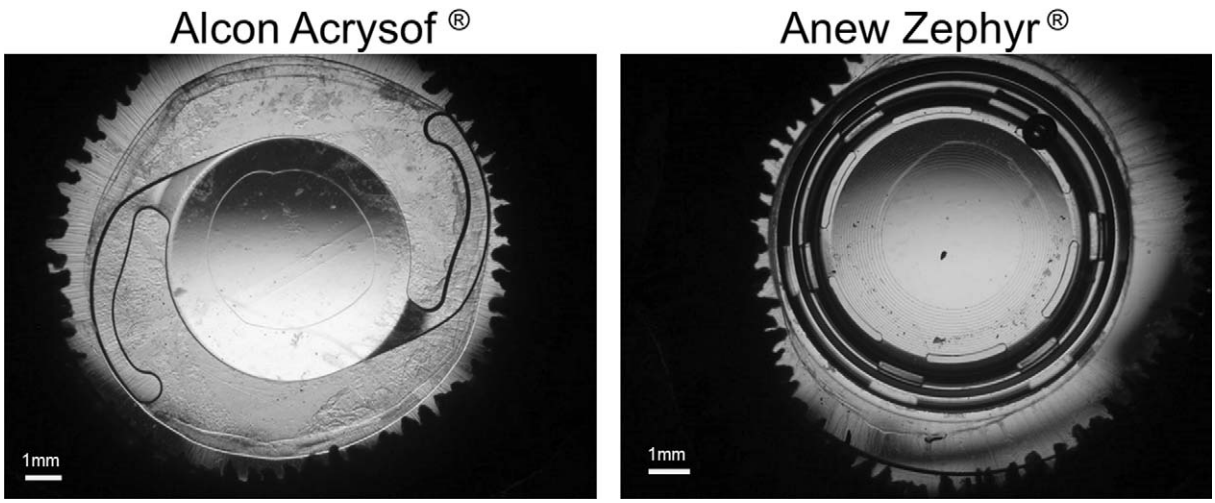

FIGURE 2. Modified dark-field images of match-paired capsular bags implanted with an Anew Zephyr IOL or an Alcon Acrysof IOL.

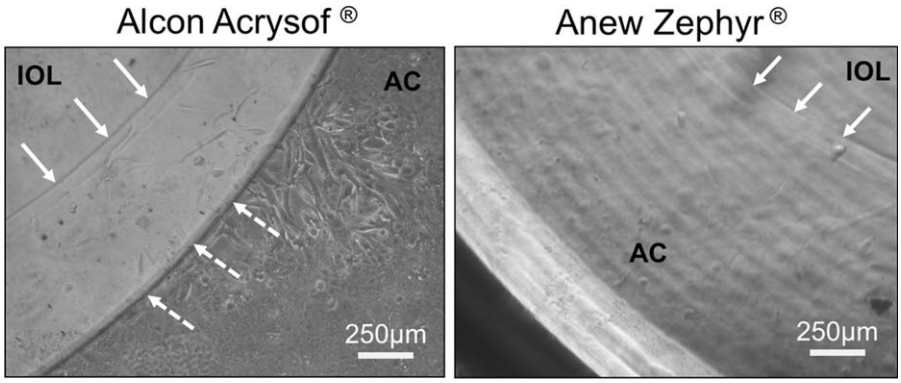

FIGURE 3. Recolonization of the AC of capsular bags implanted with an Alcon Acrysof or an Anew Zephyr IOL. Phase-contrast micrographs were captured following a 1-week period of culture in serum-free EMEM. *Dashed arrow*, IOL optic edge; *solid arrow*, rhexis edge.

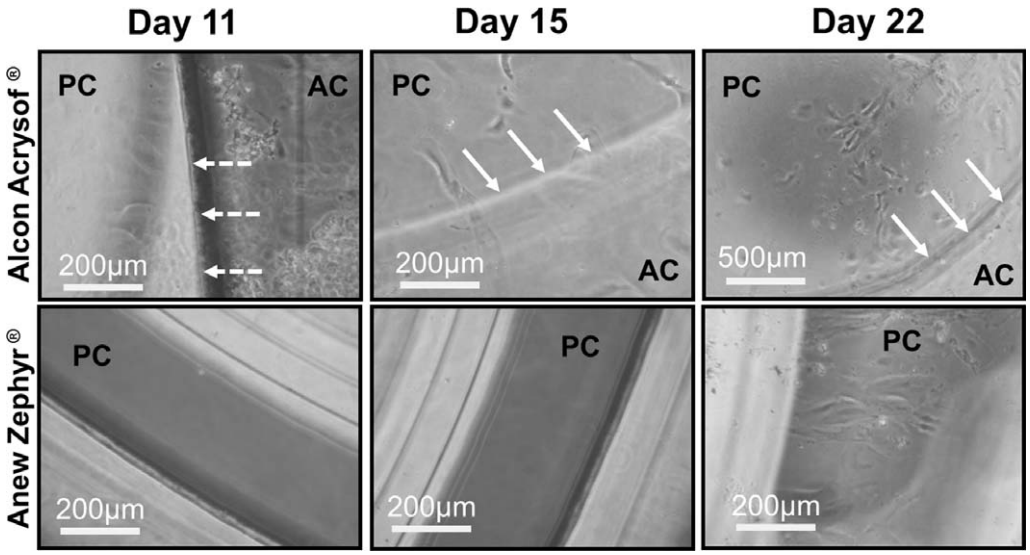

FIGURE 4. Phase-contrast micrographs showing cell growth on the posterior capsule of match-paired capsular bags implanted with an Anew Zephyr or an Alcon Acrysof IOL cultured in serum-free conditions. *Dashed arrow*, IOL optic edge; *solid arrow*, rhexis edge.

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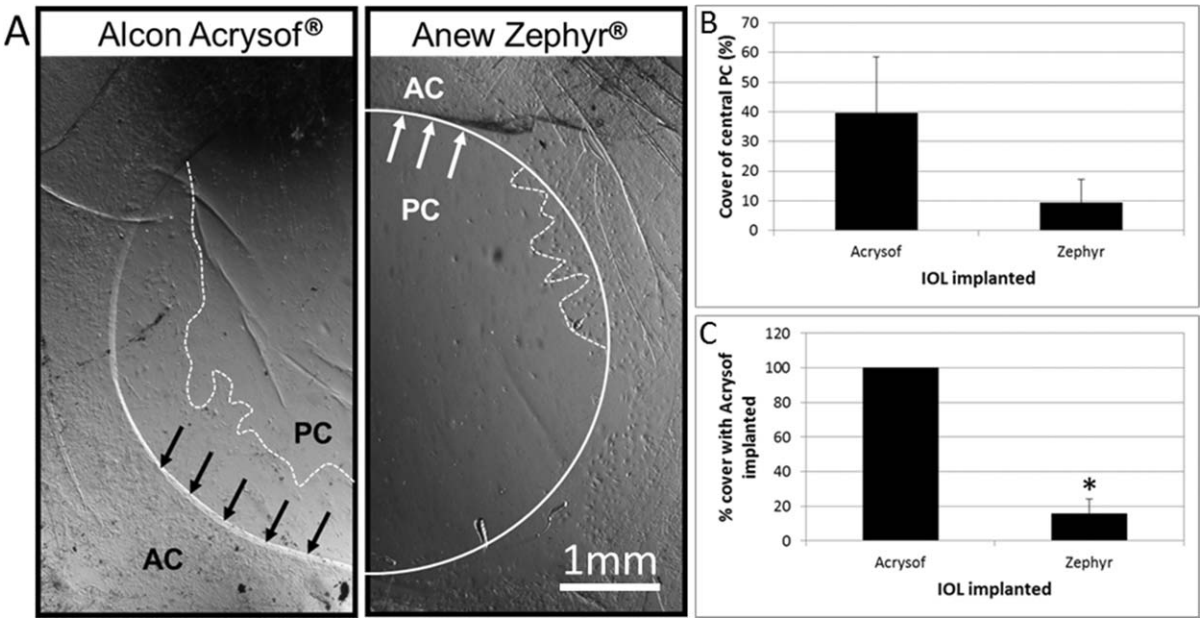

Figure 5. The Anew Zephyr IOL reduces cell coverage of the PC in serum-free conditions over a 1-month culture period. (**A**) Modified dark-field micrographs of capsular bags captured at end point following removal of the respective IOL and fixation. The modified dark-field images present the AC, capsulorhexis (*arrowed*), and PC. In the case of the Anew Zephyr IOL implanted capsular bag, a section of the AC has been folded back to expose the underlying cells on the PC; for the purpose of clarity, the *solid white line* indicates the natural location of the rhexis edge. (**B**) Pooled data showing coverage of the central PC in the presence of an Alcon Acrysof or Anew Zephyr IOL. (**C**) Pooled data showing coverage in Anew Zephyr implanted capsular bags relative to their match-paired Alcon Acrysof implanted counterpart. Data are presented as mean ± SEM ($n = 3$). *Indicates a significant difference between groups (Student's *t*-test; $P \leq 0.05$).

observations were captured using phase-contrast microscopy. Cell coverage of the central PC was determined using ImageJ1.45s analysis software (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA). To establish a measure of light scatter in the central PC, Image Pro Premier software (Media Cybernetics, Warrendale, PA, USA) was employed using a method adapted from Wormstone et al.[15] In this present study, images were placed through a single pass of a Laplacian filter, which identifies light scattering regions. These regions appear bright, and thus have a high intensity per pixel. The mean intensity of all pixels within the rhexis region was determined. Capsular bags without cells present on the PC were used to establish background levels, which was subtracted from test values.

Results

Both Anew Zephyr and Alcon Acrysof IOLs were successfully housed within the capsular bag of each donor pair (Fig. 2). In the case of the Alcon Acrysof IOL, the capsulorhexis edge lay on the anterior optic in each preparation; with the Anew Zephyr IOL, the ACs and PCs were separated. It should be pointed out that the relative number of cells remaining after surgery is similar in both match-paired bags from a single donor; however, variation in cell number following surgery between donors does occur. This is reflective of the variation also seen in cataract patients. Recolonization of the AC within both bags of a donor matched-pair also occurs in a similar fashion, therefore the differences between the matched-paired bags are largely associated with events on the PC.

The first series of capsular bags employed to compare the IOLs was maintained in serum-free EMEM, to test the influence of IOL design on LEC behavior under baseline conditions. Following 1 week of culture, cells could be clearly seen recolonizing denuded regions of the AC of capsular bags implanted with an Alcon Acrysof IOL (Fig. 3) or an Anew Zephyr IOL (Fig. 3). Observation of cell growth on the peripheral PC can be difficult in capsular bags implanted with the Alcon Acrysof IOL because of the close proximity of the AC; however, cells could be observed growing beyond the edge of the optic body within the first 2 weeks of culture. At comparable times, match-paired cultures implanted with an Anew Zephyr IOL exhibited a marked reduction in growth across the PC, which is illustrated in Figure 4. Cells continued to grow throughout culture in all preparations; however, the extent of coverage at a given time-point was always greater in the presence of an Alcon Acrysof IOL. At end point (day 28), cells could be observed on the PC beyond the capsulorhexis margin in all preparations. Mean percent coverage of the central PC with an Alcon Acrysof IOL implanted was 39.53 ± 18.93% and with an Anew Zephyr IOL 9.36 ± 7.87% (Fig. 5B). Due to general differences in the scale of wound-healing response between donors this was not a significant difference, but a common pattern was observed with each donor, such that capsular bags implanted with the Anew Zephyr IOL consistently had less coverage on the central PC at day 28 than with an Alcon Acrysof implanted. Match-paired comparison of coverage at day 28 showed a significant reduction (84.44%) in coverage with an Anew Zephyr IOL relative to that seen with the Alcon Acrysof implanted (Fig. 5C). It should also be noted that coverage was often asymmetric regardless of which IOL was implanted, suggesting a point of weakness in the barrier function of both IOLs.

A second series of match-paired capsular bag experiments was maintained in 2% HS-EMEM and 10 ng/mL TGF-β2 to provide comparison of IOLs in conditions known to drive growth and contraction.[16] In these conditions, dramatic changes were seen, such that in preparations implanted with an Acrysof or Anew Zephyr IOL cells covered the entire AC and their morphology was fibroblastic in appearance (Fig. 6). In addition matrix contraction (wrinkling) was evident in the

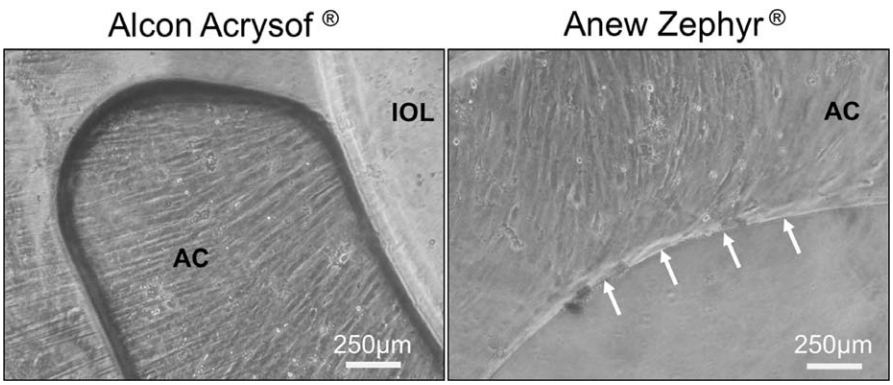

FIGURE 6. Recolonization of the AC of capsular bags implanted with an Alcon Acrysof or an Anew Zephyr IOL, following a 1-week period of culture in EMEM supplemented with 2% human serum plus 10 ng/mL TGFβ2; *solid arrow*, rhexis edge.

peripheral regions of capsular bags. The coverage observed on the PC at specific time-points varied between donors; however, it was consistently observed that coverage of the PC was retarded in the presence of the Anew Zephyr IOL (Fig. 7). For example, at Day 13, cells were observed below the Alcon Acrysof optic in all cases, but no cells were observed in the fenestrations (i.e., the peripheral PC at this time-point). At end-point this order was still apparent, but not significantly different. However, the degree of light scatter observed in the central PC, resulting from cell and matrix modification significantly differed between the two implants, such that capsular bags implanted with an Acrysof IOL presented more than double the level of light-scatter observed than their Anew Zephyr IOL implanted counterparts (Fig. 8). Further assessment of the capsular bags was made following IOL removal. This was achieved by creating radial incisions in the AC and folding it back, such that the central and peripheral PC is exposed; this allowed greater evaluation of cell distribution in this region and assessment of IOL barrier function. There was evidence of a barrier effect in association with both IOLs (Fig. 9). At day 28, there is evidence that this has been breached in places, however, a better retention of a barrier was observed with the Anew Zephyr IOL (Fig. 9).

DISCUSSION

Posterior capsule opacification is associated with a progressive deterioration in vision and its management adds substantial costs to healthcare providers, therefore, improved management of PCO is an important healthcare need.[2] A number of approaches to resolve PCO are being developed that target the biological mechanisms of the condition, such as preventing LEC migration/proliferation, transdifferentiation to myofibroblasts, matrix contraction, and in some cases annihilation of the LEC population.[2] In all cases the objective is to retain a clear and uninterrupted passage of light along the visual axis. Biological processes face clinical and regulatory issues and at present these approaches have yet to reach the clinic, and thus IOL design remains the leading approach in the management of PCO. Perhaps, the most significant advance in the last 20 years has been the incorporation of a square edge on the IOL optic,[17] which through interaction with the lens capsule forms a "barrier" to the cells and consequently impedes migration onto the central PC. This effect is not limited to material[18] and the sharpness of the IOL posterior edge appears to be the most important factor.[19] The barrier effect is believed to be optimal when the capsulorhexis is fully seated on the anterior optic surface.[20] As the anterior and PCs come in contact the cellular

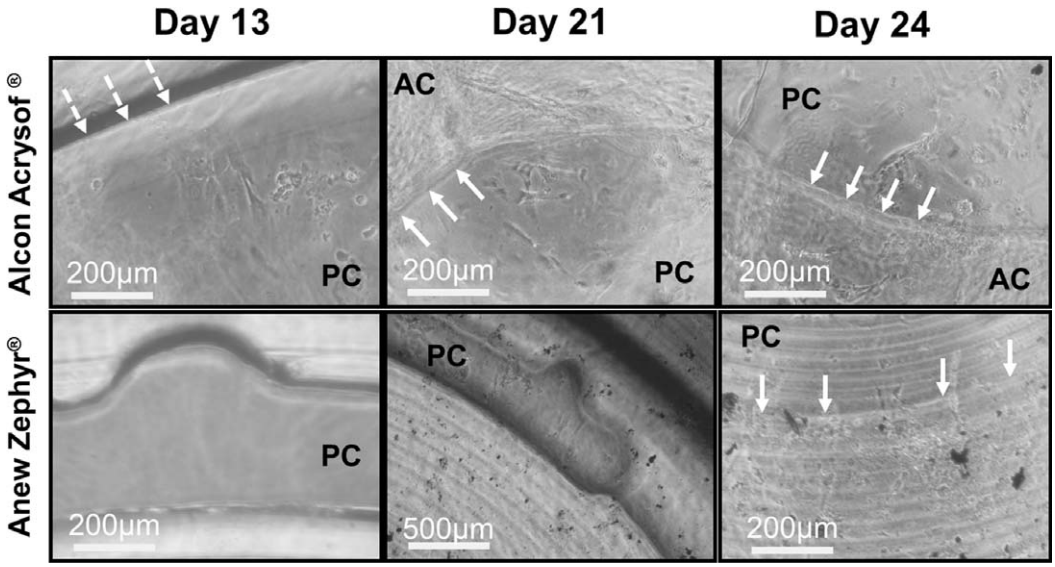

FIGURE 7. Phase-contrast micrographs showing cell growth on the PC of match-paired capsular bags implanted with an Anew Zephyr or an Alcon Acrysof IOL cultured in 2% human serum plus 10 ng/mL TGF-β2. *Dashed arrow*, IOL optic edge; *solid arrow*, rhexis edge.

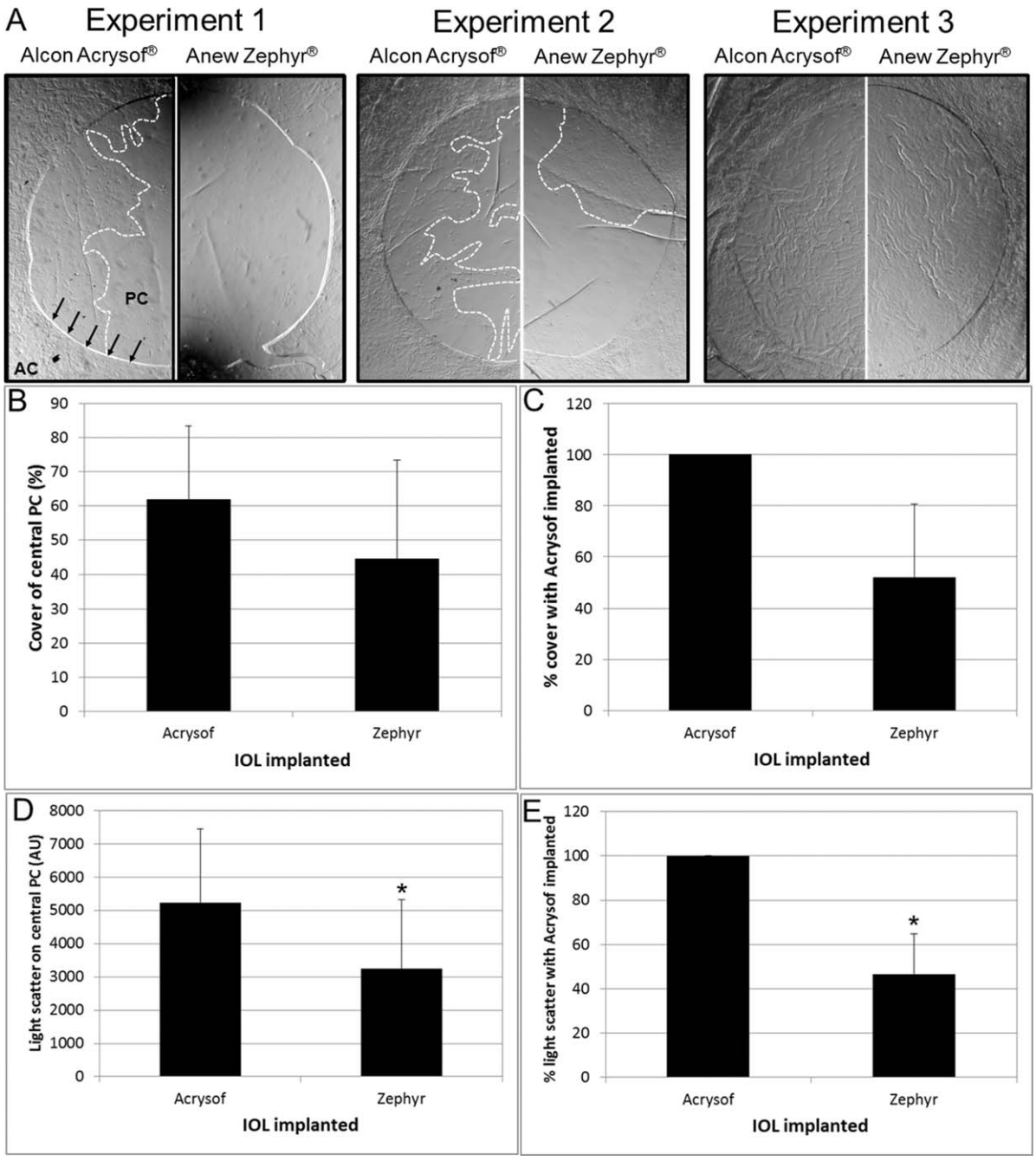

Figure 8. The Anew Zephyr IOL appears to reduce cell coverage and formation of light scattering structures on the PC of capsular bags maintained in 2% human serum plus 10 ng/mL TGF-β2 for 1 month. (**A**) Modified dark-field micrographs from three match-paired capsular bag experiments captured following removal of the respective IOL and fixation. The modified dark-field images present the AC, capsulorhexis (*arrowed*), and PC. (**B**) Pooled data showing coverage of the central PC in the presence of an Alcon Acrysof or Anew Zephyr IOL. (**C**) Pooled data showing coverage in Anew Zephyr implanted capsular bags relative to their match-paired Alcon Acrysof implanted counterpart. (**D**) Pooled data showing the level of light scatter in the central PC in the presence of an Alcon Acrysof or an Anew Zephyr IOL. (**E**) Pooled data showing the level of light scatter in Anew Zephyr implanted capsular bags relative to their match-paired Alcon Acrysof implanted counterpart. Data are presented as mean ± SEM ($n = 3$). *Indicates a significant difference between groups (Student's *t*-test; $P \leq 0.05$).

interactions effectively "shrink-wrap" the capsular bag around the IOL, which pushes the IOL against the PC creating a pressure point at the square edge against the capsule, and thus a mechanical barrier to LEC migration. However, while a significant improvement on previous designs, these square edge IOLs retard the progression of PCO rather than prevent it. Changes in IOL engineering carry a less onerous burden of regulation than biological techniques to inhibit LEC function and, therefore, prevention or further retardation in the rate of PCO formation through improved IOL designs is of obvious benefit.

A series of developments have suggested an alternative strategy to the traditional closed-bag, square edge IOL. Studies in rabbit eyes to evaluate a capsular ring, which maintains separation of the AC and PC, demonstrated significantly reduced PCO rates.[7,8] Considering the severity of PCO

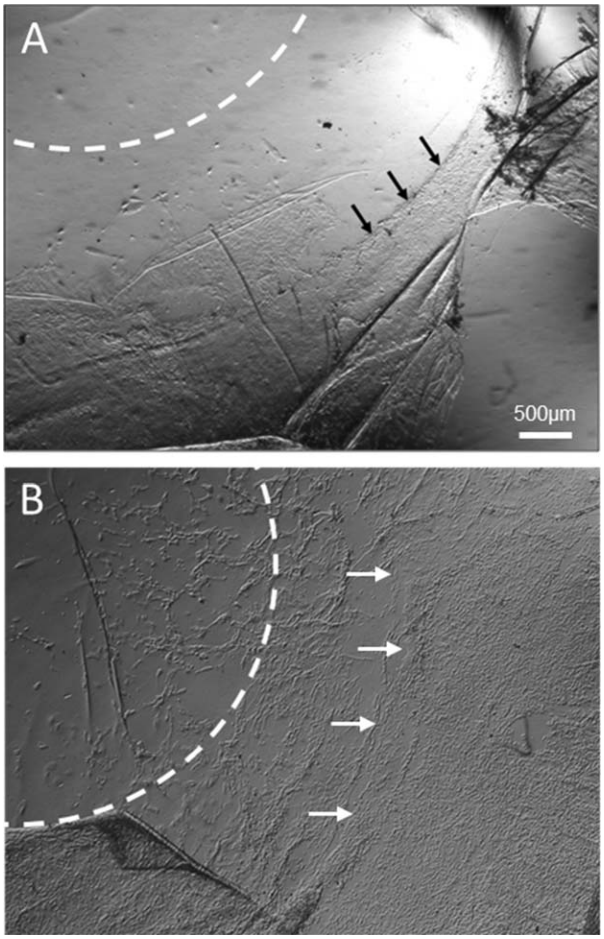

FIGURE 9. Modified dark-field micrographs showing an IOL-associated barrier effect within capsular bag preparations maintained in 2% human serum plus 10 ng/mL TGF-β2 implanted with (**A**) an Anew Zephyr IOL and (**B**) an Alcon Acrysof IOL. *Dashed line* indicates the natural location of the rhexis edge. *Arrows* indicate regions where barrier function is evident.

formation in the rabbit model, this is a significant result. Moreover, when this ring design was used in clinical studies, again the PCO rates were low.[21] Therefore, this approach holds much promise and our findings lend support to this theory as in all match-paired human capsular bag experiments, the Anew Zephyr open bag IOL significantly outperformed the current gold standard Alcon Acrysof IOL. The degree of growth and formation of light-scattering structures on the PC varied between donors, which reflects variation in patients, but on a match-paired basis for each donor these changes were significantly suppressed in preparations implanted with an Anew Zephyr IOL versus an Acrysof IOL.

We believe that the benefits observed with the Anew Zephyr IOL result both from a barrier function due to interaction of the ring haptic with the PC and through a reduced availability of growth factors within the capsular bag due to greater circulation of fluid. Findings in the current study provide evidence that the ring haptic can provide a barrier function against cell movement onto the PC. This was evident under both culture conditions, yet, this was more pronounced when human serum and TGF-β2 was present; however, once the barrier is breached, growth across and modification of the PC is relatively rapid. Despite a lack of interaction between the AC and PC it is likely that as LECs repopulate the AC producing increased tension in the bag, which creates greater force between the ring haptic and the equatorial capsule. It should be noted that in the case of the Anew Zephyr IOL the posterior component of the ring haptic is smooth. A modification to this component to create a square edge profile could provide greater interaction with the PC and further impede growth across the PC.

The other possible mechanism that could explain the improved outcomes observed with the Anew Zephyr IOL is the reduced availability of growth factors. In traditional closed-bag systems, the ACs and PCs adhere through cellular interactions, which limit fluid movement within the AC/PC space. Moreover, in this arrangement cells reside in close proximity to each other, and thus local production of growth factors and survival factors is likely to be concentrated and readily reach all cells on the two capsular surfaces. It is known that cytokines, for example, interleukins[22] and growth factors, such as hepatocyte growth factor (HGF) and fibroblast growth factor (FGF)[23–25] are produced by residual LECs cells, within human capsular bags, in response to surgery. In addition, a number of growth factors require cell or matrix interaction to convert a pro or inactive form to the active molecule or to facilitate presentation of the ligand to its corresponding receptor. It is likely that separation of the capsules plus the presence of fenestrations within the Anew Zephyr IOL design allows fluid movement within the AC/PC space, which reduces accumulation of growth factors on the matrix and limits local concentrations of cytokines. The regulation of cytokines and growth factors by open-bag devices are the subject of future studies.

In summary, the Anew Zephyr open bag IOL provides an advance on existing IOL technologies and is likely to afford added benefit to patients undergoing cataract surgery through reduced PCO rates. Open-bag strategies, in general, offer a great deal of promise.

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References

1. McCarty CA, Taylor HR. The genetics of cataract. *Invest Ophthalmol Vis Sci*. 2001;42:1677–1678.
2. Wormstone IM, Wang L, Liu CS. Posterior capsule opacification. *Exp Eye Res*. 2009;88:257–269.
3. Ranta P, Kivela T. Retinal detachment in pseudophakic eyes with and without Nd:YAG laser posterior capsulotomy. *Ophthalmology*. 1998;105:2127–2133.
4. Nishi O, Nishi K, Menapace R, Akura J. Capsular bending ring to prevent posterior capsule opacification: 2 year follow-up. *J Cataract Refract Surg*. 2001;27:1359–1365.
5. Hayashi K, Hayashi H, Nakao F, Hayashi F. Changes in posterior capsule opacification after poly(methyl methacrylate), silicone, and acrylic intraocular lens implantation. *J Cataract Refract Surg*. 2001;27:817–824.
6. Cleary G, Spalton DJ, Koch DD. Effect of square-edged intraocular lenses on neodymium:YAG laser capsulotomy rates

in the United States. *J Cataract Refract Surg*. 2007;33:1899–1906.

7. Hara T, Hara T, Sakanishi K, Yamada Y. Efficacy of equator rings in an experimental rabbit study. *Arch Ophthalmol*. 1995;113:1060–1065.
8. Hashizoe M, Hara T, Ogura Y, Sakanishi K, Honda T, Hara T. Equator ring efficacy in maintaining capsular bag integrity and transparency after cataract removal in monkey eyes. *Graefes Arch Clin Exp Ophthalmol*. 1998;236:375–379.
9. Alon R, Assia EI, Kleinmann G. Prevention of posterior capsule opacification by an intracapsular open capsule device. *Invest Ophthalmol Vis Sci*. 2014;55:4005–4013.
10. Kavoussi SC, Werner L, Fuller SR, et al. Prevention of capsular bag opacification with a new hydrophilic acrylic disk-shaped intraocular lens. *J Cataract Refract Surg*. 2011;37:2194–2200.
11. Hara T, Narita M, Hashimoto T, Motoyama Y. Long-term study of posterior capsular opacification prevention with endocapsular equator rings in humans. *Arch Ophthalmol*. 2011;129:855–863.
12. Leishman L, Werner L, Bodnar Z, et al. Prevention of capsular bag opacification with a modified hydrophilic acrylic disk-shaped intraocular lens. *J Cataract Refract Surg*. 2012;38:1664–1670.
13. Liu CS, Wormstone IM, Duncan G, Marcantonio JM, Webb SF, Davies PD. A study of human lens cell growth in vitro. A model for posterior capsule opacification. *Invest Ophthalmol Vis Sci*. 1996;37:906–914.
14. Cleary G, Spalton DJ, Zhang JJ, Marshall J. In vitro lens capsule model for investigation of posterior capsule opacification. *J Cataract Refract Surg*. 2010;36:1249–1252.
15. Wormstone IM, Anderson IK, Eldred JA, Dawes LJ, Duncan G. Short-term exposure to transforming growth factor beta induces long-term fibrotic responses. *Exp Eye Res*. 2006;83:1238–1245.
16. Dawes LJ, Illingworth CD, Wormstone IM. A fully human in vitro capsular bag model to permit intraocular lens evaluation. *Invest Ophthalmol Vis Sci*. 2012;53:23–29.
17. Hollick EJ, Spalton DJ, Ursell PG, et al. The effect of polymethylmethacrylate, silicone, and polyacrylic intraocular lenses on posterior capsular opacification 3 years after cataract surgery. *Ophthalmology*. 1999;106:49–54.
18. Nishi O. Posterior capsule opacification. Part 1: experimental investigations. *J Cataract Refract Surg*. 1999;25:106–117.
19. Nanavaty MA, Spalton DJ, Boyce J, Brain A, Marshall J. Edge profile of commercially available square-edged intraocular lenses. *J Cataract Refract Surg*. 2008;34:677–686.
20. Hollick EJ, Spalton DJ, Meacock WR. The effect of capsulorhexis size on posterior capsular opacification: one-year results of a randomized prospective trial. *Am J Ophthalmol*. 1999;128:271–279.
21. Hara T, Hara T, Narita M, Hashimoto T, Motoyama Y, Hara T. Long-term study of posterior capsular opacification prevention with endocapsular equator rings in humans. *Arch Ophthalmol*. 2011;129:855–863.
22. Dawes LJ, Duncan G, Wormstone IM. Age-related differences in signaling efficiency of human lens cells underpin differential wound healing response rates following cataract surgery. *Invest Ophthalmol Vis Sci*. 2013;54:333–342.
23. Dawes LJ, Angell H, Sleeman M, Reddan JR, Wormstone IM. TGFbeta isoform dependent Smad2/3 kinetics in human lens epithelial cells: a Cellomics analysis. *Exp Eye Res*. 2007;84:1009–1012.
24. Wormstone IM, Del Rio-Tsonis K, McMahon G, et al. FGF: an autocrine regulator of human lens cell growth independent of added stimuli. *Invest Ophthalmol Vis Sci*. 2001;42:1305–1311.
25. Wormstone IM, Tamiya S, Marcantonio JM, Reddan JR. Hepatocyte growth factor function and c-Met expression in human lens epithelial cells. *Invest Ophthalmol Vis Sci*. 2000;41:4216–4222.

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