Institution: University of East Anglia

Unit of Assessment: 5 – Biological Sciences

Title of case study:

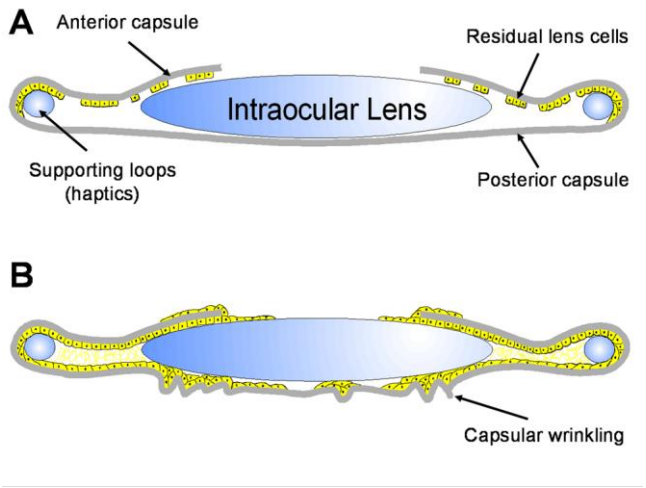
Improving success rates in the surgical treatment of cataract

1. Summary of the impact

Cataract causes blindness in millions of people worldwide. It is treated surgically by replacing the clouded lens with an artificial lens and more than 30 million such operations per year are predicted by 2020. Unfortunately, many of these patients are subsequently blighted by posterior capsule opacification (PCO) a wound-healing response by lens epithelial cells to surgical trauma. Using human donor eyes, Wormstone and Duncan developed a technique that simulated cataract operations and provided an ideal system to understand PCO biology. This technology was a key platform in developing a novel commercial intraocular lens (IOL), which shows massive reductions in PCO rates.

2. Underpinning research

Cataract renders tens of millions blind. In addition to reducing the quality of an individual's life, significant healthcare provision is required. Currently, the only means to treat cataract is by surgical intervention. Often, and especially in children, cataract surgery is blighted by a fibrotic condition known as Posterior Capsule Opacification (PCO), due to a wound-healing response to surgical trauma by lens epithelial cells, which reduces visual quality. The image below shows a representation of (A) the post surgical capsular bag and (B) the extensive growth and modification that causes PCO following cataract surgery.



Cataract surgery requires the creation of a circular opening (a process known as capsulorhexis) in the front part of the lens (anterior capsule). This opening allows access to the central fibre cells within the lens, which are typically those affected by cataract. The remaining lens tissue, comprising a ring of anterior lens capsule and the entire posterior capsule, is known as a Capsular Bag (CB), which maintains separation of the aqueous and vitreous humours. This bag can house an artificial intraocular lens (IOL), which is commonly implanted during surgery and restores the refractive power that is lost by fibre cell removal. Immediately following surgery, a marked improvement in visual quality is observed because light can pass through the lens capsular bag without meeting light-scattering structures. Unfortunately, in many patients the lens epithelial cells that line the anterior capsule survive and grow. Importantly, these cells grow on to the cell-free posterior capsule, causing them to encroach upon the visual axis. A thin cover of cells is insufficient to affect the light path, but subsequent changes to the matrix, cell organisation and phenotypic shift (trans-differentiation) give rise to light scatter. This markedly decreases visual quality and normally requires more surgery. This disruption of the posterior capsule is known as PCO; patients of all ages are affected, but it is particularly severe in children.

To study PCO progression, Duncan, Wormstone and colleagues working at UEA developed an innovative *in vitro* system that employed a simulated cataract operation on human donor eyes to produce a CB [1]. This can be cultured in controlled environmental conditions and monitored on a day-to-day basis. This allowed several clinical features of PCO to be replicated, including age-related wound-healing rates [2], matrix contraction, matrix deposition and phenotypic shift from

epithelial cells to myofibroblasts [4]. Moreover, the effects of exogenous growth factors and autocrine factors on these characteristics were evaluated [4, 5, 6]. Also, IOLs were implanted into the capsular bag and their influence on PCO was assessed [1, 3].

3. References to the research

1) Liu CSC, **Wormstone IM, Duncan G, Marcantonio JM, Webb SF**, Davies PD (1996). A study of human lens cell growth *in vitro*: a model for posterior capsule opacification. *Invest. Ophthalmol. Vis. Sci.* **37**: 906-914. (104 Citations)
http://www.iovs.org/content/37/5/906.abstract

2) **Wormstone IM**, Liu CSC, Rakic J-M, **Marcantinio JM**, Vrensen GFJM, **Duncan G** (1997). Human lens epithelial cell proliferation in protein-free medium. *Invest. Ophthalmol. Vis. Sci.* **38**: 396-404. (91 Citations)
http://www.iovs.org/content/38/2/396.full.pdf

3) **Duncan G, Wormstone IM**, Liu CSC, **Marcantonio JM**, Davies PD (1997). Thapsigargin coated intraocular lenses inhibit human lens cell growth. *Nature Medicine* **3**:1026-1028. (85 Citations)
doi: 10.1038/nm0997-1026

4) **Wormstone IM, Tamiya S, Marcantonio JM**, Reddan JR. (2000) Hepatocyte growth factor function and *c*-met expression in human lens epithelial cells. *Invest Ophthalmol Vis Sci*. **41**:4216-4222. (47 Citations)
http://www.iovs.org/content/41/13/4216.abstract

5) **Wormstone IM**, Del Rio-Tsonis K, McMahon G, **Tamiya S**, Davies PD, **Marcantonio, JM**, Duncan G. (2001) FGF: an autocrine regulator of human lens cell growth independent of added stimuli. *Invest Ophthalmol Vis Sci.* **42**:1305-1311. (35 Citations)
http://www.iovs.org/content/42/6/1305.abstract

6) **Wormstone IM, Tamiya ST**, Anderson I, **Duncan G**. (2002) TGF β2 induced matrix modification and cell transdifferentiation in the human lens capsular bag. *Invest Ophthalmol Vis Sci.* **43**: 2301-2308. (120 Citations)
http://www.iovs.org/content/43/7/2301.long

Key Grants

Since 1994, Prof. Duncan and Dr Wormstone have received continuous funding (total > £1.9 million) from The Humane Research Trust to support their work on human tissue. Also, projects that have employed the capsular bag model and which aided its development have been supported (total ~£750K) by BBSRC, Cambridge Antibody Technology, Fight for Sight, the Lord Dowding Fund, the Dunhill Medical Trust and the James Tudor Foundation.

4. Details of the impact

The innovative human CB model developed by Wormstone and Duncan at UEA has played a crucial role in the development of a new IOL, known as **the bag-in-the-lens** (BIL). BIL is commercially available from *Morcher Implants* (Product name: Type 89) and to date *Morcher* have sold 12,651 units worldwide (corroborating source A). Surgical implantation of BIL markedly reduces the incidence of PCO.

Because the CB model is generated through a simulated operation in the laboratory, it is essentially the same as that generated in a cataract patient. This makes it an ideal platform for testing novel clinical concepts in a regulated environment, which is amenable to ongoing observation and analysis. This led the Medical Director at the University Hospital Antwerp to use the Wormstone/Duncan CB model to evaluate the novel BIL. She knew of the CB model and its potential through published papers (section 3) and through discussions with Wormstone and Duncan at academic conferences. These discussions provided further assistance in applying the CB model to test the BIL, whose introduction into the eye requires a technically demanding surgical approach. This was of major value, as shown in the testimonial below:

"*I have personally employed the capsular bag model to great effect in the development of the BIL design and believe it has been an invaluable tool in translating my original concept into a device that has improved the lives of tens of thousands of cataract patients."*

(corroborating source B)

Using the Wormstone/Duncan CB model, the skills needed for this surgical procedure could be developed and honed, as follows. In contrast to conventional cataract surgery, which requires a single capsulorhexis (capsular tear) in the anterior lens capsule, the BIL technique involves the use of a twin capsulorhexis lens design, and performance of anterior and posterior capsulorhexes of the same size. According to this concept, if both capsules are well-stretched around the optic of the lens, any remaining lens epithelial cells will be captured within the remaining space of the capsular bag, and their proliferation will be limited to this space, so the visual axis will remain clear. The CB model allowed it to be ascertained that the BIL surgical technique and implantation could be applied to human lenses, and was therefore appropriate for cataract patients. Moreover, the model allowed comparison with conventional IOL designs and thus demonstrated the ability of BIL to prevent PCO formation and show that the BIL is a major advance on existing devices (corroborating sources A-C).

The beneficiaries are those patients that have had surgical implants with this new technique and who will not experience deterioration in vision nor require further surgery because of PCO. The BIL is surgically implanted into ~5000 adult and child patients a year in Europe alone, effectively restoring their vision and the Medical Director at the University Hospital Antwerp has personally implanted >8000 since the lens received European CE mark approval in 2004. Significant numbers of BILs have been implanted now and the outcomes are impressive. **Of particular interest is the application to children, who have rapid onset of blinding PCO; in nearly all cases; the BIL prevents PCO, even in these extreme cases.** The limiting factor in the uptake of this approach is the level of skill required by the surgeon to carry out this procedure, a challenge to many surgeons. Implanting BIL is not standard practice and thus is not conventionally taught. To address this issue, and to increase the pool of surgeons using the BIL procedure, wet lab and instructional courses are now run at the annual European Society of Cataract and Refractive Surgeons conference. In addition, an international panel of BIL Instructors has been established who pass on their knowledge and demonstrate the technique (corroborating source B). The weight of clinical data is strong and numbers employing BIL are growing.

Wormstone is also testing novel IOLs for *Anew Optics* using the CB model. Data generated using this model is aiding development of new IOL designs and their selection for clinical trials. In reference to this work, the CEO of *Anew Optics* has stated:

"*The findings were revealing and have made a major impact on our strategies and approach in future clinical trials. In essence, I consider your work in the capsular bag pivotal for evaluating the performance attributes of new technologies.*"

(corroborating source D)

5. Sources to corroborate the impact

A. Bag-in-the-lens (BIL) documentation from *Morcher Implants*:

(i) email from *Morcher implants* giving sales numbers of the BIL at 12,561 worldwide – held on file at UEA.

(ii) videos showing the BIL implantation procedures: http://www.morcher.com/videos/bag-in-the-lens/

(iii) details of the BIL and the surgical training courses available: http://www.morcher.com/fileadmin/content/Broschueren_Kataloge/CATALOG-89A-TASSIGNON_2012-05-02.pdf

(iv) more details of instructional courses for BIL: http://www.morcher.com/en/produkte/bag-in-the-lens.html

B. Corroborating letter, held on file at UEA, from the Medical Director, Chair & Head of the Department of Ophthalmology, University Hospital Antwerp, who developed BIL and regularly implants it into patients.

This letter describes how Wormstone and Duncan's capsular bag model was used to invented the bag-in-the-lens surgical technique. It also states that BIL has been implanted into 8000 patients since approval of the lens by the Belgian Social Security in 2004. It is now estimated that ~5000 patients a year are implanted with BIL IOLs in Europe.

C. Key publications referring directly to the use of the CB model:

(i) De Keyzer K, Leysen I, Timmermans JP, Tassignon MJ (2008). Lens epithelial cells in an in vitro capsular bag model: lens-in-the-bag versus bag-in-the-lens technique. J Cataract Refract Surg 34:687-695. doi: 10.1016/j.jcrs.2007.11.055

This study evaluated the difference in lens epithelial cell (LEC) growth between lens-in-the-bag (traditional IOL) implantation and bag-in-the-lens (novel IOL) implantation using the in vitro human capsular bag model described by Liu et al 1996.

(ii) De Groot, Vrensen GFJM, Willekens B, Van Tenten Y, Tassignon MJ (2003). *In Vitro* Study on the Closure of Posterior Capsulorrhexis in the Human Eye. *Invest. Ophthalmol. Vis. Sci*. **44**: 2076-2083. doi: 10.1167/iovs.02-0525

This work studied the closure of the posterior rhexis zone in an in vitro capsular bag model, described by Wormstone et al 1997.

D. Corroborating letter, held on file at UEA, from the CEO of *Anew Optics* which states:

"We have employed the capsular bag model to assess modified IOL designs under different environmental conditions and their ability to prevent PCO like changes. The findings were revealing and have made a major impact on our strategies and approach in future clinical trials. In essence, I consider your (Wormstone's) work in the capsular bag pivotal for evaluating the performance attributes of new technologies."