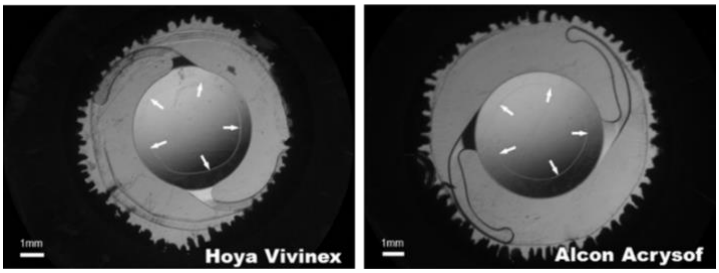
Institution: University of East Anglia		
Unit of Assessment: 5 – Biological Sciences		
Title of case study: A continuously enhanced human experimental model of cataract surgery		
Period when the underpinning research was undertaken: 2000 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Professor Michael Wormstone	Professor of Ophthalmology	1997 - present
Period when the claimed impact occurred: August 2013 – December 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Cataract, a clouding of the lens, is a global problem affecting tens of millions of people. Surgery is the only treatment, but it commonly causes secondary blindness due to a wound-healing response. **Wormstone** and colleagues, as its original inventors, have continuously refined an experimental culture system of the human lens (the capsular bag model) that enables the causes of secondary blindness to be better understood. The enhanced model has generated clinically relevant data more rapidly than clinical trials, enabled product development for artificial lenses and supported product marketing. As a result, **Wormstone**'s research and consultancy have contributed to the recent growth of Singapore-based HOYA Surgical Optics, now the third largest manufacturer within the multibillion-dollar global intraocular lens market. In addition, the model supports practitioners by allowing surgeons to make informed decisions resulting in long-term restoration of vision and benefits patients through a reduced need for follow-up surgery.

2. Underpinning Research



Cataract surgery involves implanting an artificial lens (intraocular lens) in the affected eye. However, posterior capsule opacification (a clouding behind the intraocular lens) following cataract surgery causes secondary blindness in millions of patients worldwide. In a wound-healing response, residual lens epithelial cells grow on previously cell-free regions within the line of sight and become fibrotic. Additional surgery is required to restore sight once more, causing substantial extra cost to healthcare providers and patients. For example, under Medicare, laser treatment of posterior capsule opacification costs up to USD823 (09-2020), yet it is the second most common operation in the world. So, understanding the biology behind posterior capsule opacification and establishing the capacity of an intraocular lens to suppress it are of great interest to clinicians, the intraocular lens industry and patients. Clinical trials are expensive and time-consuming, while animal models of posterior capsule opacification are not ideal because the mechanisms involved may differ from those in humans. Consequently, a human experimental system to make intraocular lens development more effective and provide better outcomes for patients has been in great demand across the world.

To meet this need, **Wormstone** and colleagues, including the late George Duncan, invented and developed the human capsular bag model at UEA. Essentially, this involves bench-top cataract surgery on human donor eyes in a laboratory setting. The product of this procedure is an isolated capsular bag (the part of the eye housing the lens). An artificial intraocular lens can be placed within the capsular bag in the same manner as a cataract patient would experience. The capsular bag (with or without an intraocular lens) can be transferred and secured to a culture dish and maintained in a controlled environment. This tissue culture system (the capsular bag model)

replicates the spatial organisation and cell composition found in real patients and so allows the features of human posterior capsule opacification to be studied. From 2000 onwards, the team refined this novel culture model through the application of match-paired experiments to discover factors regulating posterior capsule opacification [Grant A]. For example, using the model for inhibition studies, the team identified key autocrine factors such as fibroblast growth factor [R1, Grant A] and vascular endothelial growth factor [R2, Grants A & B]. In addition, the team used the model to allow the influence of external stimuli (that could arise from non-lens sources) to be established, finding that transforming growth factor β mimicked fibrotic changes seen in post-mortem posterior capsule opacification patient samples [R3, Grant A].

Since 2012, in a process of continuous enhancement, **Wormstone** and team have developed several new and improved variants of the system, which have in turn increased the clinical relevance of the model:

- *Inverted system capsular bag model*: The team developed an inverted system such that, unlike in previous versions, the anterior face of the capsular bag was adjacent to the culture dish and the posterior capsule furthest away. This allowed greater interaction between the posterior capsule and intraocular lens and, together with the use of human serum to deliver stimuli (adopted for the first time in this model and then used in all subsequent ones), made the model more reflective of the clinical setting than previous ones [R4, Grant A].
- *Suspended capsular bag model:* In this model, developed through collaboration with Prof. David Spalton, St Thomas' Hospital, London [Grants A & B], the ciliary body (a circular muscle connected to the lens) is pinned to a silicone support ring, so allowing the capsular bag to be suspended over the lumen of the ring. An intraocular lens can be placed in this model, allowing it to interact with the capsule in a manner that is again more clinically realistic [R5].
- *Graded culture suspended capsular bag model:* In patients, changes to the lens region following cataract surgery are transient, peaking in the days or weeks following surgery and returning to a baseline over time. To better reflect this clinical scenario, in 2017 **Wormstone** collaborated with HOYA Surgical Optics to modify the maintenance conditions for suspended capsular bag cultures [Grants A & C]. To achieve this, the team used human serum to drive growth and transforming growth factor β to promote fibrotic responses. Both were added in a graded manner, such that cultures were exposed to maximum levels over the first three days of culture and these levels were then reduced gradually over time. As predicted, features of posterior capsule opacification such as cell growth, light scatter and fibrotic responses could be mimicked in what is termed graded culture [R6]. Using this version of the model over a one-month culture period, the HOYA Vivinex™ intraocular lens was found to have an overall better level of anti-posterior capsule opacification performance than the market-leading intraocular lens. This predicted outcome of the model was borne out in a recent clinical study based on data obtained after an interval of three years following surgery [S5], which reported significantly lower posterior capsule opacification scores and a smaller percentage of cases needing laser treatment with HOYA Vivinex™ than with the market leader (11.4 and 18.6% of cases, respectively). The graded culture model therefore has clinical relevance and allows the anti-posterior capsule opacification performance of intraocular lenses (whether commercially available ones or prototypes) to be evaluated much more rapidly than previously.

Image: Modified dark-field images of match-paired capsular bags implanted with a HOYA Vivinex™ or an Alcon Acrysof™ intraocular lens. *Credit*: Michael Wormstone, published in [R6].

3. References to the research

Underpinning research: The underpinning research outputs have all been published in competitive, international, peer-reviewed journals and form part of a larger body of such published work (citation numbers are from Google Scholar; UEA author names are in bold):

R1 **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. *Investigative Ophthalmology & Visual Sciences* 42: 1305-1311. https://iovs.arvojournals.org/article.aspx?articleid=2162674. [85 citations]

R2 **Eldred JA**, **McDonald M**, **Wilkes HS**, Spalton DJ, **Wormstone IM**. (**2016**) Growth factor restriction impedes progression of wound healing following cataract surgery: identification of VEGF as a putative therapeutic target. *Scientific Reports* 6: 24453. DOI: 10.1038/srep24453 [14 citations]

R3 **Wormstone IM**, **Tamiya ST**, Anderson I, **Duncan G** (**2002**) TGF β2 induced matrix modification and cell transdifferentiation in the human lens capsular bag, *Investigative Ophthalmology & Visual Sciences* 43: 2301-2308. https://iovs.arvojournals.org/article.aspx?articleid=2123745. [279 citations]

R4 **Dawes LJ**, Illingworth CD, **Wormstone IM** (**2012**) A fully human in vitro capsular bag model to permit intraocular lens. *Investigative Ophthalmology & Visual Sciences* 53: 23-29. DOI: 10.1167/iovs.11-8851 [23 citations]

R5 **Eldred JA**, **Spalton DJ**, **Wormstone IM** (**2014**) An in vitro evaluation of the Anew Zephyr® open bag IOL in the prevention of Posterior Capsule Opacification using a human capsular bag model, *Investigative Ophthalmology & Visual Sciences* 55: 7057-7064. DOI:10.1167/iovs.14-15302 [27 citations]

R6 **Eldred JA**, Zheng J, Chen S, **Wormstone IM** (**2019**) An in vitro human lens capsular bag model adopting a graded culture regime to assess putative impact of IOLs on PCO formation. *Investigative Ophthalmology & Visual Sciences* 60: 113–122. DOI: 10.1167/iovs.18-25930 [9 citations]

Funding: Funding of this research has come from international companies and, as competitive, peer-reviewed funding, from UK charities. Continuous funding from The Humane Research Trust since 2000 has supported work on human tissue, the most relevant being Grant A. Other key grants were provided by Fight for Sight [Grant B] and HOYA Surgical Optics [Grant C]:

Grant A: PI: **IM Wormstone**. Title: *The Humane Research Trust Laboratory – infrastructure support*. Funder: The Humane Research Trust. Project dates: 17 January 2007 – 31 December 2022. Total value: GBP1,888,001. Grant B: PI: **IM Wormstone**. Title: *To identify the biological basis of open bag strategies for the prevention of posterior capsule opacification*. Funder: Fight for Sight. Project dates: 1 October 2012 – 30 September 2015. Total value: GBP163,942. Grant C: PI: **IM Wormstone**. Title: *Evaluation of a commercial HOYA intraocular lens and surface modified intraocular lenses using the human capsular bag model*. Funder: HOYA Surgical Optics. Project dates: 15 November 2017 – 15 March 2019. Total value GBP140,000.

4. Details of the impact

The research of **Wormstone** and team in developing and enhancing the capsular bag model has achieved significant impacts on commerce, production and practitioners in the health sector, so improving the health and wellbeing of people. Specifically, it has: (a) enabled the rapid testing of novel clinical concepts, leading to the development and marketing of ocular products for a number of companies, so generating significant revenue; (b) positively impacted practitioners (surgeons); and (c) led to better outcomes and improved vision in many patients worldwide, immensely benefiting their quality of life.

(a) Impact on development and marketing of ocular products: The capsular bag model has played a key role in the development and evaluation of several intraocular lenses (IOL) including: the "bag-in-the-lens" intraocular lens (Morcher Type 89™); AnewOptics Zephyr™; Hoya Vivinex™; and Hoya Nanex™ [R5, R6; S1-S5]. These form part of a global intraocular lens market whose size was estimated to reach USD4,200,000,000 (12-2017) in 2020. To take the leading examples:

Bag-in-the-lens intraocular lens: **Wormstone**'s research facilitated the development of this highly successful intraocular lens, which, since 2014, has been implanted in patients in more than 10,000 cataract operations in Europe [S1]. The Emeritus Head and Chair of the Department of Ophthalmology, Antwerp University Hospital, Belgium, who is the inventor of this lens and regularly implants it into patients in cataract surgery, stated, *"The capsular bag model was an*

invaluable tool in translating my original concept to a clinical product" [S1]. The clinical outcomes from the large number of implantations of this lens are impressive. Specifically, in a five-year follow-up study, under 10% of children required additional surgical treatment after receiving the bag-in-the-lens intraocular lens [S2], whereas, with conventional surgery and standard intraocular lens implantation, 100% of children would have required it.

HOYA Vivinex™ and HOYA Nanex™ intraocular lenses: Since 2017, following an approach by the company on the basis of his research record and expertise, **Wormstone** has served as a consultant for HOYA Surgical Optics, one of the largest intraocular lens manufacturers globally, to aid their product development programme [S3]. **Wormstone**'s graded culture suspended capsular bag model [R6] found that the HOYA Vivinex™ intraocular lens had an overall better level of anti-posterior capsule opacification performance than the market-leading intraocular lens. The data from these studies, obtained within months [R6], predicted clinical outcomes that took years to obtain [S4]. As the HOYA Surgical Optics Global Product and Marketing Directors stated, *"The capsular bag model is, therefore, a very powerful clinically relevant tool that can be used to evaluate and develop IOL performance"* [S3]. They also stated, *"The quality of the work and the significance of the published findings provided by Prof. Wormstone, using the capsular bag model, have greatly aided our ability to market our products"* [S3].

In 2018 **Wormstone** presented his work on the capsular bag model as a keynote speaker at the HOYA symposium in Vienna, Austria, to an audience of approximately 300 ophthalmic surgeons, assembled as potential end-users of HOYA products. This presentation, along with follow-up content, was then used by the company for its marketing. As the HOYA Surgical Optics Global Product and Marketing Directors stated, "*The presentation in Vienna was recorded and is available in the HOYA collection on the Eyetube web platform. Prof. Wormstone's work was also a key element in an advertorial published in 'The Ophthalmologist' which was followed by a feature article highlighting the capsular bag model and its demonstration of the performance of Vivinex™. A further feature article was published in 'Eurotimes'* [magazine of the European Society of Cataract and Refractive Surgeons]*. Collectively these publications have a readership of over 50,000 internationally, the majority of which are ophthalmic surgeons*" [S3, S5]. In his capacity as consultant, **Wormstone** also used the capsular bag model in the preclinical development and assessment of the HOYA Nanex™ IOL (designed for microincision cataract surgery), which was added to the HOYA clinical product portfolio in 2019 [S3].

Referring to the UEA capsular bag studies, HOYA Global Product and Marketing Directors stated, *"These activities have contributed to the continued growth and success of HOYA Surgical Optics and our products. HOYA Surgical Optics is now the world's third largest IOL manufacturer globally, and has been the fastest growing of the largest IOL manufacturers in recent years. Professor Wormstone and his work on the capsular bag model continue to impact on the success of our company..."* [S3].

(b) Impact on practitioners: **Wormstone** has delivered several invited talks at practitioner-based events, including: 100% Optical (2017) [S6]; the Cambridge Ophthalmological Symposium (2019) [S7-S8]; and two HOYA symposia (2017 and 2018), allowing him to present his research directly to ophthalmic surgeons [S3]. **Wormstone**'s presentations, in addition to his publications in peer-reviewed journals and practitioner-based magazines, have achieved impact through informing clinicians of relative intraocular lens performance [S3, S6-S8]. For example, the Associate Professor of Ophthalmology, Ludwig-Maximillians-University of Munich, Germany, a distinguished and experienced cataract surgeon, approached **Wormstone** following a keynote lecture. **Wormstone** then visited her in Munich to pass on his knowledge of the capsular bag model and provide practical feedback. This technique has been fundamental in this practitioner's research strategy and clinical practice from 2014 onwards and, as she has stated, *"The capsular bag model developed by Prof Wormstone has had a marked impact on cataract surgery....The data provided using the capsular bag model, therefore, provides scientifically rigorous findings that can inform the surgeon and aid their selection of IOL for their patients"* [S9].

(c) Impact on patients: The ultimate beneficiaries of advances made using the capsular bag model as an experimental and evaluation tool are patients. As detailed above, the bag-in-the-lens intraocular lens has led to much improved clinical outcomes for children [S1, S2]. To quote further the Emeritus Head and Chair of the Department of Ophthalmology, University Hospital, Antwerp, Belgium, it *"...has provided and maintained vision in tens of thousands of cataract patients"* [S1]. In addition, of the best-selling intraocular lenses, HOYA Vivinex™ continues to increase its market share and offers improved clinical outcomes relative to the current market leader, such that posterior capsule opacification is better managed and the need for laser surgery is reduced [R6, S4]. Ultimately, benefits to patients across the world result from decisions made by surgeons and the impact the capsular bag model has on this process is highlighted in the following statement by the Associate Professor of Ophthalmology, Ludwig-Maximillians-University of Munich, Germany: *"I have drawn on my knowledge from capsular bag studies to guide colleagues on their IOL choices, which I believe have positively impacted on many patients since 2014"* [S9].

5. Sources to corroborate the impact

S1 Letter from the Emeritus Head and Chair of the Department of Ophthalmology of Antwerp University Hospital (UZA), Antwerp, Belgium (7.9.20).

S2 Van Looveren J, Ni Dhubhghaill S, Godts D, Bakker E, De Veuster I, Mathysen DG, Tassignon MJ (2015) Pediatric bag-in-the-lens intraocular lens implantation: long-term follow-up. *Journal of Cataract & Refractive Surgery* 41: 1685-1692. DOI: 10.1016/j.jcrs.2014.12.057 [Publication reporting significant mitigation of posterior capsule opacification in children implanted with the bag-in-the-lens intraocular lens.]

S3 Letter from Global Product Director, and Global Marketing Director, of HOYA Surgical Optics (25.9.20).

S4 Leydolt C, Schartmuller D, Schwarzenbacher L, Roggla V, Schriefl S, Menapace R (2020) Posterior capsule opacification with two hydrophobic acrylic intraocular lenses: 3-year results of a randomized trial. *American Journal of Ophthalmology* 217: 224–231. DOI: 10.1016/j.ajo.2020.04.011. [Publication reporting clinical data that show better posterior capsule opacification management with HOYA Vivinex™ versus the market-leading intraocular lens; cites R6 on p. 229.]

S5 HOYA advertorial supplement -The Best of Multiple Worlds? *The Ophthalmologist* (2018)

S6 E-mail from Head of Education and OT Clinical Editor detailing **Wormstone**'s involvement in 100% Optical event and feedback/evaluation (5.10.17).

S7 Letter from Consultant Opthalmic and Vitreoretinal Surgeon and organiser of the 49th Cambridge Ophthalmological Symposium (18.9.20). [Feedback following invited talk by **Wormstone** in 2019.]

S8 **Wormstone IM** (2020) The human capsular bag model of posterior capsule opacification. *Eye* 34: 225–231. DOI: 10.1038/s41433-019-0680 [Publication associated with the 2019 Cambridge Ophthalmological Symposium.]

S9 Letter from Associate Professor of Ophthalmology, Ludwig-Maximillians-University of Munich, Germany (23.9.20).