Institution: University of Kent

Unit of Assessment: 9, Physics

Title of case study: Transformational Biomedical Diagnostics with Optical Coherence Tomography

1. Summary of the impact

The **Applied Optics Group (AOG)** at Kent has been at the forefront of fundamental research into **optical coherence tomography (OCT)** for eye-imaging since 1996. The group has invented and developed diagnostic OCT with scanning laser ophthalmoscopy (OCT/SLO). The **combination** of these two techniques at Kent was crucial to the development of a **new generation of instrumentation**, which was commercialised in 2006 and now routinely used in eye clinics worldwide. It is essential technology in the rapid and accurate diagnosis and treatment of eye diseases that would otherwise not be possible.

The new instrumentation provides rapid images at higher resolution that are much less sensitive to patient movement. The direct impact is on the **doctors** who have access to more information on the patients condition in much less time, as well as **patients** whose rapid diagnosis increases their treatment success rate. **We estimate that around five million patients worldwide have benefitted from this technology.** There is indirect impact via the profits to the University and to the company that holds the licence to manufacture the instruments.

2. Underpinning research

A ground-breaking method for imaging the human retina was pioneered at the University of Kent by Podoleanu, Jackson & Dobre through two EPSRC grants in the period 1995 – 2001, that now constitutes state-of-the-art technology in **advanced retinal imaging laboratories worldwide**.

Instrument Development and Commercialisation

Prior to the research at the University of Kent, the standard orientation of OCT images was along cross-sections, which gives low resolution images during a lengthy procedure that is extremely sensitive to patient movement. The EPSRC funded research enabled the development of methods to rapidly obtain three dimensional OCT images of the retina and skin. The new technology facilitated the next generation of high resolution images at previously unachievable en-face orientations (a direct frontal view), similar to those obtained through microscopy [1]. This pioneering approach and insight permitted immediate integration of OCT technology with confocal microscopy [2]. This led to the development of a new **dual channel instrument OCT/SLO**, which was exclusively **licensed to Ophthalmic Technology Inc (OTI), Canada**. Between 2001 and 2010, the **Applied Optics** group at **Kent** has facilitated the transition of en-face OCT, and of the OCT/SLO technology, from the **experimental setup at the University of Kent to practicing eye clinics**. Numerous supporting grants for Podoleanu as PI, exceeding £200K, have been provided by OTI, New York Eye and Ear Infirmary (NYEEI), and the Ariba Foundation to support this work via staffing, equipment and teaching replacement, as well as carrying out testing and trials. The OCT/SLO technology was initially tested on patients at New York Eye and Ear Infirmary (NYEEI), the Macula Foundation, NY, Academic Medical Centre, Amsterdam and Yokashiwava College, Japan with support from OTI. From its early days, the en-face OCT proved **vital for early diagnosis** of melanocytoma, diabetic retinopathy, choroidal neovascular membrane, and macular pucker [2]. As a result of this international collaboration and support, a demand for further development was identified, and a new **three channel instrument**, with a third fluorescence channel, **was invented at Kent** and tested on patients [6]. The OCT/SLO technology contributed to a rapid advance in diagnosis of age related macula degeneration, diabetes and other diseases of the eye became possible [5].

Further support to Podoleanu (PI) from EPSRC for “Adaptive Optics Assisted Optical Coherence Tomography for Retinal Imaging”, 2003-2006, (value £180K) led to publication [3]. This refers to a new OCT/SLO instrument where both channels operate via an adaptive optics closed

loop. This development was carried out in collaboration with Prof. C. Dainty of the National University of Ireland. This is protected by US7466423 patent and has led to a **licence agreement with Optos plc** (who bought OTI in the intervening period).

Research performed in 1993-1996 [4, and references therein] has provided the further insight that Talbot bands could be applied to spectral OCT to reduce the mirror image specific to this technology, leading to a further patent and to another **licence agreement, to spin-out company Optopod**, with Podoleanu as Director.

Patient Testing

During the commercialisation process, patient testing was required to optimise the functionality of the instruments. This attracted further funds to Podoleanu from OTI and NYEEI, where two OCT/SLO instruments were have been placed in New York, followed by an OCT/SLO fluorescence, and a 3 micron resolution OCT/SLO, the highest achievable in-vivo of any OCT technology. Successful patient testing enabled A. Podoleanu to conduct and oversee the assembly and installation of eight different prototypes between 2003-2009. The patent on a sequential spectral OCT with SLO was the subject of an agreement with **OPKO** in 2011, with technology transferred to **Optos plc**. This forms the basis of the system currently commercialised by **Optos** along with other aspects of technology protected through **14 patents** with Podoleanu as the inventor or co-inventor.

3. References to the research

The first three references (1, 2, and 3; marked with a *) best indicate the quality of the underpinning research, averaging 91 citations per paper.

1.* A. G. Podoleanu, J. A. Rogers, D. A. Jackson, Three dimensional OCT images from retina and skin, Optics Express, **7**, 292 (2000). (Cited 154 times) DOI http://dx.doi.org/10.1364/OE.7.000292

2.* A. G. Podoleanu, G. M. Dobre, R. G. Cucu et al. Combined multiplanar optical coherence tomography and confocal scanning ophthalmoscopy, Journal Biomedical Optics, Vol: 9 Issue: 1 pp: 86-92 (2004). DOI: http://dx.doi.org/10.1117/1.1627778 (Cited 61 times)

3.* D. Merino, C. Dainty, A. Bradu, A. Podoleanu, Adaptive optics enhanced simultaneous en-face optical coherence tomography and scanning laser ophthalmoscopy, Optics Express, Vol: 14 Issue: 8 pp: 3345-3353 (2006). (Cited 57 times) DOI http://dx.doi.org/10.1364/OE.14.003345

4. A. Gh. Podoleanu, Unique interpretation of Talbot Bands and Fourier domain white light interferometry, Optics Express, 15 9867 (2007). (Cited 12 times) DOI: http://dx.doi.org/10.1364/OE.15.009867

5. A. Gh. Podoleanu, R. B. Rosen, Combinations of techniques in imaging the retina with high resolution, Progress in Retinal and Eye Research, 27, No. 4, pp 464-499, (2008). DOI http://dx.doi.org/10.1016/j.preteyeres.2008.03.002 (Cited 44 times)

6. R.B. Rosen, M. Hathaway, J. Rogers, J. Pedro, G. Patricia, P. Laissue, G. M. Dobre, A. Gh. Podoleanu, Multidimensional en-Face OCT imaging of the retina Optics Express, Vol. 17 Issue 5, pp.4112-4133, doi:10.1364/OE.17.004112, (2009), (Cited 10 times) DOI http://dx.doi.org/10.1364/OE.17.004112

Selection of grants associated with the OCT work:

1. D.A. Jackson, D.J. Webb, £180K, Non-invasive optical techniques for high spatial resolution studies of the eye, 1995-1997; RA: A. Podoleanu.
2. D.A. Jackson, D.J. Webb, En face optical coherence tomography of the living human eye, 1998-2001, £450K, (RAs: A. Podoleanu & G. Dobre).
3. Marie Curie Early Stage Training Network, (ESTN), EC, HIGH RESOLUTION OPTICAL MEASUREMENTS AND IMAGING, 3 HEs and 2 SMEs in Europe, 2.4 MEuros, 1/05/2006-31/07/2010, EC, Marie Curie Training Network, over 650k Euros for AOG, supported 12 PhD students and 6 short term early stage researchers, two workshops and a Summer School;
4. EPSRC, “Adaptive Optics Assisted Optical Coherence Tomography for Retinal Imaging”, 2003-2006, supported a postdoc, components, equipment and travel, over £180K.
5. Ariba Foundation, New York Eye and Ear Infirmary, USA, “Quantification of reflectivity of

contrast media", £150K, Jan 2002 - April 2006.
6. University of Kent, PhD studentship, "Fourier domain OCT", 2002-2005. ~£39K.
7. "Distortions and randomness in low coherence interferometry applied for imaging of multilayer objects", EPSRC, £78K, Jan. 2001 - Oct. 2004, International collaboration with the School of Optics – Center for Research and Education in Optics and Lasers, University of Central Florida, Orlando, USA. This supported a PhD studentship including equipment and components and travel between Canterbury and Orlando.
8. "Optical Coherence Tomography of Skin", Pfizer, Sandwich, £70K, 2001-2003, to research an imaging system to evaluate the penetration of drugs in the skin;
9. "Assembly of optical mapping apparatus", Ophthalmic Technologies Inc., Toronto, Canada, 2000-2002, for the design and assembly of 4 imaging instruments, installed at four clinics worldwide: New York Eye and Ear Infirmary, Vitreos Retina Macula Consultants of New York, Academic Medical Centre, Amsterdam and Asahikawa Medical College, Japan, £44K (labour only, components up to £40K/apparatus supplied by OTI);

Patents
US7466423, US7995207, US5975697, US7594730, US7113818, US5975697, US7330273, US7417741, US7466423, US6769769, US7139077, US6927860, US7535577, US7995207

4. Details of the impact

The work of the Applied Optics Group has had a direct impact on the health of some 5 million people worldwide, thanks to accelerated diagnosis of eye diseases such as age related macula degeneration and diabetes.

Research at Kent has led to commercial instruments that provide the only real time SLO image in pixel-to-pixel correspondence with the OCT image. Other OCT systems use an SLR camera (Topcon) or infer the SLO image using software from OCT images after the OCT acquisition (Zeiss). The provision of these directly related SLO/OCT images is crucial in guiding ophthalmologists in choosing the retina areas to be "sampled" by OCT. The technology developed by the AOG was translated to industry through four licence agreements. The first two below were to the benefit of patients with eye disease, with the second in current commercial exploitation and used by clinics worldwide. The latter two are at an earlier stage of development, but demonstrate that researchers at Kent are continuing to explore new ways of exploiting these technologies to create worldwide impact in ophthalmology/optometry.

1. Patent US5975697 by A. Podoleanu and D.A. Jackson (1998) has been assigned to OTI, followed by a family of patents (A. Podoleanu plus AOG members). This led to commercialisation of the OCT/SLO instrument by OTI worldwide, leading to revenue to the University and inventors exceeding $300K in the period.

2. The patent on a sequential spectral OCT with SLO was the subject of an agreement with OPKO in 2011 [6], with technology transferred to Optos. They continue to exploit the technology commercially and maintain the patent in good standing.

The implications of these instruments on health care professionals and patients cannot be overstated [1]. **The technology delivers new insight into eye diseases by providing recognisable en-face patterns of specific diseases** [2]**,** for example diabetic retinopathy, age-related macular degeneration, glaucoma, stroke and heart disease [3]. Instruments based on the technology covered by these patents are in use in eye clinics worldwide. OCT SLO is a central product for Optos plc, whose shares have grown by a factor 3 since 2008 and currently operates at around £125 million annual revenue and 16m profit. A rise in revenue of 37% in the past two years bringing valuable employment to Scotland. The company has over 5,000 clinical users worldwide [5], although it does not make public details on the price and exact numbers of OCT instruments described above these can be checked [4] and cross-referenced with income from the patent agreements to the university. This shoes that a large percentage of these clinics have instruments produced directly as a result of the research done by the Kent academics and covered by Kent patents and that on average they have been installed for five years. **Each instrument typically**

treats around 1,000 patients per year. It is estimated that around 5 million patient diagnoses was aided by the application of our research [4]**.**

The other two licence agreements are at an earlier stage of development. They demonstrate that researchers at Kent are continuing to explore ways of developing these technologies to create worldwide impact in ophthalmology/optometry.

3. Adaptive Optics technology applied to the OCT/SLO has been developed, assisted by EPSRC funding with input from the National University of Ireland, Galway (Prof. C. Dainty). This has been licensed to OTI for ophthalmology/optometry. Optos plc maintains the patent and there is on-going discussion between the parties on development and commercialisation of the technology.

4. A method of spectral OCT without disturbing mirror terms has been invented by A. Podoleanu. Spin-off company Optopod was created in 2005 by Podoleanu, (Director). Optopod has obtained University approval to sub-license the technology for Ophthalmology/optometry to OTI in return for prosecution of the patent in three territories, USA, Europe and Japan. The patent was filed in 2004 and only awarded in 2011. This technology has not yet been exploited commercially by OPKO/Optos.

Twenty-two PhD students have been trained within the OCT research programme. All 22 have found employment commensurate with their qualification level. e.g. M. Hathaway and J. Rogers, as Directors of OCT research at OPKO (now Optos plc). G. Dobre was a PDRA supported by EPSRC and NYEEI grants, becoming a lecturer in the AOG in 2003. D. Woods is now employed by Michelson Diagnostics Ltd, which commercialises OCT instrumentation for skin imaging.

5. Sources to corroborate the impact

Individual users and beneficiaries:
1. *For extensive utilisation of the en-face OCT technology and of the OCT/SLO technology:* Program Director ophthalmology, Department of Ophthalmology, The New York Eye and Ear Infirmary *[Contact 1]*

2. *For PhD of a clinician on the en-face OCT technology and on the OCT/SLO technology* Former Head of department and Director Rome Eye Hospital *[Contact 2]*

3. *To confirm the claims made in relation to the underpinning research being used in the product line*, Director of Research, Optos plc *[Contact 3]*

4. *To confirm the claims made with respect to numbers of patients and units sold*, Project Manager – Technology, Optos plc *[Contact 4]*

5. Figures on user basis and income are given in the company annual report: http://www.optos.com/Global/documents/AGM_Presentation_Feb2013.pdf *showing sales in relation to OCT products of over $2m per annum (FY12)*

This press release covers the acquisition of the OCT and ultrasound business and assets by OPKO Health, Inc. and indicates that the research that was carried out in Kent:
6. http://www.optos.com/en-GB/Investors/Press-Room/Press-Releases/2011/Proposed-Acquisition-of-the-OCT-and-ultrasound-business-and-assets-of-OPKO-Health-Inc/

7. Details of worldwide OCT funding, what it was used for and what has been achieved is provided in the following link:
http://www.octnews.org/articles/2920025/optical-coherence-tomography-used-500m-of-federall/