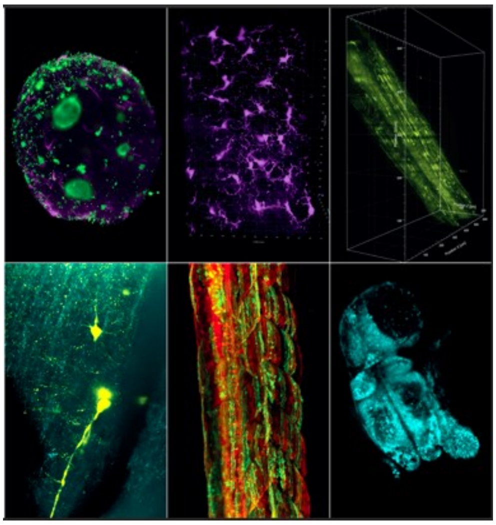
Section A		
Institution: University of St Andrews		
Unit of Assessment: UoA 09: Physics		
Title of case study: Commercialising Airy Beam Light Sheet Fluorescence Microscopy		
Period when the underpinning research was undertaken: 01 January 2012 to 31 December 2014		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by HEI:**
Kishan Dholakia	Professor	01 January 2000 - present
Period when the claimed impact occurred: January 2015 to 31 December 2020		
Is this case study continued from a case study submitted in 2014? N		

Section B

1. Summary of the impact

Our research on the physics of optical beams has led to the commercialisation of a new form of microscopy known as Airy beam light sheet fluorescence microscopy (LSFM). It is a powerful new 3D optical imaging technique that finds principal application in cell biology and neuroscience. The key innovation is the use of a special light beam profile, the Airy beam profile, which results in several advantages over existing microscopes: a 20 fold increase in the field of view whilst achieving deep sample penetration and high resolution, up to 20 times reduction in imaging time, and lower phototoxicity thus causing less damage to cells.



Biological objects imaged using Airy beamlight sheet fluorescence microscopy.

The University's Airy beam LSFM technology was exclusively licensed to M Squared Lasers Ltd. They spun out a legally and financially separate biophotonics business unit, M Squared Life Ltd, in 2016 specifically to develop and sell a new scientific instrument, the "Aurora" light sheet microscope, based on the Airy beam. The economic impact has arisen through the creation of [text removed for publication] jobs [text removed for publication], the sale of Aurora systems, which has raised over [text removed for publication] in revenue up to March 2020, and the securing of [text removed for publication] investment to grow both businesses.

End users of Aurora work on understanding diseases and processes in neuroscience and developmental biology in Universities, Research Institutes and National Laboratories and are located worldwide, including the UK, across Europe (e.g. Max Planck Institute for Molecular Biomedicine), South Africa, and the USA. Compared with competing technologies, Aurora enables end users to image a wider variety of biological samples with less photon damage and do so more rapidly and with unprecedented image quality over a larger volume. These benefits are enabling new imaging approaches not previously possible, particularly for live samples.

2. Underpinning research

The Optical Manipulation group, led by Kishan Dholakia, within the Centre for Biophotonics in the School of Physics & Astronomy at the University of St Andrews, has an extensive track record in the development of using shaped light beams for imaging studies, including seminal work on the Airy beam shape, published in 2014 [R1, R2]. This beam is a curved light field with side lobes that retains its thin size as it propagates in space. It was applied for the first time to light sheet optical imaging by the group, which is the basis of the underpinning research.

Optical imaging for biological applications is undergoing a revolution not only to achieve high resolutions at the 10nm scale but also to meet the growing demand for the imaging of larger structures (100µm to cm). In contrast to standard microscopes in which light illuminates a sample and one collects an image through the same set of optics, light sheet fluorescence microscopy (LSFM) is emerging as a powerful alternative. LSFM irradiates a section of the subject with a thin 'sheet' of light and the fluorescence or scattered light is collected at right angles to the illumination. The method is very appealing when compared to illuminating and collecting light through the same optics as it allows rapid 3D imaging of live specimens, has very low toxicity due to dramatically reduced light exposure (10 to 1,000 times lower than conventional imaging as only the part of the sample from which we wish to extract a signal is irradiated), and offers high contrast due to the targeted illumination. LSFM is the tool of choice for neuroscience and developmental biology. It also has great potential for drug discovery, histopathology, and phenotypical studies as it allows rapid (sub-second) imaging of 10s to 100s of samples.

The LSFM methodology has previously had three challenges that limited its applicability. However, we have now addressed these with our research on optical beams. The challenges were: (i) how to create a sheet-like beam of light that is ideally as thin as possible, which extends right across the field of view of the sample to provide uniform image quality across the whole field of vision; (ii) how to address (i) whilst keeping the light illumination level as low as possible to avoid any sample damage from excessive light exposure; and (iii) how to achieve increased light penetration (depth) into biological samples which are scattering and thus allow imaging at more than just the surface. Until now, these three challenges have restricted biomedical understanding and the ability to achieve high sensitivity and specificity in early diagnosis. Our approach of using the Airy beam, a transverse light pattern in two dimensions that does not change as the beam moves across the sample, addresses all three of these drawbacks. As a result, the technology can improve imaging of many biological systems, including the whole mouse brain, histopathology samples from cancer (colon, prostate, breast), and model organisms (zebra fish).

Prof. Dholakia's group showed that they could overcome the above restrictions in LSFM through the use of an Airy beam in 2014 [R3]. The beam's transversal structure has the unique property that allows the retrieval of high-resolution information (via a straightforward mathematical deconvolution algorithm) to create an image of the whole sample. In 2016, the team showed that the proposed microscope could be developed into a compact solution to imaging in neuroscience [R4] and that the approach is also compatible with more advanced fluorescence techniques in 2017 [R5]. In 2018, this was extended to tailor the Airy beam to overcome degradation of the beam due to sample scattering, allowing it to achieve deep penetration into a given sample [R6].

3. References to the research

All papers below are published in internationally recognised peer reviewed journals and the research was supported by peer-review grants.

R1. **Generation of attenuation compensating Airy beams** M. Preciado, K. Dholakia and M. Mazilu, Optics Letters, 39, (16), 4950-4953 (2014). DOI: 10.1364/OL.39.004950

R2. **A compact Airy beam light sheet microscope with a tilted cylindrical lens** Z. Yang, M. Prokopas, J. Nylk, C. Coll-Llado, F.J. Gunn-Moore, D.E.K. Ferrier, T. Vettenburg and K. Dholakia, Biomedical Optics Express 10, 3435 (2014). DOI: 10.1364/BOE.5.003434

R3. **Light-sheet microscopy using an Airy beam** T. Vettenburg, H.I.C. Dalgarno, J. Nylk, C. Coll-Llado, D.E.K. Ferrier, T. Cizmar, F.J. Gunn-Moore and K. Dholakia, Nat. Methods 11, 541-544 (2014). DOI: 10.1038/nmeth.2922

R4. **A compact light-sheet microscope for the study of the mammalian central nervous system** Z. Yang, P. Haslehurst, S. Scott, N. Emptage and K. Dholakia, Scientific Reports **6**, 26317 (2016). DOI: 10.1038/srep26317

R5. **Integrated single- and two-photon light sheet microscopy using accelerating beams**, P. Piksarv, D. Marti, T. Le, A. Unterhuber, L.H. Forbes, M.R. Andrews, A. Stingl, W.

Drexler, P.E. Andersen and K. Dholakia, Scientific Reports 7, 1435 (2017). DOI: 10.1038/s41598-017-01543-4

R6. **Light-Sheet Microscopy With Attenuation-Compensated Propagation-Invariant Beams**, J. Nylk, K. McCluskey, M. A. Preciado, M. Mazilu, Z. Yang, F.J. Gunn-Moore, S. Aggarwal, J.A. Tello, D.E. K. Ferrier and K. Dholakia, Science Advances 4, eaar4817 (2018). DOI: 10.1126/sciadv.aar4817

4. Details of the impact

The commercialisation of Airy beam light sheet fluorescence microscopy based on our research on the physics of optical beams has led to **economic impact through the creation and growth of a new business**, M Squared Life Ltd. The **sales of Aurora microscope systems to customers worldwide**, based on our licensed technology, **have created [text removed for publication] jobs [text removed for publication] and generated [text removed for publication] in revenue between 2016 and March 2020.** As a result, the M Squared group has **raised GBP32,500,000 in Tier 1 investment** in 2020 to support future growth. The new technology **benefits end users in cell biology and neuroscience by delivering improved imaging performance over that available from previous microscopes** (20 times wider field of view and up to 20 times faster imaging, lower phototoxicity, and 10 times higher signal to noise ratio). Aurora microscopes have enabled new forms of live cell imaging for biologists and clinicians. In turn, this is assisting end users in understanding diseases and neuronal processes.

Translating biophotonics research into commercial products

Prof. Dholakia's Optical Manipulation group has a broad portfolio of patents in Biophotonics. In 2015 the University of St Andrews completed a major IP licensing deal with M Squared Lasers Ltd [S1], a Glasgow-based SME with 93 employees and an annual revenue of GBP17,700,000 that has specialised in the development of advanced laser systems. Included in this deal was IP associated with light sheet imaging (Patent WO2013150273A1, 2013) and the application of such techniques within biology and medicine based on the research described in [R1] and [R2].

The intellectual steps and know-how needed for commercialisation of the Airy light sheet technology was undertaken solely by researchers from the School of Physics at St Andrews whilst many collaborators supported the application of the technology to biology [R2-R6]. Colleagues in the Schools of Biology and Medicine, University of St Andrews, the Department of Pharmacology, University of Oxford and the Medical University of Vienna provided biological samples and interpretation of biological images. Femtolasers GmbH loaned a laser for multiphoton research, and colleagues from Denmark Technical University supported us in its use.

In order to develop successfully the products based on this IP portfolio and to progress into new marketplaces in biomedicine, M Squared Lasers Ltd founded a new business subsidiary, M Squared Life Ltd in 2016 on the University of Surrey's research park in Guildford. The CEO recruited to manage the new company was chosen for his substantial experience of the biomedical imaging market, having previously been the Head of UK Instrument business at Nikon Corporation's Instrument Company, a leading supplier of microscopes for the biology and life sciences.

Prof. Dholakia and his team in the Centre for Biophotonics worked closely with M Squared Lasers and M Squared Life between 2015 and 2017 as the companies developed the light sheet technology for the market. Prof. Dholakia also assisted in developing the early adopter customer base for the microscope by hosting end user technical visits at St Andrews and providing specialist advice to end users on the specifics of optical system parameters and microscope use. Because of this close collaboration, M Squared Lasers and the University of St Andrews secured an ISCF/EPSRC funded Prosperity Partnership in 2017 to translate the light sheet research and grow the microscopy business, in which the company matched the GBP1,434,010 EPSRC funding commitment [S2]. This enabled the company to grow and develop the product range.

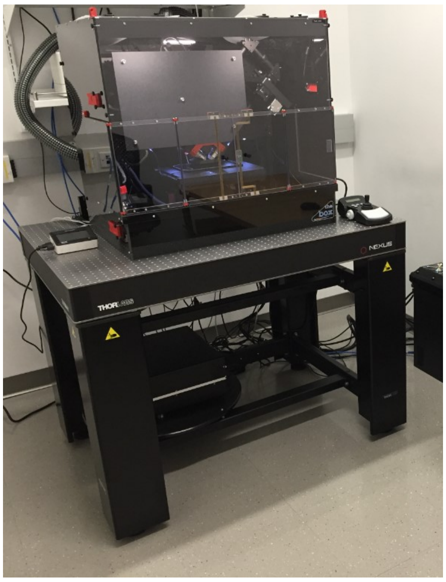
In 2017 M Squared Life was recognised with a Business Innovation Award from the Institute of Physics for bringing a new physics-based product to market which had a transformative effect on increased turnover, profitability and jobs. The Airy beam light sheet microscope enables "*scientists to perform 3D volumetric imaging of live cells and fixed tissue so they can understand more about the biological processes of diseases such as cancer and dementia*" [S3].

Aurora Airy beam microscopes contribute to the UK economy

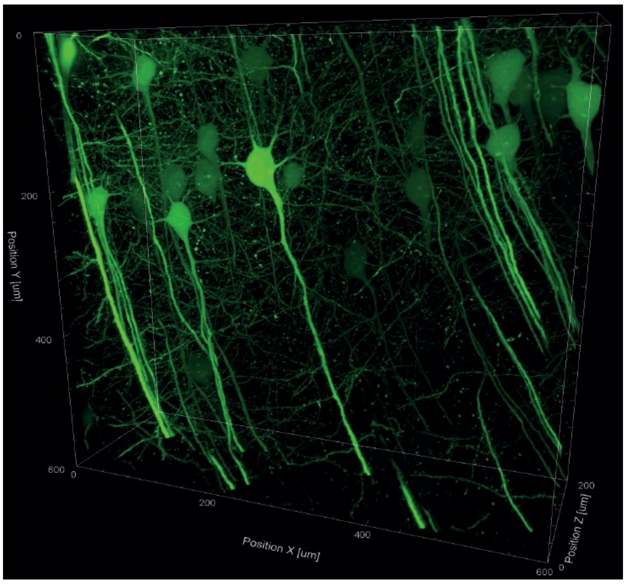
M Squared Life developed the Airy beam LSFM technology into the 'Aurora' trademarked microscopy product range [S4]. The company worked closely with early adopter customers internationally to bring the technology rapidly to market and develop Aurora as a flexible, modular system. The Head of Biophotonics at M Squared Life explained: "*The technology in this platform has allowed us to create a unique Light Sheet Microscope product in that it is able to image a wide range of biological material unlike our competitors more dedicated systems*" [S5].

Since 2016, sales of high value systems have been made to customers worldwide including "*two Max Planck Institutes, The Nils Bohr Institute, The University of Southern California and the UK National Physical Laboratory.*" [S5]. Aurora is now installed in the "*UK, USA, Germany, Sweden, Denmark, Finland & South Africa*" [S5]. The Head of Biophotonics at M Squared Life confirmed that "*As of March 2020 we generated revenues including contracts in process [text removed for publication] worth of systems.*" and that they have created *"… [text removed for publication] new high value technical and commercial positions.*" [text removed for publication] [S5]. As of [text removed for publication], they are currently handling end user enquiries worth "*in excess of [text removed for publication]*" [S5]. In context, the global light sheet microscopy market in 2019 was valued at USD105,410,000 in 2019 and is expected to reach USD181,900,000 by the end of 2026 growing at a compound annual growth rate (CAGR) of 10.27% during 2021-2026. [S5].

The commercial success of Aurora brings wider economic benefit to the M Squared group of companies as the Head of Biophotonics explains: *[text removed for publication]* [S5]. He added, "*The momentum the Biophotonics business has contributed to the M Squared group…has helped the company secure [text removed for publication] funding to further the next phase of the company's growth…*" [S5].



M Squared Life "Aurora"
light sheet fluorescence microscope



Aurora 3D image of brain cells (600x600x200μm)
Credit: Dr A. Vernon and R. Chesters, IoPPN

Improvements in live cell imaging for international end users in biomedicine

The innovative use of Airy beams in LSFM, which has been translated from our research, is **bringing tangible performance and efficiency benefits** over previous technology to **a diversity of biomedical end users in neuroscience, developmental biology, regenerative medicine and cancer research**. Understanding functional biology requires rapid 3D imaging of large volumes with sub-cellular resolution. Airy beam LSFM offers significant performance improvements over existing biological microscopes: 20 times wider field of view and up to 20 times faster imaging, lower phototoxicity and 10 times higher signal to noise ratio [S4]. These benefits enable end users to perform rapid 3D volumetric imaging of live cells and fixed tissue so they can understand more about the biological processes of diseases such as cancer and dementia. The technology is now used in facilities for neuroscience and developmental biology in Universities, Research Institutes and National Laboratories worldwide. The benefits to end users and the industry are exemplified by the following testimonials.

A Senior Research Scientist at UK National Physical Laboratory, where a system was installed in 2017, verified the benefits: "*We use the Aurora Airy beam light sheet microscope system for a wide range of volumetric fluorescence imaging experiments in our lab. In particular, we find the capability of the system to rapidly image large samples with sub µm spatial resolution make it well suited to studying 3D cell cultures and multicellular models, which is helping us to investigate structural changes in tumour organoids in response to therapeutic drug treatment*" [S4, p. 5]. This team has shown that Aurora "technology *is ideal for imaging [text removed for publication]*" [S5].

The improvements over previous technology are clearly stated by the Manager of the Live Cell Imaging Facility at the Karolinska Institutet, Sweden, which provides biological imaging facilities to around 70 medical science researchers: "*Compared to the capacity we had before acquiring the Aurora light sheet, we have improved greatly the speed of imaging, the ability to image very large samples as well as the ability to image live samples in large gels without phototoxicity.*" Furthermore, she states that "*Additionally, the Aurora light sheet benefits from a very large field of view over 780x780 µm with a resolution better than 1µm over the whole image which is an exceptional performance.*" (2020) [S6].

The Head of the BioOptics Service Unit, Max Planck Institute for Molecular Biomedicine, Germany, which provides light microscopy services to 150 researchers, states: "*the Aurora instrument provides an extremely flexible specimen area with an incredible observation volume*" and has enabled them "*to improve our temporal resolution compared to the classical approach by factor of 4 with an increased observation volume and improved resolution in Z-direction.*" (2020) [S7].

The Director of the Wohl Cellular Imaging Centre, King's College London, describes the improvement: "*we are now able to image 3D neuronal organoids … in 3D, 20x faster than with our previous imaging system. This has allowed us to visualise the 'self-organisation' of neural stem cells into neural rosette structures in 3D, which we were not able to do with traditional confocal and 2 photon imaging approaches. This system now provides the ability to rapidly acquire overall neuronal architecture uniformly within large volumes of neuronal tissue*." (2020) [S8].

5. Sources to corroborate the impact

S1. http://www.bbc.co.uk/news/uk-scotland-scotland-business-32038141 (24/03/15)
S2. https://www.electrooptics.com/news/%C2%A378-million-government-fund-aid-industry-academia-collaboration (24/07/17)
S3. Institute of Physics Business Innovation Awards Brochure, pp. 7 & 13 (2017)
S4. Aurora brochure https://www.m2lasers.com/images/M_Squared_Life_Brochure_2019.pdf pp. 10 & 5 (2019)
S5. Letter from the Head of Biophotonics at M Squared Life Ltd (14/12/20)
S6. Letter from the Live Cell Imaging Facility Manager at the Karolinska Institutet, Sweden (26/03/20)
S7. Letter from the Head of the BioOptics Service Unit at the Max Planck Institute for Molecular Biomedicine, Germany (13/03/20)
S8. Letter from the Director of the Wohl Cellular Imaging Centre, Kings College London (24/03/20)