

Impact case study (REF3b)

Institution: University of Dundee
Unit of Assessment: UoA15 – General Engineering
Title of case study: New concepts in the 3-dimensional nature of blood flow improving the treatment of people with peripheral vascular disease and requiring haemodialysis.

1. Summary of the impact (indicative maximum 100 words)

Commercialisation: Through government grants, institutional and private investors, a medical devices company (Vascular Flow Technologies) was founded.

Products: Spiral Laminar Flow™ Vascular Grafts for use in bypass for peripheral arterial disease and vascular access for haemodialysis.

Market / Sales: Spiral Laminar Flow™ Grafts are sold in 18 countries, with over 3000 grafts implanted (<1% estimated market size) and sales in excess of £1million.

Patient Outcomes: Published and presented clinical series show the grafts have increased survival rates leading to reduced re-interventions and reduced amputations.

2. Underpinning research (indicative maximum 500 words)

Previously the understanding of blood flow within the body has revolved around a 2-dimensional representation of flow within rigid vessels. Following work visualizing the internal structure of medium sized arteries, a hypothesis was developed by one of the principal investigators, Professor Stonebridge: that there is a rotational element to laminar flow with its axis at the centre of the artery.

Together with subsequent work, it is possible to bring left ventricular anatomy and function together with blood flow within large to medium arteries, as a coherent beneficial spiral laminar flow system [1-3]. Vascular grafts which generate a normal non-turbulent vascular flow environment for blood vessels and their cell lining - stable spiral laminar flow - have significant advantages over all other grafts which generate a damaging turbulent outflow.

The next stages of the project, engineering and product development, were carried out by Professor Stonebridge and Professor Houston with colleagues in engineering. This required two key inter-related innovations. The first was to develop a non-invasive, reproducible method of identifying spiral laminar flow in vivo and as part of device assessment. This has been achieved using 2 modalities; colour-Doppler ultrasound and Magnetic Resonance Imaging (MRI) [1-2]. This has confirmed that normal blood flow is spiral laminar in nature and has allowed the design and testing of a new family of prosthetic bypass grafts [1-3,5]. Such grafts are used to treat diseases such as peripheral arterial disease and renal failure (see section 4 for more information).

The second was to begin to define the advantages of such a flow pattern using engineering techniques of computational fluid dynamics, bench testing and clinical studies [4-5]. This initially examined spiral and non-spiral laminar flow through a narrowed conduit. This indicated that rotational laminar flow induced 'laminar stability' in a flow environment that would otherwise induce turbulence [4]. Clinical studies revealed an association between the absence of spiral laminar flow and the severity and progression of disease [5].

The next stage was to design and engineer a prosthetic graft that induced a flow profile within manufactured devices identical to that seen in healthy arteries. This required multiple iterations of a three part approach to design and pre-production prototype testing; computational fluid dynamics, flow bench testing (requiring the development of a patented flow pump), and pre-clinical animal testing in modelling peripheral vascular and high-flow arterio-venous flow environments. This required the development of a pre-clinical model with flows matching intended human flow rates. The subsequent spiral flow inducer is protected by 18 families of patents ranging from broad concept patents to the grafts critical geometries. Finally the prototype was engineered using a composite material design to allow commercial production and regulatory approval in the EU and US for product marketing and sales.

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3. References to the research (indicative maximum of six references)

Peer reviewed publications: (Three key references are denoted with an asterisk.)

1. **In vivo* spiral laminar flow. Stonebridge PA, Hoskins P, Allan PL, Belch JJF. Clinical Science 1996; 91: 17-21
2. *2-Dimensional Flow Quantitative MRI of Aortic Arch Blood Flow Patterns: Effect of Age, Gender and Presence of Carotid Atheromatous Disease on the Prevalence of Spiral Blood Flow. Houston JG, Gandy SJ, Sheppard DG, Dick JBC, Belch JJF, Stonebridge PA. J. Magn. Reson. Imaging 2003; 18(2):169-74. DOI: 10.1002/jmri.10341
3. Three-dimensional blood flow dynamics: spiral/helical laminar flow. Stonebridge PA. Methodist Debakey Cardiovasc J. 2011 Jan-Mar;7(1):21-6.
4. *Non spiral and spiral (helical) flow patterns in stenoses. In vitro observations using spin and gradient echo magnetic resonance imaging (MRI) and computational fluid dynamic modelling. Stonebridge PA, Buckley C, Thompson A, Dick J, Hunter G, Chudek JA, Houston JG, Belch JJ. Int Angiol. 2004 Sep;23(3):276-83.
5. Spiral laminar flow in the abdominal aorta: A predictor of renal impairment deterioration in patients with renal artery stenosis? Houston JG, Gandy SJ, Milne W, Dick JB, Belch JJ, Stonebridge PA. Nephrol Dial Transplant. 2004 Jul;19(7):1786-91. DOI:10.1093/ndt/gfh238

Research Grants

- a. SUPA/SINAPSE PhD Studentships 2010, £56,000. Fluid dynamics assessment of spiral flow inducing intravascular stents.
- b. DPFMS MRC 2010 £296,632. Extracorporeal system for pulsatile flow and respiratory motion of Thiel embalmed human cadavers "Dundee Pulsatile Flow System".
- c. Knowledge Transfer Partnership 2010, £142,292. Development of new arterial graft and stent design based on improved materials & tests prototypes & products using imaging blood flow measurement capability. KTP007891

Patents

There are 54 granted patents related to spiral flow and its testing within 18 Patent Families in Europe, USA, China, Japan, India, Taiwan, and Argentina.

4. Details of the impact (indicative maximum 750 words)

Peripheral arterial disease is a narrowing of the arteries causing reduced blood flow. Symptoms range from leg pain when exercising to severe foot pain, ulceration and gangrene with significant potential for limb amputation and affects 10.5m individuals across Europe and North America. One of the main treatment options replaces the diseased artery with a synthetic **peripheral vascular graft (PVG)**.

Haemodialysis (HD) is a common treatment for patients with end stage renal failure. Over a quarter of a million patients receive haemodialysis in Europe, increasing at a rate of 5% per year (European Renal Association - European Dialysis and Transplant Association Registry 2009). One method of establishing access to the patients' circulation required for hemodialysis is **arteriovenous graft (AVG)** implantation.

The durability of all prosthetic PVG or AVG are severely limited by the formation of blood vessel narrowing (stenosis) due to post-procedural overgrowth of vessel wall cells (intimal hyperplasia). Forty to 70% of PVG used below the groin fail within 2 years leading to prolonged hospital stays, repeated interventions, and amputation. Sixty to 80% of AVG fail at one year, resulting in poor dialysis, multiple re-interventions and loss of dialysis access.

From the research carried out by Stonebridge and Houston, the creation of vascular devices which engender spiral laminar flow were expected to improve graft patency and reduce disease progression [REFa]. This led to the start up of a company to design, market and sell such devices. **Creation of a new bioengineering design company globally marketing vascular medical devices:**

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In 2001 Vascular Flow Technologies Ltd was founded by Profs P. Stonebridge and G Houston, and Dr J Dick. The aim was to create an international, innovative medical device company and to explore non-medical/industrial applications of spiral laminar flow as a platform technology. Tayside Flow Technologies Ltd, renamed Vascular Flow Technologies Ltd (VFT) is currently a SME based in Dundee, Cambridge and Boston (Mass., USA), employing 15 full-time staff and a further 4 part-time consultants [REFb].

The company has attracted £13.5million of external investment (including £950k of government and industry grant funding (SMART and SpurPlus)). Recent investment in 2013 (£1.5million) underpins more rapid penetration of the US market [REFc]. Out licensing of the core IP within a number of areas is also in progress. This will increase the product portfolio and significantly expand the company’s potential market.

Vascular Flow Technologies currently has 2 established vascular graft product ranges (6mm and 8mm SLF™ peripheral vascular graft and a 6mm SLF™ arteriovenous vascular access graft) with regulatory approval in Europe (‘CE mark’ issued by Intertek) and the USA (‘510k substantial equivalence’ issued by the FDA) between 2007 and 2010 (Table) [REFd]

Graft	Award	Year
PV 6mm / 8mm	CE mark	2007/2008
PV 6mm /8mm	510K	2009
AV	CE mark/510K	2010
AV	510K	2010



Table: EU and USA regulatory approval

Figure: SLF™ graft

The products have been manufactured by an OEM (original equipment manufacturer); Vascutek, Renfrewshire, Scotland (a Terumo Company) since 2008. Blank expanded polytetrafluoroethylene (ePTFE) grafts are post-processed to add a precisely engineered, patented spiral induction segment to the distal end of the graft (Figure above).

The European Market for Peripheral Vascular Grafts is valued at \$100.2million with growth expected to increase at a compound annual rate of 7.3%. The grafts are marketed and distributed from Scotland. Vascular Flow Technologies established distribution networks in USA and Europe, South East Asia, and Japan between 2008 and 2013. Over 2500 grafts have been implanted worldwide in 18 countries (Australia, Austria, Belgium, Czech Republic, Denmark, Germany, Greece, Italy, Netherlands, New Zealand, Russia, Saudi Arabia, Spain, Switzerland, Thailand, Turkey, UK, and the USA). Further regulatory approval has been obtained in France and been submitted in Japan [REFb, REFc].

Vascular Flow Technologies has also entered into a unique regional partnership with a multinational vascular devices company, LeMaitre GmbH, as distributor of Spiral Flow vascular Grafts, initially, in Germany reinforcing industry recognition and impact of this new technology [REFe].

Sales within the REF period, to the end of 2012, of the graft products are in excess of £1million [REFc].

Improved patient care:

Published and presented clinical series show Spiral Laminar Flow™ grafts have increased graft survival leading to reduced re-interventions and reduced amputations [REFf, REFg]. Patient registry/clinical trials are ongoing with an EU grant (€2.6million) being offered to examine the clinical trends in haemodialysis patients including assessment of the impact of the VFT graft

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[REFh]. Other companies have begun to adopt the underlying principles in their medical device products [REFi].

Vascular Flow Technologies technology, based in the UK with UK manufactured products, has delivered a significant new platform technology applicable to medical devices to a global market.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[REFa] Adaptable technology is crucial in accommodating a variety of patient needs. Professor Alan Lumsden, Methodist DeBakey Hospital Houston. Endovascular Today. <http://evtoday.com/2012/09/supplement/what-exactly-is-radial-fit/>

[REFb] Vascular Flow Technologies Ltd. (VFT) www.vascular-flow.com

[REFc] Factual statement: CEO, Vascular Flow Technologies.

[REFd] NHS National Institute of Health Research. Spiral laminar flow peripheral bypass graft for PAOD. NIHR Horizon Scanning Centre, School of Health & Population Sciences, University of Birmingham. Sept 2009 <http://www.hsc.nihr.ac.uk/topics/spiral-laminar-flow-peripheral-bypass-graft-for-pe/>

[REFe] LeMaitre New Distributor in Germany. <http://www.vascular-flow.com/new-distributor-in-germany/>

[REFf] Spiral Flow™ Grafts Offer Superior Clinical Outcomes in Prosthetic Bypass Grafting. Veith Symposium in New York, USA. <http://www.prnewswire.com/news-releases/spiral-flowtm-grafts-offer-superior-clinical-outcomes-in-prosthetic-bypass-grafting-180145491.html>

[REFg] Spiral laminar flow prosthetic bypass graft: medium-term patency from a structured first-in-man structured registry study. Stonebridge PA, Vermassen F, Dick J, Belch JJ, Houston G. Ann Vasc Surg 2012; 26(8):1093-9.

[REFh] EU IAAP Grant Offer €2.3million - PIAP-GA-2012-324487 ReDVA: Development of hemodynamic solutions in Renal Dialysis Venous Access Failure.

[REFi] BioMinics 3D™ Stent for peripheral artery disease. <http://euroscan.org.uk/technologies/technology/view/2544>