Institution: University of Nottingham		
Unit of Assessment: 3 (Allied Health Professions, Dentistry, Nursing and Pharmacy)		
Title of case study: Translation and commercialization of a bacteria resistant coated urinary catheter: From Discovery to Society.		
Period when the underpinning research was undertaken: 2008 – 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 Morgan Alexander	Professor of Biomedical Surfaces	2010 to present
Dr Andrew Hook	Senior Research Fellow	2014 to present
Professor Martyn Davies	Professor of Biomedical Surface Chemistry	1985 to 2017
Period when the claimed impact occurred: August 2013 to date		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Research by the School of Pharmacy that led to the discovery of a new class of materials has underpinned the translation and commercialization of a paradigm-shifting biomedical device. From licensing the patented technology and continued collaboration with Nottingham researchers, Camstent Ltd have attracted in excess of GBP5,000,000 of investment, opened an ISO approved manufacturing facility in the UK with commercially attractive production capacity, and obtained a CE mark for a urinary catheter with a 'bacteria-phobic' descriptor. Following successful first-in-man trials the catheters are being used in hospitals in the UK, benefitting patients and clinicians.

2. Underpinning research

Use of implanted and indwelling medical devices in hospitals can directly cause bacterial infections, currently costing the NHS over GBP1 billion annually, of which catheter associated urinary tract infection (CAUTI) is one of the major causes, accounting for 38% of all cases. Efforts to reduce infection include sterile practice, limiting catheter duration, and routine use of antibiotics. Such use of antibiotics is problematic and unsustainable, contributing to the rise in antibiotic resistant bacteria.

A key challenge in prevention and treatment of bacterial infection associated with medical devices is tackling biofilms – an aggregate of bacteria on the surface – which cause 80% of hospital acquired infections (HAI) (National Institutes of Health). Bacteria in biofilms are 1000 times more resistant to antibiotics and clearance by the host immune system, therefore biofilm prevention is an important target to reduce infections with huge potential benefits for patients and healthcare providers (Centers for Disease Control and Prevention). Furthermore, biomineralization – the deposition and growth of mineral crystal deposits – can be particularly problematic with catheters and urease-producing bacteria such as *Proteus*, causing catheter encrustation resulting in blockage and significant removal problems.

Alexander and co-workers have expertise in developing materials for application in biological environments. In 2007, Alexander's team collaborated with researchers at the Massachusetts Institute of Technology who developed a novel materials micro-array process that enabled hundreds of unique polymers to be screened simultaneously. Working closely with Professor Paul Williams (Life Sciences, UoN) they implemented the micro-array process to screen 1000s of polymers against multiple pathogens, leading to the discovery of a new group of structurally-related polymers that dramatically reduced attachment of pathogenic bacteria (including *Pseudomonas, Proteus, Staphylococcus* and *Escherichia coli*) (R1). Coating silicone with these 'hit' materials achieved up to a 30-fold reduction in the surface area covered by bacteria *in vitro* compared to a commercial silver hydrogel coating in use in catheters at the time. *In vivo* studies using the new coatings also demonstrated a reduction in bacterial attachment, and importantly that they were non-toxic and non-irritant. The materials were patented in 2011 (R11).

Collaboration with Prof Derek Irvine (Faculty of Engineering, UoN) enabled further development of the polymer structure for enhanced material properties. The introduction of a co-monomer enabled appropriate mechanical flexibility without negating the bacteria resistant properties (R2).

Further research by the team has investigated the correlation between the nature of the hydrocarbon moiety and bacteria adhesion, which led to the generation of structure-function relationships (R3). In 2019, the researchers reported the experimental validation of their predictive tools, thereby providing mechanistic insight into the function of the materials, and demonstrated further functionality of the polymer group to function against *Enterococcus faecalis* and *Klebsiella pneumoniae* (R4).

In 2013, the researchers licensed the materials to a medical device company Camstent Ltd for product development and manufacture as a bacteria resistant catheter. The unique ability of these materials is their prevention of bacteria forming irreversible attachments to the surface, thereby inhibiting proliferation and biofilm formation. Unlike competitor devices, the Camstent catheter is not dependent on killing bacteria, so there are no eluted by-products or build-up of antibiotic resistance overtime. Preventing bacterial attachment and biofilm formation rather than using antibiotics with their known role in driving antibiotic resistance presents a paradigm shift of biomedical device design and use; 'prevention is better than cure'. In 2018, the coating was registered under the BACTIGON® trade mark. In 2019, the initial results of the first-in-man pilot study evaluating the effectiveness of 10 BACTIGON-coated catheters developed with Camstent vs 12 uncoated catheters, was published (R5). The study demonstrated that the coated catheters had reduced both biofilm formation and biomineralization compared to the uncoated catheters.

A continued multidisciplinary collaboration between and the researcher team and Camstent Ltd to develop the materials into a useable medical device has led to the impacts outlined below.

3. References to the research (research staff in **bold** from the School of Pharmacy, UoN)

R1. **Hook, A.L.**, Chang, C-Y., **Yang, J**., Luckett, J., Cockayne, A., Atkinson, S., Mei, Y., Bayston, R., Irvine, D.J., Langer, R., Anderson, D.G., Williams, P., **Davies, M.C**. and **Alexander, M.R**. Combinatorial discovery of polymers resistant to bacterial attachment. *Nature Biotechnology* **30** (2012) 868-875. DOI: 10.1038/nbt.2316.

R2. Adlington, K., Nguyen, N.T., Eaves, E. **Yang, J**., Chang, C.-Y., Li, J., Gower, A.L., Stimpson, A., Anderson, D.G., Langer, R., **Davies, M.C**., **Hook, A.L**., Williams, P., **Alexander, M.R.** and Irvine, D.J. Application of Targeted Molecular and Material Property Optimization to Bacterial Attachment-Resistant (Meth)acrylate Pol Application of Targeted Molecular and Material Property Optimization to Bacterial Attachment-Resistant (Meth)acrylate Polymers. *BioMacromolecules* **17** (2016) 2830-2838. DOI: 10.1021/acs.biomac.6b00615

R3. Sanni, O., Chang, C.Y., Anderson, D.G., Langer, R., **Davies, M.C**., **Williams, P.M.**, Williams, P., **Alexander, M.R**. and **Hook A.L**. Bacterial attachment to polymeric materials correlates with molecular flexibility and hydrophilicity. *Advanced Healthcare Materials* **4** (2015) 695-701. DOI: 10.1002/adhm.201400648

R4. Dundas, A.A, Sanni, O., Dubern, J.-F., Dimitrikas, G., **Hook, A.l**, Irvine, D.J., Williams, P. and **Alexander, M.R.** Validating a Predictive Structure-Property Relationship by Discovery of Novel Polymers which Reduce Bacterial Biofilm Formation. *Advanced Materials* **31** (2019) 1903513. DOI: 10.1002/adma.201903513

R5. Jeffery N., Kalenderski K., Dubern J., Lomiteng A., Dragova M., Frost A., Macrae B., Mundy A., **Alexander M.R.**, Williams P. and Andrich D. A new bacterial resistant polymer catheter coating to reduce catheter associated urinary tract infection (CAUTI): A first-in-man pilot study. *European Urology Supplements* **18** (2019) e377 DOI: 10.1016/S1569-9056(19)30282-9

Grants:

R6. Wellcome Trust Technology Transfer Translation Award: High throughput micro arrays for discovery of polymers resistant to bacterial colonisation. Grant holders: Williams P., **Alexander M.R.** and **Davies M.C**. GBP1,300,000 (2008-2012) Grant Number: 085245

R7. Wellcome Trust Joint Senior Investigator Award: Bacterial Surface Sensing: To stick or not to stick? Grant holders: Williams P. and **Alexander M.R.** GBP2,000,000 (2014-2019) Refs. 103882/Z/14/Z & 103884/Z/14/Z

R8. EPSRC Programme Grant: Next Generation Biomaterials Discovery. Grant Holders: PI: **Alexander M.R.;** Co-Is include **Rose F.R.A.J.**, **Davies M.C.**, **Williams P.M**., **Yang J**., **Shakesheff K.M.**, **Alexander C**., Irvine D.J. and Williams P. GBP5,365,958 (2015 to 2020) EP/N006615/1

Awards:

R9. The Camstent-University of Nottingham work has been shortlisted in the Most Innovative Contribution to Business-University Collaboration category at THE Awards 2018.

Patent and trade marks:

R10. BACTIGON® has been registered as a UK trade mark (3326867, Class 5, 19-10-2018, UK)

R11. US (9,981,068B1) and EP (2704565B1) patents (priority date: 04-05-2011) 'Polymers which resist bacterial attachment'.

4. Details of the impact

Fundamental, discovery research led by Alexander has resulted directly in the development, translation and commercialisation of a Bacteriaphobic® urinary catheter through the collaboration with a specialist medical device company Camstent Ltd. This discovery and the commercial product offers a superior strategy to prevent CAUTI's over current methods, which focus on antibiotics to kill the attached organisms.

The 2012 Nature Biotechnology article detailing the discovery of bacteria-resistant materials gained wide media coverage and considerable interest from industry to develop the discovery into new technology. In 2013, Camstent Ltd changed their business direction from blood resistance to focus on commercialization of the technology discovered at the University of Nottingham. Camstent Ltd secured an exclusive licencing deal to develop the technology into products for urology that commonly lead to HAIs. With continued support from UoN researchers, Camstent have developed their first commercially available, CE mark approved Bacteriaphobic® urinary catheter [A]. The growth of Camstent during the REF period is intimately linked to the discovery of the materials at the University of Nottingham and the continued research support provided, "*the nature and outcomes of the research collaborations between Camstent Ltd and the University of Nottingham has resulted in the successful development and commercialisation of our first coated urinary catheter product and growth of Camstent Ltd*.", CTO and Founder of Camstent confirms [B]. This can be summarised in several milestones:

i. Licencing milestone

In 2013, the patent of the antibacterial polymer developed by Alexander and colleagues was licensed by the University of Nottingham to Camstent Ltd for their exclusive use to coat urinary tract Foley catheters [C].

ii. Investment milestones

To December 2020, Camstent has raised in excess of GBP5,000,000 of investment through a series of funding rounds supported by promising proof-of-concept results established with University of Nottingham support. As indication of the excitement and interest in the technology in June 2017, Camstent exceeded a target investment round by almost three-fold to a total of GBP850,000 from existing and new investors. The investment was pledged towards a CE mark application of the Foley catheter, to develop clinical and marketing partnerships towards sales, and to expand the development of other medical products. In a separate investment round in March 2019, Camstent raised an additional GBP600,000, which was used towards funding clinical evaluations, pursuing regulatory milestones, making key appointments to the Executive Team, and doubling the manufacturing and laboratory space [D].

iii. Manufacturing milestones

In 2017, with Alexander and colleagues providing the technical knowhow to set up the polymer manufacturing process, Camstent Ltd established a manufacturing facility in Bedfordshire, UK. The facility is medical devices-compliant and certified for the manufacture of coated urinary Foley catheters (ISO 13485). The opening of the facility was an important milestone that allowed the production of coated catheters for early sales, product trials and regulatory approval, with the maximum capacity of 10,000 catheters per month [B, E].

iv. Regulatory research milestones

The Camstent Ltd coated urinary catheter achieved European Union CE mark approval in 2017 (CE 0088, Certificate Number LRQ 00000604/B). The CE mark allows for the catheters to be sold in the UK and across Europe. More recently in November 2019, the catheter achieved the descriptor of Bacteriaphobic® following claim approval from the notified body, and National UK trade mark following publication of the first-in-man clinical trial that demonstrated the coatings ability to resist bacteria [F]. This was a significant step towards commercialization, as the catheter could now claim to repel bacterial attachment.

v. Clinical milestones

Camstent Ltd secured Innovate UK funding to carry out a qualitative evaluation of the performance of the Bacteriaphobic® catheters in 31 patients. The evaluation determined the perceived comfort and ease of insertion/withdrawal of the catheters, adequate drainage of urine from the bladder, safety, packaging, labeling, instructions for use, all of which is key for both patients and clinicians. The catheter coating forms a smooth surface that lowers the frictional forces associated with insertion and withdrawal, minimising patient discomfort, acute irritation and reducing tissue trauma. 30 of the 31 patients reported positive comfort experiences on catheter insertion [G]. A UK lead urologist and Honorary Associate Professor at University College London Hospitals NHS Foundation Trust, who trialled the catheters in her patients, said "*The surface of the catheter is very smooth and hardly requires any lubrication for insertion which is great for the patient. Our patients are all satisfied with the new product and we will continue to use Camstent catheters… as the new standard for post-operative urinary diversion after Reconstructive Urological Surgery."* [H]

An intermediate scale first-in-man pilot study during 2018-2021 involving six hospitals in the UK compared biofilm formation in 75 BACTIGON®-coated versus 75 standard silicon catheters in 150 hospitalised patients. This study concluded the BACTIGON®-coated catheters reduced the mass of bacteria detected on catheters after use by 65% to 95% compared to uncoated catheters [I]. The Head of Nottingham Colorectal Service at Nottingham Universities Trust who partook in the non-randomised clinical study stated, "*Attempts to reduce CAUTI infections have really made very little impact so far….reducing infections is essential to prevent complications and reduce length of hospital stay I therefore agreed to run a study of the Camstent catheters…the catheters were deemed easy to insert by clinicians and the results demonstrated a reduction in biofilm formation compared to our standard catheters.*" [J]

vi. Sales and agreements milestones

The Camstent Bacteriaphobic® catheter is available for sale on Camstent's website: *"available in standard and female lengths, and in sizes 12 & 14 Fr"* and has recently secured regulatory approval to expand the range of coated catheters to include more sizes and speciality tips [K]. In 2019, Camstent secured a deal with the global distributor of medical devices Pennine Healthcare. Since then, Pennine have secured the placement of the Camstent catheters on NHS procurement of four UK hospitals who are regularly purchasing catheters from Camstent Ltd [B].

vii. Company diversification and future outlook

Camstent is making significant progress to secure FDA approval to sell its product in the United States, and is conducting a 300-patient multi-centre clinical trial with the University of Nottingham to document the significant impact the coating is expected to have on infection rates

and length of hospital stay [I]. Camstent is currently pursuing partnership and licencing opportunities for wider use of the coating in medical products across global markets. In late 2020, a supplementary trial is beginning in collaboration between Camstent, the University of Nottingham and the Norfolk & Norwich Trust to apply the coating to suprapubic catheters used for patients with trauma of spinal injury. This is evidence of company strategy and future product diversification as a result of their collaboration with the Nottingham research team.

The collaboration between Camstent Ltd and the University of Nottingham research group has been paramount to the success of this commercial venture. Chief Technical Officer at Camstent said "*Professor Morgan Alexander and Professor Paul Williams brought un-matched insight to material chemistry, understanding of clinical microbiology, and comprehensive analytical test facilities that made transfer of the University's technology to clinical customers possible*." [B]

The UK lead urologist at UCL Hospitals NHS Foundation Trust comments that "*We are very pleased that there is finally a catheter available with antibacterial surface coating we have been waiting decades for!*" [H]

In summary, researchers at the University of Nottingham have enabled the translation and commercialization of a medical device from their discovery of a new class of biomaterial through to the clinic.

5. Sources to corroborate the impact that has occurred

A. Camstent webpages providing information on the device. URL: www.camstent.com (accessed 05/01/21 – also PDF).
B. Corroborative statement from CTO, Director and Founder of Camstent Ltd (PDF).
C. Exclusive licence between The University of Nottingham and Camstent Ltd for use of materials for catheter development (PDF).
D. Camstent press release of funding rounds. URL: www.camstent.com/camstent-raises-600k-and-doubles-manufacturing-and-lab-space/ (accessed 03/12/20 – also PDF).
E. Camstent press release of manufacturing facility. URL: www.camstent.com/camstent-opens-pilot-manufacturing-facility/ (accessed 05/01/21 – also PDF).
F. Confirmation of BACTIGON® and Bacteriaphobic® trade marks from UK government trade marks listing: https://trademarks.ipo.gov.uk/ipo-tmcase/page/Results/1/UK00003326867 https://trademarks.ipo.gov.uk/ipo-tmcase/page/Results/1/UK00003422986 (also on PDF).
G. Reports on 'lubricity' of Camstent device vs non coated and Patient Comfort study (PDF).
H. Corroborative statement from urologist, UCL Hospitals NHS Foundation Trust (PDF).
I. FDA application (PDF).
J. Corroborative statement from colorectal surgeon, Nottingham University Hospitals Trust (PDF).
K. Camstent webpage with device data sheet and sales listing. URL: www.camstent.com/product_sales/ (accessed 03/12/20 – also PDF).