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| **Institution:** The University of Nottingham | | |
| **Unit of Assessment:** UoA5 | | |
| **Title of case study:** Development of a Bactigon® -coated bacterial-resistant urinary catheter results in commercialisation and company growth. | | |
| **Period when the underpinning research was undertaken:** 2008-present | | |
| **Details of staff conducting the underpinning research from the submitting unit:** | | |
| **Name(s):** Paul Williams | **Role(s) (e.g. job title):** Professor of Molecular Microbiology | **Period(s) employed by submitting HEI:** 1985-present |
| **Period when the claimed impact occurred:** August 2013-present | | |
| **Is this case study continued from a case study submitted in 2014?** No | | |

## 1. Summary of the impact

Research conducted by Professor Paul Williams and collaborators at the University of Nottingham resulted in the development of Bactigon®, a novel biomaterial that is resistant to bacterial biofilm formation. Bactigon® has been licensed to Camstent Ltd, a platform medical materials and coating process UK company, to develop a coated indwelling urinary catheter. This has resulted in the significant growth of Camstent: Camstent has raised GBP5,000,000 of investment as of December 2020, has established an approved manufacturing facility in the UK, has achieved European Union CE mark certification for human use and the descriptor of Bacteriaphobic® under the National UK trade mark law, and has started to successfully sell Bactigon®-coated catheters in NHS hospitals.

## 2. Underpinning research

Biofilm formation on the surface of medical devices causes 80% of Healthcare Associated Infections (HAIs). Biofilms are bacterial aggregates bound to each other and to a substrate, for example to a medical device, and embedded within an extracellular matrix. They typically show high resistance to antibiotic treatment.

Indwelling urinary tract catheters are the most commonly employed prosthetic medical devices. However, these promote bacterial biofilm formation and ultimately catheter-associated urinary tract infections (CAUTIs). Treatment for CAUTIs usually involves catheter removal, antibiotic therapy and an unplanned prolonged hospitalization, all of which creates an economic and health burden. An added global burden is antimicrobial resistance, as a CAUTI diagnosis needs antibiotic treatment. The development and commercialisation of bacterial biofilm resistant materials for coating urinary tract catheters therefore offers major economic and health benefits.

Novel strategies that inhibit bacterial attachment to the substrate and inhibit biofilm formation have the potential to hugely benefit patients, healthcare providers and the tax-payer. Professor Williams studies the molecular mechanisms of cell-cell communication and biofilm formation of pathogenic bacteria. The signalling mechanisms regulating how bacteria interact with surfaces are still poorly understood, and therefore hypothesis-driven rational design of novel materials resistant to bacterial biofilm formation has been limited.
In 2008, funded by a Wellcome Trust Translational Award **[10],** Professor Williams (School of Life Sciences) established a collaboration with biomaterials researchers Professors Alexander and Davies (School of Pharmacy). Professor Williams developed a novel high-throughput, unbiased microbiological screen for materials refractory to bacterial biofilm formation using Alexander and Davies' polymer microarray. The assay enabled the systematic screening of thousands of co-polymers with multiple pathogens under *in vivo* simulating growth conditions. From 1300 unique poly(meth)acrylate materials in over 20,000 biological assays a new group of structurally related materials comprising ester and cyclic or aromatic hydrophobic moieties were identified that dramatically reduced attachment and

biofilm formation by diverse pathogens, including *Pseudomonas aeruginosa, Staphylococcus aureus, Proteus* and *Escherichia coli*. This novel material was later trademarked Bactigon® **[9]**. Coating medical-grade silicone with Bactigon® resulted in 30-fold reduction in bacterial coverage compared with a commercial silver hydrogel coating *in vitro* and achieved a 10-fold reduction in biofilm formation *in vivo* in a mouse implant infection model compared with silicone **[1].**

Further targeted screens of (meth)acrylate monomers and the application of machine learning by Professor Williams and colleagues identified further novel materials that resist bacterial attachment **[2, 7].** In addition, data generated in these high-throughput screens was used to derive polymer structure function models of pathogen attachment, which resulted in the identification of polymer surface chemistries that reduced bacterial attachment, accelerating new materials development **[3, 4].**

Worldwide, the annual number of urinary tract infections is in the region of 150 million, some 75-80% of which are catheter associated urinary tract infections (CAUTIs). Consequently, considerable efforts are being made to find new biocompatible polymers that can be used as coatings for silicone-based urinary catheters to reduce bacterial biofilm formation. With this in mind, the University of Nottingham (UoN) licensed the patent **[8]** for the polymer to Camstent Ltd, a medical materials company, for its use to coat urinary catheters. Professors Williams, Alexander and Davies collaborated with Professor Irvine (Faculty of Engineering) and Camstent, to optimize the mechanical properties and scale up production of Bactigon® to be used for coating of silicone urinary catheters **[5].** Additionally, a new covalent attachment method made the coating durable to mechanical stresses for the long-term use of the device and highly resistant to biofilm formation **[6]**.

**3. References to the research**

**Key publications** (University of Nottingham UoA5 researchers, at the time of publication, are highlighted in bold)


1 Hook AL, **Chang CY**, Yang J, **Luckett J**, **Cockayne A**, **Atkinson S**, Mei Y, Bayston R, Irvine DJ, Langer R, Anderson DG, **Williams P**[*], Davies MC[*] and Alexander MR[*] (2012) Combinatorial discovery of polymers resistant to bacterial attachment. *Nature Biotechnology* 30(9), 868-875. doi:10.1038/nbt.2316. (*These authors jointly directed this work).

2 Hook AL, **Chang CY**, Yang J, **Atkinson S**, Langer R, Anderson DG, Davies MC, **Williams P**, Alexander MR. (2013) Discovery of Novel Materials with Broad Resistance to Bacterial Attachment Using Combinatorial Polymer Microarrays. *Adv. Mater.* 25: 2542-2547. doi: 10.1002/adma.201204936.

3 Epa VC, Hook AL, **Chang C**, Yang J, Langer R, Anderson DG, **Williams P**, Davies MC, Alexander MR and Winkler DA (2013) Modelling and prediction of bacterial attachment to polymers. *Adv. Funct. Mater.* 24: 2085-2093. doi: 10.1002/adfm.201302877

4 Sanni O, **Chang CY**, Anderson DG, Langer R, Davies MC, Williams PM, **Williams P,** Alexander, MR and Hook AL (2014) Bacterial attachment to polymeric materials correlates with molecular flexibility and hydrophilicity. *Adv. Healthcare Materials* 4:695-701. doi: 10.1002/adhm.201400648

5 Adlington K., Nguyen NT, Eaves E, Yang J, **Chang CY**, Li J, Gower AL, Stimpson A, Anderson DG, Langer R, Davies MC, Hook AL, **Williams P**, Alexander MR, Irvine DJ (2016). Application of targeted molecular and material property optimization to bacterial attachment-resistant (meth)acrylate polymers. *Biomacromolecules* 17:2830–2838. doi: 10.1021/acs.biomac.6b00615

6 Magennis EP, Hook AL, **Williams P**, Alexander MR. (2016) Making silicone rubber highly resistant to bacterial attachment using thiol-ene grafting. *ACS Appl Mater Interfaces* 8: 30780–30787. doi: 10.1021/acsami.6b10986

7 Dundas A A, Sanni, O, **Dubern J-F**, Dimitrakis G, Hook AL, Irvine DJ, **Williams P**, Alexander MR. (2019) Validating a predictive structure-property relationship by discovery of novel polymers which reduce bacterial biofilm formation. *Adv. Mater.* 31: 1903513 doi: 10.1002/adma.201903513


**Key Patents and registrations**

**8** Patent: Polymers which resist bacterial attachment. Inventors: **Williams P**, Alexander MR, Davies MC, Langer R and Anderson DG. WO 2012/150467, EP 2704565B1 (priority date 04.05.2011), US 9,981,068 B2 (patent granted in 2018), web link

**9** BACTIGON® was successfully registered as a UK Trade Mark in 2018 (3326867, class 5, UK), web site

**Grants**

**10** 2008-12, Wellcome Trust Technology Transfer Translation Award, "High throughput micro arrays for discovery of polymers resistant to bacterial colonisation", Alexander PI, **Williams CoI**, GBP1,293,880

**11** 2015-21, EPSRC Programme Grant, "Next Generation Biomaterials Discovery", Alexander PI, **Williams** CoI, GBP5,365,957

**12** 2014-19 Wellcome Trust Joint investigator Award in Science, "Bacterial Surface Sensing: To stick or not to stick?", **Williams** and Alexander**,** GBP933,419 (to Williams)

## 4. Details of the impact

Professor Williams and colleagues at UoN developed Bactigon®, a novel biomaterial resistant to biofilm formation. The biomaterial has been licensed to a UK company for the coating of urinary catheters. The company has raised investment for the development of the product, which has started commercialisation in the UK.

Bactigon® has been licensed to Camstent, which has developed and commercialized a Bactigon®-coated urinary catheter

Camstent Ltd is a UK-based SME focused on the application of specialised coatings to indwelling consumable medical products. Camstent's first commercial product is a Bactigon®-coated Foley (indwelling urinary) Catheter that aims to prevent biofilm formation and CAUTIs. The growth of Camstent over the last seven years is intimately linked to the UoN materials and microbiology research and the continued research support provided. Chief Technical Officer and Founder of Camstent said '*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.'* **[S1]**. This can be summarised in several milestones:

i. Licensing milestone

In 2013 the patent for the antibacterial polymer developed by Professor Williams and colleagues was licensed by the UoN to Camstent Ltd for their exclusive use to coat urinary tract Foley Catheters **[8]**.

ii. Investment milestones

To December 2020, Camstent has raised in excess of GBP5,000,000 of investment through a series of funding rounds aided by proof-of-concept product results established with the support of UoN researchers. Investors included business angels (including the London Business Angels) and private investors.

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.

In June 2018, Camstent secured GBP74,448 of Innovate UK funding **[S2]** to carry out a qualitative evaluation of the performance of the Bactigon®-coated catheters in 31 patients. CTO and Founder of Camstent said *"With the University license and joint proof-of-concept results, Camstent entered investment markets after receiving early support from UKRC and InnovateUK. To date, the company has raised in excess of £5 million"* **[S1]**.

iii. Manufacturing milestones

In 2017, with input from the UoN academic team providing the technical knowhow to set up the polymer manufacturing process, Camstent established an R&D facility in Bedfordshire, UK. The facility is medical devices compliant and certified for the manufacture of coated urinary Foley Catheters by the UK's Notified Body (ISO 13485), thanks to the successful implementation of a rigorous product development and test process. 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 production capacity of 10,000 catheters per month **[S1]**.

iv. Regulatory milestones

The Camstent coated urinary catheter achieved European Union CE mark certification in 2017 **[S3].** The CE mark recognises that the product has met all standards for safety and quality and can be marketed in the UK and across Europe.
More recently in November 2019, the catheter achieved the descriptor of Bacteriaphobic® under the National UK trademark **[S4]** and the potential to supress infections was added to the clinical labelling **[S1]**. This was a significant step towards commercialisation, as the catheter could now claim to repel bacterial attachment.
Camstent has initiated discussions with the Food and Drug Agency (FDA) in the USA to gain approval to sell the coated catheter into the USA market. The FDA pre-submission was jointly prepared by Camstent and the UoN research team, submitted in January 2020 and feedback was received in March 2020 (FDA Case Reference Q200218, '*Camstent Coated Foley Catheter*'). Camstent and UoN researchers are currently addressing specific queries from this feedback and a final formal submission is planned for 2021. FDA approval will open the vast USA market.

v. Clinical milestones

Using Innovate UK funding mentioned above **[S2]**, Camstent Ltd completed a qualitative evaluation of the performance of the Bactigon®-coated 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, etc., all of which are key factors 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 **[S5].** A UK lead urologist and Honorary Associate Professor at University College London 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'* **[S5].**
A current intermediate scale first-in-man clinical trial involving five hospitals in the UK compares biofilm formation in 75 Bactigon®-coated versus 75 standard silicon catheters in 150 hospitalised patients. Biofilm density on the catheter will be measured and correlated with incidence of HAI in each patient group. The progress of this study has been hindered by Covid-19, as many elective surgical procedures where catheter use was planned have been postponed, but it is projected to conclude in 2021.

vi. Recruitment milestones

Camstent Ltd has grown since the licensing of the UoN patent in 2013 and currently employs 12 employees and contractors involved in development, clinical and manufacturing work. In July 2019, Camstent appointed Mark Harwood as new Chief Executive Officer. Mr Harwood has extensive experience in the medical device sector and of growing SMEs into global players. He was appointed to oversee sales, marketing and manufacturing, including regulatory and quality processes **[S1]**.

vii. Sales and agreements milestones

The catheter is available for sale on the Camstent website **[S6]** and Camstent has recently secured regulatory approval to expand the range of coated catheters to include more sizes and specialty tips. In 2019, Camstent secured a distribution agreement with the global distributor of medical devices Pennine Healthcare. Since then, Pennine Healthcare have secured the listing of the catheters on NHS procurement of four UK hospitals, which are regularly purchasing catheters from Camstent Ltd **[S1]**.

viii. Company diversification and future outlook

Camstent Ltd is currently undergoing discussions with the UoN research team for the licensing of the coating material to be used in other medical devices, such as endotracheal tubes and central venous catheters. Chief Technical Officer at Camstent said *"The company is pursuing partnership and licensing opportunities for wider use of the coating in medical products across global markets. The technical team continues collaborations with the core University of Nottingham professors and their students, focused on creating materials able to repel blood and protein, on higher performing materials that can be applied to metal and plastic, and on the basic science and teaching needed to drive clinical care improvements from laboratory discoveries to clinical adoption"* **[S1]**. This is evidence of company strategy to steer towards future product diversification as a result of their collaboration with the UoN research team.

The collaboration between Camstent Ltd and the UoN 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. From the beginning, chemists from Camstent and University of Nottingham researchers collaborated to find product solutions. From making the coating robust and flexible to making it smooth and comfortable, from defining consistent coating processes to cost effective sterilisation, the teams progressively addressed market requirements for performance and safety"* **[S1]**.

The UoN research group won the *'Faculty of Science'* category of the *UoN Knowledge Exchange and Impact Awards 2018* for its *"potential to reduce the burden of hospital-acquired infections, and benefit many patients around the world. This is just the first of many potential commercial applications of the technology"* **[S7]**. Camstent-UoN were also shortlisted for the *'Most Innovative Contribution to Business-University Collaboration'* category of the *2018 Times Higher Education Awards* **[S8]**.

**5. Sources to corroborate the impact** (websites were last accessed on 18/01/2021)

**S1** Corroborative letter from the Chief Technical Officer at Camstent
**S2** Innovate UK funding, 'Effectiveness of a novel bacteriaphobic coating for preventing catheter-acquired infections in man', 2018-19, GBP74,448, web link
**S3** CE Certificate
**S4** The National UK trade mark gives Camstent catheter the Bacteriaphobic® descriptor, web link
**S5** Post Market Clinical Follow Up Report: Coated Foley Urinary Catheters'
**S6** Camstent website web link
**S7** UoN Knowledge Exchange and Impact Awards 2018: Camstent-UoN winners of the Faculty of Science Award, web link
**S8** THE (Times Higher Education) Awards 2018: Camstent-University of Nottingham shortlisted for in the Most Innovative Contribution to Business-University Collaboration category, web link