Institution: University of East Anglia

Unit of Assessment: 8 - Chemistry

Title of case study:

Medical implants with biocompatible electropolymer surfaces

1. Summary of the impact

Our research has shown that functionalised poly(pyrroles) grown electrochemically on medical steels and other alloys as adherent, highly conformal coatings can enhance surface biocompatibility and provide a platform for implantable medical devices. *Chameleon Biosurfaces Ltd*. was founded to exploit this research by producing coatings for medical devices, including coronary artery stents and pacemaker implants. Up to 2009, *Chameleon Biosurfaces Ltd.* received £1.48M of venture capital and seedcorn funding. In 2011 all assets of *Chameleon Biosurfaces Ltd.* were sold to the US biomedical company *Biotectix LLC*.

2. Underpinning research

The research underpinning this impact spans the period 1993 to 2013. Initial research undertaken by Professor **Chris Pickett**'s research group was based at the John Innes Centre on the Norwich Research Park. A change of research direction coincided with Professor Pickett's move to the School of Chemistry, University of East Anglia (UEA) in 2005.

The academic research programme addressed the construction of electrode interfaces in which bioinorganic reaction centres were confined within an electropolymer matrix. It was found that such electropolymers could be grown on medical stainless steels, which opened the possibility for biomedical implant applications. A spin-out company, *Chameleon Biosurfaces Ltd.*, was established to pursue these applications. In 2003, *Chameleon Biosurfaces Ltd.* performed an initial rabbit dorsal muscle implant study with four types of electropolymer, establishing that the materials were well tolerated in the *in vivo* environment. This result, together with their high conformality and adhesion to medical steels, suggested that the electropolymers could be of benefit in the area of polymer-coated drug-eluting coronary stents. However, while commercially available coronary drug eluting stents were successful in inhibiting restenosis, in 2005 there were significant emerging problems with late stent thrombosis. This was variously attributed to polymer detachment, poor biocompatibility and delayed re-endothelialisation.

Late stent thrombosis defined the medical problem which *Chameleon Biosurfaces Ltd.* sought to address when the company relocated to UEA in 2005. Dedicated laboratory and office space was provided within the School of Chemistry and four personnel employed by *Chameleon Biosurfaces Ltd.*: Dr Jane Knott was employed to undertake synthesis of innovative pyrroles; Dr Steven Ryley was appointed as a senior scientist and worked on the project until December 2008; Dr John Tolland undertook biophysical studies of the electropolymer coatings; Mr Christian Greef was employed as a research technician in 2007 for 20 months.

The research at UEA led to the synthesis and electropolymerisation of unprecedented, highly functionalised poly(pyrroles), bearing cysteine and other motifs capable of binding synthetic ferredoxin and hydrogenase clusters (references 1 and 2). In 2007, a histological study of functionalised poly(pyrrole) coated stents following implantation in porcine coronary arteries was undertaken in conjunction with the St Joseph Medical Center, Atlanta (USA). This showed that the new functionalised poly(pyrrole) coatings were biocompatible *in vivo* over a period of three months, presenting a low polymer burden (reference 3).

Subsequent research on antithrombolytic electropolymers led to the synthesis of pyrrole monomers, with molecular motifs related to allicins, and studies of their electropolymerisation. These studies showed that such surface functionality resulted in low levels of platelet binding, agglomeration and thrombus formation. Real-time dynamic studies of the behaviour of the electropolymer coatings were carried out on whole blood samples, in collaboration with Professor Richard Farndale at Cambridge University. Importantly, sulfur and/or allyl functionality of these

pyrroles conferred excellent adhesion to medical steel substrates. The research on these innovative, low thrombogenicity electropolymer materials was patented (reference 4).

Follow-on fund support from the BBSRC (2006 – 2007) enabled studies of drug confinement in the electropolymer matrices for neurostimulator coatings. Alongside this, *Biotectix LLC* funding supported research on the functionalisation of poly(3,4-ethylenedioxythiophene) (PEDOT) electropolymers also for application in the neurostimulator area.

UEA Research Personnel:

Professor Chris Pickett: UEA 2005 to date
Dr Jane Knott: Post-doctoral research associate (2006-2007) BBSRC Follow-on Funding
Dr Tim Boote: PhD student (2006 – 2010) funded on an ICASE award (Antithrombolytic Electropolymers); postdoctoral research associate (2010 to 2011) funded by *Chameleon Biosurfaces Ltd.* and *Biotectix LLC*.

3. References to the research

(UEA authors in bold)

(1) Electropolymeric materials incorporating subsite structures related to iron-only hydrogenase: active ester functionalised poly(pyrroles) for covalent binding of {2Fe3S}-carbonyl/cyanide assemblies
Ibrahim, **SK**; **Liu**, **XM**; **Tard**, **C**; **Pickett**, **CJ**
Chemical Communications 2007, 1535-1537.
doi: 10.1039/b617399c

(2) Artificial hydrogenases: assembly of an H-cluster analogue within a functionalised poly(pyrrole) matrix
Ibrahim, **S**; **Woi**, **PM**; Alias, Y; **Pickett**, **CJ**
Chemical Communications 2010, 46, 8189-8191.
doi: 10.1039/c0cc02962a

(3) Novel surface modification for reducing polymer burden on drug-eluting stents is highly compatible with pig coronary arteries
Shinke, T; Brants, I; Robinson, KA; **Tolland**, **J**; **Knott**, **J**; **Ibrahim**, **S**; Jabara, R; Chronos, N; **Mackenzie**, **IA**; **Pickett**, **CJ**.
American J. Cardiology 2007, 100, issue 8A, Supp.S, 161L-161L
Conference Abstract. Presented at 19th Annual Transcatheter Cardiovascular Therapeutics Symposium, Washington DC (USA), Oct 20-25, 2007.

(4) Patent: Polymer coatings on medical devices
EP2155275 (A2) (Publication date: 2010)
Inventors: **CJ Pickett**, **TJ Boote**, **SK Ibrahim**, **JM Knott**, **JD Tolland**

Key Research Funding:

Anti-thrombolytic electropolymers (2006 to 2010)
EPSRC ICASE Studentship
Pickett, CJ
£60,864

In vitro biocompatibility and release characteristics of polypyrrole -bupivacaine coatings for neurostimulators (2006 to 2007)
BBSRC Follow-on Fund
Pickett, CJ
£87,962

Biotectix LLC contract with *Chameleon Biosurfaces Ltd.* (2011)
£35,100

4. Details of the impact

In the period 2001 to 2009, *Chameleon Biosurfaces Ltd.* received a total of £1.48M of venture capital and seedcorn funding from a number of sources: the ICENI University Seedcorn Fund; Rainbow Venture Capital; Aitua; London Seed Capital; Great Eastern Investment and Create Ventures. The activities of *Chameleon Biosurfaces Ltd*. at UEA were funded by £1.13M of this venture capital, secured between 2005 – 2009.

Initial work focussed on showing that the electropolymers developed by Pickett's group were well tolerated *in vivo*. Subsequently there was considerable industrial interest in the development of the electropolymers as coatings for implantable medical devices – for which there is a multi-billion $US global market – where the aim of the technology is to address key limitations of current devices such as foreign body reactions, stability and long-term electrical performance.

In 2009 and 2010, *Chameleon Biosurfaces Ltd.* completed contracts with two international medical device companies [redacted] (2009) and [redacted] (2009 and 2010) to study the electropolymer coatings on stents and pacemaker implants respectively. The latter study resulted in IPR on the coating methodology for use in heart stimulation applications. [corroborating source A]

A second patent was filed in 2010 that detailed the preparation and biophysical characterisation of low thrombogenicity electropolymer materials that could be used in coronary stent applications. [corroborating source B]

Following the successful conclusion of these contracts, in 2011 *Biotectix LLC*, a leading developer of implantable medical devices based in Ann Arbor Michigan, acquired all *Chameleon Biosurfaces Ltd.* issued and pending US and international patents [corroborating sources A to C] together with all technical and commercial data on the electropolymers for an undisclosable sum.

Biotectix LLC, a wholly-owned subsidiary of *Allied Minds*, is developing a new class of conducting polymer materials and coatings, for implantable medical devices and sensors. The goal is to improve the safety, longevity, reliability, biological integration and function of implantable biomedical devices for electro-stimulation and sensing applications. Following the acquisition, all *Chameleon Biosurfaces Ltd.*'s materials technology transferred to Ann Arbor. *Biotectix LLC* continues to maintain the granted IPR and is actively pursuing applications of the electropolymers in implantable medical devices for cardiovascular, cochlear and neuro-modulation.

The General Manager at *Biotectix LLC*, James Arps, stated at the time that:

> "the Chameleon technology is highly complementary to the conductive thiophene-based polymer materials we are actively commercializing. Importantly, the acquisition further solidifies our leading IP position in this field while giving us additional materials options with our co-development partners in the medical device field."

[corroborating source D]

The continuing importance of this acquisition in increasing the commercial opportunities available to *Biotectix LLC* is clear from the statements by the Director of R&D provided in 2012:

> 'Implantable medical devices for cardiovascular and neuromodulation applications, together represent a multi-billion dollar global market. Hence there is a significant commercial opportunity for value-added technologies including BT's [*Biotectix's*] medical coatings that address the needs for smaller, safer, multifunctional next generation clinical medical devices.'
>
> 'The acquisition of *Chameleon Biosurfaces* assets further solidifies BT's leading IP position in this field...'

[corroborating source E]

In 2011, following the acquisition of IPR from *Chameleon Biosurfaces Ltd.*, *Biotectix LLC* funded further electropolymer studies at UEA which have already been of considerable benefit to *Biotectix LLC* producing more than 5 new molecular species that continue to be evaluated for further development by *Biotectix LLC*. [corroborating source E]

5. Sources to corroborate the impact

[A] **Coating on titanium nitride**
UK patent application 1012808.0 (Submitted: 2010)
US patent: **Implantable Electrode** US 2012/0029585 (publication date: 2012)
Inventor: CJ Pickett
This patent application covers applications of Chameleon Biosurfaces Ltd. electropolymers for heart stimulation applications.

(details held on file at UEA)

[B] **Polymer coatings on medical devices**
EP2155275 (A2) (Publication date: 2010)
Inventors: CJ Pickett, TJ Boote, SK Ibrahim, JM Knott, JD Tolland
This patent describes low thrombogenicity electropolymer materials including their preparation and biophysical characterisation.

(details held on file at UEA)

[C] **Electro-release systems, modified electrodes and their use**
US 6,132,752 (publication date: 2000)
Also EU, Canadian, Australian and other derived granted patents.
Inventors: CJ Pickett , SK Ibrahim
This patent family described how electrical stimulation of an implanted electropolymer device containing a bound drug could control the release of that drug.

(details held on file at UEA)

[D] Press releases posted on 28th March 2011 regarding the *Biotectix LLC* acquisition of assets and technology from *Chameleon Biosurfaces Ltd.*:

http://www.pharmiweb.com/pressreleases/pressrel.asp?ROW_ID=38278

http://www.businessweekly.co.uk/biomedtech-/11596

(Accessed on 7th November 2013 and held on file at UEA)

[E] Supporting letter from *Biotectix LLC*

(held on file at UEA)