Institution: University of Warwick

Unit of Assessment: UOA5 - Biological Sciences

Title of case study: Bench to bedside: Transformational point-of-care diagnostic device underpinned by novel purine biosensors

Period when the underpinning research was undertaken: 1 January 2003 -31 December 2019

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:
Nicholas Dale	Ted Pridgeon Professor of Neuroscience, Founder and Chief Scientific Officer of Sarissa	February 2000- present

Period when the claimed impact occurred: 1 August 2013- 31 December 2020

Is this case study continued from a case study submitted in 2014? N

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

Professor Nicholas Dale's research has underpinned development of the world's first point-of-care diagnostic device for the measurement of purines in whole blood - SMARTChip. Dale's research identified microelectrode purine biosensors which enable rapid recognition of medical emergencies involving patients with ischemia. Commercialised through spin-out company, Sarissa Biomedical Ltd, SMARTChip and its associated reader have progressed to large-scale diagnostic accuracy evaluation trials for the recognition of stroke across four NHS Hospital Trusts in the UK. The company employs 12 staff and has attracted GBP3,800,000 of inward investments.

2. Underpinning research (indicative maximum 500 words)

Purine-based signalling agents have the potential to be used as real-time indicators of metabolic stress such as stroke. A key barrier to adoption of purines as a diagnostic biomarker has been the difficulty of measuring them in a clinical setting. Since 2000, Professor Nicholas Dale's research developed and validated microelectrode purine biosensors [3.1]. With Dr Enrique Llaudet (Research Assistant and co-Founder of Sarissa, University of Warwick, 2000-2007), Dale patented a unique process for coating enzymes onto microelectrodes based on electrochemical deposition of sol gels (patent WO2004048603). This methodology enabled further enzymatic biosensors to be developed [3.2]. Funded by the Wellcome Trust, Dale and Dr Faming Tian (Postdoctoral Research Assistant, Chief Scientist in Sarissa) developed Ruthenium Purple (RP) as a mediator for biosensors [patent WO2008081193; 3.3]. This key advance enabled accurate measurement of purines in whole unprocessed blood at clinically relevant concentrations for the first time. These two patents are assigned to Sarissa Biomedical Ltd, which was founded by Dale and Llaudet to exploit their intellectual property. These methods underpin the fabrication and analytical performance of the SMARTChip, and this is the diagnostic technology platform that underpins Sarissa's commercial diagnostic strategy.

The development of microelectrode biosensors enabled Dale and collaborators (Professor Bruno Frenguelli, Warwick 2007- current) to show that purines are rapidly released from brain tissue in *in vitro* models of stroke [3.4, 3.5]. Purines have a very short half-life in blood (seconds to minutes) and are present at low micromolar concentrations, a thousand times lower than the healthy fasting concentration of glucose, for example. Before Dale's research, accurate measurements could only be achieved by using expensive, complex and time-consuming high-performance liquid chromatography methods, which precluded their clinical use, especially in emergency settings. The results validated Warwick's electrochemical biosensors as rapid and highly sensitive devices for measuring purines under physiological conditions and laid the foundations for using measurements of purines as diagnostic biomarkers in clinical settings.

Dale's first clinical device - SMARTCap (patent, US9791401B2, EP13799648.4) – presented the microelectrode RP biosensors in a vacutainer, a widely used blood collection device. Between 2012 and 2014, Dale collaborated with Warwick Honorary Professor Chris Imray (University Hospitals of Coventry and Warwickshire, UHCW) to investigate purine release into the blood following the onset of ischaemia which was imposed by a carotid clamp during carotid endarterectomy. SMARTCap enabled real-time, patient-side measurements of purines in blood for the first time. Importantly, purines were shown to be sensitive indicators of ischaemia, rising quickly following application of the carotid clamp, remaining elevated through the clamp period and returning to normal following release [3.6]. Following on, between 2014 and 2015 Dale, Imray and Professor Christine Roffe (Keele University and University Hospital of North Midlands) undertook the first point-of-care study using SMARTCap, comparing purine levels in the blood of stroke patients and in healthy controls. The findings gave proof of principle evidence that moderate and severe strokes all gave significant elevation of blood purines above the controls [3.7]. This work has led to two new patent applications held by Sarissa Biomedical Ltd, including the development of SMARTChip.

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

[3.1] **Llaudet, E.,** Botting, NP., Crayston, JA. and **Dale, N.** (2003). A three-enzyme microelectrode sensor for detecting purine release from central nervous system. **Biosens Bioelectron** *18*, 43-52. doi.org/10.1016/S0956-5663(02)00106-9
[3.2] **Llaudet, E., Hatz, S., Droniou, M.** and **Dale, N**. (2005) Microelectrode biosensor for real-time measurement of ATP in biological tissue. **Anal Chem** *77*, 3267-3273. doi.org/10.1021/ac048106q
[3.3] **Tian, F., Llaudet, E.** and **Dale, N**. (2007) Ruthenium Purple-mediated microelectrode biosensors based on sol-gel film. **Anal Chem** *79*, 6760-6766. doi.org/10.1021/ac070822f
[3.4] Frenguelli, BG., **Wigmore, G., Llaudet, E.** and **Dale, N.** (2007). Temporal and mechanistic dissociation of ATP and adenosine release during ischemia in the mammalian hippocampus. **J Neurochem** *101*, 1400-1413. doi.org/10.1111/j.1471-4159.2006.04425.x
[3.5] Frenguelli, BG., **Llaudet, E**. and **Dale, N.** (2003). High-resolution real-time recording with microelectrode biosensors reveals novel aspects of adenosine release during hypoxia in rat hippocampal slices. **J Neurochem** *86*, 1506-1515. doi.org/10.1046/j.1471-4159.2003.01957.x
[3.6] Tian, F., Bibi, F., **Dale, N**. and **Imray CHE.** (2017) Blood purine measurements as a rapid real-time indicator of reversible brain ischaemia. *Purinergic Signalling 15, p237–246 doi.org/10.1007/s11302-019-09647-4*
[3.7] **Dale, N.,** Tian. F., Sagoo, R., Phillips, N., **Imray, C**. and Roffe, C. (2019) Point-of-care measurements reveal release of purines into venous blood of stroke patients. *Purinergic Signalling 15, 237–246, doi.org/10.1007/s11302-019-09647-4*

Key grants:

PI Nicholas Dale, Commercialisation of purine biosensors: essential tools for scientific and clinical communities, Wellcome Trust, 11/2003-10/2005, GBP249,200
PI Nicholas Dale, SMARTChip: a field-deployable blood test for stroke, capable of detecting brain ischaemia from the earliest stages of pathology, NIHR, Intervention for Innovation Programme, 01/2014- 05/2017, GBP575,268

Patents:

WO2004048603 Coatings, Method of Producing Sol-gels and Sol-gel Biosensors granted 2004
WO2008081193 Ruthenium Purple Biosensor, granted 2008
WO/2016/198839 Methods and devices to detect the presence of a condition associated with ATP depletion in a subject, published 2016 by Sarissa (Granted in the US: US10889846B2 12/1/2021)
WO/2016/198838 Methods and devices to detect stroke in a subject, published 2016 by Sarissa US9791401B2 and EP13799648.4 Cap including device with biosensor and holder published 2013 by Sarissa. Granted in US 2017, Intention to grant from EPO received Sept 2020.

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

Rapid, point-of-care diagnosis of stroke

Sarissa Biomedical Ltd was formed to commercialise the biosensor research of Professor Nicholas Dale and led to the development of the SMARTChip system for the rapid identification of patients with ischemia (restricted blood supply). The first application is for stroke, where there is a patient population of approximately 5,000,000 per year in the USA and Europe alone. Additional disease areas include myocardial infarction, traumatic brain injury and peripheral artery disease. In total, these conditions impact over 50,000,000 patients per year in the USA and Europe.

Stroke is the fourth most common cause of death in the UK and the major cause of adult disability. Both thrombolytic medications which dissolve blood clots and mechanical thrombectomy are highly effective at minimising the impact of ischemic stroke but only if used early after the acute event. Currently, few diagnostic tools exist to help stroke clinicians and first-responders assess the patient and no blood tests are used specifically in the diagnosis of stroke. The first advantage of SMARTChip is to help eliminate stroke mimics from entering the stroke pathway. Mimics are a major drain on acute stroke unit resources with typically 50% of patients arriving at stroke units being mimics [5.1].

Product development for the advanced prototype SMARTChip system has been completed and the manufacturing process validated. Sarissa Biomedical, as part of a consortium, has been awarded a GBP1,998,604 Small Business Research Initiative contract from Innovate UK to conduct a large-scale clinical trial with partners including Newcastle University's Stroke Research Group, Northumbria Healthcare NHS Foundation Trust and Oxford AHSN, for hospital staff to test the SMARTChip. This will be done in combination with the FAST (Face, Arms, Speech, Time) algorithm to more accurately differentiate patients that have had a stroke from those displaying stroke mimics [5.2]. Following the completion of full product development, Sarissa Biomedical expects to launch the product after obtaining UK, European and US regulatory clearance [5.3].

Stroke care is responsible for approximately 5% of total NHS costs in the UK. The aging population, increasingly complex emergency treatments and redirection of patients towards fewer highly specialised stroke units, all amplify the clinical and financial value of any improvement in the accuracy of early diagnosis. *"The main value of the new Sarissa SMARTChip diagnostic would be to significantly reduce the number of patients wrongly labelled as stroke. Using a model built with conservative assumptions about the likely performance of the new diagnostic and the cost savings and health gains that would result from more stroke and mimic patients arriving in the most appropriate care setting, it has been estimated that the value to the NHS would be an average GBP1,227 financial saving per use"* [5.1,5.3].

Over the REF assessment period, Sarissa Biomedical has transitioned from a biotechnology company primarily servicing preclinical scientific communities to an early-stage medical device company with a market-ready product, employing 12 staff members, and establishing dedicated research, production and quality and regulation departments.

"Between 6,000 to 9,000 sensors are produced annually, with a market value of over GBP240,000, which are used by clinicians and the wider scientific community to investigate stroke, sepsis, schizophrenia, Huntingdon's Alzheimer's, Epilepsy and Parkinson's. It has been financed by a combination of equity investments, revenue from biosenors sold to the academic and research communities, and grants. Since 2013, Sarissa has received a total of GBP2,625,000 in VC and Enterprise Investment Scheme funding" [5.3]. A further GBP1,200,000 investment from a consortium of investors including the MEIF Proof of Concept & Early Stage Fund was received in 2020 and will enable Sarissa to invest in product manufacture and carry out a clinical study with the NHS and Newcastle University Stroke Research Group [5.4].

Product development and manufacture of SMARTChip

Feedback on the first proof-of-concept biosensor array test in 2012 – SMARTCap - and support from the NIHR's Invention for Innovation (i4i) award in 2013 and Innovate UK Small Business Research Initiative in 2017, led to Sarissa modifying the design. SMARTChip was developed in 2016 for use by paramedics and healthcare professionals in emergency settings with a minimal amount of training. The new test includes the SMARTChip sensor, a ceramic strip with screen-printed electrode array to which a finger-prick of blood is applied, and the hand-held SMARTChip reader, which measures the purine levels in approximately 3-5 minutes. A Certificate of Registration was awarded by the British Standards Institution in August 2018 under ISO 13485:2016 and has retained its certification through 2020 [5.5, 5.6].

SMARTChip (left) and the SMARTChip Reader

Sarissa has invested in electronics design, advanced materials and automation to enable cost effective production of SMARTChip at volume including:

- Contracting Assembled Electronic Solutions (Stratford) between 2017-2019 for the development and manufacture of SMARTChip readers and associated software, Sun Chemical Ltd (Slough) 2018-2020 to develop novel printing methods to achieve correct quality and yields for the SMARTChip base transducer and new supply contracts with Flexmedical Solutions Ltd (Livingstone) and Metrohm Dropsens (Oviedo, Spain).
- Collaborating with Aston University and WMG via a Knowledge Transfer Partnership in 2018 to develop automated processes to scale the SMARTChip coating, procedures for pre- and post-processing of chips, and to further refine the design to improve production and ease of use. Sarissa invested in a robot to automate the initial coating steps, providing a capacity of approximately 15,000 chips per robot per year.

SMARTChip's clinical trials demonstrate diagnostic performance

The development of SMARTChip is an important breakthrough in the development of a tool for clinicians and paramedics to quickly and correctly diagnose stroke, leading to improved patient outcomes. A number of clinical trials have exemplified the new diagnostic technology, and supported Sarissa's growth:

- Professor Chris Imray (UHCW) and Professor Christine Roffe (Royal Stoke University Hospital) investigated whether purines were elevated in the blood of stroke patients in emergency departments using Sarissa's prototype biosensor array, SMARTCap. The trial reported that blood purines were significantly elevated in minor, moderate and severe strokes (ClinicalTrials.gov Identifier: NCT02308605, 2014-2015, funded by the National Institute for Health Research Invention for Innovation Programme)
- Professor Imray (UHCW) validated the sensitivity of SMARTChip in detecting acute cerebral ischaemia in 40 patients undergoing elective carotid endarterectomy at UHCW NHS Trust, University Hospitals of North Midlands NHS Trust and University Hospitals Birmingham NHS Foundation Trust (ClinicalTrials.gov Identifier NCT02545166, 2016-2019). Sage Open Med 7 doi.org/ 10.1177/2050312119865120
- Professor Roffe (Royal Stoke University Hospital), Professor Smith (Royal Salford), Professor Imray (UHCW) and Dr Christopher Price (Newcastle University) used SMARTChip to measure purine levels in the blood of stroke patients on admission to hospital and investigate correlation with the infarct/ haemorrhage size (ClinicalTrials.gov Identifier: NCT02795481, 2016-2019).
- Dr Price (Newcastle University) is leading the PRISM trial (Purines for Rapid Identification of Stroke Mimics) to define the diagnostic performance of SMARTChip in discriminating strokes from non-strokes. In the largest SMARTChip trial to date and a major NIHR Portfolio trial, one hundred SMARTChip readers are being deployed across four NHS Hospital Trusts (Northumbria Specialist Emergency Care Hospital, Salford Royal Hospital, Royal Blackburn Hospital, Royal Stoke University Hospital) and twenty

seven ambulance stations (North East Ambulance Service NHS Foundation Trust, North West Ambulance Service NHS Trust and West Midlands Ambulance Service NHS Foundation Trust). There has been significant investment in the training of relevant staff to use the readers and 377 patients will be recruited (by June 2021, funded by the Innovate Small Business Research Initiative) Dr Price has stated "*The knowledge gained by Professor Dale and his research and development of the SMARTChip has enabled the participation of patients in a diagnostic accuracy study which may have a radical impact on the care of patients with suspected stroke… No other technology is currently available to rapidly inform clinicians about a diagnosis which can lead to urgent treatment to reduce disability"* [5.7].

- Northumbria Health Economists estimate that the use of the SMARTChip test could save stroke units GBP25,000,000 per annum by the redirection of stroke mimics [5.2].

Wider international clinical research and trials of SMARTChip

- Professor Beata Sperlagh, Institute of Experimental Medicine, Hungarian Academy of Sciences has used SMARTChip to test purines as an aid in early recognition of schizophrenia (2018-ongoing).
- Dr Tobias Engel (Royal College of Surgeons in Ireland) has used SMARTChip to measure purines as a marker of seizures in neonates who have suffered hypoxia/ischemia during birth and have developed neonatal encephalopathy. Dr Engel cites Professor Dale's research leading to the creation of SMARTChip as having "*opened up a new avenue for seizure and epilepsy diagnosis with the potential to transform how seizures and epilepsy will be diagnosed in the future"* [5.8]. Detection of seizures in infants is extremely difficult and in Ireland there are only two neonatal units capable of doing this. A simple biomarker test could identify babies needing further expert assessment, leading to prevention of future seizures and avoiding further brain damage [5.8].
- Sarissa is the SME partner in the Horizon 2020 Marie Curie Innovation Training Network programme PurinesDX (EUR3,500,000). Its biosensors feature prominently in the investigation by leading clinical specialists and industry partners into a broad range of brain diseases, and is training highly skilled, innovative and entrepreneurial scientists.

Recognition of SMARTChip by investors and Health Sciences networks

SMARTChip won the MidTECH award for the "Best NHS-Developed Medical Technology Innovation" at the West Midlands Academic Health Science Network (WMAHSN) Awards 2018. KTP Associate, Radovan Gallo (now Chief Engineer at Sarissa), won "Best Future Innovator" award from Innovate UK in recognition of his work with the company (2019) [5.9].

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

[5.1] Innovate UK/SBRI Stratified Medicine Final report.
[5.2] Purines for Rapid Identification of Stroke MImics (PRISM) trial, led by Northumbria Healthcare NHS Foundation Trust with Sarissa as the lead applicant, Innovate UK Small Business Research Initiative, GBP 1,998,604, https://gtr.ukri.org/projects?ref=971541
[5.3] Written statement from CEO, Sarissa Biomedical Ltd Dr John Clarkson
[5.4] Press release announcing GBP1,2000,000 investment https://www.warwicksciencepark.co.uk/business-support/coventry-based-sarissa-biomedical-secure-1-2million-investment/
[5.5] Sarissa Quality Manual
[5.6] BSI ISO13485:2016 certificate demonstrating consistent design, development, production of medical devices http://sarissa-diagnostics.com/index.php/quality-certification/
[5.7] Written statement from Chris Price, Newcastle University
[5.8] Written statement from Dr Tobias Engel, Royal College of Surgeons in Ireland
[5.9] West Midlands Academic Health Science Network (WMAHSN) 2018 MidTECH award for the "Best NHS-Developed Medical Technology Innovation" https://www.wmahsn.org/news/2018/07/13/West_Midlands_healthcare_sector_celebrated_with_innovation_awards and Knowledge Transfer Network (KTN) 2019 Best Future Innovator award https://ktn-uk.co.uk/news/ktp-best-of-the-best-awards-2019-finalists-announce