Institution: University of Exeter

Unit of Assessment: 15 General Engineering

Title of case study: Diagnosing malaria using magneto-optic sensors

1. Summary of the impact

Malaria is endemic in more than 100 countries but its rapid and accurate diagnosis in locations remote from clinical laboratory facilities remains challenging yet desperately needed. This case study describes how scientific discoveries made in the field of digital data storage have been developed and applied to deliver a rapid, reliable and low cost malaria diagnosis sensor suitable for field application. Diagnostic devices have been both laboratory-tested and clinically trialled on over 900 patients under adverse field conditions in malaria endemic countries with very promising results. The **health impact** includes not only significantly reducing unnecessary treatments but potentially saving millions of lives.

2. Underpinning research

For many years, Professor David Newman studied the magneto-optic spectroscopy of materials to optimise their performance as digital data storage media (1). This was based on the premise that the magnetic state of a material produces changes in many of its physically measurable parameters including its optical properties. After joining Exeter Engineering in 2003, and now based in the Functional Materials Group, Newman realised that this must also apply to organic molecules in biological systems. So, in principle, any disease which modifies the biochemistry of physiological systems dependent on iron should be detectable through magneto-optic measurements.

The basis of the detection approach is exploitation of a magneto-optic mechanism observable in liquids and gases called the Cotton-Mouton effect. In most fluids this is very small, but interestingly many biological fluids when subjected to an applied field generate a much larger effect, the Extraordinary Cotton-Mouton Effect (ECME). So, if the pathology of a particular disease modifies the biochemistry of a physiological system to produce a change in the ECME of some testable fluidic component of the system, for example blood, then the disease ought to be detectable through this mechanism.

It was decided to test this idea on the highly significant disease of malaria. The pathological action of the infecting parasite is known to produce substantial structural impact on the haemoglobin within red blood cells. The toxic haem component of the blood is rendered harmless to the parasite by its conversion to haemozoin in the form of rod shopped nano-crystals. These structures were expected to generate a detectable ECME signal that would correlate with disease progression.

The foundational research required to test this hypothesis was carried out by a consortium of seven academic and industrial partners led by Newman and funded by an EC 6th Framework grant [i]. Undertaken between 2005 and 2009, this involved developing new magneto-optic instrumentation to handle liquid samples and establishing the sensitivity required to detect and quantify the changes wrought by the malaria parasite on the haemoglobin in red blood cells (2, 3). By artificially creating calibrated samples typical of the blood taken from malaria patients it was determined that the Cotton-Mouton effect is, under laboratory conditions, a rapid and sensitive (≈5pgm/µl) volumetric assay for haemeozoin. Formal blind laboratory studies using real patient blood samples collected in malarial endemic regions were then carried out and confirmed the potential of the technique (4). An even more exciting discovery was that the principle is also realisable in non-invasive format (5) by accessing the blood supply below the fingernail. This could significantly minimise cross infection risks to health-workers although significant challenges remain in instrumentation miniaturisation.

To ensure maximum impact, reliability and effectiveness a series of clinical field trials was

conducted in the most adverse environments. This was needed since the sensitivity of the diagnosis depends on the amount of haemozoin present in a patient's blood, which in turn is related to the different stages of the parasites life cycle as indicated by blood parasite count. These are described in section 4.

3. References to the research

1. Carey R, Newman DM & Thomas BWJ. (1995) Magneto-Optic Recording, *Journal of Physics D: Applied Physics,* **28**, 2207-2227. **
2. Newman DM, Heptinstall J, Matelon RJ, Savage L, Wears ML, Beddow J, Cox M, Schallig HD, Mens PF. (2008) *A magneto-optic route toward the in vivo diagnosis of malaria: preliminary results and preclinical trial data, Biophysics Journal,* **95**,. 2, 994-1000. **
3. Newman DM, Matelon RJ, Wears ML, Savage L, Heptinstall J, Beddow J, Cox M. (2009) *Magneto-Optics in the Service of Medicine - Diagnosis via the Cotton-Mouton Effect-, PhotonicsGlobal@Singapore, IPGC 2008. IEEE.* DOI: 10.1109/IPGC.2008.4781387
4. Mens PF, Matelon RJ, Nour BYM, Newman DM, Schallig HDFH. (2010) *Laboratory evaluation on the sensitivity and specificity of a novel and rapid detection method for malaria diagnosis based on magneto-optical technology (MOT), Malaria Journal,* ***9****, 207-215.* **
5. Newman DM, Matelon RJ, Wears ML, Savage LB. (2009) *The In Vivo Diagnosis of Malaria: Feasibility Study Into a Magneto-optic Fingertip Probe, IEEE Journal of Selected Topics in Quantum Electronics,* ***16****, 573-580.* **

** Papers that best indicate quality of underpinning research.

Research funding

i. Newman, D. (PI) *Novel magneto-optical sensors for malaria diagnosis*, EC 6th Framework Programme. Priority: IST-NMP-2 Bio-Sensors for Diagnosis and Healthcare, FP6-016494, €1,450,000, 2005-2009.

ii. Newman, D. (PI) *Novel magneto-optical biosensors for malaria diagnosis.* Bill & Melinda Gates Foundation Grand Challenges Explorations Initiative, Grant Number 53086, $100,000, 2009-2010.

iii. Newman, D. (PI) *Novel magneto-optical biosensors for malaria diagnosis*. Bill & Melinda Gates Foundation Grand Challenges Explorations Initiative, Global Health Grant Number OPP1024428, $996,171, 2011 - present.

4. Details of the impact

Malaria diagnosis is challenging and is currently either carried out symptomatically or by the use of antigen detecting rapid diagnostic test (RDT) sticks. However, studies by the World Health Organisation [a] found detection rates reduced to less than 75% for more than half the RDT devices tested with some products returning values as low as 25%. Consequently in many regions where malaria is endemic there is a tendency to treat patients automatically (and particularly children under five) presenting with fever for malaria. Often this is incorrect and such over-prescribing is one of the major factors driving development of drug resistance in the malarial parasite.

The laboratory trials had proven to be highly successful and promising to the point that the global medical industry recognised the fledgling device as one of the top ten medical devices of **2010** [b]. The clinical field trials were therefore important to confirm this promise and were focused particularly on the issue of over-prescribing, but also on accurate and timely diagnosis. In addition, the device needed to be impervious to environmental effects and able to return a reliable diagnosis in less than two minutes under the most adverse field conditions irrespective of the operator.

Field trials were held in Kenya in **2008** [c] based on 682 patients showing clinical signs of uncomplicated malaria. The original prototype instrument was evaluated under blind clinical conditions against expert microscopy. It returned initial sensitivity and specificity values of 85%

and 64.5% respectively although it was noted that several cases of high level infection (parasitaemia) were missed. This prototype was the size of a small filing cabinet but its performance was promising enough [d, e] to secure prestigious funding from the *Bill and Melinda Gates Foundation* (ii, iii) for its miniaturisation and continued development.

A radical redesign realised the diagnostic platform in a portable hand-held format about the size and weight of a credit card reader. Several such devices have subsequently been manufactured in-house at Exeter. It is estimated that each device could be mass produced for less than $200 with tests costing 25 cents each, much lower than current RDTs. Devices in this format were field trialled over the summer months of **2012** in collaboration with Prof. Francois Nosten and Dr Stephane Proux at the Shokolo Malaria Research Unit (SMRU) in Thailand [6, f]. This was a study of a population of 155 patients composed primarily of migrants from across the Burmese border and yielded what at first seemed disappointing results; sensitivity 41% to 56% - specificity 96% to 100%. However the false positive count was essentially zero, indicating the haemozoin concentration in these samples was at or below the device detection limit. This finding was reinforced by expert diagnostic microscopy that reported that infection was at the very early stages in all samples tested. Thus these suppressed results are likely a consequence of the atypical study population but nevertheless they do indicate it is essential to further boost instrument sensitivity at the bottom end of its range to pick up very early infection. This is possible as design of the portable devices was based on the data obtained in Kenya. Despite this, results clearly indicate that these instruments are the most sensitive of all means of detecting haemozoin in blood and that they will function under conditions where microscopy is completely impractical and RDT's environmentally compromised.

The technique as patented [g] compared very favourably with other existing and developing diagnostic technologies in UNITAID's **2011** review [h] of the malaria diagnostic landscape for the World Health Organisation. When commercialised and following further development, the sensor is well placed to reach the Global Health Diagnostic Forum's goal [i] for malaria diagnosis. This is to substantially reduce the more than 400 million unnecessary treatments administered each year but also to save upwards of 1.8 million adjusted lives per year.

Finally and significantly, it has become clear that the technology is immediately applicable to the diagnosis or other classes of disease and also realisable as a generic multi-spectrum point-of-care device. It is potentially able to sensitively diagnose any disease or condition for which a biomarker and biomarker receptor have been identified and even diagnose several diseases simultaneously from a single fluid sample. Both these advances have been protected by patent applications filed in **2011** [j].

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

a. *Malaria Rapid Diagnostic Test Performance: Results of WHO product testing of malaria RDTs: Round 1 (2008): ISBN 978 92 4 159807 1.* PDF supplied.
b. Report by the Medical Device Developments editor lists our magnetic-optical device as one of ten technologies that have caused the most excitement in 2010 in terms of how they will alter patient care in the years ahead. http://www.medicaldevice-network.com/features/feature106579/
c. Netherlands Trial Register (2008). *Clinical evaluation of a magnetic device for the diagnosis of malaria*. NTR Number NTR1532: http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1532
d. Press announcement of Gates Foundation award (2011) http://www.bbc.co.uk/news/uk-england-devon-1413854
e. Lead, Discovery & Translational Sciences team, Bill and Melinda Gates Foundation, 440 5th Ave N., Seattle, WA 98109, USA.
f. The trial was registered and the protocol approved under the Oxford Tropical Research Ethics

Committee (Oxford University). Reference: 22-12. PDF approval letter supplied http://www.tropicalmedicine.ox.ac.uk/oxtrec

g. *Patent*. Newman DM. Hemtinstall, J. *Devices and Methods for Detecting β-haematin and haemozoin.* This is the primary patent protecting the diagnosis of malaria by magneto-optics. International Patent Application Number PCT/GB2007/004300 filed 10/ 11/2006. US Patent granted 3/07/2012 No 8,214,006. Currently undergoing examination in the EU, China and India. http://www.google.com/patents/WO2008056171A2

h. UNITAID (2011). *Malaria Diagnostic Technology Landscape*, see pages 55-59 and appendix pages 85 and 86, UNITAID Secretariat, World Health Organisation, Ave Appia 20, CH-1211 Geneva 27, Switzerland. http://www.unitaid.eu/en/marketdynamics/malaria-diagnostics-landscape

i. Urdea M, Penny LA, Olmsted SS, Giovanni MY, Kaspar P, Shepherd A, Wilson P, Dahl CA, Buchsbaum S, Moeller G & Hay Burgess, DC. (2006). Requirements for high impact diagnostics in the developing world*, Nature, 73-79 doi:10.1038/nature05448.* http://www.nature.com/nature/journal/v444/n1s/pdf/nature05448.pdf

j. *Patents*
Newman DM. *Detection of Neurodegenerative Disease.* This patent protects the extension of the primary patent to the diagnosis of a raft of neurodegenerative diseases. UK Patent Application Filed 26/08/2011, Number 1114733.7. PDF supplied.
Newman DM. *Method and Device for Detecting an Analyte*. This patent protects the IP associated with a whole class of techniques with the potential to enhance magneto-optic detection and signalling to allow the development of multi-spectrum volumetric assay in a point-of-care diagnostic device. UK Patent Application Filed 01/09/2011, Number 1115120.6. PDF supplied.