Institution:
UNIVERSITY OF LIVERPOOL and LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Unit of Assessment:
UOA1 - Clinical Medicine

Title of case study:
Sepsis diagnostic & Company spin-out

1. Summary of the impact

Research at the University of Liverpool (UoL) has developed and proven a straightforward diagnostic test method for bacterial blood infections. This was urgently needed as sepsis is a medical emergency that lacks adequate and rapid diagnostic tests particularly for low cost early detection. UoL's research has demonstrated that a simple optical test that can be conducted during routine testing of coagulation is an effective diagnostic, prognostic and monitoring marker for sepsis that can be routinely applied in clinical settings. There are now established UK and international laboratory standards in place. In 2010 a spinout company was formed to exploit four patents and incorporate the technology into a point-of-care device suitable for all clinical settings. The company, Sepsis Ltd, has attracted £1.45m of investment.

2. Underpinning research

Sepsis is a bacterial infection of the blood that causes whole body inflammation and is the leading cause of death worldwide. It affects 18 million people and 30% of cases die from it. In addition, sepsis is increasing by 1.5% each year. This is because of an ageing population and antibiotic-resistant bacteria. A major problem is that prompt diagnosis of sepsis is difficult. Early diagnosis is crucial to avoid complications, secure appropriate antibiotic treatment and can be life-saving. There is a pressing need for rapid detection systems that can indicate bacterial infection at the patient bedside because conventional blood cultures take over 24 hours to produce a result.

The pioneering research, led by Prof Cheng Hok Toh at the UoL, was first published in 1997 following investigations into the routine coagulation test for sepsis used in intensive care setting [1]. It was found that during this course of this measurement of the activated partial thromboplastin time (aPTT), optical measurements could distinguish between samples where sepsis was present and not. This optical measurement was called the aPTT biphasic waveform and is straightforward to generate.

The next step in the UoL research was to investigate the potential of the aPTT biphasic waveform as a diagnostic, prognostic and monitoring marker for sepsis and sepsis related complications. There were two threads to this research. The first was based on further prospective and large clinical cohort studies to ascertain the sensitivity and specificity of the aPTT biphasic waveform measurements for this application. It was found that this new measurement was sensitive, rapid and selective. Of particular importance was the finding that it was more sensitive than the established aPTT coagulation test; it could detect sepsis at an earlier stage which enables earlier diagnosis and treatment. It was found to be at least as sensitive as the two existing sepsis biomarker measurements – procalcitonin and C reactive protein, which are expensive and take hours for a result and therefore, not routinely used in the UK. This is the first significant research output, that aPTT biphasic waveform measurements have been found to be a superior indicator in clinical sample for the presence of sepsis [3].

The second thread to the UoL research was to investigate the underlying molecular mechanism and establish its function. It was found to involve a calcium-dependent complex between C reactive protein and very low density lipoprotein, which can slow down normal bacterial clearance by the body. It is the knowledge of this molecular mechanism that has enabled the development of new assays for sepsis [2]. These assays form the key technology platform for routine point-of-care use of the laboratory-based aPTT waveform directly into clinical settings. Four patents have also arisen from this research [4-7].

3. References to the research

Key Publications

1. Downey C, Kazmi R, **Toh CH**. Novel and diagnostically applicable information from optical waveform analysis of blood coagulation in disseminated intravascular coagulation. B J Haem 1997; 98: 68-73. Citations: 47 Impact Factor: 4.942

2. **Toh CH**, Samis J, Downey C, Walker J, Becker L, Bruffato N, Tejidor L, Jones G, Houdijk W, Giles AR, Koschinsky M, Ticknor L, **Paton R**, **Wenstone R**, Nesheim ME. Biphasic transmittance waveform in the APTT coagulation assay is due to the formation of a calcium dependant complex of C-reactive protein with very-low-density-lipoprotein and is a novel marker of impending disseminated intravascular coagulation. Blood 2002, 100, 2522-2529. Citations: 70 Impact Factor: 9.060

3. **Toh CH**, Ticknor LO, Downey C, Giles AR, **Paton R, Wenstone R**. Early identification of sepsis and mortality risks through simple, rapid clot-waveform analysis. Intensive Care Medicine 2003, 29, 55-61. Citations: 46 Impact Factor: 5.258

Patents arising directly from the research.

4. WO00046603A1 (2000) describes "A method and apparatus for predicting the presence of haemostatic dysfunction in a patient sample." http://www.wipo.int/pctdb/en/wo.jsp?WO=2000046603

5. WO01013125A1 (2000) describes "A Method for predicting the presence of haemostatic dysfunction in a patient sample." http://www.wipo.int/pctdb/en/wo.jsp?WO=2001013125

6. WO01096864A2 (2001) describes "A method for detecting a lipoprotein-acute phase protein complex and predicting an increased risk of system failure of mortality." http://www.wipo.int/pctdb/en/wo.jsp?WO=2001096864

7. WO03073099A1 (2003) describes "A Method for diagnosing and monitoring haemostatic dysfunction, severe infection and systemic inflammatory response syndrome." http://www.wipo.int/pctdb/en/wo.jsp?WO=2003073099

Key grants

2005-2007. **MRC** (G0400488). The role of very low density lipoprotein in enhancing thrombin generation in sepsis. £89,408, **Toh CH**, N Rhodes, M Leuwer.

2007-2010. **NIHR Biomedical Research Centre** Project 3515, A Prospective Study of the aPTT Waveform and Lipoprotein-Complexed C Reactive Protein Assays in the Early Diagnosis and Prognosis of Sepsis. £330,820, **Toh CH**, Welters I, Williamson PR

2010. **NIHR Innovation for Invention Future Product Development Stage 1:** (II-FS-0509-12093). A Point-of-Care Test for Sepsis based on Calcium-induced Turbidity in Blood, £100k, **Toh CH**, Myers P.

2010-2012. **Technology Strategy Board**. Rapid point-of-care detection of bacterial sepsis. £160k, **Toh CH**

2011-2014. **NIHR Innovation for Invention Late Stage Development:** ((II-LS-1010-10045). A Point-of-Care Test for Sepsis based on Calcium-induced Turbidity in Blood, £300k, **Toh CH**, Myers P.

4. Details of the impact

The impacts in this section have all occurred in 2008 or later and have occurred as a direct result

of the UoL research.

As already mentioned, sepsis is a major cause of mortality and morbidity. In England, Wales and Northern Ireland, 27% of adult admissions to critical care in the period December 1995 to January 2005 were found to progress to severe sepsis within the first 24 hours. Hospital mortality in 2004 in this geography was estimated to be 44.7% for those with severe sepsis or 14,000 cases. Other estimates are higher. Prompt diagnosis and treatment is essential with one study reporting a 7.6% increase in mortality for each hour that antibiotic treatment was delayed in patients with septic shock [18,19].

Following publication of the UoL research, there was recognition that the aPTT biphasic waveform measurements could be important through enabling earlier diagnosis to lead onto clinical benefits for patients and economic benefits for health system providers. Several influential journal editorials drew international attention to the research outputs [14-17]. This led to demonstration of the benefits in two disease areas where infection is a common and important complication, namely heart bypass surgery and the treatment of cancer [8,9]. The superiority of the aPTT biphasic waveform over the leading sepsis biomarker, procalcitonin, in clinical settings has also been investigated and confirmed [10].

This work led the British Committee for Standards in Haematology, a leading professional body in the UK, to invite Toh and others to specify laboratory standards for diagnosing the sepsis-related complication of disseminated intravascular coagulation (DIC). These were published in 2009 [11] and included the aPTT waveform. These measurements are being promoted by laboratories among their clinical customers and also by haematologists requiring these measurements to improve clinical outcomes. Whilst initially focussed on patients in intensive care settings, the rapid, reliable and low cost measurement is leading to the test being used in emergency rooms, post-surgical wards and oncology. This increase in testing for sepsis is leading to earlier diagnosis and appropriate treatment. Through improved diagnosis, it is also reducing the use of antibiotics through an accurate distinction between bacterial and viral disease [16]. The research is therefore clearly and directly impacting upon clinical and laboratory medicine practitioners in the UK and also specialists, including haematologists, emergency and critical care physicians and paediatricians. Patients are benefiting through improved treatment and reduction in the burden of sepsis on the NHS.

In a similar way, Toh was asked to contribute to the International Society on Thrombosis Haemostasis's work to establish standards internationally for diagnosing DIC and for laboratories offering the aPTT biphasic waveform test to ensure that there is international consistency in its application. Guidelines were published in Feb 2013 and work on standardising the use of aPTT biphasic waveform measurements throughout the world is ongoing [12]. They are impacting upon laboratories, clinicians and patients in a similar way to the UK.

These advances have also been integrated into UK and international training in haematology [13].

A new spinout company, Sepsis Ltd, was formed in 2010 and has acquired the four patents arising from the UoL research. Its objective is to develop devices incorporating aPTT biphasic waveform technology that can be used at points of care for the routine testing of sepsis, from GP surgeries to emergency rooms. The company has secured £250k of investment funding and £1.2m from the Technology Strategy Board. It has already developed a prototype device and by the end of 2013 will employ 3 people.

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).

8. Delannoy, et al. Effect of cardiopulmonary bypass on aPTT waveform analysis, serum

procalcitonin and CRP concentrations. Crit Care 2009; 12: R180.

9. Hussain, et al. The biphasic transmittance waveform: an early marker of sepsis in patients with neutropenia. Thromb Haemost 2008; 100: 146-8.

10. Zakariah A, et al. Combination of biphasic transmittance waveform with blood PCT levels for diagnosis of sepsis in acutely ill patients. Crit Care Med 2008; 36: 1507-12.

11. Clinical guidelines: Guidelines for the diagnosis and management of disseminated intravascular coagulation. Br J Haematol 2009; 94: 387-94.

12. Wada H, Thachil J, Di Nisio M, Mathew P, Kurosawa S, Gando S, Kim HK, Nielsen JD, Dempfle CE, Levi M, Toh CH; Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines. (2013) The Scientific Standardization Committee on DIC of the International Society on Thrombosis Haemostasis. http://www.ncbi.nlm.nih.gov/pubmed/23379279

13. Postgraduate Haematology (Wiley-Blackwell) 6th Edition (2010), edited by Victor Hoffbrand, Daniel Catovsky, Edward GD Tuddenham and Tony Green. Chapter on Acquired Coagulation Disorders features the aPTT biphasic waveform.

Journal editorials on the aPTT biphasic waveform in sepsis

14. ten Cate H. The biphasic waveform in plasma: identifying the sepsis-coagulation crossroad. J Thromb Haemost 2004; 2: 1534-5.

15. Thomas K. Transmitting and absorbing new information on the early identification of sepsis patients: aPTT waveform. Crit Care Med 2006; 34: 1829-31.

16. Dempfle CE, Borggrefe M. The hidden sepsis marker: aPTT waveform analysis. Thromb Haemost 2008; 100: 9-10.

17. Schneider CP, Angele MK, Hartl WH. aPTT waveform analysis as specific sepsis marker in cardiopulmonary bypass surgery. Crit Care 2010; 14: 104.

Evidence of the serious nature of septic shock

18. Harrison DA, et al. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. Critical Care 2006, 10:R42 doi:10.1186/cc4854 http://ccforum.com/content/10/2/R42

19. Gaieski D, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med 2010; 38; 3. DOI: 10.1097/CCM.0b013e3181cc4824