Institution: Queen's University, Belfast

Unit of Assessment: 8

Title of case study: Utilisation of Fluorescent PET (Photoinduced Electron Transfer) Sensor Molecules in Blood Analysis

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

Research on fluorescent PET sensors by de Silva at Queen's University Belfast was directly, and collaboratively, built into the Roche/Optimedical OPTI blood electrolyte analyser, which has had sales of US$50M in the past five years equating to 10 million sensors sold. The market for this sensor is global and it is used every day worldwide in hospital critical care units, ambulances, general-practice surgeries and veterinary care, often in life or death circumstances. The research, therefore, has led to both economic impact as well as significant health benefits.

2. Underpinning research (indicative maximum 500 words)

De Silva in QUB has been the pioneer of research into fluorescent PET (photoinduced electron transfer) sensors as a technique to target species such as protons, sodium and calcium that are crucial in many biological and medical contexts. The research at QUB which started in 1993, developed an understanding of the mechanism associated with PET sensors (references 1 and 2 *in section 3*), based on Nobel Prize winning Marcus Theory which explains the rates of the electron transfer reactions. The mechanistic understanding obtained allowed the design of a modular sensor consisting of a fluorescent unit and a receptor unit joined through a spacer molecule (Figure 1). When optically excited, this allows the transfer of an electron to/from the fluorescent unit from/to the receptor, as occurs in plant photosynthesis, so that fluorescence is killed off. When the receptor captures a suitable cation, however, such as sodium, the increased positive charge prevents the electron transfer, allowing fluorescence. Additionally, the research demonstrated that changes in conformation caused by species occupying the receptor can enhance the fluorescence switching effect. Critically, as a result of the understanding formulated by the Queen's group, the combination of components has been able to be manipulated to selectively detect analytes at concentrations as low as 10^{-7} M, thus enabling, for example pH, calcium, sodium and potassium ion concentration to be determined from the same sample in a flow through system via a number of sensors in series. Furthermore, the Queen's group developed the fluorescent PET sensors to be designed so that a substantial number of other cationic, anionic and neutral species are also accommodated to trigger fluorescence leading to the technology to be transferred to a commercial process and the design of sensors and devices for much wider applications, for example in the field of molecular logic based computation (reference 3 *in section 3*), of which the initial sensors acted as YES gates. Other molecules, which behaved as AND gates, (references 3-6 *in section 3*) also emerged. From this research, Roche/Optimedical collaborated with the Queen's team to develop commercial sensors for sodium, potassium and calcium which were tested in collaboration with scientists at AVL Bioscience Corporation, Roswell, GA leading to the final OPTI blood electrolyte analyser product.

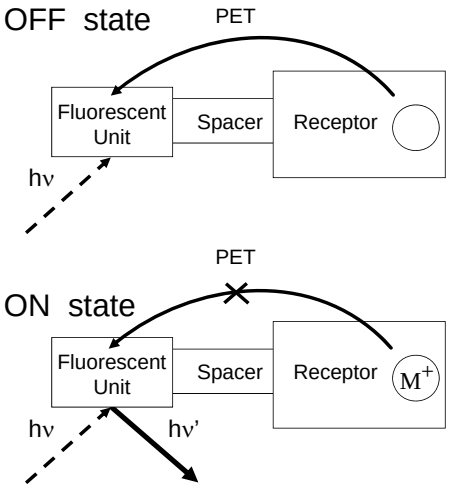

Figure 1 Mechanism of PET sensor action

3. References to the research (indicative maximum of six references) * signify the references which best indicate the quality of the underpinning research

*1. Fluorescent switches with high selectivity towards sodium ions: correlation of ion-induced conformation switching with fluorescence function. A.P. de Silva, H.Q.N. Gunaratne, T. Gunnlaugsson and M. Nieuwenhuyzen, *Chem. Commun.* 1996, 1967, DOI: 10.1039/cc9960001967.

*2. New Fluorescent Model Compounds for the Study of Photoinduced Electron Transfer: The Influence of a Molecular Electric Field in the Excited State. A.P. de Silva, H.Q.N. Gunaratne, J.-L. Habib-Jiwan, C.P. McCoy, T.E. Rice and J.-P. Soumillion, *Angew. Chem. Int. Ed. Engl.* 1995, **34**, 1728, DOI: 10.1002/anie.199517281.

3. A molecular photoionic AND gate based on fluorescent signalling. A.P. de Silva, H.Q.N. Gunaratne and C.P. McCoy, *Nature* 1993, 364, 42, DOI: 10.1038/364042a0.

*4. Switching between molecular switch types by module rearrangement: Ca^{2+}-enabled, H^{+}-driven 'Off–On–Off', H^{+}-driven YES and PASS 0 as well as H^{+}, Ca^{2+}-driven AND logic operations. J.F. Callan, A.P. de Silva and N.D. McClenaghan, *Chem. Commun.* 2004, 2048, DOI: 10.1039/b405909c.

5. Membrane Media Create Small Nanospaces for Molecular Computation. S. Uchiyama, G.D. McClean, K. Iwai and A.P. de Silva, *J. Am. Chem. Soc.* 2005, **127**, 8920, DOI: 10.1021/ja0513638.

6. Direct detection of ion pairs by fluorescence enhancement. A.P. de Silva, G.D. McClean and S. Pagliari, *Chem. Commun.* 2003, 2010, DOI: 10.1039/b305262a.

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

Based on the seminal research undertaken by de Silva, Roche developed, in conjunction with QUB, a blood analyser which was commercialised and has been the market leader in point-of-care analyzers ever since (Figure 2). Throughout the period 2008-13 this R&D programme has led to sales of US$50M of the diagnostic cassettes used in the OPTI device) (see reference 1 *in section 5)* clearly demonstrating economic impact of the fundamental research undertaken in QUB.

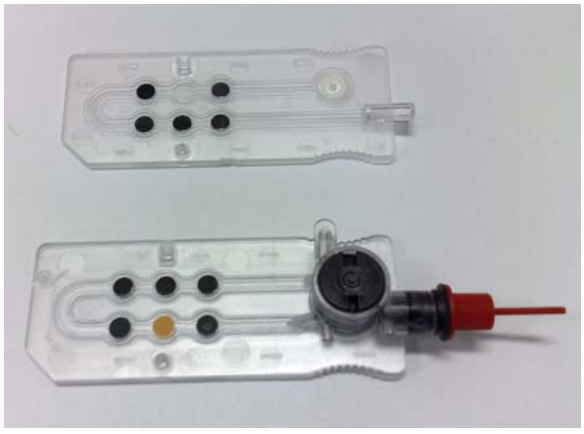

Figure 2 OPTI cassettes sold by Optimedical Inc (www.optimedical.com). The black spots carry the appropriate sensor molecules covalently attached.

As well as economic impact, the formulation of these sensors has had wide spread health benefits worldwide. "The sensors are used in various locations within hospitals, emergency centers, ambulances, helicopters, airplanes, pulmonary centres and in any location where time critical diagnostic testing is needed." (see reference 2 *in section 5*). For example, they monitor blood for levels of common salt components such as sodium, potassium and calcium rapidly allowing emergency units to arrange for a certain type of blood with the necessary salt levels to be ready following transport of a patient from triage to hospital, for example. The ability to analyse the blood

rapidly (within 30 s) has also changed the working patterns of health professionals, for example, in Japan, general practitioners use the device to give patients results in their surgeries rather than have to send away blood samples for analysis. In addition, the technology is so robust that paramedics in ambulances in Sri Lanka used the Optimedical analyzer during the civil war, which ended in 2009, when casualties were a daily occurrence. These devices have recently been used in a similar vein in Libya (see reference 3 *in section 5*). Furthermore, the technology has been adapted for veterinary treatments and is incorporated into the IDEXX VetLab Suite demonstrating the breadth of the impact delivered (see reference 4 *in section 5*).

The high quality fundamental research undertaken in the area of PET fluorescent sensors by de Silva in QUB has had significant economic impact benefiting both the companies involved as well as the wider economy. Importantly, there have also been health and societal benefits to the development of the OPTI blood analyser in terms of speed of the analysis which has resulted in patients' peace of mind and more importantly efficient life saving transfusion of compatible blood aiding the recovery of patients globally.

In 2008 Prof de Silva won the Royal Society of Chemistry's Award for Sensors sponsored by GE Healthcare for his contribution towards 'switch and tell' sensor molecules, the invention of molecular logic and the industrial impact of the research undertaken (reference 5 *in section 5*).

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

1. Supporting letter from Optimedical Company (which is the current name of the Roche/AVL Division) by Senior Scientist.
2. http://www.optimedical.com/
3. http://www.optimedical.com/news/2011/OPTI_Medical_Analyzers_In_Libya.pdf
4. http://www.idexx.com/view/xhtml/en_us/corporate/investors/annual-review/2009/2009-opti-medical.jsf
5. http://www.rsc.org/ScienceAndTechnology/Awards/Archive/SensorsAward/Index.asp