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| **Institution: Middlesex University** | | |
| **Unit of Assessment: UofA3 Allied Health Professions, Dentistry, Nursing and Pharmacy** | | |
| **Title of case study:** Effective methods to study and locate the physical properties of gold nanoparticles in medical application to improve clinical effectiveness | | |
| **Period when the underpinning research was undertaken:** 2014 and ongoing | | |
| **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:** |
| Prof Richard Bayford | Professor of Biophysics and Engineering | 1986 to date |
| Dr Song Wen | Senior lecturer | 2012 to date |
| Prof Ajit Shah | Professor of Bioanalytical Science | 2010 to date |
| **Period when the claimed impact occurred: 2014 to date** | | |
| **Is this case study continued from a case study submitted in 2014?** No | | |

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

Key impacts are:

- Providing new methods for Emergex vaccines (industry) to improve the targeting and hence the effectiveness of their vaccines in humans (4.1).
- Working jointly with Proxima Concepts to create new aptamers and bioproducts attached to gold (4.2).
- Working with industrial partners to develop a new AI-based approach for generation of novel peptide aptamers for targeting of diseases including COVID-19 (4.1,4.2).
- Working with Ascend Diagnostics to develop a new generation of mass spectrometer with improved characterisation of molecules attached to gold nanoparticles (4.3).
- Bioimpedance/nanoparticles for colorectal cancer screening with St Mary's Hospital, Imperial College London and KCH for brain cancer are influencing clinical practice (4.4, 4.5).
- A new device which can be used for detecting virus-associated diseases with Chinese partners (4.6).

**2. Underpinning research.**

Our work has focused on the use and understanding of gold nanoparticles less than 5 nm in size along with their use in the delivery of therapeutic drugs for cancer and other therapies which is of considerable importance for pharmaceutical research and industry.

**Gold Nanoparticles (GNPs) and Electrical Impedance Tomography (EIT):** GNPs are gold particles, with a diameter of 1-100 nm. They are widely employed in biomedical applications based on their unique properties and multiple surface functionalities. Thus, they provide a versatile platform for binding to antibodies, proteins and drugs. The inert nature of gold and the small particle size make GNPs an ideal platform for the attachment of a variety of molecules. EIT provides impedance changes that result from the injection of small electrical currents into an electrode array. We developed a novel approach to tracking GNPs based on the insight that they can be stimulated to generate a temperature differential, and this can be detected using EIT [1].

**Initial research (2009):** In collaboration with Midatech Spain Ltd we investigated the effects of using specific radio frequencies (RF) to heat GNPs with the aim of using the heat generated to kill cancer cells. We found that heating small nanoparticles (<2nm) can be done with minimal side effects on surrounding normal tissues [2]. Importantly, we found that the size and nature of the molecules attached to the nanoparticle change the frequencies at which it heats. We also found

that we can minimize heating of surrounding tissue through subtle frequency changes. This has proved useful in the GNPs developed by our industrial partners.

**Colorectal cancer (2011 - ongoing)**: Colorectal cancer (CRC) is one of the most common types of cancer in the UK (35,000 diagnosed each year). Using funding from the EPSRC Grand Challenge grant (EP/R04192X) (£1.8M), our research extended to the development of a method that used EIT to image GNPs in colorectal cancer [3]. A key novel aspect of this work was the use of GNPs for imaging this cancer. We conjugated a variety of biomolecules to GNPs to target cancer biomarkers and exploited their ability to enhance the impedance of diseased tissue. By replacing radioactive labelling with nanoparticles, we have designed a safer alternative to PET systems to target cancer cells (*Patent granted*) (5.3).
Validation was undertaken to demonstrate increased uptake and delivery efficiency of GNPs into the CRC cells by targeting folate receptor alpha and Tyrosine Kinase receptors together. In parallel to this we worked with the Lord Darzi group at Imperial College London and their lead Surgeon to create a device to locate colorectal cancer using EIT and nanotechnology.

**Technology development (2016 - 2019):** Alongside this, and together with the development of new EIT hardware (CRADL H2020), we further formulated the theoretical aspects of the technology [2,4,5]. This was also funded through an EPSRC Bright ideas fund EP/G061572 (£250K)[1]. In addition, we have used liposomal nanotechnology to demonstrate reduced toxicity and improved drug delivery [6].

**Application for cancer and vacancies (2018 - ongoing):** A key feature of our technology is that it can be widely applied. At present we are continuing to develop this technology with Emergex Vaccines. They have provided us with conjugated GNPs for locating COVID-19. We have also recently been working with Proxima Concepts to develop new GNP-based aptamer constructs for a range of clinical applications.

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

[1] Nazanin Neshatvar, Rui Damaso , Nima Seifnaraghi , Andreas Demosthenous and Richard Bayford (2019) Towards a System for Tracking Drug Delivery Using Frequency Excited Gold Nanoparticles *Sensors* , *19* (21), 4750; https://doi.org/10.3390/s19214750.

[2] Nordebo, Sven, Dalarsson, Mariana, Ivanenko, Yevhen, Sjoeberg, Daniel and Bayford, Richard (2017) *On the physical limitations for radio frequency absorption in gold nanoparticle suspensions.* Journal of Physics D: Applied Physics, 50 (15) . ISSN 0022-3727(doi:10.1088/1361-6463/aa5a89).

[3] Lund, Torben, Callaghan, Martina, Williams, Phil, Turmaine, Mark, Bachmann, Christof, Rademacher, Tom, Roitt, Ivan and Bayford, Richard (2011) *The influence of ligand organization on the rate of uptake of gold nanoparticles by colorectal cancer cells.* Biomaterials, 32 (36) . pp. 9776-9784. ISSN 0142-9612 (doi:10.1016/j.biomaterials.2011.09.018).

[4] Dalarsson, Mariana, Nordebo, Sven, Sjöberg, Daniel and Bayford, Richard (2017) *Absorption and optimal plasmonic resonances for small ellipsoidal particles in lossy media.* Journal of Physics D: Applied Physics, 50 (34) . ISSN 0022-3727 (doi:10.1088/1361-6463/aa7c8a).

[5] Nordebo, Sven, Dalarsson, Mariana, Ivanenko, Yevhen, Sjöberg, Daniel and Bayford, Richard (2017) *Parameter studies on optimal absorption and electrophoretic resonances in lossy media.* 2017 XXXIInd General Assembly and Scientific Symposium of the International Union of Radio Science (URSI GASS). In: 2017 XXXIInd General Assembly and Scientific Symposium of the International Union of Radio Science (URSI GASS), 19-23 Aug 2017, Montreal. ISBN 9789082598704. (doi:10.23919/URSIGASS.2017.8105294).

[6] Wang X, Li D, Ghali L, Xia R, Munoz L, Garelick H, Bell C and Wen X (2016). Therapeutic Potential of Delivering Arsenic Trioxide into HPV-Infected Cervical Cancer Cells Using Liposomal Nanotechnology. Nanoscale Res Lett 11:94. (doi: 10.1186/s11671-016-1307-y).

Grants
ERPRC Colorectal cancer, EP/RO4192X, £1.8M
EPSRC Bright ideas EP/G061572, £250k CRADL H2020 5.5M EUROs Prof Bayford coordinator
Midatech provided equipment (£250K)

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

New drug therapies currently cost up to £4bn to reach the stage of Food and Drug Administration (FDA) approval and currently approximately 99% of freely circulating drugs administered do not reach the target site. The attachment of drugs and biomarkers to our GNP allows a novel imaging to locate these nanoparticles in humans in real time. Our work in tracking GNPs has impacted on improving the delivery of therapeutic drugs and therapies. In addition, it impacts the development of new vaccines by improving the targeted therapies to optimise therapeutic intervention.

To this end we are working with industrial partners to develop ground-breaking technologies, which advances nanomolar biophysics and engineering by using a unique method to monitor a range of therapies including cancer, dementia and COVID-19. This provides a paradigm-shift treatment modality that adds a strong tool to the collective treatment arena, which could significantly reduce the side effects associated with other treatments like chemotherapies.

Specific current impacts are as follows:

4.1 We have been working with Emergex Vaccines (formally Midatech), a company that is involved in development of synthetic vaccines for infectious diseases to extend the application of EIT for the detection of cancer [5.1]. Midatech provided equipment (£250K) to develop a method to heat GNPs for therapeutic use. This work led to the identification of appropriate radio frequencies to heat GNPs. This led to a joint patent (WO/2010/052503: Detection of Cancer) in place with Midatech Pharma, a company focused on improving drug biodelivery and biodistribution [5.2]. (This work is subject to an NDA, which limits the information we can disclose in this document and recently a new patent has been filed on imaging of GNPs [5.3]).

4.2 Proxima Concepts Limited is an international bio-pharmaceutical R&D company that uses drug delivery and discovery technologies and works with the biotechnology industry to address the needs of healthcare and medical therapeutics. We have worked together using their novel artificial intelligence (AI) approach to create new peptide aptamers to link to gold for targeting troponin as a point of care device for detection of stroke and SARS. This has enabled new applications for the aptamers and impact on the range of uses for their products. For example, COVID-19 vaccines and biosensors [5.3]. This has opened new markets for the company and attracted new international investors.

4.3 An important aspect of our GNP work has been the characterisation of drugs and biomarkers that are bound to our GNPs. Rapid characterisation has been achieved using matrix assisted laser desorption ionisation time of flight mass spectrometry (MALDI-TOF MS) As a result of this work, the instrument manufacturer Ascend Diagnostics (formerly ASTA) has developed the next generation of this instrument. The new instrument has improved software and hardware features which significantly improve data output (5.4).

4.4 Translation of bioimpedance for colorectal cancer screening with St Mary's Hospital, Imperial College London and has been used on some patients with anal cancer. The work allowed them to apply and be awarded an ICHT Charity grant and Royal College of Surgeons Research Fellowship to support the salary of a research fellow who undertook the colorectal work at the ICHT site.

Collaboration has continued, using clinical data held at and managed by Middlesex University and analysis of that data in shaping some of our own work which will create opportunities for clinical trials in the future.

The benefits here are primarily related to the development of new diagnostic but also effective treatment schemes, but we also see ongoing benefit in patient support, clinical decision-making and treatment triage. [5.5]

4.5 The work above [4.4] has led to the application of bioimpedance/nanoparticles methods for brain cancer initially at UCLH and then at KCH. The work focuses on image guided surgery using a new robotic system to identify what part of the tissue has cancer during surgery [5.6].

4.6 We have been working with Nanjing University of Science and Technology to design a new device to detect virus associated diseases. The Institute of Nano-Resolution Optics at Nanjing University have pioneered the research in polarization parametric indirect microscopic imaging (PIMI), a new super resolution imaging method. This instrument allows optical detection of nanosized biomolecules, such as viruses, through nanopore arrays without labelling. This has transformed the way in which nanosized biomolecules are detected. The Middlesex University team are working alongside researchers from Nanjing University to solve challenging technical difficulties in the processes of device design, conjugating nanoparticles with antibodies for detection and post imaging processing procedures to widen and promote the application using machine learning techniques.

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

5.1 Emergex Vaccines Holding have pioneered a new approach to vaccine development to address some of the world's most acute health threats such as Zika, Ebola, pandemic flu and antibiotic-resistant bacteria and is working with us to develop the new imaging method to validate these ground-breaking approaches to making vaccines, using purely synthetic components to activate T-cells of the immune system to destroy virus-infected human cells. MU work helped to expand the range of GNPs produced and used for therapeutic heating. Our novel imaging method has been adopted for studies in COVID-19 animal models to locate and validate their new vaccine and other GNPs based therapies (see Emergex support letter).

5.2 Patent: (WO/2010/052503) Detection of Cancer. Nanoparticle imaging (MUH,011-EP // L&C 29760). This helped Midatechpharma to raise investment funding and the patent is 50% assigned to the company. (Details can be made available if required subject to an NDA)

5.3 Proxima Concepts and Vaxcine are working with us on the design of aptamers for nanoparticles for troponin and COVID-19 (see Vaxcine support letter). Our work impacted the development of aptamers for biosensors. This has enabled new applications for their aptamers which has had an impact on the range of application for the products.

5.4 Ascend Diagnostics (see support letter) The work on nanoparticles as part of the collaborative project has led to improvement in software and hardware in their MALDI-TOF mass spectrometer. This has ultimately led to the development of the next generation instrument which is in the process of being commercialised.

5.5 St Mary's Hospital London, part of Imperial College Healthcare NHS Trust. Our bioimpedance/nanoparticles technology has impacted them by permitting discrimination between benign and malignant colorectal tissue and helping with clinical practices (see Imperial letter of support).

5.6 The bioimpedance/nanoparticles technology has impacted work by consultant neurosurgeons at Kings College Hospital by permitting discrimination between benign and malignant brain tissue and helping with clinical practices (see Kings support letter).

5.7 The Institute of Nano-Resolution Optics at Nanjing University are experts in developing a detection scheme based on the modification of light transmission through a plasmonic nanopore. Other work has impacted on optical detection of translocated single DNA molecules without the need of any labelling, which provides a platform for label free nanotweezing and single-molecule Raman spectroscopy. (see Nanjing Letter of Support)