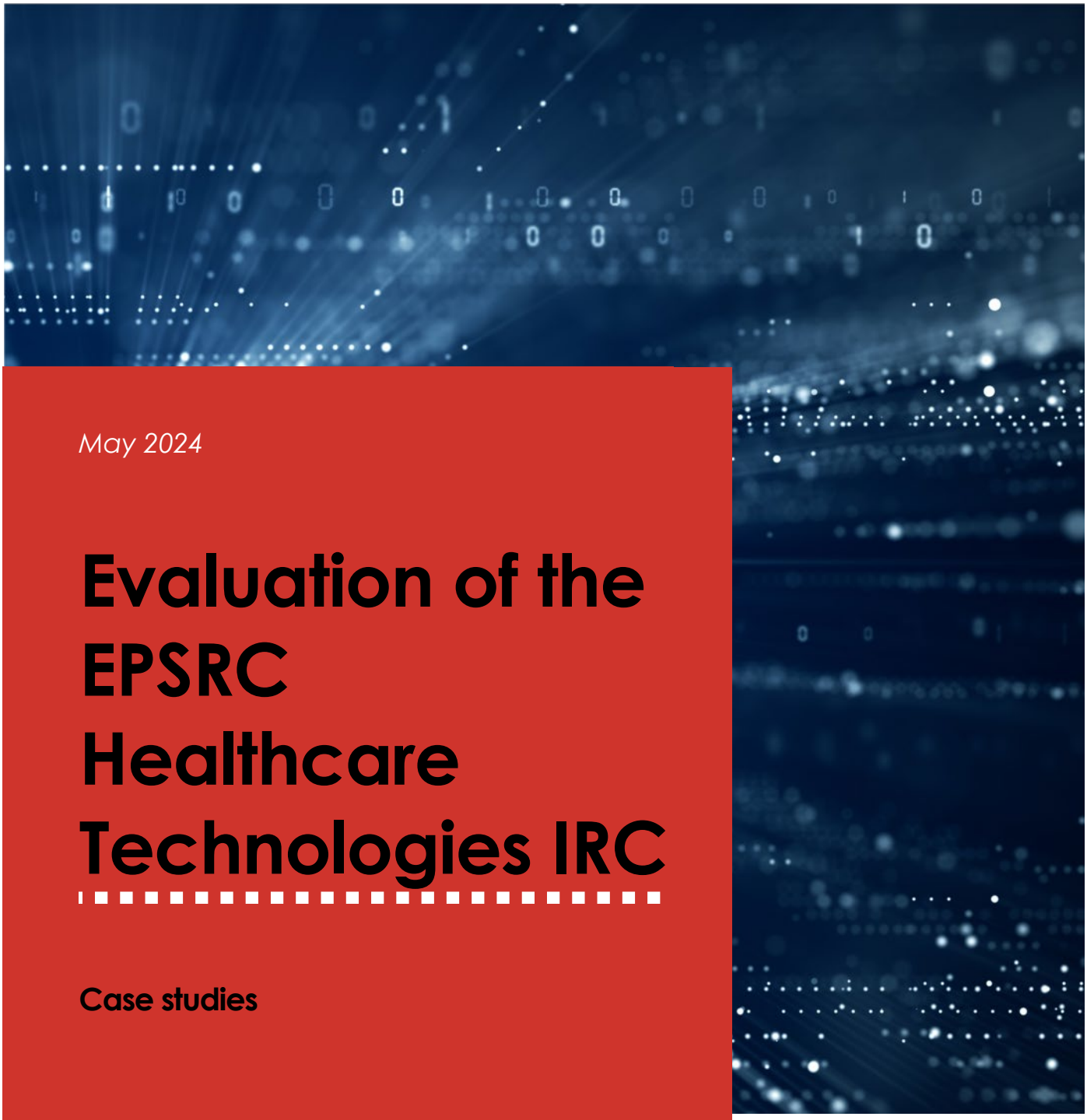
technopolis group



May 2024

Evaluation of the EPSRC Healthcare Technologies IRC

Case studies

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1 Rationale for case study selection

The study team set out to develop case studies to illustrate significant (actual and expected) outcomes and impacts emerging from the Healthcare Technologies Interdisciplinary Research Collaboration (IRC) programme, relevant for each impact area of the programme's logic model. The overarching rationale for case study selection was based on ensuring a balanced view across and between the IRC portfolio, providing evidence on outcomes and impacts relevant to the programme as a whole but also to key individual projects. The selection criteria were based on (1) funding size and mechanism involved; (2) type(s) of outcomes and impact as set out in the logic model; (3) type(s) of actors involved (researchers, industrial partners, hospitals, etc); (4) coverage of the evaluation questions; and (5) availability of evidence and access to key informants.

A long list of case studies was developed by the study team and iterated with IRC leads and EPSRC. This iteration allowed for an assessment of case study strengths and feasibility, in particular relation to criteria (5): availability of evidence and access to key informants. The final list of case studies is shown in Table 1 below.

Table 1 Final list of case studies

IRC	Case study title
IRC i-sense	Early warning of infectious diseases using symptoms reported online
	Ultra-Sensitive Enhanced NanoSensing of Anti-Microbial Resistance (u-Sense)
	Using nanozymes to achieve ultra-sensitivity in diagnostic tests
	m-Africa: mobile phone-connected diagnostic for HIV prevention and management
IRC Proteus	Spinout Singular Photonics: ultra-fast image sensors
	A Frugal Point-of-Care System for Fluorescent Detection of Microbial Keratitis
	Our Health Interdisciplinary Research Programme: Exploring community-based participatory research
IRC SPHERE	The use of multi-modal multi-sensor technology to measure symptoms and activities of daily living in Parkinson's disease
	Opportunistic Passive Radar for Non-Cooperative Contextual Sensing (OPERA)
IRC TeDDy	Dynamic hydrogels as a platform for local drug delivery
	Spinout Vector Bioscience: nanomaterials for drug delivery applications
Cross-IRC	IRC programme Partnership Resource Funding
	IRC programme's contribution to skills and career development

The final list consists of 13 case studies which vary in depth, impact area and/or project stage. Two cross-IRC case studies were developed to provide insights on innovative management aspects of the IRC funding and their contributions to skills & career development. In addition, 10 case studies were developed to showcase the outcomes and impacts emerging from one or more projects from all four IRCs. For these, some case studies are highly focused on knowledge and research impact, while others provide evidence of outcomes and impacts across multiple areas (for example, economic, research and societal).

2 Case studies

2.1 Early warning of infectious diseases using symptoms reported online

Summary

Surveillance systems are used by public health agencies to obtain early warnings of outbreaks and mitigate the health and economic impact of infectious diseases. To improve surveillance systems, new digital epidemiology approaches have been developed to understand disease activity and outbreaks in real-time. Key challenges for surveillance systems include obtaining data from a large number of individuals and from those who have not sought medical assistance.

Between 2013 and 2019, researchers from IRC i-sense and partner organisations used web search data from Twitter, Bing and other sources to develop new digital epidemiology approaches for estimating infection rates and disease spreading. Their work produced several highly cited publications and contributed to outcomes with significant impact:

- The first ever assessment of influenza vaccine effectiveness using internet data was conducted, which contributed to Public Health England's (now UK Health Security Agency - UKHSA) decision to introduce a national influenza vaccination program for children.
- Dashboards known as the 'Flu Detector' were developed for daily estimation of influenza rates in England. This tool was incorporated into PHE's surveillance system in 2018, becoming the first system of its kind to be adopted by a national health agency.
- Computer models were developed to estimate COVID-19 prevalence, providing accurate forecast of regional infection surges 7 to 10 days before case counts. UKHSA highlighted how the data influenced national level policies and decision-making, shaping response to COVID-19 pandemic.

Introduction

Infectious diseases are illnesses caused by microorganisms such as viruses and bacteria that can be spread from one individual to another. In the UK, it was estimated in 2017 that infectious diseases account for 7% of deaths and £30 billion in annual costs[1]. Further unprecedented impact was observed in the UK economy in 2020, with GDP falling nearly 20% due to the COVID-19 pandemic[2]. To mitigate the health and economic impact of infectious diseases, countries rely on surveillance systems that report new cases of influenza-like illness (ILI) to health authorities. In the UK, the UK Health Security Agency maintains a system of syndromic surveillance to obtain early warnings of disease outbreaks[3]. The system primarily relies on collecting and analysing health data of individuals who use the healthcare system via GPs (sentinel networks), A&E, ambulance systems and other services.

A key challenge for syndromic surveillance systems is the lag time between individuals using the healthcare system and the information reaching the relevant health authority, which is generally 1 to 2 weeks. In addition, syndromic surveillance systems do not usually obtain information from individuals with early signs of infectious disease who do not (yet) seek any medical assistance. To address these challenges, digital epidemiology approaches to

[1] https://researchbriefings.files.parliament.uk/documents/POST-PN-0545/POST-PN-0545.pdf

[2] https://www.ons.gov.uk/economy/grossdomesticproductgdp/articles/gdpandeventsinhistoryhowthecovid19pandemicshockedtheukeconomy/2022-05-24

[3] https://www.gov.uk/government/collections/syndromic-surveillance-systems-and-analyses

surveillance have been developed. These approaches harness internet data to understand disease activity and outbreaks in real-time and from a large number of individuals including those who have not sought medical assistance[4]. One of these approaches was Google Flu Trends (GFT), a system launched in 2008 which used Google search queries to monitor indirect signals of ILI. GFT was implemented in several countries, with some success. However, further assessments of the computer model in 2013 indicated poor reliability in monitoring seasonal or pandemic influenza, with significant overestimation of disease prevalence[5].

Thus, there was a clear need for better computer models and statistical approaches behind surveillance of infectious disease supported by internet data. By improving the accuracy and reliability of these computer models, surveillance systems for infectious disease would be able to benefit from real-time information and from a wider coverage of individuals in comparison to traditional methods.

Project activity

In 2013, EPSRC's Interdisciplinary Research Collaboration (IRC) i-sense set out to advance research in early warning systems to monitor and prevent spread of diseases. Under its 'Track' research strand at i-sense, Professor Cox led a project to explore innovative methods to analyse internet data to identify outbreaks. The project, named 'Modelling infectious diseases using web search data' (from now on referred to as 'the project'), had two main objectives:

- To create and/or improve existing computer models for estimating infectious disease using internet data, in order to reduce the 1 to 2 weeks delay between individuals using the healthcare system and the data reaching the relevant health authority.
- To develop models that could be applied to countries in which surveillance systems may lack resources.

The project was led by Professor Cox and Dr Lampos, with key inputs from project partners Dr. Yom-Tov at Microsoft Research and Dr Pebody at Public Health England. The project partners provided intellectual contributions throughout the project. Microsoft Research played a pivotal role in the project by providing internet search data from its search platform Bing[6] as well as by granting access to subscription-based Twitter data via Twitter Firehose, with estimated costs exceeding 1 million USD. In addition to this data, the project made use of Google Health Trends, a semi-public database with frequency of searched words related to health[7], as well as sentinel surveillance data from GPs, made available by the Royal College of General Practitioners.

Research findings and outputs

Between 2013 and 2019, i-sense researchers and project partners published a series of impactful papers in the fields of computer science and digital epidemiology, introducing innovative methodologies and enhanced techniques for modelling infectious diseases using internet data. These research outputs can be summarised as follows:

(1) Improvements to computer science models to estimate influenza-like illness (ILI) rates.
(2) New methods for estimating ILI rates in different geographical locations.
(3) Identification of disease outbreaks and early indicators of disease risk.
(4) Assessment of influenza vaccination effectiveness.
(5) Dashboards for improving syndromic surveillance with internet data

[4] https://academic.oup.com/cid/article/47/11/1443/282247
[5] https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1003256; see also Butler, D. When Google got flu wrong. *Nature* 494, 155–156 (2013). https://doi.org/10.1038/494155a
[6] https://www.bing.com/
[7] https://trends.google.com/trends/fullscreen/m/IN

The findings of these research outputs are discussed below.

Improving computer science models to estimate ILI rates

In 2014, Dr Lampos was seconded by Google as part of his involvement with i-sense. This secondment enabled collaboration with researchers at Google Flu Trends team. In 2015, Dr Lampos et al presented a new and improved approach to analysing online search queries in order to track ILI[8]. Their work analysed the model behind Google Flu Trends and other established methods to modelling infectious diseases, aiming to evaluate their performance and understand shortcomings. In addition, the researchers demonstrated that a new approach using a mathematical method (called Gaussian Process in combination with autoregressive modelling) was better at predicting influenza rates in comparison to existing methods. Further to this work, i-sense researchers sought to address a key challenge in the estimation of ILI rates from Google search data: reducing spurious features of the text analysed to infer ILI, to improve reliability of the prediction. In this work published in 2017, researchers used Twitter data and neural word embeddings, a machine learning technique, to determine the semantic relationship between textual features and ILI[9]. This approach improved search query accuracy by over 28%, ultimately making the models for estimating ILI rates from internet search data more reliable.

New methods for estimating ILI rates in different geographical locations

In order to improve the applicability of the computer models developed in the project, i-sense researchers worked on the problem of training models across different geographical locations and in health systems with varying quality and availability of surveillance systems data. Using the United States and England as case studies, they showed in 2018 that using a multi-task machine learning approach can improve prediction of ILI by nearly 15% in comparison to previously used single-task approaches[10]. In 2019, the researchers proposed a new statistical framework for predicting ILI rates in countries with poor or no surveillance data[11]. To achieve this, they proposed a computer model trained on data from locations in which there is robust syndromic surveillance data. Then, a transfer learning solution was proposed for the computer model to be trained on locations with poor or no syndromic surveillance data, using an unsupervised machine learning technique. This approach delivered a transferable model capable of prediction ILI rates in locations with poor or no syndromic surveillance systems, with significant implications for implementation in low and middle-income countries. The transferable model was tested with data from France, Spain and Australia, showing strong statistical performance.

Identifying disease outbreaks and early indicators of disease risk

In 2015, i-sense researchers worked in collaboration with Microsoft Research to develop algorithms capable of identifying outbreaks of communicable diseases in mass gatherings, such as religious events and festivals, using internet data. Detecting disease outbreaks in mass gatherings can be challenging for traditional surveillance methods, as participants disperse quickly after the event. The researchers used Twitter and Bing search query data related to ten different events. Three different methods were used to compare disease symptom-related words in a 30-day period before and after the events took place. The methods identified

[8] https://www.nature.com/articles/srep12760
[9] https://dl.acm.org/doi/10.1145/3038912.3052622
[10] https://dl.acm.org/doi/10.1145/3178876.3186050
[11] https://dl.acm.org/doi/10.1145/3308558.3313477

statistically significant symptoms in the events, confirming the feasibility of using internet data to identify signs of outbreaks, in particular when combining data sources and methods[12].

i-sense and Microsoft Research also collaborated in a study to identify early indicators of disease risk. Traditional epidemiology methods rely on clinical studies and medical databases, which can be costly and not account for underreported diseases (for example, diseases associated with social stigmas). The researchers proposed a new method to automatically analyse Bing search query data and identify precursors behaviours associated with health events[13]. While establishing direct causal link between online behaviours and health events is not always possible, the new method has the potential to mitigate the effect of underreported diseases and it provides an automated and cost-effective way to identify risk factors. The study revealed both known and new risks associated with health events, representing a significant breakthrough in using internet data to identify risk factors.

The first ever assessment of influenza vaccination using internet data

In 2015, building on initial work conducted at i-sense, Dr Lampos, Professor Cox (i-sense), Dr Yom-Tov (Microsoft Research) and Dr Pebody (PHE) proposed the first ever statistical framework for assessing the effectiveness of influenza vaccination using machine learning techniques to analyse user-generated content in internet platforms Bing and Twitter[14]. In 2013/14, a pilot influenza childhood vaccination program was launched in seven regions of England, but its impact was uncertain due to difficulties in assessing influenza indicators in piloted vs non-piloted locations[15]. To address this, the researchers developed a computer model capable of using Bing searches and Twitter posts to estimate rates of influenza-like illnesses (ILI). This model was used to identify 'control' groups of places similar to the locations in which the vaccination program was piloted. Then, the researchers compared the predicted rates of ILI between the controls groups and the locations where the vaccination program was delivered. This approach can provide advantages to traditional methods for assessing vaccine effectiveness, in particular, in situations with insufficient epidemiological sources of data or where geographical focused signal is required.

Dashboards for improving syndromic surveillance with internet data

In 2018, researchers at i-sense collaborated with Public Health England (PHE) to assess how computer models using internet data for disease surveillance can be improved to be adopted by public health agencies[16]. The researchers analysed two machine learning models trained on ILI rates provided by the Royal College of General Practitioners, with predictions based on Twitter posts and Google search queries. Their findings showed that the model based on Google search queries performed well for predicting the onset, intensity, peak activity, and duration of influenza season. The team concluded that there is substantial potential for such models to add value to existing surveillance systems as a complementary tool and to support public health strategies. Building on this work, Dr Lampos and Professor Cox developed dashboards for daily estimations of influenza rates in England. This online tool, named 'Flu Detector' or 'i-senseFlu', was incorporated into PHE's syndromic surveillance in 2018, becoming the first system of its kind to be adopted by a national health agency.

Outcomes, impacts and unexpected benefits

[12] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4090384/

[13] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4327439/

[14] https://link.springer.com/article/10.1007/s10618-015-0427-9

[15] https://pubmed.ncbi.nlm.nih.gov/24925457/

[16] https://www.nature.com/articles/s41598-018-32029-6

The project on modelling infectious diseases using web search data produced several outcomes with large and significant impact in health systems, in the economy and for interdisciplinary research. An overview of the project's outcomes and impact is provided below.

Influenza vaccination

The assessment of influenza vaccine effectiveness using internet data conducted by i-sense researchers contributed to PHE's decision to introduce a national influenza vaccination program for children. In PHE's own assessment, childhood influenza vaccination reduces influenza prevalence in the general population by 20%. By supporting PHE's assessment to launch the vaccination programme, the project has delivered significant health and economic impact. The impact of seasonal influenza is associated with a loss to the UK's economy of £644 million (almost 0.05% of GDP) and 4.8 million lost working days. In addition, the NHS is impacted by an average of 5,000 excess absent staff every month and longer A&E waiting times[17].

Informing decision-making for influenza and COVID-19 national policies

The i-sense project's flu detector was included in PHE's weekly influenza reports. The tool detected the onset of influenza season in 2019 earlier than the gold-standard sentinel networks of GPs[18], which contributed to national decisions around antiviral prescription and showcased the power of using artificial intelligence approaches in digital epidemiology.

During the COVID-19 pandemic, researchers at i-sense worked to adapt the technologies developed to support the UK's response to the outbreak[19]. PHE requested i-sense to develop a model to estimate the prevalence of COVID-19, based on previous work on ILI rates described in the research outputs section. The model developed was included in PHE weekly COVID-19 surveillance reports[20], providing an essential input for epidemiological understanding COVID-19 measures, such as national lockdown. The model provided an accurate forecast of regional infections surges 7 to 10 days before case counts[21]. PHE representatives highlighted how the data influenced national level policies and decision-making, shaping response to the COVID-19 pandemic[22]. In addition, i-sense researchers and project partner Microsoft Research provided an assessment of COVID-19 regional prevalence in England, which helped PHE teams with detecting clusters of disease prevalence. According to a consultant epidemiologist at PHE:

> *"This [i-sense] system…provided an essential surveillance system for early indication of changes in COVID-19 activity. This was particularly notable at the start of the pandemic when the covid-19 Google search surveillance system gave us one of our earliest indicators that the national lockdown was successfully reducing COVID-19 activity"*[23].

Research excellence and further funding

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[17] https://www.rand.org/pubs/research_reports/RRA2165-1.html
[18] https://www.i-sense.org.uk/sites/default/files/37180.01_ISENSE_FORWEB_LOW.pdf
[19] https://www.i-sense.org.uk/covid-19/covid-19-response
[20] https://www.gov.uk/government/news/flu-and-covid-19-surveillance-report-published
[21] https://www.nature.com/articles/s41598-022-06340-2
[22] https://www.ukri.org/news/report-reveals-impact-of-covid-19-research-and-innovation-funding/
[23] UCL REF Impact Case Study

The publications produced as a result of the project collectively account for a large number of citations (over 320 citations). The publications were cited by articles spanning a wide range of countries and a diverse range of disciplines, showcasing the project's impact. The research excellence of the project is also evidenced by comments made by Google's Engineering Director:

'i-sense, in part, led to the Google Flu Trends team moving from the US to London, the creation of new jobs in London, and influencing Google policy to open access to search data for academics and Public Health England.'[24]

IRC i-sense attracted further funding as a result of the project's success in estimating infectious diseases using internet data. This included EPSRC COVID-19 award (£500,000) and Google grant (USD 200,000) to work on tools for COVID-19 surveillance. In addition, project partner Microsoft Research awarded a PhD scholarship (£37,000) to one of Professor Cox's students for a separate project. The collaboration with Microsoft Research also opened internship opportunities for University College London PhD students in UK, USA and Israel.

Contribution of IRC investment

The IRC i-sense brought together epidemiologists and other health experts through workshops, lectures and other activities. These networks of experts provided key inputs for researchers at i-sense to understand the wider context of the project and its potential applicability in different areas. As a result, i-sense was able to tackle research beyond the project's main objectives, such as assessing the effectiveness of childhood influenza vaccination. Without the IRC, i-sense researchers would not have benefited from these networks and thus they would have been unable to understand the epidemiological challenges and the full potential of the computer models in different settings and scenarios. In addition, researchers highlighted the IRC management team was essential in promoting regular engagement between partners, which enable learning across organisations and facilitated collaboration. The long-term funding of IRC was also a key enabling factor to ensure research progress within the project, as it provided job stability to the researchers involved in the project.

Key learnings

- The IRC i-sense network enabled the exploration of new research avenues within the project.
- The proximity to a wide range of experts and collaboration with project partners Microsoft and Public Health England enabled direct health and economic impact by ensuring applicability of the research outputs to surveillance systems.
- The IRC programme funding provides career stability and leadership to enable long-term impact of the research outputs.

[24] https://www.i-sense.org.uk/sites/default/files/37180.01_ISENSE_FORWEB_LOW.pdf

2.2 Ultra-Sensitive Enhanced NanoSensing of Anti-Microbial Resistance

Summary

Rapid and early identification of antimicrobial resistant (AMR) infections in patients allows for quick medical treatment, which reduces the fatality rate and healthcare costs. To select the appropriate treatment, it is important to identify not only which bacterial species is present in a patient sample, but also to which antibiotics the bacteria are resistant. However, few accurate technologies capable of rapidly identifying AMR strains are currently available.

In 2018, the u-Sense project, funded through a Next Step Plus award to IRC i-sense, set out to develop diagnostic tests capable of detecting bacteria as well as antibiotic resistance. u-Sense completed in April 2024. Researchers used an ultra-sensitive detection method, Surface-Enhanced Raman Scattering (SERS), to simultaneously detect two protein biomarkers for Clostridium difficile, the main cause of infectious diarrhoea in hospitalised patients. This test is now ready for clinical evaluation.

In addition to the above, the project collaborators combined several novel approaches to target identification, amplification and signal detection, and are developing a test capable of detecting five resistance genes to the last-line antibiotic carbapenem. Results from this work are expected to be published in the near future. In addition, u-Sense collaborators at Imperial College London are progressing a 'simplified', affordable SERS detection system that can be used at the point of care.

Introduction

Antimicrobial resistance (AMR) is escalating globally and represents a pressing worldwide concern affecting public health and food security.[25,26] It is mainly caused by the excessive and inadequate use of antibiotics, which increases the prevalence of resistance genes in bacterial strains, leading to treatment failure and a reduction in the number of antibiotic treatment options available. AMR thus leads to longer hospital stays, higher medical costs and increased mortality. Globally, bacterial AMR was estimated to account for between 3.62–6.57 million deaths in 2019.[27] In Europe, the burden of five types of infection with antibiotic-resistant bacteria has been estimated at 170 disability-adjusted life-years (DALYs) per 100,000 people in 2015, similar to the cumulative burden of influenza, tuberculosis, and HIV.[28] A report published by the UK government highlighted that in the absence of action to reduce AMR, ten million lives a year and a cumulative US$100 trillion of economic output are at risk by 2050.[29]

Rapid and early identification of AMR infections in patients allows for quick medical treatment, which reduces the fatality rate and healthcare costs (and thus the impact of AMR).[30] To select the appropriate treatment, it is important to identify not only which bacterial species is present

[25] World Health Organization (2020) Antibiotic resistance. https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance

[26] Hassanain, WA; Johnson, CL et al (2022) Recent advances in antibiotic resistance diagnosis using SERS: focus on the "Big 5" challenges. Analyst 147: 4674

[27] Murray, C. J. et al (2022) Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 399, 629–655

[28] Cassini A; Högberg LD; Plachouras D et al (2019) Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 19(1):56-66. doi: 10.1016/S1473-3099(18)30605-4.

[29] O'Neill, J. (2016) Tackling drug-resistant infections globally: final report and recommendations. APO20 https://apo.org.au/node/63983

[30] Hassanain, WA; Johnson, CL et al (2022) Recent advances in antibiotic resistance diagnosis using SERS: focus on the "Big 5" challenges. Analyst 147: 4674

in a patient sample, but also to which antibiotics the bacteria are resistant.[31] In addition, techniques that can evaluate the effect of antibiotics at different dosages and the level of clinical response at different stages of the treatment protocol are important to understand and improve therapeutic approaches. However, few accurate technologies capable of rapidly identifying AMR strains are currently available. Development of such point-of-care diagnostic tests is complicated by the fact that bacterial resistance can result from a variety of underlying mechanisms. Current detection approaches each have drawbacks, such as long time-to-result, high cost, limited sensitivity and reliability, or the need for extensive sample preparation.

The u-Sense project set out to tackle the need for a point-of-care diagnostic test for bacteria and antibiotic resistance by integrating a range of novel approaches and expertise from across disciplines, e.g. bioinformatics, biomedical engineering, and analytical chemistry.

Project/activity

The u-Sense project set out in 2018 involving a multidisciplinary collaboration between several i-sense partners, at Newcastle University (Professor Anil Wipat and Dr Neil Keegan) and Imperial College London (Professor Molly Stevens), and a new partner at the University of Strathclyde (Professor Duncan Graham and Professor Karen Faulds).[32] Led by Dr Neil Keegan, University of Newcastle, u-Sense completed in April 2024.

During the first five years of i-sense, researchers at Newcastle University had developed a novel bioinformatics system, termed IDRIS. The system comprises a database of all bacterial sequences and annotations deposited in RefSeq (a public reference sequence collection) which it can query for protein biomarkers.[33] IDRIS was hence available for u-Sense to modify and search for DNA based molecular diagnostic targets. However, to enable translation of the technology and yield direct benefit for patients, a key need remained: the development of a sensitive, reliable method for detection and evaluation of bacteria in clinical samples that would allow assessment of multiple biomarkers at the same time, i.e. on a single test strip (multiplexed detection).[34] A novel sensitive detection technique, Surface-Enhanced Raman Scattering (SERS), presented a promising candidate for such a diagnostic.

As part of u-Sense, a multidisciplinary team of i-Sense collaborators with expertise in bioinformatics, molecular biology/biosensors, nanomaterials and device engineering came together with an external team of researchers from the University of Strathclyde with expertise in SERS.[35] By combining SERS with the tools and expertise developed as part of i-Sense, the u-Sense project aimed to produce a rapid, easy-to-use and cost-effective diagnostic system for the detection of AMR sequences suitable for use across a variety of settings.

Findings, Outcomes and Impacts

The u-Sense project combines four key steps:

1) Identification of nucleic acid sequences indicative of AMR,

2) Development of quick, reliable and low-cost diagnostic tests based on the identified sequences,

3) Use of an ultra-sensitive and selective detection method, SERS, and

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[31] https://gtr.ukri.org/projects?ref=EP%2FR018391%2F1#/tabOverview Accessed 27 Sep 2023

[32] https://gtr.ukri.org/projects?ref=EP%2FR018391%2F1#/tabOverview Accessed 27 Sep 2023

[33] https://www.iscb.org/cms_addon/conferences/ismb2016/posterlist.php?cat=A Accessed 27 Sep 2023

[34] Hassanain, WA; Johnson, CL et al (2022) Recent advances in antibiotic resistance diagnosis using SERS: focus on the "Big 5" challenges. Analyst 147: 4674

[35] https://gtr.ukri.org/projects?ref=EP%2FR018391%2F1#/tabOverview Accessed 27 Sep 2023

4) Fabrication of a portable, affordable prototype for detection by SERS.

At the time of the evaluation, the u-Sense project was still on-going (end date: April 2024), each of the key technical steps have achieved progress.

1) Identification of nucleic acid sequences indicative of AMR

Antibiotic resistance is encoded within the bacterial genome and can be transferred between bacteria through mobile genetic elements. The original IDRIS system allowed the selection of antigenic epitopes (areas of molecules which can be recognised and bound by an antibody) to a given strain or species. The u-Sense project extended IDRIS to mine genomic sequence databases for genetic features that encode antibiotic resistance traits, to create a database of genetic information of AMR bacteria.[36]

As the project progressed, the team decided to focus on a target assay for resistance to the last-line antibiotic carbapenem, which currently is among the five greatest AMR challenges for the European population based on the estimated burden of disease.[37] Carbapenem resistance genes enable bacteria to produce enzymes, called carbapenemases, that inactivate carbapenem and stops the antibiotic from working.

The u-Sense team used a database of bacterial sequences (the Comprehensive Antimicrobial Resistance database) and sequence alignments to help design a test that targets the five most common bacterial genes conferring carbapenem resistance.[38] In addition, the bioinformatics team used machine learning models to predict new variants of beta-lactamases, a broader class of antibiotics, that would likely arise in future evolutionary events. This early-stage work was based on a previous attempt to 'forward evolve' a protein family and is ongoing. The approach would be very useful to predict how resistance genes are likely to evolve and how diagnostic tests would need to adapt to the changes in genetic sequence.[39]

The bioinformatics work is led by Professor Anil Wipat at the School of Computing Sciences, Newcastle University.

2) Development of quick, reliable and low-cost diagnostic tests

Using the sequences identified in point 1 above, u-Sense is currently developing a carbapanemase multiplex test, capable of detecting the five most common resistance genes in patient samples.[40] The team is employing a next generation molecular technique, Recombinase Polymerase Amplification (RPA), that is fast, sensitive and can operate at room temperature (but is optimal at 37C degrees). [41] It can hence be used in field settings. Such a test would allow clinicians to identify very quickly if - and which type of - carbapenem resistance is present in a patient sample, providing the opportunity to supplement antibiotic

[36] https://gtr.ukri.org/projects?ref=EP%2FR018391%2F1#/tabOverview Accessed 27 Sep 2023

[37] Hassanain, WA; Johnson, CL et al (2022) Recent advances in antibiotic resistance diagnosis using SERS: focus on the "Big 5" challenges. Analyst 147: 4674

[38] Dr Neil Keegan, Newcastle University. Personal communication, 11 Oct 2023

[39] Prof Anil Wipat, Newcastle University. Personal communication, 11 Oct 2023

[40] Dr Neil Keegan, Newcastle University. Personal communication, 11 Oct 2023

[41] https://gtr.ukri.org/projects?ref=EP%2FR018391%2F1#/tabOverview Accessed 27 Sep 2023

treatment with the correct inhibitors of the resistance mechanism. The results from this work are expected to be published in the near future.

This work is led by Dr Neil Keegan, Diagnostic and Therapeutic Technologies Research Group at Newcastle University.

3) Use of an ultra-sensitive and selective detection method

SERS is a novel method that is extremely sensitive and allows detection of multiple targets simultaneously. Prior to u-Sense, work within i-Sense had identified a unique biomarker on the surface of the *Clostridium difficile* bacterium, the main cause of infectious diarrhoea in hospitalised patients.[42] However, 'conventional' methods to detect these biomarkers on lateral flow tests lacked sensitivity.[43]

As part of u-Sense, the groups at Newcastle and Strathclyde Universities set out to test and optimise the use of SERS in a lateral flow test for *C. difficile* infection. This requires the detection of a marker specific for the surface of *C. difficile* to identify and quantify the level of bacteria present, and of a toxin (protein toxin B) to distinguish between *C. difficile* colonisation and true infection. Exploiting the high sensitivity of SERS, the team was able to simultaneously detect both protein biomarkers on a single test strip and quantify the level of protein present, within 20 minutes, using a handheld Raman spectrometer (rather than a benchtop machine).[44] The researchers hence demonstrated that the SERS diagnostic platform has the capability to detect protein biomarkers in a highly selective, sensitive, fast and cost-effective manner, requiring only minimal sample pre-treatment steps and simple manual operation.

Building on this work, the team are currently using the SERS diagnostics platform as the readout for the RPA diagnostic that detects multiple DNA sequences, targeting the five common carbapenem resistance genes.[45] The results from this work are close to being published.

The development of SERS for use in AMR diagnostics is led by Professor Duncan Graham at the Pure and Applied Chemistry Department, University of Strathclyde.

4) Fabrication of a portable SERS detection prototype

Portable readout equipment for detection by SERS is already available on the commercial market, but it has broad functionality to accommodate a variety of use cases and hence added expense. The u-Sense project set out to design a miniaturised, cost-effective spectrometer device, specialised for use on diagnostic tests.[46] This 'simplified' SERS detection system is cheaper, scalable, and suitable for use outside of the laboratory, for example, in the hospital or the GP surgery.

The u-Sense team developed an initial large test setup for benchmarking which was used to record SERS spectra of selected SERS reporters (dyes) on gold-coated nanoneedles.[47] Based on the success of this setup, a working, affordable, miniaturised alpha prototype and

[42] Lawry, BM; Johnson, CL et al (2028) Species-specific detection of C. difficile using targeted antibody design. Anal. Chem. 90: 13475-13482

[43] https://theanalyticalscientist.com/fields-applications/c-difficile-but-not-impossible Accessed 27 Sep 2023

[44] Hassanain, WA; Spoors, J; Johnson, CL et al (2021) Rapid ultra-sensitive diagnosis of clostridium difficile infection using a SERS-based lateral flow assay. Analyst 146:4495. DOI: 10.1039/d1an00726b

[45] Prof Duncan Graham, University of Strathclyde; Dr Neil Keegan, Newcastle University. Personal communication, 10 Oct 2023

[46] https://gtr.ukri.org/projects?ref=EP%2FR018391%2F1#/tabOverview Accessed 27 Sep 2023

[47] Prof Molly Stevens, Imperial College London. Personal communication, 11 Oct 2023

associated software (*in-house* developed graphical user interface) were built and tested using high Raman scattering reference samples. While working, the evaluation showed some potential pitfalls within the design that would prevent its use in a clinical test. As a result, an improved beta prototype was designed. The development of the beta prototype is still in progress.

In parallel, the group also worked on developing algorithms to process SERS data aiming at increasing the sensitivity and specificity of the diagnostic test. The purpose of the algorithm development was to mitigate the reduced signal-to-noise ratio, which is an inherent result of miniaturisation. The algorithm development is ongoing.

The development of the handheld SERS detection device is led by Professor Molly Stevens, Institute of Biomedical Engineering at Imperial College London.

While still ongoing, u-Sense is starting to yield outcomes. The collaborations formed through u-Sense (and the wider i-sense consortium) were highlighted as a 'real lasting success': "*Through u-Sense, people really came together with a common goal of what they wanted to do, a common goal of what they wanted to achieve. It was a good first step to building relationships with each other.*"[48] These collaborations are anticipated to go beyond the lifetime of the project. For example, groups at Newcastle and Strathclyde are considering further joint grants, building on the collaboration and results of u-Sense.

Contribution of IRC investment

The IRCs facilitate the building of strong interdisciplinary teams, with each group contributing essential expertise to advance the technology under development. This integration of teams from across disciplines was highlighted as a key strength for the u-Sense project: "*It's the culmination, in a truly interdisciplinary way, of how we bring all those components together. None of us could do it by ourselves.*"[49]

As a Next Step Plus award, u-Sense enabled the i-sense research groups to build on technology they had developed under i-sense, and include an additional partner with crucial expertise in a key method to progress the technology further: "*The initial work [as part of i-Sense] was great. But building on it and being allowed to bring in the right partners to meet the required sensitivity is something that I think the EPSRC got really right with this grant. It was fundamental to us taking a good piece of research and expanding the reach of the impact through additional capability.*"[50]

Challenges

The emergence of Covid was a challenge for the u-Sense project. With experimental work coming to a halt during the lockdown period, the project timeline was delayed, which caused several issues especially around commercialisation.

- While research grants were extended to accommodate the delay caused by the COVID-19 pandemic, patent office timelines remained unchanged. The team had filed a UK patent application for the *C. difficile* SERS lateral flow assay in May 2018[51], which was progressed to a PCT (international) patent application in 2019[52]. During this time, the test was found to not yet be sufficiently sensitive for commercialisation.[53] By 2021,

[48] Dr Neil Keegan, Newcastle University. Personal communication, 21 Sep 2023

[49] Dr Neil Keegan, Newcastle University. Personal communication, 21 Sep 2023

[50] Dr Neil Keegan, Newcastle University. Personal communication, 21 Sep 2023

[51] 1807367.6: C.Difficile biomarkers and antibodies

[52] GB2019/051240

[53] Dr Neil Keegan, Newcastle University. Personal communication, 21 Sep 2023

the team had managed to improve the technology to the desired sensitivity and published the results.[54] However, this data, which would have justified entering the national phase for the patent, came too late: the application had been discontinued in 2020.

- COVID-19 made accessing the necessary clinical samples challenging and the decision was taken to publish the results of the *C. difficile* diagnostic work, rather than wait to gain the data with clinical samples which would have been the basis of a patent filing. This has resulted in rapid sharing of this capability and the commercial opportunity for this technology remains open for exploitation.
- The COVID-19 pandemic also caused a significant change in u-Sense engagement with industrial partners, with the private sector having to reprioritise their own business activities to manage the consequences. Business engagement has taken time to be restored to pre-COVID-19 levels, resulting in a slowing down of possible partnerships and commercialisation for u-Sense.

Next steps

Several publications are currently in preparation and are expected to be submitted in the short-term.[55] In addition, the researchers are exploring applications for funding to maintain the momentum created by this collaborative research programme.

The research focussing on detection of *C. difficile* biomarkers (protein) and carbapenemase biomarkers (DNA) showed that incorporating SERS into a diagnostic platform is suitable for rapid, ultra-sensitive detection in point-of-care settings.[56] The next step is an evaluation of the *C. difficile* test's accuracy when used with clinical samples. The team is currently in discussions with clinical microbiologists at the Royal Bolton Hospital on how the *C.difficile* test could best be implemented in the clinical pathway, opening the door for clinical assessment.[57] Similarly, the researchers are consulting with clinical microbiologists at The Newcastle Upon Tyne Hospitals NHS Foundation Trust, on how the carbapenem resistance test could be implemented in the clinical pathway, bringing the diagnostic one step closer to use for patient benefit.[58]

[54] Hassanain, WA; Spoors, J; Johnson, CL et al (2021) Rapid ultra-sensitive diagnosis of clostridium difficile infection using a SERS-based lateral flow assay. Analyst 146:4495. DOI: 10.1039/d1an00726b

[55] Dr Neil Keegan, Newcastle University. Personal communication, 21 Sep 2023

[56] Hassanain, WA; Spoors, J; Johnson, CL et al (2021) Rapid ultra-sensitive diagnosis of clostridium difficile infection using a SERS-based lateral flow assay. Analyst 146:4495. DOI: 10.1039/d1an00726b

[57] https://gtr.ukri.org/projects?ref=EP%2FR018391%2F1#/tabOverview Accessed 27 Sep 2023

[58] Dr Neil Keegan, Newcastle University. Personal communication, 21 Sep 2023

2.3 Using nanozymes to achieve ultra-sensitivity in diagnostic tests

Summary

While early detection of infections such as HIV is key to successful treatment, the application of lateral flow immunoassays (LFIAs) in early disease diagnostics is often limited due to insufficient sensitivity and the short time frames available for testing. As a result, current LFIA technology cannot detect the low levels of biomarkers present in the early stages of the disease.

In 2016, a team from IRC i-sense set out to develop a LFIA for ultra-sensitive detection of p24, the viral capsid protein of HIV and the earliest biomarkers of infection. The team developed a LFIA up to 20 times more sensitive than the leading commercial rapid tests for p24, giving a signal that can be detected by the naked eye or a mobile phone. To achieve this, the team incorporated two novel approaches – nanozyme particles to amplify the test signal, and nanobodies to optimise binding of the target molecule at the test line. With mobile device adoption continuing to spread globally, this type of test promises to enable access 'for all', including in otherwise resource-limited settings.

The results of the work were published, and the team has continued to improve the nanozyme platform, achieving promising results for the use of nanozymes in diagnostic tests for biomarkers of both communicable and non-communicable diseases. The work has led to two patent applications (currently pending). A spinout company, Zyme Dx, was created to take the nanozyme diagnostic platform forward into clinical testing and commercialisation. The development work has also received follow-on funding from public and non-profit funders.

Introduction

Lateral flow tests, also called lateral flow immunoassays (LFIAs), are among the most widely used point-of-care (PoC) diagnostic devices to confirm the presence or absence of a target analyte, such as a pathogen or disease biomarker.[59,60] One type of LFIA works by mixing patient samples with nanoparticles bound to antibodies that adhere to a specific target if it is present in the sample. On the diagnostic test device, the antibody-target complex moves via capillary flow past a test line, an area on the test membrane that captures and immobilises the complex. This causes the complex to accumulate and concentrate in a small area, which shows up as a coloured line if the nanoparticle-target complex is present. In some tests, the density of the line can provide an indication of the quantity of target present.

While early detection of infections such as HIV is key to successful treatment, the application of LFIAs in early disease diagnostics is often limited due to insufficient sensitivity and the short time frames of PoC testing.[61,62] As a result, current LFIA technology cannot detect the low levels of biomarkers present in the early stages of disease. However, a test capable of diagnosing HIV earlier would be transformative, e.g., for the diagnosis of infants whose mothers are known to

[59] O'Farrell, B (2009) Evolution in Lateral Flow–Based Immunoassay Systems. In: Wong, R., Tse, H. (eds) Lateral Flow Immunoassay. Humana Press. https://doi.org/10.1007/978-1-59745-240-3_1

[60] Hristov, DR; Rodriquez-Quijada, C et al (2019) Designing Paper-Based Immunoassays for Biomedical Applications. Sensors (Basel) 19: 554

[61] May, MT (2016) Better to Know: the importance of early HIV diagnosis. The Lancet Public Health 2: E6-E7

[62] Loynachan, CN; Thomas, MR et al (2018) Platinum Nanocatalyst Amplification: Redefining the Gold Standard for Lateral Flow Immunoassays with Ultrabroad Dynamic Range. ACS Nano 2018, 12, 1, 279–288

be HIV positive, and to ensure early intervention with antiretroviral therapies where they have the potential to be most beneficial. While diagnostic platforms with higher sensitivity than current LFIAs are available, these use techniques that are relatively resource demanding, require technical expertise to run and interpret, and utilise equipment that is unsuitable for or unavailable in resource-limited settings.

A different approach to boosting LFIA sensitivity is to amplify the colour signal, making it possible to detect even low levels of the target molecule. Nanozymes are a technology that can achieve this amplification.[63] Nanozymes are inorganic nanomaterials which catalyse chemical reactions that mimic the activity of natural enzymes, in a highly efficient manner. In addition, they are extraordinarily stable in harsh environments, for example in high temperatures, which makes them suitable for use in the field. Nanozymes are thus promising candidates to boost the sensitivity of LFIAs.

Project and project findings

In 2016, a team from i-Sense set out to explore the use of nanozymes in LFIAs for ultra-sensitive detection of p24, the viral capsid protein of HIV and the earliest biomarkers of infection.[64] The project brought together two groups at Imperial College London, one led by Professor Molly Stevens and one led by Professor Rachel McKendry, in collaboration with researchers at the London Centre for Nanotechnology and the Department of Chemistry, University College London. I-Sense facilitated this collaboration and the team met monthly to discuss results and share ideas. The results of the work were published in ACS Nano in 2018.

Together, the i-Sense team developed a lateral flow test that incorporated nanozyme technology to boost the colour signal at the test line, sufficiently strong to be detected by the naked eye or a mobile phone. To achieve this, the team incorporated two novel approaches – nanozyme particles to amplify the test signal, and nanobodies optimise binding of the target molecule at the test line.

Researchers in the group led by Professor Stevens worked on the nanozyme signal amplification. The team optimised the preparation and particle size of a platinum nanocatalyst (PtNC) for use in LFIAs and tested its performance with plasma samples containing p24. At high p24 concentrations, the LFIA showed a clear black line visible with the naked eye where the PtNC accumulated (due to the absorbance of the nanoparticles). At lower concentrations, the target signal was amplified by taking advantage of the PtNC's catalytic activity: after addition of hydrogen peroxide and a colourless dye, the PtNCs-target complex catalyses oxidation of the dye, resulting in the deposition of a coloured product. Through this approach, the team was able to detect even low levels of p24 by naked eye in under 20 minutes, with the test being up to 20 times more sensitive than the leading commercial rapid tests for p24. A further advantage of the PtNC approach was that the two-step detection regimen, i.e. without and with hydrogen peroxide addition, allowed a simple assessment of the quantity of p24 present in the sample.

Researchers in the group led by Professor McKendry developed a nanobody for rapid capture target complexes at the test line. Nanobodies are antibody fragments that are much smaller and more stable than conventional antibodies but are still highly selective for their targets.

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[63] Shamsabadi, A; Haghighi, T et al (2023) The Nanozyme Revolution: Enhancing the Performance of Medical Biosensing Platforms. Adv. Mater. 2300184. https://doi.org/10.1002/adma.202300184

[64] Loynachan, CN; Thomas, MR et al (2018) Platinum Nanocatalyst Amplification: Redefining the Gold Standard for Lateral Flow Immunoassays with Ultrabroad Dynamic Range. ACS Nano 2018, 12, 1, 279–288

Nanobodies also have the advantage that they can be efficiently mass-produced in bacteria, facilitating at-scale manufacture. The team modified a p24-specific nanobody in such a way that it could bind to p24 on one side of the molecule and to a binding system that could rapidly 'grab' onto the LFIA test line on the opposite side. This spatial separation of binding sites avoided interference despite the small size of the nanobody, and resulted in fast and efficient binding of the PtNCs-target complex as it is pulled past the test line by capillary action.

The research hence resulted in an easy-to-use highly sensitive LFIA for p24 with a colour output that can be read by the naked-eye or by mobile phone camera and provides a semi-quantitative assessment of the level of p24 in the sample. With mobile device adoption continuing to spread globally, including in otherwise resource-limited settings, this type of test promises to enable access 'for all', eliminating the need for costly laboratory equipment and extensive training to interpret test results.

Outcomes and Impacts

Since the successful production of the ultra-sensitive p24 LFIA, the team has continued to improve the nanozyme platform, for example by adjusting the test to make it more affordable and by simplifying the test device to minimise user steps.[65] The researchers have also achieved promising results for the use of nanozymes in diagnostic tests that detect or monitor other biomarkers, for example enzyme activity or the presence of nucleic acid biomarkers in non-communicable diseases such as cancer and cardiovascular disease.[66,67] One of these projects was supported by an i-Sense mobility grant, which funded a postdoctoral research associate to work at the laboratory of a collaborator at the Massachusetts Institute of Technology (MIT) in Boston. Using a CRISPR technology platform, this work promises to overcome the limited sensitivity of current LFIAs in detecting low-level nucleic acid biomarkers, without the need for technically-complex preamplification of the target.

As a result of the research to which i-Sense contributed, the group filed two patent applications (pending).[68] In August 2023, a company, Zyme DX, was spun out of Imperial College to further develop the technology for commercialisation.[69,70] The company recently recruited a CEO with experience in the diagnostic device industry and is currently looking to secure private investment. The development work has also received follow-on funding from several UK public and non-profit funders. The National Institute for Health and Care Research (NIHR) is providing the company with £150,000 through its Invention for Innovation (i4) programme to gather additional data for its business case and tailor the device for use in an NHS setting.[71] Grants from non-profit organisations are supporting development of the technology for use across a range of disease indications including cardiovascular disease, cancer, and other infectious

[65] Dr Leah Frenette, personal communication. 26 Sep 2023

[66] Loynachan, CN; Soleimanym AP et al (2019) Renal clearable catalytic gold nanoclusters for in vivo disease monitoring. Nat. Nanotechnol. 14, 883–890

[67] Broto, M; Kaminski, MM et al (2022) Nanozyme-catalysed CRISPR assay for preamplification-free detection of non-coding RNAs. Nat. Nanotechnol. 17: 1120-1126

[68] Patents pending, 2219191.0/GB/PRV and PCT/EP2022/070866. Dr Leah Frenette, personal communication. 18 Oct 2023

[69] https://ibkrcampus.com/traders-insight/securities/macro/diagnostics-for-all/ Accessed 3 Oct 23

[70] Dr Leah Frenette, personal communication. 26 Sep 2023

[71] https://fundingawards.nihr.ac.uk/award/NIHR205784 Accessed 1 Dec 2023

diseases.[72] The follow-on funding also includes £454,973 from EIT Health (2020)[73] and a grant of approximately £3 million from a large biopharma company supporting Imperial College London.

Contribution of IRC investment

The IRC approach provided the framework for a successful collaboration between research groups at different universities, and a broader research community in the diagnostic technology space, facilitating progress in developing the nanozyme technology. Researchers working under the "Test" stream of i-Sense met up monthly to exchange ideas. While different groups were pursuing different technological approaches, they encountered common challenges, such as how to reduce background signal, which they were able to discuss jointly. Thus, being part of i-Sense helped researchers to brainstorm solutions.

In addition, through annual meetings, i-Sense brought together key opinion leaders in the field giving researchers a clear idea of the patient/user needs and health system requirements before beginning to solve the technical problems. It also allowed researchers to consider other avenues of impact outside their area of expertise, such as integrating the LFIAs into mobile health systems.

The long-term funding of the IRC programme provided the time to see the technical development from concept to early prototype while nurturing the personal development of the key researchers.

Next steps

Zyme DX, the spin-out company stemming from the nanozymes work, is planning to take the nanozyme diagnostic platform forward into clinical testing, at which point there is potential to involve larger industry partners. Ultimately, the technology may lead to simple, rapid, ultra-sensitive and affordable diagnostic tests targeted at different diseases that can be used in the clinic, at the GP surgery, or even at home.

[72] Dr Leah Frenette, personal communication. 26 Sep 2023

[73] https://www.i-sense.org.uk/news/i-sense-research-receive-funding-eit-covid-19-rapid-response-call Accessed 18 Oct 2023

2.4 m-Africa: mobile phone-connected diagnostic for HIV prevention and management

Summary

Closing the gap between HIV testing and treatment is essential to reduce HIV incidence, transmission and mortality, and to ease the burden on primary healthcare. Mobile health (mHealth) approaches have the potential to widen access to HIV testing and improve access to care. Combining HIV disease diagnostics with mobile-phone technologies that link to care providers would enable individuals to self-test at home, report the results to healthcare professionals and access care if needed.

IRC i-sense researchers in collaboration with the Africa Health Research Institute (AHRI) in South Africa developed a mHealth app that uses a machine learning model to interpret the results of commercially available lateral flow tests for HIV. The app can improve the accuracy of HIV lateral flow test interpretation compared to visual inspection and thus contribute to reducing the number of false positive/negative test results. This in turn has the potential to support field worker training, strengthening healthcare system efficiency and improving patient outcomes. This project produced key outputs for the use of mHealth and machine learning for diagnostic analysis beyond testing for HIV:

- The machine learning model developed was used by researchers at Imperial College London to analyse over 500,000 COVID-19 lateral flow tests. The findings support the use of machine learning-enabled automated reading of at-home lateral flow tests to improve the accuracy of population-level community surveillance.
- While the mHealth app developed could not be implemented across South Africa due to limitations in the healthcare system, AHRI researchers are planning to apply the machine learning image data collection approach to patient immunisation cards and paper-based medical records to automatically create electronic patient records.

Introduction

Human immunodeficiency virus (HIV), the virus that causes AIDS (acquired immunodeficiency syndrome), is one of the world's most serious infectious disease threats. In 2022, an estimated 39 million people globally were living with HIV, 1.3 million were newly infected with the virus and over 600,000 died, despite advances in HIV treatment, prevention and care scale up.[74]

South Africa has the highest rate of HIV infection, with over 8 million people living with HIV[75]. Within South Africa, the province of KwaZulu-Natal (KZN) is disproportionately affected, with nearly 1 in 3 people living with HIV, and only half of those that have been diagnosed are receiving care[76]. Factors contributing to the high infection rate include limited uptake of testing due to the stigma associated with HIV[77]. As a result, people are unaware of their infection status, which increases the potential for disease transmission. In addition, limited access to HIV clinics and capacity of the healthcare systems impedes care delivery.

[74] UNAIDS Global HIV & AIDS statistics — Fact sheet. https://www.unaids.org/en/resources/fact-sheet

[75] Department of statistic South Africa. Mid-term population estimates (2020). Available here.

[76] Vandormael A, Bärnighausen T, Herbeck J, et al. Longitudinal Trends in the Prevalence of Detectable HIV Viremia: Population-Based Evidence From Rural KwaZulu-Natal, South Africa. *Clin Infect Dis*. 2018;66(8):1254-1260.

[77] Wood, C., S., Thomas, M. R., Budd, J., Mashamba-Thompson, T., P., Herbst, K., Pillay, D., Peeling, R. W., Johnson, A., M., McKendry, R. A., and Stevens, M. M. 'Taking connected mobile-health diagnostics of infectious diseases to the field' *Nature* (2019).

Closing the gap between HIV testing, treatment and prevention is essential to reduce HIV incidence, transmission and mortality, and to ease the burden on primary health care. Moreover, commonly used lateral flow tests are typically read by eye, risking incorrect interpretation and data loss. Mobile health (mHealth) approaches have the potential to decentralise access to healthcare, offering individuals a more convenient and efficient means of diagnosis and care delivery outside of the primary healthcare setting[77]. Combining HIV disease diagnostics with mobile-phone technologies that link to care providers would enable individuals to self-test at home, report the results to healthcare professionals and access care if needed. Furthermore, the reporting of test results provides a mechanism to monitor and manage infectious disease outbreaks. Although South Africa has made progress in implementing mHealth approaches, more research is needed to develop mHealth technologies and understand the feasibility and acceptability of introducing them into current healthcare pathways.

Project background

In 2017, i-sense researchers secured follow-on funding from the Medical Research Council Global Challenges Research Fund to adapt the mHealth tools and protocols developed in i-sense to inform the development of a mobile phone-assisted diagnostic test for HIV in South Africa[78]. The m-Africa project was a two-year collaboration led by Professor Rachel McKendry at University College London (UCL) and Professor Deenan Pillay at the Africa Health Research Institute (AHRI). Ultimately, the m-Africa project aimed to build a mobile phone-assisted HIV diagnostic test that enables individuals to self-test at home or in the local community and – if needed – receive medical care. The ability to self-test was envisioned to widen access to HIV testing and improve access to care.

Findings, outcomes and impact

Together, the i-sense and AHRI teams developed a mobile app and a machine learning model to capture and interpret the results of commercially available lateral flow tests for HIV. To achieve this, more than 60 field workers at AHRI collected over 11,000 images of HIV lateral low diagnostic tests taken as part of routine surveillance for communities in rural KZN, using a new co-created mHealth protocol. These images formed the largest real-world image library of lateral flow tests at that time, and were used to train a deep learning algorithm to classify the images as either positive or negative for HIV.

The teams then tested the app in a pilot field study. In this study, five participants of varying experience (ranging from nurses to newly trained community health workers) used the mobile app to record their interpretation of 40 HIV test results, and to capture a picture of the tests to be read automatically by the machine learning classifier. The pilot demonstrated that the machine learning classifier was able to reduce errors in reading the test images: It correctly interpreted images with a 98.9% accuracy overall, compared to a 92.1% accuracy for traditional visual interpretation by study participants. The study also found that all five participants were able to use the app without training, indicating the feasibility and acceptability of this approach. The findings were published in *Nature Medicine*[79].

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[78] UKRI research grant (2017): m-Africa: Building mobile phone-connected diagnostics and online care pathways to support HIV prevention and management in decentralised. Available here.

[79] Turbé, V., Herbst, C., Mngomezulu, T. *et al.* Deep learning of HIV field-based rapid tests. *Nat Med* **27**, 1165–1170 (2021). https://doi.org/10.1038/s41591-021-01384-9

In parallel to developing the machine learning algorithm to interpret the results of HIV lateral flow tests, AHRI researchers collaborated with i-sense to conduct a pilot simulation study involving 30 participants. The aim of this study was to assess the feasibility and acceptability of linking the mobile diagnostic app, called 'Zenzele' (do it yourself in Isi-Zulu), to HIV healthcare support[80]. Note that Zenzele did not use the machine learning algorithm at this stage. The pilot was conducted in a clinic in KZN to simulate the home test environment. The study found that all participants were able to perform the self-test and upload the result for analysis, and that the one participant who tested positive was successfully linked to care. Post-pilot interviews captured participants' experience with self-testing and receiving test results from the device. The findings revealed that participants appreciated the privacy and convenience of the approach. A further qualitative study involving 54 in-depth interviews and nine focus group discussions was conducted with potential users, including end users and health care providers. The objective was to understand whether implementing mobile phone-assisted self-testing and linkage to care for HIV could overcome barriers to current HIV testing and care services[81]. The study found that mobile phone-assisted self-testing and linkage to care for HIV was broadly acceptable to potential users, and highlighted strengths of the home self-test approach, including privacy, convenience, and time-savings.

The m-Africa project showed that an mHealth approach can improve the data capture and accuracy of HIV lateral flow test interpretation and thus contribute to reducing the number of false positive and negative test results. This in turn has the potential to support field worker training, strengthening healthcare system efficiency and improving patient outcomes. The findings lay the foundations for a new paradigm of deep learning–enabled diagnostics in low- and middle-income countries, termed REASSURED diagnostics[82], an acronym for Real-time connectivity, Ease of specimen collection, Affordable, Sensitive, Specific, User-friendly, Rapid, Equipment-free and Deliverable.

After the m-Africa collaborators demonstrated that the machine learning model improved the accuracy of HIV lateral flow test interpretation, the approach was shared with researchers at Imperial College London who applied it to analyse over 500,000 COVID lateral flow tests as part of the REACT study, one of the largest self-testing surveys worldwide[83]. The findings support the use of machine learning-enabled automated reading of at-home lateral flow tests to improve the accuracy of population-level community surveillance.

The i-sense m-Africa research featured in the 100 Days Mission diagnostics implementation report as an exemplar for pandemic preparedness through better data capture from rapid tests[84]. This i-sense research has the potential to be applied to a range of other important diseases, including for malaria, syphilis, tuberculosis, influenza, and non-communicable diseases, and there is growing recognition of the critical importance of data capture from decentralised lateral flow tests and decision support tools for future pandemics.

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[80] Shahmanesh M, Adeagbo O, Herbst C, et al m-Africa: Zenzele, a mobile-phone enabled HIV testing and linkage to care pathway for young people in rural south Africa. Sexually Transmitted Infections 95, A72 (2019).

[81] Adeagbo O, Herbst C, Blandford A, et al. Exploring People's Candidacy for Mobile Health-Supported HIV Testing and Care Services in Rural KwaZulu-Natal, South Africa: Qualitative Study. *J Med Internet Res*. 21:e15681 (2019).

[82] Land, K. J., Boeras, D. I., Chen, X.-S., Ramsay, A. R. & Peeling, R. W. REASSURED diagnostics to inform disease control strategies, strengthen health systems and improve patient outcomes. Nat. Microbiol. 4, 46–54 (2019).

[83] Wong, N. et al. Machine learning to support visual auditing of home-based lateral flow immunoassay self-test results for SARS-CoV-2 antibodies. *Commun. Med.* 2, 78 (2022).

[84] UCL academic advises on global pandemic preparedness report: https://www.ucl.ac.uk/news/2024/jan/ucl-academic-advises-global-pandemic-preparedness-report (2024)

Barriers to implementation

The m-Africa project has demonstrated the potential benefits of the mHealth app. The mHealth technology is still at an early stage and cannot currently be implemented across South Africa. Electronic health record systems to monitor patient outcomes and schedule clinic appointments are under development, and thus it not yet possible to link the mHealth app to healthcare[85]. Moreover, field workers routinely use other types of HIV tests (e.g., blood spot tests) to verify the accuracy of HIV lateral flow tests, therefore as the mHealth app only marginally improves the accuracy of HIV diagnosis, cost-effectiveness studies would be needed before possible implementation[86].

Contribution of IRC investment

The i-sense IRC investment enabled the development of mHealth technology and expertise, which underpinned the securing of a follow-on grant for the m-Africa project to continue the development and gather evidence for how mHealth technology can be implemented in South Africa. The m-Africa project achieved more than what could have been achieved with a standalone grant of £600,000 by leveraging the existing expertise and resources available in i-sense[87]. The AHRI collaborators benefitted from input from i-sense investigators, as part of regular project meetings as well as the wider i-sense bi-annual meetings. In addition, i-sense researchers visited the AHRI to gain a deeper understanding of the local context and tailor the development of the technology. These regular exchanges were particularly beneficial for researchers at the AHRI, providing them with exposure to an interdisciplinary research environment and the opportunity to explore new avenues of research: "Seeing the [i-sense] model for collaborative work was very impactful. My career has grown by widening the type of work I do in terms of bringing the digital aspect to diagnostics.[88]"

Next steps

Building on the knowledge and expertise gained from the collaboration with i-sense, AHRI researchers are planning to apply the machine learning image data collection approach to patient immunisation cards and paper-based medical records to automatically create electronic patient records. This work is being supported as part of a £72 million renewal funding grant for the AHRI from the Wellcome Trust[89]. The UCL team have recently secured funding from the Wellcome Trust to explore the application of mHealth approaches to cholera and are beginning a new collaboration with the US regulator, the Food and Drug Administration[90].

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[85] Kobus Herbst, IRC collaborator at AHRI, Personal communication, 14 November 2023

[86] Kobus Herbst, IRC collaborator at AHRI, Personal communication, 14 November 2023

[87] Maryam Shahmanesh, IRC collaborator at AHRI, Personal communication, 20 October 2023

[88] Maryam Shahmanesh, IRC collaborator at AHRI, Personal communication, 20 October 2023

[89] https://www.ahri.org/africa-health-research-institute-secures-r1-6-billion-in-funding-to-respond-to-urgent-health-challenges/

[90] Rachel McKendry, IRC lead at UCL, Personal communication, 20 October 2023

2.5 Spinout Singular Photonics: ultra-fast image sensors

Summary

Fast and accurate point-of-care diagnostics (POC) play a crucial role in intensive care units as they can detect early complications and thus improve success of interventions. Microendoscopy may be used as a POC for examining lung tissue with real-time video to support surgery and other urgent interventions in critically ill ventilated patients. However, there are several challenges to using pulmonary microendoscopy, including low image quality and harmful side effects.

In 2013, IRC Proteus set out to develop a fibre-based optical sensing and imaging platform (FOSIP) to improve POC for lung diseases. FOSIP required researchers to develop new semiconductor technology for imaging sensors capable of improving real-time video image quality. Between 2013 and 2017, new designs and prototypes of optical detectors were developed, achieving significant improvements to imaging resolution. Proteus researchers also developed the digital architecture and custom firmware for integrating the sensors into POC. This work produced highly cited publications in several fields, including electrical engineering and medical optics; it also enabled FOSIP to be tested in ongoing human clinical trials.

The technology underpinning the new imaging sensors was patented and enabled the creation of Singular Photonics, a spinout company that will license the patent and seek to use the technology in other medical and scientific applications. The company has attracted interest from market leading companies in the field of high-precision instruments for life sciences and it has obtained pre-seed funding to develop new technologies.

Introduction

Intensive care (or critical care) medicine is an area of healthcare specialised in managing patients that are critically ill. In England, the NHS spends approximately £1,700 per day for each bed in intensive care units, with the total annual costs for intensive care accounting for nearly 5% of the entire NHS England budget in 2021[91]. In the UK, respiratory illnesses, such as lung conditions and lung cancer, are one of the leading causes of death and a significant driver of patient admission in intensive care units[92]. The estimated wider societal costs of respiratory diseases in the UK are nearly £10 billion every year[93]. In intensive care units at hospitals, fast and accurate diagnostics are critical for recognising complications and for the success of treatments. Slow or inaccurate diagnostics in intensive care can result in longer stays, higher mortality and, in the case of infections, it can also lead to over-prescription of antibiotics, increasing antimicrobial resistance and patient burden. Point-of-care diagnostics (POC) are tests that enable clinicians to conduct medical diagnostics next or close to patient care. POC are faster than standard diagnostics, which may require the involvement of an external laboratory and take days to weeks for a test result[94]. In addition to faster diagnosis, POCs enable healthcare professionals to monitor disease progression and to adjust therapies if

[91] https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/

[92] https://www.longtermplan.nhs.uk/online-version/chapter-3-further-progress-on-care-quality-and-outcomes/better-care-for-major-health-conditions/respiratory-disease/#ref

[93] https://www.longtermplan.nhs.uk/online-version/chapter-3-further-progress-on-care-quality-and-outcomes/better-care-for-major-health-conditions/respiratory-disease/#ref

[94] https://www.england.nhs.uk/long-read/integrating-in-vitro-point-of-care-diagnostics-guidance-for-urgent-community-response-and-virtual-ward-services

needed, ultimately reducing delays to treatment, length of stay in intensive care units and patient mortality[95].

Pulmonary microendoscopy is a diagnostic based on a camera attached to the tip of a flexible tube which is used to examine lung tissue. In some situations, pulmonary microendoscopy is used as a POC, with real-time video of lung tissue to support surgery and other urgent interventions in critically-ill ventilated patients. However, there are challenges with pulmonary microendoscopy, such as poor image quality and harmful side effects from the fluorescent probes used to highlight the targeted tissue (irritation, bleeding, etc). These limitations significantly reduce the accuracy of the diagnostic, posing challenges for clinicians in identifying conditions like infections, inflammations or scarring in lung tissue. Thus, there is a clear need for improving the accuracy of pulmonary microendoscopy diagnostics for the benefit of point-of-care diagnostics for critically-ill patients. In addition, improved diagnostic accuracy would also benefit standard microendoscopy diagnostics conducted periodically to identify and monitor disease progression, such as different types of cancer and precancerous tissue. By advancing technologies that underpin endoscopic diagnostics, such as high-precision imaging devices, there could also be opportunities for applications beyond the medical field.

Project objectives

In 2013, the interdisciplinary research collaboration (IRC) Proteus, led by the University of Edinburgh, set out to develop ultra-fast detectors for medical devices, with a particular focus on improving point-of-care diagnostics for lung diseases. IRC Proteus proposed a novel technology named FOSIP (fibre-based optical sensing and imaging platform), which combines multiplex optical sensing capabilities, surface-enhanced Raman spectroscopy (SERS) and fluorescent molecular probes. FOSIP would enable in-vivo and in-situ characterisation of diseased tissues via arterial sampling-line or pulmonary micro endoscopy. This novel technology would enable clinicians to obtain real-time high-quality images of targeted tissues, addressing an unmet need in endoscopic procedures. The creation of FOSIP required significant technical advances in a range of disciplines, such as chemistry and computer science. IRC Proteus therefore combined several research strands in order to integrate a range of technologies: a novel optical fibre-based system, new assays for sensing and imaging lung and blood, new inference techniques for interpreting the data and novel ultrafast optical detectors.

This case study focuses on the technical progress and commercial exploitation of one of these technologies, the ultrafast optical detectors. The overall objective of this research strand at IRC Proteus was to take advantage of the properties of complementary metal–oxide–semiconductors (CMOS) optical detectors, specifically single photon avalanche diodes (SPAD). CMOS SPAD sensors are exceptionally sensitive detectors of light with applicability in high-precision devices, such as bioimaging technologies. Each detected photon can be time-stamped, enabling discrimination of Raman and fluorescence spectroscopic signals. These detectors can play a pivotal role in mitigating the trade-off between speed (real-time imaging) and sensitivity (quality of the image). The two specific objectives of this research strand were: 1) to develop new CMOS SPAD sensors with increased imaging capabilities; 2) to build the electronic and digital systems required to integrate the sensor into an imaging device.

Project activities and outputs

CMOS SPAD sensor development and patenting

In 2013, Professor Henderson, a co-investigator at IRC Proteus, led the research strand responsible for designing new CMOS SPAD sensors. The research team consisted of Professor

[95] https://www.mdpi.com/2075-4418/11/12/2202

Henderson and two postdoctoral researchers working under his supervision. Previous designs of CMOS SPAD sensors lacked capabilities around single photon counting (super sensitive imaging abilities) and time-resolved imaging (ability to scan in 3D). The research team worked to develop a SPAD line sensor architecture to enable fluorescence and Raman spectroscopy in one imaging device[96]. The combination of spectroscopy capabilities provides complementary information on the tissue being imaged, improving imaging capability.

In 2015, the research team designed a CMOS SPAD sensor with novel capabilities for time-resolved spectroscopy. The new design would enable the sensor to detect multiple colours simultaneously (full spectral decays in parallel)[97], improving its ability to identify and quantify different molecules. A working prototype of this sensor was manufactured by IRC Proteus project partner ST Microelectronics over the course of six months. Between 2015 and 2016, further work was conducted on CMOS SPAD technology to build the digital architecture and custom firmware for rapid sensing and processing of data in SPAD sensors[98]. In 2016, a new prototype SPAD image sensor was developed using a more advanced 40 nanometres technology than previous designs, which used 130 nanometres technology. This new design allowed for better integration of different components in the sensor, improving single photo counting and time-resolved imaging capabilities[99]. This prototype brought significant improvements to image resolution, opening opportunities for both medical and scientific imaging applications. In 2017, the technology underlying the prototype was submitted for patent protection in five different regions. Among these, patents have been successfully granted in the USA[100], China and Japan, while patent applications are pending in Europe and India.

Systems integration

As the sensor design research strand progressed between 2013 and 2016, IRC Proteus engaged several other researchers to build the systems required to integrate the sensors into an imaging device (an optical scanning microscope). This work was conducted by Professor Henderson and other researchers at IRC Proteus from 2017 to 2020, namely Dr Ahmet Erdogan, Dr Elvira Williams, Dr Gareth Williams and Dr Neil Finlayson. The researchers attended weekly meetings with wider research teams at IRC Proteus to ensure alignment with other work packages (for example, creation of fibre-based optical sensing system for FOSIP). In addition, fortnightly technical meetings were conducted with the research team involved in building the systems to integrate the CMOS SPAD sensors.

The integration of CMOS SPAD sensors required characterisation of the sensors, and the development of a confocal microscopy system incorporating these sensors as well as novel software and artificial intelligence algorithms for image analysis. These activities were carried out in parallel between 2017 and 2020, achieving several technical advancements:

- Improvements to the sensor's ability for capturing light at speed and with very high spatial resolution (time correlated single photon counting)[101].

[96] https://ieeexplore.ieee.org/document/6942042

[97] https://opg.optica.org/oe/fulltext.cfm?uri=oe-23-5-5653&id=312419

[98] https://opg.optica.org/ol/abstract.cfm?uri=ol-40-18-4305

[99] https://ieeexplore.ieee.org/document/7838372

[100] https://image-ppubs.uspto.gov/dirsearch-public/print/downloadPdf/20200116838

[101] https://spie.org/Publications/Proceedings/Paper/10.1117/12.2509466?SSO=1

- Incorporation of innovative features such as a sensor design that improves sensitivity and data processing capabilities (per-pixel histogramming)[102].
- Development of a confocal microscopy system (an optical scanning microscope) enabling fluorescence lifetime imaging (chromatic confocal laser scanning system)[103].

In 2019, the research team achieved a significant milestone by integrating the CMOS SPAD sensors into a new imaging system known as a full-spectral fluorescence lifetime imaging microscope. This state-of-the-art system provides an understanding of the behaviours of fluorescent molecules in human tissue with unprecedent detail and speed[104]. The imaging system also contains capabilities for conducting fluorescence and Raman imaging simultaneously, which can provide in-depth information about samples for use in scientific research. To build on this capability, the research team also worked on a new method for Raman spectroscopy using time-correlated single photo counting[105]. They demonstrated the new method significantly improved the speed in which Raman spectroscopy can be conducted, with implications for speed and accuracy of sample analysis in scientific research.

In 2020, the research team introduced a new artificial intelligence approach for analysing images collected via fluorescence spectroscopy. They demonstrated that the use of deep convolutional neural networks outperformed traditional machine learning methods, with implications for improving the accuracy of cancer diagnosis via fluorescence spectroscopy[106].

Outcomes and Impacts

Progress towards clinical trials and point-of-care diagnostics

The development of CMOS SPAD sensors and subsequent improvements towards integration into an imaging device underpin the creation of IRC Proteus's fibre-based optical sensing and imaging platform (FOSIP). Parallel work conducted by other research teams at IRC Proteus with fibre-based optical systems and chemical probes enabled the creation of two FOSIPs: Versicolour, a widefield microscope and Kronoscan, a confocal Raman imaging microscope. These platforms enabled researchers at IRC Proteus to conduct two exploratory clinical studies with 40 patients in total, for assessing their feasibility and safety, between 2016 and 2018[107] and then between 2019 and 2022[108]. A third clinical study involving 80 patients is ongoing (2022 to 2027)[109]. This trial will test Versicolour and Kronoscan's capabilities for distinguishing between healthy and diseased lung tissue. If successful, the trial will be a key milestone for the technologies developed at IRC Proteus, with potential for disrupting point-of-care diagnostics of lung diseases and other conditions.

Towards commercialisation

In 2019, three market leading companies in the field of high-precision instruments for life sciences showed interest in the CMOS SPAD sensor developed at IRC Proteus. The companies assessed the sensor and provided positive feedback about its capabilities, indicating significant commercial interest.

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[102] https://ieeexplore.ieee.org/document/8637804

[103] https://spie.org/Publications/Proceedings/Paper/10.1117/12.2509466?SSO=1

[104] https://www.nature.com/articles/s41467-021-26837-0

[105] https://opg.optica.org/ol/abstract.cfm?uri=ol-46-17-4104

[106] https://ieeexplore.ieee.org/document/9175598

[107] https://clinicaltrials.gov/study/NCT02604862

[108] https://clinicaltrials.gov/study/NCT02676050

[109] https://www.isrctn.com/ISRCTN10996089

In 2020, IRC Proteus researchers obtained further funding of approximately £60,000 from Scottish Enterprise to conduct a feasibility study on the commercialisation of the technologies developed at IRC Proteus. Running from 2020 to 2021 and led by Dr Finlayson, the feasibility study analysed several aspects of commercialisation, such as regulatory and supply chain landscape analysis, marketing and software development. It recommended that the CMOS SPAD sensors and confocal microscopy system should be commercialised separately from the endoscopic devices (Versicolour and Kronoscan). This would allow each of the technological assets to be fully exploited within their original application (point-of-care diagnostics for lung diseases), and beyond diagnostics for lung tissues, including applications in the medical field.

In 2022, IRC Proteus researchers obtained £75,000 of further funding from Scottish Enterprise for the development of a business case for a spinout company 'Singular Photonics'. Following recommendation from the 2020 feasibility study, Singular Photonics would license the patent filed in 2017 to operate in the systems instrumentation market, supplying CMOS SPAD sensors and imaging devices to life sciences companies. The capabilities of CMOS SPAD sensors and the full-spectral fluorescence lifetime imaging microscopy system would also allow Singular Photonics to explore other markets that require high precision spectroscopy, from pharmaceuticals to battery technology research and development.

Based on the business case developed, a further £199,000 from Scottish Enterprise was granted in 2022 to researchers Dr Finlayson, Dr Jalajakumari, and Professor Henderson for creating the company Singular Photonics, supported by commercial advisors Dr Neville Freeman and Les Bayne. This grant enabled the design and development of a camera module prototype, as well as the required software and firmware. While the company has not officially started trading, the team has fully developed a prototype camera module, which is expected to be evaluated by the end of the 2023. If successful, the camera module will be a key product to be supplied by Singular Photonics to manufacturers of scientific instruments.

In October 2023, a highly experienced executive from the photonics sector joined Singular Photonics as CEO, and the company is expected to attract 10 to 15 employees in the first years of trading[110]. In addition, Singular Photonics has been selected to join Chip Start, a chip design incubator programme part of the UK's national strategy for semiconductors[111]. The company will receive mentorship and benefit from design tools and investment networking. Singular Photonics' participation in the incubator programme strongly emphasises its potential for future economic impact.

Contribution of IRC investment

According to interviews, the IRC investment provided essential long-term funding, enabling the development of CMOS SPAD sensors for use in healthcare technologies. As such, the IRC funding has been instrumental in steering research towards a challenging technical problem in healthcare technologies that might not have been pursued otherwise[112].

Researchers interviewed also reported that IRC Proteus successfully broke down barriers between disciplines, enabling researchers to learn from each other and integrate findings[113].

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[110] Personal communication, Dr. Finlayson, 25th September 2023.

[111] https://www.uktech.news/deep-tech/semiconductor-design-incubator-20231012

[112] Personal communication, Prof. Henderson, 22nd September 2023.

[113] Personal communication, Dr. Finlayson, 25th September 2023.

The management team and advisory board contributed key inputs to ensure alignment across research strands and to validate research progress from different teams[114].

Key learnings

Enablers

- Creation of a strong interdisciplinary research community.
- Regular meetings, workshops and presentations enabled flow of information and facilitated technical progress.

Challenges

- Translational activity in the field of semiconductors is fast paced, with new discoveries requiring rapid action for successful intellectual property protection. However, interviews highlighted some opportunities for protecting new discoveries made at IRC Proteus were missed due to delays around patent filing[115].
- Attracting professionals with expertise in sensing technologies is extremely difficult due to competition for skills by the private sector.

[114] Personal communication, Dr. Finlayson, 25th September 2023; Personal communication, Prof. Henderson, 22nd September 2023.

[115] Personal communication, Prof. Henderson, 22nd September 2023.

2.6 A Frugal Point-of-Care System for Fluorescent Detection of Microbial Keratitis

Summary

Microbial keratitis (MK) caused by bacteria or fungi is the most common cause of blindness in both developed and developing countries. Current diagnostic methods for MK are time consuming and exhibit a wide variation in their sensitivity and specificity. There is a need to develop highly sensitive and accurate, as well as cheap and easy-to-use, diagnostic approaches to provide timely diagnosis.

In 2018, researchers at IRC Proteus collaborated with the Aravind Eye Care Hospital in India to develop a novel rapid point-of-care diagnostic for corneal infections, suitable for use in resource limited settings. The team demonstrated how "SmartProbes" (microbe-specific fluorescent reporters previously developed by IRC Proteus) could improve MK detection. In 2019, the Next Step Plus project "Photonic Pathogen Theranostics - Point-of-care image guided photonic therapy of bacterial and fungal infection" (PPT) set out to develop a proof-of-concept, low-cost and easy to use fluorescence imaging device (FluoroPi) that could be used in combination with the SmartProbes. The research team also introduced a new approach for preparing MK samples, with implications for developing less invasive sampling techniques in healthcare facilities.

The PPT project enabled researchers to build on IRC Proteus technology and adapt it for use in resource-constrained health systems. The researchers are currently adapting the FluoroPi technology to turn it into a more robust, user-friendly version. The next iteration of the FluoroPi device will then undergo evaluation with clinical samples as part of future validation studies.

Introduction

Corneal opacity is the 5th leading cause of blindness and visual impairment globally, affecting approximately 6 million people worldwide[116]. Microbial keratitis (MK) caused by bacteria or fungi is the most common cause of the condition in both developed and developing countries. The impact of blindness or visual impairment on individuals can be devastating, leading to loss of livelihood, income and reduced life expectancy. Depending on geographical location, the incidence of MK can range from 2.5–799 cases per 100,000 population/year, with a higher prevalence in lower- and middle-income countries. For example, in India, the incident of MK is 113 per 100,000 population-year[116].

Blindness from MK can be avoided with correct diagnosis and treatment strategies. Current diagnostic methods for MK (direct smear microscopic examination and/or culture of scraped corneal material) are time consuming and exhibit a wide variation in their sensitivity and specificity[117]. Thus there is a need to develop highly sensitive and accurate, as well as cheap and easy-to-use, diagnostic approaches to provide timely diagnosis, which is crucial for successful treatment and prevention of loss of vision.

Project background

[116] Ting, D.S.J., Ho, C.S., Deshmukh, R. *et al.* Infectious keratitis: an update on epidemiology, causative microorganisms, risk factors, and antimicrobial resistance. *Eye* 35, 1084–1101 (2021). https://doi.org/10.1038/s41433-020-01339-3

[117] Ung, Lawson et al. "The persistent dilemma of microbial keratitis: Global burden, diagnosis, and antimicrobial resistance." Survey of ophthalmology vol. 64,3 (2019): 255-271. doi:10.1016/j.survophthal.2018.12.003

In 2018, Proteus IRC researchers at the University of Edinburgh initiated a collaboration with the Aravind Eye Care Hospital in India to develop a novel rapid point-of-care diagnostic for corneal infections, suitable for use in resource limited settings. The collaborators set out to test whether "SmartProbes", microbe-specific fluorescent reporters previously developed by the Proteus IRC project, could improve MK detection.[118] Two types of SmartProbes, "BAC One"[119] for bacterial and fungal infections and "BAC Two" for gram-negative bacteria[120], had already been validated for detection of bacteria in the lung. Based on samples from 267 patients with suspected MK at the corneal clinic at Aravind Eye Care Hospital, the researchers found that using these probes in combination with fluorescence microscopy resulted in equivalent or higher sensitivity, specificity, and accuracy compared to conventional diagnostic methods.

While the results were promising, the researchers recognised two barriers that would limit translation of the technology for use in resource-limited settings. Firstly, the approach requires a high-resolution fluorescence microscope, which are very expensive and require a high level of technical expertise to operate and maintain. Secondly, only tertiary care facilities have the ability to prepare the samples used for diagnostic analysis (microbial isolates from corneal scrapes), limiting patient access to diagnosis.

In order to overcome these technical challenges, the Proteus IRC Next Step project "Photonic Pathogen Theranostics - Point-of-care image guided photonic therapy of bacterial and fungal infection" (PPT) set out in 2019 with the aim of developing an affordable fluorescence imaging device and evaluating its performance in combination with the SmartProbes. In addition, the project aimed to explore less invasive approaches for the collection of corneal samples so that this step could be devolved to secondary and primary care centres. PPT involved a multidisciplinary collaboration between Proteus IRC partners at the University of Edinburgh, led by Professor Kev Dhaliwal and researchers at the Aravind Eye Care Hospital.

Findings, outcomes and impact

The PPT Next Step Plus project developed a proof-of-concept, low-cost and easy to use fluorescence imaging device (FluoroPi) and demonstrated its ability to detect MK infections using SmartProbes in a porcine model[121].

The FluoroPi device combines a Raspberry Pi single-board computer and camera, inexpensive coupling optics, and multiple light-emitting-diode sources and filters. To demonstrate its performance, the team established *ex vivo* porcine models of MK infected with two bacterial pathogens that commonly cause MK, *P. aeruginosa* and *S. aureus*. They found that FluoroPi's performance in detecting infections was similar to that of commercial fluorescence microscopes, for both, BAC One and BAC Two probes. The research team also showed that samples could be prepared via a different method, corneal impression membranes (CIM). This

[118] Gunasekaran, Rameshkumar et al. "Exploratory Use of Fluorescent SmartProbes for the Rapid Detection of Microbial Isolates Causing Corneal Ulcer." *American journal of ophthalmology* vol. 219 (2020): 341-350. doi:10.1016/j.ajo.2020.06.014

[119] Akram AR, Avlonitis N, Lilienkampf A, et al. A labelled-ubiquicidin antimicrobial peptide for immediate *in situ* optical detection of live bacteria in human alveolar lung tissue. *Chem Sci*. 2015;6(12):6971-6979. doi:10.1039/c5sc00960j

[120] Akram, Ahsan R et al. "In situ identification of Gram-negative bacteria in human lungs using a topical fluorescent peptide targeting lipid A." *Science translational medicine* vol. 10,464 (2018): eaal0033. doi:10.1126/scitranslmed.aal0033

[121] Mohanan, Syam Mohan P C et al. "FluoroPi Device With SmartProbes: A Frugal Point-of-Care System for Fluorescent Detection of Bacteria From a Pre-Clinical Model of Microbial Keratitis." *Translational vision science & technology* vol. 12,7 (2023): 1. doi:10.1167/tvst.12.7.1

is a first step towards developing a less invasive sampling approach which could be performed by trained healthcare professionals in primary or secondary care facilities. If it can be translated to the clinic, the simpler method would widen access to diagnosis within community settings so that MK infections can be treated earlier, when outcome is likely to be better. The CIM approach was inspired from research at St. Paul's Eye Unit (Liverpool University Hospital) where it is now routinely used in clinical practice[122].

The PPT project was described as a valuable opportunity for early career researchers to gain experience of interdisciplinary research and to progress their careers. Following on from PPT, Dr Bethany Mills, a postdoctoral researcher on the PPT team, was successful in securing a £1.5 million UKRI Future Leaders Fellowship in 2021. The award allows her to continue collaborating with the Aravind Eye Care Hospital to develop pathways to diagnose, treat and reduce the burden of MK in India.[123] Dr Mills was also awarded a Wellcome Institutional Translational Partnership award (approximately £50,000) to support further development of the FluoroPi device towards a commercial product.[124] In addition, the research has opened up a new avenue of research for Dr Bethany Mills to apply the approach to detect corneal MK infections in dogs and cats as part of a collaboration with the Hospital for Small Animals at the University of Edinburgh[124].

Contribution of IRC investment

The PPT project enabled researchers to build on technology that had been developed by the Proteus IRC and adapt it for use in resource-constrained health systems. A key factor for the success of the project was the continuation of a collaboration between Proteus IRC research teams in the UK and the Aravind Eye Care Hospital in India, facilitating frequent knowledge exchange in project meetings and visits: "*The ambition of this project would be impossible to realise without the partnerships we have in place, each bringing their own expertise, experiences and local knowledge. […] Spending time physically co-located is essential for understanding the nuances in expectations, passing on protocols and testing technology together.*"[125] This knowledge exchange was essential for understanding how the technology could be tailored to the needs and requirements of end users and fit into existing care pathways in India.

Next steps

To translate the FluoroPi technology, the next steps are to adapt the current prototype to turn it into a more robust, user-friendly version. The next iteration of the FluoroPi device will then undergo evaluation with clinical samples as part of future validation studies. Researchers from the Aravind Eye Care Hospital are currently engaging in discussions with a potential manufacturer, Aurolab, a not-for-profit manufacturing facility affiliated with the Aravind Eye Care Hospital, to support the commercialisation of the FluoroPi device[126]. Proteus researchers

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[122] Somerville, Tobi F et al. "An Evaluation of a Simplified Impression Membrane Sampling Method for the Diagnosis of Microbial Keratitis." *Journal of clinical medicine* vol. 10,23 5671. 30 Nov. 2021, doi:10.3390/jcm10235671

[123] https://gtr.ukri.org/projects?ref=MR%2FV026097%2F1

[124] Bethany Mills, Proteus researcher, Personal communication, 17 October 2023.

[125] Blog: Translational Healthcare Technologies partners with the University of Liverpool and Aravind Eye Care Hospital to bridge the 'valley of death' and develop point-of-care diagnostics for corneal infection. Shared by Beth Mills.

[126] Kev Dhaliwal, Proteus researcher, Personal communication, 11 October 2023.

have also developed light-activated molecules that can kill gram positive bacteria[127,128], which will be tested for their ability to kill MK infections in future studies.

[127] Mills, Bethany et al. "Riboflavin-Vancomycin Conjugate Enables Simultaneous Antibiotic Photo-Release and Photodynamic Killing against Resistant Gram-Positive Pathogens." *JACS Au* vol. 3,11 3014-3023. 24 Oct. 2023, doi:10.1021/jacsau.3c00369

[128] Ucuncu, Muhammed et al. "Polymyxin-based photosensitizer for the potent and selective killing of Gram-negative bacteria." *Chemical communications (Cambridge, England)* vol. 56,26 (2020): 3757-3760. doi:10.1039/d0cc00155d

2.7 Our Health Interdisciplinary Research Programme: Exploring community-based participatory research

Summary

Patient and public involvement and engagement (PPIE) is important to ensure that research projects address issues that matter to patients and the outcomes of the research can make a difference to their lives. However, researchers often do not know how to engage effectively with patients.

In 2017, Dr Helen Szoor-McElhinney launched the 'Our Health Interdisciplinary Research Programme' (Our Health) as part of the PPIE activities of IRC Proteus at the University of Edinburgh. Our Health is a community-based participatory research (CBPR) programme that aims to reduce health inequalities by improving health research skills and knowledge within socio-economically disadvantaged communities, working with undergraduate and post graduate students from the University of Edinburgh who benefit from learning from a CBPR approach. Our Health initially launched two interdisciplinary, community-based research pilot projects focused on research questions that had been co designed by local patient support groups. These projects involved volunteers from community partner organisations as well as undergraduate and postgraduate students from the University of Edinburgh, supported by academic experts.

The Our Health programme led to five new partnerships with community partners and further funding to continue activities. As a result of the success of the programme, In 2023, Our Health was developed into an interdisciplinary research undergraduate course called "Sensing in the Community", where students learn about the role of community engagement and carry out interdisciplinary research projects that address real-world issues. The undergraduate course is currently offered by the University of Edinburgh.

Introduction

Patient and public involvement and engagement (PPIE) in research aims to address the challenge of ensuring relevance of outcomes of research and sharing research findings with the public. Patients and members of the public are invited to inform and shape all aspects of the research process, from planning and research design to dissemination and implementation, so that research is carried out "with" rather than 'to' them[129].

This approach contributes to research that is ethical and accessible. Funding bodies increasingly require researchers to involve people with lived experience of a health condition (patients, formal and informal carers and healthcare professionals) in their research. The EPSRC Health Technologies Strategy encourages researchers to engage with PPIE activities at the outset of their research and incorporate public, patient and user perspectives to inform and shape their projects[130].

Community-based participatory research (CBPR) recognises that communities have their own expertise and knowledge in health-relevant areas and that working collaboratively between communities and academic researchers enhances learning and understanding for all parties.

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[129] NIHR (2022). Patient and Public Involvement and Engagement Resource Pack. https://www.nihr.ac.uk/documents/patient-and-public-involvement-and-engagement-resource-pack/31218. Accessed 13 October 2023

[130] EPSRC health technologies strategy. (2023).)https://www.ukri.org/publications/epsrc-health-technologies-strategy/epsrc-health-technologies-strategy/. Accessed 13 October 2023

The aim is to combine knowledge to find solutions to health problems and improve adoption, maintenance and sustainability of research outcomes. The approach can be used to reduce health inequalities, which is especially important for socially disadvantaged populations who experience disparities in health outcomes.

The project and project activities: Our Health

In 2017, Dr Helen Szoor-McElhinney launched the EPSRC Our Health Interdisciplinary Research Programme as part of the PPIE activities of the IRC Proteus. Our Health is a CBPR-based programme that aims to reduce health inequalities by improving health research skills and knowledge within socio-economically disadvantaged communities. Located at the University of Edinburgh, the programme received a total funding of £12,000 until 2023 under the EPSRC core and follow-on Proteus IRC grants[131].

Our Health involves collaborative research projects between students, community partners and IRC researchers. Students were recruited as volunteers from across the University of Edinburgh, encompassing individuals from diverse academic disciplines and levels. The students undertook a short training programme after which they were placed in groups of 4-6 individuals to work on Our Health projects for a year[132].

Projects in the Our Health programme begin by identifying health-related social issues, using IRC PPIE activities to select potential community partners with specific health-related interests for collaborative research. These community partners were from communities with a Scottish Index of Multiple Deprivation index between 1-4[133]. This index covers deprivation across seven domains: income, employment, education, health, access to services, crime and housing[134].

Initially, Our Health and potential partners hold meetings and workshops to explore perspectives and experiences of specific health and wellbeing issues[135]. Then, students form small interdisciplinary teams and work with community partners, a network of CBPR experts and researchers from the IRC to fully develop research questions, methodologies and project design.

At inception, in 2017, Our Health launched two interdisciplinary, community-based research pilots projects. The research questions were co-designed with Breathtakers and Breathe Easy Fife, local patient support groups for people who suffer from or care for someone with a lung condition, and the Cheyne Gang, a Scottish charity that runs singing groups for people who live with chronic lung diseases[136]. In the latter project, the Cheyne Gang wanted to know if the breathing techniques they used before singing impacted lung physiology and improved their symptoms. The singing group partnered with students in the Our Health programme to develop the research question and design, with support from academic and clinical researchers to refine measurement parameters. Engineering researchers then worked with the students and

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[131] Dr Helen Szoor-McElhinney. Personal communication 8 December 2023

[132] Our Health. https://www.ed.ac.uk/clinical-sciences/our-health/student-learning-reflections. Accessed 13 October2023

[133] Dr Helen Szoor-McElhinney. Personal communication 8 December 2023

[134] Scottish Index of Multiple Deprivation. https://www.gov.scot/collections/scottish-index-of-multiple-deprivation-2020/. Accessed 11 December 2023

[135] Liam Gilchrist, Alette Willis and Helen Szoor-McElhinney. Our Health: exploring interdisciplinarity and community-based participatory research in a higher education science shop. Research for All. 2022. Vol. 6(1). DOI: 10.14324/RFA.06.1.18

[136] The Cheyne Gang. http://www.communitynorth.scot/directory/the-cheyne-gang/ Accessed 27 November 2023

community partners to develop a sensor that could record accurate measurements. This project is still in progress[137].

Outcomes and Impacts

Since 2017, the Our Health programme has established **five new partnerships** with community partners and embarked on the following five projects[138]:

- Partnership with NHS Lothian as part of the COVID-19 response to co-produce a patient-led research project that explores the benefits and challenges associated with the use of digital solutions for the improvement of the out-patient care pathway. NHS Lothian supported the partnership with £8,000[139].
- Partnering with Versus Arthritis research volunteers, the project takes a CBPR approach to co-develop new research questions about key issues in arthritis faced by people living with the disease[140]. For the second phase of the partnership, the partnership was extended to involve the Cowrie Scholarship Foundation to specifically engage with people of Black African heritage who have direct experience of living with or alongside a joint/bone condition. Insights gained from these projects will guide the prioritisation of research questions and influence research funding decisions made by Versus Arthritis[141].
- Partnership with the Scottish charity Cyrenians to research multiple questions around homelessness and the impact of exclusion on health and wellbeing. This project involved a clinical fellow from the University of Edinburgh and a PhD student from the University of Stirling.
- Partnership with the Aravind Eye Hospital based in Madurai, India to research questions around patients' eyecare needs and access to essential eyecare. Aravind Eye Hospital is the largest and most productive eye care centre in the world and is committed to eradicating needless blindness in India.
- Partnership with the National Institute for Research in Tuberculosis (NIRT) in India, to investigate how COVID-19 has impacted the patient care pathways for TB patients.

The Our Health programme has enabled **community partners to engage with researchers** about their health and well-being. In the words of the programme's lead:

"Communities and patient groups now feel that research is not a closed domain. They believe that they can be part of the research process and that their expertise is important. An unexpected benefit of the programme patients said was that participating in the Our Health programme impacted their health, with a perception of reduced symptoms that made them feel healthier."

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[137] Proteus Mid-term Report (2021)

[138] https://www.ed.ac.uk/clinical-sciences/our-health/our-health-projects

[139] https://www.accord.scot

[140] Taking on Arthritis Together. https://www.ed.ac.uk/clinical-sciences/our-health/taking-on-arthritis-together. Accessed 7 December 2023

[141] https://www.versusarthritis.org/news/2023/august/how-collaborative-research-is-helping-us-take-on-arthritis-together/ Accessed 10 December 2023

Our Health Lead, Dr Helen Szoor-McElhinney[142]

The Our Health programme has also **enhanced the knowledge and skills of students and researchers**. Since 2019, about 160 students had been involved in Our Health community research projects[143]. The programme provided students with access to communities, interdisciplinary learning experiences and development of skills beyond those acquired through their current programme of study. For instance, students reported that they were able to improve their communication, time management, leadership and creative thinking skills[144].

In 2019, the Our Health programme was awarded a **further funding** of £7,000 from the University of Edinburgh's Principal's Teaching Award scheme (PTAS) to support learning and teaching enhancements at the University of Edinburgh[145]. The award enabled the Our Health team to carry out an evaluation of the programme, gathering evidence for learning purposes. In 2021, the Our Health programme secured further funding from NHS Lothian for a research associate to study how remote care affects the patient and clinician relationship[146]. The CBPR project was co-designed with NHS Lothian who provide patient and community perspectives about remote outpatient hospital care. This research is implemented with local community partners in central Scotland (Breathe Easy East Lothian, Breathe Easy Fife & Catch Your Breath)[147].

In 2023, the University of Edinburgh used the **Our Health teaching and learning model** to design and deliver an interdisciplinary health technology course called "Sensing in the Community"[148]. The course is offered to second year undergraduate students enrolled in degree programmes in the Schools of Engineering and Chemistry, Health in Social Sciences and the Deanery of Biomedical Sciences. It enables students to understand the role of novel 'sensing' health technologies within health care, as well as community engagement. It enables students to carry out interdisciplinary research addressing real-world issues, enabling the fostering of skills in research management, teamwork, and critical thinking[149].

The Our Health team has actively communicated their work on community-based research. For example, the team **shared best practice in community-based research** at the University of Edinburgh, Teaching and Learning Conference in 2020[150], the European Science Shop Conference in 2019[151] and the Times Higher Education, 2021[152]. The Our Health team shared experiences of using CBPR at the LNHS Lothian Health and Care Professions Research

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[142] Dr Helen Szoor-McElhinney. Personal communication. 21 September 2023

[143] A Community-University Interdisciplinary Research Programme. What have we achieved so far and what next?.

[144] Our Health. Student learning reflections. https://www.ed.ac.uk/clinical-sciences/our-health/student-learning-reflections. Accessed 13 October 2023

[145] The University of Edinburgh. Our Health Wins Principals Teaching Award. https://www.chem.ed.ac.uk/news-events/news/our-health-wins-principals-teaching-award. Accessed 13 October 2023

[146] NHS Lothian Remote Outpatient Hospital Care Report 2022, A Community- based Participant Action Research Project

[147] Proteus Mid-term Report (2021)

[148] Our Health. Sensing in the community. https://www.ed.ac.uk/clinical-sciences/our-health/sensing-in-the-community. Accessed 13 October 2023

[149] http://www.drps.ed.ac.uk/22-23/dpt/cxscee08018.htm Accessed 8 Dec 2023

[150] https://gtr.ukri.org/projects?ref=EP%2FR005257%2F1. Accessed 7 December 2023

[151] https://gtr.ukri.org/projects?ref=EP%2FR005257%2F1. Accessed 7 December 2023

[152] Directing research to engage and support local communities. https://www.timeshighereducation.com/campus/directing-research-engage-and-support-local-communities. Accessed 14 December 2023

Conference in 2023 and they were invited to present at the Living Knowledge Conference in 2024[153].

Contribution of IRC investment

The IRC contributed to the success of the Our Health programme in different ways. First, funding through IRC Proteus provided support to Dr McElhinney's salary and organisation of early engagement events and activities with community partners. The support enabled Our Health to build networks with researchers across Europe who were experienced in using the CBPR approach[154]. These experts contributed to the design of the Our Health programme and enabled Dr McElhinney to develop the programme at the University of Edinburgh[155].

Second, the IRC PPIE activities provided a platform for Our Health programme to select potential community partners with specific health-related interests for collaborative research[156]. Through the IRC, Our Health was able to engage with communities such as the Cheyne Gang.

Third, the IRC provided the Our Health programme with academic support. About six experienced IRC postdoctoral researchers and PhD students were involved in the Our Health programme and delivered workshops that explored the conceptual and practical application of interdisciplinary research and interactional practice[157]. This enriched the training and supervision of interdisciplinary student teams and community partners. Additionally, Proteus researchers advised the student groups during their projects and helped them refine their research methodology[158].

Next steps

The Our Health team continues to work with its community partners and researchers to improve health-related research skills and drive forward community-centred research through specific partnership projects and its Sensing in the Community university course[159]. Several UK universities have also expressed interested in using the EPSRC Our Health model[160] within their own research context.

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[153] Lothian Health and Care Professions Research Conference 2023. https://services.nhslothian.scot/hcprofessionsresearch/wp-content/uploads/sites/47/2023/11/NHS-Lothian-NMAHPPS-Research-Conference-Nov-7-2023-Full-Programme-Final.pdf.

[154] https://livingknowledge.org/

[155] Dr Helen Szoor-McElhinney, personal communication. 21 September 2023

[156] Liam Gilchrist, Alette Willis and Helen Szoor-McElhinney. Our Health: exploring interdisciplinarity and community-based participatory research in a higher education science shop. Research for All. 2022. Vol. 6(1). DOI: 10.14324/RFA.06.1.18

[157] Liam Gilchrist, Alette Willis and Helen Szoor-McElhinney. Our Health: exploring interdisciplinarity and community-based participatory research in a higher education science shop. Research for All. 2022. Vol. 6(1). DOI: 10.14324/RFA.06.1.18

[158] Proteus Mid-term report (2021)

[159] Dr Helen Szoor-McElhinney. Personal communication. 7 December 2023

[160] Dr Helen Szoor-McElhinney. Personal communication. 7 December 2023

2.8 The use of multi-modal multi-sensor technology to measure symptoms and activities of daily living with Parkinson's disease

Summary

Parkinson's Disease (PD) is the second most common neurodegenerative disease in the UK, damaging nerve cells in the brain over many years and leading to a reduction in the neurotransmitter dopamine and related control of body movement. It is therefore essential to develop ways to detect the disease and intervene at the earliest disease stage. A key challenge is that current practice requires clinicians performing standardised tests at monthly "snapshot" assessments rather than having access to the patient's real-world symptoms continually.

In 2018, researchers from IRC SPHERE set out to study how SPHERE's multi-modal multi-sensor technology can be used to measure symptoms and activities of daily living with PD. Led by a clinician specialised in neurology, the project sought to find alternatives to the current clinical assessment tool. For five days, 12 participants with PD and 12 healthy control participants stayed in the SPHERE House in Bristol, where video cameras captured participants' daily routines. The study (called PD SENSORS) produced several key research results:

- Developed new mobility-related parameters from real-world data that may be used as digital biomarkers of disease progression in PD.
- Demonstrated how video data can be used to evaluate disease severity when analysing motor activities, such as standing up and sitting down.
- Highlighted the importance of real-world observation of people's day-to-day life patterns as data showed that clinicians' presence can influence patients' mobility outcomes.

The research team has secured follow-on funding of £6.2m from EPSRC to take the protocol, findings and results of the PD SENSORS study into a new project called "Transforming the Objective Real-world measurement of Symptoms" (TORUS), to support generation of data relevant to clinical trials.

Introduction

Parkinson's Disease (PD) is a condition that damages parts of the brain over many years. It is caused by a loss of nerve cells in a part of the brain called the substantia nigra. This leads to a reduction in the neurotransmitter dopamine which helps control body movement. PD is the second most common neurodegenerative disease in the UK, affecting around 153,000 people, a number that is forecast to rise to around 172,000 people by 2030[161].

The main symptoms of PD are involuntary shaking of parts of the body, slow movement and stiff inflexible muscles[162]. It is estimated that by the time of diagnosis with PD, most patients have already lost around 50% of their dopaminergic neurons[163]. This makes it crucial that attempts to intervene with disease progression are aimed at the preclinical or early-stage disease states.

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[161] Parkinsons UK. Reporting on Parkinson's: information for journalists. https://www.parkinsons.org.uk/about-us/reporting-parkinsons-information-journalists Accessed 3 October 2023

[162] NHS. Overview Parkinson's disease. https://www.nhs.uk/conditions/parkinsons-disease/. Accessed 3 October 2023

[163] Fearnley JM, Lees AJ, Ageing LAJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 1991;114:2283–301.

Challenge

One of the tools most commonly used by clinicians to assess PD is the "Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale" (MDS-UPDRS)[164]. It evaluates various aspects of PD, including motor and non-motor symptoms of daily living, and motor complications. While the MDS-UPDRS is widely used, it relies on the clinician's observation and interpretation of a patient's performance, at limited points in time and in a clinical setting. For example, in clinical trials, each participant needs to travel to a trial site to be observed by a clinician while performing standardised tests[165]. These (at most) monthly "snapshots" are a poor representation of the hour-by-hour variation of PD patients' true symptoms. As a consequence, assessment results can be variable and may not accurately reflect the patient's real-world mobility such as engagement in social activities[166], falls[167] and other metrics which affect well-being and quality of life such as sleep[168].

Project and project findings

In 2018, Dr Catherine Morgan, a neurology specialty registrar at the North Bristol NHS Trust, took a leave from her position to pursue a PhD in the Movement Neuroscience Group at the Bristol Brain Centre, University of Bristol[169]. It was during this period that she and her supervisors developed the idea to conduct research on an alternative to the MDS-UPDRS assessment tool that would overcome some of the issues of this established approach[170].

Dr Morgan and her primary supervisor, Dr Alan Whone, a consultant neurologist, heard about the SPHERE IRC and its testing facility, the SPHERE House, from Professor Ian Craddock, lead of SPHERE, who was her secondary PhD supervisor. This prompted Dr Morgan to embark on a PhD project with SPHERE to test how sensors in people's homes could be used to detect and measure PD symptoms[171]. The study called PD SENSORS (Parkinson's Disease Symptom Evaluation in a Naturalistic Setting producing Outcome measuRes using SPHERE technology) was supported by the EPSRC SPHERE and funded by the Elizabeth Blackwell Institute for Health Research (University of Bristol), the Wellcome Trust Institutional Strategic Support Fund, Cure Parkinson's Trust, and IXICO, a UK-based imaging and digital biomarker analysis company [172].

The SPHERE House is a research facility located at the University of Bristol, UK. It is a home-like setting equipped with sensors and cameras that can capture data on the daily activities of the house's occupants. The SPHERE House enables researchers to develop and test technologies

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[164] Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., ... & LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Movement disorders: official journal of the Movement Disorder Society, 23(15), 2129-2170. https://doi.org/10.1002/mds.22340

[165] https://gtr.ukri.org/projects?ref=EP%2FX036146%2F1#/tabOverview Accessed 27 November 2023

[166] Duncan RP, Earhart GM. Measuring participation in individuals with Parkinson disease: relationships with disease severity, quality of life, and mobility. Disabil Rehabil 2011;33:1440–6.

[167] Silva de Lima AL, Smits T, Darweesh SKL, et al. Home-Based monitoring of falls using wearable sensors in Parkinson's disease. Mov Disord 2020;35:109–15.

[168] van Uem JMT, Isaacs T, Lewin A, et al. A viewpoint on wearable technology-enabled measurement of wellbeing and healthrelated quality of life in Parkinson's disease. J Parkinsons Dis 2016;6:279–87.

[169] Movement disorders research team. https://www.nbt.nhs.uk/research-innovation/our-research/current-research/movement-disorders-research-hub/movement-disorders-research-team. Accessed 30 November 2023

[170] Dr Catherine Morgan, personal communication. 18 September 2023

[171] Dr Catherine Morgan, personal communication. 18 September 2023

[172] Morgan, C., Jameson, J., Craddock, I., Tonkin, E. L., Oikonomou, G., Isotalus, H. K., ... & Whone, A. (2022). Understanding how people with Parkinson's disease turn in gait from a real-world in-home dataset. *Parkinsonism & Related Disorders*, *105*, 114-122.

that can support independent living and improve health outcomes for people in their own homes[173].

The high-level goals of Dr Morgan's project were:

1. to advance digital measures of mobility that could serve as critical markers of PD progression and be used in clinical trials, and
2. to develop a method for assessing the degree to which results obtained in a controlled laboratory experiment (for example, the clinic) correspond to those obtained in the real world (for example, the home).

For the study, 12 participants with PD and 12 healthy control participants stayed for five days in the SPHERE House. Video cameras mounted on the walls of the SPHERE House captured participants as they engaged in their daily routines, moving around freely. In total, 85 hours of video data was captured. The data was manually annotated by clinicians and evaluated[174]. In addition, researchers visited the house twice to conduct in-person clinical assessments using the MDS-UPDRS tool.

The study showed proof-of-concept for the use of mobility-related parameters from real-world data as digital biomarkers of disease progression in PD. It concluded that wall-mounted cameras in the home can reliably differentiate between PD and healthy participants, and showed that people with PD turned more slowly and with more steps compared to healthy individuals in real-world indoor settings. There were strong correlations between the turning parameters determined by the camera approach and in-person MDS-UPDRS assessments, lending confidence to the findings.

In addition, the camera data was able to identify changes in turning when PD patients temporarily paused their medication (that is to say, distinguish between the 'on' or 'off' states for PD medication). For most patients, the number of steps per turn increased in the 'off' state, while for others it decreased. This variation in mobility-related outcomes of medication highlights the need to stratify patients into PD phenotypes in clinical trials.

The data also showed that participants turned differently (took more steps and took less time for turns) when they were being observed by a clinician compared to during 'passive' observation by camera. Hence, the presence of a clinician can influence turning outcomes and indicates that real-world observation may better reflect how people move in day-to-day life.

Using the same data set, the research team then applied automated video analysis to detect and quantify when participants stood up from a sitting position (sit-to-stand transition)[175]. The automated approach performed well and strongly correlated with assessments made by human raters, indicating high reliability and robustness, and the potential for use as a digital biomarker, for example, in PD treatment trials.

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[173] The SPHERE House. https://www.bristol.ac.uk/engineering/research/digital-health/research/sphere/the-sphere-house/. Accessed 30 November 2023

[174] Morgan, C., Jameson, J., Craddock, I., Tonkin, E. L., Oikonomou, G., Isotalus, H. K., ... & Whone, A. (2022). Understanding how people with Parkinson's disease turn in gait from a real-world in-home dataset. Parkinsonism & Related Disorders, 105, 114-122. https://www.sciencedirect.com/science/article/pii/S1353802022003753

[175] Morgan, C., Masullo, A., Mirmehdi, M., Isotalus, H. K., Jovan, F., McConville, R., Tonkin, E. L., Whone, A., & Craddock, I. (2023). Automated Real-World Video Analysis of Sit-to-Stand Transitions Predicts Parkinson's Disease Severity. *Digital biomarkers*, *7*(1), 92–103. https://doi.org/10.1159/000530953

A further analysis was undertaken looking at room localisation using accelerometer and received signal strength indicator (RSSI) data. The network developed outperformed other methods for indoor localisation. A further evaluation showed that precise room-level localisation predictions, transformed into in-home gait speed features, produced accurate predictions on whether the PD participant was taking or withholding their medications[176].

To explore whether continuous monitoring of PD symptoms using passive sensors would be acceptable to patients, Dr Morgan conducted interviews with study participants on their experience of living in the SPHERE House[177]. This qualitative study concluded that use of multimodal sensors such as wrist-worn wearables, cameras in people's homes, and other ambient sensors, was broadly acceptable. It also highlighted concerns and limitations to this approach, for example, potential changes in participant behaviour due to the presence of sensors, which can inform the design of future sensor systems.

Outputs and Outcomes

The PD SENSORS study produced more than ten peer-reviewed journal articles and conference publications. Dr Morgan has disseminated her work to a wider audience and presented the study findings at various conferences, including the 2018 Bristol Brain Research Showcase, the Pervasive Computing Conference PerCom 2021 and Movement Disorders Society International Congress 2022[178].

Recently, the research team secured follow-on funding to take their findings further, including the results of the PD SENSORS study. Led by Professor Craddock, the "Transforming the Objective Real-world measurement of Symptoms" (TORUS) received EPSRC funding of nearly £6.2 million over five years (2023-2028)[179]. TORUS aims to develop a platform of sensing technologies that can be used in clinical trials of PD treatments: a wrist-worn wearable integrated with AI-enabled cameras that can continuously and objectively measure symptoms of PD.

Contribution of IRC investment

The SPHERE IRC and SPHERE House infrastructure underpinned Dr Morgan's work and was fundamental to the study, both in terms of funding and expertise. The SPHERE House was equipped with sensors and cameras which captured the movement of people living with PD and therefore provided a testbed for Dr Morgan to collect the dataset needed for the study. As at the time on embarking on the research, there was no other research group with such multimodal in-home sensing capabilities. Dr Morgan reports that it is unlikely the PD SENSORS project would have been conducted with the success that it has achieved without such an infrastructure.

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[176] Jovan, F., Morgan, C., McConville, R., Tonkin, E. L., Craddock, I., & Whone, A. (2023, August). Multimodal Indoor Localisation in Parkinson's Disease for Detecting Medication Use: Observational Pilot Study in a Free-Living Setting. In *Proceedings of the 29th ACM SIGKDD Conference on Knowledge Discovery and Data Mining* (pp. 4273-4283). https://doi.org/10.48550/arXiv.2308.02419

[177] Morgan, C., Tonkin, E. L., Craddock, I., & Whone, A. L. (2022). Acceptability of an In-home Multimodal Sensor Platform for Parkinson Disease: Nonrandomized Qualitative Study. *JMIR human factors*, 9(3), e36370. https://doi.org/10.2196/36370

[178] Dr Catherine Morgan, personal communication. 18 September 2023

[179] Transforming the Objective Real-world measurement of Symptoms" (TORUS). https://gtr.ukri.org/projects?ref=EP%2FX036146%2F1 Accessed on 30 November 2023

The strong interdisciplinary collaboration between engineers, computer scientists, movement disorders clinicians and industry enabled Dr Morgan to access and engage with experts in different fields[180].

The SPHERE IRC fostered interdisciplinarity between the fields of engineering and medicine which was essential to the study. This interdisciplinarity enabled Dr Morgan to collaborate with engineers and other researchers who supported the project with their time, by helping to collect the sensor data and providing guidance on how to explore the dataset and identify what would be clinically useful to the study[181].

Next steps

Dr Morgan has now returned to her work as a neurology specialty registrar at the North Bristol NHS Trust. She intends to continue her research and will be a co-investigator in TORUS.

PD SENSORS delivered important proof-of-concept that a real-world passive sensor approach to capturing PD symptoms is feasible and acceptable. Furthermore, it has the potential to augment data obtained through standard practices. However, the small number of participants involved in the study means that the results are not currently generalisable to the wider population of people with PD. Future studies, such as TORUS, aim to develop the real-world approach further.

[180] Dr Catherine Morgan, personal communication. 18 September 2023

[181] Dr Catherine Morgan, personal communication. 18 September 2023

2.9 Opportunistic Passive Radar for Non-Cooperative Contextual Sensing (OPERA)

Summary

Contextual sensing can be used to monitor human activity and health metrics in the home, in order to detect health issues and trigger timely interventions. These types of Ambient Assisted Living (AAL) technologies hold the promise of enabling people to live healthy, independent lives for longer, and thus reduce the burden on healthcare systems.

The OPERA Project (Opportunistic Passive Radar for Non-Cooperative Contextual Sensing) was funded by an IRC Next Step Plus award from January 2019 to March 2023. It aimed to develop contextual sensing technologies capable of passive sensing to recognise physical activity and localisation in the home. Researchers developed and integrated two passive sensing approaches with other sensing systems of the IRC SPHERE, achieving validation of their system. Their findings have produced several outputs, including 19 conference proceedings, 14 journal articles and three annotated datasets and a simulation tool (open access).

Having validated the technology in a laboratory environment (Technology Readiness Level 4), the OPERA team are now looking to secure funding to test the technology in a real-world healthcare setting (TRL5), in collaboration with the NHS. The technology developed also has the potential to be applied in fields beyond healthcare and is already being tested for use in surveillance and law enforcement.

Introduction

Ambient assisted living (AAL) technologies can facilitate independent living and enhance the quality of life for people living with long-term chronic health conditions and seniors.[182] A demographic shift is driving the demand for such technologies, with the proportion of people aged 65 and over in the UK expected to increase from 19% in 2021 to 22% by 2031.[183] By 2066, this group is projected to account for more than a quarter of the UK population.[184]

As we age, long-term conditions including heart disease, diabetes, and dementia become more prevalent: 58% of people over 60 vs 14% of people under 40% suffer from a long-term condition.[185] Reflecting this high burden of disease, around 70% of the total health and care spend in England is attributed to caring for people with long-term conditions. AAL technologies hold the promise of allowing people to live healthier and independently for longer, support caregivers and medical staff, and ultimately reduce the burden on healthcare systems.

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[182] Cicirelli G, Marani R et al (2021) Ambient Assisted Living: A Review of Technologies, Methodologies and Future Perspectives for Healthy Aging of Population. Sensors (Basel) 21:3549. doi: 10.3390/s21103549

[183] Census 2021 (2022) Voices of our ageing population: Living longer lives. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/articles/voicesofouraageingpopulation/livinglongerlives. Accessed 9 Nov 2023

Office for National Statistics. National population projections: 2020-based interim. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/bulletins/nationalpopulationprojections/2020basedinterim#changing-age-structure. Accessed 9 Nov 2023

[184] https://www.gov.uk/government/publications/trend-deck-2021-demographics/trend-deck-2021-demographics#increase-in-over-65s-to-more-than-a-quarter-of-the-uk-population-by-2066. Accessed 9 Nov 2023

[185] UK Department of Health (2012) Long Term Conditions Compendium of Information (3rd edition). https://assets.publishing.service.gov.uk/media/5a7c638340f0b62aff6c154e/dh_134486.pdf. Accessed 9 Nov 2023

Contextual sensing technology combines physical activity recognition and indoor localisation (finding the precise location of devices, people or objects in indoor environments).[186] By monitoring daily activities and health metrics in the home, these AAL technologies gather real-time data that can enable detection of health issues and timely interventions, and inform clinical research, e.g. by identifying early warning signs.

Current approaches to contextual sensing in the home include wearable devices and video. However, adoption of these technologies faces challenges, such as limited battery life and non-compliance in using wearable devices (especially among the elderly) and the high cost, limited field of view, and privacy concerns arising from the intrusive nature of video-based technologies.[187]

Passive sensors collect data on participants with minimum ongoing interaction and awareness. In a home setting, passive sensors can detect wireless signals from household Wi-Fi access points and other wireless-enabled devices as they reflect off people or objects. The data is then used to recognise physical activity and localisation.[188] This sensing technology monitors 'in the background', without the need for people to actively engage (for example, to put on a wearable). It also does not produce images or identify the people being monitored, alleviating privacy concerns.

Project/activity

By 2017, the SPHERE IRC (phase 1) had developed a platform of wirelessly networked home sensing technologies comprising wearable, video and environmental sensors. The IRC collaborators were looking to investigate new contextual sensing technologies capable of 'passive sensing' that could be integrated with their current platform.[189]

The OPERA Project (Opportunistic Passive Radar for Non-Cooperative Contextual Sensing) was an IRC Next Step Plus project, funded from January 2019 until March 2023.[190] OPERA's aim was to investigate and develop new contextual sensing capabilities for activity detection, in the SPHERE ecosystem as well as for other indoor sensing scenarios.[191] The project was led by Professor Robert Piechocki, University of Bristol and included SPHERE research groups from the University of Bristol with new collaborators from University College London (UCL) and the University of Oxford (later relocated to University of Cambridge). This brought together expertise not yet represented in SPHERE into the collaboration, in passive Wi-Fi radar (Dr Kevin Chetty, Professor Karl Woodbridge, UCL), as well as additional machine learning capabilities (Professor Nic Lane, University of Cambridge).

OPERA focussed on the two main approaches to Wi-Fi sensing, 1) sensing through passive Wi-Fi radar (UCL) and 2) channel state information (CSI) based wireless sensing (Bristol).[192] Over the course of four years, the OPERA collaborators developed and tested the capabilities of both

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[186] Bocus MJ, Piechocki R. (2022) A comprehensive ultra-wideband dataset for non-cooperative contextual sensing. Sci Data 9(1):650. doi: 10.1038/s41597-022-01776-7

[187] https://gtr.ukri.org/projects?ref=EP%2FR018677%2F1#/tabOverview. Accessed 9 Nov 2023

[188] Li, W; Piechocki, RJ et al (2021) "Passive WiFi Radar for Human Sensing Using a Stand-Alone Access Point," in IEEE Transactions on Geoscience and Remote Sensing 59: 1986-1998. doi: 10.1109/TGRS.2020.3006387.

[189] OPERA Case for Support, 2019. EPSRC IRC Next Steps Plus proposal

[190] https://gtr.ukri.org/projects?ref=EP%2FR018677%2F1#/tabOverview. Accessed 9 Nov 2023

[191] OPERA Case for Support, 2019. EPSRC IRC Next Steps Plus proposal

[192] W. Li, M. J. Bocus, C. et al (2022) "On CSI and Passive Wi-Fi Radar for Opportunistic Physical Activity Recognition," in IEEE Transactions on Wireless Communications 21: 607-620. doi: 10.1109/TWC.2021.3098526.

approaches for contextual sensing in the home, both individually and in combination, and alongside other sensing systems in the SPHERE platform. This research benefitted from availability of the SPHERE House, a terraced house in Bristol equipped with a range of sensor systems that allow activity monitoring and recording of data while the 'inhabitants' (research participants) go about their daily lives.[193]

Using the gathered data, OPERA worked on various strategies to develop a passive contextual sensing system, including synchronisation of sensor systems, integration of data from multiple systems (data fusion), development of machine learning techniques to enable activity recognition and classification, and a simulation tool for passive radar data from human motion (described in more detail the following section).

Findings, Outcomes and Impacts

OPERA advanced the development of passive sensing approaches and achieved validation of their system for human activity recognition in the SPHERE House. The collaborators shared findings in numerous publications, including 19 conference proceedings (mainly by the IEEE), 14 journal articles and 3 book chapters, and made available three annotated datasets and a tool (open access).[194]

OPERAs' key findings and outputs include:

- A comparison of the performance of the two approaches to Wi-Fi sensing: The OPERA team carried out experiments to evaluate the performance of the two approaches, passive Wi-Fi radar and CSI based wireless sensing, in detecting human activity. The results showed that the systems have different strengths, recommend that future Wi-Fi sensing applications should leverage the advantages of both systems.[195]
- Strategies for synchronising sensor systems and data fusion: OPERA's passive contextual sensing systems were used to capture human motion data alongside sensing technologies already present in the SPHERE House.[196] The team developed algorithms to keep the multiple sensors synchronised, allowing data from different systems to be integrated and sent to a central data hub for interpretation. This created a dataset of eight hours of annotated measurements, called OPERAnet, collected via the multiple sensors from six participants performing six daily activities. The dataset was made available for download and use by the wider research community.[197]
- Machine learning techniques to enable activity recognition and classification: Radar-based sensing of motion, for example, a person walking, swinging their arms, generates complex data signatures. The OPERA collaborators developed machine learning techniques that could process and interpret these large and complex datasets, to

[193] https://www.bristol.ac.uk/engineering/research/digital-health/research/sphere/the-sphere-house/. Accessed 9 Nov 2023

[194] OPERA ResearchFish submission, 2023

[195] Li, W; Bocus, MJ et al (2022) "On CSI and Passive Wi-Fi Radar for Opportunistic Physical Activity Recognition," in *IEEE Transactions on Wireless Communications*. 21: 607-620. doi: 10.1109/TWC.2021.3098526.

[196] Bocus, MJ; Li, W et al (2021) OPERAnet: A Multimodal Activity Recognition Dataset Acquired from Radio Frequency and Vision-based Sensors. Scientific Data 9:474. doi: 10.1038/s41597-022-01573-2

[197] Bocus, MJ (2022). A Comprehensive Multimodal Activity Recognition Dataset Acquired from Radio Frequency and Vision-Based Sensors. figshare. Collection. https://doi.org/10.6084/m9.figshare.c.5551209.v1

recognise and classify different types of human activity.[198] The team improved the classification accuracy further by combining simulated data with real measurement (see SimHumalator simulation tool below), showing that simulation data can enhance limited experimental radar datasets and thus address the "cold-start problem."[199,200]

- Simulation Tool: The development of algorithms that interpret the data and recognise specific motions, such as walking, grabbing, and rotating, generally requires large volumes of high-quality training data (data that 'teaches' the machine learning application to recognise patterns). For the radar approach to contextual sensing, OPERA was faced with the "cold start problem", that is to say, a lack of existing databases to train the machine learning models for activity recognition. The project created a simulation tool by integrating its radar data with data from two motion capture systems.[201,202] The resulting tool, called SimHumalator, enables researchers to simulate radar data for different motions in passive Wi-Fi sensing scenarios without the need for extensive experimental data acquisition and to generate realistic synthetic data to train machine learning algorithms.

OPERA's progress in developing passive activity sensing is reaching the wider research community. The team have presented their findings to international audiences, including at the US-based IEEE (Institute of Electrical and Electronics Engineers), a professional association with a key role in the development of technology standards.[203,204,205] In this way, the OPERA project can contribute to shaping further research and future standards in the field. The project's outputs also support current research, within the OPERA collaboration and beyond. For example, the SimHumulator tool is freely available online to other researchers and has been downloaded 250 times by research organisations around the world.[206]

The technology developed through the OPERA award has the potential to benefit other fields. For example, accurate counting of the number of individuals in a given space is useful in many applications ranging from intelligent environments and security/law enforcement, to management of areas that experience high levels of footfall such as transport hubs and shopping centres. Drawing on the insights from OPERA's health technology work, further development of the passive Wi-Fi radar approach at UCL enabled the researchers to count up to six individuals with high accuracy.[207] Unlike surveillance cameras, this approach works through solid barriers. Funded by an internal UCL grant, the group are continuing their work on

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[198] Vishwakarma, S; Li, W et al (2022). Attention-Enhanced Alexnet for Improved Radar Micro-Doppler Signature Classification. *IET Radar, Sonar and Navigation*. doi:10.1049/rsn2.12369

[199] Tang, C; Vishwakarma, S et al (2021). Augmenting Experimental Data with Simulations to Improve Activity Classification in Healthcare Monitoring. In 2021 IEEE Radar Conference (RadarConf21): Radar on the move Article 9455314 IEEE. https://doi.org/10.1109/radarconf2147009.2021.9455314

[200] Vishwakarma, S; Chetty, K; Li, W (2022) Realistic Micro-Doppler Database Generation Through Neural Style Transfer Framework. Presented at: IEEE-EMBS International Conference on Biomedical and Health Informatics.

[201] Vishwakarma, S; Li, W et al (2021) SimHumalator: An Open Source WiFi Based Passive Radar Human Simulator For Activity Recognition. Available at https://arxiv.org/pdf/2103.01677.pdf. Accessed 10 Nov 2023

[202] https://uwsl.co.uk/simhumalator/ Accessed 10 Nov 2023

[203] Personal communication, Dr Kevin Chetty, 7 Nov 2023

[204] https://isac.committees.comsoc.org/about/founding-members/. Accessed 10 Nov 2023

[205] https://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=9455240. Accessed 11 Nov 2023

[206] Personal communication, Dr Kevin Chetty, 14 Nov 2023

[207] Tang, C; Li, W et al (2022). People Counting using Multistatic Passive WiFi Radar with a Multi-Input Deep Convolutional Neural Network. Proc. SPIE PC12108, Radar Sensor Technology XXVI

passive radar sensing for use in security and surveillance, for example, through-wall sensing for counter-terrorism and law enforcement purposes.[208]

Contribution of IRC investment

The IRC investment enabled OPERA to build on existing infrastructure and expertise essential to the project. OPERA relied on research infrastructure established as part of SPHERE (SPHERE House, ethics and advisory panels), and benefitted from regular interaction and sharing of ideas with the wider network experts in the SPHERE collaboration. This would have been difficult to access if OPERA, as a Next Step Plus project, had not been connected to SPHERE.[209]

As a Next Step Plus award, OPERA enabled the SPHERE collaborators to bring in additional research expertise to progress the development of a novel approach to contextual sensing. This included groups that had not previously worked on healthcare applications. For example, the initial link between SPHERE and the passive Wi-Fi radar group (Dr Kevin Chetty, UCL Department of Security and Crime Science) was established through a small subcontract as part of SPHERE 1, facilitated by a postdoctoral researcher who moved from UCL to the University of Bristol.[210] The Next Step Plus award opportunity gave the impetus for the groups to collaborate on a larger scale. OPERA was the Chetty group's first full project in the area of health technologies; without the IRC investment, the group may have focussed on other applications, for example, in security and surveillance.

Challenges

- COVID-19 pandemic: The COVID-19 pandemic forced the researchers to adapt their original research plan. Home-bound during lockdown periods, the team re-directed their focus to research that did not require access to test equipment at the SPHERE House. Working from home on previously collected datasets, the team developed the SimHumalator, a simulation tool for passive radar data from human motion.[211] In addition, the OPERA award was extended by two years as a result of delays in data collection caused by the COVID-19 pandemic.
- In hindsight, the researchers would propose a higher budget for the purchase of hardware and equipment. This would have allowed the team to explore some add-on approaches and extend the findings, building on the core equipment covered by the award.

Next steps

OPERA was successful in advancing development of contextual sensing technology, achieving system validation in a laboratory environment (TRL4). The next step is to test the technology in a real-world situation (TRL5). To this end, the OPERA collaborators have partnered with an NHS Trust and are looking for opportunities to secure joint grant funding to test the contextual sensing system in a real-world healthcare setting.[212] In addition, the team plans to engage with engineering companies that can take the current prototype towards commercialisation.

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[208] Personal communication, Dr Kevin Chetty, 7 Nov 2023

[209] Personal communication, Dr Kevin Chetty, 7 Nov 2023

[210] Personal communication, Dr Kevin Chetty, 7 Nov 2023

[211] Personal communication, Dr Kevin Chetty, 7 Nov 2023

[212] Personal communication, Dr Kevin Chetty, 7 Nov 2023

The UCL group are also discussing potential collaborations with research groups at the University of Glasgow and several universities in Canada, to extend the system's capabilities for health care applications.

2.10 Dynamic hydrogels as a platform for local drug delivery

Summary

Current standard treatment for cancer involves surgical removal of the cancer followed by chemotherapy and/or radiotherapy to destroy any remaining cancerous cells. However, in the case of hard-to-treat cancers, complete removal of cancerous cells is difficult.

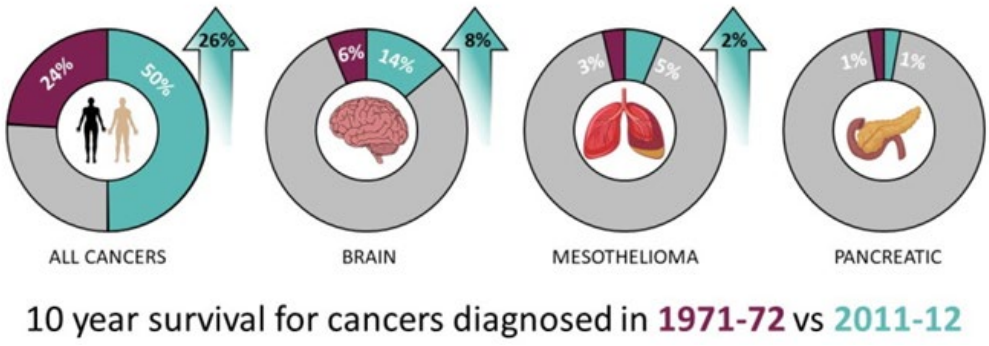
In 2018, IRC TeDDy set out to develop injectable hydrogels for drug delivery systems to improve encapsulation and release of a wide range of therapeutic drugs. Building on previous research, researchers developed a robust manufacturing scale up and sterilisation protocol for the hydrogel drug delivery system in line with good manufacturing practice (GMP) requirements. This is a key step to progressing the technology and further testing in clinical trials.

As a result of this project, researchers were able to test a variety of scale up and sterilisation protocols to produce the hydrogel formulation in sufficient quantity necessary for clinical studies. Results of this work are expected to be published in the near future and further funding will enable the manufacture of hydrogel to GMP standards.

Introduction

Cancer survival rates have doubled over the last few decades. Today more than half of patients survive cancer, however some types of cancer such as brain tumours, mesothelioma and pancreatic cancer remain hard-to-treat with less than a 14% survival rate (Figure 1). Current standard of care treatment for cancer may include surgical removal of the cancer, chemotherapy and/or radiotherapy. However, in the case of hard-to-treat cancers complete removal of the cancerous cells is not possible[213].

Figure 1. 10-year survival rates for cancer



Source: https://www.teddy.eng.cam.ac.uk/background

Brain tumours such as glioblastoma (~12,288 cases/year in UK)[214] are hard-to-treat for two reasons. First, it is challenging to remove the entire tumour without compromising normal brain function and second, the blood-brain barrier makes it difficult for chemotherapeutic drugs to enter the brain. Similar challenges are encountered for malignant mesothelioma (~2,718

[213] IRC TeDDy Case for Support

[214] Cancer Research UK: Brain, other CNS and intracranial tumours statistics. Available here.

cases/year in UK)[215], caused by exposure to asbestos, and treatment rarely removes all traces of cancerous cells due to its aggressive infiltrating nature. Pancreatic cancers (~10,425 cases / year in UK)[216] are also difficult to treat, partly because of the formation of fibrotic tissue around and within the tumour, which impedes chemotherapy drugs reaching cancerous cells.

To overcome the challenges of hard-to-treat cancers, new drug delivery systems are needed. Placement of biomaterials in the cancer surgical resection site that can locally deliver chemotherapeutic drugs over time is a promising route to improve the therapeutic outcomes of hard-to-treat cancers.

Project background

IRC TeDDy (Targeted Delivery of Hard-to-Treat Cancers) project started in 2018 with the objective of developing new strategies for targeted drug delivery in the context of hard-to-treat cancers: brain (glioblastoma), mesothelioma and pancreatic cancer[213]. The aim was to develop a multimodal biocompatible drug delivery platform using different delivery vehicles, including injectable hydrogels gels, high-capacity vehicles and implantable devices to improve the delivery of existing chemotherapeutic drugs targeting hard-to-treat cancers.

Professor Oren Scherman at the University of Cambridge led the research to further develop an injectable hydrogel drug delivery technology. He had previously developed a novel hydrogel formulation and validated its ability to release chemotherapeutic drugs to destroy brain cancer cells in *in vitro* and *ex vivo* experimental models[217,218].

The IRC provided the opportunity to develop a robust manufacturing scale up and sterilisation protocol for the hydrogel formulation in line with good manufacturing practice (GMP) requirements. This is a key step to translate the technology towards testing in clinical trials. However, developing manufacturing methodologies for hydrogels is technically challenging as current GMP methods are not well suited for this type of technology. Due to the high-water content in hydrogels, the sterilisation processes can result in significant (80%) loss of therapeutic properties of drugs encapsulated within the hydrogel[22].

Findings, outcomes and impact

IRC researchers were able to test a variety of scale up and sterilisation protocols to develop a hydrogel formulation in sufficient quantity necessary for clinical studies[219]. Furthermore, the hydrogel was shown to retain its material properties and demonstrated efficacy in a range of *in vitro* and *ex vivo* experimental models for brain cancer. Two publications are currently in preparation describing the hydrogel scale up methodologies. These publications will provide an important contribution to the academic and industry knowledge base, as literature on hydrogel manufacturing scale up methodologies is currently very limited[220].

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[215] Cancer Research UK: Mesothelioma statistics. Available here .

[216] Cancer Research UK: Pancreatic cancer statistics. Available here.

[217] Rowland MJ, Parkins CC, McAbee JH, et al. An adherent tissue-inspired hydrogel delivery vehicle utilised in primary human glioma models. *Biomaterials*. 2018;179:199-208.

[218] Parkins, Christopher C et al. "Mechanically matching the rheological properties of brain tissue for drug-delivery in human glioblastoma models." *Biomaterials* vol. 276 (2021): 120919.

[219] Professor Oren Scherman, IRC co-investigator, Personal communication, 22 Sept 2023

[220] Dr Paraskevi Kasapidou, IRC postdoctoral researcher, Personal communication, 9 Oct 2023

Professor Scherman secured additional funding from the Medical Research Council to further validate the hydrogel drug delivery system in a pre-clinical animal model[221]. The aim of the award is to determine the maximum tolerated drug dose that can be delivered by the hydrogel technology to effectively treat glioblastoma in rats. If successful, the translation of the hydrogel drug delivery technology can progress toward further toxicology studies, bringing the technology closer to a clinical trial.

The IRC was highlighted as an effective model for training the next generation of interdisciplinary researchers. IRC postdoctoral researchers had the opportunity to learn a wide range of skills across a range of disciplines[219]. Dr Paraskevi Kasapidou, an IRC post-doctoral researcher, had the opportunity to take part in a 6-month industry placement at Aqdot, funded by BBSRC's Flexible Talent Mobility Account[222]. Aqdot is a Cambridge-based supramolecular chemistry company with a focus on and expertise in developing, licensing and selling novel proprietary products. The placement enabled Dr Kasapidou to gain experience within an industrial laboratory, to develop the hydrogel manufacturing scale up and sterilisation protocols in line with GMP standards. Moreover, it was also a key step in supporting her to begin a career transition towards an industrial role. She commented that her experience at the IRC was critical for developing her 'industrial mindset' and building credibility in 'industrial translation'[220]. Dr Kasapidou now works as a formulation scientist at Janssen Pharmaceutical Companies of Johnson & Johnson developing injectable formulations in a range of disease areas.

Challenges

Although progress has been made to develop a robust manufacturing scale up and sterilisation protocol for the hydrogel drug delivery technology, the IRC team has found it challenging to secure funding for the estimated £5 million needed to complete the pre-clinical studies required to obtain regulatory approval for first-in human studies[219]. Furthermore, the UK does not have suitable GMP-certified infrastructure in place to manufacture hydrogels. Without this, the hydrogel drug delivery technology cannot proceed to being tested in clinical trials.

Contribution of IRC investment

The IRC is facilitating building a unique interdisciplinary consortium of biologists, chemists, engineers and clinicians. Regular consortium meetings were highlighted as an important mechanism to 'break down silos' between disciplines and promote new avenues of research[219]. The IRC partnership resource fund has enabled the establishment of new partnerships to complement the expertise of the consortium and further advance the validation of the hydrogel drug delivery technology:

- In 2022, Professor Judy Coulson, a cancer biologist at the University of Liverpool, joined forces with IRC[223]. The goal of the partnership is to test whether the hydrogel drug delivery technology can destroy lung cancer cells in a novel hen's egg model developed at the University of Liverpool.

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[221] IRC news (2022): IRC Investigator secures Medical Research Council (MRC) Confidence in Concept Award. Available here.

[222] IRC TeDDy news (2021): Dr Paraskevi Kasapidou has been awarded a BBSRC Flexible Talent Mobility Account award that supports knowledge exchange between industry and academia. Available here.

[223] IRC news (2022): The IRC is collaborating with the University of Liverpool where scientists have developed a new preclinical model of mesothelioma to help speed up the journey of therapeutics from lab to clinic. Available here.

- In 2023, a partnership was established with Dr Ryan Mathew, a neuroscientist and clinician, at the University of Leeds. The partnership aims to test the hydrogel's ability to release chemotherapeutic drugs to destroy cancer cells in patient-derived brain tumour 3D-cellular systems and resection-recurrence surgical mouse models, which were developed at the University of Leeds[224].

Next steps

The IRC TeDDy funding will continue until September 2024. To progress the translation of the hydrogel drug delivery technology, IRC researchers are currently looking for a contract research organisation (CRO) in the UK to take over the protocols developed and adapt them to guide the manufacture of the hydrogel to GMP standards. The search to find a suitable CRO has been expanded to the Netherlands, US and Canada, where more relevant GMP facilities are available. In addition, they are exploring opportunities to secure the further funding needed to enable the technology to move forward to first-in-human studies.

[224] IRC TeDDy news (2023): IRC announces new partnership with the University of Leeds. Available here.

2.11 Spinout Vector Bioscience: nanomaterials for drug delivery applications

Summary

Current medical treatments have limited therapeutic effect against cancer in the brain and lung, leading to low survival rates in patients. One key challenge is adapting interventions to overcome natural barriers that limit the rate of anti-cancer drug penetration, such as fibrous outer layers in tumour.

In 2018, researchers at IRC TeDDy set out to develop and validate new nanomaterials for drug delivery vehicles, such as metal-organic frameworks (MOFs). MOFs can be used to encapsulate drugs and improve the efficacy of a range of therapies. A new approach to create a modified MOF was developed, presenting delayed drug-release capabilities and lower toxicity when compared to other MOFs. This approach also improved the material's stability, integrity in solutions and enabled dry storage.

The technology underpinning the modified MOF was patented and Vector Bioscience was created as a spinout company that will license the patent and conduct translational research and development of nanomaterials for drug delivery applications. The company has attracted over £2 million pre-seed funding, which will enable further preclinical and clinical studies to collect toxicity and effectiveness data. Positive results of these studies may lead to new formulation of drugs for hard-to-treat cancer in the future.

Introduction

Significant advancements have been made in diagnosing and treating cancer in the past 50 years. The 10-year survival rate of patients diagnosed with cancer has increased nearly 30% between 1971 and 2011[225]. However, the 10-year survival rate for hard-to-treat cancers, such as glioblastoma, mesothelioma and pancreatic cancer, has seen a much lower increase over the same period (2% to 8%)[226]. As a result of lower survival rates, hard-to-treat cancers pose a major burden on society, healthcare systems and the economy, with millions of new cases and deaths reported every year around the world[227]. A key technical challenge for increasing the survival rates of hard-to-treat cancers is overcoming their resistance to conventional medical interventions. For example, mesothelioma and pancreatic cancer tumours have fibrous outer layers which limit the rate of drug penetration[228], ultimately reducing the efficacy of current anti-cancer therapies. Thus, the treatment of hard-to-treat cancers requires innovative solutions to improve targeting and delivery of anti-cancer drugs.

Research aims

In 2018, the interdisciplinary research collaboration (IRC) in Targeted Delivery for Hard-to-Treat Cancers (TeDDy) set out to develop new approaches for '*enhancing treatment efficacy and increasing the rate and extent of drug activity at the tumour site*'[229]. To achieve this, researchers at TeDDy are conducting research on a range of potential solutions, such as injectable hydrogels[230] and high-capacity drug delivery vehicles.

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[225] https://news.cancerresearchuk.org/2016/07/20/tackling-hard-to-treat-cancers-what-how-and-why/

[226] https://www.teddy.eng.cam.ac.uk/background

[227] https://acsjournals.onlinelibrary.wiley.com/doi/10.3322/caac.21660

[228] https://www.teddy.eng.cam.ac.uk/background

[229] https://www.teddy.eng.cam.ac.uk/our-approach

[230] https://www.teddy.eng.cam.ac.uk/our-approach/hydrogels

This case study provides an overview of the research and associated commercialisation activities conducted at TeDDy, relating to high-capacity drug delivery vehicles. The overarching objective of this research strand is to develop novel nanoparticular materials for drug delivery vehicles, such as metal-organic frameworks (MOF). These materials can be used to encapsulate hydrophobic drugs and macromolecules like siRNAs and mRNAs[231], and have the potential to improve the efficacy of a range of therapies. The specific aims of this research strand include the development and validation of new materials in both in-vitro and in-vivo studies.

Research activities

The interdisciplinary research team working on high-capacity delivery vehicles at TeDDy is led by Professor Fairen-Jimenez. It consists of engineers, chemists, and biologists, and builds on previous work conducted at the Adsorption and Advanced Materials Laboratory, also led by Professor Fairen-Jimenez at the University of Cambridge. Since 2012, the team has made progress in developing and testing MOF for different applications.

In 2019, the team presented a disruptive, new approach for encapsulating siRNA using highly porous MOF. They demonstrated that their method protects siRNA from enzymatic degradation, a key challenge in the delivery of gene therapies against cancers[232]. In 2020, computational and experimental methods were used to analyse the toxicity and the release mechanisms of a drug delivery systems using MOFs[233]. In the same year, the team presented a design for a new drug delivery system based on MOFs that can target mitochondria. The design can improve the efficacy of therapies while using lower doses of anti-cancer drugs, resulting in fewer side effects[234].

In 2021, the TeDDy team reached a milestone in the development of MOFs: the modification of MOFs with a chemical group called phosphate-functionalised methoxy polyethylene glycol (mPEG-PO_3)[235]. This modification significantly improved the stability of the MOF, enabling dry-storage and maintaining the integrity of the material in solutions[236]. In addition, the modified MOFs presented delayed drug-release capabilities and lower toxicity when compared to other MOFs[237]. This approach allows the translation of the MOF properties to real systems in-vivo and further into clinical trials. The key intellectual property of this work has been protected with patents filled by Cambridge Enterprise on behalf of the University of Cambridge.

Vector Bioscience

In 2021, Professor Fairen-Jimenez started Vector Bioscience, a spinout company focused on translating research on nanomaterials for drug delivery applications[238]. The company has been granted exclusive licensing rights to the patent on MOFs described above from the University of Cambridge. In the next two years, Vector Bioscience will continue to collect the preclinical

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[231] https://www.teddy.eng.cam.ac.uk/our-approach/high-capacity-vehicles. siRNAs refer to small interfering ribonucleic acids and mRNA refers to messenger ribonucleic acid.

[232] https://www.sciencedirect.com/science/article/pii/S2451929419303845

[233] https://www.sciencedirect.com/science/article/pii/S2666386420302769

[234] https://pubs.acs.org/doi/10.1021/jacs.0c00188

[235] https://pubmed.ncbi.nlm.nih.gov/34357768/

[236] https://cen.acs.org/materials/metal-organic-frameworks/New-coating-technique-protects-MOF/99/web/2021/09

[237] https://pubmed.ncbi.nlm.nih.gov/34357768/

[238] https://www.vectorbiocam.com/home

data of the material as a drug delivery vehicle, including the toxicity and effectiveness through additional in-vivo work for first-in-human studies[239].

Vector Bioscience has attracted £2.7 million in pre-seeding funding in 2022 and 2023, £500,000 from Innovate UK and £2.2 million from the European Innovation Council[240]. This funding will enable the creation of eight jobs by the end of 2023 and fund the planned in-vivo studies. If the results of in-vivo studies are positive, Vector Bioscience plans to enter into partnerships with pharmaceutical companies while developing their own pipeline of assets for oncology indications. Vector will also secure further funding to test the material in clinical trials[241]. In the next 6 to 10 years, positive results from clinical trials may lead to new formulation of drugs for hard-to-treat cancer, with high potential for reducing patient burden and saving lives.

[239] Interview conducted on 1st November 2023 with Prof. Fairen-Jimenez.

[240] https://www.cam.ac.uk/news/cambridge-spin-out-receives-ps2-2-million-to-help-improve-cancer-treatments

[241] Interview conducted on 1st November 2023 with Prof. Fairen-Jimenez.

2.12 IRC programme Partnership Resource Funding

Summary

Building critical mass in healthcare technologies involves gathering relevant expertise and resources to accelerate research and innovation. The Partnership Resource Fund (PRF) is a flexible funding mechanism of the IRC programme which required that 10% of total IRC grant value is allocated to activities for bringing new partners onboard and funding pump priming activities. At the start of the IRC Programme, each IRC outlined a plan for implementing PRF, including workshops to identify new partners and funding for new research projects to generate data or demonstrate feasibility.

In the case of IRC i-sense, the management team set up a dedicated board for managing PRF in 2013, and allocated, beyond the required 10% of the IRC grant, an additional 20% to fund small and high-risk projects ('Exploratory Projects'). The aim was to grow i-sense into a self-sustained hub of innovation, by building networks of excellence with external academic, clinical and industry partners. A total of 12 exploratory projects were funded through three rounds of internal competition, in which universities of the i-sense consortium could bid for funding ranging from £70,000 to £140,000. Under the PRF and Exploratory Projects umbrella, several other activities were conducted at i-sense, including themed workshops with experts, Knowledge Transfer Grants for translating technologies into products and practices, and 16 Mobility Fellowships awarded to researchers to work at other (international) institutions.

Overall, the PRF provided flexibility to IRC management teams to be agile and establish new collaborations, contributing to the expansion of the IRC programme network. In total, 87 distinct organisations were involved in the IRC programme over the 10-year period. Over half of these organisations are UK universities and research institutes, and about 15% are industry. Companies mostly contributed in-kind resources and provided guidance to projects. To illustrate, the PRF enabled:

- New partnerships at i-sense with industry and public authorities, leading to high impact research on digital epidemiology approaches to monitor infectious diseases outbreaks.
- Strengthened SPHERE's ecosystem of digital healthcare research, leading to the creation of a new £6 million Centre for Doctoral Training in Digital Health and Care at the University of Bristol.
- Attracted a large number of universities to the Proteus consortium in 2018, leading to several patents filled in the field of semiconductors and chemical reagents, as well as supported the creation of a Healthcare Technology Accelerator facility based at the University of Edinburgh.

Introduction

A key objective of the IRC programme is to build critical mass to tackle research challenges in healthcare technologies. Building critical mass involves gathering relevant expertise and resources to accelerate research and innovation. To achieve this, each IRC was expected to expand its networks of partners and collaborators over the years, enhancing the expertise needed to generate new knowledge and progress research findings toward new products and services. In addition, IRCs were asked to provide financial support to research projects that showed promise but needed to generate data or demonstrate feasibility. For these reasons, EPSRC funding calls for the IRC programme included a flexible funding mechanism named **partnership resource funding** (hereinafter referred to as 'PRF'). PRF's main objective was to enable IRCs to bring new partners and collaborators onboard and initiate new research

projects together. This mechanism required IRC management teams to allocate 10% of total grant value to any of the activities below[242]:

- Working with new academic partners
- Pump priming activities
- Workshops to encourage new collaborations
- Match funding for projects with partners outside of EPSRC's remit, or those further down the translational route.

This case study investigates how PRF has contributed to the development of critical mass in healthcare technologies. It aims to understand the outcomes and impacts of PRF for the IRC programme as a whole. First, it presents a brief overview of the objectives set out by the IRCs to manage PRF. Then, an overview of the IRCs' network of partners and collaborators are presented. Second, the case of the IRC i-sense is used to deep dive into the management of PRF and its associated activity 'Exploratory projects'. Third, examples of outcomes and impacts enabled by the PRF are presented. Finally, learning and recommendations for future use of PRF in interdisciplinary research collaborations are discussed. Importantly, the case study does not aim to compare the performance of IRCs in managing PRF. Information specific to each IRC is presented to contextualise how the different research areas of focus and objectives have influenced the management processes of PRF across the IRC programme.

Management of partnership resource funding and overview of IRC networks

At the start of the programme, each IRC put forward a list of objectives for implementing PRF. Overall, all IRCs set out to identify new partners and to fund new research projects. SPHERE (2013) provided a timeframe for funding pump priming activities (year 1 to 3) and for bringing a new partner onboard (year 4 to 5). Similarly, TeDDy (2018) proposed annual workshops to identify new collaborations and promising research projects. Proteus (2013) proposed to use PRF for undefined and evolving needs throughout the project, such as regulatory consultancy, sub-contracting and team building activities. I-sense (2013) set out a comprehensive strategy to create 'a self-sustained hub of innovation', through workshops, dissemination activities and leveraging existing partnerships. In addition, i-sense proposed an associated activity 'Exploratory projects', which is further explored in the next section.

Table 2 presents an overview of IRC programme partners and collaborators in the first phase (2013-18) and subsequent phase (2018-23). It provides the number of organisations from the first phase that continued to collaborate in the second phase, as well as those who joined the programme in the second phase. Importantly, data in Table 2 was compiled from programme documentation and stakeholder consultations. However, it may not be complete due to challenges in capturing all collaborations over the 5- or 10-year span. Yet, the data provides insight into the evolution of the network of partners and collaborators in the IRC programme.

Table 2 Number and type of organisations involved with each IRC between 2013 and 2023

IRC *(type of stakeholder)*	First phase (2013-2018)	Second phase (2018-2023)		IRC programme (2013-2023)
	Number of organisations	Number of organisations retained from first phase	Number of new organisations	Total unique organisations involved with the IRC
i-sense	**13**	**8**	**14**	**27**

[242] As outlined in 2012 funding call.

University	*5*	*4*	*5*	*10*
Company	*7*	*4*	*3*	*10*
Healthcare provider	*1*		*1*	*2*
Other			*5*	*5*
Proteus	**8**	**4**	**20**	**28**
University	*4*	*4*	*10*	*14*
Company	*3*		*1*	*4*
Healthcare provider			*2*	*2*
Other	*1*		*7*	*8*
SPHERE	**9**	**4**	**8**	**17**
University	*3*	*1*	*3*	*6*
Company	*2*	*2*	*2*	*4*
Healthcare provider		*0*	*1*	*1*
Other	*4*	*1*	*2*	*6*
TeDDy	**n/a**		**15**	**15**
University			*9*	*9*
Company			*3*	*3*
Other			*3*	*3*

Source: IRC application forms and stakeholder consultations via interviews and email exchange. Data does not include advisory board members. 'Others' include government authorities, research institutes and non-profit organisations.

The data above suggests the first three IRCs (Proteus, SPHERE and i-sense) retained approximately 50% of partners and collaborators in the second phase of the IRC programme. Over 40 new organisations joined the first three IRCs in the second phase, primarily universities (n = 18) and 'other' organisations (n = 14), such as research institutes, government authorities and non-profit organisations. This indicates the IRC programme has successfully enabled the network of partners and collaborators to grow from 30 organisations (first phase) to 73 organisations (second phase), including TeDDy. In total, over 85 distinct organisations have been involved in the IRC programme in both phases.

i-sense management of PRF and Exploratory projects

In 2013, the interdisciplinary research collaboration i-sense set out a comprehensive strategy for managing PRF. In addition to PRF, i-sense's management team proposed that an additional 20% of total IRC grant funds would be allocated to small and high-risk projects ('Exploratory Projects)'. In this section, these activities under i-sense's PRF strategy are described.

The PRF and the exploratory projects at i-sense were overseen by a dedicated board led by Professor Vincent Emery, a member of i-sense's management team. The board consisted of internal and external members including from universities, industry and healthcare settings. The board had oversight over several activities under the PRF, which are described in Table 3.

Table 3 Summary of activities of i-sense's partnership resource and exploratory project funding

Activities	Summary
Themed workshops	I-sense led and/or collaborated to deliver several workshops with experts on relevant topics, such as infectious diseases.

Knowledge Transfer Awards	I-sense provided funding for translation of technologies developed at i-sense (£20,000 to £40,000).
Mobility fellowships	A total of 16 mobility fellowships were awarded to researchers to visit and/or work abroad for short periods of time (£5,000 to £10,000).
Communications and Engagement	Dedicated staff was hired for delivering digital communications and public patient engagement events.
Education Alliance	Training and events to develop postdoctoral researchers and students' skills on relevant subjects, such as scientific communication.
Exploratory Projects	I-sense funding for high-risk projects to close 'expertise gaps' in the consortium. A total of 12 projects were funded.

I-sense's exploratory projects

IRC i-sense allocated 20% of IRC grant funds to 12 exploratory projects through three rounds of internal competition since 2013. This scheme provided universities of the i-sense consortium an opportunity to bid for funding, ranging from £70,000 to £140,000, for high-risk projects with potential for high impact.

The funding call required the completion of a short application form detailing project aims, activities, type of costs required, timeframe and other aspects. The applications were assessed by the PRF board against four criteria: a) alignment with i-sense's mission; b) suitability of proposed budget; c) completeness of project details; d) likelihood of impact. This assessment provided a fair mechanism for allocating funds to projects with potential for high impact. On some occasions, partial funds were offered to applications whose total project amount exceeded the budget available[243].

The funding of exploratory projects enabled research in a range of disciplines and generated data to support further studies[244]. Examples of exploratory projects funded by i-sense include:

- Analysis of ethical and regulatory challenges for building and maintaining public trust in early warning sensing system of influenza (UCL[245], LSHTM[246], PHE[247]).
- Development of low-cost mobile phone spectrometer for point-of care tests for influenza (UCL and Imperial College London).
- Exploiting microfluidics and printing technologies to detect bacterial infections (UCL, Newcastle University and PHE).
- Improving accuracy of flusurvey, a large crowd-sourced study enabling digital health detection of influenza in the community (UCL, LSHTM, PHE).

Outcomes and impact

The growth of the IRC's network discussed in previous sections contributed to several outcomes with impact on research, health and the economy. For example, i-sense's themed workshops helped to secure partnerships with industry and public authorities, enabling secondments of researchers and collaborative research[248]. I-sense's work with Microsoft Research and Public Health England produced computer science models for digital epidemiology approaches to monitor infectious disease outbreaks. This work was adapted during the COVID-19 pandemic

[243] Interview conducted on 29 September 2023 with Prof. Vincent Emery.

[244] Interview conducted on 29 September 2023 with Prof. Vincent Emery.

[245] University College London.

[246] London School of Hygiene & Tropical Medicine.

[247] Public Health England.

[248] Interview conducted on 29 September 2023 with Prof. Vincent Emery.

to support surveillance systems at the UK Health Security Agency, contributing to national policies for responding to the health emergency[249].

The research and data generated at SPHERE on sensors for characterising health-related behaviours created a unique resource for research in health, social sciences and other disciplines. The PRF enabled new partnerships to exploit this data and strengthen an ecosystem of digital healthcare research within SPHERE's consortium. This supported the creation of a new £6 million Centre for Doctoral Training in Digital Health and Care[250] and a MSc in Digital Health[251] at the University of Bristol.

The PRF also enabled a significant number of new universities to join Proteus's network in the second phase of the IRC programme. A total of 11 patents were filed by Proteus partner universities, in the field of semiconductors, chemical reagents and other tools relevant for medical optical imaging. These inventions have enabled the creation of several spinout companies in the field of life sciences, with potential for economic impact via sales of products and job creation in the UK. In addition, Proteus researchers supported the creation of a Healthcare Technology Accelerator facility based at the University of Edinburgh, which seeks to remove barriers for development and translation of novel technologies[252].

Learnings and recommendations

The examples of outcomes summarised above suggest the requirement for partnership resource funding actually enabled the IRC programme to focus on growing the network of partners and aggregate the expertise to accelerate research and innovation in healthcare technologies. According to stakeholder consultations with IRC leads, the main value of the PRF was that it provided flexibility to IRC management teams to be agile and establish new collaborations and set up new high impact projects within the IRC. This promoted change within partner universities and supported the creation of an ecosystem of research in healthcare technologies. Similarly, themed workshops and mobility fellowships were important to communicate research conducted at IRC, create new partnerships and enhance the skills of individual fellows. According to one interviewee at i-sense[253], these initiatives were key to establishing collaborations with Google, the Africa Health Research Institute and other organisations.

While the PRF mechanism was successful in enabling new collaborations throughout the IRC programme, it proved less effective in attracting active industry partners. Specifically, funding levels allocated for pump priming activities (or exploratory projects) was relatively low for companies, making it challenging for them to engage in research projects. Ten key industry partners were identified that typically contributed in-kind resources or took advisory roles in projects[254]. A key example is Microsoft Research, who joined i-sense's 'Track' research strand and provided critical input to the first ever assessment of influenza vaccination using internet data[255].

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[249] https://www.ukri.org/news/report-reveals-impact-of-covid-19-research-and-innovation-funding/
[250] https://gtr.ukri.org/projects?ref=EP%2FS023704%2F1
[251] https://www.bristol.ac.uk/study/postgraduate/taught/msc-digital-health/
[252] https://healthcare-technology-accelerator.ed.ac.uk/about-us
[253] Interview conducted on 29 September 2023 with Prof. Vincent Emery.
[254] Interview conducted on 29 September 2023 with Prof. Vincent Emery.
[255] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4327439/

Limitations

The analysis of the PRF mechanism proved challenging for the evaluation team and exposed weaknesses in IRCs collecting and recording monitoring information. This gap could not be sufficiently filled via stakeholder consultation and desk research. In some cases, staff turnover contributed to losing access to key individuals. Therefore, a more detailed examination of the implementation and outcomes of the PRFs in the context of the four IRCs was not possible.

2.13 IRC programme's contribution to skills and career development

Summary

At i-sense, mobility fellowships provided a maximum allowance of up to £10,000 per fellowship to cover travel, subsistence costs, and course fees from the Partnership Resource Fund[256]. In total, i-sense provided 16 mobility fellowships to PDRAs, PhD students and other academic staff.

Researchers made use of this opportunity to acquire new research skills through placements with leading research groups in the USA, Australia, South Africa, Myanmar and other countries. For example, a former PhD student from Imperial College London received a five-week placement at the Cluster for Advanced Macromolecular Design at the University of New South Wales in Sydney, Australia. The aim of the placement was the acquisition of polymer chemistry skills for the development of an enzyme responsive polymer-based platform for enabling early HIV detection[257].

The funding also helped researchers to gain understanding of the local challenges involved in implementing healthcare technologies. A former PhD student from University College London worked for seven weeks at Population Services International (PSI) in Myanmar, to support the introduction of HIV self-testing in the country. PSI is a global network of local organisations working to bring healthcare closer to those most in need[258]. At PSI, the PhD student designed the timeline, protocol and study for the organisation's approach for implementing HIV self-tests at scale for target populations in Myanmar. Other researchers visited and trained at the World Health Organization, Massachusetts Institute of Technology, the Africa Health Research Institute and other organisations.

Introduction

The EPSRC's Interdisciplinary Research Collaborations programme in Healthcare Technologies (hereinafter referred to as 'IRC programme') consists of three collaborations in sensing systems running from 2013 to 2023 (i-sense[259], Proteus[260] and SPHERE[261]), and one collaboration in targeted therapeutic delivery running from 2018 to 2024 (TeDDy[262]). A lead university is responsible for managing the interdisciplinary research collaborations (IRCs), which involve partnerships with other universities, industry, healthcare and other organisations. At the start of the programme, each IRC set out a list of objectives for contributing to capacity building and career development of postdoctoral researchers (PDRAs) and PhD students[263] associated with the IRC. Table 4 below provides a summary of these objectives.

[256] i-sense internal funding opportunities. https://www.i-sense.org.uk/projects/i-sense-internal-funding-opportunities. Accessed 16 November.

[257] https://www.i-sense.org.uk/science-sunny-sydney. Accessed 7 December 2023.

[258] Population Services International. https://www.psi.org/about/. Accessed 7 December 2023.

[259] EPSRC IRC in Agile Early Warning Sensing Systems for Infectious Diseases and Antimicrobial Resistance

[260] Multiplexed 'Touch and Tell' Optical Molecular Sensing and Imaging - Lifetime and Beyond

[261] A Sensor Platform for HEalthcare in a Residential Environment

[262] Targeted Drug Delivery for Hard-to-Treat Cancers

[263] Note that no fellowship funding was available to PhD students via the IRC programme

Table 4 Proposed IRC objectives for capacity building and career development

IRC	Capacity building and career development objectives
i-sense	To prepare students for future career development through an internal 'Education Alliance' programme, which would provide training, deliver workshops and organise mobility fellowships to PDRAs and other associated staff[264].
Proteus	To provide a fertile interdisciplinary environment for training a new cadre of translational scientists in the physical and biological disciplines to allow reaping of the clinical and commercial dividends of a new scientific era[265].
SPHERE	To ensure PDRAs, PhD and MSc students associated with the IRC will have the unique day-to-day experience of working with world-class clinical specialists[266].
TeDDY	To support career development of PDRAs within or outside academia through mentorship programmes, seminars, secondments, and workshops[267].

This case study investigates the implementation of the objectives outlined above and the resulting outputs and outcomes. Document review and a set of interviews with nine PDRAs and PhD students associated with the IRCs were carried out to further our understanding of the key activities conducted throughout the programme. We highlight examples, as reported by interviewees, of how these experiences contributed to the development of skills and career progression of IRC programme researchers.

Based on data made available to the study team, we estimate that at least 160 early-career and mid-career researchers benefited from these capacity building and career development activities throughout the IRC programme, including PhD students, PDRAs, Research Associates, and other academic staff.

IRC activities and outputs for skills and career development

Interdisciplinary research projects

Several PDRAs and PhD students involved with the research conducted at the IRCs noted the interdisciplinary research environment was a key element for learning new skills and new methods. The IRC programme exposed them to other disciplines, experts and clinicians from different backgrounds, enabling them to learn how interdisciplinary research can tackle difficult problems in healthcare. In addition, the interdisciplinary research environment enabled PhD students to contribute to research by producing papers and disseminating their work to a wide audience through conferences.

In interviews, researchers highlighted the importance of the IRC programme in improving their research skills. At the start of the programme, some PhD students had limited technical skills. Through mentorship activities, lab training and secondments, the IRC programme enabled them to develop in-demand technical skills, which facilitate career development within and outside academia. For example, as a result of participating in TeDDy, one PDRA at the University of Cambridge noted significant improvements in their coding skills, which would not have happened without the support from the IRC programme. Similarly, a former PDRA at SPHERE reported the development of technical skills in computer vision and machine learning. A former PhD student from Proteus highlighted that working with optical medical imaging

[264] i-sense case for support form 2013

[265] Proteus case for support form 2013

[266] SPHERE core proposal form 2013

[267] TeDDY IRC case for support form 2018

systems at the IRC enabled them to develop a broad range of 'rare skills' in physics and healthcare.

Importantly, some IRC projects helped PDRAs to gain an understanding of the challenges around conducting research in resource-limited settings. For example, a former PDRA from i-sense was involved in the mAfrica project, in partnership with the Africa Health Research Institute (AHRI) in KwaZulu-Natal, South Africa. This project involved interacting with the public and implementation of large-scale population surveys in South Africa.

IRC meetings

Regular meetings to track project progress and to promote knowledge exchange activities were highlighted by interviewees as important factors to the success of skills development. For instance, researchers at Proteus conducted meetings with the entire team to track-progress and milestones, along with weekly presentations from associated PhD students and monthly reports from project staff. As part of these meetings, PhD students were required to present their works to other IRC staff, which helped to develop their communication and presenting skills. It was also noted that the IRC programme enabled PDRAs to strengthen their leadership skills by conducting meetings and co-leading projects.

Workshops and training activities

All IRCs organised and delivered workshops and training activities to enable PhD students and PDRAs to learn new technical and non-technical skills. In 2014, i-sense established an internal programme named 'Education Alliance', to introduce new dedicated teaching and training events to grow the interdisciplinary skills of postgraduate students and researchers. Led by Dr Neil Keegan, University of Newcastle, the programme was designed to inspire i-sense members and prepare them for future careers[268]. Education Alliance workshops covered various themes such as enterprise, innovation, commercialisation, communication and presentation skills. A key example highlighted in interviews was a data visualisation masterclass, facilitated by the Guardian. The aim of the masterclass was to provide i-sense students and researchers with the tools to support their presentation and dissemination activities[269].

In addition to workshops and training, interviewees from all IRCs highlighted the importance of career talks and mentoring sessions. These activities helped PDRAs to understand career options within and outside academia[270] and connected researchers with opportunities to take up secondments in industry. Table 5 provides a non-exhaustive list of workshops and training activities delivered by each IRC[271].

[268] Education Alliance. https://www.i-sense.org.uk/research-and-training/education-alliance. Accessed 7 December 2023.

[269] Education Alliance statistics and data visualisation workshops. https://www.i-sense.org.uk/education-alliance-statistics-and-data-visualisation-workshops-0. Accessed 16 November.

[270] Dr Niamh Fox and Dr Etienne Rognin personal communication. 22 September 2023

[271] This non-exhaustive list of activities is based on data made available via interviews, email exchange and project documentation.

Table 5 Workshops and training activities by IRC

IRC	Type of activity	Themes
i-sense	Career development events	• Structured career development action plans and regular mentorship. • Careers Day: Learning from i-sense alumni: 3 funder talks, 7 alumni talks, 42 attendees. • Q&A with experts. • Virtual career workshops facilitated by coaching expert
	Conferences	• The Future of Healthcare Technology
	Workshops & training	• Enterprise, innovation & commercialisation • Annual event on networking and communication skills • Diagnostics development, evaluation, policy development and implementation • Preparing for global health response • Designing trials of diagnostic test accuracy • Data visualisation masterclass • Infographics workshop
Proteus	Career development events	• Line management for academic mentoring of early career researchers • Regular peer-to-peer support
	Workshops & training	• Public engagement and presentation skills • Grant writing • Intellectual property protection & commercialisation • Project management • Good manufacturing practice • Good clinical practice • Medical device / pharmaceutical assurance training
SPHERE	Workshops & training	• Communication skills • Research ethics • Lecturing skills • Intellectual property protection • Good clinical practice • Working with children • Scenario-based workshops for technical staff working inside private homes
TeDDy	Career development events	• Mentoring breakfast with senior academics • Careers mentoring sessions • Careers talk: Pharmaceutical R&D; Founding a start-up; Becoming an independent academic
	Conferences	• Annual meetings with all IRC members
	Workshops & training	• Intellectual property protection • Nanomaterials in therapeutics • Cancer therapies • Novel drug delivery vehicles • Medical devices innovation

I-sense Mobility Fellowships

Mobility fellowships enable researchers at IRCs to work or train at leading national and international teams in industry, healthcare, government agencies and research institutes. We use the case of i-sense's mobility fellowships to discuss the resulting outputs. At i-sense, mobility fellowships provided a maximum allowance of £10,000 per fellowship to cover travel,

subsistence costs, and course fees from the Partnership Resource Fund[272]. In total, i-sense provided 16 mobility fellowships to PDRAs, PhD students and other academic staff.

Researchers made use of this opportunity to acquire new research skills through placements with leading research groups in the USA, Australia and other countries. For example, a former PhD student from Imperial College London received a five-week placement at the Centre for Advanced Macro-molecular Design at the University of New South Wales in Sydney, Australia. The aim of the placement was the acquisition of polymer chemistry skills for the development of an enzyme responsive polymer-based platform for enabling early HIV detection[273].

The funding also helped researchers to gain an understanding of the local challenges involved in implementing healthcare technologies. A former PhD student from University College London worked for seven weeks at Population Services International (PSI) in Myanmar, to support the introduction of HIV self-testing to the country. PSI is a network of local organisations working to bring quality healthcare closer to those who need it the most[274]. At PSI, the PhD student designed the timeline, protocol and study for the organisation's approach for at-scale implementation of HIV self-tests for key populations. Other researchers visited and trained at the World Health Organisation, Massachusetts Institute of Technology, the Africa Health Research Institute and other organisation.

Outcomes and impact

The findings above suggest the IRC programme has provided an important training ground for early and mid-career researchers to acquire relevant skills in interdisciplinary research and support their career progression. Researchers at the IRCs worked in a real-world interdisciplinary research environment, benefitting from both day-to-day training and formal training activities, in technical areas such as good manufacturing practices and diagnostics development. In addition, non-technical training in a wide range of topics helped to strengthen researchers' knowledge relevant for academia and beyond, such as in research ethics and commercialisation activities.

In addition to training, other activities such as conferences and career developments events played a vital role in connecting individuals with job opportunities, placements and secondments. ResearchFish data on 'Next Destinations' (n = 117) and secondments (n = 32) suggests many PDRAs, PhD students and others associated with the IRC have moved to new roles. Several examples were provided in stakeholder consultations, with researchers moving to research institutes, universities, companies and other organisations:

- Several PDRAs reported new technical roles in established companies and start-ups in the fields of information technology, pharmaceuticals, life sciences instrumentation, semiconductors and others.
- PDRAs also reported new academic roles including lectureships and postdoctoral roles in the UK and abroad.

[272] i-sense internal funding opportunities. https://www.i-sense.org.uk/projects/i-sense-internal-funding-opportunities. Accessed 16 November.

[273] https://www.i-sense.org.uk/science-sunny-sydney. Accessed 7 December 2023.

[274] PSI. https://www.psi.org/about/. Accessed 7 December 2023.

- PhD students reported secondments and postdoctoral roles at universities and research institutes, such as the Clinton Health Access Initiative, Joint Biosecurity Centre and the National Institutes of Health in the USA

By establishing training opportunities, the programme has contributed to the UK's skills supply for research and innovation in healthcare technologies, in particular, sensing systems for healthcare and targeted therapeutics delivery. This new cohort of researchers will strengthen the UK's capacity to conduct interdisciplinary research and supply highly skilled professionals to industry, government, healthcare and other organisations, as evidenced above. It is likely that in addition to the 160+ early-career and mid-career researchers that directly interacted with the IRC programme, a much larger number of researchers will benefit from the programme in the future through their multiplier effect. Together, the findings of this case study suggest that the IRC programme had played a substantial role in enhancing specialist skills and creating capacity for UK research and innovation in healthcare technologies.

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