Institution: Loughborough University

Unit of Assessment: UOA8 - Chemistry

Title of case study: Enabling rapid analysis of diagnostic biomarkers for improved health screening

Period when the underpinning research was undertaken: 2007 to the current day

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Dr J C Reynolds	**Senior Lecturer Mass Spectrometry**	**2007 to current**
Prof C L P Thomas	**Chair of Analytical Science**	**2007 to current**
Prof C S Creaser	**Chair of Analytical Chemistry**	**2007 to 2017**
Dr M A Turner	**Experimental officer and then CAMS Lecturer**	**2013 to current**

Period when the claimed impact occurred: 2013 to current

Is this case study continued from a case study submitted in 2014? N

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

Personalised therapy and health and safety screening both require rapid, point-of-care, non-invasive measurements. Loughborough University's chemists developed novel interfaces to address this need. The interfaces were manufactured and marketed by commercial partners, leading to two impacts: 1) **Improved health screening**: Advion's *vAPCI* system allowed microbiologists to identify biomarkers for wound-infection, enabling the design of "smart" dressings, and it facilitated the detection of potential toxicants on the International Space Station and in foodstuffs; Owlstone's award-winning *ReCIVA* breath-biopsy has transformed the capabilities of clinical researchers worldwide to conduct diagnostic breath-testing; IMSPEX's *BreathSpec* has enabled worldwide efforts to differentiate COVID-19 from other respiratory conditions. 2) **Economic benefits** for Advion stem from *vAPCI* generating $1M in sales; for Owlstone through their supplying of the system to over a hundred sites worldwide, and for IMSPEX through confirmed orders worth £6.5M.

2. Underpinning research (indicative maximum 500 words)

The ability to make measurements rapidly at the point of care or location where investigation is taking place has been a major goal of analytical science. The capacity to make accurate *in-situ* measurements rapidly enables key decisions to be made immediately, improving outcomes, saving money and facilitating real time monitoring of processes and events. When the Centre for Analytical Science was founded in 2007 it brought together expertise in mass spectrometry, ion mobility spectrometry, breath analysis (CLPT) and direct analysis using ambient ionisation methods (CSC, JCR). Breath analysis was a key research focus and, by using an adaptive breath sampler concept, reproducible and reliable monitoring of breath volatiles from unwell and breathless participants was routinely conducted [**R1**]. By combining thermal desorption tube sampling (using the adaptive breath sampler) with ambient ionisation IMS-MS (ion mobility spectrometry - mass spectrometry), it became possible to analyse samples much faster, using the high resolution of IMS-MS instead of a chromatographic separation. Our work revealed that this approach enabled rapid, accurate IMS and MS-based identification of disease and drug biomarkers [**R2**].

Based on the strength of our work in adaptive breath sampling, in 2015 we were asked to input into Owlstone's *Breathfree* project which led to the development of the *ReCIVA* breath sampler. Close interaction with Owlstone Medical, a world leader in breath biopsy, enabled designs, concepts, technical challenges and solutions to be shared. The *ReCIVA* was subsequently deployed into clinical-studies in the MRC-EPSRC EMBER breathomics project, with operational

feedback supporting its development for four years [**R3**], resulting in the next-generation *Re*CIVA being released in 2019.

Moving these measurements out of the laboratory and enabling *in-situ* analysis was the next step. IMS is an ideal candidate for *in-situ* analysis as it does not require a vacuum system and can be more portable and through collaboration with clinical partners in respiratory disease feasibility studies, we demonstrated that GC-IMS can aid COPD diagnosis at the point of care [**R4**]. As a result of this, we began collaborating with Imspex Diagnostics Ltd, an ion mobility instrument manufacturer in 2015 to adapt their Breathspec instrument for point-of-care use in the H2020 mass casualty project TOXI-triage. Extensive world-wide studies in radiation, pesticide and alcohol toxicity-assessment culminated in successful international emergency field exercise demonstrations and subsequent GC-IMS deployments to USA, Canada, Europe, UK and Asia for COVID-19 testing (**R5**].

Following on from this, the Loughborough team identified mass spectrometers developed by Advion Inc, globally leading instrument manufacturers, as being suitable for *in-situ* analysis (being compact as well as robust). Direct breath sampling into the mass spectrometer was a significant challenge which we addressed by refining a micro-jet gas flow venturi pump originally developed at Loughborough for use with laser ablation ICPMS systems. This custom-made device proved very effective, and close interaction between the groups allowed the lessons learned during its fabrication to be acted upon [R6]. University funding supported the development of a transformational sample/mass spectrometer interface (JCR/MAT) based on a revised pump, capable of very-fast run times (< 30 s). Embedded support from Advion meant research on trace level analyte transport was rapidly placed into instrument designs, leading to a new product – *vAPCI* - in 2015, which has been marketed worldwide by Advion to a range of end-users and has found applications beyond its original scope.

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

[R1] C. Guallar-Hoyas, M. A. Turner, G.J. Blackburn, I.D Wilson and C.L.P. Thomas, "A workflow for the metabolomic/metabonomic investigation of exhaled breath using thermal desorption GC–MS", *Bioanalysis,* 2012, 4, 2227–2237 doi: doi.org/10.4155/bio.12.193.

[R2] J.C. Reynolds, G.J. Blackburn, C. Guallar-Hoyas, V.H. Moll, V. Bocos-Bintintan, G. Kaur-Atwal, M.D. Howdle, E.L. Harry, L.J. Brown, C.S. Creaser, and C.L.P. Thomas, "Detection of volatile organic compounds in breath using thermal desorption electrospray ionization-ion mobility-mass spectrometry", *Anal. Chem.*, 2010, 82, 2139 – 2144. doi: 10.1021/ac9027593

[R3] W. Ibrahim, M. Wilde, R. Cordell, D. Salman, D. Ruszkiewicz, L. Bryant, M. Richardson, R.C. Free, Bo Zhao, A. Yousuf, C. White, R. Russell, S. Jones, B. Patel, A. Awal, R. Phillips, G. Fowkes, T. McNally, C. Foxon, H. Bhatt, R. Peltrini, A. Singapuri, B. Hargadon, T. Suzuki, L.L Ng, E. Gaillard, C. Beardsmore, K. Ryanna, H. Pandya, T. Coates, P.S. Monks, N. Greening, C.E. Brightling, C.L.P. Thomas, S. Siddiqui, "Assessment of breath volatile organic compounds in acute cardiorespiratory breathlessness: a protocol describing a prospective real-world observational study", *BMJ Open* 2019, 9:e025486. doi: 10.1136/bmjopen-2018-025486.

[R4] M. Basanta, R.M. Jarvis, Yun Xu, G. Blackburn, R. Tal-Singer, A. Woodcock, D. Singh, R. Goodacre, C.L.P. Thomas and S.J. Fowler, "Non-invasive metabolomic analysis of breath using differential mobility spectrometry in patients with chronic obstructive pulmonary disease and healthy smokers" *Analyst*, 2010, 135, 315–320. doi: 10.1039/b916374c

[R5] D.M Ruszkiewicz, D. Sanders, R. O'Brien, F. Hempel, M.J Reed, A.C Riepe, K. Bailie, E. Brodrick, K. Darnley, R. Ellerkmann, O. Mueller, A. Skarysz, M. Truss, T. Wortelmann, S. Yordanov, C.L.P. Thomas, B. Schaaf, M. Eddleston, "Diagnosis of COVID-19 by analysis

of breath with gas chromatography-ion mobility spectrometry - a feasibility study", EClinicalMedicine, 2020, 29, 100609, doi:https://doi.org/10.1016/j.eclinm.2020.10060

[R6] L.M. Heaney, D.M. Ruszkiewicz, K.L. Arthur, A. Hadjithekli, C. Aldcroft, M.R. Lindley, C.LP. Thomas, M.A. Turner, J.C. Reynolds, "Real-time monitoring of exhaled volatiles using atmospheric pressure chemical ionization on a compact mass spectrometer", *Bioanalysis*, 2016, **8**, 1325–1336. doi: 10.4155/bio-2016-0045.

The underpinning research was published in international peer-reviewed journals and was supported by competitively awarded funding including £3.5M from MRC/EPSRC (£331K to Loughborough Chemistry) for the project "East Midlands Breathomics Molecular Pathology Node (EMBER)" (2015-2019), and £9.97M from European Commission Horizon 2020 (£1.1M to Loughborough Chemistry) for "TOXItriage" (2015-2019).

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

The three companies who have commercialised the products resulting from our research discovered our original results through publications and conference interactions and then built collaborations by loaning us equipment and working with our PhD students. **Advion**, who are global leaders in the manufacture of compact mass spectrometers and other analytical tools for reaction analysis, clinical and environmental monitoring, have their international HQ in New York State, with Loughborough working closely with their European hub in Harlow. **Owlstone Medical** are at the forefront of work to facilitate early screening for cancers via biomarkers. They are based in Cambridge and their aim is to build enough capacity to save "100,000 lives and save health care providers $1.5B" through breath test diagnosis. **IMSPEX Diagnostics**, based in South Wales, lead in the development and application of Ion Mobility Spectrometry (IMS) diagnostic testing technology. Collectively, the commercialization of our research led to two impacts:

Impact 1: Improved health screening capabilities for clinicians and researchers

The ease-of-use, analytical-sensitivity and flexibility of the vAPCI system has improved the ability of end users to better conduct biomarkers analysis and other types of screening. Work at Queens University Belfast on smart dressings for potentially infected wounds confirmed its importance in rapidly monitoring the volatile material released by deleterious bacteria. Prof Brendan Gilmore reported that

> "The vAPCI system has been an invaluable part of this work, providing us with capabilities we could not have accessed through any other system. Key to this is the speed and accessibility that vAPCI provides, allowing rapid assessment of results directly from model wounds in the microbiology laboratory, negating the requirement for samples to be taken and transported to a specialist mass spectrometry facility …. The work thus far could not have been done in its current form, or progressed, without the use of vAPCI." [**S1**]

The system has also been used to by the US FDA to conduct food safety screening. It also finds use in the rapid screening of exogenous materials such as those found in the International Space Station's manifest (it is vital that everything launched to the ISS is assessed for potential air contaminants right down to personal care products such as deodorants) [**S2**].

Figure 1: The Loughborough derived technology (L-R, Advion vAPCI, Owlstone ReCIVA and IMSPEX Breathspec).

Using the system for breath biopsy, Owlstone report that it has improved the development of probes for rapidly and non-invasively staging liver disease, along with identification of targets for almost 90 % of stage 1 cancers. Further, the fact they have used ReCIVA to assess exposure to toxicity in the work-place extends the domain of breath-testing into disease *prevention*. Indeed, in a short time Owlstone Medical have developed ReCIVA breath-testing to the point where it may be considered as a standard component in large-scale clinical research programmes. Inclusion in studies by AstraZeneca, GlaxoSmithKline, the Cleveland Clinic, the NHS and Actelion Pharmaceuticals Ltd testifies to this claim. As noted by Billy Boyle, the CEO of Owlstone Medical:

> "Your research demonstrated, convincingly, how pressure-controlled adaptive-breath sampling in combination with thermal desorption methodologies provided reproducible analytical methods for characterising breath biochemistry. These concepts lie at the heart of our ReCIVA and Breath-Biopsy®….We have supplied ReCIVA to over 100 clinical and academic sites worldwide." [**S3**]

Finally, IMSPEX have deployed their Breathspec GC-IMS breath analyser to various radiotherapy, emergency departments, and toxicity centres across Europe and into Asia. This drove the development of single use bio-secure at-patient breath-samplers and the introduction of better instrument gas-management systems. We ran 2 large multi-national crisis exercises involving seven nations and 25 organisations where IMSPEX convincingly demonstrated their capability. After this, their point-of-care breath-test system was adopted world-wide during 2020 as teams across the world adopted their system in their COVID-19 test development strategies. Santi Dominguez, Chairman and CEO IMSPEX Diagnostics Ltd stated that

> "Your project's emergency medicine focus led us to introduce easy-to-use, rugged and biosecure breath-samplers for use in emergency departments and for point-of-care applications. We also developed and introduced stand-alone gas-management systems that enable rapid deployment of our Breathspec; including in-community, and ambulance-based, applications with breath-tests taking less than 1 min." [**S4**]

Impact 2: Economic benefits to Advion, Owlstone and IMSPEX

For each company, our work has directed the development and efficacy of their products, in the process delivering a concomitant financial benefit to the company.

a) Advion

The vAPCI interface has been sold to academic researchers, industry and government agencies in the UK, Europe, Asia, and North America. The economic benefit for Advion has been significant, according to Dr Mark Allen (Vice President, Managing Director – Europe) [**S2**]:

> "The value of this to my organisation is measured in more than instruments sales (approx. $1M associated with the vAPCI and other ion sources) as it allows us to analyse a broader compound space and markets otherwise unexplored."

b) Owlstone

Owlstone adopted our adaptive-sampler concept through our collaborative participation in the BreathFree consortium that resulted in the realisation of their ReCIVA breath sampler. This product was awarded the Mac Robert Award in 2018 and enabled them to develop their Breath Biopsy system. In 2016 Owlstone formed Owlstone Medical, and Owlstone Medical has since grown rapidly. As they note [**S3**]:

> "I have seen our ReCIVA and Breath Biopsy® becoming a standard component of disease research and biomarker discovery. We have applied advanced and innovative breath-testing to liver disease, COVID-19 diagnosis and prognosis, occupational exposure, autoimmune diseases, pulmonary hypertension and cancer. We have established ourselves as world-leaders in the field of breath-testing backed by $93M in investment, with ~£3M revenues in 2018-2019."

c) IMSPEX

As the CEO of IMSPEX confirms, the results of work with Loughborough have had significant impact on its global presence:.

> "The impact of your research has been profound. There was a 1,100% increase in our orders to £6.5M already in the order book in 2021. We have retained significant new customers who are operating at a transformative pace and scale, e.g. Verily Life Sciences (USA), and British Columbia Cancer (Canada). We have entered a new round of funding for our company to develop this capability. Without Loughborough's work, leadership and support, especially that described in their Lancet EClinMed paper, we would not have been in the strong position we find ourselves. We would not have been able to respond, and partner, in the delivery of 40 (with a further 100 in the current order book) rapid point-of-care systems for respiratory disease breath tests, including COVID-19 detection, as quickly and effectively as we have." [S4]

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

[S1] Testimony letter from Prof Brendan Gilmore, Queen's University Belfast (2020)
[S2] Testimony letter from Mark Allen, Vice President and Managing Director Advion (2020)
[S3] Testimony letter from Billy Boyle, CEO of Owlstone Medical (2020)
[S4] Testimony letter from Santi Dominguez, Chairman and CEO IMSPEX Diagnostics (2020)