Institution: Nottingham Trent University (NTU)

Unit of Assessment: A03 – Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Translating biomedical nanotechnology into commercially viable, nutritionally enhanced plant feeds for the horticultural industries.

Period when the underpinning research was undertaken: 2006 – 2020

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

Names:	Roles:	Periods employed by submitting HEI:
Gareth W V Cave	Principal Lecturer	2005-present
Robert Rees	Professor of Tumour Biology	1996-2020
Selman Ali	Senior Lecturer in Immunology	1996-2020
Philip Bonner	Senior Lecturer in Applied Biosciences	1991-present

Period when the claimed impact occurred: August 2015 to 31 December 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

NTU's patented research in nanoparticle coating and production,` originally for cancer drug delivery, have been commercialised in 'nano fertiliser' plant and crop mineral biofortification products by new NTU spin-out Pharm2Farm Ltd. Pharm2Farm was acquired by Remote Monitored Systems PLC. through a £2.37 million share issue, and has a current market valuation of £40 million. Pharm2Farm's global sales of biofortification products, direct and via third parties, span the territories of Australia, South Korea, India, Canada, and USA, and have provided increases in turnover for suppliers and retailers and yield and income for farmers.

2. Underpinning research

NTU iron oxide nanoparticle technology was developed originally by Cave in immunology research to allow MRI detection and tracking of exosomes in cancer drug delivery, working alongside colleagues Robert Rees and Selman Ali in the NTU Biomedical Research Unit (**G1**) (**R1**), and in collaboration with MRI Imaging experts in the NTU Engineering Research Unit. The 13 nm size super paramagnetic iron oxide nano particles were synthesized by adapting standard literature protocols (**R1**). Cave's continuing work in collaboration with MRI Imaging experts in the NTU Engineering Research Unit demonstrated how super paramagnetic iron oxide nano particles could be exploited in a novel localised MRI readable DNA system, replacing the traditional approach of using fluorescent markers (**R2**).

Realising the yet greater potential for further innovation in new nano-bio-technology systems, Cave extended the scope of the research into developing new coating and high throughput synthetic methods to scale up nano particle fabrications significantly above research volumes and into extending the techniques to metal compounds beyond iron. Innovations followed that built on the expertise that Cave developed on fabricating the iron oxide nanoparticles for MRI contrast agents that underpinned the above research accomplishments in cancer immunology and in MRI readable DNA systems (**R1**, **R2**).

The first key innovation to result from this research was a patented (**R3**) method to coat a range of different varying metal oxide nanoparticles, typically in the size range 2 nm to 100 nm, with organic compounds, by mechanically combining the mineral nanoparticles with an organic biomolecule, via electrostatic interactions, in a dry mixing process. The fields of the work disclosed in the invention encompassed creating bioavailable materials to address trace element deficiency in humans, as well as new methods to increase levels of micronutrients in food crops. The second key innovation to result from this research was a patented (**R4**) continuous flow process for producing suspensions of mineral nanoparticles. In the proof-of-concept research Cave demonstrated volume production of high uniformity (size and shape) nanoparticles based on a process whereby liquid materials react on the surface of a spinning disk, with particle size controlled by temperature, concentration and the retention time on the spinning disc. This reactor was capable of producing over one kilogram of nanoparticles per hour compared with one kilogram per day with the commercially available technology at the time, reducing solvent use, and providing a high level of nanoparticle uniformity. The patented reactor design and processing techniques

were further optimised with commercial partners to produce over ten kilograms per hour with a reactor footprint of only one square meter.

A confidential clinical trial conducted by NTU researchers and a major pharmaceutical company in 2013 demonstrated the efficacy of the bioavailability concepts (**R3**) in humans (*n* = 40), demonstrating that NTU's vitamin C coated iron mineral nanoparticles significantly increased ferritin levels by 21%, with respect to the control, and 3% more compared to traditional iron supplements. In animals, NTU researchers conducted a study in Ross-308 broiler chickens (*n* = 384) over 35 days, which demonstrated that supplementing the bird's diet with nanoparticles of zinc coated with methionine, in place of conventional zinc supplements, resulted in a 5% increase in bird growth (**R5**). Cave's innovative biofortification ideas and techniques (**R2**) and (**R3**) were applied to commercial livestock production within the joint NTU-Agrimin Innovate UK research translation KTP grant (**G2**). This project developed, and demonstrated the efficacy of, boluses with embedded mineral nanoparticles of a range of trace elements to provide slow-release bioavailable copper, cobalt, zinc, manganese and selenium nutrients for cattle and sheep for up to 6 months. An independent trial, commissioned by Agrimin, in a herd of Holstein (*n* = 20) cows demonstrated that nanoparticles of copper coated in lysine, improved the bioavailability of the mineral by 50%. In addition, unlike conventional copper supplements, the nanoparticles were not affected by dietary antagonist such as molybdenum and sulphur.

Cave's crop biofortification concepts were developed, working with NTU colleague and protein purification expert Philip Bonner, in on a BBSRC funded research collaboration with the Agriculture and Horticultural Development Board (**G3**). This research led to a novel way to enrich potatoes with iron, zinc, selenium and calcium *via* their parent mineral nanoparticles, coated with amino acids as a nanoparticle fertiliser formulation. The amino acid coating enables a sustained breakdown and delivery of the mineral to the plant *via* the root zone, achieved by the transporter-mediated root uptake of amino acid metal chelate formed *in situ*. This biofortification of staple food crops process offers a far cheaper alternative to vitamin supplements and a tool kit towards fighting hidden hunger. The process was also demonstrated in tomato and chilli plants and then optimised to triple the levels of trace minerals in the crops, reduce harvest time by up to two weeks and typically improve yields by 40%.

3. References to the research (NTU researchers underlined)

Underpinning research quality has been evidenced by rigorous externally peer reviewed outputs:

R1. "Artificial exosomes as tools for basic and clinical immunology". De la Pena H, Madrigal JA, Rusakiewicz S, Bencsik M, Cave GWV, Selman A, Rees R, Travers PJ, Dodi IA, *Journal of Immunological Methods* 2009, **344**(2), pp 121-132. doi:10.1016/j.jim.2009.03.011
R2. "Towards MRI microarrays". Hall A, Mundell VJ, Blanco-Andujar C, Bencsik M, McHale G, Newton MI, Cave GWV, *Chemical Comms.* 2010, **46**(14), pp 2420-2422. doi:10.1039/b925020d
R3. "Coating Metal Oxide Particles", Cave GWV, Mundell JL, UK Patent GB201204579A, (15 March 2012), equivalents EP2825515A2/US10154628B2/US2015027050A1/WO2013136082A3
R4. "Reactor", Cave GWV, UK Patent GB201515000A, Priority Date 24 August 2015, equivalents EP3341117A1/US2018280910A1/WO2017033005A1
R5. "Bioavailability of Methionine-Coated Zinc Nanoparticles as a Dietary Supplement Leads to Improved Performance and Bone Strength in Broiler Chicken Production", Ashraf Alkhtib, Dawn Scholey, Nicholas Carter, Gareth W.V. Cave, Belal I. Hanafy, Siani R.J. Kempster, Subbareddy Mekapothula, Eve T. Roxborough and Emily J. Burton, *Animals* 2020, **10**(9), p1482. doi:10.3390/ani10091482 [Publication delayed until after commentarial licencing embargo]

The quality of the underpinning research has been further evidenced by rigorous externally peer reviewed grants from prestigious funding organisations that have invested in the research:

G1. Anthony Nolan PhD studentship, Dodi A, Rees R, Cave GWV, Selman A, 2005-2008
G2. Innovate UK KTP, Cave GWV and Agrimin Ltd, 2017-2020 (KTP010517, reference 509960)
G3. BBSRC CASE studentship with the Agriculture and Horticultural Development Board Potato Council, Cave GWV, Bonner P and Harper G. 2014-2018 (BB/K012878/1)

4. Details of the impact

Impacts on commerce and the economy: spin-out company Pharm2Farm Ltd. has commercialised NTU's patented technologies, created jobs, attracted investment, and significant growth led to the company's £2.37 million acquisition

Pharm2Farm Ltd. was incorporated as an NTU spin-out company in August 2015. It has licenced Gareth Cave's granted patents (**R3**, **R4**) and is commercialising Cave's ground-breaking research innovations in nanoparticle biofortification and virucides, including nanoparticle fabrication techniques that reduced the cost of nano particle production from over £1000 per kilogram to [text removed for publication] per kilogram, making volume production possible. Pharm2Farm Ltd. adopted, further developed, and scaled up Cave's novel coated nanoparticle manufacture techniques (**R3**, **R4**) and brought to market a range of commercial 'nano plant fertiliser' plant feed products based on this technology. These plant feed products, which have been sold and supplied globally, include own brands Seasons™ and Spectrum™, and nanoparticles supplied as active ingredients into third party manufacturers (**S1**).

Braveheart Investment Group PLC., a fund management and strategic investment group, acquired a 33% holding in Pharm2Farm Ltd. on 8 July 2019. Braveheart invested a further £200k into Pharm2Farm Ltd. on 2 December 2019, to increase its holding from 33.33% to 51.72% (**S2**). Braveheart's Chief Executive Officer said, "*The interest shown in P2F products and technology since we acquired our original investment has significantly exceeded our expectations*" (**S2**).

AIM-listed Remote Monitored Systems PLC. acquired Pharm2Farm Ltd. from Braveheart Investment Group and Cave in August 2020 through the issue of 600 million new shares (**S3**). The Director of Remote Monitored Systems PLC wrote, "*Acquisition was satisfied by the issue of 600,000,000 new ordinary shares of 0.01 pence each in RMS, equating to approximately £2,370,000 based on RMS's closing share price on 20 August 2020 (0.38p; £5.4 million market capital)", and added, "The market valuation of P2F was based primarily on Dr Cave's knowledge and know-how and the underpinning patented process, licenced from Nottingham Trent University, for producing and functionalising nanoparticles*" (S4). The Director of Remote Monitored Systems PLC added that the share price had risen from to 0.38p on 20 August 2020 to 3.00p by the date of their testimonial letter, the close of trading day 15 Jan 2021, and "*This rapid and dramatic increase in the current market valuation of RMS is widely attributed to the step changes that Dr Cave and his team have achieved in implementing their platform nano technology into real work applications*" (**S4**).

The Director of Innovation, Pharm2Farm Ltd. commented that, "*the licensing of Dr Cave's nanoparticle manufacturing scale-up technology from NTU has led to significant investment from both the Braveheart Investment Group plc and new investors, Remote Monitored Systems plc,*" (**S1**). This funding facilitated Pharm2Farm's move into a new 400 m^2 commercial clean room manufacturing and distribution facility that employed 10 full time staff, in addition to contracted support staff. In January 2021, the Director of Innovation at Pharm2Farm Ltd. attributes, "*Dr Cave's research and technology breakthroughs, support, drive and commitment has been instrumental for Pharm2Farm's rapid expiation from a company valued at £75,000 in August 2019 to a current valuation (31 December 2020) of over £40,000,000*" (**S1**).

Impacts on commerce and the economy: Pharm2Farm Ltd. created a new a product range, incorporating NTU's patented technologies, which has achieved global sales, and have provided increases in turnover for suppliers and retailers and yield and income for farmers

The product range created by Pharm2Farm Ltd. includes their home and garden plant foods, Seasons™ "*that incorporates Dr Cave's advanced nanoparticle plant feed*" (**S1**), and their hydroponic feeds range, Spectrum™, "*designed with Dr Cave and incorporate his plant feed nanotechnology*" (**S1**). Seasons™ is sold throughout the UK, at nurseries, national garden centre chains and at Asda supermarkets and Spectrum™ products are sold in around [text removed for publication] shops in the UK (**S1**).

Pharm2Farm Ltd. also supply directly to commercial growers , including supermarket suppliers of tomato, chilli and strawberries, and supply the nanoparticles as active ingredients into third party agrochemical manufacturers with the UK and EU, including [text removed for publication]., [text

removed for publication]., [text removed for publication]. and [text removed for publication]. (S1). The Director of Innovation at Parm2Farm Ltd. confirmed that, "*Dr Cave's technology and the corresponding global license agreement has opened new markets and territories to Pham2farm, examples include South Korea, India, Canada, and USA*" (**S1**).

ÔpennLabs Europe Ltd., a nanotechnology firm based in the UK and France, has created a new line of plant nutrient and growth stimulant products as a direct result of adapting bespoke nanoparticles supplied by Pharm2Farm, with direct support from Cave. This has allowed the company to "*disrupt existing markets for silicon-based nutrient products and compete in sectors, including North America and Australia*" (**S5**). It has resulted in a "*3,500% increase in turnover since 2018 and the creation of three new full-time employment positions*" (**S5**).

End retailer Liverpool-based hydroponic shop NPK Technology Ltd. took on nanoparticle Iron and Silicon products in 2015 for their business, and reported that *"Since then we have sold over 12,500 units of nano particle material to our customers who have had excellent results and are now repeat customers for that product. Financially, the product has helped our business increase its nutrition turnover* [text removed for publication]*, which we believe having this novel product allowed us to gain more customers for other products as well"* (**S6**).

South Korean urban basil farmers, Griin Co Ltd., [text removed for publication] utilise nano silica and iron, supplied by Pharm2Farm Ltd. They report that the nanoparticle plant food has increased their average harvest yield [text removed for publication] (**S7**).

Srirama Raithu Sangham, a co-operative agricultural organisation in India, have been using nano fertiliser formulations, supplied by Pharm2Farm Ltd. to grow their chilli crops over a land area of over 750 hectares since 2017. This has "…*reduced the time for fruit ripening and harvesting time from 155 days to 118 days*" with the impact that "*on average each farmer has secured annual agricultural income of Rs.250000/Hectare (£2500 GBP)*" (**S8**)

5. Sources to corroborate the impact (* participant in the process of impact delivery)

S1.* Testimonial letter: Director of Innovation, Pharm2Farm Ltd.
S2. Web-link: RNS information published in Financial Times online, Company Announcements (12 Dec 2019) https://markets.ft.com/data/announce/detail?dockey=1323-14345380-7R85RN2AR5FF9JERU3AL3M6E6U
S3. Web-link: "Proactive Investors LLC" financial media portal report (24 Aug 2020) https://www.proactiveinvestors.com/companies/news/927329/remote-monitored-systems-inks-deal-to-acquire-pharm2farm-927329.html
S4.* Testimonial letter: Director, Remote Monitored Systems PLC
S5. Testimonial letter: Chief Technology Officer, ÔpennLabs Europe Ltd., UK
S6. Testimonial letter: Owner, NPK Technology Ltd., UK
S7. Testimonial letter: Founder and Chief of Executive Office, Grinn Co Ltd, Korea
S8. Testimonial letter: Chair Person, Srirama Raithu Sangham cooperative, India