Institution: University of Cambridge		
Unit of Assessment: 5		
Title of case study: New commercial ventures to accelerate therapeutic antibody discovery		
Period when the underpinning research was undertaken: 2007 - 2011		
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:**
John McCafferty	Director of Research Affiliated Lecturer	Jul 2007- Sep 2012 Oct 2015 – Sep 2020
Period when the claimed impact occurred: 2013 - present		
Is this case study continued from a case study submitted in 2014? N		

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

University of Cambridge academics, including John McCafferty, contributed to the invention of phage display, a revolutionary antibody discovery technology. Using outcomes from the research, Dr McCafferty established the biotechnology company IONTAS, now at the forefront of antibody innovation. The company combines drug discovery services alongside the development of new antibody technologies that enhance and optimise antibody drug discovery, facilitating the development of new medicines. With 32 employees and 2019 assets of GBP 2,377,000, IONTAS is an expanding, recently merged, company that contributes to the economy in the UK and in Portugal, through its parent company, Fairjourney Biologics. The research and technology also created the opportunity to launch a new drug development company, Maxion Therapeutics.

2. Underpinning research (indicative maximum 500 words)

The use of monoclonal antibodies, man-made proteins that act like human antibodies in the immune system, is rapidly expanding in the world of biotechnology. With their ability to bind with high affinity and specificity to a wide variety of targets, monoclonal antibodies (mAbs), have emerged as an important tool in medicine, biochemistry and molecular biology. It is, therefore, necessary to establish cost-effective methods to discover and generate mAbs at scale.

Bacteriophages (or phage) are viruses of bacteria that can be used to produce proteins of interest (PoI) in large amounts. In the phage display technique, a gene encoding a PoI is inserted into a phage coat protein gene, causing the phage to display the PoI on the outside, while containing the gene for the protein inside, resulting in a connection between genotype and phenotype. The phage can then be amplified through host bacteria that replicate them. This approach can be used with many millions of genes to create libraries of proteins that can be screened in order to detect interaction between the displayed protein and other molecules.

Using phage display, antibody fragments can be displayed and presented to different proteins to select for antibodies with specific characteristics. Unlike earlier methods that relied on production in mice, phage display can be used to generate fully human antibodies, reducing the likelihood of the human body identifying the injected antibody as foreign and generating its own immune response. Due to the robust nature and high stability of phages, this technology has gained advantages over the other antibody isolation approaches (Int J Biol Macromol, 2019, doi:10.1016/j.ijbiomac.2019.06.006).

The work carried out in the assessment period by Dr John McCafferty and colleagues is centred on the generation of mAbs using phage display. This work was crucial for simplifying and improving many facets of the phage display process and enhancing its commercial viability. In 2007, Dr McCafferty and colleagues showed that by using their technology it was possible to

generate a high-quality antibody display library of over 10 billion clones, which was then used to isolate antibodies to hundreds of targets [R1], demonstrating the potential of phage display in genome-wide mAb generation. However, it was still necessary to overcome some challenges. A common issue with phage display stems from the misfolding of proteins associated with the use of the bacterium *E. coli* to express mammalian proteins. A possible solution was to prepare a library of gene fragments and to select those that express well. In 2008, McCafferty et al. described a new method for preparing a random gene fragment library and selecting for soluble protein expression [R2]. Prior to this, methods used to circumvent the problem were laborious and costly, and required a mapped protein domain. The new method was particularly useful since it could be performed without prior knowledge of target protein domain architecture.

The success of an antibody in a particular application is dependent on a combination of specificity, affinity, and the properties of the antigen binding site. To generate such antibodies in a scalable fashion, McCafferty and colleagues took part in an international pilot study in 2010, creating a large panel of antibodies to a family of 20 human signalling molecules [R3]. They showed that affinity maturation, the process of improving antibody affinity to antigens, could be carried out in parallel on multiple antigens. The resulting antibodies were successfully used to identify interacting partners of a signalling protein (Shc1). Following this proof-of-concept, to provide a scalable approach for mapping protein interaction networks, it was necessary to increase the availability of antibodies with sufficient affinities. In 2011, McCafferty and colleagues demonstrated such an approach for the generation of suitable antibodies using phage display and affinity maturation [R4].

Whilst many commercially available antibodies to human proteins existed, research in the area had been hindered by their inconsistent validation and poor performance. To overcome this, McCafferty and colleagues demonstrated that using phage display, high-affinity, high-specificity antibodies could be produced and validated, laying the groundwork for a pipeline for the supply of such antibodies [R5].

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

R1. Schofield, D.J., **McCafferty, J**. et al. Application of phage display to high throughput antibody generation and characterization. Genome Biology. 2007. 8, Article number: R254, doi:10.1186/gb-2007-8-11-r254

R2. Dyson MR, Perera RL, Shadbolt SP, Biderman L, Bromek K, Murzina NV, **McCafferty J**. Identification of soluble protein fragments by gene fragmentation and genetic selection. Nucleic Acids Res. 2008. 36 (9): e51 PMID: 18420658, doi: 10.1093/nar/gkn151

R3. Pershad K, Pavlovic JD, Graslund S, Nilsson P, Colwill K, Karatt-Vellatt A, Schofield DJ, Dyson MR, Pawson T, Kay BK, **McCafferty J**. Generating a panel of highly specific antibodies to 20 human SH2 domains by phage display. Protein Eng. des. Sel. 2010. 23 (4): 279-88 PMID: 20164219, doi:10.1093/protein/gzq003

R4. Collwil, K, Renewable Protein Binder Working Group, [**McCafferty, J** as member], Graslund, S. A roadmap to generate renewable protein binders to the human proteome. Nat Methods. 2011. 15 (8): 551-8 PMID: 21572409, doi:10.1038/nMeth.1607

R5. Dyson MR, Zheng Y, Zhang C, Colwill, K, Pershad K, Kay BK, Pawson T, **McCafferty J**. Mapping protein interactions by combining antibody affinity maturation and mass spectrometry. Anal. Biochem. 2011. 417 (1): 25-35 PMID: 21704603, doi: 10.1016/j.ab.2011.05.005

All research outputs have been published in peer-review journals.

Competitive funding received
Wellcome Trust Programme Grant, 2007-2012, GBP1,119,000

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

Research from Cambridge University on phage display has opened up access to human antibodies in a way that has proved commercially profitable, and revolutionary for the development of antibody therapeutics.

Commercial impact

Dr McCafferty founded the company IONTAS to generate human antibody drug leads for client companies using phage display on a fee-for-service basis. IONTAS was established in 2012, initially embedded within the Department of Biochemistry at the University with four employees. In the first two years, the company focused on building a reputation for successful delivery of products within Dr McCafferty's existing network of contacts in the therapeutic antibody discovery community [E1], generating profit from the outset and growing a community of repeat customers. As the business grew it relocated to the Babraham Research Park, and again in 2016 to its present-day location in dedicated premises south of Cambridge, with 7,500 sq. ft of lab and office space [E2]. Following an atypical route, IONTAS did not receive external funds from investors, and its growth was solely from revenue generated by the company. By 2020 IONTAS had grown to a team of 32 employees with assets of GBP 2,377,000 [E3]. IONTAS' success was recognised when it was named small business of the year at the Cambridge News Business Excellence Awards in 2019, highlighting its sustained growth and increased market strength whilst remaining profitable [E4].

The success of IONTAS is further highlighted by their acquisition in early 2020 by their main competitor, FairJourney Biologics (Porto, Portugal), facilitated by investment [undisclosed amount] from GHO Capital, a European health care investor. Their collaboration brings together complementary services and technology to enable faster identification of effective antibodies, with an immediate focus on SARS-CoV-2 antibodies [E5]. FairJourney say that "this junction allows antibodies to be identified without the need for further optimisation thereby reducing the risk of delays during development and subsequent scale to manufacture" [E5]. The CEO of FairJourney Biologics said of the collaboration that the two companies "share the same values in offering a premium service with innovative technology. This deal represents an important step in the continued growth and internationalisation of FairJourney" [E6]. As part of the transaction with FairJourney, McCafferty has also launched a new drug development company, Maxion Therapeutics, making use of IONTAS' emerging KnotBody technology [E5]. The KnotBody technology is also a product of McCafferty's research on phage display.

Antibody development

Two key lines of work at IONTAS that are revolutionising antibody development are Knotbodies and Mammalian Display Technology.

<u>Knotbodies</u>

Using phage display technology, IONTAS has invented a novel antibody format ("KnotBodies") that facilitates the targeting of ion channels: key therapeutic targets which therapeutics had previously struggled to target with the required potency and specificity. The KnotBody format combines the ion channel-modulating functionality of naturally occurring venom-derived small peptides called knottins, with the extended half-life, specificity and in vivo capabilities of monoclonal antibodies [E7].

<u>Mammalian Display Technology</u>

IONTAS have developed a proprietary and patented mammalian display system [E8], using Dr McCafferty's research outlined above, i.e. the linkage of antibody genes to the antibodies they encode. However, by using mammalian rather than bacterial cells, the work is done in cell types that are ultimately used for antibody production. As well as allowing for the direct screening of millions of clones, the mammalian display system also has the potential, during the early discovery phase, to identify and avoid clones with biophysical liabilities that can lead to product failure and derailment, such as a propensity to aggregate. This allows the team to "fix" problematic antibodies and, better still, identify them during discovery and avoid them in the first

place [E8]. FairJourney Biologics CEO highlighted Mammalian Display Technology as being time-saving and cost-saving for industry as the process allows developable products to be generated without repeat iterations [E6].

COVID-19
In September 2020, IONTAS and FairJourney announced the discovery of 15 potent antibodies that neutralise SARS-COV-2 virus in tests. The antibodies have been shown to block infection by SARS-CoV2 virus at doses as low as 20 picomolar (pM) in pseudoviral assays and 100 pM in live coronavirus assays, matching or surpassing the best antibodies reported. All 15 antibodies are optimally suited to clinical development and manufacturing [E9].

Customer satisfaction
IONTAS has built its reputation for delivering reliable products that other companies find challenging. The company Adaptate Biotherapeutics used the IONTAS Mammalian Display Technology in December 2019 to select antibodies with optimal biophysical properties for novel immuno-oncology targets. The Chief Executive Officer of Adaptate Biotherapeutics, said: "IONTAS has developed an impressive track record in delivering therapeutic antibodies. We selected them as our partner because of their extensive experience in overcoming antibody project challenges using their industry-leading platforms. We anticipate that the combination of IONTAS' antibody discovery capabilities and our innovative approach to gamma delta T cell-targeted therapeutics will facilitate the accelerated entry of our oncology portfolio to the clinic" [E10].

Medicxi, a venture capital life science company engaged IONTAS after an unsuccessful attempt with another service provider. They were founding another company, Super X, and were engaged in efforts to develop an antibody lead molecule with challenging requirements in terms of specificity and function. The venture partner at Medicxi gave testimony to IONTAS' services: "In the end the project proved to be too difficult [for the initial service provider] and no lead molecules were generated. We were aware of IONTAS and their excellent reputation…we re-ignited the project and were not disappointed. John…and the IONTAS team…delivered the lead molecules we sought within the specified timelines. The knowledge that we can rely on IONTAS to deliver "developable" molecules with required properties, on time, significantly de-risks our investment decisions" [E11].

Work carried out at IONTAS, building upon previous research carried out by Dr McCafferty at the University of Cambridge, has been crucial in de-risking and accelerating therapeutic antibody discovery services by furthering phage display technology. This has facilitated new collaborations between leading researchers and organisations, stimulated investment and created new enterprises, leading to employment of 32 people.

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

E1. IONTAS celebrates 5 years article
E2. Business weekly article detailing IONTAS relocation
E3. Companies House record showing staff numbers
E4. Small business of the year article
E5. Invest Porto article detailing merger with FairJourney Biologics
E6. FairJourney Biologics testimonial
E7. Knotbodies publication – Biophysical Journal
E8. Mammalian Display Technology patent (page 1 provides summary of claims)
E9. Cambridge Independent COVID antibody article
E10. Adaptate testimonial
E11. Medicxi testimonial