Institution: University College London

Unit of Assessment: 12 - Engineering

Title of case study: Purification technology for intensified and flexible manufacture of biotherapeutics

Period when the underpinning research was undertaken: 2007 - 2020

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:
Daniel Bracewell	Professor of Bioprocess Analysis	2002-present

Period when the claimed impact occurred: 2013 - 2020

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

1. Summary of the impact

Research by Professor Bracewell at UCL developed a technique to manufacture nanofibre materials that could be used in chromatography (the separation of mixtures in solution) to produce biopharmaceuticals, such as antibodies. The increased efficiency of the nanofibres, compared to traditional purification technologies, led to the development of a spin-out company, Puridify, which was acquired for [TEXT REMOVED FOR PUBLICATION] in 2017. The economic impact of the research extends further than Puridify, as the company's Fibro technology for purification is now on sale and has been used by clients including AstraZeneca, resulting in a 6-fold increase in efficiency of biopharmaceutical manufacture and an acceleration of the drug-discovery process.

2. Underpinning research

Nanofibres have been used for a range of purposes, including textiles, medical materials, filtration devices, bioengineering materials and energy cells. In the medical sector, nanofibres have been used to produce artificial organ components, implant material, tissue replacement and wound dressing and are the subject of much recent attention. In 2007, Professor Daniel Bracewell at UCL, and Professor Bob Stevens at STFC Rutherton Appleton laboratories, began collaborating on fabricating novel nanofibre adsorbents for bioprocessing, such as the manufacture of therapeutic proteins, using electrospinning technology. Work began in 2008 via an EPSRC CDT project to which Oliver Hardick, a PhD student, was appointed.

The aim was to improve on the purification technology that currently dominates the market in manufacturing biopharmaceuticals. Currently, beaded resin technology is the standard material used in chromatography (the separation of a mixture in a solvent using another substance). With this approach, a therapeutic protein such as an antibody can be purified, and the right molecule is extracted by filtering it through an adsorptive material. While this adsorption-based separation technology is effective, it relies on diffusion to reach all the sites available. This limits the speed of separation and therefore the productivity. To intensify the separation and increase productivity in manufacturing a new material that would enable convective (i.e. directed) rather than diffusive transfer of mass was required. This nanofibre-based technology would be considerably more efficient.

The underpinning research behind this purification technology had to begin at the most fundamental level – development of the fabrication techniques to synthesise the nanofibre based adsorbent. The initial objective was to create materials with high surface area to provide high binding capacity but avoid the diffusional mass transfer limitations (the slowed rate of movement) found in existing adsorbents. The fabrication methodology and fundamental properties of these novel cellulose nanofibre adsorbents is summarised in (**R1**).

The work at UCL then characterised the performance of this new adsorbent material for bioprocessing. This data became the basis for the first underpinning patent of the nanofibre technology, initially supported by UCLB and was subsequently published by peer review in (**R2**). This research demonstrated an adsorbent operating at flowrates of 100 times that of typical adsorbent materials, resulting in a potential10-fold increase in productivity. The UCL team then demonstrated how the convective nature of mass transfer facilitated by this new material enables operation at high flowrates to radically shorten operational times thus providing productivity improvements of over an order of magnitude (**R3**) for protein bioprocessing relative to the existing adsorbent technology. This progress took the technology to the point where in 2013 a company (Puridify) could be spun-out using this underpinning data and patent application.

Research then proceeded via collaboration between UCL and Puridify using several rounds of TSB, BBSRC, EPSRC and Innovate UK funding and a PhD studentship. In the first grant 2014/5 (BB/M004848/1, £140,778 to UCL) the PhD student and postdoctoral researcher at UCL focused on improved fabrication techniques for cellulose nanofibre adsorbent (**R4**). The next grant was directed at the design of the adsorbent housing to provide a packed bed configuration for bioprocess separation and scale-up (EP/M017222/1, £608,611 to UCL) with two postdocs at UCL (2015-17) looking at experimental and computational fluid dynamics aspects respectively.

In a final project in 2016-17 (EP/N013395/1, £363,240 to UCL) Innovate UK funding allowed the researchers to expand the use of the nanofibre separation technology to new/next generation therapeutic products particularly focused upon viral vectors. These products offer huge potential to improve patient outcomes but present unique manufacturing challenges due to their relative complexity and labile nature compared to protein therapeutics. The research examined both the recovery of adenovirus sourced from collaborators at Oxford University (**R5**), and lentivirus sourced from UCL (**R6**). In both cases the research showed that the capacity, speed of operation, and recovery of active viral vector product exceeds anything published elsewhere. This research saw the technology advance through the technology readiness levels culminating in a product called “Fibro PrismA” and the sale of the spin-out company to GE Healthcare who have gone on to launch the product to their customers

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

R1. Hardick O, Stevens B, **Bracewell DG**. (2011). Nanofibre fabrication in a temperature and humidity-controlled environment for improved fibre consistency, *J Mater Sci,* 46: 3890. DOI 10.1007/s10853-011-5310-5

R2. Hardick O, Dods S, Stevens B, **Bracewell, DG**. (2013). Nanofiber adsorbents for high productivity downstream processing. *Biotechnol. Bioeng*., 110: 1119-1128. DOI:10.1002/bit.24765

R3. Hardick O, Dods S, Stevens B, **Bracewell DG**. (2015). Nanofiber adsorbents for high productivity continuous downstream processing, *Journal of Biotechnology*, 213, 74-82. DOI: 10.1016/j.jbiotec.2015.01.031

R4. Dods SR, Hardick O, Stevens B, **Bracewell DG**. (2015). Fabricating electrospun cellulose nanofibre adsorbents for ion-exchange chromatography, *Journal of Chromatography A* 1376, 74-83. DOI:10.1016/j.chroma.2014.12.010

R5. Turnbull J, Wright B, Green NK, Tarrant R, Roberts I, Hardick O, **Bracewell DG**. (2019). Adenovirus 5 recovery using nanofiber ion-exchange adsorbents. *Biotechnology and Bioengineering*. 116: 1698-1709. DOI:10.1002/bit.26972

R6. Ruscic, J, Perry C, Mukhopadhyay T, Takeuchi Y, **Bracewell DG**. (2019). Lentiviral vector purification using nanofibre ion exchange chromatography. *Mol. Therapy - Methods & Clinical Dev,* 15, 52-62. DOI: 10.1016/j.omtm.2019.08.007

4. Details of the impact

In 2013, as Hardick completed his doctorate, the nanofibre adsorption technology developed at UCL was sufficiently developed to launch a spin-out company (Puridify), led by Hardick. Puridify, building on research from the UCL team, offered a solution to a variety of manufacturing difficulties for biopharmaceuticals. The collaboration between UCL and Puridify has resulted in a jointly patented new chromatography medium, now commercially available as Fibro PrismA. The impacts of the research have been significant; both its commercial impact on Puridify, and its impact on clients, helping to advance the development of life saving treatments.

Commercial Impact on Puridify

The global market for chromatography resin, a key component of biopharmaceutical manufacture is projected to grow from USD2,100,000,000 (12-2020) in 2019 to USD3,000,000,000 (12-2020) by 2024; a Compound Annual Growth Rate of 7.2%. The market is largely driven by the increasing demand for therapeutic antibodies. The efficiency gains over resin, made possible by Puridify and its Fibro technology platform (commercially available as Fibro PrismA) have huge potential not only of time saved, but also of scalability. The Fibro technology offers faster work rates, and allows a manufacturer to switch more easily between different biopharmaceutical products, potentially making advanced treatments more accessible to low- and middle-income countries.

These efficiency gains make the company extremely attractive to funders and investors. In 2013, the year Puridify was founded, the company won the first Oxbridge Biotech Roundtable (OBR) life-sciences business plan competition. SR One, the venture capital arm of GlaxoSmithKline, provided GBP100,000 and lab space at the Stevenage BioScience Catalyst as a result. This collaboration later led to Puridify winning the 2016 BioProcess International Award for “Best Collaboration” with GlaxoSmithKline to advance industrial evaluation of Puridify’s FibroSelect The company also acquired investment from SR One (**S1**), UCLB and Imperial Ventures (GBP850,000 in 2014) (**S2**). It received non-diluting funding from Innovate UK (then TSB) for further collaboration with Bracewell at UCL, in recognition of the importance of its research-led work.

This series of grants allowed the company to progress through the technology readiness levels starting with improvements in the material, progressing into device design and finally looking into future application of the technology in viral vector purification (2014-2018). In 2015 Puridify had a Series A funding round successfully raising GBP2,200,000 from SR One, UCLB and Imperial Ventures (**S3**). By 2016, Puridify had 14 scientists at their site at Stevenage and 4 postdoctoral researchers working with Professor Bracewell at UCL via Innovate UK funding. The company has also won six Innovate UK Awards since 2013. Bracewell and Hardick were recognised as finalists in the BBSRC Innovator of the year competition in 2015 (**S4**).

In 2017, GE Healthcare (the chromatography resin market leader) bought Puridify, recognising its innovation and potential and to gain “*access to exciting technology that could give considerable improvements for some customers in their purification step”* (**S5**). [TEXT REMOVED FOR PUBLICATION]. This patent, and the technology developed stem directly from research conducted with Bracewell. GE Healthcare maintained the Stevenage site and has grown its 17 staff (at the time of purchase) to 25, and expanded its facilities. In 2018 they opened a pilot scale manufacturing facility for their proprietary nanofibre adsorbent technology on the site (**S6**). GE Healthcare was itself purchased by Danaher in 2020 and renamed Cytiva. As Cytiva, the company then launched the nanofiber based adsorbents as a commercial product in spring 2020, while tripling office space and further expanding the workforce. Cytiva is initially focusing on the purification of therapeutic monoclonal antibodies (**S7**).

Impact on Clients

Since the commercial release of Fibro PrismA in 2020, customer testimonials of the product have drawn attention to large increases in productivity (**S8**). The biologics expression team at AstraZeneca, evaluating fibro against standard chromatography, saw a 6-fold increase in throughput. The purification officer, called the resulting efficiency gains “*substantial… saving two*

staff one day each per week, so we can focus on more challenging work. It makes a big difference to us." (**S8**).
The Principal Scientist at LifeArc, says, "*The main benefits of Fibro PrismA are speed and efficacy. As an organization that focuses on translation and progressing work from early lab-based findings, Fibro PrismA is helping us to accelerate the research that brings transformative medicines to patients. We have seen an immediate impact on project timelines, including some of our Covid-19 related work*" (**S8**).

As these testimonies show, the impact is not simply felt in efficiency gains, but the corollary progress in the development of therapies that contribute to wider wellbeing. Fibro lowers the bars to entry for the manufacture of biopharmaceuticals. This technology, and the research that made it possible, is driving further innovation. As Puridify CEO and Bracewell's former PhD student, says "*We see the continued growth of smaller players in the industry and Fibro is directly intended to be a more attractive option to these players. Following the launch of HiTrap Fibro PrimsA we have seen strong uptake from across the globe and a broad user base which provides a good base for the launch of Fibro products for GMP manufacturing due early in 2021*" (**S9**).

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

S1. SR One, the venture capital arm of GlaxoSmithKline, and Oxbridge Biotech Roundtable (OBR) have awarded £100,000 and a laboratory support package to Puridify (2013).
S2. Imperial Innovations seed funding (2014).
S3. Puridify completes series A funding (2015).
S4. BBSRC Innovator of the year finalist 2015.
S5. Puridify sale to GE Healthcare (2017).
S6. Expansion at Stevenage (2018); plans announced to open a 3,000 square-foot production facility for the technology at the Bioscience Catalyst Open Innovation Campus in Stevenage, UK.
S7. Launch of Fibro select (2020) by Cytiva.
S8. Customer testimonials: AstraZeneca and LifeArc.
S9. Testimonial from Puridify CEO.