

Institution: The University of Edinburgh		
Unit of Assessment: UoA5		
Title of case study: Fundamental research on exhausted T-cells leads to creation of a spinout providing immune-oncology assays to the pharmaceutical industry, supporting drug development efforts		
Period when the underpinning research was undertaken: 2005 - 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:
Prof Steve Anderton	Personal Chair of Therapeutic Immunology/RCUK Fellow	2000 - 2020
Prof Anna Williams	Personal chair of Regenerative neurology	2008 - Present
Period when the claimed impact occurred: 1 st Aug 2013 – 31 st Dec 2020		
Is this case study continued from a case study submitted in 2014? Y/N. N		
1. Summary of the impact Attribution: University of Edinburgh (UoE) research in immunology by Steve Anderton has led to the creation of Aquila BioMedical, a Contract Research Organization (CRO), founded in 2011 to facilitate drug development. Impact on the UK economy: The company, based at the Edinburgh BioQuarter, employs 32 members of staff (most trained to PhD level) and is generating substantial revenues (GBP3,813,592 in 2019). Impact on the pharmaceutical industry: The company provides an enabling technology that accelerates drug development and has enhanced productivity in global pharmaceutical development, with 103 projects for 44 companies delivered in 2019 alone. Reflecting the importance of the technology, in October 2017, Aquila was acquired by Concept Life Sciences and since February 2018 has been part of Spectris plc, a FTSE250 company. Beneficiaries: the UK economy and the pharmaceutical industry worldwide. Significance and Reach: Aquila provides innovative research solutions for drug discovery, especially in biologics, which constituted 11 out of 50 drugs approved by the FDA in 2019. The company provides services globally, with 10% of partners in the US and others in the UK, Japan, Canada, Europe and Australia.		
2. Underpinning research The majority of Aquila's service provision for their clients is based on Anderton's research carried out at the University Edinburgh (UoE). Anderton's research has focused on the signals that lead to the activation of T cells that cause autoimmune and allergic pathology. As a product of this research, Anderton developed three assays that were of benefit to the pharmaceutical industry; a Myelin Basic Protein Tracker Mouse, an Exhausted T-Cell Assay, and a Treg Suppression Assay. Myelin Basic Protein (MBP) Tracker Mouse: A major strand of Prof. Anderton's research has been using Experimental Autoimmune Encephalitis (EAE) (a mouse model of Multiple Sclerosis) to investigate T cell responses during autoimmune disease. T cells are central mediators of disease in this model, and MBP is one of		

the self-antigens that these T cells recognise. Between 2001-2004, Anderton generated an 'MBP Tracker mouse' in his lab by crossing an existing T-Cell Receptor transgenic mouse Tg4 (reactive against the major epitope of MBP) with an existing Ly5.1 mouse line. His research demonstrated that when these Ly5.1+ Tg4 cells are transferred to a Ly5.2+ recipient mouse, the disease causing Tg4 cells can be identified and tracked during EAE, [3.1, 3.2]. In conjunction with this, Prof. Anderton's PhD student has optimised specialist histology, including multiplexed immunofluorescence and immunohistochemistry, to allow the visualisation of these cells within the tissue [3.3]. This provides the basis for studying the function of T cell responses during an autoimmune response, and how potential therapies may alter T cell function. This is now one of the standardised services offered by Aquila.

Exhausted T-Cell Assay:

T cell exhaustion occurs in chronic inflammatory settings, and describes a phenomenon where T cells lose their ability to function and become less responsive to challenge. This can prevent the immune response over-reacting and causing pathology, but in the case of tumours the development of T cell exhaustion can prevent effective killing of the tumour. In 2014, based on research performed in the Anderton laboratory [3.1], Aquila branched out into immuno-oncology, and repurposed the TCR transgenic CD4⁺ T cells from the MBP Tracker mouse to study T cell exhaustion. Tg4 T cells can be stimulated with altered MBP peptides that have different affinities for the Tg4 T cell receptor (TCR). Low affinity MBP peptides result in weak T cell activation, whilst high affinity MBP peptides can act as superagonists. When Tg4 cells are stimulated with an altered MBP peptide that acts as a superagonist they become exhausted, mimicking the exhausted state of T cells in the tumour microenvironment [3.4]. This provides a defined model to study mechanisms of T cell exhaustion, and how T cell exhaustion may be therapeutically manipulated.

Treg Suppression assay:

Foxp3⁺ Regulatory T cells (Tregs) are a central immunosuppressive cell that plays a vital role in preventing the development of autoimmune responses and immune pathology. However, excessive Treg activity can also hamper the development of protective immunity to infections and tumours. In the past 20 years, Prof. Anderton has published a wide range of papers on FoxP3⁺ Treg cells in autoimmune diseases and cancer. Based on this research, Aquila offers standardised Treg suppression assays to test the ability of potentially therapeutic compounds to boost or reduce Treg activity [3.5].

More recently, in collaboration with Williams, Aquila has developed a Neuroscience service offering based on an **ex-vivo CNS slice assay**, which allows a pharmaceutical company to evaluate adverse central nervous system effects arising from a lead compound [3.6], preserving the structure and cellular diversity of the original tissue, which can be visualised using either qPCR or immunohistochemical techniques.

3. References to the research

[3.1] Ryan, K.R., D. McCue and S.M. Anderton. 2005. Fas-mediated death and sensory adaptation limit the pathogenic potential of autoreactive T cells. *J. Leukoc. Biol.* 78: 43-50. DOI: <https://doi.org/10.1189/jlb.0205059>

[3.2] McPherson R.C., J.E. Konkel, C.T. Prendergast, J.P. Thomson, R. Ottaviano, M.D. Leech, O. Kay, S.E. Zandee, C.H. Sweenie, D.C. Wraith, R.R. Meehan, A.J. Drake and S.M. Anderton. "Epigenetic modification of the PD-1 (Pdc1) promoter in effector CD4⁺ T cells tolerized by peptide immunotherapy." *elife* 3 (2014): e03416. <https://doi.org/10.7554/eLife.03416>

[3.3]. Zandee, SEJ, O'Connor, RA, Mair, I, Leech, MD, Williams, A & Anderton, SM 2017, 'IL-

10-producing, ST2-expressing Foxp3(+) T cells in multiple sclerosis brain lesions', Immunology and Cell Biology. <https://doi.org/10.1038/icb.2017.3>

[3.4]. Anderton SM, Radu CG, Lowrey PA, Ward ES, Wraith DC. Negative selection during the peripheral immune response to antigen. *J Exp Med*. 2001;193(1):1–11. doi: <https://doi.org/10.1084/jem.193.1.1>

[3.5]. Stephens, Leigh A., Katy H. Malpass, and SM. Anderton. "Curing CNS autoimmune disease with myelin- reactive Foxp3+ Treg." *European journal of immunology* 39.4 (2009): 1108-1117. DOI: <https://doi.org/10.1002/eji.200839073> .

[3.6] Dombrowski, Yvonne, et al. "Regulatory T cells promote myelin regeneration in the central nervous system." *Nature neuroscience* 20.5 (2017): 674-680. <https://doi.org/10.1038/nn.4528>

4. Details of the impact

In nine years, Aquila biomedical has progressed from a spinout from the University of Edinburgh to a revenue-positive company, part of a multinational services company. While Aquila provides services aimed at early-stage drug development and this means that no product has yet reached market with their assistance, Aquila is a leading company among Scottish CROs.

Aquila is a leader in the provision of immuno-oncology assays and contract research in the immunology area. Immuno-oncology is a promising area of drug development that aims to refresh T-cells that are currently in an 'exhausted' state: *i.e.* unable to respond to antigen. This is a key potential therapy for cancer and an active area in drug discovery programmes. Anderton's research provided unique underpinning assays that form the basis of Aquila's offering. Anderton formed a CRO in 2011, with licensing of the MBP Tracker mouse IP as the catalyst for the Aquila start up [5.1].

Beneficiaries and nature of impact:

The UK economy: Aquila BioMedical Ltd is a medium sized CRO that arose from Steve Anderton's expertise and under-pinning research, with GBP3,813,592 in revenue in 2019, increasing from GBP3,771,611 from 2018 [5.2]. Aquila was purchased by Concept Life Sciences in 2017 [5.3].

"Aquila provides bespoke therapeutically focussed scientific programs of work, with advanced technologies, that have made it an integral part of Concept Life Sciences' and Spectris plc's service offerings to the pharmaceutical industry, and this could not have been achieved without the underpinning research from Prof Anderton." [5.1].

In 2018, Concept Life Sciences became part of Spectris plc, an FTSE250 company with 10,000 staff worldwide [5.4].

Productivity in the pharmaceutical industry: Aquila provided contracted services to 44 clients globally in 2019 [5.1] allowing them to make better decisions for drug development in early preclinical phases, facilitating go/no-go decisions for discovery programmes. The exhausted T-cell generated as part of SA's research programme are highly relevant to immuno-oncology research, and an important tool to test the efficacy of clients' compounds in reversing T cell exhaustion and restoring normal effector function, the underpinning mechanism of cancer immunotherapy.

"Aquila's key expertise is in the process of 'intelligent drug discovery': answering research questions and helping to close in on drug targets. Prof Anderton's research underpins these offerings, and the development of Aquila as a company allowed excellent basic science to be scaled up and translated into services that met business needs. Concept's world-class 'future of biology' platform uses systems developed at Aquila and based around Prof. Anderton's research, with a key assay of T cell exhaustion directly linked to an exclusive

licence agreement established between Aquila and the University of Edinburgh.” [5.1]

Aquila was one of the first CROs to offer immune-oncology services and one of the first CROs to be built from an immunology base. The exhausted T-cell assay is an important tool to test the efficacy of compounds in reversing T cell exhaustion and restoring normal effector function.

Prior to the purchase of Aquila, Concept Life Sciences focused on development of small molecule drugs, but the purchase of Aquila has allowed Concept Life Sciences to provide services for biologics development. The assays provided allow companies to progress rapidly through the preclinical phases towards the first clinical trials. Aquila was a clear factor in the subsequent acquisition of Concept Life Sciences by Spectris plc, a FTSE250 company in February 2018.

“Concept’s motivation for the purchase of Aquila was due to their focus on unparalleled quality and ability to serve their customer base – the pharmaceutical industry.” [5.1]. An example of this is Macrophage Pharma, who have outsourced their main research and development activities to Aquila [5.5]. The success of this partnership has enabled them to obtain multiple rounds of investment.

Significance of Impact:

Economy: Aquila generated GBP3,813,592 revenue in 2019, with performance continuing to be strong in 2020. Aquila currently employs 32 staff (most trained to PhD level) [5.1], and provides:

“a career path for highly trained post-docs who don’t want to follow an academic route but are highly skilled and have a comprehensive knowledge of the literature. As an example ... a PDRA in the Marriage lab leverages her tech capabilities and literature research skills to support Aquila’s clients who span everything from pharma start-ups to global drug companies, all of whom trust Aquila with their drug programmes, providing them with capabilities that they can’t do themselves” [5.6].

Aquila’s services allow clients to make better decisions in early preclinical phase through provision of data-rich, high value assays. The total value of biologics as a segment of the pharmaceuticals market had a value of USD232,000,000,000 in 2016 [5.7], while immuno-oncology therapies are now worth in the region of GBP14,000,000,000, and are expected to be worth GBP34,000,000,000 by 2024 [5.8]. Aquila’s assay services provide rapid screening capabilities facilitate go/no-go decisions for cancer therapy discovery programmes. From providing data to secure series A funding for early-stage clients to supporting clinical trials by providing multiplexed histology services, Aquila uniquely provides an assay which could measure reversal of T cell exhaustion or offers such a broad range of assays in the immuno-oncology service.

Reach of impact:

Aquila has a global reach. In 2019 alone, Aquila delivered 103 projects for 44 companies, with 10% in the US, and the remainder from UK, Europe, Australia, Canada and Japan [5.1]. Recent examples are a partnership with Merus in the Netherlands, with whom Aquila developed a T-cell exhaustion assay [5.9], AstronauTx, who are using the recently developed ex-vivo CNS slice assay [5.1] and Macrophage Pharma [5.6].

5. Sources to corroborate the impact

[5.1] Testimonial: Regional Director of Aquila Biomedical and, Chief Operating Officer of Concept Life Sciences

[5.2] Annual report and unaudited financial statements for year ending 31st December 2019.
<https://find-and-update.company-information.service.gov.uk/company/SC393914/filing-history/MzI4MDcwMzY0MmFkaXF6a2N4/document?format=pdf&download=0>

[5.3] Press release for Concept Life Sciences' acquisition of Aquila Biomedical:
<https://www.conceptlifesciences.com/2017/10/30/concept-life-sciences-announces-acquisition-aquila-biomedical/>

[5.4] Press release for Spectris's acquisition of Aquila Biomedical:
<https://www.spectris.com/media/press-releases/2018/26-jan-2018>

[5.5] Press release for Aquila and Macrophage Pharma's research collaboration:
<https://www.pharmaceutical-technology.com/news/aquila-support-macrophages-immuno-oncology-programme/>

[5.6] i- Testimonial: Director and Founder Biotech Innovation & Future Health. ii- Evidence of date of testimonial.

[5.7] Biopharmaceutical Market Size: <https://www.alliedmarketresearch.com/biopharmaceutical-market>

[5.8] Immuno-oncology market growth: <https://drug-dev.com/multi-blockbuster-drugs-will-drive-immuno-oncology-market-to-34-billion-by-2024/>

[5.9] Press release for Aquila and Merus's joint industrial/academic Eurostars grant:
<https://ir.merus.nl/news-releases/news-release-details/merus-nv-receives-eu15-million-eureka-eurostars-grant-aquila>