Institution: The University of Manchester

Unit of Assessment: 5 (Biological Sciences)

Title of case study: Commercial development and patient benefit of Adoptive Cell Therapy (ACT) for cancer

Period when the underpinning research was undertaken: 2000 - 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:
Robert Hawkins	Cancer Research UK Professor (Honorary from 2019)	1998 - present
Peter Stern	Professor (Honorary from 2013)	1989 - present
Fiona Thistlethwaite	Honorary Professor Honorary Senior Lecturer	2019 - present 2007 - 2019
David Gilham	Reader	1998 - 2016

Period when the claimed impact occurred: August 2013 – July 2020

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

1. Summary of the impact

Immunotherapy is revolutionising cancer treatment. University of Manchester (UoM) researchers have been at the forefront of developing a branch of immune-oncology, Adoptive Cell Therapy (ACT), through molecular and pre-clinical research to delivery within the NHS as standard-of-care treatment. Development and commercialisation of ACT products has led to economic impact, with the UoM spin-out company Immetacyte expanding from 40 employees in 2019 to merger with Instil Bio in 2020 (raising USD172,000,000 in financing). Worldwide, thousands of patients have now benefited from these life-saving treatments and in the UK alone, around 200 patients per year currently receive commercial products.

2. Underpinning research

Despite successes in the field of oncology, there remains a huge unmet need in both haematological and solid malignancies. Hawkins developed the concept of using a patient's own T lymphocytes as a 'living drug' to induce an anti-cancer response. At the start of this work, whilst theoretically possible, none of the required technologies were established. From 2000, Hawkins' basic and translational research programme within the UoM, supported by underpinning work in immunology (Stern) provided the pre-clinical evidence on how to optimise anti-tumour response and techniques such as efficiently transducing cells and how to expand them under the correct conditions. This led to clinical trials and ultimately commercialisation of ACT.

UoM's early work centred on developing constructs to efficiently target/activate T-cells by antibody-based receptors (so-called Chimeric Antigen Receptor T cells or CAR-T cells). Key aspects of receptor design were optimised using protein engineering approaches to efficiently target a range of cancer associated antigens, with the aim of developing an effective therapy for a variety of malignant diseases [1]. Research on cancer vaccines and antibody-targeted therapies identified the glycoprotein 5T4 as a potential targetable tumour antigen which was also explored for CAR-T cell based therapy [2]. The team identified critical aspects of immune regulation which impact on the effectiveness of cancer immunotherapy in general and cellular therapy in particular [3]. This included early work on the immune suppressive tumour microenvironment including regulatory T cells and how the effects of these might be mitigated

through, for example, depletion and conditioning chemotherapy [4]. Building on these novel findings, they developed the first UK trials of ACT for cancer.

UoM basic research on CD19 CAR-T cells suggested B-cell leukaemias and lymphomas were particularly good targets for CAR-T cell therapy, and the team delivered all necessary translational studies [4] to undertake one of the earliest clinical trials targeting CD19 using the UoM Good Manufacturing Practice (GMP) facility. This single centre phase I trial used first-generation CAR-T and demonstrated an objective response rate of 75%. Subsequent trials run in the US with second-generation CD19 CAR-T have observed a similar objective response rate including durable remissions, such that some patients who had exhausted all other lines of therapy have been cured. These findings have led to rapid commercialisation with two approved therapies (Yescarta and Kymriah) currently available as standard-of-care in the UK (section 4).

In contrast to CD19 for haematological malignancies, finding suitable targets for ACT in solid tumours has been more challenging. UoM's pre-clinical research demonstrated the potential of Carcinoembryonic antigen (CEA) as a target for CAR-T cells [1] but their trial uncovered toxicity due to normal tissue reactivity [5] – other groups had similar findings and targeting solid tumours with CAR-T cells has so far been less successful than targeting haematological malignancies. To broaden the ACT opportunities, UoM increasingly focused on exploiting the potential of tumour-infiltrating lymphocytes (TIL), natural tumour-specific T-cells found within many common solid tumours. They also developed novel methods to isolate key tumour reactive T-cell receptors [6].

3. References to the research

1. Guest RD, **Hawkins RE**, Kirillova N, Cheadle EJ, Arnold J, O'Neill A, Irlam J, Chester KA, Kemshead J, Shaw D, Embleton J, **Stern PL, Gilham DE**. (2005). The Role of Extracellular Spacer Regions in the Optimal Design of Chimeric Immune Receptors: Evaluation of Four Different scFvs and Antigens. Journal of Immunotherapy 28(3): 203-11. DOI: 10.1097/01.cji.0000161397.96582.59
2. Griffiths RW, **Gilham DE**, Dangoor A, Ramani V, Clarke NW, **Stern PL, Hawkins RE**. (2005). Expression of the 5T4 oncofoetal antigen in renal cell carcinoma: a potential target for T-cell-based immunotherapy. Br J Cancer 93(6): 670-7. DOI: 10.1038/sj.bjc.6602776
3. Griffiths RW, Elkord E, **Gilham DE**, Ramani V, Clarke N, **Stern PL, Hawkins RE**. (2007). Frequency of regulatory T cells in renal cell carcinoma patients and investigation of correlation with survival. Cancer Immunol Immunother 56(11): 1743-53. DOI: 10.1007/s00262-007-0318-z
4. Cheadle EJ, **Hawkins RE**, Batha H, O'Neill AL, Dovedi SJ, **Gilham DE**. (2010). Natural expression of the CD19 antigen impacts the long-term engraftment but not antitumor activity of CD19-specific engineered T cells. J Immunol 184(4): 1885-96. DOI: 10.4049/jimmunol.0901440
5. **Thistlethwaite FC, Gilham DE**, Guest RD, Rothwell DG, Pillai M, Burt DJ, Byatte AJ, Kirillova N, Valle JW, Sharma SK, Chester KA, Westwood NB, Halford SER, Nabarro S, Wan S, Austin E, **Hawkins RE** (2017). The clinical efficacy of first-generation carcinoembryonic antigen (CEACAM5)-specific CAR T cells is limited by poor persistence and transient pre-conditioning-dependent respiratory toxicity. Cancer Immunol Immunother 66 (11): 1425-1436. DOI: 10.1007/s00262-017-2034-7
6. Spindler M, Nelson A, Wagner E, Oppermans N, Bridgeman J, Heather H, Adler A, Asensio M, Edgar R, Lim Y, Meyer E, **Hawkins R**, Cobbold M, Johnson D (2020). Massively parallel interrogation and mining of natively-paired human TCR repertoires. Nat Biotech 38(5): 609-619. DOI: 10.1038/s41587-020-0438-y

4. Details of the impact

Context

There remains a high unmet need for cancer patients with both haematological and advanced solid malignancies, *e.g.* median survival for patients with relapsed refractory Diffuse large B-cell lymphoma is around 6 months. Following UoM preclinical work (section 2) in 2007, one of the world's first CD19 CAR-T trials in lymphoma was run in Manchester. This trial demonstrated the potential of the therapy (response rate 75%) and had a significant impact on the ACT landscape today by providing the platform for subsequent larger trials with second-generation CD19 CAR-T trials in the US.

Pathways to impact

Critical collaborations: Between 2005 and 2017, UoM led (Hawkins Co-ordinator) several major EU consortia in ACT – the ATTACK (Adoptive T-cell Therapy to Achieve Cancer Killing) series of grants. ATTACK brought together major European sites in the ACT field, facilitating development of expertise and infrastructure to deliver this type of therapy. This funding enabled key links with leading US investigators and in 2008 Hawkins founded a spinout small and medium-sized enterprise (Cellular Therapeutics Ltd, CTL), a partner in the EU grants.

Delivery capability: Delivery of GMP-compliant production processes and facilities was a critical requirement to delivering early clinical trials, and was initially established with the National Blood Service then as a UoM GMP facility. Following UoM's demonstration of the pre-clinical efficacy of CD19-CAR-T therapy [4] they identified a significant shortfall of UK manufacturing capabilities for ACT products which hampered the progression to clinical trials. To address this, Hawkins established CTL to manufacture ACT in Manchester. Initially sharing facilities at UoM, CTL became independent in 2015.

Implementation in Manchester: In 2018 a Manchester-based, 12-partner consortium, Innovate Manchester Advanced Therapy Centre Hub (iMATCH), led by Thistlethwaite, received funding to become one of three National Advanced Therapy Treatment Centres (ATTCs). iMATCH has funding of GBP9,000,000 (from Innovate UK and commercial partners). Its impact on the ACT landscape in Manchester is through a comprehensive programme integrating activities of nine commercial (including Instil Bio), two clinical (Manchester University NHS Foundation Trust, MFT, and Christie NHS Foundation Trust, CFT) and an academic partner (UoM incorporating Manchester Cancer Research Centre and CRUK Manchester Institute) to scale up and deliver ACT in Manchester and beyond. The aims of iMATCH include: maximising patient access through integration of sample collection, development of electronic sample tracking systems, clinical data capture systems, scale up in the clinical setting, training and education to safely deliver these complex therapies at scale.

Reach and significance of the impact

Commercial impact:

CTL manufactured GMP-grade CAR-T cells, T Cell Receptor (TCR) gene modified T cells, TIL and Natural Killer (NK) cells and manufactured the first Cell and Gene Therapy Catapult commercial product for cells expressing WT1 (Wilms' tumour suppression gene 1) TCR [A]. CTL became Immetacyte in 2018 (2019 turnover GBP5,800,000, 40 employees). Immetacyte has developed patented approaches to engineering TIL to enhance efficacy that are being tested in trials led from UoM (Thistlethwaite). In 2019 it formally partnered with InsTIL Bio [B], a US biotechnology company (Series A financing USD25,000,000). In March 2020 Immetacyte and Instil Bio Inc merged and subsequently raised USD172,000,000 in a Series B financing – enabling larger scale trials and commercial development of TIL products in Europe and US (expected 150 employees in UK and 150 in US by mid-2021).

Since formation in 2018, iMATCH has achieved impact through job creation (>18 FTE jobs) and increased private funding/expenditure. There has been commercialisation of outputs, *e.g.* commercial partners (Aptus Clinical and Datatrial) have developed an electronic Trial Master File, now sold as a commercial product [C]. iMATCH has also attracted additional funding such as the Innovate UK-funded ATTC network project, SAMPLE (Standard Approach to atMP

tissue collection) (GBP2,500,000) which is a 10-partner consortium led by Thistlethwaite and developing a National Framework for the key components required to scale up activity in ACT.

Policy impact:

Between 2010 and 2015 Hawkins was expert advisor on the House of Lords Regenerative Medicine Committee, which developed The 'Advanced Therapies Manufacturing Action Plan' [D]. In 2017 this resulted in GBP30,000,000 allocated from the Industrial Strategy Challenge Fund to establish the ATTC Network [E] through competitive applications to become centres of excellence, the first network of its kind globally. Hawkins was also a key clinical/scientific expert on the committee which led to the early evaluation of CD19 CAR-T cell therapy by the National Institute for Health and Care Excellence (NICE) in 2017 and facilitated the approval of CAR-T CD19 therapies in the UK [F].

Patient benefits:

In 2019 NICE assessed the cost effectiveness of both commercial CD19 CAR-T products (Axicabtagene ciloleucel and Tisagenlecleucel, brand names Yescarta and Kymriah respectively) and approved them for reimbursement within the NHS [G]. Later that year both CFT and MFT transplant units were in the first wave of nine NHS England-approved centres and are now delivering CAR-T as standard of care, enabling patients from Manchester (and across the UK) to access this life-saving treatment [H]. Together the Manchester centres treat approximately 50 patients per year (the number is increasing) with CD19 CAR-T products, resulting in complete and durable responses in these patients who would otherwise have had a prognosis measured in a small number of months. In 2019, approximately 200 patients were treated across the UK (163 in lymphoma alone [I]).

Through iMATCH, adults and children with a range of malignancies, frequently with no other treatment options, can now access the largest UK programme of ACT cancer clinical trials. 12% of global trials in the Advanced Therapy space are in UK, with 30/127 in Manchester (December 2019).

Thousands of patients worldwide have been treated with CD19 CAR-T therapy both in trials and now within standard-of-care pathways with commercial products. This success, in which UoM researchers have played a pivotal role, has sparked widespread interest and investment including from all major pharma companies such that the ACT field now has more agents in clinical trials than any other branch of immune-oncology and the global cell and gene therapy market is projected to be worth USD11,960,000,000 by 2025 [J].

5. Sources to corroborate the impact

A. Cell and Gene Therapy Catapult announcement of Cell Therapy Catapult award of major contract to Cellular Therapeutics Limited to accelerate WT1 Clinical Programme (3 August 2015).

B. InstilBio website which details the pipeline and focus of the company.

C. Aptus Clinical announcement of launch of commercial Clinical Data Management Service resulting from iMATCH (18 September 2019).

D. Report (dated 11 March 2016) 'Exploring the assessment and appraisal of regenerative medicines and cell therapy products'. Produced in response to the House of Lords' inquiry into Regenerative Medicine, by an expert group convened to develop an action plan for the NHS. This report presents the findings of independent research commissioned to inform this appraisal and the deliberations of a panel convened by NICE to evaluate the mock appraisal, and evidences Hawkins' involvement in this process (named as Advisory Group member on page 295).

E. UK government announcement of the establishment of the Advanced Therapy Treatment Centres (2 October 2017), which Hawkins was instrumental in.

F. Minutes of NICE Technology Appraisal Committee meeting (25 January 2017) evidencing Hawkins' involvement (named as invited expert on pages 3, 5, 6).

G. NICE announces approval of Axicabtagene ciloleucel and Tisagenlecleucel for reimbursement within the NHS: 'NICE recommends a CAR T-cell therapy for adults with some types of non-Hodgkin lymphoma' (Tisagenlecleucel) (7 December 2018); 'NICE recommends another revolutionary CAR T-cell therapy for adults with lymphoma' (Axicabtagene ciloleucel) (1 February 2019). This resulted from the meeting of the NICE Technology Appraisal Committee involving Hawkins [F].

H. Evidence that CFT and MFT are in wave 1 providers (9 centres in England) to deliver commercial CAR-T products: https://www.england.nhs.uk/cancer/cdf/car-t-therapy/

I. Conference abstract confirming the number of lymphoma patients who received CAR-T cell products in the UK in 2019: 'Outcome of high-grade lymphoma patients treated with CD19 CAR-T – updated real-world experience in the UK', EHA Library. Kuhnl A. et al. 06/12/20; 295063; S243.

J. BIS Research report (6 August 2019): 'Global Cell and Gene Therapy Market to Reach $11.96 Billion by 2025'.