Institution: University College London		
Unit of Assessment: 1 - Clinical Medicine		
Title of case study: Next-generation programmed T cell therapies for cancer treatment: innovation, validation and development through the spin-out company, Autolus Ltd		
Period when the underpinning research was undertaken: 2005 – present		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): **Martin Pule**	**Role(s) (e.g. job title):** **Senior Lecturer**	**Period(s) employed by submitting HEI:** **Sept 2005 - Present**
Period when the claimed impact occurred: 2014-present		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Research at UCL's Cancer Institute has developed CAR T-cell therapy– a personalised approach to eradicate cancer cells in patients with lymphoid cancers. In clinical studies, CAR T-cell therapy has been used successfully to treat over 80 patients to date. In 2014, Dr Pule and UCL colleagues founded a spin-out company - Autolus Ltd, to develop the technology, which was listed on NASDAQ in 2018. With a global HQ in London, Autolus now employs over 400 people and has raised investment of more than USD500,000,000. The company is celebrated by government as a biotech exemplar and is highlighted in the UK's 2017 and 2018 Industrial Strategy Life Sciences Sector Deals.

2. Underpinning research

Blood cancers, including lymphomas, claim approximately 15,000 lives each year in the UK. Unlike standard chemotherapy and radiotherapy which are toxic to healthy cells, genetically engineered T cells that specifically target cancer cells and spare healthy cells, are providing a new generation of personalised medicines**.** T-cells are a key component of the immune system. They circulate in the blood where they search for and kill infected cells and can move to sites of disease, replicating themselves and causing inflammation. These properties make T-cells well equipped to eradicate cancers but, because cancers are derived from normal tissues, they are not recognized as 'foreign' by T cells. However, T-cells can be genetically engineered to recognize cancers. One approach is to reprogramme T cells to express so-called chimeric antigen receptors (CARs) which target a specified protein (antigen) on the cancer cell surface. T-cells taken from a patient's blood can be reprogrammed to express a specific CAR and then re-infused back into the patient where they recognize cancer antigens and reject tumours.

CAR T-cell therapy has shown considerable promise in the treatment of lymphoid cancers, and research coordinated through UCL's CAR T programme has led to significant advances in CAR T-cell design and targeting, with safe and effective CAR T-cells being tested in patients with refractive/relapsing paediatric B cell acute lymphoblastic leukaemia and also in paediatric neuroblastoma.

CARs with more physiological signalling targeting B cell malignancies

Early clinical experience with CD19 CAR T-cell therapy for B-precursor acute lymphoblastic leukaemia (B-ALL) identified two significant limitations: immunotoxicity and rapid clearance of the CAR T cells from the circulation. The UCL team developed a new type of CD19 receptor (CAT19) with fast binding kinetics which mimic physiological signalling. In a trial of 14 patients with relapsed/refractory paediatric B-ALL, following infusion of engineered CAT19 cells, 12

patients achieved molecular remission with low toxicity and 11 of 14 patients had circulating CAR T cells at one year follow up (**R1**).

CAR arrays which target more than one antigen.
Targeting a single antigen is often insufficient because either some cancer cells in a tumour do not express that antigen and can escape the therapy (a major cause of treatment failure with CD19 CAR T-cells); or in cases where a cancer cannot be distinguished from normal tissue by a single antigen. The UCL team addressed these limitations by developing different approaches to either target multiple antigens (**R2**), or to control the activation pathway (cell signalling pathway) of the CAR T cells based on either the presence of two antigens, or the presence of one and the absence of another antigen (**R3,R4**). This research has allowed simultaneous targeting of CD19 and CD22 on malignant B cells, which is now being trialled in patients with B-ALL.

CARs for T-cell malignancies
The UCL team also developed a strategy to target T-cell lymphomas. They designed a CAR T cell that targeted a variation in the clonally re-arranged T-cell receptor, which is expressed by nearly all T-cell lymphomas. This approach allows deletion of the lymphoma in its entirety, but preserves approximately half of the normal T-cells, reducing the risk of immunosuppression (**R5**).

CARs which safely target disialoganglioside (GD2) on solid tumours
Most cancer antigens also appear at some level on normal tissue cells. GD2 is expressed at high density in several neuroectodermal cancers but at low level on peripheral nerves and brain parenchyma. The UCL team developed a GD2 CAR designed to discriminate between high-level pathological expression and low-level physiological expression. This CAR (huK666) was tested in a phase I clinical study in children with relapsed/refractory neuroblastoma; at a therapeutic dose level, three out of six patients responded with CAR T-cell expansion. Importantly, no on-target off-tumour toxicity was observed (**R6**). This clinical data is among the most important CAR T-cell clinical data in a solid cancer, allowing the development of more complex and potent therapies for GD2+ tumours built on this receptor.

3. References to the research

R1 Ghorashian S, Kramer A, Onuoha S, Wright G, Bartram J, Richardson R, Albon SJ, Casanovas-Company J, Castro F, Popova B, Villanueva K, Yeung J, Vetharoy W, Guvenel A, Wawrzyniecka PA, Mekkaoui L, Cheung GW, Pinner D, Chu J, Lucchini G, Silva J, Ciocarlie O, Lazareva A, Inglott S, Gilmour KL, Ahsan G,Ferrari M, Manzoor S, Champion K, Brooks T, Lopes A, Hackshaw A, Farzaneh F, Chiesa R, Rao K, Bonney D, Samarasinghe S, Goulden N, Vora A, Veys P, Hough R, Wynn R, Pule M, Amrolia P (2019). Enhanced CAR T cell expansion and prolonged persistence in pediatric patients with ALL treated with a low-affinity CD19 CAR. *Nat. Med.* 25, 1408–1414. DOI: 10.1126/scitranslmed.abd6169.

R2. Lee LSH, Draper BO, Chaplin N, Philip B, Chin M, Galas-Filipowicz D, Thomas S, Kokalaki E ,Francis J, Yong KW, Pule MA (2016). An APRIL Based Chimeric Antigen Receptor to Simultaneously Target BCMA and TACI in Multiple Myeloma (MM) Has Potent Activity in Vitro and in Vivo. *Blood* 128, 379–379. https://doi.org/10.1182/blood.V128.22.379.379

R3 Kong, K., Cordoba, S. & Pulé, M. Signalling system patent application. WO2015GB52494.

R4.Pulé, M., Kong, K. & Cordoba, S. Cell patent application. WO2016135470.

R5 Maciocia PM, Wawrzyniecka PA, Philip B, Ricciardelli R, Akarca AU, Onuoha SC, Legut M, Cole DK, Sewell AK, Gritti G, Somja J, Piris MA, Peggs KS, Linch DC, Marafioti T, Pule MA (2017). Targeting the T cell receptor β-chain constant region for immunotherapy of T cell malignancies. *Nat. Med.* **23**, 1416–1423. DOI: 10.1038/nm.4444

R6 Straathof S, Flutter B, Wallace R, Jain N, Loka T, Depani S, Wright G, Thomas S, Cheung

WK, Gileadi T, Stafford S, Kokalaki E, Barton J, Marriott C, Rampling D, Ogunbiyi O, Akarca AU, Marafioti T, Inglott S, Gilmour K, Al-Hajj M, Day W, McHugh K, Biassoni L, Sizer N, Barton C, Edwards, D, Dragoni I, Silvester J, Dyer K, Traub S, Elson L, Brook S, Westwood N, Robson L, Bedi A, Howe K, Barry A, Duncan C, Barone G, Pule MA, Anderson J (2020). Antitumor activity without on-target off-tumor toxicity of GD2–chimeric antigen receptor T cells in patients with neuroblastoma *Science Translational Medicine* Vol. 12, Issue 571 DOI: 10.1126/scitranslmed.abd6169.

4. Details of the impact

Every year in the UK around 40,000 people are diagnosed with a blood cancer, of which there are hundreds of different types. Lymphomas are blood cancers that affect B cells or T cells – two types of blood lymphocytes. Research led by UCL has developed CAR T cell therapy for B cell and T cell lymphomas and created a spin-out company, Autolus Ltd. The company has now established a pipeline of effective CAR T cell therapies to target lymphomas including Acute Lymphoblastic Leukemia (ALL) and large B cell lymphoma together with other cancers such as neuroblastoma, small lung carcinoma and prostate cancer and has, in clinical studies run by UCL, successfully treated more than 80 patients to date.

Clinical Innovation

Underpinned by pre-clinical and clinical research performed at UCL, Autolus is using a suite of proprietary and modular T cell programming technologies to engineer precisely targeted, controlled and highly active T cell therapies that recognize cancer cells, break down their defence mechanisms and eliminate them. Autolus has a pipeline of product candidates in development for the treatment of blood cancers and solid tumours.

Two thirds of adult patients with B-ALL relapse or are refractory to first line therapy. AUTO1, the most advanced of Autolus' clinical programmes, is a novel investigational CD19 targeting CAR T cell therapy and has been tested in a Phase 1b/2 study in adult ALL and a Phase 1 study in paediatric ALL (**S1**). In November 2019, AUTO1 was granted orphan drug designation by the US Food and Drug Administration (FDA) for the treatment of ALL patients, 60% of whom are under the age of 20 (**S2**). In December 2020, data from the ALLCAR Phase 1 study reported that of 19 patients with resistant/relapsing ALL who received AUTO1, 84% achieved minimum residual disease-negative complete response at one month, with low toxicity. In all treated patients, event-free survival at six and 12 months was 69% and 52% respectively. Autolus's CEO said "We are excited about the long-term remissions observed without a need for an additional stem cell transplant. Remarkably, this outstanding result was achieved with a well-tolerated safety profile in this fragile adult ALL population" (**S3**). The trial, led by the UCL team, has been extended to treat a further 30 patients with either diffuse large B-cell lymphoma, chronic B lymphocytic leukemia or B-cell non-Hodgkins lymphoma.

AUTO3, a programmed T cell therapy containing two independent CARs targeting CD19 and CD22, is currently being tested in a Phase 1/2 study in 35 patients with diffuse large B cell lymphoma (DLBCL). AUTO3 has also been granted orphan drug designation by the FDA for the treatment of ALL (**S4**). Autolus has also recently reported positive preclinical data from its AUTO5 (in T cell lymphoma), AUTO6NG (in small cell lung cancer), and AUTO7 (in prostate cancer) programs (**S5**).

Business success and economic impact

Recognising that the funding required to enable rapid technological development of these emerging therapies could most effectively be secured through a spinout company, Dr Pule founded Autolus in 2014 with UCL Business Plc (UCLB), the wholly-owned technology transfer company of UCL, aided by additional funding from a BBSRC Sparking Impact award.

This support helped facilitate dialogue with venture capital firms, ultimately securing in January 2015, GBP30,000,000 investment from Syncona LLP, a subsidiary of Wellcome which targets exceptional science in areas of high unmet medical need. This investment represented at the

time the largest series A funding ever raised by a European biotechnology company (**S6**). This was followed in March 2016 by an additional GBP40,000,000 series B funding and then in September 2017 by a further USD80,000,000 (GBP59,000,000) in series C funding from new investors.

In June 2018, Autolus Therapeutics raised USD150,000,000 from the Initial Public Offering (IPO) of its shares and began trading on the NASDAQ exchange (**S7**). Subsequent share offerings in 2019 and 2020 raised a further USD184,000,000 in net proceeds. The registration statement filed by Autolus with the US Securities and Exchange Commission (SEC) ahead of its IPO identifies the UCL team's work as the company's foundation stone, "Our proprietary and modular T cell programming technologies were invented by Dr Martin Pule, our scientific founder and Senior Vice President and Chief Scientific Officer. Dr Pule has been an innovator in the field of genetic engineering of T cells for cancer treatment for almost 20 years".

Autolus has established its global headquarters and research operations in the UK, creating 400 jobs, including more than 150 high-skilled manufacturing positions and 50 cutting-edge research roles (**S8**). Up to 50 additional manufacturing staff are being recruited, mainly to work at the Cell and Gene Therapy Catapult (CGT Catapult) GBP70,000,000 large-scale GMP manufacturing centre in Stevenage. The CGT Catapult is part of the Innovate UK-funded catapult network, designed to transform the UK's innovation capability in key industry sectors, and in 2016 Autolus became the first company signed up to collaborate with its manufacturing arm (**S9**).

Autolus is recognised as a UK industrial success story, featured in the government's Life Sciences Sector Deals, Parts 1 and 2, published in 2017 and 2018 respectively as part of the UK Industrial Strategy (**S10**). The government's 2018 Industrial Strategy: Life Science Sector Deal Part 2 publication highlights Autolus as a case study in the Business Environment section ("Making the UK a global hub for advanced therapies manufacturing"), noting the company's plans to "expand their global headquarters and research laboratories, generating 100 high-value UK jobs". In October that year, Autolus was one of a small number of biotech companies invited to discuss UK industrial strategy with then Secretary of State for Business, Energy and Industrial Strategy, Greg Clark (**S11**).

5. Sources to corroborate the impact

S1. Autolus Pipeline of Clinical Programs: https://www.autolus.com/pipeline
S2. https://autolus.gcs-web.com/news-releases/news-release-details/autolus-therapeutics-receives-fda-orphan-drug-designation-auto1
S3.Autolus Therapeutics presents compelling AUTO1 data from ALLCAR Phase 1 study in Adult Acute Lymphoblastic Leukemia (ALL) during the 62nd ASH Annual Meeting https://www.globenewswire.com/news-release/2020/12/05/2140158/0/en/Autolus-Therapeutics-presents-compelling-AUTO1-data-from-ALLCAR-Phase-1-study-in-Adult-Acute-Lymphoblastic-Leukemia-ALL-during-the-62nd-ASH-Annual-Meeting.html
S4.https://autolus.gcs-web.com/news-releases/news-release-details/autolus-therapeutics-receives-fda-orphan-drug-designation-auto3
S5. https://autolus.gcs-web.com/news-releases/news-release-details/autolus-therapeutics-reports-second-quarter-2020-financial
S6. https://bbsrc.ukri.org/documents/1610-autolus-ltd-pdf/
S7. https://autolus.gcs-web.com/news-releases/news-release-details/autolus-announces-pricing-initial-public-offering
S8. F1 document filed with SEC: https://autolus.gcs-web.com/static-files/371bda81-690f-42b7-b4b2-e8857b74ae1b
S9. https://autolus.gcs-web.com/news-releases/news-release-details/autolus-manufacture-cell-and-gene-therapy-catapult-collaboration
S10.https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/665452/life-sciences-sector-deal-web-ready-version.pdf (pp. 14, 29)
]https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/768570/life-sciences-sector-deal-2-web-ready-update.pdf (pp.11, 17)

S11.Oct-Dec 2018 BEIS ministerial meetings:
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/788293/october-december-2018-disclosure-ministerial-meetings.csv/preview