

<b>Institution:</b> Keele University		
<b>Unit of Assessment:</b> UoA12 Engineering		
<b>Title of case study:</b> Advancing Regenerative Medicine: from the bench to a NICE-approved treatment for early osteoarthritis		
<b>Period when the underpinning research was undertaken:</b> 2000-2020		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
Prof Sally Roberts PhD	Biologist; Prof of Orthopaedic Research	2001 - present
Prof James Richardson FRCS, PhD	Instigator of Cell Therapy Programme; Surgeon & Prof of Orthopaedics	1995 – 2018 (deceased)
Dr Jan Herman Kuiper PhD	Statistician, engineer; SL in Biomechanics	2001 - present
Dr Karina Wright PhD	Cell Biologist; SL in Orthopaedics & Bioengineering	2009 - present
Dr Helen McCarthy PhD	Histologist; PDRA	2010 - present
Dr Claire Mennan PhD	Cell Biologist; PDRA	2011 - present
Dr Charlotte Hulme PhD	Biochemist; PDRA	2015 – present
Dr Andrea Bailey PhD Dr Bernhard Tins FRCR Mr Peter Gallacher FRCS Mr Paul Jermin FRCS	Physiotherapist Consultant Radiologist Consultant Orthopaedic Surgeon Consultant Orthopaedic Surgeon	Collaborative NHS staff
Robert Taylor	Research User Group	
<b>Period when the claimed impact occurred:</b> 2014 onwards		
<b>Is this case study continued from a case study submitted in 2014?</b> N		
<b>1. Summary of the impact</b> (indicative maximum 100 words) <p>Our research in applied cell engineering in knee joints has had impact on (i) public policy, (ii) health and quality of life, (iii) economy and (iv) practitioners and professional services. It has provided evidence affecting regulatory decisions, prognostic tools, and new clinical standards benefitting patients, clinical practitioners, and commercial companies. The research involved a team of clinicians, engineers and scientists and has translated cell therapy for knee cartilage, autologous chondrocyte implantation (ACI), to help prevent osteoarthritis. Our research and cost-benefit data led to National Institute for Health &amp; Care Excellence (NICE) approval in 2017 and eligibility for NHS funding.</p>		

**2. Underpinning research** (indicative maximum 500 words)

The underpinning research was performed by a multidisciplinary team from Keele and the Robert Jones & Agnes Hunt Orthopaedic Hospital (RJA), comprising orthopaedic surgeons (Richardson, Gallacher & Jermin), physiotherapists (Bailey), radiologists (Tins), engineers (Kuiper), scientists (Roberts, Wright, McCarthy, Hulme, Mennan), and patient and public advocacy.

Untreated cartilage defects can progress to osteoarthritis, characterised by joint pain, functional limitations, reduced quality of life, and risk of progression to joint replacement (arthroplasty). This programme of research has focussed on a regenerative medicine approach, autologous chondrocyte implantation (ACI), which aims to help cartilage repair by implanting healthy chondrocytes cultured in our Good Manufacturing Practise (GMP) facility, the John Charnley Laboratory. The aim of ACI is to provide long-term clinical benefit by enhancing cartilage repair. A cohort of >500 patients, has supported assessment of the long-term efficacy of ACI treatment and improved understanding of the cartilage repair process [Kuiper, Richardson, Roberts, Tins 3.1, 3.2, 3.3].

We observed that a small percentage of patients had little or only a short-term benefit from ACI [3.3,3.4]. Through this we identified patient-specific factors that favoured longer-term benefits, such as being male, younger, having a small number of previous operations, and limited osteoarthritic damage to the knee [3.3]. Using these data, a prognostic tool was developed to aid treatment decisions for both the surgeon and patient, helping identify those patients who will benefit most from ACI (Oswestry Risk of Knee Arthroplasty Index (ORKA-1)). Within one year of publication, a centre in New York had trialled and validated this tool [5.8]. Our team has developed a web-based App (<https://ork.app/>) further implementing the tool, allowing patients and their surgeons to enter their unique data. The app then determines the likely benefit ACI will provide for that patient, enabling a streamlined and improved process for treatment decisions. Further personalisation of treatment is now possible via our biomarkers studies demonstrating, for example, that high levels of the enzyme, ADAMTS-4, are associated with lack of response to ACI [3.4].

Our research was instrumental in establishing an international scoring benchmark, firstly in the original International Cartilage Research Society (ICRS) visual assessment scale (ICRS I) [3.5]. Collaborating with other histopathologists as part of the monitoring committee of the clinical trial of the 1<sup>st</sup> ACI product to obtain a marketing authorisation, manufactured by Tigenix (Chondrocelect), this assessment scale was then developed into a new system (ICRS II) published in 2010 [3.6]. This new scoring system has become an international standard for evaluating cartilage repair in clinical treatments, trials, and research models, as well as for evaluating the effectiveness of commercial products.

Continual monitoring of patients after cell implantation and their outcomes proved to be a key factor in demonstrating cost effectiveness of ACI and its subsequent NICE approval. Much of the data presented to NICE (2017) came from the Keele/RJA multicentre trial, ACTIVE (<http://www.isrctn.com/ISRCTN48911177>). At the time of approval (October 2017) and at present, we are the only Medicines and Healthcare products Regulatory Agency (MHRA) licensed chondrocyte manufacturing facility in the UK.

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

**3.1** Bhosale A, Kuiper JH, Johnson WEB, Harrison P, Richardson JB. Midterm to Long-Term Longitudinal Outcome of Autologous Chondrocyte Implantation in the Knee Joint A Multilevel Analysis. Am J Sport Med. 2009;37 (Suppl 1):131S-138S.

**3.2** Roberts, S, Mccall, IW, Darby, AJ, Menage, J, Evans, EH, Harrison PE, Richardson, JB. Autologous chondrocyte implantation for cartilage repair: monitoring its success by magnetic resonance imaging and histology. Arthrit Res Ther. 2003; 5:60-74.

**3.3** Dugard MN, Kuiper JH, Parker J, Roberts S, Robinson E, Harrison P, Richardson JB. Development of a tool to predict outcome of autologous chondrocyte implantation. *Cartilage*. 2017 8:119-30.

**3.4** Wright KT, Kuiper JH, Richardson JB, Gallacher P, Roberts S. The absence of detectable ADAMTS-4 (aggrecanase-1) activity in synovial fluid is a predictive indicator of autologous chondrocyte implantation success. *Am J Sport Med*. 2017; 45:1806-14.

**3.5** Mainil-Varlet P, Aigner T, Brittberg M, Bullough P, Hollander A, Hunziker E, Kandel R, Nehrer S, Pritzker K, Roberts S, Stauffer E. Histological assessment of cartilage repair: a report by the Histology Endpoint Committee of the International Cartilage Repair Society (ICRS). *J Bone Joint Surg*. 2003;85-A Suppl 2:45-57.

**3.6** Mainil-Varlet P, Van Damme B, Nesic D, Knutsen G, Kandel R, Roberts S. (2010) A new histology scoring system for the assessment of the quality of human cartilage repair: ICRS II. *Am J Sport Med* 2010; 38:880-90.

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

##### Impacts on public policy

NICE approved autologous chondrocyte implantation (ACI) for treating articular cartilage defects in October 2017 after a long period of clinical trials and scientific research [5.1], in which Keele researchers were key. Our research on the long-term benefits of ACI contributed strong evidence leading to approval of the technique for wider use and funding within the NHS [5.2] ACI is the first cell therapy to get such regulatory approval. Survival analysis suggested that long-term results are better with ACI than with microfracture and health-economic modelling showed ACI to be cost-effective across a range of scenarios, with a best estimate of £8,000 per quality adjusted life year (QALY) compared to alternative treatments [5.1].

The recommendations by NICE showed the impact of determining the mechanisms and benefits of ACI for knee cartilage repair. Specifically, the NICE committee commented that “*Clinical trial evidence shows that ACI can improve the symptoms of articular cartilage defects of the knee. There is evidence that it is likely to be more successful in people who have not had any previous knee repair surgery, and in people who have very little osteoarthritic damage in the knee.*” Much of this evidence comes from our multicentre trial, ACTIVE (<http://www.isrctn.com/ISRCTN48911177>), [5.1].

##### Impacts on health:

The focus of our research on ACI has been on understanding how cell therapy enhances the cartilage healing process and identifying patient-specific factors that influence a successful treatment outcome. The ongoing translation of this research also resulted in providing autologous cell therapy at our institution to treat more than 500 cartilage defect patients up until July 2020, improving their health and quality of life [5.3].

Three typical patients are Marianne (fitness instructor), Christopher (mechanical engineer) and Melissa (intensive care nurse). Marianne featured on BBC’s One Show (November 2019; updated on BBC Morning Live 27 November 2020 [5.4a]), together with Roberts (Keele) and Gallacher (surgeon), and the story was covered in The Times (14<sup>th</sup> Jan 2020) [5.4a]. Marianne explained how she was diagnosed with early onset osteoarthritis three years ago and had the ACI procedure on her knee. Before the surgery she was in a lot of pain, struggling to walk and forced to leave her job as a fitness instructor. She is now recovering well, free of pain, back running and has landed a new dream job [5.4a].

Christopher had suffered with debilitating knee problems following a mountain bike accident in 2009. He started ACI treatment as part of a trial in April 2016 and has since found a dramatic improvement: “*I’ve made huge progress since the trial. I’m back at work, and I’m able to move around again. It’s made a huge difference to my quality of life.*” [5.4b].

Melissa had previously enjoyed a busy and active lifestyle. After more than a decade of suffering with arthritis, she found it causing increasingly excruciating pain, making her consider giving up

work. Following the ACI treatment, her life has returned to normal. She is working and even undertook the 'River Severn challenge' incorporating a 40 mile walk and swimming 220 miles in June 2019 [5.4c].

In addition, the John Charnley Laboratory has been used to provide cells for a study of autologous bone marrow-derived mesenchymal stromal/stem cells (MSCs) to treat patients with recalcitrant (long-lasting) non-union fracture of their bones, who were considering amputation of their leg. Thanks to our treatment, 21 patients achieved a union of their fracture [5.5].

#### *Impacts on industry and economics*

Our work has impacted on commercial providers of products related to ACI. The histology scoring scheme developed by Keele researchers (ICRSII; [3.6]) was used as the primary outcome during the assessment by the European Medicines Agency (EMA) for Marketing Authorisation of ChondroCelet by Tigenix [5.6]. Seven international randomised clinical trials of cartilage repair used histology as an outcome measure, utilising the ICRS-II score [5.7].

NICE's first approval of ACI was based on long-term evidence from Keele researchers amongst others [5.1; 5.2]. This evidence was subsequently extended to NICE's second approval of a cartilage cell therapy product, Chondrosphere® (Spherex, CO.DON) in March 2018, despite the company having no long-term follow-up beyond 4 years [5.8]. The government funded Small Business Research Initiative (SBRI), identified ACI as a priority for musculoskeletal conditions worthy of support in July 2018, including the contribution that regenerative medicine could make to this health condition. (<https://sbrihealthcare.co.uk/wp-content/uploads/2018/07/Krysia-and-Sally.pdf>). Small and medium size enterprises were awarded Phase 1 (<£100k) and Phase 2 (<£1m) funding respectively to advance the development and uptake of ACI technology further (<https://mogrify.co.uk/mogrify-awarded-1-1m-additional-funding-from-sbri-healthcare>).

#### *Impact on practitioners and professional services*

In August 2018 the first external validation of the ORKA-1 was published. This study considered an ACI patient cohort in the United States [5.9]. The authors concluded that "*The ORKA-1 is a helpful tool for surgeons to estimate an individual patient's likelihood of ACI survival.*" Further impacts of the use of ORKA-1 by fellow professionals and its impact have materialised, such as its use in a recent NICE scoping exercise for an additional novel cartilage repair treatment [5.10]. Our impact on practitioners is also evidenced by the 'James Richardson Award' (<http://arthritistissueengineering.org.uk/blog/james-richardson-award>), created in 2018 by the International Cartilage and Joint Preservation Society (ICRS) to honour Professor Richardson's impact on Cell Therapy and Regenerative Medicine and encourage other mentors and innovators in the field of cartilage repair.

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

**5.1** Technology appraisal guidance TA477: "Autologous chondrocyte implantation for treating symptomatic articular cartilage defects of the knee", National Institute for Health and Care Excellence (NICE), Oct 2017 <https://www.nice.org.uk/guidance/ta477>

**5.2** Mistry H, Connock M, Pink J, Shyangdan D, et al. Autologous chondrocyte implantation in the knee: systematic review and economic evaluation. Health Technol Assess. 2017 Feb;21(6):1-294. DOI: [10.3310/hta21060](https://doi.org/10.3310/hta21060).

**5.3** Individual users/beneficiaries who could be contacted by the REF team to corroborate claims – Consultant Knee and Shoulder Surgeon, Royal Orthopaedic Hospital, Birmingham (personal details (name, position, contact details) entered under Corroborators on the REF submission system)

**5.4a** Story of Marianne W: <https://www.thetimes.co.uk/article/could-this-be-the-miracle-cure-for-your-dodgy-knee-7mvlzhqg5>, [www.versusarthritis.org how-we-re-improving-treatment-options-for-people-with-osteoarthritis-through-research](http://www.versusarthritis.org/how-we-re-improving-treatment-options-for-people-with-osteoarthritis-through-research), "The pain meant I was losing so much"

<https://www.versusarthritis.org/news/2020/february/the-pain-meant-i-was-losing-so-much/> and <https://www.bbc.co.uk/iplayer/episode/m000prwy/morning-live-series-1-27112020> (segment is on from 32:08.) (download held within Keele's repository)

**5.4b** Story of Christopher B: <https://www.rjah.nhs.uk/Our-Services/Orthopaedic-Surgery/Cartilage-Transplantation/Patient-Case-Study-Christopher-Bloore.aspx>

**5.4c** Story of Melissa C: <https://www.bbc.co.uk/news/uk-england-shropshire-48913407>

**5.5** Bhattacharjee A, Kuiper JH, Roberts S, Harrison PE, Cassar-Pullicino VN, Tins B, Bajada S, Richardson JB. Predictors of fracture healing in patients with recalcitrant nonunions treated with autologous culture expanded bone marrow-derived mesenchymal stromal cells. Journal of Orthopaedic Research®. 2019 Jun;37(6):1303-9. DOI: [10.1002/jor.24184](https://doi.org/10.1002/jor.24184)

**5.6** EMEA ChondroCelect assesment [https://www.ema.europa.eu/documents/assessment-report/chondrocelect-epar-public-assessment-report\\_en.pdf](https://www.ema.europa.eu/documents/assessment-report/chondrocelect-epar-public-assessment-report_en.pdf)

**5.7** [US Clinical Trials using ICRS-II score](#)

**5.8** Technology appraisal guidance TA508: "[Autologous chondrocyte implantation using chondrosphere for treating symptomatic articular cartilage defects of the knee](#)", National Institute for Health and Care Excellence (NICE), Mar 2018.

**5.9** Ackermann J, Barbieri Mestriner A, Arango D, Ogura T, Gomoll AH. Validation of the Oswestry Risk of Knee Arthroplasty Index (ORKA-1) for patients undergoing autologous chondrocyte implantation. Cartilage. 2018 Aug 27: DOI: [10.1177/1947603518796146](https://doi.org/10.1177/1947603518796146)

**5.10** Autologous chondrocyte implantation using 3D collagen matrix (novocart 3D) for treating articular cartilage defects of the knee [ID2707], NICE, June 2020. <https://www.nice.org.uk/guidance/gid-ta10667/documents/draft-scope-pre-referral>