**IS ORTHOPAEDICS LEADING THE WAY IN GETTING CELL THERAPY TO THE CLINIC?**

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# The translation of Advanced Therapeutic Medicinal Products (ATMPs) from the laboratory bench to their use in patients is probably more difficult than for any other pharmaceutical product. Whilst there have been very significant progresses in introducing ATMPs in the form of chimeric antigen receptor (CAR)-T cells for the treatment of leukaemia and lymphoma, the number of patients which will be impacted on is relatively small. The field of orthopaedics provided the first ATMP to be licensed and to obtain a Marketing Authorisation in 2009 from the European Medicines Agency, with the chondrocyte cell therapy (Chondrocelect) for repair of cartilage defects in the knee via autologous chondrocyte implantation (ACI). ACI was one of the first ATMPs to be approved by NICE in the UK in 2017. This application has a much bigger potential patient base, being relevant to millions if such a product can be used successfully to treat early osteoarthritis; in addition, unlike some of the CAR-T cells, it is likely to have few if any potential adverse reactions. In terms of clinical trials, some of the largest of ATMPs are also for orthopaedic products, for example, ACI is being trialled in ACTIVE (ISCRCTN 48911177, n=390 patients) and a mesenchymal progenitor cell for disc degeneration and back pain (MSB-DR003, NCT02412735, n=404 patients).

# The path is not straightforward, however, as orthopaedic products were also some of the first to be withdrawn from the market place (MACI and Chondrocelect in 2014 and 2016, respectively)1.

# For ATMPs to have a more widespread take-up in orthopaedics, they need to be rendered simpler to apply than for example in the current ACI technique. The use of allogeneic cells, such as may be sourced from umbilical cord tissue, and transforming ACI from a procedure requiring two surgeries with fairly prescriptive timelines to a simple intra-articular injection, should aid this development considerably. Likewise better patient selection, which could improve the typical 80% success rate currently with ACI, would further improve the cost-benefit which could be gained. Recent studies of the proteome of synovial fluid have shown differences between patients who do or do not respond to ACI and development of this knowledge into a simple serological biomarker assay should improve cost-effectiveness of ACI further.

# 1Seimetz D, Heller K and Richter J (2019) Approval of First CAR-Ts: Have we Solved all Hurdles for ATMPs? *Cell Medicine* 11:1-16