All fields of endeavour have their ups and downs, but gene therapy arguably suffers more than most. The predominant early concern was safety. In the broad sweep of events since the first approved gene transfer to a human in 1989, there have been two major setbacks as a result of well-publicized patient deaths. The first, that of Jesse Gelsinger in 1999, deflated what had until then been a decade of increasing optimism and achievement that saw the approval of approximately 485 gene therapy trials. After a hiatus, progress resumed only for momentum to be reversed once again, this time by the occurrence of leukaemia in children receiving gene therapy for severe combined immunodeficiency disease (SCID). Nevertheless, at about this time, the Chinese authorities approved the world’s first gene therapeutic, Gendicine (Shenzhen SiBiono GeneTech, Shenzhen, China), for the treatment of head and neck cancer (Table I). Approval of a gene therapy by Western countries did not occur until 2012, when the European Medicines Association (EMA) authorized Glybera (UniQure, Amsterdam, The Netherlands) for lipoprotein lipase deficiency.

Since then, in the absence of additional major safety issues and with technological advances in vector design and manufacturing, 13 gene therapies have now gained full or conditional market approval in various parts of the world (Table I), although one of these has since been rescinded (Invossa; Kolon TissueGene, Rockville, Maryland) and another withdrawn for commercial reasons (Glybera). Another, conditionally approved product, Zalmoxis (MolMed, Milan, Italy), is on hold because the primary endpoint has not been met in a current Phase III trial. By the end of 2017, the last year for which complete data are available, approximately 2600 gene therapy clinical trials had been completed.

Interest in orthopaedic applications of gene therapy began in the late 1980s and its development has been buffeted by many of the same issues affecting the field as a whole. Most progress has been made with the development of intra-articular gene therapies for treating arthritis, where the introduction of cells expressing the interleukin-1 receptor antagonist (IL-1Ra) into rheumatoid joints was an early success. Progress in the further development of this ex vivo, retroviral approach was prevented by a number of factors, including the risk from insertional mutagenesis of the type that caused the occurrence of leukaemia in the SCID trial mentioned above.

By then, adeno-associated virus (AAV) vector technology had improved considerably, and Phase I and II trials were conducted, which used this vector to deliver etanercept to joints with rheumatoid arthritis (RA). Although these trials showed promise, a patient in the Phase II study died from a fungal infection. After an investigation by the United States Food and Drug Administration (FDA), the clinical hold was lifted. However, there has been no further activity from this clinical programme. Elsewhere, recombinant AAV encoding interferon-beta under the transcriptional control of an inflammation-inducible promoter was developed for injection into joints with RA. This has shown promise in preclinical testing and clinical trials are underway (NCT02727764, NCT03445715).

Meanwhile, a novel ex vivo protocol for the intra-articular treatment of osteoarthritis (OA) was introduced, using allogeneic chondrocytes transduced with retrovirus to express high levels of transforming growth factor-beta. This therapeutic, known as Invossa, was approved in South Korea in 2017 (Table I) and Phase III clinical trials in the United States began in 2018 (NCT03203330). Then everything stopped. Earlier this year, it came to light that the genetically modified cells being injected intra-articularly were not chondrocytes but HEK293 cells. The HEK293 line, established from human embryonic kidney, is often
engineered to produce retrovirus vectors of the type used to prepare Invossa. The circumstances under which the HEK293 cells contaminated Invossa and other matters surrounding this case are under investigation. Meanwhile, the Korean licence for Invossa has been revoked and the Phase III United States trial has been suspended by the FDA.

In the latest arthritis gene therapy protocol to start clinical trials, knee joints of nine patients with OA will be injected with recombinant AAV that encodes IL-1Ra (NCT02790723); the first patient in this Phase I study was injected in June 2019. ClinicalTrials.gov also reports a Phase I study where plasmid DNA encoding a variant of human interleukin (IL)-10 will be injected into the knees of patients with OA (NCT03477487). In August 2019, its status was given as “active, not recruiting”.

There is considerable interest in using gene transfer in the context of orthopaedic tissue regeneration. The underlying strategy is to deliver regenerative gene products, especially morphogens and growth factors, in the sustained fashion necessary for robust healing. Traditional delivery methods, in contrast, implant these proteins in combination with a scaffold, which usually results in suboptimal, rapid burst release kinetics. Gene transfer holds additional promise when delivering products such as transcription factors and non-coding RNA, whose sites of action are intracellular.

Applications in bone healing, cartilage repair, and the regeneration of intervertebral disc, tendons, and ligaments largely remain at a preclinical stage of research, but show promise in rodent and rabbit models. It has proved difficult to replicate these successes in large animal models, although Bez et al recently achieved impressive healing of critical size, tibial defects in pigs using bone morphogenetic protein-6 delivered via plasmid DNA in conjunction with sonication. Invossa has been implanted within a fibrin gel for the repair of human cartilage defects (NCT01825811) with encouraging, but unpublished, results.

There has been relatively little research into the application of gene therapy for treating genetic diseases of the skeletal system. These are quite rare and the most common, osteogenesis imperfecta, is a dominant negative mutation that not only requires transfer and expression of a wild-type cDNA, but also repression of the mutant gene. In such cases, gene editing using CRISPR-Cas technology may offer a more straightforward path forward.

Although cancer gene therapy is a thriving field, so far there has been little clinical application to malignancies of...
orthopaedic interest beyond early trials using CAR-T cells (NCT01953900) and Rexin-G (Epeius Biotechnologies, San Marino, California) to target osteosarcoma (Table I).16

As safety concerns recede and the number of approved gene therapeutics increases, the field of gene therapy has gathered considerable recent momentum. Particularly encouraging is the rapidly expanding involvement of large pharmaceutical companies with the experience and resources to accelerate the clinical development of gene therapeutics.

However, a number of constraints continue to limit progress. In particular, the production of vectors under Good Manufacturing Practice (GMP) conditions remains inefficient and expensive. In many cases, contract manufacturers have long queues. These factors partly explain the very high cost of gene therapeutics. Glybera became the world’s first million-dollar drug; it sold poorly and was withdrawn from the market in 2017. The latest gene therapy to be approved, Zolgensma (Novartis, Basel, Switzerland) for spinal muscular dystrophy, has been priced at $2.1 million per dose, another new record.

Genetic drugs for treating disorders of bones and joints should be much more affordable. Not only is the patient pool for diseases such as OA very large, but most applications envisage local treatment with a relatively small amount of vector. Under these conditions, orthopaedic conditions could become the domain where gene therapy becomes widely applied.17

References
1. Rosenberg SA, Aebersold P, Cornetta K, et al. Gene transfer into humans—immunotherapy of patients with advanced melanoma, using tumor-infiltrating lymphocytes modified by retroviral gene transduction. N Engl J Med 1990;323:570-578.
2. Raper SE, Chirmule N, Lee FS, et al. Fatal systemic inflammatory response syndrome in a ornithine transcarbamylase deficient patient following adenoviral gene transfer. Mol Genet Metab 2003;80:148-158.
3. Hacein-Bey-Abina S, Von Kalle C, Schmidt M, et al. LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science 2003;302:415-419.
4. Zhang WW, Li L, Li D, et al. The first approved gene therapy product for cancer ad-p53 (Gendicine): 12 years in the clinic. Hum Gene Ther 2018;29:160-179.
5. Richards S. Gene therapy arrives in Europe. The Scientist 2012. https://www.the-scientist.com/news-opinion/gene-therapy-arrives-in-europe-40230 (date last accessed 8 October 2019).
6. Kotterman MA, Chalberg TW, Schaffer DV. Viral vectors for gene therapy: translational and clinical outlook. Annu Rev Biomed Eng 2015;17:83-99.
7. Ginn SL, Amaya AK, Alexander IE, Edelstein M, Abedi MR. Gene therapy clinical trials worldwide to 2017: an update. J Gene Med 2018;20:e3015.
8. Evans CH, Ghizzavani SC, Robbins PD. Gene delivery to joints by intra-articular injection. Hum Gene Ther 2018;29:2-14.
9. Evans CH, Robbins PD, Ghizzavani SC, et al. Gene transfer to human joints: progress toward a gene therapy of arthritis. Pro Natl Acad Sci U S A 2005;102:8696-8703.
10. Meese PJ, Wei N, Fedman EJ, et al. Safety, tolerability, and clinical outcomes after intraarticular injection of a recombinant adeno-associated vector containing a tumor necrosis factor antagonist gene: results of a phase 1/2 Study. J Rheumatol 2010;37:692-703.
11. Meese PJ, Hobbs K, Chalmers A, et al. Local delivery of a recombinant adenoassociated vector containing a tumour necrosis factor alpha antagonist gene in inflammatory arthritis: a phase 1 dose-escalation safety and tolerability study. Ann Rheum Dis 2009;68:1247-1254.
12. Evans CH, Ghizzavani SC, Robbins PD. Arthritis gene therapy’s first death. Arthritis Res Ther 2009;11:10.
13. Bevaart L, Aalbers CJ, Vierboom MP, et al. Safety, biodistribution, and efficacy of an AAV-5 vector encoding human interferon-beta (ART-I02) Delivered via intra-articular injection in rhesus monkeys with collagen-induced arthritis. Hum Gene Ther Clin Dev 2015;26(2):103-112.
14. Evans CH, Huard J. Gene therapy approaches to regenerating the musculoskeletal system. Nat Rev Rheumatol 2015;11:234-242.
15. Bez M, Sheyn D, Tawackoli W, et al. In situ bone tissue engineering via ultrasound-mediated gene delivery to endogenous progenitor cells in mini-pigs. Sci Transl Med 2017;9:eaal3128.
16. Chauva SF, Chua VS, Fernandez L, et al. Phase I/II and phase II studies of targeted gene delivery in vivo: intravenous Rexin-G for chemotherapy-resistant sarcoma and osteosarcoma. Mol Ther 2009;17:1651-1657.
17. Evans CH. Orthopaedics: gene therapy’s dark horse. Gene Ther 2004;11:343.

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