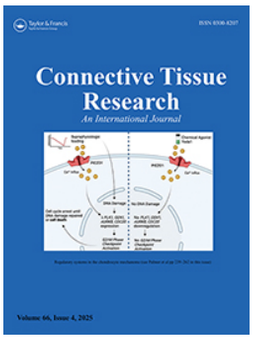

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Gene therapy pipelines for osteoarthritis: current innovations, operational challenges, and future directions

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ABSTRACT

Background: Osteoarthritis (OA) is a multifactorial joint disease characterized by progressive cartilage degradation, synovial inflammation, and subchondral bone remodeling. Despite its significant global health burden, there are currently no disease-modifying pharmacological therapies for OA. Gene therapy, leveraging viral and non-viral vectors to deliver therapeutic transgenes into the joint environment, shows significant promise.

Significant discoveries: This mini-review highlights recent innovations in OA gene therapy pipelines, focusing on Platforms employing recombinant adenovirus, adeno-associated virus (AAV), and herpes simplex virus vectors. Strategies include AAV-mediated delivery of interleukin-1 receptor antagonist (IL-1Ra) and truncated nkx3.2 transcription factor to modulate inflammation and promote chondrocyte survival. Non-viral approaches, such as plasmid DNA encoding interleukin-10, are also under investigation.

Critical barriers: Emerging data from preclinical and clinical studies demonstrate the feasibility of achieving sustained, intra-articular transgene expression with therapeutic efficacy in animal models and early-phase human trials. However, challenges persist, including immune barriers to repeat dosing, variability in vector performance, and the high costs of treatment. Additionally, agerelated declines in transduction efficiency, the heterogeneity of OA, and systemic metabolic influences complicate therapeutic outcomes.

Outlook: To overcome current regulatory obstacles, future research must prioritize the refinement of vector systems to enhance safety, potency, and specificity, as well as the development of combination therapies integrating genetic and conventional approaches, targeting pain and improving function. Gene therapy has transformative potential for improving OA management and an important priority is multidisciplinary collaboration to translate preclinical innovations into accessible, effective treatments for a highly heterogeneous and aging patient population.

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Introduction

Osteoarthritis (OA) is a chronic, progressive and systemic mechano-inflammatory whole joint disease characterized by the breakdown and loss of articular cartilage, synovial inflammation, and subchondral bone remodeling[1,2]. As a multifactorial disorder, OA primarily affects load-bearing joints such as the knees, hips, and spine, leading to pain, stiffness, and impaired mobility. OA also affects smaller joints such as ankles, shoulder and the hand. Pathophysiologically, OA involves a dynamic interplay of mechanical stress, pro-inflammatory mediators, and altered cellular signaling within the joint microenvironment[3]. Key molecular features of OA include extracellular matrix (ECM) degradation driven by proteases including matrix metalloproteinases (MMPs) and aggrecanases[4], dysregulation of chondrocyte homeostasis, plus immunometabolic alterations[5] and low-grade inflammation[6] mediated by pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). Despite its high prevalence and significant impact on quality of life, there are no approved disease-modifying pharmacological treatments for OA, highlighting the critical need for advancements in therapeutic strategies targeting both symptom management and structural preservation[7]. Regenerative medicine, cell-

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based, and gene-based therapies hold significant promise for addressing the global health challenges posed by OA.

This mini-review summarizes the current state of knowledge regarding viral and non-viral gene therapy platforms that are currently being developed and tested for OA, delving into challenges and opportunities. We will discuss recombinant adenovirus (Ad) and adeno-associated virus (AAV) vectors for delivering cDNA encoding the interleukin-1 receptor antagonist (IL-1Ra)[8] in the synovial joint. We will also touch upon research focusing on adeno-associated viral vector delivery of the truncated form of the nkx3.2 transcription factor, which plays key roles in determining chondrogenic cell fate, endochondral ossification, and chondrocyte survival[9,10]. This paper will also discuss naked non-viral plasmid DNA encoding interleukin 10 currently being trialed (NCT04124042) for the treatment of knee OA and herpes simplex virus 1 (HSV-1) encoding carbonic anhydrase 8 for therapeutic delivery to the intra-articular space and indirect targeting of the dorsal root ganglion for achieving analgesic action through modulation of the Kv7 voltage-gated potassium channel, which is still in preclinical development[11]. Finally, consideration will be given to important operational practicalities, the challenges of repeat administration, immunogenicity, and the high cost of treatment, which is primarily driven by the cost of goods sold (COGS) currently. The high cost relates to development and manufacturing and is less related to re-dosing and the chronic nature of OA. We will also address issues relating to vector payload, duration of treatment, and potential adverse side-effects of the treatment (safety and efficacy) and allay any concerns in the scientific community about genome integration for gene therapy platforms using adenovirus, adeno-associated virus, and herpes simplex virus.

A detailed discussion of the background and history of gene therapy in osteoarthritis and how it has evolved over the last three decades is beyond the scope of this review article. Therefore, in the subsequent sections, we will focus immediately on significant discoveries and current innovations in gene therapy pipelines for OA and the choice of vectors for transgene delivery.

Significant discoveries

It is now well established that transgenes can be introduced into the diarthrodial joints of laboratory animals and expressed intra-articularly with therapeutic effects in animal models of OA[12]. Both *ex vivo* and *in vivo* strategies can be used for gene transfer. A variety of vectors have been employed in these studies for *in vivo* delivery, including lentivirus (LV), Ad, HSV, and AAV (Figure 1). Of these, high-capacity adenovirus (HCAd), also referred to as helper-dependent adenovirus (HDAd), and AAV have entered clinical trials. Although pre-clinical studies have generally found non-viral vectors to have poor transfecting ability in joints with transient transgene expression, there have been clinical trials using plasmid DNA (NCT03477487; NCT04124042) (Table 1).

Vectors injected into the joints of laboratory animals typically transduce the synovium first (Figure 1C), although AAV has also been shown to transduce chondrocytes *in situ* throughout the full thickness of the cartilage in equine joints[8,12–14]. There is little escape of the vector from the injected joint[14]. With OA being a chronic condition, the expression of an anti-arthritic transgene needs to persist at therapeutic concentrations to avoid frequent redosing. Because the innate immune system presents a major barrier to redosing, persistent transgene expression is best achieved using an immunologically silent vector to deliver an autologous transgene. Many current protocols incorporate transient immunosuppression at the time of viral vector administration to help prevent the development of neutralizing antibodies (NAbs). Injection of AAV encoding equine interleukin-1 receptor antagonist (IL-1Ra) into equine joints, for instance, elevates the local synthesis of equine IL-1Ra for at least 6 months[13]. Data from a recently completed clinical trial (NCT02790723.) confirm that this principle also applies to human knee joints with OA for at least 1 year[15].

Lessons learned

At this point, it remains unclear which transgenes or combinations of transgenes might produce the best therapeutic effects. Indeed, with OA being such a heterogeneous disease[1,2,5], it is unlikely that one gene therapeutic would be effective in all patients. Among the candidate genes are those encoding anti-inflammatory molecules (e.g., IL-1Ra, IL-10, IL-4), growth factors to promote cartilage matrix synthesis (e.g., TGF-, IGF-1, TGF-β-18), proteinase inhibitors to protect the matrix of cartilage (e.g., TIMPs), anti-nociceptive products, NF-κB antagonists, etc[4,7,12]. There is little information from pre-clinical investigations on the value of combination therapy involving gene therapy combined with a traditional pharmaceutical.

Most pre-clinical investigations have used strong constitutive promoters to drive the expression of therapeutic transgenes[8]. Still, there is interest in using

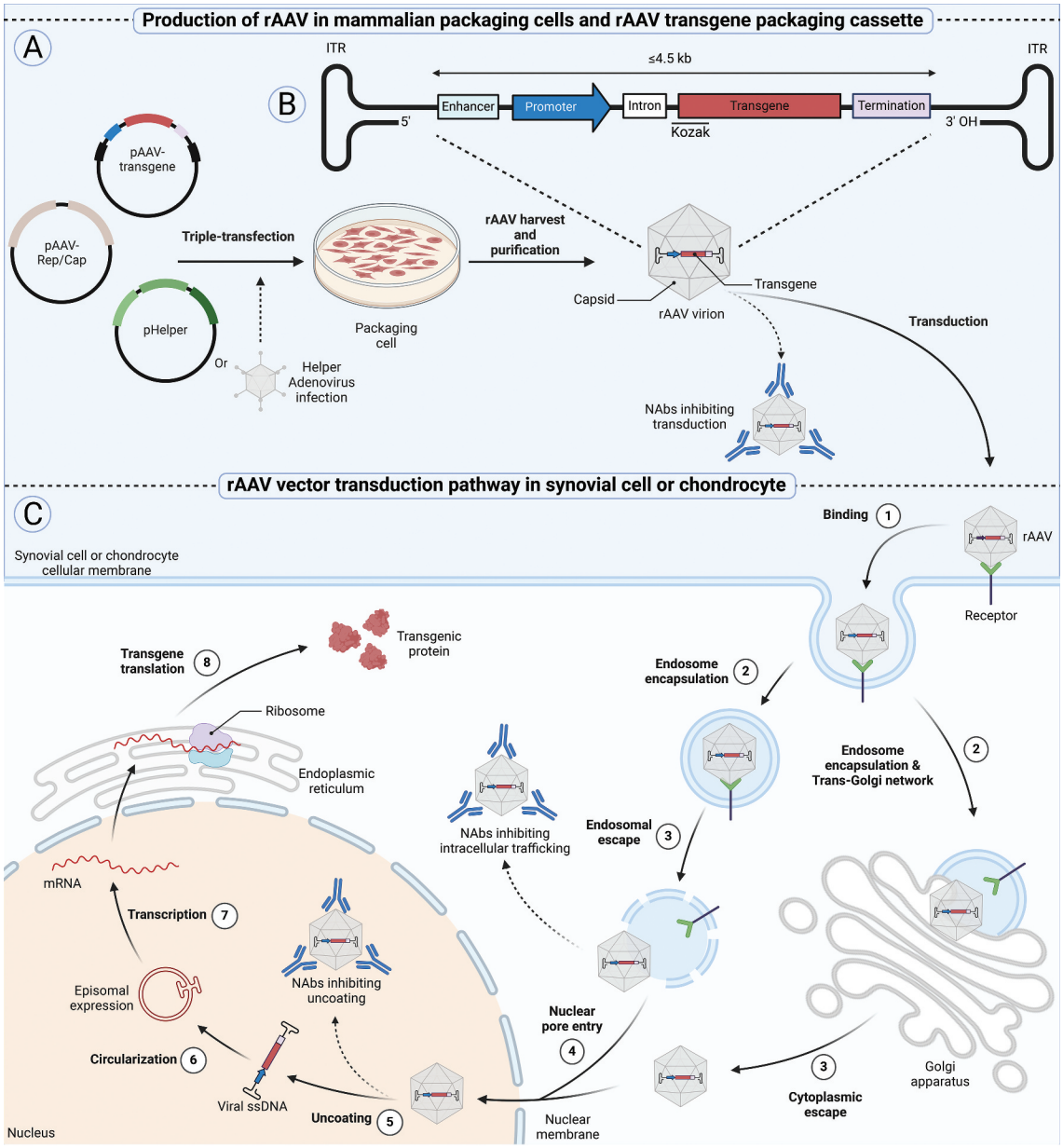

Figure 1. Recombinant adeno-associated virus (rAAV) production via triple-transfection and transduction pathway in synovial cells and chondrocytes. (A) production of rAAV in mammalian packaging cells via triple-transfection. Packaging cells, such as HEK-293, are transiently transfected with three plasmids: pAAV-transgene plasmid, pAAV-Rep/Cap plasmid (containing replication and capsid encoding genes), and pHelper plasmid (coding for *E4, E2a* and *VA* genes). Alternatively, a helper adenovirus infection can replace the pHelper plasmid. (B) Basic rAAV transgene packaging cassette. The packaging capacity of the rAAV vector is ≤ 4.5 kb. ITR—inverted terminal repeats. (C) rAAV vector transduction pathway in synovial cells or chondrocytes. rAAV primarily transduces synovial cells, with some vectors reaching and transducing chondrocytes when the rAAV is intra-articularly administered. 1) rAAV virion binds to the primary receptor. 2) endosomal encapsulation and trans-Golgi network processing of the rAAV virion. Conformational changes in the rAAV capsid occur in endosomes and Golgi. 3) late endosomal escape or cytoplasmic escape from the Golgi. 4) nuclear entry through the nuclear pore complex. 5) uncoating and release of the rAAV genome inside the nucleus. 6) conversion to double-stranded DNA and circularization. 7) transcription of the transgene. The transgene DNA remains episomal and does not integrate into the synovial cell or chondrocyte genome. 8) transgene translation. In the absence of *rep*, *cap*, and helper genes, rAAV particles for transduction are not produced. Neutralizing antibodies (NAbs) may inhibit transduction, intracellular trafficking, or uncoating processes, creating a clinical bottleneck for redosing. Choosing the rAAV serotype is also critical for transduction efficiency and represents another clinical bottleneck. Additionally, dropout rates from clinical trials pose a significant challenge. Created in BioRender.

Table 1. Clinical trials for intra-articular administration of osteoarthritis gene therapy.

Sponsor	Gene therapy	Mechanism of action (transgene)	Delivery platform	Development stage	Gene therapy patient exposure to date	Conditioning regimen	Lead indication	Clinical references	Status
Arthrogen BV	ART-102	IFN-β	Recombinant adeno-associated virus (rAAV), AAV5	Phase I	4	NA	Inflammatory hand arthritis	NCT02727764	Completed
Genascence Corporation	GNSC-001	IL-1Ra	Recombinant adeno-associated virus (rAAV), AAV2.5	Phase Ib	66	Yes	Knee osteoarthritis	NCT02790723 NCT05835895	Active, not recruiting
ICM	ICM-203	Nkx3.2-D2	Recombinant adeno-associated virus (rAAV), AAV5.2	Phase I/IIa	8	NA	Knee osteoarthritis	NCT04875754 NCT05454566	Not yet recruiting
Pacira BioSciences	PCRX-201	IL-1Ra	Adenovirus (HCAd, high-capacity adenovirus)	Phase II	162	Yes	Knee osteoarthritis	NCT04119687 NCT06884865	Recruiting
Xalud Therapeutics	XT-150	IL-10	Non-viral plasmid DNA (pDNA)	Phase II/III	389	No	Knee osteoarthritis	NCT03282149 NCT03477487 NCT04124042 NCT05196919	Completed

IFN-β, Interferon β; IL-10, interleukin 10; IL-1Ra, Interleukin-1 receptor antagonist; Nkx3.2-D2, A truncated form of NKx3.2 (NK3 homeobox 2) encoding amino acids 123–320.

inducible promoters to match the level and timing of transgene expression with the exacerbations and remissions of OA. Such a strategy promises to produce a better therapeutic effect and also accommodates the concern that the prolonged, constitutive expression of certain transgenes may be detrimental to the joint. Promising results have been reported for promoters constructed with multiple NF-κB response elements and one such inducible promoter has been used in a Phase I clinical trial (NCT04119687).

A small number of clinical trials have been initiated, which are early-phase studies (Table 1). So far, these trials have not reported serious adverse events at a systemic level, but local inflammation has been observed. In one study (NCT02727764) using AAV5 to deliver interferon β to the carpometacarpal joints and the proximal interphalangeal joints of the hand, subsequent tenosynovitis was sufficiently severe to terminate the trial. However, such severe symptoms were not observed when using AAV of a different serotype to deliver IL-1Ra to knee joints. Nevertheless, the inflammatory response to the delivery of IL-1Ra cDNA using HCAd was sufficiently robust to require the co-administration of corticosteroids.

Potential explanations for the variability in incidence and severity of side effects between studies include neutralizing antibody presence to the viral vector, age, and transgene selection. There is also the possibility that different joints mount different responses to the intra-articular injection of gene therapeutics and that these responses vary by different joint tissue compartments and disease states.

Knowledge gaps

Excluding genetically modified cell therapies such as chimeric antigen receptor T (CAR-T) cells, there are only 11 approved gene therapies globally[#], indicating that the overall gene therapy sector is still in its infancy. Compounding this, gene therapy for OA is one of the few highly prevalent chronic conditions to advance into the clinic along with select ophthalmologic and neurological indications. Taken together, there are knowledge gaps for gene therapy in general and for OA in particular.

As OA is generally an age-related disease, transduction efficiency in the target population is a question. Older cells typically exhibit lower transduction compared to young cells due to alternations in cell membrane properties and cellular processes associated with aging[16]. Additionally, a key variable to transduction efficiency is the presence of NAbs, which increase with age due to cumulative exposure[17].

It is indeterminate whether the mere presence of NAbs or a certain titer/threshold would affect efficacy. The degree to which the immune system limits the transduction of joint tissues and the level and duration of transgene expression combined with decreased transduction efficiency with aging may moderate the efficacy of gene therapy in the OA population. Conditioning regimens (e.g., oral or intra-articular steroid course) may mitigate NAbs, but the details (e.g., dose, duration, administration, etc.) remain to be elucidated. It also remains to be understood how to overcome immune barriers to intra-articular gene therapy, including how to dose and re-dose, if the latter is feasible when NAbs to the viral vector are present.

The selection of the optimal vector for transgene transduction is unknown, which is a consideration for both sensitivity to age-related changes and immunogenicity[16]. AAV has been the most common vector in OA gene therapy due to its low immunogenicity, ability to transduce quiescent cells such as chondrocytes, small capsid size, and non-integrating episomal expression[8,18] (Figure 1C). However, the limitation of AAV is the small packaging capacity (≤4.5 kb) (Figure 1B).

As a multifactorial disorder, targeting a single pathway in OA may either not achieve the desired effect or, with gene therapy specifically[19], the desired effect over the desired period (e.g., months/years). Further, constitutive promoters in gene therapy may not be ideal in a condition, where physiologic levels are important for reestablishing homeostasis. Constitutive promoters drive gene expression continuously, which may induce unwanted long-term effects due to the lack of regulation, adaptivity to homeostatic conditions, and toxicity. For inducible promoters, there is the question of drug-drug interactions (DDI), which may cause interference, especially if the mechanism of action is anti-inflammatory, as the promoter would likely be attuned to the level of inflammation.

Currently, one of the proposed benefits of gene therapy for OA is local delivery via an intra-articular injection[7,12,18]. However, the systemic inflammatory environment in metabolic OA[20] may overwhelm the local knee environment, which is an important consideration when nearly 60% of OA may be metabolic in nature (e.g., metabolic syndrome)[20,21]. While this may only apply to gene therapies targeting an anti-inflammatory effect, we would note that this is most of the pipeline in development.

The value proposition for gene therapy is centered on extended duration of activity—a single injection

providing months or years of benefit. However, outside the 2-year data for PCRX-201/FX-201 presented at the American College of Rheumatology (ACR) meeting (November 2024), there is limited published information regarding follow-up studies on this gene therapy pipeline for OA. From a safety and efficacy perspective, additional observational studies and regulatory scrutiny is necessary.

Critical challenges

One of the major challenges in current OA gene therapy pipelines is demonstrating safety and efficacy across an epidemiologically relevant and clinically representative age spectrum for a sufficient observation period acceptable for the regulators. This information is crucial for drawing conclusions regarding efficacy prior to approval and underscores the major clinical and regulatory challenges.

Beyond these considerations, operational challenges may arise from access, distribution, and injection confirmation. Although OA gene therapies are not anticipated to be priced as high as gene therapies for rare and orphan diseases, there is a relatively low-price ceiling created by knee arthroplasty (TKA) for patients, who are surgically eligible and age-appropriate. For younger patients (<55 years), there may be greater price flexibility driven by the overall safety and efficacy profile with a focus on the durability of the therapeutic effect. Payors are likely to be sensitive to responses in a representative OA patient population. They may restrict access above a certain age, and in North America, this is likely to be around 55 years of age. For example, the safety and efficacy of meniscal implants (e.g., 55 years) and Matrix-induced Autologous Chondrocyte Implantation (MACI) (e.g., 65 years) have not been effectively demonstrated in patients 55 and 65 years of age or older, respectively; and thereby, are not covered by payors.

Distribution and storage are important logistical considerations that are rarely discussed in scientific communications. Gene therapies are commonly stored and distributed at −80°C. While this level of cold chain logistics expanded significantly during the COVID pandemic due to similar requirements for the associated vaccines, the cold chain did not reach the offices of physicians. For gene therapy to expand beyond hospital centers, either "last mile" logistics or improved stability (e.g., 2°C to 8°C for days and weeks) needs to be established. The research community needs to consider the use of cryopreservation chemicals and stabilizers. Chemical agents for extending the shelf-life of vaccines and gene therapies may include cryoprotectants such as glycerol, dimethyl sulfoxide (DMSO), trehalose, and sucrose. Cryoprotectant agents collectively protect viral vectors during freezing and thawing by preventing the formation of ice crystals that can damage their structure. However, thus far no studies have used or tested them for this purpose in OA gene therapy pipelines. In addition, there is potential for using surfactants, chelating agents and antioxidants such as sorbitol and mannitol for extending the shelf and transport life of gene therapies. Although some of these agents have been included in intra-articular hyaluronic acid (HA) injections a number of important regulatory hurdles and challenges still remain. Pricing expectations for OA gene therapy appear to be within the range of HA to TKA. If gene therapy costs land in the mid-to-high end of the range, payors may require confirmation of injection within the intra-articular space. This is because an estimated 15% to 20% of knee injections, guided by anatomical landmarks or ultrasound imaging, are outside the capsule[22].

To address these challenges, gene therapy is well-positioned to achieve disease modification status and qualify as a disease-modifying OA drug (DMOAD). However, the bar to achieve this may be high with statistically significant and clinically relevant improvements expected for pain, function, and anatomy, as measured radiographically, and a delay in surgical eligibility and procedure. Challenges in manufacturing arise from production pricing and difficulties in production. For application, issues include transducing capabilities, immunogenicity, and preexisting NAbs.

Conclusions

In the future, refining vector systems to enhance potency, reduce immunogenicity, and control transgene expression will be essential. Engineering viral capsids to evade the immune system and optimizing the design of the vector cassette are promising approaches[23]. Furthermore, many naturally occurring viruses remain underexplored as potential tools for gene delivery. Potential vectors for future investigation include baculovirus, lentivirus, and hybrid vectors combining features of AAV and adenovirus. While AAVs remain the primary focus, HCAd vectors are also under consideration due to their enhanced transgene capacity and lower immunogenicity. We need to develop simple, safe, and effective non-viral gene delivery systems with prolonged transgene expression under physiologically inducible promoters. Combination therapies involving gene therapeutics and non-viral therapies are another

potential strategy. Stratification is also extremely important in this context, and exploratory research is underway to stratify heterogeneous OA populations based on molecular endotypes[24] and imaging[25]. This will help to identify subgroups that could be responders or non-responders to specific gene therapies. Identification, validation, and qualification of combinations of biomarkers improvement will also be a consideration. Validating biomarkers involves multi-stage clinical testing, standardization of assays, and integration into patient stratification protocols.

Outlook

The integration of genomics, transcriptomics, and proteomics has already begun to reshape our understanding of OA heterogeneity and presents a foundation for precision medicine strategies. Considering the complex interplay between genetic, inflammatory, metabolic, and biomechanical factors underpinning OA pathogenesis, gene therapies employing AAV-mediated delivery of therapeutic transgenes, particularly IL-1Ra, are demonstrating significant potential. Gene therapy can target key inflammatory and catabolic mediators to preserve cartilage integrity and reduce intra-articular inflammation. Advancements in vector design can potentially mitigate immune responses, enhancing transgene efficacy and duration of action. Collectively, these innovations offer a paradigm shift from symptomatic pharmacological management to genuine disease modification in OA. Future research should integrate insights from omics studies, especially single-cell and spatial transcriptomics and proteomics of the synovium with advanced gene delivery platforms to refine personalized therapies that address the heterogeneity of OA pathophysiology. As our understanding of joint biology evolves, translating these findings into clinical practice will significantly improve outcomes for millions affected by this debilitating disease.

Note

https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products.

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Disclosure statement

Karman Ng and Ron Ellis were formerly employees of Pacira Biosciences. Jean-Yves Reginster is President of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and Co-Founder and Board member of the International Osteoporosis Foundation (IOF). Christopher H. Evans is co-founder of the gene therapy company Genascence.

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