Gene Therapy in Osteoarthritis: *a Scoping Review*

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PURPOSE. **Osteoarthritis (OA)** is the most common degenerative joint disease, affecting **500 million people worldwide**. It is characterized by a progressive loss of cartilage associated with synovitis and subchondral bone remodeling. Despite the high prevalence of OA, there is to date no treatment to cure or delay the progression of OA. Recent advances have, however, been made in the development of a range of biological drugs that position gene therapy as a promising option to overcome the limitations of traditional therapeutics in OA. ***The objective of this paper was to provide a scoping review of the preclinical and clinical studies reporting the effect of gene therapies for OA.***

METHODS. This review followed the **JBI methodology** for scoping reviews and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses for Scoping Reviews (**PRISMA-ScR**) checklist. All research studies that explore *in vitro*, *in vivo*, or *ex vivo* gene therapies that follow a viral or non-viral gene therapy approach were considered. Only studies published in English were included in this review. There were no limitations to their date of publication, country of origin, or setting. Relevant publications were searched in **Medline ALL** (Ovid), **Embase** (Elsevier), and **Scopus** (Elsevier) in January 2022. Study selection and data charting were performed by two independent reviewers. The data-charting form included the following items: author and year of publication, aims and objectives, country of the study, participants, the context of the study, disease models, delivery methods targets, and effects. Key data extracted from the selected articles included any information relevant to the search questions. Data were analyzed and summarized quantitatively through numerical counts as well as descriptively. Data were presented graphically or in tabular form.

RESULTS

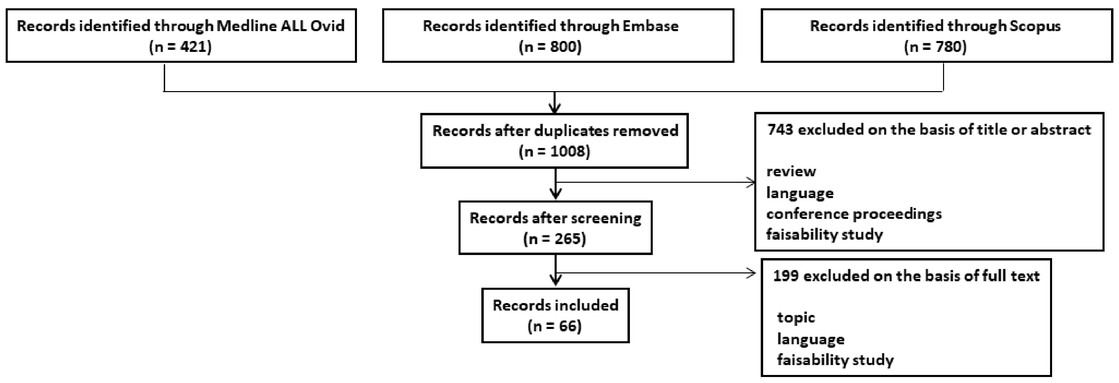

Figure 1
PRISMA flowchart outlining the study selection procedure: An initial search identified **2,001** studies, **1,008** of which remained after the removal of duplicates. All but **265** of these studies were excluded at the stage of abstract review. Furthermore, **199** additional studies were excluded after reviewing the full manuscript due to the topic, language, or study concept. Overall, **66** studies responded to the inclusion criteria and constituted the study data.

Author and year	NCT number	Study Design	Delivery Methods	Targets
Ha C-W et al. 2012	NCT02341391	Clinical Phase I, single center, open-label, dose-escalation	TissueGeneC	TGFβ1
Cherian JJ et al. 2015	NCT01221441	Clinical phase II: multi-center, double-blinded, placebo-controlled, randomized	Retrovirally transduced allogenic human chondrocytes (TissueGene-C)	TGFβ1
Ha C-W et al. 2015	NCT02341378	Clinical phase IIa, multicenter, single -blind	GEC-TGF-β1 (TissueGeneC)	TGFβ1
Kim M-K et al. 2018	NCT02072070	Clinical Phase III, multicenter, double-blind	TissueGeneC	TGFβ1
NA	NCT03282149 NCT03477487 NCT03769662	Clinical phase I	hIL-10var pDNA (XT-150)	IL-10
NA	NCT04124042	Clinical phase II: multi-center, double-blinded, placebo-controlled, randomized	hIL-10var pDNA (XT-150)	IL-10
Sellon S et al. 2022	NCT02790723	Clinical Phase I, single center, open-label, dose-escalation	Sc-rAAV2.5IL-1Ra	IL-1Ra
Kelley S et al. 2021	NCT04119687	Clinical Phase I, single center, open-label, dose-escalation	HDAd-IL-1Ra (FX201)	IL-1Ra

Table 1
Clinical trials on gene therapy in OA.

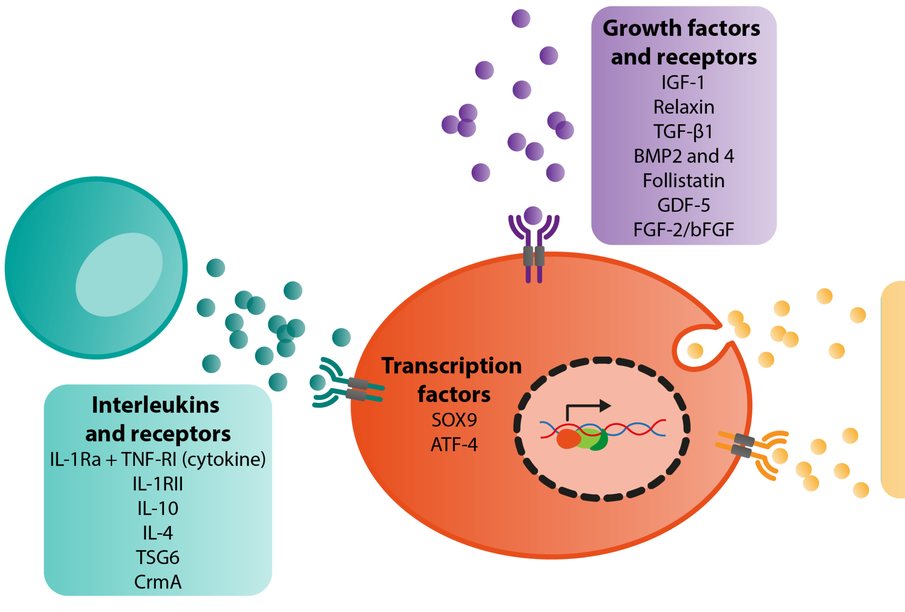

Figure 2
Summary of evidence: We found a total of **24** different targets for gene therapy in the context of OA. These included studies examining **interleukins** (IL-1Ra alone or in combination with another target, IL-1RII, IL-10, IL-4, TSG6, CrmA), **growth factors**, **and receptors** (IGF-1, relaxin, TGF-β1, BMP2 and 4, follistatin, GDF-5, FGF2/bFGF), **transcription factors** (SOX9 alone or in combination with another target, and ATF-4) and **other key targets** such as PRG4 (alone or in combination with another target), LOXL2, GlcAT-1, GGCX, kallistatin, RHEB and HSP70.

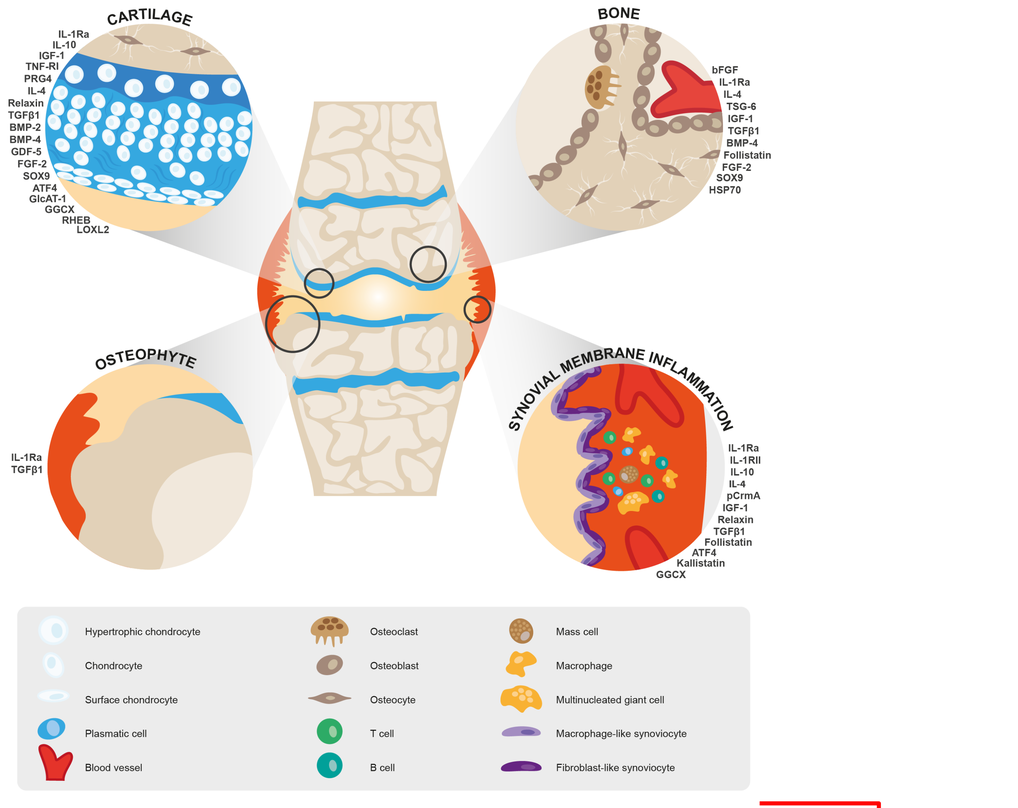

Figure 3
Schematic representation of targets identified for gene therapy of OA and their therapeutic potential.

CONCLUSIONS. **In the last decade, research in the field of gene therapy has been in full expansion, as evidenced by an increasing number of scientific articles on the subject. In the absence of any disease modifying OA drug, gene therapy is a highly promising treatment for OA, even though it still is in its early stages and further development is required to bring more targets to the clinical stage.**