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Review Article

MODERN CELLULAR THERAPIES IN ORTHOPEDICS

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ABSTRACT

Cellular therapies, so-called *"living drugs"*, are reshaping the landscape of clinical and experimental medicine and are increasingly recognized as a new class of pharmaceutics. They provide unprecedented opportunities for treatment of a range of diseases, including orthopedic disorders, which represent a significant burden in global health. Traditional treatments in orthopedics often address symptoms rather than restore damaged tissues or target malignancies. Initially, cellular therapies, particularly those involving stem and progenitor cells, have emerged as a promising frontier in regenerative orthopedics. Additionally, genetically engineered immune cell therapies, such as chimeric antigen receptor (CAR)-T/NK cells, have been proposed for applications in onco-orthopedics, offering targeted approaches to bone and soft tissue sarcomas, but also, in parallel to CAR-bearing regulatory T cells, in a range of autoimmune diseases. This review provides an overview of current cellular therapies, either in clinical use or under investigation in orthopedics, with a focus on platelet-rich plasma- or chondrocyte-based approaches, mesenchymal stromal cells (MSC), induced pluripotent stem cells (iPSC), and potential applications of CAR-based immune cell therapies. Their biological basis, mechanisms of action, preclinical evidence, clinical applications, challenges, and future directions are discussed.

KEYWORDS: Orthopedics, Cellular Therapies, Regenerative Medicine, Chimeric Antigen Receptors

1. Introduction

Cellular therapies, unlike conventional small molecules or biologics, harness the intrinsic regenerative, modulatory, or cytotoxic capacities of living cells to achieve therapeutic effects that cannot be replicated by the inert compounds. As such, cellular therapies redefine the concept of a "drug," positioning cells themselves as both the therapeutic agent and the means of inducing the biological restoration [1]. Indeed, this 'living-drug' model is revolutionizing pharmaceutical sciences, challenging regulatory frameworks, manufacturing practices, and clinical paradigms, while simultaneously offering unprecedented opportunities for personalized and durable treatments in numerous medical areas, including orthopedics. From platelets releasing growth factors that stimulate tissue healing and chondrocytes restoring articular cartilage, through mesenchymal stromal cells driving tissue repair, to genetically immune cells targeting otherwise intractable malignancies or autoreactive cells causing autoimmune disorders, orthopedic cellular therapies embody a paradigm shift toward personalized, dynamic, and adaptive interventions.

Musculoskeletal disorders and injuries represent one of the most prevalent causes of disability worldwide [2]. With an aging world population, increasing life expectancy, and rising incidence of degenerative osteoarthritis or autoimmune diseases, such as rheumatoid arthritis, grows the demand for effective and durable treatments in orthopedics [3]. Traditional therapies, ranging from pharmacological interventions to surgical procedures, often fail to restore the full structural and functional integrity of musculoskeletal tissues. For example, joint replacement surgeries, though highly successful in restoring mobility, do not fully replicate the complex biomechanical features of the native joints and carry risks of revision surgery over time. Similarly, fracture repair, tendon reconstruction, and cartilage repair often encounter complications such as incomplete healing, scar formation, or loss of tissue function.

In recent decades, advances in regenerative medicine, cell biology, and genetic engineering have opened new

opportunities for addressing these unmet clinical needs in three prevalent areas in orthopedics (see Figure 1): tissue regeneration, combating cancer growth, and alleviating inflammation [4-6].

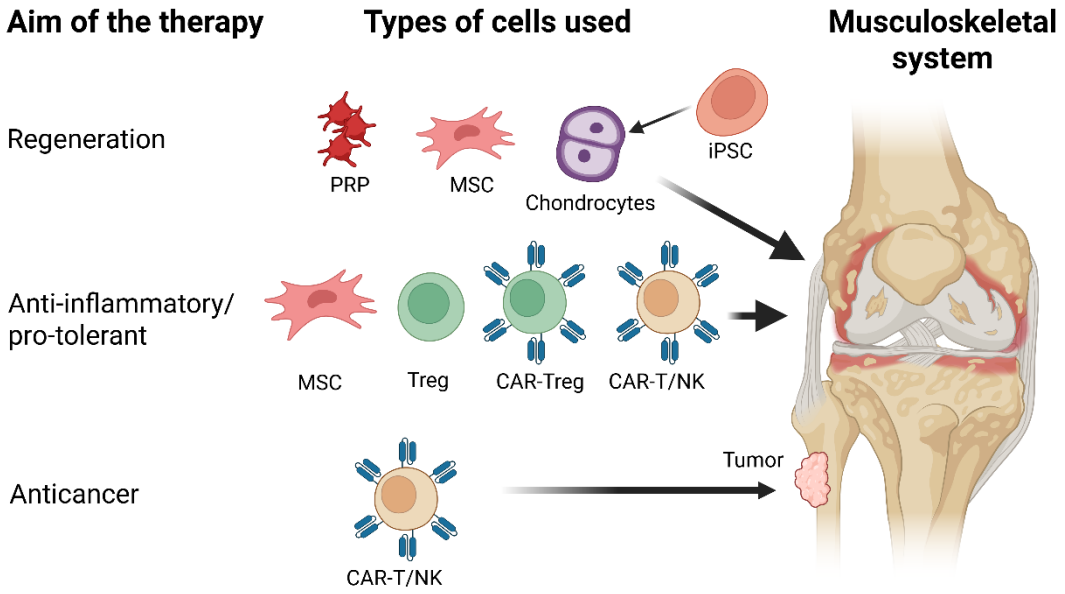

Figure 1. Examples of cell therapies in orthopedics (see text for details). Abbreviations: CAR-T/NK – chimeric antigen receptor-bearing T/NK cells, CAR-Treg – chimeric antigen receptor-bearing regulatory T cells, iPSC – induced pluripotent stem cells, MSC – mesenchymal stromal cells, PRP – platelet-rich plasma, Treg – regulatory T cells. (Created in BioRender. Zagozdzon, R. (2025) https://BioRender.com/sczdc7u)

Out of these, therapies that use living cells to regenerate or replace damaged tissues have emerged as one of the most promising approaches in orthopedic medicine [7, 8]. These therapies aim not only to alleviate symptoms but also to restore structural and functional integrity through biological repair [4]. The concept builds upon the regenerative capacity of certain cell types, such as progenitor cells or differentiated cells expanded in vitro, which can both directly replace damaged elements and modulate the local environment to stimulate endogenous healing via paracrine and immunomodulatory mechanisms [7, 9]. Established or experimental regenerative cellular therapies in orthopedics include autologous platelet-rich plasma (PRP) or chondrocyte implantation, mesenchymal stromal cell (MSC) therapy, and, potentially, induced pluripotent stem cell (iPSC)-derived strategies. Conversely, targeted immune cells, such as CAR-T cells, can potentially eliminate cancer cells or suppress the autoimmune cells that are mediating the damage to the musculoskeletal system.

This review provides an overview of modern cellular therapies in orthopedics. Emphasis is given to the biological mechanisms of action, preclinical models, clinical applications, challenges, and emerging future directions.

2. Cell-based regenerative approaches in orthopedics

Modern cellular therapies in orthopedics encompass a wide spectrum of approaches that utilize living cells to repair or regenerate musculoskeletal tissues. As mentioned above, the principal categories PRP, chondrocyte-based therapies, MSC, and, recently, a proposition to utilize iPSC. These cell types have been selected due to their biological relevance, ability to differentiate into key tissue lineages, and potential for immunomodulatory or trophic effects. Unlike acellular or molecular-based strategies, cellular therapies aim to introduce a biologically active component capable of responding to the microenvironment and dynamically contributing to healing. Below, the most relevant cellular regenerative approaches are described.

2.1. Platelet-rich plasma

PRP therapy, first introduced in the late 1980s for maxillofacial and dental surgery applications, has since gained significant attention in orthopedic medicine for its potential to enhance tissue healing and regeneration [10]. PRP is an autologous blood product obtained by centrifugation, which concentrates platelets and their associated growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and others [10]. These bioactive molecules play key roles in modulating inflammation, cell proliferation, angiogenesis, and extracellular matrix remodeling, and can also provide the pain relief. Since its adoption in orthopedics in the early 2000s, PRP therapy has been widely investigated for the treatment of tendinopathies, ligament injuries, muscle tears, osteoarthritis, and bone defects. However, despite encouraging preclinical results and widespread clinical use, the efficacy of PRP remains controversial due to variations in preparation protocols, platelet concentrations, and injection regimens. Therefore, proper standardization and well-controlled clinical trials are necessary to precisely define the therapeutic potential of PRP [11].

Indeed, criticism towards PRP application in orthopedics often centers on its high variability and lack of standardization, which makes it difficult to compare results across studies or predict clinical outcomes. Key

methodological challenges include inconsistent preparation methods, including differences in platelet concentration, leukocyte content, activation protocols, and centrifugation systems, which produce biologically distinct products all labeled as "PRP." Additionally, many trials suffer from heterogeneous patient populations, inadequate controls, and inconsistent dosing schedules, limiting the strength of evidence. The placebo effect is also difficult to rule out because PRP injections are procedural and invasive. Finally, the mechanisms of action remain insufficiently defined, making it challenging to tailor PRP formulations to specific orthopedic conditions or identify which patient subgroups are most likely to benefit.

2.2. Chondrocyte-based therapies

Chondrocyte-based therapies represent one of the earliest forms of cell therapy in orthopedics to reach clinical practice [12]. Autologous chondrocyte implantation (ACI) involves harvesting healthy chondrocytes from a non-weight-bearing region of the joint, expanding them in vitro, and implanting them into a region of cartilage defect. This approach was first introduced in 1994 by Brittberg et al. for the repair of focal articular cartilage defects in the knee [13]. The goal of ACI is to restore hyaline-like cartilage and improve joint function, thereby delaying or preventing the progression to osteoarthritis. Over time, this procedure has evolved through several generations, including matrix-assisted chondrocyte implantation (MACI), where cells are seeded onto a biomaterial scaffold for improved handling and integration [14]. Also three-dimensional culture systems and/or allogeneic cell sources could be utilized.

The rationale for ACI is to provide a population of cells capable of producing cartilage-specific extracellular matrix, thereby filling defects with hyaline-like cartilage rather than fibrocartilage typically seen after microfracture procedures. Clinical outcomes of ACI and MACI have been generally positive, with many patients reporting durable improvements in pain and function over long-term follow-up [15, 16]. Nevertheless, limitations include the dedifferentiation of chondrocytes during in vitro expansion, leading to loss of chondrogenic phenotype, and difficulty in achieving seamless integration with host cartilage. Furthermore, the requirement for a two-step procedure (harvesting and implantation) adds complexity and patient burden.

Recent innovations in chondrocyte-based therapies include co-culture with MSC to improve matrix formation and reduce hypertrophy, and the development of 3D co-culture/aggregation systems that enhance functional cartilage properties and extracellular-vesicle (EV) yield. Co-culture and structured 3D co-culture approaches have been shown to enhance chondrogenesis, suppress hypertrophic differentiation, and improve the quality of engineered cartilage compared with monocultures [17-20]. The use of juvenile allogeneic chondrocytes has also been proposed and explored because juvenile cells display superior proliferative and matrix-producing capacity and may be used as off-the-shelf allogeneic products with limited immunogenicity in preclinical and early clinical work [21]. Research continues to optimize expansion and redifferentiation protocols to maintain or restore the chondrogenic phenotype, including growth-factor priming, altered expansion conditions, and transition to 3D culture systems, in order to limit dedifferentiation and enhance matrix production on implantation [22-24].

Despite promising long-term outcomes for selected patients treated with ACI/MACI in multiple series, persistent challenges include donor-site morbidity after autologous harvest, chondrocyte dedifferentiation during 2D expansion, high procedural and manufacturing costs, and substantial variability in clinical success across studies and products [22, 25, 26]. In more detail, the main criticism of isolated chondrocyte–based therapies in orthopedics, including autologous chondrocyte implantation and its variants, often focuses on their inconsistent clinical outcomes, particularly when treating larger or more complex cartilage defects. Methodologically, these approaches face challenges such as variability in chondrocyte quality after in-vitro expansion, where cells can dedifferentiate and lose their native cartilage-producing phenotype. Surgical technique introduces further variability, as outcomes depend on defect preparation, graft containment, and postoperative loading protocols. Many studies also lack long-term, standardized comparisons with simpler or less costly alternatives such as microfracture or MSC-based therapies, making it difficult to define clear indications. Additionally, the need for a two-stage surgical procedure increases patient burden and introduces selection bias in clinical studies. Together, these issues create uncertainty regarding reproducibility, cost-effectiveness, and optimal patient selection for isolated chondrocyte therapies.

2.3. Mesenchymal stromal cells

Mesenchymal stromal cells (previously referred to as 'mesenchymal stem cells') are among the most extensively studied and widely applied cell types in orthopedic regenerative medicine [27]. Originally isolated from bone marrow, MSC are multipotent progenitors capable of differentiating into osteoblasts, chondrocytes, and adipocytes. Over time, MSC have also been identified in numerous other tissues including adipose tissue, synovium, periosteum, and perinatal tissues such as umbilical cord or placenta. Their abundance, ease of isolation, and immunomodulatory properties make them attractive for clinical application.

The source of MSC harvest is of importance [28]. Bone marrow-derived MSC (BM-MSC) are considered the gold standard but have limitations including invasive harvesting procedures, declining yields with donor age, and donor-to-donor variability. Adipose-derived MSC (AD-MSC) have emerged as a more accessible alternative, with higher yields from minimally invasive liposuction procedures [29]. Synovium-derived MSC demonstrate particularly strong chondrogenic potential, making them attractive for cartilage repair [30]. Perinatal MSC, while allogeneic, exhibit enhanced proliferative capacity and reduced immunogenicity, potentially making them suitable for off-the-shelf products [31].

In orthopedic context, MSC exert their effects through several mechanisms [32]. First, they can directly differentiate into musculoskeletal lineages, thereby contributing to new tissue formation. For example, MSC implanted into osteochondral defects in animal models can form cartilage-like or bone-like structures. Second, and perhaps more importantly, MSC exert potent paracrine effects. They secrete a wide array of cytokines, growth factors, and extracellular vesicles that modulate the local

inflammatory response, recruit endogenous progenitor cells, and stimulate angiogenesis. This ability to orchestrate a pro-regenerative microenvironment has been increasingly recognized as central to their therapeutic action [33].

Preclinical research has been central to demonstrating the feasibility and mechanisms of MSC-based therapies in orthopedics. Animal models including rodents, rabbits, sheep, and pigs have been used extensively to study cartilage, bone, tendon, and ligament regeneration [34-36]. In cartilage repair models, MSC delivered into osteochondral defects frequently generate cartilage-like tissue, improve histological scores, and restore biomechanical properties. Importantly, MSC often improve the quality of repair through paracrine effects, even when their direct engraftment into new tissue is limited [37]. In bone healing, MSC have been shown to accelerate fracture repair, enhance callus formation, and improve mechanical strength [38]. They have been tested in non-union and large bone defect models, often in combination with scaffolds [22]. For tendon and ligament injuries, MSC delivered locally can improve tendon histology, reduce adhesions, and increase biomechanical strength [39]. Early studies suggested that MSC modulate inflammation and fibrosis while supporting regeneration of tendon fibers. These preclinical studies have been a stimulus for translation of MSC-based therapies into clinical medicine in orthopedics [34].

Despite their promise, challenges remain in standardizing MSC products in clinical medicine. Variability in cell isolation, expansion conditions, and donor characteristics can result in heterogeneous cell populations with inconsistent therapeutic effects. Regulatory definitions also differ internationally, creating obstacles for global translation [40, 41].

2.4. Induced pluripotent stem cells

Induced pluripotent stem cells, created by reprogramming adult somatic cells into a pluripotent state, are expected to provide a transformative advance in regenerative medicine [42]. Functionally similar to embryonic stem cells, iPSC can give rise to virtually any cell type, including chondrocytes, osteoblasts, and other musculoskeletal cells relevant to orthopedics [43]. Their use bypasses ethical concerns associated with embryonic stem cells and enables patient-specific, autologous therapies [43].

In orthopedics, iPSC hold promise for generating unlimited numbers of chondrocytes for cartilage repair, osteoblasts for bone regeneration, and potentially complex tissue constructs [44]. Preclinical studies have shown that iPSC-derived chondrocytes can integrate into cartilage defects and produce hyaline-like matrix [45]. Similarly, iPSC-derived osteoblasts and osteogenic progenitors have demonstrated bone-forming capacity in animal models of bone defects and fractures [46].

However, translation of iPSC into clinical therapies remains in its early stages. Major concerns include the risk of tumorigenicity due to residual undifferentiated cells, genetic and epigenetic instability during reprogramming, and the need for robust differentiation protocols that ensure phenotypic fidelity and safety. Additionally, the concern is the use of integrating reprogramming vectors, which can leave behind insertional mutations that predispose cells to malignant transformation; this has driven a shift toward non-integrating methods such as episomal plasmids, Sendai virus, mRNA, or recombinant proteins. Even with safer vectors, iPSC may retain residual epigenetic memory from their somatic cell of origin, influencing differentiation trajectories and potentially leading to heterogeneous or incompletely differentiated cell populations. Any contamination with undifferentiated cells introduces the possibility of teratoma formation, underscoring the importance of rigorous purification, differentiation fidelity, and release criteria. Regulators treat iPSC-derived products as high-risk advanced therapy medicinal products (ATMP), requiring extensive genomic stability testing, lineage-specific potency assays, tumorigenicity studies, long-term follow-up plans, and stringent GMP controls over reprogramming and differentiation processes. Therefore, manufacturing iPSC-derived products remains technically complex and costly.

Despite these challenges, the potential of iPSC to provide personalized, renewable sources of therapeutic cells continues to drive significant research investment and innovation [47].

2.5. Clinical applications of regenerative cellular therapies in orthopedics

Some of the cellular therapies have now entered clinical practice in selected orthopedic indications, while many more are in ongoing clinical trials.

PRP has become one of the most commonly used biologic therapies in orthopedic practice, applied in a wide range of degenerative and traumatic musculoskeletal conditions [40, 48]. In knee osteoarthritis, intra-articular PRP injections have been shown to improve pain and joint function compared with hyaluronic acid or placebo in several randomized clinical trials, although results remain heterogeneous due to differences in PRP preparation and patient selection [49, 50]. PRP is also used in tendinopathies such as chronic lateral epicondylitis and patellar tendinopathy, where local injections can promote healing by delivering concentrated growth factors that enhance collagen synthesis and reduce inflammation [51]. Additionally, in rotator cuff repair and anterior cruciate ligament (ACL) reconstruction, PRP has been explored as an adjunct to surgical procedures, with some studies reporting accelerated recovery and improved structural integration, though meta-analyses indicate inconsistent long-term benefits [52].

For cartilage repair, ACI and its evolution into MACI represent established procedures with decades of clinical use [12]. Numerous studies report significant improvements in pain and function, particularly in younger patients with focal cartilage defects. Long-term follow-up indicates durability of results, though not all patients achieve optimal outcomes. Chondrocyte-based approaches for intervertebral disc regeneration are being explored, with preliminary studies suggesting symptomatic improvement in discogenic back pain.

MSC-based therapies have been extensively studied in osteoarthritis [53]. Intra-articular injections of autologous or allogeneic MSC have demonstrated improvements in pain and function, often accompanied by MRI evidence of cartilage preservation or partial regeneration. Trials using

bone marrow, adipose, or umbilical cord MSC suggest safety and efficacy, though results remain heterogeneous due to differences in cell preparation and delivery methods. In bone healing, MSC have been applied in cases of delayed union or nonunion, with several reports of enhanced healing and reduced need for secondary surgeries. MSC combined with scaffolds or grafts have also been tested for large bone defects, showing promising results. For tendons and ligaments, clinical trials remain limited. However, small studies report improved healing in rotator cuff repairs and anterior cruciate ligament (ACL) reconstruction when MSC are added to conventional surgery.

Overall, clinical evidence supports the safety of regenerative cellular therapies in orthopedics, though efficacy varies, and further large-scale randomized controlled trials are warranted.

2.6. Other challenges and risks of regenerative approaches

Despite the substantial promise of regenerative cellular therapies, significant challenges remain in their widespread adoption and clinical standardization.

One of the foremost issues is variability. MSC, for example, are heterogeneous populations whose properties vary depending on source tissue, donor age, isolation method, and culture conditions. This variability complicates standardization, regulatory approval, and reproducibility of results.

Safety concerns are also of importance. For MSC, risks include unwanted differentiation, ectopic tissue formation, and immunogenic reactions, particularly with allogeneic products. For iPSC, the risk of tumorigenicity remains a critical barrier, necessitating stringent purification and validation of differentiated cell populations.

Manufacturing challenges include the need for Good Manufacturing Practice (GMP)-compliant facilities, quality control assays, and scalable production methods. Costs associated with these requirements can pose a substantial limiting factor.

Also, regulatory frameworks for cellular therapies are evolving but remain inconsistent across jurisdictions, creating barriers to clinical translation [54]. Finally, long-term durability of benefits has not yet been conclusively demonstrated for many indications, underscoring the need for extended follow-up in clinical studies.

3. Engineered immune cell-based therapies

In addition to regenerative approaches, modern cellular therapies in orthopedics are beginning to explore the potential of genetically engineered immune cell therapies for musculoskeletal illnesses, primarily malignancies, but also autoimmune diseases [55].

Indeed, engineered immune cell-based approaches bring a profound conceptual change in cellular therapies with potential application in orthopedics. The regenerative cell-based therapies used in orthopedics primarily aim to support tissue repair and regeneration by enhancing the local healing environment, supplying progenitor cells, or restoring native cell populations within cartilage, tendon, or bone. These approaches rely on endogenous biological processes like extracellular matrix production, modulation of inflammation, or differentiation into musculoskeletal cell types. In contrast, engineered immune-cell therapies such as CAR-T and CAR-Treg represent active, highly targeted immunomodulatory interventions designed to recognize specific antigens and exert controlled immune responses. In orthopedics, CAR-T technologies would function less as regenerative tools and more as precision immune modulators, for example, eliminating pathogenic inflammatory cell subsets (CAR-T) or enforcing tolerance and reducing destructive inflammation (CAR-Treg). Thus, while traditional orthopedic cellular therapies focus on repairing or replacing damaged tissue, CAR-based approaches focus on reprogramming immune function, offering mechanistic precision but not direct regenerative capacity.

Additionally, manufacturing for orthopedic regenerative therapies such as PRP, chondrocytes, or MSC, typically focuses on cell isolation, expansion, and preparation with relatively straightforward processing steps, often autologous, minimally manipulated, and compliant with point-of-care or GMP culture workflows. These products generally involve short production timelines, limited genetic alteration, and standardized expansion protocols focused on preserving cell phenotype and viability. Conversely, CAR-T and CAR-Treg manufacturing is far more complex, customized, and genetically intensive. It requires isolation of specific immune cell subsets, viral or nonviral gene engineering to introduce chimeric antigen receptors, clonal selection, controlled activation, multi-stage expansion, extensive safety testing, and cryopreservation, often tailored to each patient. The result is a customized, multi-week bioprocess with robust regulatory scrutiny due to genetic modification and potent immune activity. Thus, while orthopedic cell-based products follow a regenerative biomanufacturing model, CAR-engineered therapies operate under a precision gene-engineering paradigm with markedly greater complexity, cost, and risk management requirements.

However, the potential benefits justify the attempts for utilizing CAR-T or CAR-Treg therapies in clinical medicine, including orthopedic disorders.

3.1. Potential of CAR-based therapies in onco-orthopedics

For oncological indications, primary bone tumors, such as osteosarcoma, Ewing sarcoma, and chondrosarcoma, as well as metastatic lesions in bone, remain difficult to treat with conventional surgery, chemotherapy, and radiotherapy alone. New approaches are urgently needed [56, 57]. Among these, the experimental use of chimeric antigen receptor (CAR)-engineered T cells (CAR-T) and natural killer cells (CAR-NK) in orthopedic disorders is nascent but conceptually transformative [58, 59].

CAR-T cell therapy was first developed in the late 1990s and achieved clinical success in onco-hematology during the 2010s, paving the way for its exploration in non-oncologic diseases [60]. The biological foundation of this approach lies in the genetic modification of immune effector cells to express modular synthetic receptors that recognize specific target antigens in an antibody-like manner, and then transduce intracellular activation and co-stimulation signals. Altogether, this design enables precise and MHC-independent cytotoxic responses of CAR-bearing cells, most commonly T lymphocytes [61]. Indeed, CAR-T cells are typically autologous T lymphocytes genetically modified to express CARs that recognize tumor-associated antigens. In onco-orthopedics, candidate targets include

HER2, GD2, B7-H3, and other sarcoma-associated surface proteins [56, 62].

Preclinical models have demonstrated that CAR-T cells can infiltrate tumor tissue, mediate cytotoxicity, and reduce tumor burden [58]. However, challenges such as the immunosuppressive tumor microenvironment, heterogeneous antigen expression, and risk of on-target/off-tumor toxicity remain significant hurdles [57].

CAR-NK cells, in turn, represent an alternative approach with several potential advantages [63, 64], including reduced risk of graft-versus-host disease, shorter persistence that may improve safety, and innate tumor-recognition properties [65]. Early studies have suggested feasibility of CAR-NK approaches against sarcoma-associated antigens, though clinical data remain sparse [66].

The integration of CAR-T and CAR-NK cell therapies into onco-orthopedics represents a new frontier where regenerative and anti-tumor strategies may converge. For example, CAR-based therapies could be combined with regenerative cell therapies to both eradicate tumor tissue and subsequently restore structural integrity following tumor resection [56]. Although still at an early stage, this area highlights the expanding scope of cellular therapies in orthopedics beyond regeneration alone [40].

3.2. Potential treatment of orthopedic autoimmune diseases with CAR-bearing immune effector cells

Following the observation of 'immunological reset' after bystander elimination of non-malignant CD19-positive cells in onco-hematology, there is emerging early-stage evidence that CAR-T (and related) cell therapies can be of value for treatment systemic autoimmune/rheumatic disorders [67], which then may in future extend into musculoskeletal/orthopedic applications. Up to date, a systematic review found that about 80+ patients with various refractory autoimmune diseases (including some cases of rheumatoid arthritis, RA) received CD19- or CD19/BCMA-targeted "off-label" CAR-T treatments. In consequence, clinical trial registrations (e.g., NCT05869955, NCT05859997) show CAR-T therapy being explored in conditions such as systemic lupus erythematosus (SLE) [68], systemic sclerosis [69] and inflammatory myopathies [70]. There is a hope, that these results will translate into new treatments of orthopedic autoimmune disorders (e.g., joint-specific RA, enthesitis, or cartilage destruction) [71].

It must be noted, however, that the use of CAR-T cells in non-oncological orthopedics is still highly experimental . In addition to elimination of the autoreactive immune cells, proposed applications focus on targeting pathogenic inflammatory cells involved in chronic joint degeneration, such as synovial fibroblasts or macrophage subsets, in conditions like osteoarthritis or rheumatoid arthritis. Preclinical work suggests that CAR-T cells engineered against specific fibroblast surface markers could reduce destructive inflammation and limit tissue catabolism, offering a mechanism distinct from systemic immunosuppressants. While promising in concept, these strategies remain in early research stages, requiring extensive safety validation given the potency and persistence of CAR-engineered immune cells.

3.3. Potential of using Treg-based approaches in orthopedics

Regulatory T cells (Treg) are in our organism the mainstay of self-antigen-specific autotolerance [72, 73], which has been highlighted by the 2025 Nobel Prize in Physiology or Medicine. In consequence, Tregs hold significant potential in the treatment of autoimmune orthopedic diseases due to their ability to suppress aberrant immune responses and restore self-tolerance [74]. By modulating inflammatory pathways and inhibiting the activity of autoreactive T and B cells, Tregs can reduce synovial inflammation, prevent cartilage and bone destruction, and promote tissue repair [75]. Preclinical studies in models of rheumatoid arthritis and osteoarthritis have demonstrated that adoptive transfer or in situ expansion of Tregs can alleviate joint inflammation and preserve structural integrity [76]. This effect can be further potentiated by an introduction of CAR into Treg (CAR-Treg cells) [77].

Indeed, the experimental use of chimeric antigen receptor regulatory T cells (CAR-Tregs) in autoimmune orthopedic disorders represents a novel immunotherapeutic approach aimed at restoring immune tolerance and preventing chronic joint destruction [78]. In this strategy, autologous regulatory T cells (Tregs) are genetically engineered to express a synthetic chimeric receptor that enables them to recognize specific autoantigens or inflamed tissue components in an MHC-independent manner, thereby enhancing their localization and suppressive activity within affected joints. By selectively targeting pathogenic immune responses, such as those driven by autoreactive T and B cells or proinflammatory cytokine networks, CAR-Tregs have the potential to re-establish immune homeostasis and promote tissue repair in diseases such as rheumatoid arthritis, ankylosing spondylitis, and lupus-related osteoarticular inflammation. Since the first preclinical demonstrations of CAR-Treg feasibility in autoimmune and transplant models around 2016 [79], several studies have reported their capacity to suppress local inflammation and mediate antigen-specific immune regulation in vivo [80, 81]. Reviews summarizing this early work have highlighted the potential of CAR-Tregs for autoimmune and transplantation indications [82-84]. Furthermore, preclinical studies using antigen-specific or FoxP3-engineered regulatory T cells in models of rheumatoid arthritis have demonstrated that adoptive transfer or in situ expansion of Tregs can alleviate joint inflammation, protect cartilage integrity, and reduce synovial fibrosis [85-87]. Together, these findings suggest that engineered regulatory T cells, potentially including CAR-Tregs, may offer a biologically targeted and durable strategy for restoring immune tolerance and preserving joint structure in autoimmune musculoskeletal diseases.

4. Conclusions

Cell-based therapies represent a transformative frontier in orthopedic medicine, offering the potential not only to alleviate symptoms but also to restore tissue structure and function. Chondrocyte-based approaches, mesenchymal stromal cells, and induced pluripotent stem cell-derived strategies each bring unique advantages and challenges in regenerative medicine. In parallel, engineered immune cell therapies, including CAR-T and CAR-NK cells, open new possibilities for onco-orthopedic applications by providing targeted strategies against sarcomas and other bone-associated malignancies, but also in autoimmune diseases

(please see Table 1 for the summary). Preclinical and early clinical studies (see Table 2 for examples) provide strong evidence for the feasibility and safety of these diverse approaches, though efficacy remains variable and long-term durability is not yet fully established. Key challenges include standardization, safety, cost, and regulatory hurdles. Future research aimed at optimizing regenerative and immune-based cellular therapies, enhancing biological potency, and integrating with bioengineering innovations holds great promise. As the field matures, cellular therapies may become an integral component of orthopedic care, offering regenerative, anti-inflammatory or anticancer solutions to conditions that currently lack curative treatments.

Table 1. Summary of the characteristics, benefits and risks/limitations for cellular therapies in orthopedics.

Therapy	Key features	Benefits (orthopedics)	Risks / Limitations
PRP	Autologous concentrate of platelets and plasma containing growth factors/cytokines; prepared at point-of-care.	May reduce pain and improve function for tendinopathies and early osteoarthritis; low immunologic risk; outpatient.	Highly variable preparations and protocols; inconsistent evidence; temporary effects; dosing not standardized.
Autologous chondrocytes (ACI / MACI)	Patient chondrocytes harvested, expanded ex vivo and implanted (with or without scaffold) into focal cartilage defects.	Tissue-specific repair for focal defects; can restore hyaline-like cartilage; durable symptom relief in selected younger patients.	Two-stage surgery, donor-site morbidity, high cost, technically demanding; not suitable for widespread osteoarthritis.
MSC	Multipotent cells (bone marrow, adipose, etc.) with trophic and immunomodulatory secretion; used as injection or scaffold-seeded cells.	Anti-inflammatory effects; potential to support cartilage repair and improve joint environment; minimally invasive delivery.	Heterogeneous cell populations and potency; low engraftment/differentiation in vivo; mixed clinical outcomes; regulatory /manufacturing variability.
iPSC-derived cells	Induced pluripotent stem cells reprogrammed from somatic cells then differentiated (e.g., to chondrocytes) for implantation or tissue engineering.	Potential unlimited, patient-matched cell supply; advanced tissue engineering and disease modelling possibilities.	Complex, costly manufacturing; risk of residual pluripotent cells (tumorigenicity); regulatory and safety hurdles; early-stage for orthopedics.
CAR-T cells	T cells engineered with chimeric antigen receptors to target specific antigens on cells.	Conceptually could remove pathogenic/ inflammatory cell populations selectively; very potent targeted activity.	Proven in oncology but not established in orthopedics; risk of severe systemic toxicities (cytokine release syndrome, neurotoxicity), off-target effects; complex manufacturing and high cost.
Treg	$CD4^+CD25^+FoxP3^+$ cells isolated/expanded or induced to suppress immune responses and inflammation.	Can reduce autoimmune/inflammatory joint damage and create a pro-regenerative environment; may limit chronic inflammation.	Difficulty expanding stable functional populations; phenotype instability; potential for systemic immunosuppression; limited orthopedics data.
CAR-Treg	Regulatory T cells engineered with CARs to direct suppressive function to antigen-expressing tissues.	Antigen-specific, localized immunosuppression - reduces systemic effects while promoting tolerance and tissue repair.	Very early-stage; manufacturing complexity; unknown long-term stability/safety; risk of losing regulatory phenotype or off-target suppression.

Table 2. Examples of clinical trials of cell-based therapies in regenerative orthopedics or onco-orthopedics.

NCT number	Indication	Cell type / Intervention	Phase / Status
NCT03138317	Knee osteoarthritis	Autologous Platelet-Rich Plasma (PRP) intra-articular injections	Interventional (Completed)
NCT04852380	Knee osteoarthritis	Autologous PRP intra-articular injections	Interventional (Recruiting/Completed depending on site)
NCT00414700	Focal cartilage defects of the knee	Autologous chondrocyte implantation (ChondroCelect®)	Phase III (Completed)
NCT04296487	Chondral defect (knee)	Autologous chondrocyte implantation (ACI)	Interventional (Completed/Active)
NCT03477942	Knee osteoarthritis / focal chondral defect	Autologous bone marrow–derived MSC (IA injection)	Phase I (Recruiting)
NCT05933434	Mild–moderate knee osteoarthritis	Allogeneic adipose-derived MSC IA injection vs placebo	Phase 1/2 (Recruiting)
NCT06078059	Knee osteoarthritis	Allogeneic umbilical cord–derived MSC	Randomized, open-label exploratory (Active)
NCT00902044	HER2-positive sarcoma /solid tumors (onco-orthopedics)	Autologous HER2-specific CAR-T cells	Phase I/II (Completed)
NCT06475495	Rheumatoid arthritis (refractory)	Autologous anti-CD19 CAR-T cells	Phase I/II (Active/Not yet fully reported)

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