Latest Innovations in Knee Osteoarthritis:

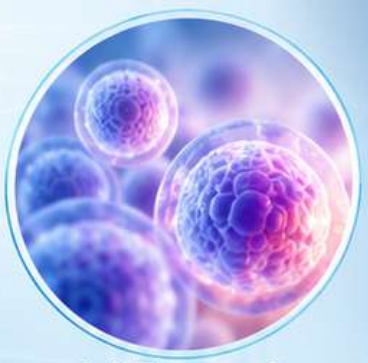
From Molecular Research to Next-Generation Therapies

Exploring the science and technology shaping the future of knee osteoarthritis treatment

Molecular Targets

Targeted Drug Delivery

Gene Therapy



Cell Therapy & Regenerative Medicine

Toward more effective, targeted and disease-modifying treatments for healthier joints

Latest Innovations in Knee Osteoarthritis

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Knee Osteoarthritis: Moving Ahead to Find Better Cure

Knee osteoarthritis (KOA) is one of the most common forms of osteoarthritis and a major cause of chronic pain, impaired mobility, and reduced quality of life. As populations age and obesity and other lifestyle-related risk factors become more prevalent, the burden of knee osteoarthritis is expected to continue increasing. Treatment strategies for KOA are gradually moving beyond symptom relief toward molecularly targeted and potentially disease-modifying therapies.

What Is Knee Osteoarthritis?

Knee osteoarthritis is a progressive degenerative disease involving the entire joint rather than cartilage alone. The disease is characterized by deterioration of articular cartilage, changes in subchondral bone, synovial inflammation, vascular alterations, and instability of surrounding structures such as ligaments and tendons.

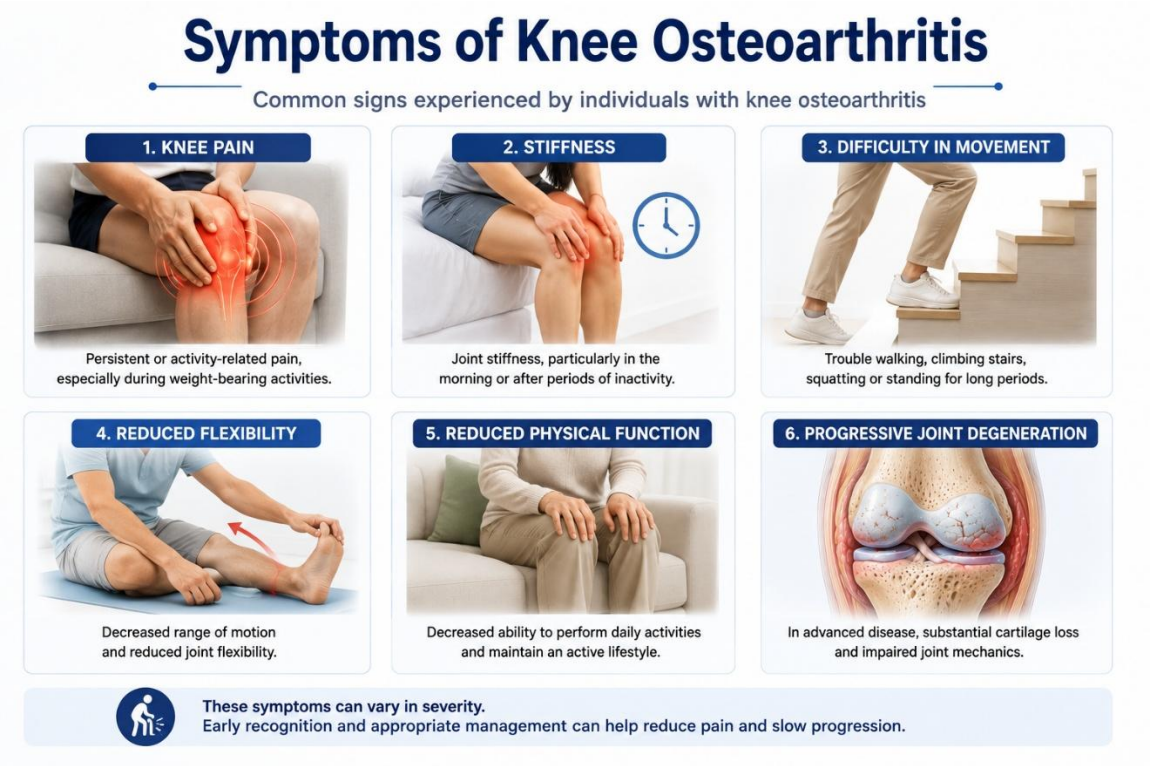
A central feature of KOA is the disruption of cartilage homeostasis. The extracellular matrix, which contains structural components including collagen and proteoglycans, gradually breaks down. As cartilage is damaged, chondrocytes attempt to compensate, but this response can also increase the production of inflammatory mediators and matrix-degrading molecules. The result is a self-perpetuating cycle of inflammation, tissue destruction, and joint dysfunction.

Key Structural Changes in Knee Osteoarthritis

- **Synovial inflammation**
- **Cartilage thinning and degradation**
- **Changes in the underlying subchondral bone**

Symptoms of Knee Osteoarthritis Symptoms

The symptoms of knee osteoarthritis can vary depending on disease severity, but commonly include:

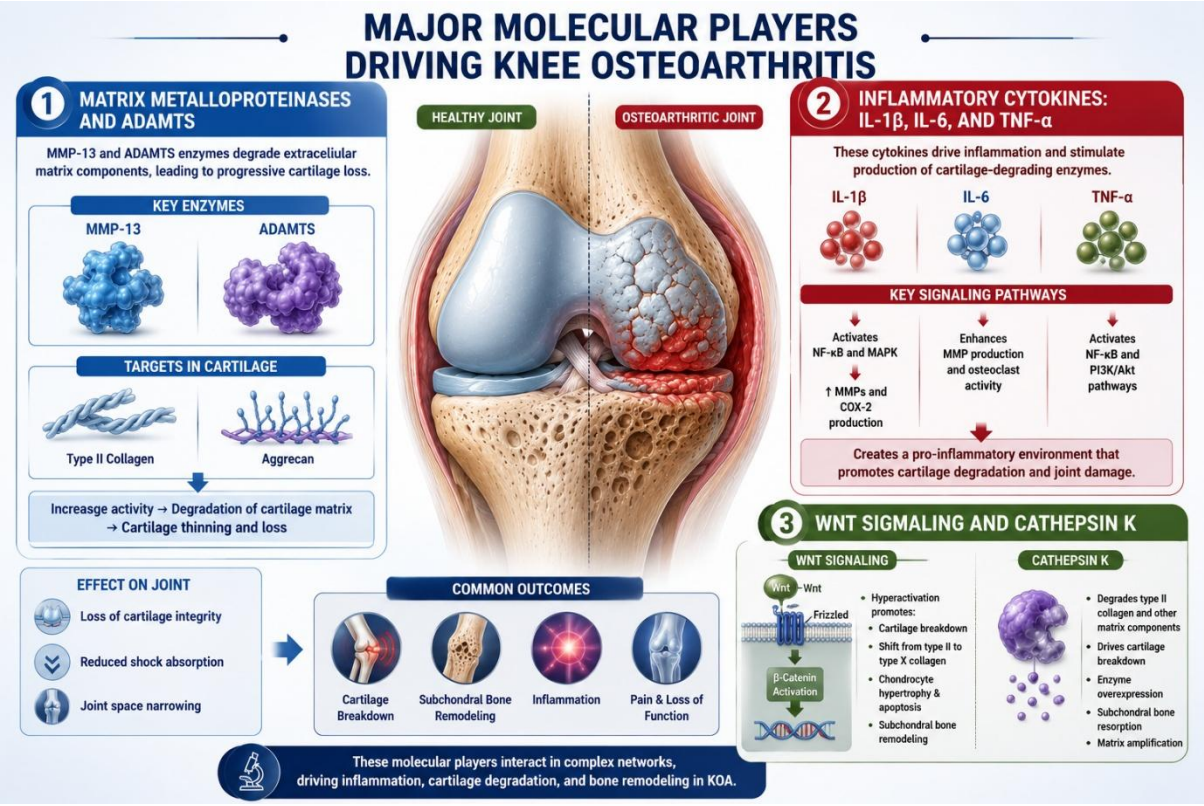


- Persistent or activity-related knee pain
- Joint stiffness and reduced flexibility
- Difficulty walking, climbing stairs, or standing for long periods
- Reduced physical function
- Progressive joint degeneration
- In advanced disease, substantial cartilage loss and impaired joint mechanics

Current management focuses largely on reducing these symptoms. Exercise, weight management, patient education, physical therapy, analgesics, nonsteroidal anti-inflammatory drugs, and intra-articular corticosteroids remain important treatment approaches. However, the currently available treatments generally provide symptomatic benefit and that no established medication can reliably stop or reverse KOA progression.

Major Molecular Players Driving Knee Osteoarthritis

Understanding the molecular mechanisms of knee osteoarthritis is essential for developing targeted therapies.



Matrix Metalloproteinases and ADAMTS

Matrix metalloproteinases, particularly **MMP-13**, and members of the ADAMTS family are important enzymes involved in cartilage destruction. These molecules degrade components of the extracellular matrix, including type II collagen and aggrecan. Their increased activity contributes directly to progressive cartilage loss.

For this reason, **MMP** and **ADAMTS** inhibitors are being investigated as potential disease-modifying osteoarthritis drugs.

AQU-019, an allosteric MMP-13 inhibitor, has shown promising preclinical properties. Similarly, **GLPG1972/S201086** was developed to inhibit ADAMTS5 and demonstrated chondroprotective activity in preclinical research. However, despite acceptable tolerability, its Phase II development did not achieve the required clinical efficacy endpoints.

Inflammatory Cytokines: IL-1β, IL-6, and TNF-α

Inflammation is another major component of KOA. Interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) promote inflammatory signalling and stimulate the production of cartilage-degrading enzymes.

- **IL-1β** activates pathways including NF-κB and MAPK, promoting the expression of MMPs and cyclooxygenase-2.
- **IL-6** can enhance MMP production and osteoclast activity, while
- **TNF-α** activates inflammatory pathways including NF-κB and PI3K/Akt. Together, these signalling networks create an environment that promotes inflammation and structural damage.

Wnt Signalling and Cathepsin K

The **Wnt signalling** pathway also contributes to joint degeneration. Hyperactivation of this pathway promote cartilage breakdown, cell death and abnormal shift in structural proteins from type II to type X collagen leading to matric degradation, chondrocyte hypertrophy, apoptosis and subchondral bone remodelling. **Lorecivivint**, a Wnt pathway inhibitor, has progressed through clinical trials and has shown encouraging results, including pain reduction and improved joint function after intra-articular administration.

Cathepsin K is another important molecular target. it destroys joint cartilage and subchondral bone by splitting type II collagen and other matrix components, driving the progressive wear and loss of joint tissue leading to cartilage breakdown, enzyme overexpression, subchondral bone resorption and matric amplification. The inhibitor **MIV-711** demonstrated reduced bone remodelling and less cartilage loss compared with placebo in a Phase II trial. However, structural improvement did not translate into statistically significant pain reduction during the relatively short study period, highlighting an important challenge in KOA research: changes in joint structure and symptom improvement do not always occur simultaneously.

Drug Landscape for Knee Osteoarthritis

Pharmacological Treatments (approved)	Targeted Therapies (under Trials)	Advanced Therapies (under development)
• Topical NSAIDs (Diclofenac) • Oral NSAIDs (Ibuprofen, Meloxicam, Indomethacin, naproxen) • COX-2 inhibitors (Celecoxib, Etoricoxib) • Analgesics (Acetaminophen, Paracetamol) • Weak opioid (Tramadol) • Topical analgesic (Capsaicin) • Intra-articular corticosteroids (Triamcinolone acetonide, methylprednisolone acetate) • Extended-release corticosteroid (Triamcinolone acetonide extended-release, Zilretta) • Viscosupplementation (Hyaluronic acid and cross-linked HA products)	• Wnt/CLK/DYRK inhibitor (Lorecivivint, SM04690) • ADAMTS-5 inhibitor (GLPG1972/S201086) • ADAMTS-5 nanobody (M6495) • MMP-13 inhibitor (AQU-019 and related MMP-13 programs) • Cathepsin K inhibitor (MIV-711) • FGF-18 analogue (Sprifermin) • MEPE-derived peptide (TPX-100) • ANGPTL3-derived therapy (LNA043) • Senolytic (UBX0101) • iNOS inhibitor (Cindunistat, SD-6010) • IL-1α/β antibody (Lutikizumab, ABT-981)	• Anti-NGF antibody (Tanezumab, Fasinumab) • Anti-ADAMTS-5 biologic (M6495) • IL-1 blockade (Lutikizumab) • Cell and gene therapy (TG-C) • Gene therapy (XT-150) • Liposomal corticosteroid (TLC599, liposomal dexamethasone)

Innovations for Early Diagnosis of ROA

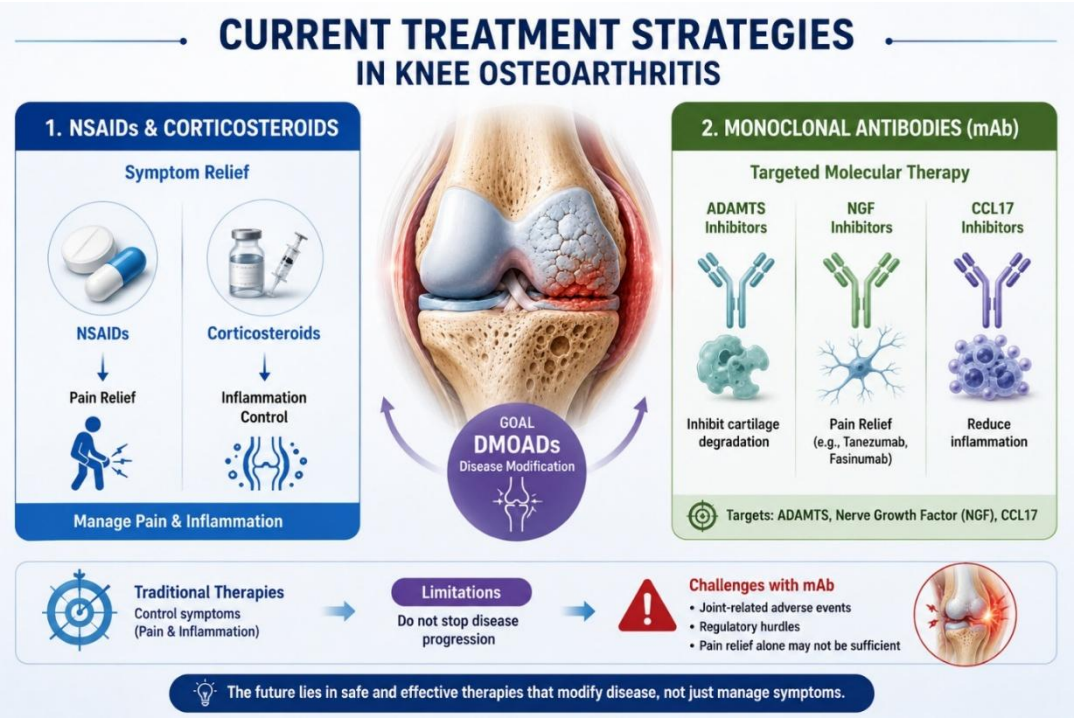
At present, clinical assessment and imaging remain central to evaluating disease severity and structural changes. Molecular characterization may become increasingly important in future KOA management.

Magnetic resonance imaging has been a major breakthrough that has been used to monitor cartilage thickness, cartilage loss, bone remodelling, and subchondral bone changes during clinical trials.

Next diagnostic step ahead

A future diagnostic strategy may combine imaging with molecular biomarkers such as inflammatory cytokines, MMP activity, ADAMTS activity, and characteristics of the joint microenvironment. Such approaches could potentially identify biologically distinct forms of KOA and allow treatment to be selected according to the dominant disease mechanism.

Treatment of KOA: From Pain Relief to Targeted and Disease-Modifying Strategies



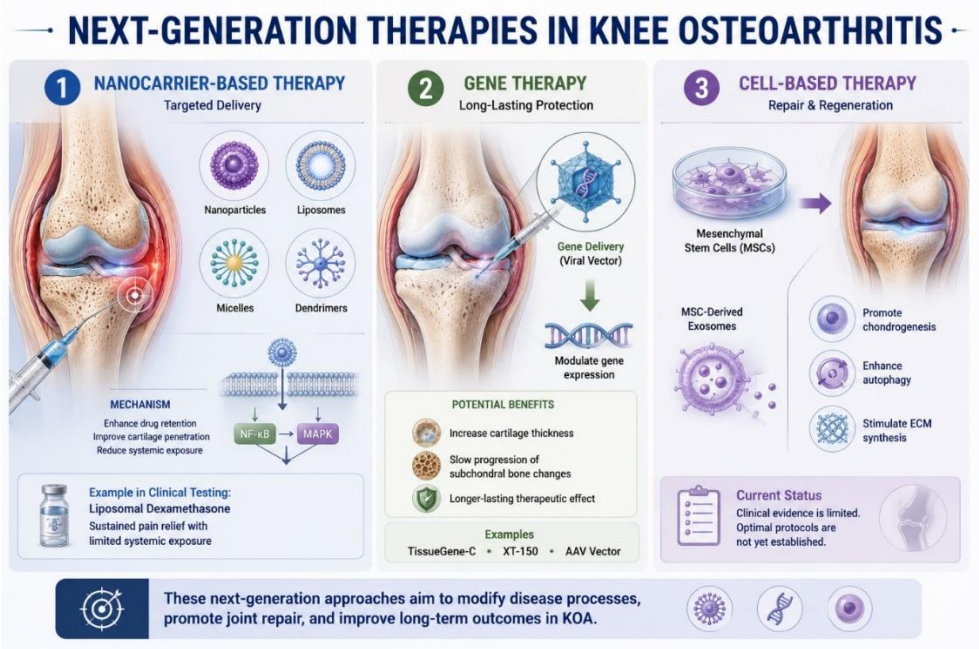
Current treatment strategies using NSAID, corticosteroids and mAb

One of the most important developments in knee osteoarthritis research is the search for disease-modifying osteoarthritis drugs, often referred to as **DMOADs**.

Traditional treatments such as **NSAIDs and corticosteroids** primarily control pain and inflammation while targeted therapies attempt to interfere with the molecular processes responsible for cartilage destruction, inflammation, bone remodelling, or abnormal signalling.

On the other hand, monoclonal antibodies have been investigated against targets including **ADAMTS, nerve growth factor, and CCL17**. Antibodies against nerve growth factor, such as **Tanezumab and Fasinumab**, produced substantial pain relief in some studies. However, concerns regarding joint-related adverse events created major barriers to regulatory approval and clinical development. This illustrates that suppressing pain alone may not be sufficient if the underlying disease process continues or safety risks emerge.

Nanotechnology, Gene Therapy, and Regenerative Medicine



1. Nanocarrier-based therapy is another promising area of KOA research. Nanoparticles, liposomes, micelles, and dendrimers can potentially improve drug retention within the joint, increase cartilage penetration, and reduce systemic exposure.

The nanocarriers can deliver active compounds directly to the knee joint and influence inflammatory pathways such as NF-κB and MAPK. Liposomal formulations have already

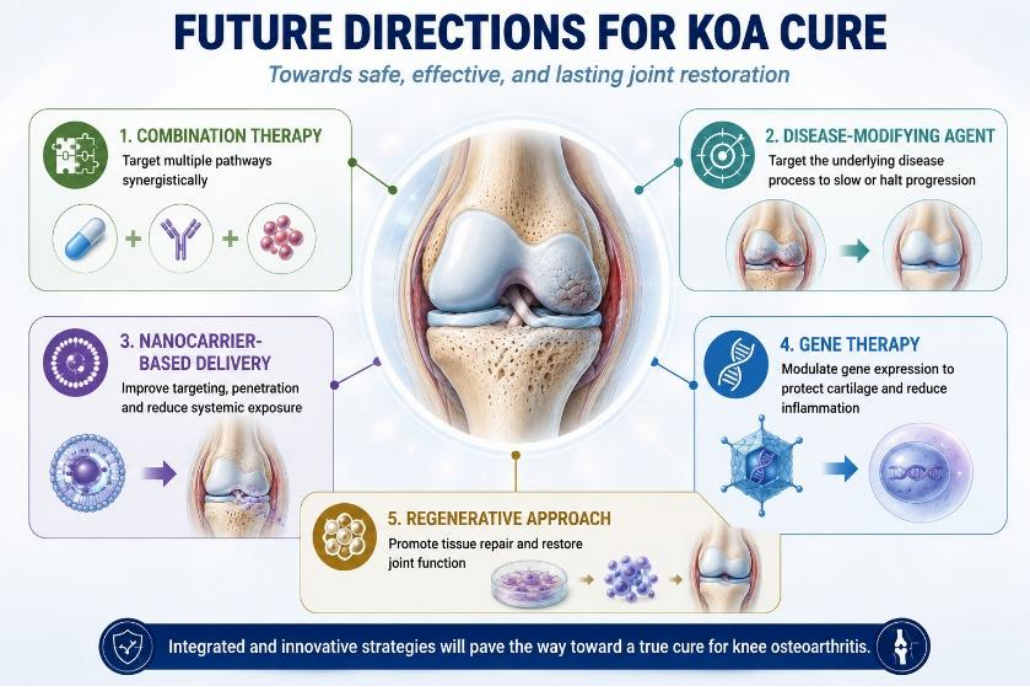
reached clinical testing. For example, **Liposomal Dexamethasone** was developed to provide sustained pain relief and improve joint function while limiting systemic exposure.

2. Gene therapy may offer longer-lasting therapeutic effects by suppressing harmful gene activity or increasing the expression of protective factors. **TissueGene-C** has shown evidence of increased cartilage thickness and slower progression of subchondral bone changes in clinical research. Other approaches, including **XT-150** and **adeno-associated viral vector** therapies, are also being investigated, although several remain in early-stage development.

3. Cell-based therapies are also attracting attention. **Mesenchymal stem cells** may support cartilage repair and regulate inflammation, while mesenchymal stem cell-derived exosomes may promote chondrogenesis, autophagy, and extracellular matrix synthesis. Nevertheless, current clinical evidence remains limited, and optimal treatment protocols have not yet been established.

Can Knee Osteoarthritis Be Cured?

Based on the reviewed evidences, there is currently no established cure that can reliably reverse knee osteoarthritis or permanently restore a severely damaged joint. Advanced cases may require surgical interventions, including osteotomy or knee arthroplasty.



However, the future of KOA treatment may be very different. The combination of molecular profiling, targeted drug delivery, gene therapy, regenerative medicine, and advanced imaging could support a more personalized approach. Instead of treating every patient with the same

therapy, future treatment may target the dominant mechanism in an individual joint, whether inflammation, cartilage degradation, abnormal bone remodelling, or another biological pathway.

The most promising direction may therefore be:

- A combination therapy
- A disease-modifying agent
- A nanocarrier-based delivery
- A gene therapy
- A regenerative approach.

However, major challenges remain, including long-term safety, manufacturing cost, treatment standardization, scalability, and the need to identify the most effective molecular targets.

The Future of Knee Osteoarthritis Treatment

Knee osteoarthritis research is entering an important transition. The goal is no longer limited to relieving pain. Scientists are increasingly focusing on:

- Preservation of cartilage
- Regulation of inflammation
- Modifying destructive molecular pathways
- Regeneration of damaged joint tissue.

Although a definitive cure for KOA has not yet been achieved, targeted inhibitors, monoclonal antibodies, nanomedicine, gene therapy, stem cells, and exosome-based therapies provide multiple pathways toward more effective treatment.

The future of knee osteoarthritis management may depend on identifying the right molecular target, delivering the therapy precisely to the affected tissue, and combining structural protection with meaningful symptom relief.

Reference:

Chen, L., Huang, F. L., Tang, Q., Zhao, Z. K., Ye, Z. Y., & Liang, J. H. (2025). Targeted therapy for knee osteoarthritis: From basic to clinics. Medicine, 104(33), e43686. https://doi.org/10.1097/MD.0000000000043686.