Designing Drug Delivery Systems for Articular Joints

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No disease-modifying drug exists for osteoarthritis due to poor drug delivery within joints. Engineered biomaterials could address this challenge by improving the duration and targeting of therapies.

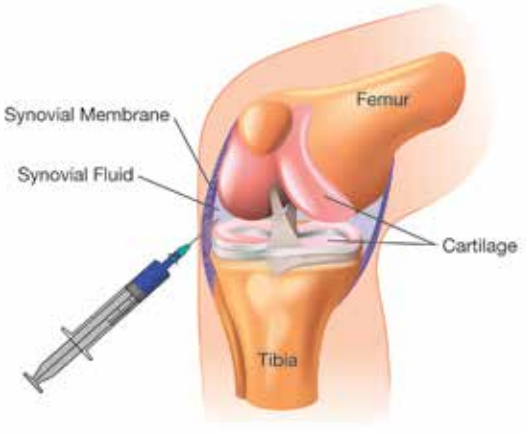
Osteoarthritis is a debilitating disease of individual joints, marked by progressive joint tissue degeneration, which causes pain and loss of mobility. It is a widespread disease that affects 30 million people in the U.S., including 19% of adults aged 45 and older *(1)*. However, despite decades of research and development, no disease-modifying drug for osteoarthritis has been approved for use in humans *(2)*. Such a drug could slow disease progression by reducing the rate of cartilage degeneration or even regenerating new tissue. The current standard of care focuses on pain relief only after symptoms are present. Even approved drugs in this category, such as corticosteroids and hyaluronic acid suspensions, are subject to debate with respect to their safety and/or efficacy *(3–5)*.

Underlying the clinical failures of disease-modifying drugs and the shortcomings of approved drugs is inadequate drug delivery to target joint tissues *(6, 7)*. Despite the use of intra-articular injection as a technique for local delivery to the joint, free drugs are unable to remain within the joint space for adequate time periods and thereby do not reach their biological targets at sufficient levels *(8)*.

The key obstacle for drug delivery in osteoarthritis is the hostile pharmacokinetics of the joint. Upon injection into the articular joint capsule (Figure 1), the drug enters synovial fluid, which is subject to rapid physiological turnover *(8)*. The fluid and the drug contained within it are rapidly drained via the venules and lymphatic vessels located in the synovial membrane; hence, most drugs are lost to systemic circulation *(9)*.

Free drugs are cleared from articular joints in a matter of hours to days, with some dependence on the molecular weight of the drug molecule. In contrast to this short therapeutic time frame, most clinicians seek to minimize the frequency of repeat intra-articular injections. Time between injections varies based on the physician's judgment and the drug being used, but an interval of 2–12 weeks is considered reasonable. It is therefore unsurprising that many treatments for osteoarthritis are ineffective.

Moreover, articular cartilage, which is often the therapeutic target of disease-modifying drugs, presents a formidable biological barrier to drug delivery. Cartilage is avascular (*i.e.,* it has no blood vessels), and thus penetration of drugs through the tissue to interact with the resident cell type, chondrocytes, occurs only by diffusion through the cartilage. Diffusive transport through cartilage is significantly hindered by its dense, highly anionic extracellular matrix and small



▲ **Figure 1.** Intra-articular injection is commonly used for local drug delivery into knee joints. However, upon injection into the fluid-filled joint capsule encased in the synovial membrane (or synovium), the drug is typically lost to systemic circulation within a matter of hours to days.

pore size of less than 15 nm *(10)*. Diffusion through cartilage is slower than the clearance rate of the joint, so free drug in the joint space is typically cleared before it can penetrate the depth of cartilage at a therapeutic concentration.

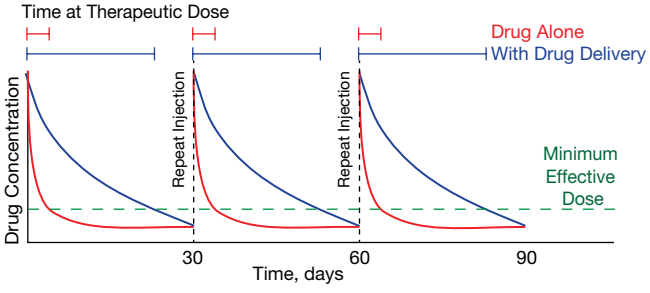
Fortunately, advanced formulation techniques for intra-articular injection using engineered biomaterials show promise in overcoming these delivery challenges. Even modest improvements in intra-articular penetration and half-life could have a considerable impact on therapeutic drug exposure time between injections (Figure 2).

This article provides an overview of some of the design strategies used in drug delivery systems for joints, and discusses important considerations and challenges for clinical translation of these technologies.

Strategies to avoid joint clearance: Microparticles

One approach to prevent clearance of a drug from synovial fluid is to encapsulate the drug in a biomaterial package that is simply too large to enter the synovial microvasculature. The biomaterial, with its longer joint residence time, can serve as a controlled release depot for the drug over a much longer timescale than an injection of a free drug (Figure 3). This tactic can also reduce the maximum concentration of the drug to which joint tissues are exposed. A reduced maximum concentration of drug is particularly important for corticosteroids, which have shown concerning side effects at repeated high doses *(5, 11)*, as well as for potent biologic drugs.

Flexion Therapeutics used this approach in developing FX-006, a therapy that was recently approved by the U.S. Food and Drug Administration (FDA). FX-006 is a poly(lactic-co-glycolic acid) (PLGA) microparticle that encapsulates triamcinolone acetonide (TA), a clinically used corticosteroid that targets synovial tissue to reduce inflammation and pain. The PLGA microparticles have a median size of 42 μm, which is large enough to prevent clearance through joint microvasculature *(12)*.



▲ **Figure 2.** Improved drug delivery would extend the residence time of intra-articular drug therapies in joints, which would markedly increase the total time at therapeutic dose over the course of treatment. Clinicians aim to reduce injection frequency as much as possible while still maintaining an effective drug concentration. Advanced drug delivery systems developed by researchers can make this goal possible.

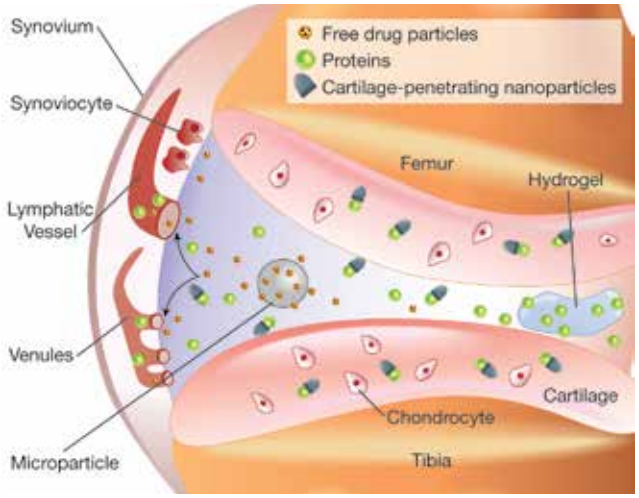
In humans, TA released from FX-006 was measurable in synovial fluid in most patients through 12 weeks post-injection, whereas TA in crystalline suspension was below the lower limit of quantification by six weeks *(13)*. The greatly improved pharmacokinetics of FX-006 produced statistically significant improvements in joint pain, function, and stiffness that warranted FDA approval of the therapy.

Importantly, the possibility that clinical improvement can be achieved using already approved therapeutics for osteoarthritis pain suggests that further advanced delivery approaches could enable the success of true disease-modifying drugs. A cartilage drug delivery system could sufficiently improve the efficacy of a previously failed disease-modifying drug to show clinical benefit.

Strategies to avoid joint clearance: Hydrogels

Like microparticles, hydrogels serve as drug material reservoirs that are too large to clear from the joint, thereby extending the time of therapy (Figure 3). This technique has been used to extend time between injections in viscosupplementation therapy — a medical procedure in which commercial hyaluronic acid formulations are injected into a joint with the goal of enhancing joint lubrication and alleviating pain.

One advantage over microparticles is that hydrogels are capable of encapsulating disease-modifying biologic drugs, such as growth factors or cytokine receptor antagonists, without loss of bioactivity. Polymer microparticle formulations often involve degradable polymers that are not water-soluble and require solvent or heat for processing — harsh conditions that are likely to denature most biologics drugs.



▲ **Figure 3.** In articular joints, free drugs and unbound nanoparticles are quickly cleared into lymphatic vessels and venules in the synovium. Microparticles and hydrogels are retained within the synovial fluid and slowly release drugs until they degrade. Cartilage-penetrating nanocarriers enter the tissue and interact with cells, although those that do not bind to cartilage are cleared.

Betre *et al.* designed a system using thermoresponsive elastin-like polypeptides (ELPs) that undergo a solution-gel transition upon injection at human body temperature to form micron-sized aggregates *(14)*. These aggregated ELPs had a half-life of 3.7 days in rat joints, and a release span of 28 days without accumulation in non-target tissues such as the liver or lungs *(15)*. ELP proteins can be expressed as fusions with biologic drugs, which would enable controlled drug release based on enzymatic degradation of the fusion linker.

Strategies to penetrate cartilage: Tissue binding

The aforementioned techniques are effective at prolonging exposure of the drug to the joint space, but do not provide a means for encapsulated drugs to navigate the cartilage extracellular matrix to interact with chondrocytes. This is acceptable for therapies with molecular targets within synovial tissue or fluid, as is the case for many pain-alleviating therapies. However, a disease-modifying effect can often be most effectively achieved by targeting the chondrocytes directly (Figure 3).

A challenge in designing biomaterials for cartilage penetration while avoiding rapid synovial clearance is the pore size of cartilage extracellular matrix. Research by our groups and others has shown that cartilage has an effective pore size of less than 15 nm, which precludes the use of microparticles, hydrogels, and many types of nanoparticles as cartilage-penetrating carriers *(10)*. Smaller nanocarriers would be capable of transport through cartilage, but such carriers are susceptible to rapid clearance from the joint by the lymphatic vessels and venules in the synovium.

To enable cartilage penetration while mitigating clearance, scientists have endeavored to design small nanomaterials that are capable of binding to cartilage at rates faster than the joint clearance rate. Early work by Rothenfluh *et al.* established this concept using a phage-panned peptide, WYRGRL (described in single-letter amino acid code), optimized for high-affinity binding with Type II collagen, a major constituent of cartilage extracellular matrix *(16)*. When the researchers conjugated WYRGRL to fluorescent nanoparticles, the nanoparticles exhibited increased fluorescence intensity relative to untargeted nanoparticles within mouse cartilage four days after intra-articular injection. Nanoparticles with a volume-average size of 30 nm (measured by dynamic light scattering) were present throughout the depth of thin (~50 µm) mouse cartilage, but 90-nm (volume-average sized) nanoparticles were restricted to the surface.

Hu and colleagues applied the same concept to the chelating small molecule DOTAM *(17, 18)*. DOTAM conjugated with three WYRGRL peptides (DOTAM-$(WYRGRL)_3$) was retained in the mouse joint for seven days and penetrated at least 200 µm into *ex vivo* porcine cartilage. Interestingly, DOTAM-$(WYRGRL)_3$ exhibited more cartilage binding and penetration than DOTAM-$(WYRGRL)_1$, suggesting that increasing the binding to cartilage can improve transport into the tissue *(17)*.

Cartilage-penetrating nanocarriers: Cationic proteins

In a manner analogous to the concept of using biomolecular peptide-protein interactions, electrostatic interactions between cationic biomaterials and anionic cartilage can accelerate penetration into cartilage, and electrostatic binding interactions can augment retention within the tissue.

This concept was thoroughly explored in our group by Bajpayee *et al.* with a cationic 7-nm protein, avidin, and its neutral counterpart, neutravidin *(10)*. These two proteins are nearly identical in size and structure, yet avidin, with a net charge of +20, was able to penetrate 1,000-µm-thick *ex vivo* bovine cartilage within 24 hr, whereas neutravidin penetrated only 50–100 µm within the same time frame *(10)*.

In rat joints, avidin was detected up to seven days after intra-articular injection and had an intra-tissue half-life of 1.2 days *(19)*. In rabbit joints, which contain thicker cartilage, the intra-tissue half-life of avidin ranged from 1.0 to 6.4 days, depending on the location of the cartilage within the joint and its thickness *(20)*. These findings suggest that the electrostatic binding mechanism of cartilage retention and penetration is more effective in thicker cartilage *(21)*.

Cartilage-penetrating nanocarriers: Synthetic polyelectrolytes

Our research groups are also developing polyelectrolyte complex systems to deliver biologic therapeutics, such as growth factors, throughout the depth of cartilage.

To encapsulate insulin-like growth factor 1 (IGF-1) without loss of bioactivity, we created a nanoscale polyelectrolyte complex (nanoplex) by controlling the complexation of cationic IGF-1 with anionic poly (L-glutamic acid) and then introducing cationic poly (L-arginine) to modify the surface with excess positive charge *(22)*. The nanoplex had a 16-nm mean diameter as measured by cryogenic transmission electron microscopy (cryo-TEM) and bioactivity equivalent to that of free IGF-1. The IGF-1 nanoplex achieved a joint residence time of 30 days, whereas IGF-1 alone was cleared within seven days. The nanoplex also penetrated through at least 500 µm of *ex vivo* bovine cartilage tissue, a degree of penetration on par with that of IGF-1 alone.

To further engineer the surface charge of IGF-1 systems, we designed a unimolecular polyelectrolyte nanocarrier for IGF-1. By covalent modification of some fraction of cationic side groups of the nanocarrier with polyethylene glycol (PEG) oligomers, we created a small library of <10-nm polyelectrolyte molecules with varying surface charge.

This library was screened for binding to bovine carti-

lage explants and counter-screened for toxicity in human chondrocytes. We observed increased cartilage binding with increasing surface charge, corresponding to less PEGylation (*i.e.,* covalent conjugation with polyethylene glycol). However, below a certain threshold of PEGylation, the polycations exhibited dose-dependent cytotoxicity. We identified polyelectrolytes with optimal cationic surface charge for substantial cartilage binding with no cytotoxicity. These optimally PEGylated polyelectrolytes could fully penetrate 1,000 μm in *ex vivo* bovine cartilage.

Interestingly, more-charged formulations required more time to achieve full penetration, but reached higher concentrations throughout the tissue at equilibrium. These optimally charged polyelectrolyte-IGF-1 conjugates are currently undergoing further testing in a rat model of osteoarthritis.

Translational considerations: Drug selection

Within the past decade, the emergence of the wide array of advanced drug delivery technologies for articular joints constitutes an important milestone toward the development of a disease-modifying osteoarthritis drug. The disease-modifying therapeutic candidates currently under investigation span a wide range of modalities and tissue targets. A particular delivery system may be better suited for one potential therapeutic than another. For clinical development of a drug delivery system for osteoarthritis, candidate drug selection is a crucial consideration.

Small-molecule therapeutics can be readily encapsulated at high concentrations within micro- or nanoparticle systems or hydrogels. The high minimum effective dose of small molecules (relative to biologics) often necessitates a large payload of drug. Delivering such a large payload with molecular-carrier-drug conjugates necessitates introducing high concentrations of carrier compound, which could exceed the maximum tolerated dose of the carrier.

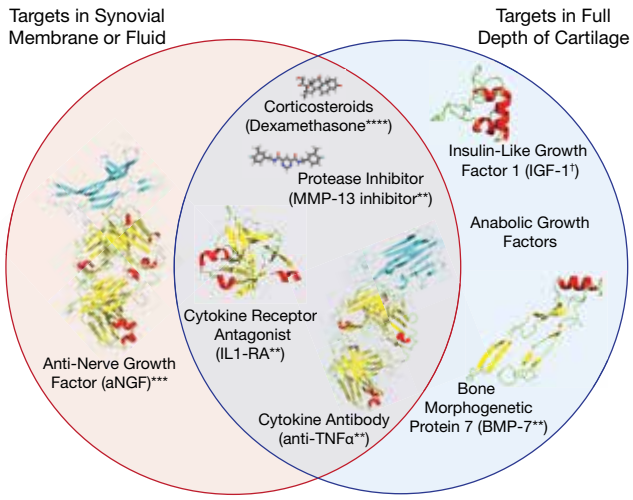
In contrast, biologics can be effective at remarkably low doses, yet are difficult to encapsulate into synthetic micro/nanoparticles without loss of bioactivity due to the solvent, temperature, or chemical crosslinking conditions often used in the production of these carriers. Molecular conjugates, self-assembled nanomaterials, electrostatic complexes, or fusion proteins, however, can often couple the carrier and therapeutic together under benign conditions.

Another key consideration in drug selection is the biological target of the drug. Many disease-modifying compounds that are focused on cartilage regeneration or homeostasis (*i.e.,* preventing cartilage degeneration) target chondrocytes dispersed throughout cartilage, so a cartilage-penetrating drug delivery system is required for maximum effect (Figure 4). Drugs that mitigate pain and/or inflammation may need to target only the synovial fluid or membrane to have some therapeutic benefit, enabling them to take advantage of drug delivery systems with longer joint half-lives but no inherent cartilage penetration capability, such as microparticles or injected gels.

It is worth noting that many drugs have targets in both synovial tissue and cartilage (Figure 4) and that the therapeutic effects of such drugs may differ based on their biological target(s) *(21)*. Corticosteroids such as dexamethasone are well-studied molecules that appear to have this effect. When they act primarily on synovial tissue, their function appears to be reducing pain and inflammation. However, these molecules appear to have protective, anticatabolic effects on chondrocytes that could be disease-modifying at an early stage of the disease *(23, 24)*. Thus, depending on the delivery system, the same drug could produce two different effects. This phenomenon highlights both the role of tissue targeting and the importance of understanding desired clinical outcomes when selecting a drug delivery system for osteoarthritis.

Translational considerations: Clinical

One of the goals in designing advanced drug delivery systems for articular joints is to improve the clinical efficacy of potential disease-modifying molecules undergoing trials. Often, these molecules have shown substantial promise in preclinical studies, but exhibit poor pharmacokinetics in humans and consequently do not show enough efficacy to warrant FDA approval or further development. Drug delivery systems could make a great impact in this area, yet it is



▲ **Figure 4.** Several classes of potential disease-modifying drugs with targets in synovial fluid, synovial membrane, and/or articular cartilage are currently undergoing clinical trials *(21)*. Note: Antibodies are shown as the antigen-binding fragment, F_{ab}, interacting with its biomolecular target (cyan). Current status in clinical trials is indicated, where † is preclinical, * is Phase I, ** is Phase II, *** is Phase III, and **** is clinically approved. Structures provided by the RCSB Protein Data Bank and PubChem under accession codes: 2GF1 (IGF-1), 1BMP (BMP-7), 1ILT (IL1-RA), 3WD5 (aTNFα F_{ab}), 4EDW (aNGF F_{ab}), 5743 (Dex), 5289110 (MMP13).

vital that selection of the drug delivery system is synergistic with the clinical study.

Referring again to the corticosteroid example, a trial focused on using dexamethasone to reduce inflammation and pain would be best served with a drug delivery system to maximize synovial residence time without regard to cartilage penetration. Conversely, in a trial to achieve disease-modifying effect, dexamethasone would need to be targeted to chondrocytes using a cartilage-penetrating formulation; these trials would likely also involve a younger patient population.

For example, while a trial in late-stage osteoarthritis may serve to benefit a larger patient population, drugs are unlikely to show disease-modifying effects in this population, regardless of improved drug delivery. This patient population will, on average, have severe and often irreversible cartilage degeneration. Not only would cartilage-binding delivery systems be less effective in such damaged tissue, but evidence suggests that past a certain point of the disease, cartilage cannot be regenerated *(25)*. Thus, a disease-modifying drug trial would best be conducted in earlier-stage osteoarthritis patients or those that are at great risk for the disease, such as a post-traumatic injury population.

While early-stage patients could see life-altering improvement in their osteoarthritis from a disease-modifying therapy, they typically do not exhibit easily measured symptoms like pain. Biomarkers such as MRI-based cartilage thickness measurements or synovial protein levels could

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be used to prove disease-modifying effect, but no such biomarker has yet to be qualified as an approvable clinical endpoint for disease-modifying effect in osteoarthritis.

For a disease-modifying therapy to be successful, there is great need for the development of biomarkers that:

- are sensitive to the effects of disease-modifying drugs over a practical timeframe
- represent clinically meaningful improvement in the overall disease
- can achieve regulatory approval as a clinical outcome of treatment.

Even when used only in preclinical studies, biomarkers that are readily detected and quantified will further understanding in the field.

Closing thoughts

The past decade of drug development for osteoarthritis has seen the failure of an unformulated drug due to poor pharmacokinetics, as well as the approval of an advanced formulation based on improved pain-reduction efficacy via enhanced pharmacokinetics. There appears to be growing consensus within the community of osteoarthritis researchers that drug delivery will play a key role in addressing the ongoing challenge of developing a disease-modifying therapy. In light of these developments, the recent advances in cartilage drug delivery as outlined in this article are particularly exciting. However, more research is required before articular drug delivery systems can reach their clinical potential.

Further quantification of the effects of carrier charge and size on tissue transport properties will be necessary to precisely engineer cartilage-binding systems. An understanding of the intracellular trafficking of these systems will also be crucial. Most biologic drugs currently under development for osteoarthritis interact with an extracellular receptor, but as nucleic acid therapeutics emerge, there will be an increasing need for cartilage-penetrating nanocarriers to deliver cargoes across the cellular membrane. And, as always, reproducible synthesis of a well-characterized drug delivery system is vital to clinical translation.

The approval of the first disease-modifying drug for osteoarthritis remains a salient goal for researchers in the field. For decades, unfavorable intra-articular pharmacokinetics have been a major roadblock in the path to this goal. Thus, there is tremendous opportunity for advanced drug delivery techniques to propel candidate therapeutics forward toward clinical success.

As concurrent research in osteoarthritis biomarkers and mechanisms of cartilage penetration progresses, we expect to see increased clinical development in the osteoarthritis space and anticipate the continued use of advanced delivery strategies based on engineered biomaterials. With such biomaterials providing a solution to the pharmacokinetics problems that have vexed previous therapies, a disease-modifying drug for osteoarthritis may arrive in the near future. CEP

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