Drug delivery to chondrocytes

Asked why he robs banks, the gangster Willie Sutton famously replied: “because that’s where the money is”. The same logic can be applied to intra-articular therapy. Why inject drugs into joints? – Because that’s where the arthritis is. But robbing banks is easier.

The main problem is that anything injected into a joint tends to come back out again very quickly. This restricts the effectiveness of intra-articular treatments to acute conditions, such as injuries and flares. There is a pressing need for technologies to retain drugs in joints and thus permit sustained therapeutic responses in chronic conditions such as osteoarthritis (OA). Furthermore, accumulating large amounts of a therapeutic within the joint space is not very helpful if the target cells are chondrocytes and the agent cannot penetrate the extracellular matrix of cartilage. A paper by Bajpayee et al. in this issue of Osteoarthritis and Cartilage addresses these matters.

Thanks to the pioneering studies of Peter Simkin, University of Washington, Seattle and Rodney Levick, St George’s Medical School, London, we have a good understanding of the pharmacokinetics of the knee joint. Small molecules, such as NSAIDs and glucocorticoids, diffuse out of the joint space very quickly via the sub-synovial capillaries. And it is no good trying to address this by forming large conjugates, because macromolecules are also rapidly cleared, in this case via the lymphatics, in a manner that is independent of their size. Proteins and glycosaminoglycans (GAGs), for instance, have intra-articular half-lives of only a few hours. Larsen et al. have compiled the intra-articular half-lives of various relevant molecules (Table I).

Because frequent, repeated intra-articular injections are not feasible, several alternative strategies have emerged in attempts to solve the problem of drug retention. Gene transfer is one of them. The idea is to introduce cDNAs into the cells of the joint so that the encoded products endogenously for an extended period of time. This technology works best when the drug is a pro-drug. Because that’s where the arthritis is. But robbing banks is easier.

Alan Grodzinsky and his colleagues at MIT have pioneered alternative strategies in which drugs or drug carriers are modified to bind to the extracellular matrix of cartilage. This approach nicely converts the matrix from a barrier to an accomplice when delivering molecules to chondrocytes. In their first successful demonstration of this approach, collaborating with Richard Lee and co-workers of Harvard Medical School, insulin-like growth factor-1 was engineered to contain a heparin-binding domain. In the current issue of Osteoarthritis and Cartilage, Bajpayee et al. report a refinement of this tactic using avidin as the anchor.

Avidin has several unique advantages in the present context. With a diameter of about 7 nm, it is small enough to diffuse into intact cartilage, whose cut-off has been estimated at around 10 nm. It is highly cationic, leading to Donnan (electrostatic) interactions that generate at least a six-fold upward partitioning factor at the synovial fluid–cartilage interface. This increases the intra-tissue concentration gradient, significantly enhancing avidin’s transport and uptake inside the cartilage. Moreover, its favorable net positive charge enables weak and reversible ionic binding with GAGs (Ko ~ 150 μM) allowing avidin to diffuse throughout the whole depth of the cartilage. Despite weak binding, it has long intra-tissue residence time because of the extremely high binding site density of the negatively charged groups (Nm ~ 300 μM). This ensures that cartilage not only accumulates considerable amounts of avidin throughout its entire thickness but also releases it internally (see Fig. 1). If avidin is conjugated to a drug, the latter then becomes available to chondrocytes. Avidin’s effectiveness as a delivery vehicle to cartilage has been confirmed in vivo in rats and rabbits.

A popular alternative is to combine drugs with slow-release nano- or micro-particles for intra-articular injection. The problem here is that these particles, too, are rapidly cleared by the lymphatics. Moreover, micron-sized particles are too big to penetrate cartilage. Even though nano-sized particles may do so, in the absence of an intra-cartilage retention mechanism they will diffuse right back out again. As things stand, the duration and magnitude of clinical benefit using particles as delivery vehicles is only incrementally greater than that of the free drug.

Table I

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Molecular weight</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>151</td>
<td>1.1</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>234</td>
<td>0.4</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>358</td>
<td>0.4</td>
</tr>
<tr>
<td>Cortisone; hydrocortisone</td>
<td>360, 363</td>
<td>0.4–4.2</td>
</tr>
<tr>
<td>Evans Blue</td>
<td>963</td>
<td>0.9</td>
</tr>
<tr>
<td>Albumin</td>
<td>6.7 × 10⁴</td>
<td>1–13</td>
</tr>
<tr>
<td>Hyaluronan</td>
<td>0.1–6 × 10⁹</td>
<td>10–26</td>
</tr>
<tr>
<td>Aggrecan</td>
<td>2.5 × 10⁴</td>
<td>12.5</td>
</tr>
</tbody>
</table>

From Larsen et al., reference 3.
The latest paper\(^1\) evaluates an avidin-dexamethasone conjugate. Dexamethasone was selected following our discovery that it dramatically protects cartilage from the combined effects of injurious compression and inflammatory cytokines without compromising matrix synthesis or other aspects of chondrocyte metabolism\(^13\). This finding has resulted in a clinical trial to evaluate the possibility that a single, intra-articular injection of dexamethasone after injury to the joint can prevent the onset of post-traumatic OA\(^14\). The intra-articular transience of dexamethasone is, however, a concern.

Bajpayee et al.\(^1\) covalently attached dexamethasone to avidin using ester or pH-sensitive hydrazone linkers, designed to release dexamethasone quickly (t\(_{1/2} = 14\) h) or slowly (t\(_{1/2} = 57\) h in an acidic environment), respectively. Looking ahead to possible clinical application, a PEGylated version of avidin was also synthesized to reduce immunogenicity. The potency of these molecules was determined in an in vitro assay system where disks of bovine articular cartilage were exposed to interleukin-1. This resulted in depletion of proteoglycan from the matrix, inhibition of GAG synthesis and cell death. Avidin-delivered dexamethasone protected against each of these responses. A single application of unconjugated dexamethasone was less effective than a similar single application of an avidin-dexamethasone conjugate, with a 1:1 mix of the slow and fast releasing formulations being the most potent. No cytotoxicity was observed.

These promising data have motivated evaluation of new conjugates in animal models of joint disease, which may lead to clinical trials in human and veterinary medicine. Novel approaches such as these have much to offer in the continuing quest to develop disease-modifying drugs for OA.

**Author contributions**

CHE wrote this editorial.

**Conflict of interest**

None.

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**References**


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