Osteoarthritis (OA) remains untreated primarily due to a lack of cartilage targeting drug delivery methods and concerns around systemic toxicity. The dense meshwork of negatively charged aggrecan-glycosaminoglycans (GAGs) and collagen in cartilage hinders diffusive transport of most macromolecules administered into intra-articular (IA) space, which is further complicated by their short joint residence time. We have shown that the high negative fixed charge density (FCD) of cartilage can be converted from a barrier to drug entry into a depot by adding optimally charged cationic domains to drugs such that electrostatic interactions can enhance their transport, uptake and retention rather than hindering them (Fig 1). We show that the weak and reversible binding nature of charge interactions is an essential characteristic for penetration through full cartilage thickness to reach cells in deep zones; strong binding, on the other hand, can hinder diffusive transport slowing down penetration of drug or its carrier trapping it in tissue surface. We also discovered that charge-based binding can be stabilized by short-range hydrophobic and H-bonds, using which we have designed carriers for delivery of small molecules, proteins and genetic materials to cells in late stage OA cartilage that may have lost significant GAGs. These biomaterials can enable translation of new OA drugs and of those that failed clinical trials due to targeting/toxicity concerns. We have also synthesized cationic contrast agents that can enable computed tomography of cartilage for early OA diagnosis. We are now synthesizing a new class of cartilage penetrating cationic exosomes for drug delivery and extending applications of charge-based delivery to other negatively charged tissues like meniscus, fracture-callus, intervertebral-discs, mucosa, and eye.

Fig 1: Cartilage homing charged biomaterials. (a) Electrostatic interactions enable rapid and full depth penetration, high uptake and long-term binding of optimally charged carriers into negatively charged cartilage. Electrostatic binding can be further stabilized by short-range H-bonds and hydrophobic interactions, using which we design carriers for targeting varying severity of arthritic cartilage. (b) Charged carriers result in 100-400x uptake, 10x faster penetration rate, and several weeks long retention even in presence of synovial fluid (SF); results show there exists an optimal net charge (+14) that results in highest uptake and rapid penetration of a carrier into cartilage; higher charge (+20) results in stronger binding with GAGs that hinders intra-cartilage penetration and uptake. (c) Physical concept: High negative FCD of cartilage results in a steep drop in electrical potential (ΔΦ) at SF-cartilage interface generating a strong, inward pointing electric fields that results in high upward Donnan partitioning of optimally charged cationic carriers accelerating their transport into cartilage. Weak-reversible binding enables full tissue thickness penetration. Despite this weak binding, high density of negatively charged binding sites enables long residence time. (d) Cartilage targeting charged biomaterials synthesized in our lab: Cationic Peptide Carriers (CPC) and multi-arm avidin (mAv) for delivery of small molecules and proteins, and cationic MSC derived exosomes for delivery of anchored drugs or encapsulated miRNA/siRNA. (e) Example successful applications: mAv increased exposure of conjugated drug, dexamethasone (Dex) to target chondrocytes inside cartilage and significantly improved repair efficacy compared to unmodified Dex as shown by Safranin-O images; CPC+8 was used to deliver anionic ioxaglate (IOX) contrast agent. CPC-IOX enabled high resolution tomography of cartilage with 32x lower concentration of IOX; cationic exosomes can be uptaken by cells.