Journal of Tissue Engineering
Volume 9: 1–12

DOI: 10.1177/2041731418776514
journals.sagepub.com/home/tej
SAGE

Intra-articular biomaterials-assisted delivery to treat temporomandibular joint disorders

Khandmaa Dashnyam[1,2], Jung-Hwan Lee[1,3], Nandin Mandakhbayar[1,2], Guang-Zhen Jin[1,3], Hae-Hyoung Lee[1,3] and Hae-Won Kim[1,2,3]

Abstract

The temporomandibular joint disorder, also known as myofascial pain syndrome, is considered one of the prevalent chronic pain diseases caused by muscle inflammation and cartilage degradation in head and neck, and thus influences even biopsychosocial conditions in a lifetime. There are several current treatment methodologies relieving inflammation and preventing degradation of the joint complex. One of the promising non-surgical treatment methods is an intra-articular injection of drugs such as corticosteroids, analgesics, and anti-depressants. However, the side effects of drugs due to frequent injections and over-doses, including dizziness, dry mouth, and possible drug dependency are considered limitations. Thus, the delivery of therapeutic molecules through the use of nano/microparticles is currently considered as a promising strategy primarily due to the controlled release. This review highlights the nano/microparticle systems for effective intra-articular therapeutics delivery to prevent cartilage degradation and protect subchondral bone in a temporomandibular joint.

Keywords

Temporomandibular joint, therapeutics delivery, nano/microparticles, intra-articular injection, temporomandibular joint disorder, myofascial pain syndrome

Date received: 17 March 2018; accepted: 23 April 2018

Introduction

The temporomandibular joint (TMJ) is a bilateral joint (synovial articulation) between the condyle (head of mandible) and part of skull (upper temporal bone). In addition to the above two skeletal structures, TMJ additionally consists of lateral pterygoid muscle, articular disk, surrounding capsule, and three ligaments (sphenomandibular, temporomandibular, and stylomandibular ligament) from front to back in a sagittal plane. The surrounding capsule consists of a dense fibrous membrane and is filled with synovial fluid, providing nutrition for the avascular central area of the disk, lubricating during opening and closing of mouth, and providing a space for therapeutic molecules used to cure diseases.[1–3] Because of the biconcave shape of the articular disk, the central area of TMJ lacks blood and nerve innervation, inflammatory-associated pain or swelling is

[1]Institute of Tissue Regeneration Engineering (ITREN), Dankook University, Cheonan, South Korea
[2]Department of Nanobiomedical Science & BK21 PLUS Global Research Center for Regenerative Medicine, Dankook University, Cheonan, South Korea
[3]Department of Biomaterials Science, College of Dentistry, Dankook University, Cheonan, South Korea

Corresponding authors:
Jung-Hwan Lee, Institute of Tissue Regeneration Engineering (ITREN), Dankook University, Cheonan 330-714, South Korea.
Email: ducious@gmail.com

Hae-Won Kim, Department of Nanobiomedical Science & BK21 PLUS Global Research Center for Regenerative Medicine, Dankook University, Cheonan 330-714, South Korea.
Email: kimhw@dku.edu

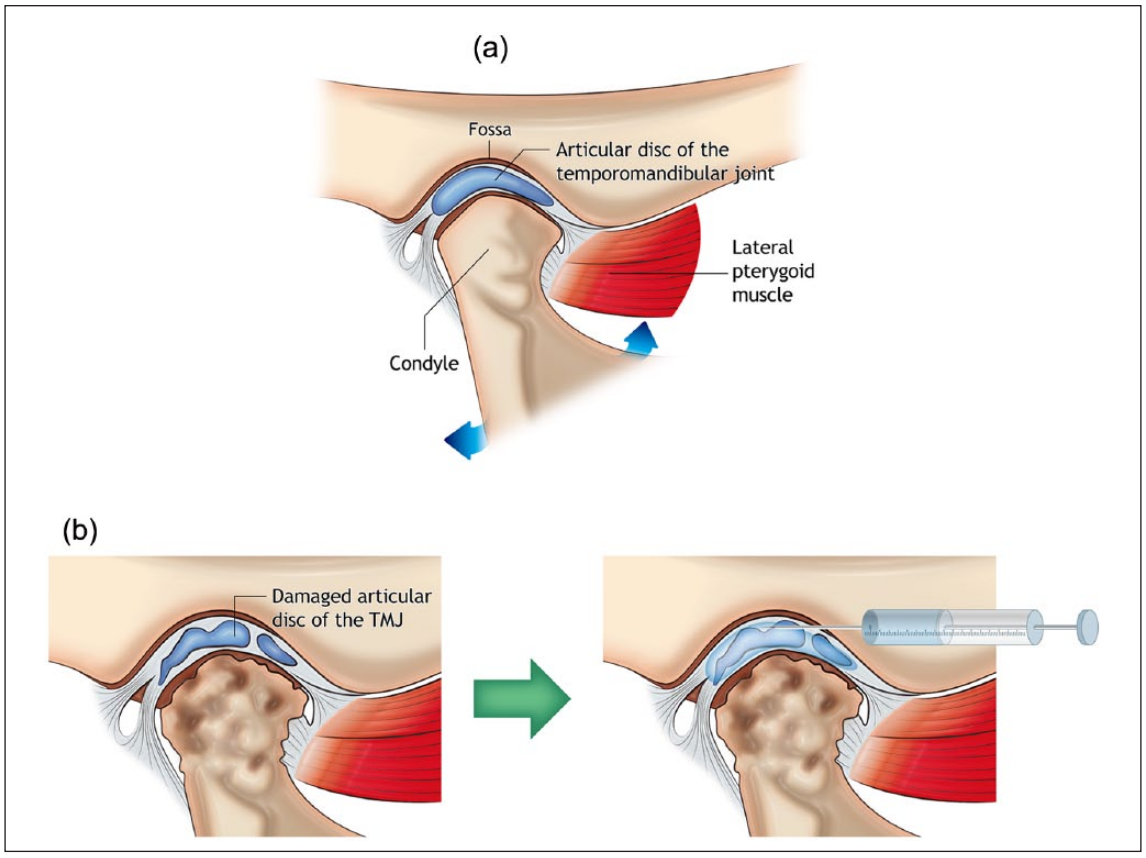

Figure 1. (a) Schematic image of the anatomical structure of temporomandibular joint (TMJ) and the most common target sites for treating temporomandibular disorder (TMD). The image shows components of normal joint anatomy, including the articular disk of TMJ, mandibular fossa, the head of the mandibular condyle, lateral pterygoid muscle, and TMJ capsule enclosing the disk. (b) TMD morphology; the head of the mandibular condyle and the articular disk lose their structures and functions. Intra-articular injection: injection with syringe and needle can deliver proper biomolecules into TMJ capsule for treating TMD.

from the peripheral region which is full of blood vessels and nerves.

Temporomandibular joint disorder (TMD), also known as myofascial pain syndrome (MPS), is a general term to describe pain and malfunction of the masticatory actions. The cause of the onset of TMD is poorly understood but considered from multiple reasons of psychosocial, habitually occlusal, mentally, genetic, or hormonal factors.[4] Although TMD is not life-threatening, it can be critical to the quality of life[5,6] because it becomes prevalent even in young generations, chronic, irreversible, and usually difficult to manage, leading to increasing number of TMD patients and undesirable effects on patients' professional and social lives.[7,8] The most common symptom of TMD is acute or chronic pain, followed by restricted mandibular movement and noises during jaw movement, leading to progressive TMJ degeneration and limitation of talking, chewing, and other basic daily mouth activities.[9] Interestingly, unlike other degenerative joint diseases such as arthritis which are more common in the elderly, TMD even affects up to one-third of adolescents and young adults.

TMD is generally classified into three categories according to the symptoms: myofascial pain, internal derangement of the joint with/without reduction, and inflammatory joint disease. Conventional treatment aims at decreasing hypertonic muscles and increasing TMJ mobility. Based on this, current clinical treatments (Figure 1) are divided into four groups: noninvasive, minimally invasive, invasive, and alloplastic replacement. The first stage of clinical treatment for TMD is noninvasive therapy which includes physical treatment using low-level laser or ultrasonic device, behavioral interventions often with occlusal splint, or pharmacologic approaches (i.e. taking analgesics, anti-depressants, muscle relaxant, or non-steroidal anti-inflammatory drugs (NSAIDs)). However, above conventional noninvasive treatment is often limited to regenerate severe or chronic TMD and systemic side effects such as gastrointestinal toxicity, cardiovascular risk, and anaphylaxis, disorders to the other tissues can be raised especially from oral administration in a dose-dependent manner.[10]

Second, minimally invasive therapies include the injections and arthrocentesis where a needle is used to flush and drain the joint space for removing inflammatory mediators and enhancing lubrication. The intra-articular injection is considered as a more promising method to deliver drugs or biomolecules to the target site, leading to a reduction of the

risk of the systemic side effects.[11] Currently, there are several injectable drugs such as NSAIDs, corticosteroid (glucocorticoids, triamcinolone acetonide, and dexamethasone), platelet-rich plasma (PRP) from blood and hyaluronic acid (HA) which relieve pain and improve maximal incisal opening.[12,13] However, the side effects of injected (bio) molecules, including dizziness, dry mouth, and possible drug dependency are considered limitations of the procedures.[4,14–16] Thus, biomaterial-based carriers have been developed mainly to deliver the drugs controllably into the specific anatomical area.[17–23]

Surgical treatments of invasive intervention or alloplastic replacement are also considered when advanced or chronically degenerative TMD is present and mouth opening is extremely limited.[24] They are quite effective in cleaning up inflammatory granular tissues and their degenerative cytokines, but they need high demand of cost and time. In case of alloplastic replacement, unpredictable outcomes are sometimes produced from uncontrollable inflammation and immune responses after replacement surgery using the artificial disk. Thus, minimally invasive intra-articular injection is highlighted as a promising general treatment even in severe TMD patients due to their high efficiency of regeneration and relatively easy procedure according to the development of stem cell biomaterial–based tissue regeneration.

There are many successful in vitro or in vivo studies on intra-articular injections to TMD patients using nano/micro biomaterials, (stem) cells, drugs, or their composite (Table 1). However, the clinical outcomes of intra-articular injections to TMD patients are by far still controversial because reports have revealed diverse outcomes from "therapeutic" to "degenerating."[31,56] In addition, like other inflammatory disease in the joint area (i.e. osteoarthritis), no agents are available to reverse the ongoing TMD to a healthy state. Current clinical therapies using intra-articular injections are only effective in pain relief at an early stage of disease but fail to alleviate severe or chronic pain lacking regenerative potential.[57]

To overcome the limitations of current intra-articular injections, nano and microscale biomaterials with or without (stem) cells or curable molecules (RNA, proteins, drugs, and macromolecules) have been introduced. They can effectively relieve pain and symptoms for long time, reduce systemic side effects of injections and tissue damages, control the release of drug and macromolecules delivered, and in turn increase regeneration process.[58] This review discusses current therapeutic strategies of using injectable biomaterial-based delivery carriers for the treatment of TMD.

Delivery vehicles of therapeutic molecules

Delivering drugs through oral administration to the targeted site takes long (1–5 h) and leads to the decrease of drug efficiency due to their gastrointestinal adsorption and systemic circulation.[59,60] Corticosteroid injection has a palliative (not curative) effect, is only used in severe acute pain, and generally for limited doses only. The effect of steroid on the disk is widely reported to irritate. Therefore, intra-articular injection of (therapeutic) biomaterials (i.e. HA and corticosteroids) has been widely used in clinics because high drug concentrations are possibly delivered with minimal side effects compared with systemic administration. However, rapid clearance of the injected biomolecules requires repeated injections, which causes complications like infection, fibrous tissue formation, and consequent joint damage.[52,56] Such obstacles are possibly tackled through the use of nano and microparticles that can deliver therapeutic molecules, such as anti-inflammatory drugs, steroids and genes, and release them in a sustained manner. In addition, nano and microparticles interact with cells at the intra and extracellular space depending on their size (Figure 2). Thus, another strategy to enhancing regeneration of TMD is through regulating the interaction between (newly conjugated or residual) cells and injected intra-articular biomaterial.

Nanoparticle-based drug delivery system

Nanoparticles have been widely used in biomedical applications due to their unique properties such as large surface-to-mass ratio, quantum properties, and ability to load and deliver small-sized biomolecules (proteins and drugs).[11,17] Nanoparticles are solid or colloidal particles with sizes ranging from tens to hundreds of nanometers.[17] Particle size is a typical factor that determines toxicity, delivery capability, and in vivo distribution. Nanoparticles readily enter into cells by an endocytosis mechanism. Thus, they can deliver small-sized biomolecules intracellularly to control cell fate.[61,62] Also, degraded products (i.e. ions) of nanoparticles can sometimes be therapeutic, exerting co-delivery functions with drugs (i.e. ion-drug).[62]

Biodegradable synthetic (poly (lactic-co-glycolic acid) (PLGA) and poly lactic acid (PLA) or natural polymers (chitosan and gelatin) are mainly developed into nanoparticles. For example, drugs for antinociceptive or anti-inflammatory effects were incorporated into biodegradable synthetic nanoparticles for controlled delivery, which revealed high antinociceptive activity and healing process.[63] HA has also been delivered for anti-inflammatory action. HA has the binding ability to CD44 receptor expressed on the surface of chondrocytes which are the major target cell source for regeneration of TMJ.[30] When HA moiety was coated on the surface of the biodegradable polymer while incorporating therapeutic drugs, the targeted delivery to chondrocytes was successful to elicit therapeutic effects.[30,64] A direct use of protein moiety to target cell type was also made with interleukin-1 receptor antagonist (IL-1Ra), which targeted synoviocyte cells in TMJ capsule.[39] The nanoparticles increased the retention time of IL-1Ra in rat joint over 14 days and inhibited IL-1-mediated inflammatory signaling through IL-1Ra and IL-1 receptor

Table 1. Summary of studies regarding intra-articular drug delivery through biomaterials.

No.	Year	Materials	Type	Drug or cell	Test model	Outcome	References
1	2012	Gelatin	Microsphere	Ibuprofen	Rat TMJ	Nociceptive response reduction and sustained drug release	Kramer et al.[25]
2	2009	PLGA + superparamagnetic iron oxide nanoparticles	Microsphere	Dexamethasone	Mice knee	Sustained release and inflammation reduction	Butoescu et al.[26]
3	2009	–	–	TGF-β	Rabbit TMJ	Potential benefit in protecting articular cartilage	Man et al.[27]
4	2009	Hyaluronic acid	Hydrogel	–	TMJ patient	Inflammation reduction and maintenance of improvements over a 6-month follow-up period	Manfredini et al.[28]
5	2009	PLGA + superparamagnetic iron oxide nanoparticles	Microsphere	Dexamethasone	Mice knee	Pronounced retention of magnetic particles and internalization efficiency.	Butoescu et al.[19]
6	2010	–	–	Tenoxicam	Human patient TMJ	Reduced TMJ pain and no complications	Aktas et al.[29]
7	2010	PLGA, PLA, and hyaluronic acid	Nanoparticles	FITC–dextran	Rat knee	No inflammation	Zille et al.[30]
8	2010	PLGA	Microparticles	–	Rat TMJ	Biocompatible and suitable for drug delivery	Mountziaris et al.[31]
9	2011	Hyaluronic acid	Hydrogel	–	Rat TMJ	Inhibiting the progression of osteoarthritic changes	El-Hakim and Elyamani[32]
10	2011	PLGA	Microspheres	Lornoxicam	Rabbit/rat knee	Good efficiency in synovial fluid and prolonged retention	Zhang et al.[33]
11	2011	PLGA	Microspheres	Methylprednisolone	Rat knee	Inflammatory response and prolonged retention	Panusa et al.[34]
12	2011	PC: DOPE: cholesterol:stearylamine	Nanoparticles (liposomes)	Chondroitin sulfate	In vitro	Good interaction with collagen	Zarnescu et al.[35]
13	2011	Chitosan and hyaluronic acid	Nanoparticle	–	In vitro	Safe and effective non-viral vector for gene delivery	Lu et al.[36]
14	2012	–	–	Monosodium iodoacetate	Rat TMJ	Successfully induced OA in TMJ by using MIA and evaluated structure of the TMJ	Wang et al.[37]
15	2012	Genipin-cross-linked chitosan	Microsphere	Flurbiprofen	Rat knee	Prolonged release and biocompatible	Kawadkar et al.[38]
16	2012	Tetraethylene glycol methacrylate and cyclohexyl methacrylate	Nanoparticles	Interleukin-1Ra	Rat knee	No inflammatory response and prolonged retention	Whitmire et al.[39]
17	2012	PLGA	Microsphere	siRNA-PEI	Rat TMJ	Sustain drug release and increased meal duration	Mountziaris et al.[40]
18	2012	–	–	Corticosteroid and triamcinolone hexacetonide	Human patient TMJ	Delivered in the absence of imaging guidance	Stoll et al.[41]
19	2013	–	–	Simvastatin	Rat TMJ	Inhibit inflammatory response	George et al.[42]

Table 1. (Continued)

No.	Year	Materials	Type	Drug or cell	Test model	Outcome	References
20	2013	Sulforaphane and PLGA	Microsphere	–	Rat knee	the significant delay in the progression of OA with the use of SFN-PLGA	Ko et al.[43]
21	2013	PLGA-cross-linked PEG	Microsphere	Brucine	Sheep knee	Decreased degradation rate and slight inflammation	Bédouet et al.[44]
22	2014	PEG	Hydrogel/ microsphere	Ibuprofen	Sheep shoulder	Sustain release for several months	Bédouet et al.[45]
23	2014	–	–	BSP/BDP	Rabbit TMJ	BSP/BDP 0.1–0.3 ml/0.7–1.5 mg range is optimal dose for TMJ OA	Kostina and Valamina[46]
24	2014	–	–	Alendronate	Rat TMJ	Early treatment of alendronate blocked the up-regulation of matrix metalloproteinase (MMP)-13 expression in the chondrocytes	Chen et al.[47]
25	2014	Poly(acrylamide)	Hydrogel	–	Human patient knee	Bio-stable, mechanical cleaning should be performed immediately	Tonbul et al.[48]
26	2015	Hyaluronic acid	Hydrogel	–	Rat knee	Pain release and decreased mechanical hyperalgesia	Ikeuchi et al.[49]
27	2015	–	Steroid	p-Dexamethasone	Rat TMJ	Inflammation reduction and reduced bone density	Knudsen et al.[50]
28	2015	–	–	Triamcinolone acetonide	Knee patient	A clinically relevant improvement in pain relief in patients	Bodick et al.[51]
29	2016	Chitosan/b-glycerophosphate/ hyaluronic acid	Hydrogel	–	Rabbit TMJ	Controllable drug release	Talaat et al.[52]
30	2016	Chitosan	Microsphere	Lornoxicam	Rat knee	Anti-inflammatory effect and biocompatible	Abd-Allah et al.[23]
31	2016	PCL	Microsphere	Etoricoxib	Rat knee	A better drug-retention capacity	Arunkumar et al.[53]
32	2016	–	–	Synovial mesenchymal stem cell	Mouse knee	Improved articular cartilage regeneration	Mak et al.[54]
33	2017	–	–	Adipose mesenchymal stem cell	Human patient knee	Significant improvements in pain levels and function compared with baseline	Pers et al.[55]

PLGA: poly(lactic-co-glycolic acid); PLA: poly lactic acid; PC: phosphatidylcholine; DOPE: dioleoylphosphatidylethanolamine; PEG: polyethylene glycol; PCL: polycaprolactone; TMJ: temporomandibular joint; TGF-β: transforming growth factor beta; FITC: fluorescein isothiocyanate; OA: osteoarthritis; MIA: monosodium iodoacetate; siRNA: small interfering RNA; PEI: poly(ethylenimine); SFN: sulforaphane; BSP: betamethasone sodium phosphate; BMP: betamethasone dipropionate.

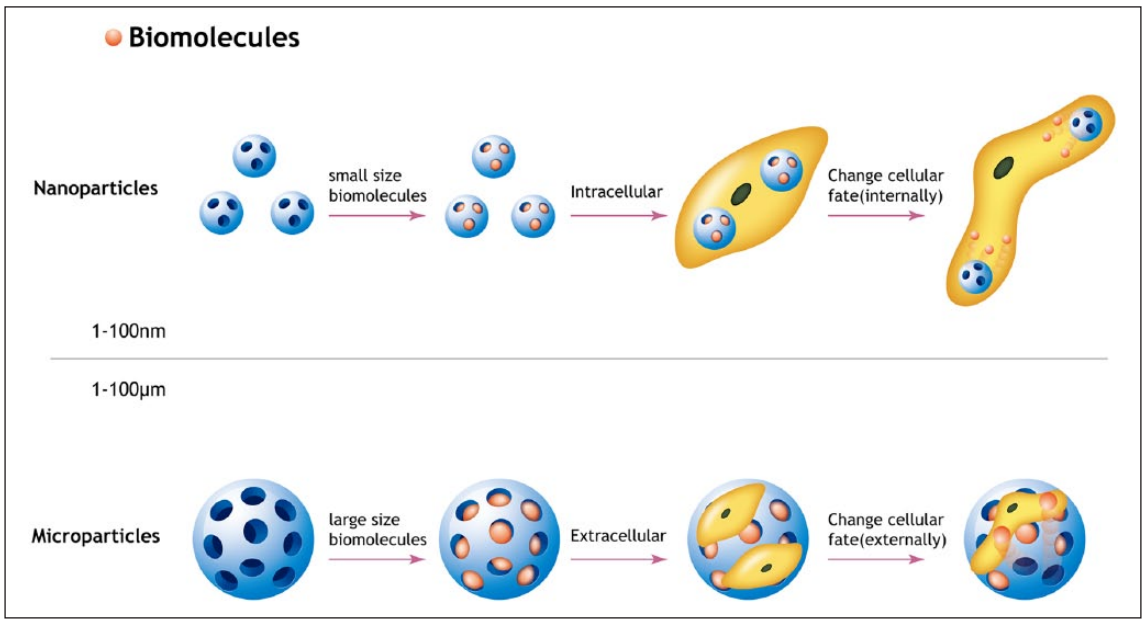

Figure 2. Nano and microparticles have the potential to deliver various biomolecules and drugs and act intracellularly or extracellularly depending on the particle size.

biding. Furthermore, the non-viral gene was delivered via chitosan/HA nanoparticles (100–250 nm), successfully transferring an exogenous gene (~20% for 5 days) into primary chondrocytes for protecting degradation of the cartilage.[36] Collectively, the nanoparticle-based delivery system seems to be suitable for delivering various types of biomolecules (i.e. drugs and genes), releasing them in a controlled manner and even targeting specific cell sources (chondrocytes or synoviocytes) to regenerate TMD.

Recently, mechanical stress or inflammatory reaction in articular tissue is reported to increase reactive oxygen species (ROS) level, leading to cartilage destruction in TMJ.[65,66] Therefore, the control of ROS generation during inflammation is highlighted as one of the strategies to prevent cartilage and bone degradation in TMJ. Antioxidant biomolecules or antioxidant nanoparticles have recently been suggested as potential options for such purposes.[67,68] However, the underlying mechanism is still not clearly understood and further researches regarding the roles of antioxidant and how to combine this with drug delivery strategies aforementioned remain. Moreover, there are some challenges for the clinical uses of nanoparticles developed so far, such as biocompatibility for Food and Drug Administration (FDA) approval and limited physiochemical properties associated with agglomeration, which need further improvement.[69–71]

Microparticle-based drug delivery system

Microparticles have three-dimensional (3D) spherical shapes with sizes of ten to hundreds of micrometers that are suitable to deliver large-sized drugs or biomolecules. In particular, microparticles can be tuned to deliver cells within macro/micro-porous inner structure or onto the surface, enabling co-delivery of cells and biomolecules (or drugs).[72,73] Because of micron-scale, when microparticles contact with cells, they interact mainly extracellularly, unlike the intracellular interaction of nanoparticles. Therefore, intra-articular injected microparticles contact directly with the joint cavity and avoid from the macrophage engulf and removal.[74,75] This allows microparticles to retain in target regions while releasing therapeutic molecules to target cells (i.e. synovial lining cells or chondrocyte). One exemplar study showed that intra-articular injection of dexamethasone-loaded poly (D, L-lactic acid) (PDLA) microspheres (size range, 40–110 μm) in healthy rabbits exhibited no drug detection in the serum over 24 h, suggesting most of the drug successfully localized in the synovial cavity.[76] Small (1–20 μm) biodegradable microspheres presented faster degradation in rabbit joints than large microparticles (35–105 μm), suggesting the importance of microparticle size for TMD applications.[77]

Microparticles are a good candidate due to their high loading capacity of biomolecules and controllable release benefited from different morphologies (bulk, porous, and hollow, etc.) or functionalization. Typical composition of microparticles varies from synthetic (polycaprolactone (PCL), poly(L-lactide) (PLLA), PLGA, poly (propylene sulfide) (PPS), and (polyphosphazene based)[56] to natural polymers (collagen, gelatin, alginate, HA, and chitosan).[78] Common drugs loaded in microparticles are steroidal (i.e. methylprednisolone and dexamethasone) and NSAIDs (i.e. ibuprofen, flurbiprofen, lornoxicam, and brucine). Besides, anti-inflammatory small interfering RNA (siRNA) was also used with PLGA microspheres functionalized with poly(ethylenimine) (PEI), and the system

demonstrated a controllable release of siRNA, consequently reducing inflammation in TMJ.[40,43]

Compared with solid microparticles, hydrogel microparticles are often preferred because they can provide extracellular matrix (ECM) mimicking native tissues.[79] Alginate-based hydrogel microparticles were first introduced due to their good biocompatibility and easy process to fabricate.[80,81] Other biopolymers such as PLGA, HA, and PLLA were also developed into hydrogel microparticles. Bédouet et al.[44] designed nondegradable or degradable polyethylene glycol (PEG) hydrogel depending on the type of cross-linker to evaluate degradability and the consequent inflammatory response when delivered to the shoulder joint. After 4 weeks' implantation in sheep shoulder joint, histological analysis presented degradable PEG hydrogel microparticles cross-linked by (PLGA–tri ethylene glycol (TEG)–PLGA) dimethacrylate indicated less inflammatory cells around compared with nondegradable hydrogel control. The covalent bond between drug and polymer can sustain the releases. Degradable PLGA-PEG (40–100 µm) hydrogel microparticles were functionalized with a methacrylic derivative of ibuprofen drug using a degradable cross-linker oligo(ethylene-glycol) methacrylate and poly(PLGA-PEG) dimethacrylate. Ibuprofen loaded in PEG hydrogel microparticles by a covalent bond showed reduced burst release and more sustained release up to months, resulting in the enhanced preservation of the anti-inflammatory response and cyclooxygenase-inhibition.[45,82]

Furthermore, microparticles have the potential to deliver or tune stem cells due to their large surface area and tailored 3D architecture where cells adhere and differentiate into specific cell lineage. The microparticles also release biomolecules while the cell-produced ECM can mimic host environment for less anti-inflammatory and enhanced healing process.[73,83] Therefore, microparticles as cell carriers have been used also in TMD area, which described in the following section.

However, some challenges still exist for the clinical applications of microparticles. For instance, large diameter gauge for injection can induce pain during procedures, and limited amounts of microparticles for small articular space can restrict therapeutic functionality.[11,84] Also, the in vivo biocompatibility of microparticles associated with their derivatives/byproducts and the possible fragmentation makes it difficult to get the FDA approval.[19,53,85]

Intra-articular stem cell delivery

Stem cells self-renew and differentiate to target cells, and produce ECMs that are favorable for regenerative process.[86] Therefore, stem cell–based therapies have the potential to bring substantial benefit to patients suffering a wide range of diseases and injuries.[87] Many studies have tried for different tissues including heart, bone, tendon, and neuron, and some stem cell therapies were FDA-approved for clinical uses.[88] Given the potential of this strategy, a lot of effort has also been dedicated to TMD through intra-articular delivery with or without biomaterials.

The majority of TMJ structures derive from mesenchymal cells during morphogenesis. Mesenchymal stem cells (MSCs) maintain physiologically for tissue remodeling/turnover and, upon injury or disease, differentiate into target tissue including cartilage, bone, ligaments, and musculature to start tissue repair/regeneration. MSCs isolated from synovial fluid in TMJ have markers typically including CD44, CD73, CD90, and CD 105 but not the hematopoietic stem cells markers such as CD34 and CD45.[89] Among the stem cell sources, MSCs from TMJ, knee joints, bone marrow, adipose tissue, and dental pulp has been widely used for intra-articular injections.[54,55] More recently, MSCs differentiated from induced pluripotent stem cells (iPSCs) were suggested as a candidate cell source due to the noninvasive cell collection (i.e. from skin) and unlimited self-renewal capacity of iPSCs.[90] Of course, synovium-derived MSCs displayed superiority in proliferation and differentiation to chondrocytes compared with MSCs from other tissues, supporting the beneficial use of these cells for TMJ repair and regeneration.[91,92] Cell density also matters in the tissue regeneration of TMJ. An unsatisfactory tissue maturation was made using a low number of pre-differentiated MSCs (5×10^6 cells/mL) in immune-deficient mice, whereas tissue maturation and osteochondral integration were made using high number of pre-differentiated MSCs (20×10^6 cells/mL).[93,94] At present, clinical study to optimize MSCs number for TMJ regeneration is under investigation, while intra-articular injection for treatment of osteoarthritis of the knee was recently made clinically. The low-dose (1.0×10^7 cells), mid-dose (5.0×10^7), and high-dose (1.0×10^8) groups, the high-dose of adipose tissue derived MSCs into the osteoarthritic knee, improved function with regeneration of hyaline-like articular cartilage, and reduced pain of the knee joint without causing adverse events.[95]

However, acute donor-cell death within a short period after cell delivery remains a critical hurdle for clinical translation. Biomaterials including micro/nanoparticles offer a potential vehicle for an effective delivery and maintaining cells close to implanted tissue while driving cellular fate into a target lineage (Figure 3).[96–98] Recently, the in vivo differentiation or survival of stem cell grafts has been proposed by the controlled release of biomolecules conjugated to injected micro/nanoparticles; growth factors (i.e. betamethasone dipropionate (BMP)-2, basic fibroblast growth factor (bFGF), or transforming growth factor beta (TGF-β)) and drugs (i.e. dexamethasone, corticosteroid, or other single chemicals).[99] In another approach, pre-differentiated MSCs into certain cell lineages (chondrocyte or osteoblast) by in vitro culture with micro/nanoparticles were utilized for the advanced MSCs delivery strategy due to the enhanced biological interaction of pre-differentiated MSCs to a target tissue. As to the type of other carriers

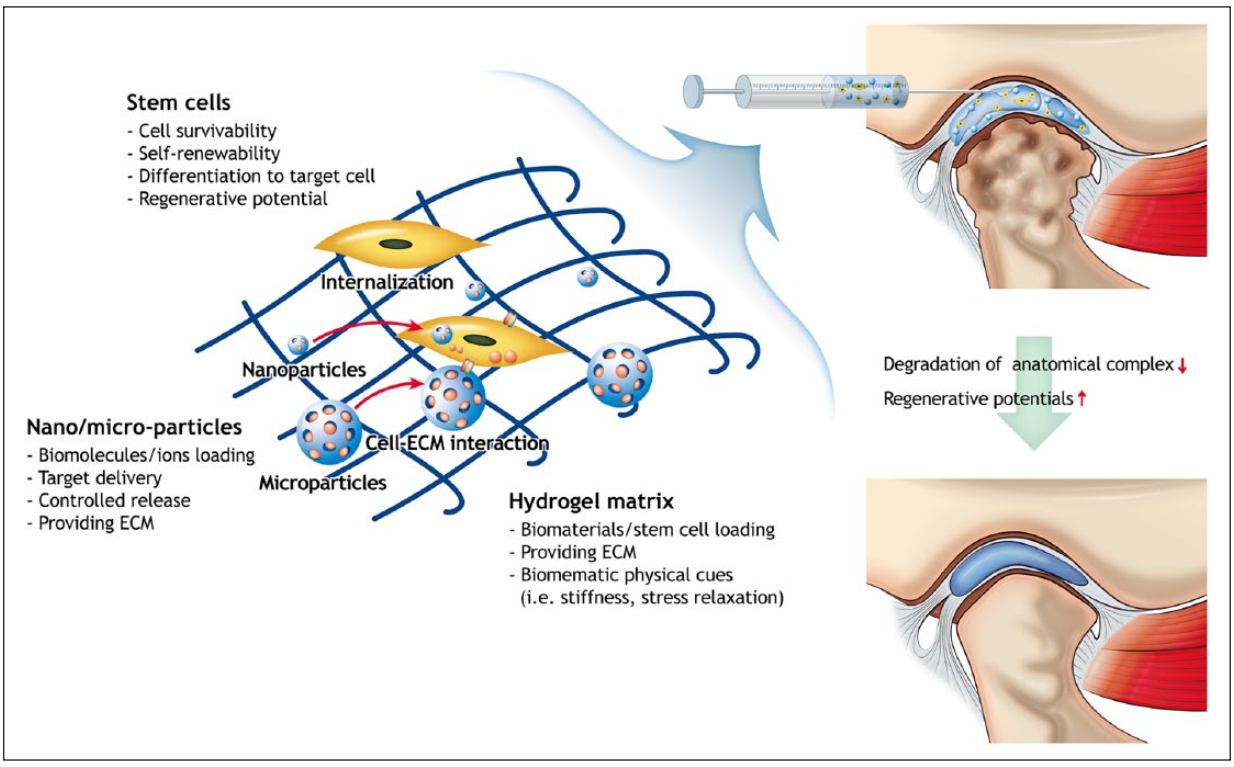

Figure 3. Intra-articular stem cell delivery with nano/microparticles for accelerating the regeneration of damaged TMJ.

such as 3D scaffolds and their use as stem cell delivery for TMD, readers are recommended to a reference.[7]

For intra-articular delivery of stem cells, typical hydrogel-based microparticles were initially utilized, which allow injection after gelation. However, the cell-loading capacity to conventional hydrogels is limited because incorporation of stem cells increases viscosity and thereby leads to decrease of injectability of mixture and stem cells delivered. To enhance loading capacity of stem cells, in situ forming hydrogels have been developed and evaluated to encapsulate stem cells more.

In situ forming hydrogels were revealed to encapsulate stem cells more and even homogeneously due to their solution state when injected, which become gel in body temperature (~37°C) or normal pH conditions (~7).[100] Poly(*N*-isopropylacrylamide) (PNIPAM), polyesters, chitosan, polyphosphazenes, polycarbonates, polycyanoacrylates, polyorthoesters, poly(ethylene glycol)-b-poly(L-alanine), polypeptides, and their composite hydrogels have been developed.[101,102] When the thermo-sensitive in situ forming gels can deliver biomolecules for chondrocyte targeting, the effects are synergized. For example, chitosan-based thermo-sensitive hydrogel incorporated with HA and beta-glycerophosphate was used for intra-articular injectable vehicles to the TMJ in a rabbit model. The hydrogel could release therapeutic biomolecules (HA and beta-glycerophosphate) with improved stability.[52] Besides, on demand gelation from external stimuli, including magnetism or heating over body temperature (~40°C), is another promising tool to improve stem cells delivery/differentiation potential from hydrogel-based microparticles.[103] These findings highlight that the intra-articular injected degradable hydrogel microparticles stay in synovial cavity up to a few months while delivering biomolecules to the inflamed joint and providing ECM structure for TMJ regeneration, not scavenged by macrophages.

In particular, the hydrogels can be designed to have chemical (ECM composition; for example, collagen type 1 and glycosaminoglycans (GAGs)) or physical properties (e.g. stiffness and stress relaxation) that can mimic the TMJ tissues.[58,104] Among them, the static stiffness value has been a key factor in hydrogels until the emergence of stress relaxation, a time-dependent stress change.[105] This stress relaxation mimics the viscoelastic responses of ECM in the target tissue, determining cellular mechanotransduction and consequent ECM-integrin networks remodeling. Recently, the stress relaxation effects were revealed on chondrocytes behaviors; the chondrocytes in rapidly relaxing hydrogels could produce cartilage ECM significantly, whereas those in slowly relaxing hydrogels suffered limited volume expansion due to persistent elastic stresses from the surrounding matrix, leading to a degeneration of cartilage.[106] Taken some of the recent key findings related to tunable physical/chemical properties, in situ forming hydrogels with TMJ mimic stiffness and stress relaxation may be promising for future stem cell delivery and regeneration of TMD.

With the advance in nanotechnology, clinicians experience the significant therapeutic potential of stem cells through nanoparticle delivery, and at the same time faces the need to reduce harmful side effects related to nanoparticles.[84,107] Nanoparticles are biomedical materials developed to host and deliver therapeutic and diagnostic molecules, ranging from drugs, peptides, proteins, genetic molecules, ions, or their combination, intracellularly or extracellularly.[62,107] Especially, when nanoparticles are co-delivered with stem cells through an intra-articular injection, they internalize by endocytosis and the loaded therapeutic molecules intracellularly functioning are efficiently delivered to specific cellular components such as mitochondria and nucleus, possibly accelerating their carrier performance and the biological fate for TMJ regeneration.[108] Nanoparticles can also be incorporated into hydrogel-based microparticles that support and deliver stem cells. Such a combinatory approach remains as a promising future study for the therapeutic treatment of TMD through biomaterial-based intra-articular delivery.

Concluding remarks

TMD is considered one of the complex joint diseases caused by inflammation and irreversible degeneration, degrading the quality of life associated with malfunctions in chewing and opening mouth. Intra-articular injection, albeit highlighted as a minimally invasive clinical treatment, still suffers low regenerative potential of single injection or complications from the repeated injection. With the development of injectable biomaterials (nano/microparticles and hydrogels), the intra-articular injection holds great promise for therapeutic roles in TMD with the effective and controlled delivery of drugs and stem cells. More in vitro and animal studies to optimize the compositions and formulations of injections will gain clinical acceptance in the near future.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Science, ICT & Future Planning (2015R1C1A1A01052127 and 2018R1A2B3003446).

References

1. Embree MC, Chen M, Pylawka S, et al. Exploiting endogenous fibrocartilage stem cells to regenerate cartilage and repair joint injury. *Nat Commun* 2016; 7: 1–13.
2. Ledogar JA, Smith AL, Benazzi S, et al. Mechanical evidence that Australopithecus sediba was limited in its ability to eat hard foods. *Nat Commun* 2016; 7: 1–9.
3. Murphy MK, Macbarb RF, Wong ME, et al. Temporomandibular joint disorders: a review of etiology, clinical management, and tissue engineering strategies HHS public access. *Int J Oral Maxillofac Implants* 2013; 28: 393–414.
4. Stoustrup P, Kristensen KD, Verna C, et al. Intra-articular steroid injection for temporomandibular joint arthritis in juvenile idiopathic arthritis: a systematic review on efficacy and safety. *Semin Arthritis Rheum* 2013; 43: 63–70.
5. Chu WC, Zhang S, Sng TJ, et al. Distribution of pericellular matrix molecules in the temporomandibular joint and their chondroprotective effects against inflammation. *Int J Oral Sci* 2017; 9: 43–52.
6. Liu HX, Liang QJ, Xiao P, et al. The effectiveness of cognitive-behavioural therapy for temporomandibular disorders: systematic review. *J Oral Rehabil* 2012; 39: 55–62.
7. Van Bellinghen X, Idoux-Gillet Y, Pugliano M, et al. Temporomandibular joint regenerative medicine. *Int J Mol Sci* 2018; 19: 446.
8. Samuelson WM, Peterson K, Mahon RT, et al. TMJ diseases and disorders: difficult but not impossible to solve. *Chest* 2004; 126: S705–S787.
9. Mujakperuo Helen R, Watson M, Morrison R, et al. Pharmacological interventions for pain in patients with temporomandibular disorders. *Cochrane Database Syst Rev* 2010; 10: CD004715.
10. Qi X, Qin X, Yang R, et al. Intra-articular administration of chitosan thermosensitive in situ hydrogels combined with diclofenac sodium-loaded alginate microspheres. *J Pharm Sci* 2016; 105: 122–130.
11. Huang G and Zhang Z. Micro- and nano-carrier mediated intra-articular drug delivery systems for the treatment of osteoarthritis. *J Nanotechnol* 2012; 2012: 748909.
12. Kim C, Jeon OH, Kim DH, et al. Local delivery of a carbohydrate analog for reducing arthritic inflammation and rebuilding cartilage. *Biomaterials* 2016; 83: 93–101.
13. Roy ME and Nayfeh TA. Intra-articular infusion knee arthroplasty. *Bone Joint J* 2016; 98: 31–36.
14. Henry DA. Side-effects of non-steroidal anti-inflammatory drugs. *Baillieres Clin Rheumatol* 1988; 2: 425–454.
15. Sostres C, Gargallo CJ, Arroyo MT, et al. Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs, aspirin and coxibs) on upper gastrointestinal tract. *Best Pract Res Clin Gastroenterol* 2010; 24: 121–132.
16. Inagaki T, Miyaoka T, Shinno H, et al. Treatment of temporomandibular pain with the selective serotonin reuptake inhibitor paroxetine. *Prim Care Companion J Clin Psychiatry* 2007; 9: 69–70, http://www.ncbi.nlm.nih.gov/pubmed/17599175 (accessed 18 April 2018).
17. Chinnagounder Periyasamy P, Leijten JCH, Dijkstra PJ, et al. Nanomaterials for the local and targeted delivery of osteoarthritis drugs. *J Nanomater* 2012; 2012: 673968.
18. Arakeri G and Brennan PA. Dose-dependent sustained local release of dexamethasone from biodegradable thermosensitive hydrogel of PEG-PLGA-PEG triblock copolymers in the possible prevention of TMJ re-ankylosis (Arakeri's TMJ release technique). *Med Hypotheses* 2012; 78: 682–686.
19. Butoescu N, Jordan O, Burdet P, et al. Dexamethasone-containing biodegradable superparamagnetic microparticles

for intra-articular administration: physicochemical and magnetic properties, in vitro and in vivo drug release. *Eur J Pharm Biopharm* 2009; 72: 529–538.
20. Allen KD, Adams SB and Setton LA. Evaluating intra-articular drug delivery for the treatment of osteoarthritis in a rat model. *Tissue Eng Part B Rev* 2010; 16: 81–92.
21. Komano Y, Yagi N, Onoue I, et al. Arthritic joint-targeting small interfering RNA-encapsulated liposome: implication for treatment strategy for rheumatoid arthritis. *J Pharmacol Exp Ther* 2012; 340: 109–113.
22. Wason MS and Zhao J. Cerium oxide nanoparticles: potential applications for cancer and other diseases. *Am J Transl Res* 2013; 5: 126–131.
23. Abd-Allah H, Kamel AO and Sammour OA. Injectable long acting chitosan/tripolyphosphate microspheres for the intra-articular delivery of lornoxicam: optimization and in vivo evaluation. *Carbohydr Polym* 2016; 149: 263–273.
24. Willard VP. Tissue engineering of the temporomandibular joint. In: Ducheyne P, Healy K, Hutmacher DW, et al. (eds) *Comprehensive biomaterials*. New York: Elsevier, 2011, pp. 221–235.
25. Kramer PR, Windsor B, Carson K, et al. Cross-linked gelatin microcapsules for drug delivery in a arthritic TMJ, 2012. DOI: 10.5772/27800.
26. Butoescu N, Seemayer CA, Foti M, et al. Dexamethasone-containing PLGA superparamagnetic microparticles as carriers for the local treatment of arthritis. *Biomaterials* 2009; 30: 1772–1780.
27. Man C, Zhu S, Zhang B, et al. Protection of articular cartilage from degeneration by injection of transforming growth factor-beta in temporomandibular joint osteoarthritis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009; 108: 335–340.
28. Manfredini D, Bonnini S, Arboretti R, et al. Temporomandibular joint osteoarthritis: an open label trial of 76 patients treated with arthrocentesis plus hyaluronic acid injections. *Int J Oral Maxillofac Surg* 2009; 38: 827–834.
29. Aktas I, Yalcin S and Sencer S. Intra-articular injection of tenoxicam following temporomandibular joint arthrocentesis: a pilot study. *Int J Oral Maxillofac Surg* 2010; 39: 440–445.
30. Zille H, Paquet J, Henrionnet C, et al. Evaluation of intra-articular delivery of hyaluronic acid functionalized biopolymeric nanoparticles in healthy rat knees. *Biomed Mater Eng* 2010; 20: 235–242.
31. Mountziaris PM, Sing DC, Mikos AG, et al. Intra-articular microparticles for drug delivery to the TMJ. *J Dent Res* 2010; 89: 1039–1044.
32. El-Hakim IE and Elyamani AO. Preliminary evaluation of histological changes found in a mechanical arthropatic temporomandibular joint (TMJ) exposed to an intra-articular hyaluronic acid (HA) injection, in a rat model. *J Cranio-Maxillofacial Surg* 2011; 39: 610–614.
33. Zhang Z, Bi X, Li H, et al. Enhanced targeting efficiency of PLGA microspheres loaded with lornoxicam for intra-articular administration. *Drug Deliv* 2011; 18: 536–544.
34. Panusa A, Selmin F, Rossoni G, et al. Methylprednisolone-loaded PLGA microspheres: a new formulation for sustained release via intra-articular administration. A comparison study with methylprednisolone acetate in rats. *J Pharm Sci* 2011; 100: 4580–4586.
35. Zarnescu O, Moldovan L, Trif M, et al. Light and electron microscopy characterization of a collagen–liposome-entrapped chondroitin sulfate composite as intra-articular drug delivery system. *J Control Release* 2011; 152: e113–e114.
36. Lu HD, Zhao HQ, Wang K, et al. Novel hyaluronic acid-chitosan nanoparticles as non-viral gene delivery vectors targeting osteoarthritis. *Int J Pharm* 2011; 420: 358–365.
37. Wang XD, Kou XX, He DQ, et al. Progression of cartilage degradation, bone resorption and pain in rat temporomandibular joint osteoarthritis induced by injection of iodoacetate. *PLoS ONE* 2012; 7: e45036.
38. Kawadkar J, Jain R, Kishore R, et al. Formulation and evaluation of flurbiprofen-loaded genipin cross-linked gelatin microspheres for intra-articular delivery. *J Drug Target* 2013; 21: 200–210.
39. Whitmire RE, Scott Wilson D, Singh A, et al. Self-assembling nanoparticles for intra-articular delivery of anti-inflammatory proteins. *Biomaterials* 2012; 33: 7665–7675.
40. Mountziaris PM, Tzouanas SN, Sing DC, et al. Intra-articular controlled release of anti-inflammatory siRNA with biodegradable polymer microparticles ameliorates temporomandibular joint inflammation. *Acta Biomater* 2012; 8: 3552–3560.
41. Stoll ML, Good J, Sharpe T, et al. Intra-articular corticosteroid injections to the temporomandibular joints are safe and appear to be effective therapy in children with juvenile idiopathic arthritis. *J Oral Maxillofac Surg* 2012; 70: 1802–1807.
42. George MD, Owen CM, Reinhardt AL, et al. Effect of simvastatin injections on temporomandibular joint inflammation in growing rats. *J Oral Maxillofac Surg* 2013; 71: 846–853.
43. Ko JY, Choi YJ, Jeong GJ, et al. Sulforaphane-PLGA microspheres for the intra-articular treatment of osteoarthritis. *Biomaterials* 2013; 34: 5359–5368.
44. Bédouet L, Pascale F, Moine L, et al. Intra-articular fate of degradable poly(ethyleneglycol)-hydrogel microspheres as carriers for sustained drug delivery. *Int J Pharm* 2013; 456: 536–544.
45. Bédouet L, Moine L, Pascale F, et al. Synthesis of hydrophilic intra-articular microspheres conjugated to ibuprofen and evaluation of anti-inflammatory activity on articular explants. *Int J Pharm* 2014; 459: 51–61.
46. Kostina IN and Valamina IE. Microstructure of temporomandibular joint cartilage after intra- articular betamethasone sodium phosphate/betamethasone dipropionate injection during the early stage of experimental osteoarthrosis. *Int J BioMed* 2014; 4: 99–103.
47. Chen K, Zhang N, Ding L, et al. Early intra-articular injection of alendronate reduces cartilage changes and subchondral bone loss in rat temporomandibular joints after ovariectomy. *Int J Oral Maxillofac Surg* 2014; 43: 996–1004.
48. Tonbul M, Adas M, Bekmezci T, et al. Intra-articular polyacrylamide hydrogel injections are not innocent. *Case Rep Orthop* 2014; 2014: 150709.
49. Ikeuchi M, Izumi M, Aso K, et al. Effects of intra-articular hyaluronic acid injection on immunohistochemical characterization of joint afferents in a rat model of knee osteoarthritis. *Eur J Pain* 2015; 19: 334–340.
50. Knudsen M, Bury M, Holwegner C, et al. Effect of dexamethasone prodrug on inflamed temporomandibular joints in juvenile rats. *Arthritis Res Ther* 2015; 17: 267.

51. Bodick N, Lufkin J, Willwerth C, et al. An intra-articular, extended-release formulation of triamcinolone acetonide prolongs and amplifies analgesic effect in patients with osteoarthritis of the knee. *J Bone Joint Surg Am* 2015; 97: 877–888.
52. Talaat W, Haider M, Al Kawas S, et al. Chitosan-based thermosensitive hydrogel for controlled drug delivery to the temporomandibular joint. *J Craniofac Surg* 2016; 27: 735–740.
53. Arunkumar P, Indulekha S, Vijayalakshmi S, et al. Poly (caprolactone) microparticles and chitosan thermogels based injectable formulation of etoricoxib for the potential treatment of osteoarthritis. *Mater Sci Eng C* 2016; 61: 534–544.
54. Mak J, Jablonski CL, Leonard CA, et al. Intra-articular injection of synovial mesenchymal stem cells improves cartilage repair in a mouse injury model. *Sci Rep* 2016; 6: 23076.
55. Pers YM, Rackwitz L, Ferreira R, et al. Adipose mesenchymal stromal cell-based therapy for severe osteoarthritis of the knee. *Stem Cells Transl Med* 2016; 5: 847–856.
56. Mountziaris PM, Kramer PR and Mikos AG. Emerging intra-articular drug delivery systems for the temporomandibular joint. *Methods* 2009; 47: 134–140.
57. Tanaka E, Detamore MS and Mercuri LG. Degenerative disorders of the temporomandibular joint: etiology, diagnosis, and treatment. *J Dent Res* 2008; 87: 296–307.
58. Pérez RA, Won JE, Knowles JC, et al. Naturally and synthetic smart composite biomaterials for tissue regeneration. *Adv Drug Deliv Rev* 2013; 65: 471–496.
59. Janssen M, Mihov G, Welting T, et al. Drugs and polymers for delivery systems in OA joints: clinical needs and opportunities. *Polymers* 2014; 6: 799–819.
60. Stoustrup P, Kristensen KD, Küseler A, et al.Intra-articular vs. systemic administration of etanercept in antigen-induced arthritis in the temporomandibular joint. Part II: mandibular growth. *Pediatr Rheumatol Online J* 2009; 7: 6.
61. De Jong WH and Borm PJA. Drug delivery and nanoparticles: applications and hazards. *Int J Nanomedicine* 2008; 3: 133–149.
62. Seo SJ, Chen M, Wang H, et al. Extra- and intra-cellular fate of nanocarriers under dynamic interactions with biology. *Nano Today* 2017; 14: 84–99.
63. Clemente-Napimoga JT, Moreira JA, Grillo R, et al. 15d-PGJ2-loaded in nanocapsules enhance the antinociceptive properties into rat temporomandibular hypernociception. *Life Sci* 2012; 90: 944–949.
64. Detamore MS and Athanasiou KA. Evaluation of three growth factors for TMJ disc tissue engineering. *Ann Biomed Eng* 2005; 33: 383–390.
65. Lee MC, Kawai Y, Shoji H, et al. Evidence of reactive oxygen species generation in synovial fluid from patients with temporomandibular disease by electron spin resonance spectroscopy. *Redox Rep* 2004; 9: 331–336.
66. Kawai Y, Kubota E and Okabe E. Reactive oxygen species participation in experimentally induced arthritis of the temporomandibular joint in rats. *J Dent Res* 2000; 79: 1489–1495.
67. Ponnunrangam S, O'Connell G, Chernyshova IV, et al. Beneficial effects of cerium oxide nanoparticles in development of chondrocyte-seeded hydrogel constructs and cellular response to interleukin insults. *Tissue Eng Part A* 2014; 20: 1–39.
68. Hirst SM, Karakoti AS, Tyler RD, et al. Anti-inflammatory properties of cerium oxide nanoparticles. *Small* 2009; 5: 2848–2856.
69. Rizzello L, Cingolani R and Pompa PP. Nanotechnology tools for antibacterial materials. *Nanomedicine* 2013; 8: 807–821.
70. Eichaker LR, Cho H, Duvall CL, et al. Future nanomedicine for the diagnosis and treatment of osteoarthritis. *Nanomedicine* 2014; 9: 2203–2215.
71. Rubinstein I and Weinberg GL. Nanomedicines for chronic non-infectious arthritis: the clinician's perspective. *Nanomedicine* 2012; 8(Suppl 1): S77–S82.
72. Dashnyam K, Jin GZ, Kim JH, et al. Promoting angiogenesis with mesoporous microcarriers through a synergistic action of delivered silicon ion and VEGF. *Biomaterials* 2017; 116: 145–157.
73. Park JH, Pérez RA, Jin GZ, et al. Microcarriers designed for cell culture and tissue engineering of bone. *Tissue Eng Part B Rev* 2013; 19: 172–190.
74. Kang ML, Ko JY, Kim JE, et al. Intra-articular delivery of kartogenin-conjugated chitosan nano/microparticles for cartilage regeneration. *Biomaterials* 2014; 35: 9984–9994.
75. Mountziaris PM, Sing DC, Chew SA, et al. Controlled release of anti-inflammatory siRNA from biodegradable polymeric microparticles intended for intra-articular delivery to the temporomandibular joint. *Pharm Res* 2011; 28: 1370–1384.
76. Ramesh DV, Tabata Y and Ikada Y. Biodegradable microspheres for local drug release in the articulus. *J Bioact Compt Polym* 1999; 14: 137–149.
77. Liggins RT, Cruz T, Min W, et al. Intra-articular treatment of arthritis with microsphere formulations of paclitaxel: biocompatibility and efficacy determinations in rabbits. *Inflamm Res* 2004; 53: 363–372.
78. Wang X, Schröder HC, Feng Q, et al. The deep-sea natural products, biogenic polyphosphate (bio-polyp) and biogenic silica (bio-silica), as biomimetic scaffolds for bone tissue engineering: fabrication of a morphogenetically-active polymer. *Mar Drugs* 2013; 11: 718–746.
79. Khunmanee S, Jeong Y and Park H. Crosslinking method of hyaluronic-based hydrogel for biomedical applications. *J Tissue Eng* 2017; 8: 2041731417726464.
80. Sun J and Tan H. Alginate-based biomaterials for regenerative medicine applications. *Materials* 2013; 6: 1285–1309.
81. Kong HJ, Smith MK and Mooney DJ. Designing alginate hydrogels to maintain viability of immobilized cells. *Biomaterials* 2003; 24: 4023–4029.
82. Kim HK, Chung HJ and Park TG. Biodegradable polymeric microspheres with "open/closed" pores for sustained release of human growth hormone. *J Control Release* 2006; 112: 167–174.
83. Cai Y, Chen Y, Hong X, et al. Porous microsphere and its applications. *Int J Nanomedicine* 2013; 8: 1111–1120.
84. Dashnyam K, El-Fiqi A, Buitrago JO, et al. A mini review focused on the proangiogenic role of silicate ions released from silicon-containing biomaterials. *J Tissue Eng* 2017; 8: 2041731417707339.
85. Palmieri G, Rinaldi A, Campagnolo L, et al. Hyaluronic acid nanoporous microparticles with long in vivo joint

residence time and sustained release. *Part Part Syst Charact* 2017; 34: 1600411.
86. Trounson A and McDonald C. Stem cell therapies in clinical trials: progress and challenges. *Cell Stem Cell* 2015; 17: 11–22.
87. Chalisserry EP, Nam SY, Park SH, et al. Therapeutic potential of dental stem cells. *J Tissue Eng* 2017; 8: 2041731417702531.
88. Segers VFM and Lee RT. Stem-cell therapy for cardiac disease. *Nature* 2008; 451: 937–942.
89. Sun YP, Zheng YH, Liu WJ, et al. Synovium fragment-derived cells exhibit characteristics similar to those of dissociated multipotent cells in synovial fluid of the temporomandibular joint. *PLoS ONE* 2014; 9: e101896.
90. Zheng X, Carstens JL, Kim J, et al. Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. *Nature* 2015; 527: 525–530.
91. Yoshimura SI, Egerer J, Fuchs E, et al. Functional dissection of Rab GTPases involved in primary cilium formation. *J Cell Biol* 2007; 178: 363–369.
92. Somuncu ÖS, Taşlı PN, Şişli HB, et al. Characterization and differentiation of stem cells isolated from human newborn foreskin tissue. *Appl Biochem Biotechnol* 2015; 177: 1040–1054.
93. Alhadlaq A and Mao JJ. Mesenchymal stem cells: isolation and therapeutics. *J Stem Cells Dev* 2004; 13: 436–448.
94. Stosich MS and Mao J. Stem cell–based soft tissue grafts for plastic and reconstructive surgeries. *Current* 2005; 19: 251–260.
95. Jo C, Lee Y and Shin W. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. *Stem Cells* 2014; 32: 1254–1266.
96. Lee AS, Inayathullah M, Lijkwan MA, et al. Prolonged survival of transplanted stem cells after ischaemic injury via the slow release of pro-survival peptides from a collagen matrix. *Nat Biomed Eng* 2018; 2: 104–113.
97. Donnelly H, Smith C-A, Sweeten PE, et al. Bone and cartilage differentiation of a single stem cell population driven by material interface. *J Tissue Eng* 2017; 8: 2041731417705615.
98. Sancho-Tello M, Martorell S, Mata Roig M, et al. Human platelet-rich plasma improves the nesting and differentiation of human chondrocytes cultured in stabilized porous chitosan scaffolds. *J Tissue Eng* 2017; 8: 2041731417697545.
99. Uchida T, Shirasawa M, Ware LB, et al. Receptor for advanced glycation end-products is a marker of type I cell injury in acute lung injury. *Am J Respir Crit Care Med* 2006; 173: 1008–1015.
100. Chung HJ and Park TG. Self-assembled and nanostructured hydrogels for drug delivery and tissue engineering. *Nano Today* 2009; 4: 429–437.
101. Yun EJ, Yon B, Joo MK, et al. Cell therapy for skin wound using fibroblast encapsulated poly(ethylene glycol)-poly(L-alanine) thermogel. *Biomacromolecules* 2012; 13: 1106–1111.
102. Liow SS, Dou Q, Kai D, et al. Thermogels: in situ gelling biomaterial. *ACS Biomater Sci Eng* 2016; 2: 295–316.
103. Zhao Q, Chen W, Chen Y, et al. Self-assembled virus-like particles from rotavirus structural protein VP6 for targeted drug delivery. *Bioconjug Chem* 2011; 22: 346–352.
104. Engler AJ, Sen S, Sweeney HL, et al. Matrix elasticity directs stem cell lineage specification. *Cell* 2006; 126: 677–689.
105. Chaudhuri O, Gu L, Darnell M, et al. Substrate stress relaxation regulates cell spreading. *Nat Commun* 2015; 6: 1–7.
106. Lee HP, Gu L, Mooney DJ, et al. Mechanical confinement regulates cartilage matrix formation by chondrocytes. *Nat Mater* 2017; 16: 1243–1251.
107. Lee JH, El-Fiqi A, Mandakhbayar N, et al. Drug/ion co-delivery multi-functional nanocarrier to regenerate infected tissue defect. *Biomaterials* 2017; 142: 62–76.
108. Lee JH, Mandakhbayar N, El-Fiqi A, et al. Intracellular co-delivery of Sr ion and phenamil drug through mesoporous bioglass nanocarriers synergizes BMP signaling and tissue mineralization. *Acta Biomater* 2017; 60: 93–108.