Functional articular cartilage repair: here, near, or is the best approach not yet clear?

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Abstract | In this Review we describe three approaches for cartilage tissue repair at the rheumatology–orthopaedics interface: disease-modifying osteoarthritis (OA) drug (DMOAD) treatment; cell-based therapies, and intrinsic cartilage repair by joint distraction. DMOADs can slow the progression of joint damage. Cell-based therapies have evolved to do the same, through selection of the most potent cell types (and combinations thereof), as well as identification of permissive boundary conditions for indications. Joint distraction techniques, meanwhile, have now demonstrated the capacity to stimulate actual intrinsic tissue repair. Although this progress is promising, true biological joint reconstruction remains distant on the developmental pathway of 'regenerative medicine'. Prolonged functional repair—that is, cure of diseases such as OA—remains an unmet medical need and scientific challenge, for which comparative and constructive interaction between these physical, chemical and cellular approaches will be required. Careful selections of patients and combinations of approaches will need to be made and tested to demonstrate their cost-effectiveness. Only with such rational and integrated assessment of outcomes will the promising results of these approaches be consolidated in clinical practice.

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Introduction

For centuries, the dogma has been that cartilage repair is an unattainable goal. Bone, the support for articular cartilage, is considered to be a substantially more dynamic tissue than cartilage, whereas modulation of tissue inflammation in the synovial lining of joints has proven to be feasible. These three tissues are strongly interrelated and together govern joint homeostasis—biochemically and mechanically determining tissue activity, turnover, and the capacity for repair. Classically, rheumatology encompasses biochemical modulation of this homeostasis (through medication) whereas orthopaedics focuses on restoring mechanical homeostasis (through surgery). Within the boundaries of these disciplines, a new field is arising to fill the gap between early and late-stage treatment for joint disorders such as osteoarthritis (OA): the development of cartilage tissue structure-modifying treatments.

Three approaches for cartilage tissue repair at this rheumatology–orthopaedics interface are described in this Review: disease-modifying OA drug (DMOAD) treatment; cell-based therapies, and intrinsic cartilage repair by joint distraction. The progression of joint damage can be slowed by DMOAD therapy as well as through cell-based treatments, which have evolved through selection of the most potent cell types (and combinations thereof), as well as identification of permissive boundary conditions (such as optimum age, lesion size and so on) for surgical cell therapy indications. Now, joint distraction techniques have not only increased the number of potential approaches to cartilage repair, but have also demonstrated the capacity to stimulate actual intrinsic tissue repair. Nevertheless, true biological joint reconstruction remains distant on the developmental pathway of 'regenerative medicine'. Prolonged functional repair—that is, cure of diseases such as OA—remains an unmet medical need and scientific challenge, for which comparative and constructive interaction between these physical, chemical and cellular approaches will be required. Here, we outline progress in DMOAD and cell-based therapies, focusing particularly on studies that support the feasibility of the concept of functional repair of articular cartilage. Next, we comprehensively review data from studies of joint distraction. Finally, we discuss homeostatic mechanisms in the joint and how the different developmental approaches to joint restoration might be combined to elicit the best results.

DMOADs: reality or make-believe?

None of the current potential DMOAD treatments (Table 1) have yet been approved for the treatment of OA by regulatory authorities worldwide, as criteria for approval of a DMOAD include both structural and clinical improvement,[1,2] Although some compounds have slowed structural progression, no symptomatic benefits have been shown. Nonetheless, research into the development of innovative agents persists and some promising findings have been reported.

Competing interests
D. B. F. Saris declares associations with the following companies: Regentis, Sanofi, Smith & Nephew and TiGenix. See the article online for full details of the relationships. S. C. Mastbergen and F. P. J. G. Lafeber declare no competing interests.

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Key points

- The quest for disease-modifying osteoarthritis drugs (DMOADs) is becoming increasingly fruitful; modalities that alter bone turnover—and, indirectly, cartilage damage—seem to be most effective
- Long-term outcomes of cell-based therapies are good; quality has improved with European advanced therapeutic medicinal products regulation; the current goal is combining cartilage components, mesenchymal stem cells and trophic factors into a one-stage therapy
- Joint distraction can induce tissue-structure modification in degenerated knee joints, accompanied by prolonged symptomatic improvement that supports the concept of cartilage repair translating into real clinical benefit
- Joint distraction itself might represent an integrated approach to tackling the separate chondroprotective, chondroreparative and bone turnover-modifying mechanisms targeted by DMOADs and cell-based therapies
- Combining DMOAD and cell-based therapies with joint distraction might be a worthwhile approach towards functional tissue repair, as distraction provides a temporary biomechanical joint homeostasis that facilities repair mechanisms

Approaches to DMOAD development

Unfortunately, no 'gold standard' or reference exists for the development of DMOADs and other tissue structure-modifying approaches. No treatment, including surgical options, has yet resulted in clear cartilage repair of unquestionable quality; thus, a comparison for assessing the clinical efficacy of new tissue structure-modifying therapies is lacking. At preclinical stages, much can be learned from the alteration and modulation of specific pathways in small animal species, including genetically modified mouse models of disease. Larger animal models (such as dogs and goats), however, have the advantage of enabling more detailed whole-joint analyses, including study of the interactions between different tissues facilitating translation of findings to the human situation.[3]

The decision to carry out arthroplasty depends on multiple variables and does not, therefore, constitute a 'hard' primary endpoint for clinical trials.[4–6] Alternative clinical endpoints that assess chondroprotective and reparative activities of potential DMOADs are clearly necessary.[7] High-level biomarker technologies allowing specific, sensitive and quantitative assessments of the turnover status of the joint tissues (synovium, bone, and cartilage) are needed. Joint-space narrowing (JSN) remains the only accepted structural endpoint in trials, despite demonstrations that MRI-based cartilage measurements are more closely associated with OA symptoms than JSN,[8] and are better able to predict knee arthroplasty.[9] Several biochemical markers exist for quantification of the underlying tissue degeneration and formation. Initiatives such as the BIPED (Burden of Disease, Investigative, Prognostic, Efficacy of Intervention and Diagnostic) biomarker classification provide specific biomarker definitions and improve our ability to develop and analyze biomarkers[10] and, as such, our search for tissue structure-modifying activity. Clearly, improvements of imaging, including radiography, as well as biomarker technologies are prerequisite for the field of tissue regeneration to advance.

Current most promising DMOADs

New mediators and pathways relevant to OA are continually being discovered. As such, several promising DMOADs are under development (Table 2; extensive reviews of DMOADs have been published in this journal[11] and elsewhere[12]).

Table 1 | Completed trials of potential DMOADs

Compound (trial sponsor)	Study*	Participants‡, duration and dosage	Primary endpoint	Outcome
Risedronate	BRISK: Spector *et al.* (2005)[121] KOSTAR: Bingham *et al.* (2004)[4]	*n* ≈ 95 per group, 1 year, 5 & 15 mg daily *n* ≈ 305 per arm, 2 years, 5 mg & 15 mg qd, 35 mg/week (in Europe) & 50 mg/week (in the USA)	JSN+WOMAC/ PGA	Both studies found no significant difference from placebo for any of the regimens used
Doxycycline	Brandt *et al.* (2005)[122]	*n* ≈ 215 per group, 2.5 years, 100 mg doxycycline bid	JSN	30% reduction in JSN with treatment, compared with placebo (0.30 mm vs 0.45 mm JSN, *P* <0.009)
Glucosamine sulfate (Rottapharm)	Pavelká *et al.* (2002)[123]	*n* = 100 per group, 3 years, 1,500 mg GS qd	JSN	Significant reduction in JSN with treatment, compared with placebo (0.04 mm JSN vs –0.19 mm JSN *P* <0.01)
Chondroitin sulfate (IBSA)	STOPP: Kahan *et al.* (2009)[124]	*n* ≈ 310 per group, 2 years, 800 mg CS qd	JSN	Significant reduction in JSN with treatment compared with placebo (–0.07 vs –0.31 mm *P* <0.0001)
Glucosamine sulfate/ chondroitin sulfate (NIH)	GAIT: Sawitzke *et al.* (2008)[125]	*n* ≈ 110 per group, 2 years, 500 mg GS tid, 400 mg CS tid, combination GS+CS tid, 200 mg celecoxib	JSN	Both compounds no significant difference from placebo

*All studies listed are randomized controlled trials. ‡Approximate patient numbers per group are provided for brevity as applicable. Abbreviations: bid, *bis in diem* (twice daily); BRISK, British study of risedronate in structure and symptoms of knee OA; CS, Chondroitin sulfate; DMOAD, disease-modifying OA drug; GAIT, Glucosamine/chondroitin arthritis intervention trial; GS, glucosamine sulfate; IBSA, Institut Biochimique SA; JSN: joint-space narrowing; KOSTAR, knee OA structural arthritis; OA, osteoarthritis; PGA: patient global assessment of arthritis; qd, *quaque die* (every day); STOPP, study on OA progression prevention; tid, *ter in die* (three times a day); WOMAC, Western Ontario and McMaster University OA index.

Table 2 | Potential DMOADs currently in clinical development for OA

Compound	Clinical trial identifiers	Stage completed	Mode of action
Strontium ranelate	ISRCTN413233722[29,30]	Phase III	Remodelling of subchondral bone and articular cartilage
Calcitonin	NCT00486434,[25] NCT00704847[24]	Phase III	Remodelling of subchondral bone and articular cartilage
FGF-18	NCT00911469,[126] NCT01033994[22]	Phase I	Pro-anabolic growth factor
SD-6010	NCT00565812[13]	Phase III	iNOS inhibitor
PG-530742, PG-116800	NCT00041756[127]	Phase II	Broad-range inhibition of MMPs
Aggrecanase (AGG-523)	NCT00427687[128]	Phase I	Inhibition of ADAMTS-4/5
BMP-7 (also known as OP-1)	NCT01133613[18]	Phase III	Pro-anabolic growth factor

Abbreviations: ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; BMP-7, bone morphogenetic protein-7; DMOAD, disease-modifying OA drug; FGF-18, fibroblast growth factor-18; iNOS, inducible nitric oxide synthase; MMP, matrix metalloproteinase; OA, osteoarthritis; OP-1, osteogenic protein-1.

iNOS inhibitors

Nitric oxide and its primary metabolites are toxic to cells and create extracellular matrix damage. Data obtained *in vivo* and *in vitro* have suggested that selective inhibitors of the enzyme inducible nitric oxide synthase (iNOS) might not only be effective agents for symptomatic treatment of OA, but might also exert disease-modifying activity.[13,14] Phase I and II studies with the oral iNOS inhibitor cindunistat have been conducted, and a Phase III DMOAD trial in knee joint degeneration was completed in 2012.[13] In this 2-year study, cindunistat did not slow the rate of JSN versus placebo in more than thousand patients with OA, although in those with less severe joint damage *post hoc* evaluation revealed a beneficial effect on JSN at 48 weeks.

Protease inhibitors

Clear evidence shows that the earliest histopathological lesions in cartilage degeneration are depletion of proteoglycans and a breakdown of the collagen network mediated by members of the matrix metalloproteinase (MMP) family and aggrecanases of the 'a disintegrin and metalloproteinase with thrombospondin motifs' (ADAMTS) family.[15] Highly specific inhibitors of MMP-13 (also known as collagenase 3) have shown promising results in protecting cartilage in experimental models of joint degeneration[16] and several MMP-13-specific inhibitors are in preclinical development. Combined inhibition of aggrecanases and collagenases might, however, be needed for full cartilage-protecting effects to be realized.[17]

Bone morphogenetic protein 7

Preclinical studies have revealed bone morphogenetic protein 7 (BMP-7, also known as osteogenic protein 1; OP-1) to be a unique growth factor that exhibits both strong anabolic activity (such as stimulation of the expression of type II collagen, aggrecan and hyaluronan, among other structural proteins) and anti-catabolic properties (inhibition of aggrecanases and MMP-13). BMP-7 inhibits the progression of OA and has the ability to repair cartilage *in vivo* in various animal models of articular cartilage degradation. The first phase I clinical trials of BMP-7 in symptomatic OA have been performed, with the results supporting continued investigation of this approach.[18]

Fibroblast growth factor 18

Fibroblast growth factor 18 (FGF-18) activates FGF receptors, triggering signalling pathways that are important in bone and cartilage biology, including chondrogenesis and osteogenesis.[19] In animals, FGF-18 showed considerable anabolic effects on chondrocytes: it stimulated proteoglycan synthesis and cartilage growth.[20] In a rat model of injury-induced joint degeneration, FGF-18 dose-dependently increased cartilage thickness.[21] Two phase I studies of the recombinant human protein (rhFGF18) administered intra-articularly in patients with knee OA have been completed, and a phase II trial is ongoing. Results showed a statistically significant dose-dependent improvement in total femorotibial cartilage volume ($P<0.05$), as well as diminished JSN at 1 year post injection.[22] All 42 patients receiving rhFGF18 experienced symptomatic improvement, although the response in the placebo group was higher than with active treatment. This early result shows that rhFGF18 has potential DMOAD activity but that further clinical investigation is clearly needed.

Calcitonin

The thyroid hormone calcitonin has been posited as a DMOAD because subchondral bone changes are key to the development and progression of OA. Preliminary findings from oral treatment with calcitonin suggest that it can preserve healthy bone, prevent osteophyte changes, slow the deposition of weaker reparative bone in the subchondral region, and maintain normal contour and shape of the articular surfaces.[23] In addition to these effects on bone, potential direct effects on cartilage have been reported.[23] One phase III efficacy trial of oral salmon calcitonin in knee OA was terminated in men "due to an imbalance in prostate cancer events";[24] another phase III trial has been completed[25] but the findings have been published to the scientific community only in Abstract form to date.[25] In this double-blind, randomized placebo-controlled study, twice-daily calcitonin treatment over 2 years in patients with knee OA resulted in

substantial symptom-modifying efficacy, with significant improvements seen in clinical scores of symptoms such as pain and function. The primary endpoint of improvement in radiographic JSN was not reached, but a significant increase was found in cartilage volume, suggesting structure-modifying capacity.[25] Thus, additional clinical research into this primarily bone-directed potential DMOAD is warranted.

Strontium ranelate

Originally developed as a treatment for osteoporosis,[26] strontium ranelate has been shown *in vitro* to stimulate the cartilage matrix formation of isolated chondrocytes.[27] *Post-hoc* analysis focusing on cartilage repair of data from cohorts in trials in osteoporosis has suggested chondroprotective abilities of the drug.[28] The first results of a trial of strontium ranelate in knee OA,[29] in which both the efficacy and safety of two oral doses of strontium ranelate versus placebo over 3 years were evaluated, were published in 2012;[30] strontium ranelate was associated with significantly less progression of JSN than placebo. This structure-modifying activity was accompanied by moderate improvement in symptoms.[30] In another study available online in 2012, findings in dogs supported the protective effect of strontium ranelate on cartilage, which is thought to occur via modulation of bone turnover.[31] Moreover, modulation of rat bone marrow mesenchymal stem cells (MSCs) by strontium ranelate *in vitro*, promoting their osteoblastic but inhibiting their adipocytic differentiation, was reported in 2012.[32] Together, these findings make strontium ranelate a promising DMOAD, although its actual mode of action in OA needs further study to enable more targeted use of the drug.[33]

Considerations in DMOAD development

The persisting effort over the past years into development of new DMOADs has led to promising leads and candidate therapies for which actual clinical usefulness is near. To make real DMOADs a routine clinical reality, attention is needed in the development path; more sensitive outcome measures at the imaging[34] and biochemical levels,[35] and the characterization of clinically meaningful improvements, will facilitate the validation of DMOADs as well as other cartilage repair approaches. An important factor to consider is the imbalance in joint homeostasis in degenerative joint diseases such as OA, creating conditions that are far from optimal for DMOADs to function. For example, continuous wear and tear of damaged cartilage surfaces, inflammatory conditions, and the low cell-density of adult cartilage determining cartilage tissue turnover rate, all contribute to constraint of the potential for repair. Not surprisingly, at the other end of the spectrum of joint-restorative approaches, modulation of joint homeostasis and cell-based therapies are being developed.

Cell-based therapies: a step ahead

Cartilage cell therapy—autologous chondrocyte implantation (ACI)—was the first clinical example of what has rapidly grown into the field of regenerative medicine. Nevertheless, research into this approach has shown us that true establishment of such technology has a long and complex way to go. Meanwhile, it has helped us to better understand the challenge of structural tissue regeneration versus repair, and functional restoration versus treatment of clinical symptoms.

Why and for whom?

A focal articular cartilage lesion is characterized by an isolated loss of cartilage tissue and function in an otherwise healthy articular joint.[36] Patients younger than 45 years show the highest prevalence of focal lesions, because their lifestyle is typically more active than in older people, making joints prone to local damage that leads to more generalized damage only over time.[7,38] Symptoms such as knee pain, swelling, catching and locking cause a decrease in activities of daily living and sports performance. In fact, the quality of life of patients with a diagnosed focal cartilage lesion is impaired to the same extent as that of patients with OA eligible for arthroplasty.[39,40] As we discuss in the following sections, cartilage cell therapy has a role in the treatment of symptomatic joint damage because natural healing is ineffective, and because current treatment options for large defects do not provide a lasting effect. ACI has been approved by the EMA and FDA for use in restoring chondral and osteochondral lesions. It has become clear that focussing only on cartilage and not addressing subchondral bone or intra-articular synovial (fluid) factors will prevent us from successfully addressing the clinical need. Thus, a combined approach of cellular, structural and biochemical factors seems to be required. The recent implementation of guidelines for cell therapy has led to the development of advanced therapeutic medicinal product (ATMP) regulation, under which cartilage cell therapy finds its place.

Route from idea to bedside of ATMPs

After initial *in vitro* and *in vivo* experiments in the 1970s and 1980s, a pivotal moment came with the first cartilage cell implantation in a cohort of patients.[39] The hallmark publication in 1994[40] of the outcome of ACI was the first proof of cartilage cell biological principal and clinical effectiveness. Sixteen patients received femoral condylar transplants and seven had patellar transplants; after an average 39 months (range 16–66 months), clinical symptoms had declined, surface restoration was good, and histological signs of hyaline cartilage restoration could be found. 2 years after surgery most treated patients had good-to-excellent results.[40]

For years after this first demonstration of ACI using a periosteal flap technique, researchers worked on defining the indications and limitations, better understanding the role and fate of implanted and resident cells, the function of the periosteal cover and how to improve the surgical procedure.[41–44] Establishment of the principal of using autologous chondrocytes and expanding them using cell culture procedures sparked a flurry of interest from international biotech companies, all trying to find a place in this new and exciting market. This initial enthusiasm was,

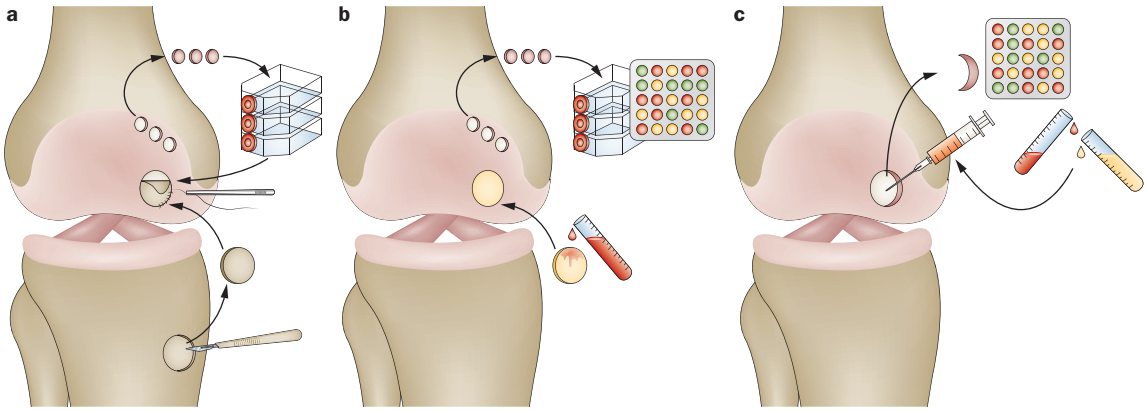

Figure 1 | Cell-based therapy approaches. Cartilage cell therapy has evolved through a few generations, with stepwise improvements in technology, safety and ease of use. This technovolution is schematically represented across the three parts of this figure. **a** | First-generation approach: cartilage fragments, harvested from the least weight-bearing part of the knee joint, were enzymatically digested to release chondrocytes, which were expanded in culture and reinserted into the defect in a second surgery using a periosteal cover, multiple small sutures and fibrin glue sealant (in the second-generation approach a synthetic collagen or resorbable biofilm cover was introduced). **b** | Third-generation approach: the chondrocytes are characterized and well-defined molecular biological measures are applied to ensure the highest percentage of cartilage producing chondrocytes are reimplanted. The second surgery has been altered into a mini arthrotomy or even arthroscopic procedure; using a biomaterial carrier the cells are reliably fixed into the defect. **c** | The next, fourth-generation approach aims at a one-stage surgical procedure in which cells are immediately released from cartilage that is acquired by cleaning the defect, such that no additional biopsy damage is made. Mixing these autologous cartilage components with allogeneic mesenchymal stem cells selected for chondrogenic potential allows us to reimplant the mix during the same surgery in a fibrin glue/hydrogel carrier material.

however, followed by signs of uncertainty about product differences,[45] clinical effectiveness, safety and production process robustness.

Technovolution of cell therapy

Natural selection of technical advances and the use of technology to improve quality of life has been called technovolution: a concept that is clearly applicable to the development of cartilage cell therapy. Four generations in the technovolution of ACI can be described to date, including current 'next generation' approaches. First-generation ACI, using culture-expanded autologous chondrocytes under a periosteal cover with good long-term results, was followed by the first matrix assisted ACI technique, in which a cover of synthetic collagen or resorbable biofilm decreases secondary hypertrophy (Figure 1a).[46] The third generation approach, in which cells are cultured in a re-differentiation phase using an open-structure collagen matrix, eliminates the need for sutured stitching and improves ease of use, limiting surgical exposure; this technique has enabled the introduction of arthroscopic delivery of cartilage cell therapy.[47–50] The introduction of bioactive matrices, such as those containing hyaluronic acid and collagen, has improved both surgical handling and patient-related outcomes.[47,48] Furthermore, the current technique of characterized chondrocyte implantation (CCI; Figure 1b), in which cultured cells are characterized using molecular biological screening with a defined panel of predictive genes and the culture process is optimized to select and support the highest number of chondrogenic cells, is an important development because it establishes release criteria and production guidelines for cell culture products to be used in clinical care to the same standard as medicinal pharmaceutical products, for which regular production and distribution can be relied upon.[50]

In parallel with the quality development in cell production, considerable progress has been made in outcomes evaluation, clinical trial design and defining the optimal patient profile for cartilage regeneration treatment. Whereas cell therapy is a realistic option up to the age of 50–55 years in a variety of patients and clinical situations, the active, healthy male patient aged <30 years with a solitary post-traumatic defect of recent occurrence in an otherwise stable and undamaged knee is accepted as the ideal indication.[42,51,52]

Technological advances and the ability to influence the biodiversity and development of cells in culture (technovolution) have had an essential role in refining ATMPs. Follow-up studies have shown persisting effectiveness of cartilage cell therapy, with several studies following patients up to 5 years and some studies demonstrating good results at 10–15 and even 20 years after treatment.[53–57] These cohort studies have clarified that patient age, gender, cartilage defect age, defect size and location and concomitant (peri)articular deformity are predictors of clinical outcome and thus essential in defining the surgical indication. Defect location and defect age proved to influence patient-reported outcomes in a randomized controlled trial in 118 patients at 3 years after surgery.[56,58,59] Medial defects were associated with a 30–50% better improvement when compared with lateral defects.[56,57] Defect age, in terms of symptom-to-treatment delay, proved to influence postoperative improvement; patients without delay (treated <3 years since onset of symptoms) had 20–27% better outcomes

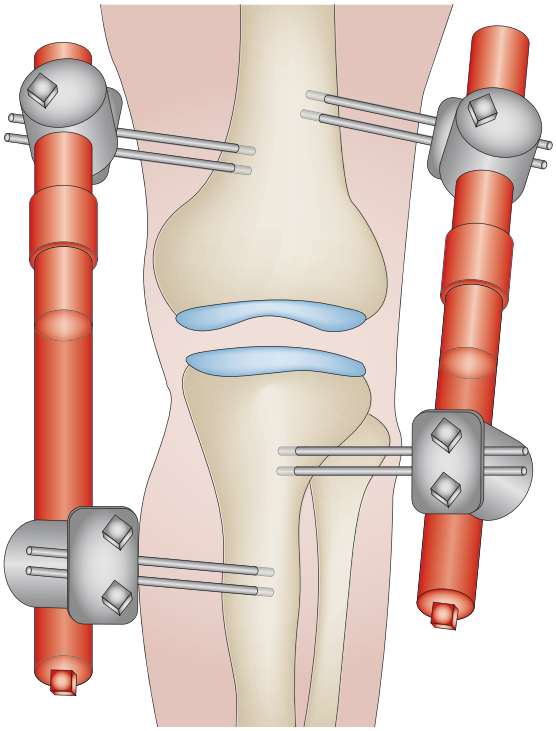

Figure 2 | Visualization of fixed knee-joint distraction apparatus. Half pins are drilled through soft tissue into the bone of the tibia and femur. Tubes (Stryker®) connect both fixations medial and lateral and allow gradual stable distraction of the joint. This distraction method was used by Intema, F. *et al.* (2011)[90] and by Wiegant *et al.* (2012)[94]; see also Table 4.

than those who waited >3 years from onset).[55] Patients younger than 30 years had significantly higher clinical improvement than patients >30 years of age.[58]

New generation approaches

Clearly, joint reconstruction technologies are evolving. New approaches being developed aim at various improvements, such as arthroscopic delivery of chondrocyte implants, application of cell-free biomaterials with the instructive capacity to guide cells and with factors to facilitate regeneration or even to improve natural healing, and one-stage off-the-shelf techniques using allogenic support cells. Further away on the horizon, transitioning from fundamental exploration to *in vitro* and preliminary *in vivo* examination, are the roles of gene transfection, siRNA, and microRNA technologies that remain too far from clinical application to be explored in this Review.

Arthroscopic delivery of chondrocytes requires either an injectable carrier or an isotropic open 3D mesh biomaterial that supports chondrogenic differentiation during the last period of cell culture. It allows more rapid recovery, improves patient comfort and allows early rehabilitation goals to be met sooner, when compared with current techniques in which the requirement for opening the full joint creates considerable discomfort and morbidity. The next frontier in improving delivery would be a one-stage procedure without need for cell culture (Figure 1c). The low cell number in native cartilage and the large surface area to volume ratio of cartilage defects currently necessitate culture expansion of chondrocytes for cell therapy. *In vitro* and *in vivo* work has shown that combining MSCs with cartilage components might enable us to provide a one-stage surgical cell therapy solution.[60–63] Combined cellular technologies that use autologous and allogenic cells in various strategies are in development; the IMPACT trial[64] of autologous chondrons (chondrocytes with their pericellular matrix intact) derived from cartilage taken from the defect rim and combined with MSCs from a stem-cell bank into one procedure is the first such trial in humans. Findings from a proof-of-concept study in rabbits suggest that smart biomaterial scaffolds might facilitate intrinsic repair mechanisms, stimulating the homing of endogenous cells to the defect without the need for cell transplantation.[65]

Considerations

Cartilage cell therapy using cultured autologous chondrocytes has now found its place in daily treatment in several hospitals worldwide. Nevertheless, persistent issues remain to be addressed, including the short-term and long-term cost–benefit and ethical risk profiles of these therapies. Furthermore, an urgent need exists to expand the indications past defect treatment to preventing OA. Mechanisms of joint homeostasis[44] ensure that strategies that aim at treating cartilage will fail unless intricate interactions between cartilage, (subchondral) bone and synovial tissue are accounted for. Thus, a combined approach including cells, biomechanical optimization, and attention to periarticular and intra-articular environments is key. Analysis of synovial fluid after anterior cruciate ligament (ACL) injury has revealed recruitment of MSCs to the joint;[66] bone-marrow derived MSCs used in cartilage repair during microfracture have produced good outcomes in follow-up studies;[57,67] and initial intra-articular applications of MSCs in clinical research settings in OA have been promising.[68–70] Further exploration of the mechanisms that underlie interactive biological repair mechanisms involving MSCs is warranted, and has the potential, in our opinion, to unite DMOADs, cell therapies, and mechanical interventions such as joint distraction.

Joint distraction

Enabling intrinsic joint repair, joint distraction is a surgical procedure in which the two bony ends of a joint are gradually separated to a certain extent and for a certain period of time by use of an external fixation frame (Figure 2). Although several different frames have been used, in all cases the process induces 2–3 months of full mechanical unloading of the affected joint, preventing further wear and tear of the damaged joint tissue.[71] Repair of joint tissues, in addition to clinical benefit, has been demonstrated,[45] as will be discussed in the next paragraphs.

Evidence of tissue repair by joint distraction

Most studies of joint distraction to date have been performed for treatment of ankle OA (Table 3).[72–83]

Table 3 | Studies of joint distraction in patients with degenerative ankle joint disease

Study; design	Number of patients; age; disorder	Type and duration of treatment; duration of follow-up*	Symptomatic outcome‡	Structural outcome	Adverse events	Failure rate
van Valburg *et al.* (1995);[82] retrospective	*n* = 11; 35 ± 13 years; OA equine deformity	Ilizarov fixed,§ 1.5–3.0 months; 1.7 ± 0.5 years	Significant improvements in pain and mobility	Modest increase in radiographic JSW	Not reported	Not reported
Kanbe *et al.* (1997);[73] case report	*n* = 1; 19 years; chondrolysis	Orthofix® apparatus, 1 month; 3 years	Significant improvements in pain and mobility	Significant increase in radiographic JSW; fibrocartilage formation by histology	Not reported	Not reported
van Valburg *et al.* (1999);[83] prospective	*n* = 17; 40 ± 11 years; (post trauma) OA	Ilizarov fixed,§ 3 months; 2 years	Significant improvement in pain; modest improvement in mobility	Modest increase in radiographic JSW	Pin tract infections	4/17
Marijnissen *et al.* (2002);[75] Part I: prospective	*n* = 57; 44 ± 11 years; (post trauma) OA	Ilizarov fixed,§ 3 months; 2.8 ± 0.3 years	Significant improvements in pain and mobility	Significant increase in radiographic JSW; Significant decrease in BD	Pin tract infections	13/57
Marijnissen *et al.* (2002);[75] Part II: randomized controlled	Control arm: *n* = 9, 44 years; treatment arm: *n* = 8; 45 years; OA	Debridement with or without Ilizarov fixed,§ 3 months; 1 year	Stronger improvements in pain and mobility with distraction than without distraction	With distraction: limited increased radiographic JSW + decreased BD; Debridement alone: small ns decreased radiographic JSW + increased BD	Pin tract infections	None
Ploegmakers *et al.*[77] (2005); retrospective & prospective	*n* = 22, 37 ± 11 years; OA	Ilizarov fixed,§ 2 months; 10 years (7–15 years)	Significant improvements in pain and mobility.	Not evaluated	1 Sudeck's atrophy	6/22
Sabharwal & Schwechter (2007);[78] case report	*n* = 1; 15 years; post trauma chondrolysis	Ilizarov fixed,§ 3 months; 5.5 years	Significant improvements in pain and mobility	Significant increase in radiographic JSW; significant decrease in BD	Not reported	Not reported
Paley *et al.* (2008);[76] retrospective	*n* = 23; 45 (17–62) years; post trauma OA	Hinged Ilizarov,§ apparatus, 4 months; 5.3 (2–13) years	Significant improvements in pain and mobility	Not evaluated	Pin tract infections	2/23
Lamm & Gourdine-Shaw (2009);[74] retrospective	*n* = 3; 41 years; post trauma arthritis	Debridement + hinged Ilizarov,§ 4 (+1 cast) months; 1 years	Not reported	Increase in cartilage thickness on MRI; decrease in BD and BC	Not reported	Not reported
Tellisi *et al.* (2009);[80] prospective	*n* = 25; 43 years (16–73 years); OA	Fixed Ilizarov,§ 3 months; 2.5 (1–5) years	Significant improvements in pain and mobility	Modest increase in radiographic JSW	Pin tract infections	2/25
Intema *et al.* (2011);[72] prospective	*n* = 26; 41 ± 9 years; post trauma OA	Fixed versus hinged Ilizarov,§ 3 months; 2 years	Not reported	Significant decreases in BD and BC as assessed by CT	Not reported	Not reported
Saltzman *et al.* (2012);[79] RCT	Fixed: *n* = 18, 42 years; hinged: *n* = 18; 43 years; post trauma OA	Fixed versus hinged Ilizarov,§ 3 months; 2 years	Significant improvements in pain and mobility significantly greater for hinged distraction	Not evaluated	Pin tract infections and 8 neuropraxia	Fixed: 3/18; hinged: 1/18
van Meegeren *et al.* (2012);[81] report of 3 cases	*n* = 3; 18–33 years; haemophilic arthropathy	Ilizarov,§ 2–3 months; 3 (2–4) years	Significant improvements in pain and mobility	Significant increases in radiographic JSW and cartilage thickness on MRI; significant decreases in BD and BC	Not reported	Not reported

*Treatment and follow-up durations expressed as means ±SEM, or range between brackets. ‡Use of the word 'significant' in this Table refers to clinically relevant effects as well as to a statistically significant effects. §The Ilizarov apparatus is a thin wire circular frame fixed or with a hinge. Abbreviations: BC, bone cysts; BD, subchondral bone density; JSW, joint-space width; OA, osteoarthritis.

The relatively high number of such studies, in comparison, for example, to trials in knee OA, is surprising because ankle arthrodesis (joint fusion) is considered a safe and cost-effective treatment, albeit at the expense of joint motion. Nevertheless, a risk of adjacent-joint degeneration in time after a tibiotalar arthrodesis has been recognized. In 7 of the 12 ankle-joint OA distraction studies, cartilage tissue repair activity was demonstrated by a sustained increase in joint-space width (JSW) on radiographs.[73,75,78,80–83]. Additional beneficial changes

in bone density were found in 3 studies.[75,78,81] Except for two,[75,79] the studies in Table 3 were all retrospective analyses. Although JSW measurements can be subject to misinterpretation influenced by positioning of the joint during acquisition of the images, the radiographic findings have been confirmed by MRI studies,[75,81] which are less influenced by positioning artefacts due to the 3D approach. The most convincing results demonstrating functional tissue repair to date were obtained by a group from Iowa,[72] and showed almost complete normalization of subchondral bone 2 years after ankle distraction in the 26 patients with advanced post-traumatic ankle OA. In each patient, cystic areas were filled in and sclerotic areas decreased in bone density; repair of cysts clearly correlated with clinical benefit.[72] Unfortunately, no data are available regarding cartilage tissue repair in this cohort.[79]

Joint-sparing surgery at a relatively young age (that is, <65 years) is a more pressing need in cases of knee and hip degeneration than for ankle OA. Nevertheless, only four such studies in patients with knee OA and three in those with hip OA have been performed to date (Table 4).

Results regarding joint tissue repair in the hip or knee[84–91] have mostly been obtained by retrospective analysis of radiographs; only two studies[85,90] were based on prospective evaluation. All, though, have demonstrated clear increases in radiographic JSW (Table 4). Two studies confirmed cartilage repair in the knee by arthroscopic evaluation,[84,87,88] and two others did so by MRI.[84,90] The most convincing study, by Intema *et al.*,[90] provided detailed blinded objective quantitative morphometric MRI data, radiographic data and biochemical marker data from a prospective (though uncontrolled) cohort of 20 patients aged <60 years with tibiofemoral OA. The MRI data demonstrated filling in of fully denuded areas of bone. Notably, this result was reported previously for osteotomy by arthroscopic evaluation.[92] Mechanical resilience of the cartilage was demonstrated by a clear increase in JSW on radiographs taken during full weight bearing and analyzed using digital evaluation of standardized acquisitions.[93] Evaluation of markers of type II collagen demonstrated an increase of synthesis over release after joint distraction, suggesting the hyaline nature of the new cartilage tissue, and subchondral bone density (sclerosis) decreased.[90] These 1-year follow-up findings were sustained for at least a second year.[94]

Besides studies in large joints, some investigators have reported joint-tissue repair by distraction in hand and foot joints (Table 4).[95–97] Radiographic evidence of cartilage and bone repair in this setting has been reported only in two case studies,[96,97] in one case supported by MRI data.[96] Despite being only from isolated case reports, the reported intrinsic repair activity of the joints was enormous, with full resurfacing of the bony joint contours fully supported by a cartilage layer.[97]

Although discarded in the selection procedure used in collating Table 3 & Table 4 because of the language of publication or because distraction was not primarily performed for treatment of joint degeneration, other studies of joint distraction of various joints could be discussed. For example, Judet and Judet[98] reported as long ago as 1978 in the French literature that hinged distraction of the knee, ankle and elbow can be beneficial. In the 1990s, Canadell *et al.*,[99] Morrey[100] and van Roermund *et al.*[97] focused on distraction of stiff joints but included patients with joint degeneration; all reported good results with evidence of joint-tissue repair. More recently, an internal distraction device has been developed; cadaveric tests were reported in 2011,[101] and a study in sheep was published in 2012[102]—promising results were obtained and the approach has reached a clinical stage. Data on distraction of degenerated ankle joints, as seen in haemophilic arthropathy, have also been published, with clear increase in radiographic JSW and normalization of subchondral bone, accompanied by clinical benefit.[81]

The astonishing remodelling of the bone–cartilage joint surface observed in finger joints[95,97] by use of joint distraction has also been demonstrated in several animal studies of the knee joint (Supplementary Table 1). In three studies in animal knees,[103–105] joint distraction added to repair of the whole joint after resection of the entire articular (bone–cartilage) surface of the tibial plateau. Furthermore, in a large osteochondral defect rabbit model, bone and cartilage tissue repair was observed using histochemistry.[106] No studies in humans have reported absence of tissue repair by joint distraction, but two of the animal studies listed in Supplementary Table 1 have done so; those by van Valburg *et al.*[107] and by Karadam *et al.*,[108] in which even adverse effects on cartilage integrity were reported. The latter investigation, however, used a model of cartilage chondrocyte death, which arguably might not be a representative model of joint degeneration.[108] Beneficial changes in chondrocyte metabolic activity were demonstrated in the dog ACL transection model used by van Valburg *et al.*;[107] a lack of detectable cartilage repair in this setting might well be attributable to a lack of follow-up. One study, in rabbits,[109] has tested distraction of experimentally-induced degeneration of the spinal disc. After 28 days of the treatment, clear histological evidence of tissue-structure repair was observed using various techniques.[109]

More proof of functional repair is needed

In most of the human studies we have discussed, clinical benefit from joint distraction seems to be not only clear but also sustained over mid-term to even long-term follow-up. Most of the studies, however, have been of limited quality. Only two prospective randomized studies have been published, both on ankle distraction and with 1-year[75] and 2-year[79] follow-up periods. In the randomized section of their study, Marijnissen *et al.*[75] compared debridement of the ankle joint with distraction in a total of 17 patients and demonstrated distraction to be favourable. Saltzman *et al.*[79] compared hinged and fixed distraction of the ankle in 36 patients; both methods induced improvement as measured using the ankle OA scale, but ankle distraction with motion was significantly more effective than the fixed. Although clinical improvements were thus demonstrated, tissue structure repair was evaluated only in the

Table 4 | Studies of joint distraction in patients with degenerative disease of hip, knee, or hand and foot joints

Study; design	Number of patients; age (range); disorder	Type and duration of treatment; duration of follow-up*	Symptomatic outcome‡	Structural outcome	Adverse events	Failure rate
Hip joints						
Aldegheri *et al.* (1994);[85] prospective	*n* = 80; (9–69) years; OA, osteonecrosis or chondrolysis	DeBastiani hinged, 1.5–2.5 months; 5–8 years	Significant improvements in pain and mobility	Significant increase in radiographic JSW	3 pelvic pin pain	4 arthritis
Thacker *et al.* (2005);[91] retrospective	*n* = 11; 13.9 (9–17) years; arthritis, osteonecrosis or chondrolysis	Hinged custom, 4.4 (3–7) months; 4.8 (2.0–6.1) years	Significant improvements in pain and mobility	Significant increase in radiographic JSW	1 pin tract infection	Not reported
Gomez *et al.* (2009);[89] retrospective	*n* = 28; 14.7 ±2.5 years; avascular necrosis	EBI/BIOMET hinged, 4.2 ± 1.5 months; 4.8 (1.0–15.5) years	Significant improvements in pain and mobility	Not evaluated	Pin tract infections +1 leg-length change	Additional surgery necessary over time in 12/28
Knee joints						
Deie *et al.* (2007)[87] & (2010);[88] retrospective	*n* = 6; 49 (42-63) years; generalized OA	BMS + hinged custom distraction, 2–3 months; 2.6–3.0 years	Significant improvements in pain and mobility	Significant increase in radiographic JSW; arthroscopic evidence of cartilage repair	Pin tract infections	2 pin tract infections
Abouheif *et al.* (2010)[84] case report	*n* = 1; 18 years; osteochondral defects	Bone graft + custom hinged distraction, 3 months; 4.5 years	Significant improvements in pain and mobility	Significant increase in radiographic JSW; significant normalization of bone arthroscopic evidence of: cartilage resurfacing; significant increase in cartilage thickness on MRI; + significant bone normalization	1 Sudeck's atrophy	Not reported
Intem *et al.* (2011)[90] prospective	*n* = 20; 48 ± 7 years; OA	Stryker® tubes‖, 2 months; 1 year	Significant improvements in pain and mobility	Significant increase in radiographic JSW; significant increase in cartilage volume on MRI; increase in type II collagen synthesis	Pin tract infections and 2 lung embolism	None
Aly *et al.* (2011);[86] controlled trial	*n* = 19 *vs* *n* = 42; (39–65) *vs.* (41–68) years; primary OA	Ilizarov§ + debridement vs debridement alone, 1 month; 5.5 *vs* 4.3 years	Significant more improvement in pain and mobility in the distraction vs. debridement alone	Significant increase in radiographic JSW with distraction vs decrease in JSW with debridement alone	Pin tract infections and 2 embolism	Not reported
Hand and foot joints						
DeVries *et al.* (2008);[96] case report	*n* = 1; 15 years; metatarsophalangeal osteochondrosis	Bone graft + custom distraction, 1.5 months; 1–5 years	Significant improvements in pain and mobility	Significant increase in radiographic JSW, significant increase in cartilage thickness on MRI and normalization of bone	Not reported	Not reported
Bain *et al.* (1998);[95] prospective	*n* = 26; 41 ± 9 years; proximal interphalangeal dislocation/fracture	Compass® hinged, 1.5 (0.5–2.0) months; 0.75 years	Significant improvement in pain	Not evaluated	Pin tract infection + 1 septic arthritis	1 due to dislocation
van Roermund *et al.* (1998);[97] case report	1; 42 years; distal interphalangeal thumb dislocation/ fracture	Hinged Ilizarov§, 3.7 months; 2 years	Significant improvements in pain and mobility	Radiographic normalization of cartilage and bone	Not reported	Not reported

*Treatment and follow-up durations expressed as means ± SEM, or range between brackets. ‖Stryker® tubes (see also Figure 2). ‡Use of the word 'significant' in this Table refers to a clinically relevant effect as well as to a statistically significant effect. §The Ilizarov apparatus is a thin wire circular frame fixed or with a hinge. Abbreviations: BMS, bone marrow stimulation (subchondral); JSW, joint-space width; OA,osteoarthritis.

study by Marijnissen *et al.*;[75] the data tended to favour distraction, but were not statistically significant.

Besides the lack of prospective randomization and small-scale nature of existing joint-distraction data, variation of patient characteristics is also an important consideration. Most studies have been in patients who have undergone multiple surgical procedures over the years before distraction was applied—such patients have

final-stage joint degeneration for which distraction was the only remaining option before replacement or fusion (arthrodesis) of the joint. Indeed, it can be anticipated that patients with less severe damage might benefit at least as well from distraction therapy. The study in which filling in of cartilage tissue in denuded bone areas was demonstrated[90] suggests that distraction might also be beneficial for treatment of local defects; however, such studies have not been reported on.

Potential adverse events

Adverse events cannot be ignored. Almost all studies that have reported on adverse events report the occurrence of pin tract infections, often in more than half of patients (Table 3, Table 4). Although treatable with local antibiotics and not leading to osteomyelitis, these infections represent a substantial burden to patients during treatment. Moreover, secondary prosthesis surgery might be hampered as a consequence of the increased risk of infection. Nevertheless, no such instances have been reported, whereas in some studies (Table 3, Table 4), prostheses were subsequently placed in patients for whom joint distraction failed to save the original joint (around a quarter to a third of patients, over the reported follow-up periods, although the proportion is often not clearly stated). Also, thrombosis (including lung embolism) and neuropraxia (including Sudeck's atrophy) were observed in 4 patients (3 in the lung) and in 11 patients (persisting in 3 of them), respectively, out of the total 429 treated patients (Table 3, Table 4). Although these risks are applicable to the use of external fixation frames in general, they cannot to be ignored in evaluating joint distraction therapies; unfortunately, however, many studies lack detailed data.

Mobile versus immobile distraction

All studies of the hip[85,89,91] or finger joints[95,97] and some of those in the ankle[74,76,79,82] and in the knee[84,87,88] used hinged distraction, with joint motion possible during the distraction period, rather than stiff distraction. None of the studies using fixed distraction in humans have reported persisting joint contractures. However, distraction with motion is more convenient for patients than a stiff joint. Moreover, as we have mentioned, ankle distraction with motion seems to have a clear clinical benefit over the fixed technique.[79] Whether tissue structure repair is also more likely or more extensive using hinged rather than stiff distraction has never been studied. Correlation between the extent of subchondral bone normalization and clinical benefit in the ankle joint, as reported after a trial of distraction by Amendola and colleagues,[72,79] suggests that structural repair might indeed be better using hinged distraction. Moreover, studies in animals have demonstrated clearly better tissue repair activity for hinged distraction when compared with stiff distraction.[107,108]

Prospects for knee joint distraction

Overall, existing data show that tissue structure modification in OA and in knee OA specifically—the most relevant challenge in clinical practice—can be accomplished by joint distraction. A remarkable increase in structural parameters (rather than a slowing of loss of tissue integrity), provides proof of concept that repair of cartilage is possible and that this change can translate into real clinical benefit.[110] Clearly, larger prospective randomized studies with longer follow-up periods, preferably using quantitative MRI and CT for detailed evaluation of soft and hard joint tissues, should be undertaken. Randomization between joint distraction and conventional surgical treatments is needed. Good clinical results of subchondral bone stimulation (microfracturing) and high tibial osteotomy have been reported, although actual cartilage tissue repair was not clear.[58,111] Prospective comparison between surgical approaches and cell-based therapies, with actual tissue repair demonstrated, is also required. Owing to variations in inclusion criteria, retrospective comparison between these approaches is not of value. Only through randomized controlled trials will we know which treatments work best for which patients in the short and long term.

Combined joint-restorative mechanisms

The development of tissue-modifying therapies has the potential to change the clinical landscape of degenerative joint disease. Furthermore, detailed outcomes of such studies are yielding insights into the mechanisms of intrinsic joint repair. Nevertheless, more knowledge is required to fully assess and interpret the results. Could joint distraction be used in future as a gold standard against which to assess the efficacy of developmental tissue structure repair approaches including DMOADs and cell-based therapies? Is it opportune to suggest that a combination of a bone directed DMOAD and a cartilage-directed cell-based therapy has a better outcome than either treatment alone? During joint distraction, joint homeostasis is substantially altered in many ways (Figure 3), seemingly in favour of cartilage tissue repair. Perhaps the efficacy of DMOAD therapy and/or cell-based therapy can be improved by combining these approaches with joint distraction.

During distraction, axial forces on joint tissues are partly taken over by the distraction frame. This reduction in mechanical pressure results in substantial peri-articular osteopenia that normalizes after distraction.[72,75,90] The current most effective DMOAD therapies, strontium ranelate and calcitonin, primarily modulate bone turnover; thus, it is tempting to speculate that this bone turnover is causal in the subsequent cartilage repair that DMOADs and distraction can elicit.[72,112] Interesting in this respect is the effect of osteotomy. This technique, in which unicompartmental unloading of the knee joint is accompanied by substantial bone turnover due to wedging of tibial bone, has also been reported to result in cartilage repair up to 2 years after treatment, as judged by arthroscopic evaluation[92] and dGEMRIC MRI.[111] Bone turnover as a result of osteotomy might, if not triggering the effect, at least add to subsequent cartilage repair activity.

On the other hand, the astonishing cartilage repair activity observed after joint distraction cannot solely

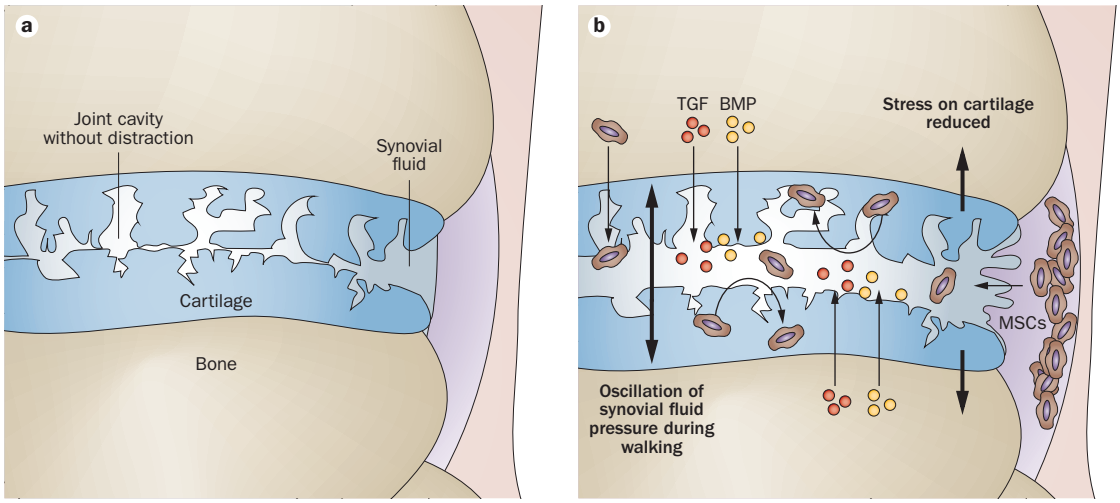

Figure 3 | Homeostatic joint mechanisms implicated in the effects of joint distraction on degenerative joint disease. **a** | Damaged joint without distraction. Loss of JSW due to articular cartilage surfaces wear and tear. **b** | Distraction changes joint homeostasis. The absence of mechanical stresses on the articular cartilage surfaces prevents wear and tear and might initiate intrinsic cartilage repair activity, as well as potentially supporting the effects of cell-based therapies and DMOADs by reducing counteracting processes. Coiled springs in the distraction tubes cause oscillating synovial fluid pressure changes during loading and unloading of the joint, improving nutrition of cartilage. Moreover, such fluid pressure changes have been demonstrated to attract and stimulate MSCs. MSCs are abundant in joint tissues including the synovium, fat pad, synovial fluid, bone marrow and cartilage, and release trophic factors that can induce chondrocyte-mediated cartilage repair. Distraction also results in considerable peri-articular bone changes, changes that are also induced by bone-directed DMOADs such as strontium ranelate and calcitonin. Altered activity of osteoblasts and osteoclasts may add (by for example, release of trophic factors such as TGF and BMP to cartilage repair. Abbreviations: DMOAD, disease-modifying osteoarthritis drug; JSW, joint-space width; MSCs, mesenchymal stem cells; TGF, transforming growth factor; BMP, bone morphogenic protein.

result from matrix synthesis by resident cartilage tissue—areas of denuded bone are filled with new cartilage tissue.[90] This observation pleads for the involvement of recruitment and/or stimulation of stem cells in the repair mechanism. Joints are a rich source of stem cells (in subchondral bone, the synovial fat pad, synovial tissue, and even cartilage itself).[113–116] Intermittent fluid oscillations in the joint during joint distraction,[82,90] considered important in cartilage nutrition, are reported to attract and retain MSCs into the joint[117] and can stimulate MSCs in co-culture with chondrocytes, leading to cartilage matrix synthesis.[118] In data published in 2012, an increase in MSCs was observed after cruciate ligament rupture, and was related to severity of the damage.[60,119] Recruitment of MSCs might represent an endogenous repair mechanism.

The most recent approaches in cell-based therapies make use of the potentiating effects of MSCs in chondrocyte transplantation, aiming for one-step procedures.[60–65,120] Furthermore, MSC trophic factors are suggested to support cartilage repair activity, according to a 2011 study using human cells.[63] In DMOAD territory, the observation that strontium ranelate influences MSC differentiation is also of interest with regard to the roles of these cells in achieving joint repair. Rat bone marrow MSCs treated with strontium *in vitro* were stimulated to differentiate into osteoblasts and not adipocytes;[32] however, the effect of this drug on chondrocyte differentiation has not yet been tested.

Joint distraction might provide a biochemical and biomechanical environment that facilitates (and could even be prerequisite for) cartilage repair. Mechanisms of the DMOAD and cell-based approaches, which might lead to partial joint-tissue repair, are more isolated than those of joint distraction, which offers an integrated way to optimally combine mechanisms to facilitate (intrinsic) repair. As such, comparative and constructive interaction between these physical, chemical and cellular approaches, with sometimes-common processes involved, is likely to be the most productive way forward in the quest for functional repair of articular cartilage.

Conclusions

Unmet needs related to the huge socioeconomic problem of joint degeneration—whether at the stage of local cartilage defects, early generalized joint damage or prolonged severe tissue damage as seen in end-stage OA—have encouraged perseverance in the search for joint tissue repair modalities. Clearly, this persistence has been fruitful. Characterized chondrocyte implantation, DMOADs that influence bone turnover, and joint distraction are promising approaches that suggest that sustained and functional repair of joint tissue is near to becoming a clinical reality.

Future studies of joint restorative approaches should focus on two key aspects: selection of patients and how best to combine therapeutic approaches. Selecting the best treatment for an individual patient according to the type and stage of their disease might be facilitated by ongoing

efforts to define distinct phenotypes of OA.[15] Randomized comparative studies between conventional surgical therapies, cell-based therapies, and joint distraction are needed to provide more data on their relative efficacies in different cohorts. On the other hand, combining approaches might be a productive next step. A combination of primarily bone-targeted DMOADs with cartilage cell-based therapies would seem logical. Similarly, improving biomechanical joint homeostasis by use of joint distraction might facilitate the effects of cell-based therapies. We should be mindful, however, of not making the mistake of using these treatment modalities for patients with too broad a set of characteristics. Extending the indications for restorative therapies too widely would decrease overall efficacy and would unnecessarily drive the costs of treatment for joint degeneration to undesirable levels. Careful selections of patients and combinations of approaches will need to be made and tested to demonstrate their cost-effectiveness. Only with such rational and integrated assessment of outcomes will the promising results of these approaches be consolidated in clinical practice.

Review criteria

References for the sections on disease-modifying drugs and cell-based therapies, including unpublished work, were selected by the authors on the basis of their relevance to and promise for joint restorative approaches; no particular searches were performed. References for the section on joint distraction were selected using a more systematic approach. The PubMed, EMBASE, and Cochrane library databases were searched for "distraction OR arthrodia(s) tasis AND joint OR articul*" (September 2012). Titles, Abstracts and then full text of identified papers were screened using various inclusion and exclusion criteria (Supplementary Figure 1) to identify publications focusing on restoration of degenerative joint damage using an external fixation device in clinical or animal *in vivo* studies. Analyses that lacked original data, studies in patients with intra-articular fractures and soft-tissue joint contractures, intra-operative use of distraction without the purpose of tissue regeneration, or permanent implantation of distraction devices were among excluded studies. Further papers were identified by screening the reference lists of relevant publications.

1. Report No. CPMP/EWP/784/97 (Committee for Proprietary Medicinal Products [CPMP], London, 1998).
2. FDA. Guidance for induistry: clinical development programs for drugs, devices and biological products intended for the treatment of OA. *U.S. Food and Drug Administration* [online], http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071577.pdf (1999).
3. Mastbergen, S. C. & Lafeber, F. P. Animal models of osteoarthritis—why choose a larger model? *US Musculoskeletal Review* **4**, 11–14 (2009).
4. Bingham, C. O. 3rd. *et al.* Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. *Arthritis Rheum.* **54**, 3494–3507 (2006).
5. Bruyere, O. *et al.* Total joint replacement after glucosamine sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomised, placebo-controlled trials. *Osteoarthritis Cartilage* **16**, 254–260 (2008).
6. Dougados, M. *et al.* Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. Evaluation of the Chondromodulating Effect of Diacerein in OA of the Hip. *Arthritis Rheum.* **44**, 2539–2547 (2001).
7. Manno, R. L. *et al.* OARSI-OMERACT initiative: defining thresholds for symptomatic severity and structural changes in disease modifying osteoarthritis drug (DMOAD) clinical trials. *Osteoarthritis* **20**, 93–101 (2012).
8. Wluka, A. E., Wolfe, R., Stuckey, S. & Cicuttini, F. M. How does tibial cartilage volume relate to symptoms in subjects with knee osteoarthritis? *Ann. Rheum. Dis.* **63**, 264–268 (2004).
9. Cicuttini, F. M., Jones, G., Forbes, A. & Wluka, A. E. Rate of cartilage loss at two years predicts subsequent total knee arthroplasty: a prospective study. *Ann. Rheum. Dis.* **63**, 1124–1127 (2004).
10. Bauer, D. C. *et al.* Classification of osteoarthritis biomarkers: a proposed approach. *Osteoarthritis Cartilage* **14**, 723–727 (2006).
11. Hunter, D. J. Pharmacologic therapy for osteoarthritis–the era of disease modification. *Nat. Rev. Rheumatol.* **7**, 13–22 (2011).
12. Martel-Pelletier, J., Wildi, L. M. & Pelletier, J. P. Future therapeutics for osteoarthritis. *Bone* **51**, 297–311 (2012).
13. Hellio le Graverand, M. P. *et al.* A 2-year randomized, double-blind, placebo controlled, multicenter study of oral selective iNOS inhibitor, cindunistat (SD-6010), in patients with symptomatic osteoarthritis of the knee. *Ann. Rheum. Dis.* **72**, 187–195 (2012).
14. Pelletier, J. P. *et al.* Selective inhibition of inducible nitric oxide synthase reduces progression of experimental osteoarthritis in vivo: possible link with the reduction in chondrocyte apoptosis and caspase 3 level. *Arthritis Rheum.* **43**, 1290–1299 (2000).
15. Bijlsma, J. W., Berenbaum, F. & Lafeber, F. P. Osteoarthritis: an update with relevance for clinical practice. *Lancet* **377**, 2115–2126 (2011).
16. Baragi, V. M. *et al.* A new class of potent matrix metalloproteinase 13 inhibitors for potential treatment of osteoarthritis: Evidence of histologic and clinical efficacy without musculoskeletal toxicity in rat models. *Arthritis* Rheum. **60**, 2008–2018 (2009).
17. Fosang, A. Knock-in mice reveal in vivo consequences of MMP activity for OA [abstract SP0022]. *Ann. Rheum. Dis.* **71** (Suppl. 3), 6 (2012).
18. Hunter, D. J. *et al.* Phase 1 safety and tolerability study of BMP-7 in symptomatic knee osteoarthritis. *BMC Musculoskelet. Disord.* **11**, 232 (2010).
19. Haque, T., Nakada, S. & Hamdy, R. C. A review of FGF18: Its expression, signaling pathways and possible functions during embryogenesis and post-natal development. *Histol. Histopathol.* **22**, 97–105 (2007).
20. Ellman, M. B., An, H. S., Muddasani, P. & Im, H. J. Biological impact of the fibroblast growth factor family on articular cartilage and intervertebral disc homeostasis. *Gene* **420**, 82–89 (2008).
21. Moore, E. E. *et al.* Fibroblast growth factor-18 stimulates chondrogenesis and cartilage repair in a rat model of injury-induced osteoarthritis. *Osteoarthritis Cartilage* **13**, 623–631 (2005).
22. McPherson, R., Flechsenhar, K., Hellot, S. & Eckstein, F. A randomized, double blind, placebo-controlled, multicenter study of rhFGF18 administered intraarticularly using single or multiple ascending doses in patients with primary knee osteoarthritis (OA), not expected to require knee surgery within 1 year. *Osteoarthritis Cartilage* **19** (Suppl. 1), 35–36 (2011).
23. Karsdal, M. A., Sondergaard, B. C., Arnold, M. & Christiansen, C. Calcitonin affects both bone and cartilage: a dual action treatment for osteoarthritis? *Ann. N. Y. Acad. Sci.* **1117**, 181–195 (2007).
24. US National Library of Medicine. *ClinicalTrials.gov* [online], http://www.clinicaltrials.gov/ct2/show/NCT00704847 (2012).
25. Karsdal, M. A. *et al.* Oral calcitonin demonstrated symptom-modifying efficacy and increased cartilage volume: results from a 2-year phase 3 trial in patients with osteoarthritis of the knee. *Osteoarthritis Cartilage* **19** (Suppl. 1), 35 (2011).
26. Marie, P. J., Ammann, P., Boivin, G. & Rey, C. Mechanisms of action and therapeutic potential of strontium in bone. *Calcif. Tissue Int.* **69**, 121–129 (2001).
27. Henrotin, Y. *et al.* Strontium ranelate increases cartilage matrix formation. *J. Bone Miner. Res.* **16**, 299–308 (2001).
28. Alexandersen, P., Karsdal, M. A., Byrjalsen, I. & Christiansen, C. Strontium ranelate effect in postmenopausal women with different clinical levels of osteoarthritis. *Climacteric* **14**, 236–243 (2011).
29. Cooper, C. *et al.* Efficacy and safety of oral strontium ranelate for the treatment of knee osteoarthritis: rationale and design of randomised, double-blind, placebo-controlled trial. *Curr. Med. Res. Opin.* **28**, 231–239 (2012).
30. Reginster, J. Y. *et al.* Efficacy and saftey of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial. *Ann. Rheum. Dis.* **72**, 179–186 (2013).
31. Pelletier, J. P. *et al.* Strontium ranelate reduces the progression of experimental dog osteoarthritis by inhibiting the expression of key proteases in cartilage and of IL-1beta in the synovium. *Ann. Rheum. Dis.* **72**, 250–257 (2013).

32. Li, Y. *et al.* Effects of strontium on proliferation and differentiation of rat bone marrow mesenchymal stem cells. *Biochem. Biophys. Res. Commun.* **418**, 725–730 (2012).
33. Lafeber F. P. & van Laar J. M. Strontium ranelate: ready for clinical use as disease-modifying osteoarthritis drug? *Ann. Rheum. Dis.* **72**, 157–161 (2013).
34. Guermazi, A., Roemer, F. W. & Hayashi, D. Imaging of osteoarthritis: update from a radiological perspective. *Curr. Opin. Rheumatol.* **23**, 484–491 (2011).
35. van Spil, W. E., DeGroot, J., Lems, W. F., Oostveen, J. C. & Lafeber, F. P. Serum and urinary biochemical markers for knee and hip-osteoarthritis: a systematic review applying the consensus BIPED criteria. *Osteoarthritis Cartilage* **18**, 605–612 (2010).
36. Buckwalter, J. A. & Mankin, H. J. Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. *Instr. Course Lect.* **47**, 487–504 (1998).
37. Harris, J. D., Siston, R. A., Pan, X. & Flanigan, D. C. Autologous chondrocyte implantation: a systematic review. *J. Bone Joint Surg. Am.* **92**, 2220–2233 (2010).
38. Lindahl, A., Brittberg, M. & Peterson, L. Health economics benefits following autologous chondrocyte transplantation for patients with focal chondral lesions of the knee. *Knee Surg. Sports Traumatol. Arthrosc.* **9**, 358–363 (2001).
39. Brittberg, M. … More bricks to the building of cartilage knowledge? *Knee Surg. Sports Traumatol. Arthrosc.* **17**, 1275–1277 (2009).
40. Brittberg, M. *et al*. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N. Engl. J. Med.* **331**, 889–895 (1994).
41. Bentley, G. *et al.* A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. *J. Bone Joint Surg. Br.* **85**, 223–230 (2003).
42. Jakobsen, R. B., Engebretsen, L. & Slauterbeck, J. R. An analysis of the quality of cartilage repair studies. *J. Bone Joint Surg. Am.* **87**, 2232–2239 (2005).
43. Lohmander, L. S. Articular cartilage and osteoarthrosis. The role of molecular markers to monitor breakdown, repair and disease. *J. Anat.* **184** (Pt 3), 477–492 (1994).
44. Saris, D. B., Dhert, W. J. & Verbout, A. J. Joint homeostasis. The discrepancy between old and fresh defects in cartilage repair. *J. Bone Joint Surg. Br.* **85**, 1067–1076 (2003).
45. Marijnissen, A. C. & Lafeber, F. P. Re: E. B. Hunziker. Articular cartilage repair: basic science and clinical progress. A review of the current status and prospects. Osteoarthritis and Cartilage 2002; **10**, 432–463 *Osteoarthritis Cartilage* **11**, 300–301; author reply 302–304 (2003).
46. Zeifang, F. *et al.* Autologous chondrocyte implantation using the original periosteum-cover technique versus matrix-associated autologous chondrocyte implantation: a randomized clinical trial. *Am. J. Sports Med.* **38**, 924–933 (2010).
47. de Windt, T. S., Concaro, S., Lindahl, A., Saris, D. B. & Brittberg, M. Strategies for patient profiling in articular cartilage repair of the knee: a prospective cohort of patients treated by one experienced cartilage surgeon. *Knee Surg. Sports Traumatol. Arthrosc.* **20**, 2225–2232 (2012).
48. Filardo, G., Kon, E., Di Martino, A., Iacono, F. & Marcacci, M. Arthroscopic second-generation autologous chondrocyte implantation: a prospective 7-year follow-up study. *Am. J. Sports Med.* **39**, 2153–2160 (2011).
49. Kon, E. *et al.* Arthroscopic second-generation autologous chondrocyte implantation compared with microfracture for chondral lesions of the knee: prospective nonrandomized study at 5 years. *Am. J. Sports Med.* **37**, 33–41 (2009).
50. Saris, D. B. *et al.* Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture. *Am. J. Sports Med.* **36**, 235–246 (2008).
51. Roos, E. M. & Lohmander, L. S. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual. Life Outcomes* **1**, 64 (2003).
52. Roos, E. M., Roos, H. P., Lohmander, L. S., Ekdahl, C. & Beynnon, B. D. Knee Injury and Osteoarthritis Outcome Score (KOOS)–development of a self-administered outcome measure. *J. Orthop. Sports Phys. Ther.* **28**, 88–96 (1998).
53. Knutsen, G. *et al.* A randomized trial comparing autologous chondrocyte implantation with microfracture. Findings at five years. *J. Bone Joint Surg. Am.* **89**, 2105–2112 (2007).
54. Knutsen, G. *et al.* Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. *J. Bone Joint Surg. Am.* **86-A**, 455–464 (2004).
55. Peterson, L. *et al.* Two- to 9-year outcome after autologous chondrocyte transplantation of the knee. *Clin. Orthop. Relat. Res.* 212–234 (2000).
56. Saris, D. B. *et al.* Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. *Am. J. Sports Med.* **37** (Suppl. 1), 10–19 (2009).
57. Vanlauwe, J. *et al.* Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. *Am. J. Sports Med.* **39**, 2566–2574 (2011).
58. Bekkers, J. E., Inklaar, M. & Saris, D. B. Treatment selection in articular cartilage lesions of the knee: a systematic review. *Am. J. Sports Med.* **37** (Suppl. 1), 148–55 (2009).
59. de Windt, T. S., Bekkers, J. E., Creemers, L. B., Dhert, W. J. & Saris, D. B. Patient profiling in cartilage regeneration: prognostic factors determining success of treatment for cartilage defects. *Am. J. Sports Med.* **37** (Suppl. 1), 58–62 (2009).
60. Hendriks, J., Riesle, J. & van Blitterswijk, C. A. Co-culture in cartilage tissue engineering. *J. Tissue Eng. Regen. Med.* **1**, 170–178 (2007).
61. Leijten, J. C., Georgi, N., Wu, L., van Blitterswijk, C. A. & Karperien, M. Cell sources for articular cartilage repair strategies: shifting from monocultures to cocultures. *Tissue Eng. Part B Rev.* **19**, 31–49 (2013).
62. Mo, X. T. *et al.* Variations in the ratios of co-cultured mesenchymal stem cells and chondrocytes regulate the expression of cartilaginous and osseous phenotype in alginate constructs. *Bone* **45**, 42–51 (2009).
63. Wu, L. *et al.* Trophic effects of mesenchymal stem cells increase chondrocyte proliferation and matrix formation. *Tissue Eng. Part A* **17**, 1425–1436 (2011).
64. European Medicines Agency. *EU Clinical Trials Register* [online], https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-001570-29 (2012).
65. Lee, C. H. *et al.* Regeneration of the articular surface of the rabbit synovial joint by cell homing: a proof of concept study. *Lancet* **376**, 440–448 (2010).
66. Sekiya, I. *et al.* Human mesenchymal stem cells in synovial fluid increase in the knee with degenerated cartilage and osteoarthritis. *J. Orthop. Res.* **30**, 943–949 (2012).
67. Gudas, R. *et al.* Ten-year follow-up of a prospective, randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the treatment of osteochondral defects in the knee joint of athletes. *Am. J. Sports Med.* **4**, 2499–2508 (2012).
68. Centeno, C. J. *et al.* Safety and complications reporting update on the re-implantation of culture-expanded mesenchymal stem cells using autologous platelet lysate technique. *Curr. Stem Cell Res. Ther.* **5**, 81–93 (2010).
69. Davatchi, F., Abdollahi, B. S., Mohyeddin, M., Shahram, F. & Nikbin, B. Mesenchymal stem cell therapy for knee osteoarthritis. Preliminary report of four patients. *Int. J. Rheum. Dis.* **14**, 211–215 (2011).
70. Koh, Y. G. & Choi, Y. J. Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis. *Knee* **19**, 902–907 (2012).
71. Lafeber, F. P., Intema, F., Van Roermund, P. M. & Marijnissen, A. C. Unloading joints to treat osteoarthritis, including joint distraction. *Curr. Opin. Rheumatol.* **18**, 519–525 (2006).
72. Intema, F. *et al.* Subchondral bone remodeling is related to clinical improvement after joint distraction in the treatment of ankle osteoarthritis. *Osteoarthritis Cartilage* **19**, 668–675 (2011).
73. Kanbe, K., Hasegawa, A., Takagishi, K., Kaneko, H. & Nakajima, Y. Arthroscopic findings of the joint distraction for the patient with chondrolysis of the ankle. *Diagn. Ther. Endosc.* **4**, 101–105 (1997).
74. Lamm, B. M. & Gourdine-Shaw, M. MRI evaluation of ankle distraction: a preliminary report. *Clin. Podiatr. Med. Surg.* **26**, 185–191 (2009).
75. Marijnissen, A. C. *et al.* Clinical benefit of joint distraction in the treatment of severe osteoarthritis of the ankle: proof of concept in an open prospective study and in a randomized controlled study. *Arthritis Rheum.* **46**, 2893–2902 (2002).
76. Paley, D., Lamm, B. M., Purohit, R. M. & Specht, S. C. Distraction arthroplasty of the ankle–how far can you stretch the indications? *Foot Ankle Clin.* **13**, 471–484, ix (2008).
77. Ploegmakers, J. J. *et al.* Prolonged clinical benefit from joint distraction in the treatment of ankle osteoarthritis. *Osteoarthritis Cartilage* **13**, 582–588 (2005).
78. Sabharwal, S. & Schwechter, E. M. Five-year followup of ankle joint distraction for post-traumatic chondrolysis in an adolescent: a case report. *Foot Ankle Int.* **28**, 942–948 (2007).
79. Saltzman, C. L., Hillis, S. L., Stolley, M. P., Anderson, D. D. & Amendola, A. Motion versus fixed distraction of the joint in the treatment of ankle osteoarthritis: a prospective randomized controlled trial. *J. Bone Joint Surg. Am.* **94**, 961–970 (2012).
80. Tellisi, N., Fragomen, A. T., Kleinman, D., O'Malley, M. J. & Rozbruch, S. R. Joint preservation of the osteoarthritic ankle using distraction arthroplasty. *Foot Ankle Int.* **30**, 318–325 (2009).
81. Van Meegeren, M. E. *et al.* Joint distraction results in clinical and structural improvement of haemophilic ankle arthropathy: a series of three cases. *Haemophilia* **18**, 810–817 (2012).
82. van Valburg, A. A. *et al.* Can Ilizarov joint distraction delay the need for an arthrodesis of the ankle? A preliminary report. *J. Bone Joint Surg. Br.* **77**, 720–725 (1995).

83. van Valburg, A. A. *et al.* Joint distraction in treatment of osteoarthritis: a two-year follow-up of the ankle. *Osteoarthritis Cartilage.* **7**, 474–479 (1999).
84. Abouheif, M. M. *et al.* Repair of a large osteochondral defect in the knee joint using autologous and artificial bone graft combined with motion preserving distraction arthroplasty: a case report. *Arch. Orthop. Trauma Surg.* **130**, 231–236 (2010).
85. Aldegheri, R., Trivella, G. & Saleh, M. Articulated distraction of the hip. Conservative surgery for arthritis in young patients. *Clin. Orthop. Relat. Res.* 94–101 (1994).
86. Aly, T. A., Hafez, K. & Amin, O. Arthrodiatasis for management of knee osteoarthritis. *Orthopedics* **34**, e338–e343 (2011).
87. Deie, M. *et al.* Knee articulated distraction arthroplasty for the middle-aged osteoarthritic knee joint. *Tech. Knee Surg.* **9**, 80–84 (2010).
88. Deie, M., Ochi, M., Adachi, N., Kajiwara, R. & Kanaya, A. A new articulated distraction arthroplasty device for treatment of the osteoarthritic knee joint: a preliminary report. *Arthroscopy* **23**, 833–838 (2007).
89. Gomez, J. A. *et al.* Articulated hip distraction: a treatment option for femoral head avascular necrosis in adolescence. *J. Pediatr. Orthop.* **29**, 163–169 (2009).
90. Intema, F. *et al.* Tissue structure modification in knee osteoarthritis by use of joint distraction: an open 1-year pilot study. *Ann. Rheum. Dis.* **70**, 1441–1446 (2011).
91. Thacker, M. M., Feldman, D. S., Madan, S. S., Straight, J. J. & Scher, D. M. Hinged distraction of the adolescent arthritic hip. *J. Pediatr. Orthop.* **25**, 178–182 (2005).
92. Koshino, T., Wada, S., Ara, Y. & Saito, T. Regeneration of degenerated articular cartilage after high tibial valgus osteotomy for medial compartmental osteoarthritis of the knee. *Knee* **10**, 229–236 (2003).
93. Marijnissen, A. C. *et al.* Knee Images Digital Analysis (KIDA): a novel method to quantify individual radiographic features of knee osteoarthritis in detail. *Osteoarthritis Cartilage* **16**, 234–243 (2008).
94. Wiegant, K. *et al.* Structural tissue changes and prolonged clinical improvement by joint distraction in treatment of end-stage knee osteoarthritis; the 2 years follow-up. *Osteoarthritis Cartilage*, **19** (Suppl. 1), 36 (2011).
95. Bain, G. I., Mehta, J. A., Heptinstall, R. J. & Bria, M. Dynamic external fixation for injuries of the proximal interphalangeal joint. *J. Bone Joint Ssurg. Br.* **80**, 1014–1019 (1998).
96. DeVries, J. G., Amiot, R. A., Cummings, P. & Sockrider, N. Freiberg's infraction of the second metatarsal treated with autologous osteochondral transplantation and external fixation. *J. Foot Ankle Surg.* **47**, 565–570 (2008).
97. van Roermund, P. M. *et al.* Function of stiff joints may be restored by Ilizarov joint distraction. *Clin. Orthop. Relat. Res.* 220–227 (1998).
98. Judet, R. & Judet, T. [The use of a hinge distraction apparatus after arthrolysis and arthroplasty (author's transl)]. Revue de chirurgie orthopedique et reparatrice de l'appareil moteur [French] **64**, 353–365 (1978).
99. Cañadell, J., Gonzales, F., Barrios, R. H. & Amillo, S. Arthrodiastasis for stiff hips in young patients. *Int. Orthop.* **17**, 254–258 (1993).
100. Morrey, B. F. Posttraumatic stiffness: distraction arthroplasty. *Orthopedics* **15**, 863–869 (1992).
101. Clifford, A., O'Connell, M., Gabriel, S., Miller, L. E. & Block, J. E. The KineSpring load absorber implant: rationale, design and biomechanical characterization. *J. Med. Eng. Technol.* **35**, 65–71 (2011).
102. Allen, M. J. *et al.* Evaluation of the safety of a novel knee load-bypassing device in a sheep model. *J. Bone Joint Surg. Am.* **94**, 77–84 (2012).
103. Kajiwara, R. *et al.* Effective repair of a fresh osteochondral defect in the rabbit knee joint by articulated joint distraction following subchondral drilling. *J. Orthop. Res.* **23**, 909–915 (2005).
104. Nishino, T. *et al.* Joint distraction and movement for repair of articular cartilage in a rabbit model with subsequent weight-bearing. *J. Bone Joint Surg. Br.* **92**, 1033–1040 (2010).
105. Nishino, T. *et al.* Effect of gradual weight-bearing on regenerated articular cartilage after joint distraction and motion in a rabbit model. *J. Orthop. Res.* **28**, 600–606 (2010).
106. Yanai, T., Ishii, T., Chang, F. & Ochiai, N. Repair of large full-thickness articular cartilage defects in the rabbit: the effects of joint distraction and autologous bone-marrow-derived mesenchymal cell transplantation. *J. Bone Joint Surg. Br.* **87**, 721–729 (2005).
107. van Valburg, A. A. *et al.* Joint distraction in treatment of osteoarthritis (II): effects on cartilage in a canine model. *Osteoarthritis Cartilage* **8**, 1–8 (2000).
108. Karadam, B., Karatosun, V., Murat, N., Ozkal, S. & Gunal, I. No beneficial effects of joint distraction on early microscopical changes in osteoarthrotic knees. A study in rabbits. *Acta Orthop.* **76**, 95–98 (2005).
109. Kroeber, M. *et al.* Effects of controlled dynamic disc distraction on degenerated intervertebral discs: an *in vivo* study on the rabbit lumbar spine model. *Spine (Phila Pa 1976)* **30**, 181–187 (2005).
110. McAlindon, T. E., Driban, J. B. & Lo, G. H. Osteoarthritis year 2011 in review: clinical. *Osteoarthritis Cartilage* **20**, 197–200 (2012).
111. Parker, D. A., Beatty, K. T., Giuffre, B., Scholes, C. J. & Coolican, M. R. Articular cartilage changes in patients with osteoarthritis after osteotomy. *Am. J. Sports Med.* **39**, 1039–1045 (2011).
112. Burr, D. B. & Gallant, M. A. Bone remodelling in osteoarthritis. *Nat. Rev. Rheumatol.* **8**, 665–673 (2012).
113. Jones, E. A. *et al.* Synovial fluid mesenchymal stem cells in health and early osteoarthritis: detection and functional evaluation at the single-cell level. *Arthritis Rheum.* **58**, 1731–1740 (2008).
114. Jones, E. A. *et al.* Isolation and characterization of bone marrow multipotential mesenchymal progenitor cells. *Arthritis Rheum.* **46**, 3349–3360 (2002).
115. Koelling, S. *et al.* Migratory chondrogenic progenitor cells from repair tissue during the later stages of human osteoarthritis. *Cell Stem Cell* **4**, 324–335 (2009).
116. Vinardell, T., Buckley, C. T., Thorpe, S. D. & Kelly, D. J. Composition-function relations of cartilaginous tissues engineered from chondrocytes and mesenchymal stem cells isolated from bone marrow and infrapatellar fat pad. *J. Tissue Eng. Regen. Med.* **5**, 673–683 (2011).
117. Richter, W. Mesenchymal stem cells and cartilage in situ regeneration. *J. Intern. Med.* **266**, 390–405 (2009).
118. Grad, S., Eglin, D., Alini, M. & Stoddart, M. J. Physical stimulation of chondrogenic cells *in vitro*: a review. *Clin. Orthop. Relat Res.* **469**, 2764–2772 (2011).
119. Nohmi, S. *et al.* Post injury changes in the properties of mesenchymal stem cells derived from human anterior cruciate ligaments. *Int. Orthop.* **36**, 1515–1522 (2012).
120. Mobasheri, A., Csaki, C., Clutterbuck, A. L., Rahmanzadeh, M. & Shakibaei, M. Mesenchymal stem cells in connective tissue engineering and regenerative medicine: applications in cartilage repair and osteoarthritis therapy. *Histol. Histopathol.* **24**, 347–366 (2009).
121. Spector, T. D. *et al.* Effect of risedronate on joint structure and symptoms of knee osteoarthritis: results of the BRISK randomized, controlled trial [ISRCTN01928173]. *Arthritis Res. Ther.* **7**, R625–R633 (2005).
122. Brandt, K. D., Mazzuca, S. A., Katz, B. P. *et al.* Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. *Arthritis Rheum.* **52**, 2015–2025 (2005).
123. Pavelká, K. *et al.* Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch. Intern. Med.* **162**, 2113–2123 (2002).
124. Kahan, A., Uebelhart, D., De Vathaire, F., Delmas, P. D. & Reginster, J. Y. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* **60**, 524–533 (2009).
125. Sawitzke, A. D. *et al.* The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: a report from the glucosamine/chondroitin arthritis intervention trial. *Arthritis Rheum.* **58**, 3183–3191 (2008).
126. US National Library of Medicine. *ClinicalTrials.gov* [online], http://www.clinicaltrials.gov/ct2/show/NCT00911469 (2011).
127. Krzeski, P. *et al.* Development of musculoskeletal toxicity without clear benefit after administration of PG-116800, a matrix metalloproteinase inhibitor, to patients with knee osteoarthritis: a randomized, 12-month, double-blind, placebo-controlled study. *Arthritis Res. Ther.* **9**, R109 (2007).
128. US National Library of Medicine. ClinicalTrials.gov [online], http://www.clinicaltrials.gov/ct2/how/NCT00427687 (2007).

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