Open Access Rheumatology: Research and Reviews

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Novel treatments for osteoarthritis: an update

This article was published in the following Dove Press journal:
Open Access Rheumatology: Research and Reviews

Yong Wu[1,*]
En Lin Goh[2,*]
Dong Wang[3]
Shaocheng Ma[3]

[1]Leicester Medical School, University of Leicester, Leicester, UK; [2]Faculty of Medicine, Imperial College London, London, UK; [3]Biomechanics Research Group, Imperial College London, London, UK

*These authors contributed equally to this work

Abstract: Osteoarthritis is the most prevalent chronic joint condition worldwide. The principles of osteoarthritis treatment are to alleviate pain and stiffness as well as maintain function, with current consensus guidelines recommending the use of a combination of conservative measures including physical therapy, analgesia, and surgical interventions such as arthroplasty. In recent years, several pharmacological therapies have emerged as potential alternatives. Although a disease-modifying osteoarthritis drug has yet to be identified, promising results have been reported in recent trials especially with serotonin–norepinephrine reuptake inhibitors, IL-1 antagonists, and antibodies to nerve growth factor. The present review aims to summarize and discuss the latest results of novel treatments for osteoarthritis and potential targets for future research.

Keywords: osteoarthritis, novel treatment, future therapy, review

Introduction

Osteoarthritis is a degenerative joint disease characterized by articular cartilage destruction, synovial membrane inflammation, and subchondral bone remodeling.[1] This condition is estimated to affect more than 10% of the population over the age of 60 years and is a major cause of morbidity, disability, and limitations on quality of life.[2–4] With the rise in life expectancy, the prevalence of osteoarthritis is projected to increase further, resulting in a greater healthcare burden. The principles of treatment are to alleviate pain and stiffness and maintain function, with current consensus guidelines recommending the use of a combination of physical therapy, analgesia with paracetamol or NSAIDs, and surgical intervention where necessary.[2]

The majority of individuals with osteoarthritis are managed successfully with a combination of the aforementioned treatments, but there is still a significant group of patients in whom these treatments do not provide adequate pain relief. Furthermore, there remains a lack of treatments available that have demonstrated effectiveness in stopping or reversing the degenerative process. Randomized controlled trials (RCTs) evaluating nonsurgical treatments on this topic are of poor methodological quality due to the lack of standardized outcomes and small sample sizes.[5,6] Research has also focused predominantly on patients with osteoarthritis of the hip and knee, with less emphasis on the hands, which is more complex.

Recent progress in osteoarthritis research has improved our understanding of the pathophysiology of the disease.[7] Specifically, the identification of the TGF-β and Wnt/β-catenin signaling pathways provide hope for a disease-modifying osteoarthritis drug.[8,9] In recent years, several novel agents have emerged as potential treatment alternatives

Correspondence: Shaocheng Ma
Biomechanics Research Group, Imperial College London, South Kensington Campus, 774, 7th Floor, City and Guilds Building, London, SW7 2AZ, UK
Tel +44 07 518 913 344
Email shaocheng.ma10@imperial.ac.uk

http://dx.doi.org/10.2147/OARRR.S176666

to improve pain, stiffness, and function with the possibility of altering disease progression. This review aims to provide an update on the most promising treatments and summarize the evidence base behind these agents.

Emerging therapies

Serotonin–norepinephrine reuptake inhibitors

Recent evidence has implicated central sensitization as an important factor in mediating pain in osteoarthritis.[10–12] The findings of Arendt-Nielsen et al lend support to this theory, where the authors observed abnormal windup in their cohort of patients with knee osteoarthritis.[13] This finding may explain the limited efficacy demonstrated by analgesics such as paracetamol and NSAIDs that target peripheral sensitization. Both noradrenergic and serotonergic neurons modulate nociceptive processing in the spinal cord and periaqueductal gray area and are potential targets in improving pain in osteoarthritis.[14,15] Chappell et al performed the first RCT comparing duloxetine with a placebo in 256 patients with knee osteoarthritis.[16] In this trial, patients treated with duloxetine exhibited significant improvements in average pain score, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, and Patient Global Impression of Severity index, which were observed within the first week of treatment. A subsequent RCT by Frakes et al reported that the addition of duloxetine to oral NSAID therapy was superior to oral NSAID therapy alone in reducing pain and improving function in patients with moderate to severe knee osteoarthritis.[17] The most frequent adverse effects associated with duloxetine therapy included dry mouth, nausea, constipation, fatigue, and reduced appetite. These studies led to the approval of duloxetine for the treatment of chronic knee osteoarthritis by the Food and Drug Administration (FDA). Duloxetine is recommended by the American College of Rheumatologists in patients with inadequate response to conventional pharmacological agents.[18] There are currently ongoing trials investigating milnacipran, which is used in fibromyalgia for osteoarthritis. A theoretical advantage of this drug over duloxetine is that it exhibits balanced affinity for noradrenergic and serotonergic reuptake transporters, thereby conferring superior efficacy.[19,20]

Strontium ranelate

The rationale for testing strontium ranelate for the treatment of osteoarthritis was first proposed following post hoc analysis of spine radiographs from osteoporosis studies.[21] A smaller proportion of patients treated with strontium ranelate experienced an increase in overall arthritis score and joint space narrowing compared with patients treated with a placebo. Strontium ranelate inhibits subchondral bone resorption by regulating the activity of osteoprotegerin, RANK ligand, and matrix metalloproteinases (MMPs) produced by osteoblasts.[22] Correspondingly, this may have a direct effect on cartilage, thereby restoring the balance between the catabolic and anabolic effects of chondrocytes that occurs in osteoarthritis. This is supported by the observation that strontium ranelate promotes proteoglycan synthesis, which stimulates cartilage matrix formation in vitro.[23] In their study on dogs, Pelletier et al observed that strontium ranelate treatment led to decreased expression of IL-1β and MMPs, which was accompanied by a reduction in osteoarthritis cartilage lesions and subchondral bone thickening.[24] A recent RCT performed by Reginster et al enrolled 1,371 patients with symptomatic knee osteoarthritis.[25] Patients were randomized to receive either strontium ranelate or a placebo daily for three years. The primary endpoint of this study was the change in joint space width (JSW) in the medial compartment. Secondary endpoints included pain and function. At the end of the study, patients taking strontium ranelate had 30% reduction in the rate of decline in JSW, which was accompanied by modest symptomatic improvement. It must be noted that there was a minimal effect on the overall WOMAC score and WOMAC pain subscore and a symptomatic benefit was only evident with a higher dose.

IL-1 receptor antagonists

The role of IL-1 in osteoarthritis has been well described. Analysis of synovial fluid of both human and experimental models of osteoarthritis revealed significantly elevated levels of IL-1, which correlated with the severity of radiographic changes.[26] In in vitro and in vivo models, IL-1 stimulates the production of MMPs while reducing the production of aggrecan and proteoglycans, resulting in an imbalance in the catabolic and anabolic responses of stimulated chondrocytes.[27] These studies have implicated IL-1 signaling as the significant driving factor in the degenerative process occurring in the osteoarthritis joint, thereby making it a potential therapeutic target. In animal models, the use of an IL-1 receptor antagonist was associated with positive results in terms of cartilage preservation.[28] However, the positive effects of IL-1 receptor antagonist have yet to be replicated in human trials. An RCT by Chevalier et al on 170 patients comparing two doses of anakinra (a recombinant modified human IL-1 receptor antagonist protein) with a placebo showed improvements in the WOMAC pain score after four days although this was not sustained till 12 weeks.[29] A subsequent study

performed by Cohen et al compared AMG 108, a fully human, immunoglobulin G2 (IgG2) monoclonal antibody against IL-1 receptor type 1 with a placebo in a two-part RCT.[30] At the study endpoint, patients who received AMG 108 had greater pain improvement as reported by the WOMAC pain score, although this was not significant. Notably, patients with a high baseline level of pain (WOMAC index >325) experienced greater pain improvements so the lack of significant difference may be the result of the small number of patients in that subgroup, which may contribute to the overall negative result. However, there is concern regarding the safety profile of AMG 108, which was found to decrease the neutrophil count and may have significant clinical implications. Despite the negative results, IL-1 receptor antagonist may exhibit a degree of clinical and structural benefit, which may be more apparent in patients with severe osteoarthritis.[29] Current findings warrant further interrogation of the efficacy and safety profile in patients with severe osteoarthritis.

Antibodies to nerve growth factor (NGF)

NGF plays an important role in the development of the nervous system and pain. It is postulated that NGF signaling modulates the expression of peripheral and central pain-related substances and sensitizes adjacent nociceptive neurons in response to inflammation.[31] Several experimental models have demonstrated that proinflammatory cytokines such as IL-1β and mechanical overloading increase levels of NGF, which explains the elevated levels of NGF found in synovial fluid of patients with osteoarthritis.[32–34] These findings led to the development of tanezumab, a highly selective humanized IgG2 monoclonal antibody against NGF. In the initial proof-of-concept study on 450 patients with moderate-to-severe knee osteoarthritis, tanezumab use resulted in three times greater improvement in knee pain, stiffness, and physical function compared with the placebo.[35] A subsequent RCT conducted by Brown et al reported significant improvements in the WOMAC and Patient Global Assessment scores in the tanezumab group.[36] However, several safety issues remain unanswered. In particular, tanezumab therapy was associated with an increased incidence of osteonecrosis, a finding that led the FDA to put the development program on hold in 2010. Following analysis of the 87 cases of osteonecrosis, Pfizer reported that only two cases displayed evidence of osteonecrosis, with a significant proportion of patients instead experiencing a syndrome of rapidly progressive and destructive osteoarthritis or subchondral insufficiency fractures of the affected joint.[37] This was associated with higher doses of tanezumab and concomitant NSAID therapy. It is plausible that the significant pain relief associated with tanezumab treatment encourages more intensive use of the compromised joint leading to further wear and tear of the damaged cartilage. Based on evidence from phase III trials, tanezumab is efficacious at improving pain and function in osteoarthritis. However, the occurrence of osteonecrosis and rapidly progressive osteoarthritis warrant further evaluation as to whether these events occur because of inhibition of the NGF signaling pathway or due to the pharmacological profile.

Regenerative therapy

The role of cell-based therapy in cartilage repair has grown rapidly as this strategy offers a long-term solution for the repair and regeneration of cartilage, which can delay or reverse the progression of osteoarthritis. Mesenchymal stem cells (MSCs) are a potential cell source as they can be easily obtained from a variety of tissue types including bone marrow, adipose tissue, and synovium. Furthermore, MSCs are intrinsically capable of rapid proliferation, chondro-differentiation, and immunosuppression. Davatchi et al studied the effect of autologous bone marrow-derived MSCs in four patients with moderate-to-severe knee osteoarthritis.[38] Following injection of these MSCs into the knee joints, the authors reported mild improvements in pain at one year, which were sustained after five years.[39] Orozco et al conducted a similar study using bone marrow-derived MSCs on 12 patients with moderate-to-severe osteoarthritis.[40] Compared with the former study, a higher quantity of MSCs were used in this study. At one year follow-up, the VAS and WOMAC pain scores improved by 68% and 75%, respectively, which were statistically significant. Additionally, there was a significant decrease in poor cartilage areas, with improvement of cartilage quality in 11 of the 12 patients. However, harvesting MSCs from bone marrow is difficult, painful, and associated with complications. Thus, adipose tissue-derived MSCs may prove to be a more feasible alternative. An initial study by Koh et al utilized MSCs harvested from the inner side of the infrapatellar fat pad, which were prepared with platelet-rich plasma and administered to 18 patients.[41] There were significant improvements in the WOMAC, VAS, and Lysholm scores as well as cartilage growth after two years of follow-up. However, a case–control study by Koh and Choi using the same technique failed to demonstrate any superiority compared with the placebo comprising platelet-rich plasma despite improvements from baseline.[42] The effects of MSC-based therapies on clinical and structural outcomes are encouraging, but these have been confined to small case series. Larger scale studies with longer

follow-up are required to fully assess the efficacy, safety, and feasibility of this treatment strategy.

Future therapies

MMP-13 and ADAMTS-5 are key matrix degrading enzymes in the pathogenesis of osteoarthritis. In the murine model of osteoarthritis, CL82198, an MMP-13 inhibitor effectively slowed progression of cartilage destruction, increased extracellular matrix production, and inhibited chondrocyte apoptosis.[43] However, these findings have yet to be replicated in humans. To date, the only clinical study of an MMP inhibitor (PG-116800) was terminated because of musculoskeletal toxicity without clinical benefit.[44] PG-116800 demonstrates affinity for a wide range of MMPs, including MMP-1 and MMP-7, which are thought to be implicated in the development of musculoskeletal toxicity.[45] Thus, further research is necessary to fully assess the safety and efficacy of MMP inhibitors.

Chen et al investigated the use of an ADAMTS-5 inhibitor to treat osteoarthritis of the knee joint in rats.[46] In this study, the combination of an ADAMTS-5 inhibitor (114810) and hyaluronic acid hydrogel ameliorated cartilage degeneration and promoted cartilage regeneration after 8 weeks, thereby confirming ADAMTS-5 as a promising target for osteoarthritis treatment. Additionally, syndecan-4 has been identified as an important regulator of ADAMTS-5 activation.[47] The use of a syndecan-4-specific antibody therefore has the potential to prevent ADAMTS-5 activation and consequently, prevent the progression of osteoarthritis.

The majority of research into therapeutic targets has focused on the articular cartilage, but subchondral bone may play an important role in the disease process. TGF-β has been identified as an important mediator of subchondral bone development. Zhen et al reported TGF-β1 activation in subchondral bone in response to altered mechanical loading in an anterior cruciate ligament transection model of mouse osteoarthritis.[48] Furthermore, the authors noted that inhibition of TGF-β activity in subchondral bone attenuated degeneration of articular cartilage. Additionally, the Wnt/β-catenin signaling may prove to be another promising target.[49] In a recent study, Dkk-1 inhibition of this pathway was found to ameliorate the osteoarthritis in the mouse model.[50] These findings underline the importance of considering osteoarthritis as a disease of the whole joint.

Apocynin and paeonol (APPA) are plant-derived compounds with anti-inflammatory and chondroprotective properties. Apocynin inhibits the neutrophil oxidative burst, while paeonol suppresses the expression of iNOS and cyclo-oxygenase-2.[51–53] Hence, the combination of these compounds (APPA) may prove beneficial in improving pain and function as well as limiting disease progression in osteoarthritis. In animal models, APPA treatment has demonstrated improvements in pain and function, with comparable effects to NSAIDs.[54,55]

Conclusions

Progress in osteoarthritis research has resulted in the identification of signaling pathways with potential mechanistic targets. This has led to the emergence of a variety of symptomatic and disease-modifying therapies in recent years. It is evident that osteoarthritis is not solely a disease caused by "wear and tear" of the joint rather a complex interplay between catabolic and anabolic effects of chondrocytes, which involves the entire joint. Given the multiple pathways involved in this disorder, it is unlikely that targeting a single molecule by a specific mechanism will be effective at combating the disease. As with other chronic disorders, the future of osteoarthritis treatment may lie in combination therapy.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Glyn-Jones S, Palmer AJR, Agricola R, et al. Osteoarthritis. *Lancet*. 2015;386(9991):376–387.
2. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. *Lancet*. 2011;377(9783):2115–2126.
3. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. *Clin Geriatr Med*. 2010;26(3):355–369.
4. Hoogeboom TJ, den Broeder AA, de Bie RA, van den Ende CH. Longitudinal impact of joint pain comorbidity on quality of life and activity levels in knee osteoarthritis: data from the Osteoarthritis Initiative. *Rheumatology*. 2013;52(3):543–546.
5. Towheed TE. Systematic review of therapies for osteoarthritis of the hand. *Osteoarthritis Cartilage*. 2005;13(6):455–462.
6. Lue S, Koppikar S, Shaikh K, Mahendira D, Towheed TE. Systematic review of non-surgical therapies for osteoarthritis of the hand: an update. *Osteoarthritis Cartilage*. 2017;25(9):1379–1389.
7. Chen D, Shen J, Zhao W, et al. Osteoarthritis: toward a comprehensive understanding of pathological mechanism. *Bone Res*. 2017;5:16044.
8. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum*. 2012;64(6):1697–1707.
9. Shen J, Li S, Chen D. TGF-β signaling and the development of osteoarthritis. *Bone Res*. 2014;2(1):1–7.
10. Imamura M, Imamura ST, Kaziyama HH, et al. Impact of nervous system hyperalgesia on pain, disability, and quality of life in patients with knee osteoarthritis: a controlled analysis. *Arthritis Rheum*. 2008;59(10):1424–1431.
11. Gwilym SE, Keltner JR, Warnaby CE, et al. Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. *Arthritis Rheum*. 2009;61(9):1226–1234.
12. Lee YC, Lu B, Bathon JM, et al. Pain sensitivity and pain reactivity in osteoarthritis. *Arthritis Care Res*. 2011;63(3):320–327.
13. Arendt-Nielsen L, Nie H, Laursen MB, et al. Sensitization in patients with painful knee osteoarthritis. *Pain*. 2010;149(3):573–581.

14. Aimone LD, Jones SL, Gebhart GF. Stimulation-produced descending inhibition from the periaqueductal gray and nucleus raphe magnus in the rat: mediation by spinal monoamines but not opioids. *Pain*. 1987;31(1):123–136.
15. Peng YB, Lin Q, Willis WD. Involvement of alpha-2 adrenoceptors in the periaqueductal gray-induced inhibition of dorsal horn cell activity in rats. *J Pharmacol Exp Ther*. 1996;278(1):125–135.
16. Chappell AS, Desaiah D, Liu-Seifert H, et al. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. *Pain Pract*. 2011;11(1):33–41.
17. Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. *Curr Med Res Opin*. 2011;27(12):2361–2372.
18. Hochberg MC, Altman RD; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res*. 2012;64(4):465–474.
19. Vaishnavi SN, Nemeroff CB, Plott SJ, Rao SG, Kranzler J, Owens MJ. Milnacipran: a comparative analysis of human monoamine uptake and transporter binding affinity. *Biol Psychiatry*. 2004;55(3):320–322.
20. Onghena P, van Houdenhove B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. *Pain*. 1992;49(2):205–219.
21. Bruyere O, Delferriere D, Roux C, et al. Effects of strontium ranelate on spinal osteoarthritis progression. *Ann Rheum Dis*. 2008;67(3):335–339.
22. Tat SK, Pelletier JP, Mineau F, Caron J, Martel-Pelletier J. Strontium ranelate inhibits key factors affecting bone remodeling in human osteoarthritic subchondral bone osteoblasts. *Bone*. 2011;49(3):559–567.
23. Henrotin Y, Labasse A, Zheng SX, et al. Strontium ranelate increases cartilage matrix formation. *J Bone Miner Res*. 2001;16(2):299–308.
24. Pelletier J-P, Kapoor M, Fahmi H, et al. Strontium ranelate reduces the progression of experimental dog osteoarthritis by inhibiting the expression of key proteases in cartilage and of IL-1β in the synovium. *Ann Rheum Dis*. 2012annrheumdis-2012-201710.
25. Reginster JY, Badurski J, Bellamy N, et al. Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial. *Ann Rheum Dis*. 2013;72(2):179-86annrheumdis-2012-202231.
26. Mcnulty AL, Rothfusz NE, Leddy HA, Guilak F. Synovial fluid concentrations and relative potency of interleukin-1 alpha and beta in cartilage and meniscus degradation. *J Orthop Res*. 2013;31(7):1039–1045.
27. Arend WP, Malyak M, Guthridge CJ, Gabay C. Interleukin-1 receptor antagonist: role in biology. *Annu Rev Immunol*. 1998;16(1):27–55.
28. Caron JP, Fernandes JC, Martel-Pelletier J, et al. Chondroprotective effect of intraarticular injections of interleukin-1 receptor antagonist in experimental osteoarthritis. Suppression of collagenase-1 expression. *Arthritis Rheum*. 1996;39(9):1535–1544.
29. Chevalier X, Goupille P, Beaulieu AD, et al. Intraarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum*. 2009;61(3):344–352.
30. Cohen SB, Proudman S, Kivitz AJ, et al. A randomized, double-blind study of AMG 108 (a fully human monoclonal antibody to IL-1R1) in patients with osteoarthritis of the knee. *Arthritis Res Ther*. 2011;13(4):R125.
31. Shang X, Wang Z, Tao H. Mechanism and therapeutic effectiveness of nerve growth factor in osteoarthritis pain. *Ther Clin Risk Manag*. 2017;13:951–956.
32. Aloe L, Tuveri MA, Carcassi U, Levi-Montalcini R. Nerve growth factor in the synovial fluid of patients with chronic arthritis. *Arthritis Rheum*. 1992;35(3):351–355.
33. Pecchi E, Priam S, Gosset M, et al. Induction of nerve growth factor expression and release by mechanical and inflammatory stimuli in chondrocytes: possible involvement in osteoarthritis pain. *Arthritis Res Ther*. 2014;16(1):R16.
34. Saxby DJ, Lloyd DG. Osteoarthritis year in review 2016: mechanics. *Osteoarthritis Cartilage*. 2017;25(2):190–198.
35. Lane NE, Schnitzer TJ, Birbara CA, et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. *N Engl J Med*. 2010;363(16):1521–1531.
36. Brown MT, Murphy FT, Radin DM, Davignon I, Smith MD, West CR. Tanezumab reduces osteoarthritic knee pain: results of a randomized, double-blind, placebo-controlled phase III trial. *J Pain*. 2012;13(8):790–798.
37. Food U, Administration D. *Tanezumab Arthritis Advisory Committee Briefing Document*. Vol. 2012. Silver Spring: FDA; 2015.
38. Davatchi F, Abdollahi BS, Mohyeddin M, Shahram F, Nikbin B. Mesenchymal stem cell therapy for knee osteoarthritis. Preliminary report of four patients. *Int J Rheum Dis*. 2011;14(2):211–215.
39. Davatchi F, Sadeghi Abdollahi B, Mohyeddin M, Nikbin B. Mesenchymal stem cell therapy for knee osteoarthritis: 5 years follow-up of three patients. *Int J Rheum Dis*. 2016;19(3):219–225.
40. Orozco L, Munar A, Soler R, et al. Treatment of knee osteoarthritis with autologous mesenchymal stem cells: a pilot study. *Transplantation*. 2013;95(12):1535–1541.
41. Koh YG, Jo SB, Kwon OR, et al. Mesenchymal stem cell injections improve symptoms of knee osteoarthritis. *Arthroscopy*. 2013;29(4):748–755.
42. Koh YG, Choi YJ. Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis. *Knee*. 2012;19(6):902–907.
43. Wang M, Sampson ER, Jin H, et al. MMP13 is a critical target gene during the progression of osteoarthritis. *Arthritis Res Ther*. 2013;15(1):R5.
44. Krzeski P, Buckland-Wright C, Bálint G, 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*. 2007;9(5):R109.
45. Holmbeck K, Bianco P, Caterina J, et al. MT1-MMP-deficient mice develop dwarfism, osteopenia, arthritis, and connective tissue disease due to inadequate collagen turnover. *Cell*. 1999;99(1):81–92.
46. Chen P, Zhu S, Wang Y, et al. The amelioration of cartilage degeneration by ADAMTS-5 inhibitor delivered in a hyaluronic acid hydrogel. *Biomaterials*. 2014;35(9):2827–2836.
47. Echtermeyer F, Bertrand J, Dreier R, et al. Syndecan-4 regulates ADAMTS-5 activation and cartilage breakdown in osteoarthritis. *Nat Med*. 2009;15(9):1072–1076.
48. Zhen G, Wen C, Jia X, et al. Inhibition of TGF-β signaling in mesenchymal stem cells of subchondral bone attenuates osteoarthritis. *Nat Med*. 2013;19(6):704–712.
49. Lories RJ, Corr M, Lane NE. To Wnt or not to Wnt: the bone and joint health dilemma. *Nat Rev Rheumatol*. 2013;9(6):328–339.
50. Funck-Brentano T, Bouaziz W, Marty C, Geoffroy V, Hay E, Cohen-Solal M. Dkk-1-mediated inhibition of Wnt signaling in bone ameliorates osteoarthritis in mice. *Arthritis Rheumatol*. 2014;66(11):3028–3039.
51. 't Hart BA, Simons JM, Knaan-Shanzer S, Bakker NP, Labadie RP. Antiarthritic activity of the newly developed neutrophil oxidative burst antagonist apocynin. *Free Radic Biol Med*. 1990;9(2):127–131.
52. Hougee S, Hartog A, Sanders A, et al. Oral administration of the NADPH-oxidase inhibitor apocynin partially restores diminished cartilage proteoglycan synthesis and reduces inflammation in mice. *Eur J Pharmacol*. 2006;531(1-3):264–269.
53. Chae HS, Kang OH, Lee YS, et al. Inhibition of LPS-induced iNOS, COX-2 and inflammatory mediator expression by paeonol through the MAPKs inactivation in RAW 264.7 cells. *Am J Chin Med*. 2009;37(1):181–194.
54. Glasson S, Larkins N. APPA provides symptom relief in clinical canine osteoarthritis. *Osteoarthritis Cartilage*. 2012;20:S287.
55. Larkins N, King C. Effectiveness of apocynin-paeonol (APPA) for the management of osteoarthritis in dogs: comparisons with placebo and meloxicam in client-owned dogs. *Matters*. 2017;3(7):e201608000001.