Abstract
Osteoarthritis (OA), by far the most common form of arthritis, has a growing impact on health care. Progress in understanding its pathophysiological processes has led to the identification of promising therapeutic targets, with disease-modifying osteoarthritis drugs (DMOADs) having the most potential. Numerous nonpharmaceutical measures and pharmacological interventions that slow the progression of the disease also have been developed. Several new classes of molecules that inhibit one or more OA pathophysiological processes have been discovered, and a number of these are under clinical evaluation to test their potential to alter the disease process in humans. Recent data from clinical trials have demonstrated that agents able to specifically block key disease mechanisms can effectively retard the progression of structural changes in knee OA patients. These studies are ushering the field into a new era in the development of DMOADs and, hence, the prospect of a cure for this disease.

Osteoarthritis (OA), in the context of the aging population, is a very significant medical problem that has a major impact on the quality of life of a rapidly growing number of patients. It is hoped that the several therapeutic strategies that have been developed and new therapies currently in development will prevent or slow down the progression of this debilitating disease.

Although the development of disease-modifying osteoarthritis drugs (DMOADs) is a rather complex process, the large body of new information generated by research provides guidance in the development of new and novel therapeutic strategies to delay the progression of structural changes in OA. It is also understood that a comprehensive therapeutic intervention in OA should integrate an understanding of the major pathophysiological factors that contribute to the progression of the disease at both the clinical and molecular levels. To that effect, clinical trials have identified the important contributions of a number of risk factors for disease progression. This type of information is essential for a comprehensive and effective approach to the treatment of the disease.

This article aims at providing a global perspective of the issues related to DMOAD approaches used in clinics today, as well as an update on the current strategies for developing a new generation of disease-modifying drugs and agents. A review of the most attractive therapeutic targets, as well as results from recent DMOAD trials will also be presented. Issues related to these trials, including study design, imaging technology, and safety concerns, will be discussed. The prospect of the use of DMOADs in the management of OA patients in the future will also be reviewed.

Pathophysiological Mechanisms, Risk Factors for Disease Development and Progression, and Therapeutic Targets
The issues related to OA disease development and progression have been the subject of a number of interesting studies and review articles.1-7 To summarize, in many instances, a large number of risk factors, as well as molecular and structural changes, are believed to act in combination to progressively induce changes seen in OA. Therefore, therapeutic intervention aimed at reducing or stopping the disease progression must integrate these into a global strategy, which is required for any therapeutic intervention
to be effective.3

Pathophysiological Mechanisms
In brief, the morphological changes observed in OA include alterations in the cartilage, subchondral bone, and synovial membrane.1,2,8 These changes are believed to be related to a complex network of biochemical pathways, which implicate the diffusion of catabolic factors and cytokines between the different joint tissues to the cartilage. There is evidence that the molecular cross-talk between the above tissues is an integral part of the disease pathogenesis.

Current knowledge points to an important involvement of the metalloprotease (MMP) class in the OA process.1,2,8 Collagenase-3 (MMP-13) was demonstrated to play a major role in cartilage degeneration. It is also suggested that another enzyme, aggrecanase-2, or ADAMTS-5 (a disintegrin and MMP domain with thrombospondin motifs), plays a predominant role in the proteolysis of OA cartilage aggrecan.9,10 Growth factors are likely candidates to be involved in cartilage regeneration. Among these, tumor growth factor (TGF-β) and insulin-like growth factor (IGF-1) have been studied extensively with respect to their expression and roles in OA. Recently, other factors, such as the bone morphogenic proteins (BMP), have received more attention with respect to their implication in OA. BMPs are known for their role in the maintenance and repair of bone, cartilage, and other tissues in adults. Interestingly, BMP activity and bioavailability can be controlled by specific antagonists. There have been demonstrations of a possible role for some BMP antagonists in OA pathogenesis. Importantly, in OA cartilage, a differential topographical distribution and synthesis regulation was found between some members of the BMP antagonists, suggesting a differential role in this tissue during the stages of the disease.

Even if cartilage destruction is a major characteristic of the OA condition, synovial inflammation is of fundamental importance in the progression of cartilage lesions. Findings point to the importance of the production by the OA synovial membrane of a number of proinflammatory cytokines in the catabolic process in OA, IL-1β being among the prime cytokines in the etiopathogenesis of the disease.1,2

Recent studies also suggest that very early in the OA process, biological and morphological disturbances occur at the subchondral bone, and that alterations in this tissue are responsible for early pathological changes in cartilage.13,14 Its key role in either the initiation or progression of OA, or both, will be discussed.

Risk Factors for Disease Development and/or Progression (Table 1)
It is now well recognized that OA is not solely a disease of cartilage. It affects all joint tissues and, in addition to the abovementioned synovium and subchondral bone, it also affects menisci, ligaments, capsule, and muscle.4 The degradation of cartilage occurs in the context of a failure of a number of tissues of the joint and is, therefore, the result of a complex interaction of mechanical factors and biochemical changes.

New insights gained from clinical studies have enhanced our understanding of the factors associated with disease development and progression. It is well known that individuals who are overweight (high body mass index [BMI]) are at high risk for developing OA of the knee, as well as of the hips and hands. The mechanism by which excess weight causes OA is still poorly understood.

Misalignment of the limbs associated with longstanding obesity is typical in OA and may be a predisposing factor for rapidly progressing knee OA.5,6 Results from studies also raise the possibility that varus-valgus laxity can increase the risk of knee OA and cyclically contribute to disease progression.6 Varus alignment is associated with a four-fold increase in the odds of progression of medial joint space narrowing (JSN). Valgus alignment was also associated with a five-fold increase in the odds of lateral progression. Therefore, knee misalignment appears to be a clear risk factor for progression of knee OA.

Exercise is an effective intervention in OA and is an important component in its prevention. A study7 demonstrated that running did not accelerate the development of radiographic or clinical OA of the knee. However, knee injuries, which occur commonly in sports, were recently demonstrated to be associated with a marked increase in the likelihood of developing knee OA.15 Anterior cruciate ligament (ACL) damage is clearly associated with the occurrence

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<th>Table 1</th>
<th>Major Risk Factors for Knee Osteoarthritis Progression and Preventive Measures</th>
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<td>Risk Factors</td>
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<td>Demographic</td>
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<td>• Gender (female)</td>
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<td>• Occupational</td>
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<td></td>
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<tr>
<td></td>
<td>• Meniscal lesions (tear, extrusion)</td>
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<td>• Subchondral bone hypersignal (edema)</td>
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of OA and its progression. Isolated meniscal tear or partial or total rupture of the ACL, without major concomitant injuries, increases the risk for knee OA by ten-fold.

Meniscal damage is now considered to be an important part of the overall pathophysiology of knee OA. Recent studies showed a highly significant loss of cartilage volume, measured by quantitative magnetic resonance imaging (MRI), in patients with severe medial meniscal tear and extrusion and in those with subchondral bone lesions. The presence of bone resorption is also recognized as a risk factor for OA progression. A recent study demonstrated that general bone resorption (indicated by serum biomarker measurements) is increased in patients with progressive knee OA. These results shed new light on the role of bone changes in the pathogenesis of OA and may provide interesting strategic therapeutic targets.

**Therapeutic Strategies for DMOAD Development (Table 2)**

Treatment aimed at reducing or stopping OA progression is best approached globally, at both the clinical and molecular levels. The elimination of risk factors, such as high BMI and joint misalignment, and also possibly the correction of other structural damage, may in certain instances reduce the progression of the disease. From a pharmacological perspective, a large number of molecular pathways involved in OA pathophysiology have been explored as potential therapeutic targets, and many compounds and agents have been tested in preclinical and clinical trials. Some have already shown positive effects on the progression of hip or knee OA, and recent studies, particularly those using new quantitative MRI technology, have provided interesting information on the planning and conducting of DMOAD trials.

**Contemporary DMOAD**

In clinical trials, oral diacerein, an inhibitor of IL-1β, was associated with significant improvement in the symptoms of patients with hip and/or knee OA. The ECHODIAH (Evaluation of the Chondromodulating Effect of Diacerein in Osteoarthritis of the Hip) study evaluated the structure-modifying effects of diacerein in patients with primary hip OA in a 3-year study. The percentage of patients with radiographic progression was significantly lower in patients receiving diacerein than in patients receiving placebo. Selectively targeting IL-1β is likely among the most promising OA treatment strategies. However, there remains a need for additional pivotal studies on diacerein, particularly with respect to its effects on other joints, such as the knee.

Among the nutraceuticals, glucosamine has been extensively evaluated for its efficacy in relieving the symptoms of OA and for its disease-modifying potential. A landmark 2-year study demonstrated that glucosamine sulphate was capable of reducing knee OA progression as assessed by radiographs. These findings were also corroborated in two additional studies using similar trial designs.

Chondroitin sulphate (CS) produces a gradual decrease in the clinical symptoms of OA that can last for an extensive period of time after the treatment is stopped. Chondroitin sulphate could also work as an antiinflammatory and chondroprotective agent by acting on the cartilage structure. Two recently published studies looked specifically at CS in patients with knee OA. A first trial examined the effects of CS in knee OA patients who were randomly assigned to receive either 800 mg CS or placebo for 2 years. The primary outcome was joint space loss over 2 years, as assessed by radiographs. The patients receiving placebo had progressive JSN after 2 years, whereas there was no change for those receiving CS. These findings were recently corroborated in two studies that also looked at the effectiveness of CS treatment on knee OA in a 1-year and a 2-year clinical trial. These studies provided solid support to the structure-modifying properties of CS in OA patients. An important study on DMOAD effects of CS and glucosamine-HCl in knee OA, sponsored by the U.S. National Institutes of Health, is

**Table 2** Tissue Specific Therapeutic Targets for DMOAD Development

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<td>Inhibiting Catabolism</td>
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<td>- Protease inhibitors of MMP and ADAMTS</td>
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<td>- Inducible nitric oxide synthase (iNOS) inhibitor</td>
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<td>- Cell-signaling pathway inhibitors: MAPK, JNK, p38, ERK1/2, etc.</td>
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<tr>
<td>- Combined inhibitor of eicosanoids (5-LOX and COX)</td>
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<tr>
<td>Stimulating Anabolism</td>
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<td>- Growth factors: TGF-β, BMPs, FGF</td>
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<td>II Synovial Membrane</td>
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<td>- Cytokines and IL-1β inhibitors: ICE inhibitor, neutralizing antibodies, soluble receptors, receptor inhibitor, PPARγ agonists, etc.</td>
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<td>- ROS inhibitors</td>
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<td>III Subchondral Bone</td>
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<td>- Inhibitors of bone resorption: bisphosphonate, strontium ranelate, calcitonin, protease inhibitors (MMP-13, cathepsin K), osteoprotegerin, RANKL inhibitors and neutralizing antibodies</td>
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<td>- Stimulation of bone formation: PTH, SERM, estrogens</td>
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nearing completion and should provide further enlighten-
ment on the disease-modifying potential of these agents
in knee OA patients.

Joint lubrication is naturally provided, at least in part,
by hyaluronic acid (HA) in the synovial fluid. It is believed
that a decrease in joint lubrication in OA can be remedied
by intra-articular viscosupplementation. This approach
has been used for many years, but the actual impact on
knee structure was not studied until recently. In a 1-year
clinical trial with sodium hyaluronate on radiographic
changes in OA of the knee, no significant differences
were found between HA and saline treatment groups on
knee OA radiographic progression. So far, no conclusive
data are available on the potential DMOAD effect of HA
treatment in OA. Obviously, more data on the effect of
viscosupplementation on structure is needed in order to
evaluate whether it can prevent progression of OA in
the knee or other joints.

Promising Results from the Most Recent Studies
Two recent studies using drugs that specifically block some
of the OA biochemical pathways have been completed.
These studies provide interesting new information on tar-
geted DMOADs.

It is recognized that MMPs play a role in the patho-
logic breakdown of the joint extracellular matrix in OA.
It is known that tetracycline analogues can inhibit some
MMPs. Low-dose regimens of a tetracycline analogue,
namely doxycycline, reduce the extracellular matrix
breakdown. A study recently examined the effects of
doxycycline on knee OA progression. The primary
outcome measure was JSN in the medial tibiofemoral
compartment. Obese females with unilateral radiographic
knee OA were randomly assigned to receive 30 months of
treatment with doxycycline or placebo. The loss of joint
space width (JSW) in the index knee in the doxycycline
group was less than in the placebo group. In brief, this
study showed that doxycycline can reduce the progres-
sion of established OA in this patient population. It
provides the first proof of concept of the effectiveness
of anti-MMP strategies for developing DMOADs. Inhibition
of the MMP superfamily is a very logical objective in
OA. Further studies are needed, however, before teta-
cycline and its analogues, or even MMP inhibitors, can
be considered to be effective treatment to prevent knee
OA progression.

Prostaglandins and leukotrienes have complementary
effects in perpetuating the inflammatory process. Blocking
both prostaglandin and leukotriene B4 production could
have synergistic effects and achieve optimal antiinflam-
matory activity and anti-cytokine effects. A novel dual
cyclooxygenase/5-lipoxygenase (COX/5-LOX) inhibitor
(licofelone) is in phase III clinical development. This
compound is an arachidonic acid substrate analogue that
inhibits both COX and 5-LOX. In animal models, licofe-
lone reduces the experimentally induced canine OA. The
DMOAD effects of licofelone treatment versus naproxen
on knee OA were evaluated in a 2-year study. In contrast to
naproxen, licofelone significantly reduced the progression
of cartilage degradation as assessed by quantitative MRI in
these patients at the same time as it significantly reduced
the symptoms of the disease. Interestingly, the effect of
licofelone was found to be more pronounced in patients
who had the most rapid disease progression. The results of
this study are encouraging and provide additional strong
proof of concept for the development of DMOADs.

The Most Attractive Therapeutic Targets
This section reviews a number of strategies believed to
involve the most logical and promising targets for the
development of future DMOAD therapies.

Synovial Inflammation and Inflammatory
Mediators
Synovial inflammation and the release of a number of
mediators, such as cytokines, eicosanoids, and growth
factors by the inflamed tissue, are important in the de-
velopment and progression of OA. Among the inflam-
atory factors, the proinflammatory cytokine IL-1ß
plays a central role in OA pathophysiology. Factors that
regulate its synthesis or activity are therefore favored
targets. Various strategies can be used and include
receptor blockades, neutralization of the cytokine by
soluble receptors or monoclonal antibodies, blocking the
formation of active IL-1ß, inhibiting the IL-1ß cellular
signaling pathways, and using the recombinant human
IL-1 receptor antagonist, IL-1Ra. IL-1ß, being primarily
synthesized as a precursor (pro-IL-1ß), must be cleaved
by the IL-1ß-converting enzyme (ICE or caspase-1) to
generate the mature cytokine. Interestingly, inhibiting
this enzyme blocks the activation of two very potent
proinflammatory cytokines: IL-1ß and IL-18.

IL-1 activity is mediated by its binding only to the
type I IL-1 receptor with the induction of multiple
phosphorylation-dependent signaling pathways that
regulate gene expression. These pathways include the
serine-threonine kinases of the MAP kinase family and
NF-kB cascades. To date, at least one experimental in
vivo study has reported a therapeutic effect of a specific
extracellular signal-regulated protein kinase inhibitor
(Erk1/2), namely PD198306, in the experimental rabbit
model of OA.

Inducible nitric oxide synthase (iNOS), producing
NO and byproducts, is able to induce the inflammatory
compound of OA responsible for an increase in the
symptoms of the disease, tissue damage, and destruc-
tion. Therefore, it is believed that reducing the levels of
iNOS will reduce the symptoms and also slow the disease
progression. This hypothesis is supported by positive
findings in vivo on the progression of lesions in studies
conducted in an experimental canine model of OA. Clinical studies with iNOS inhibitors should be underway soon in knee OA patients.

**Inhibition of Cartilage Degradation**

Enzymes such as the MMPs, which can degrade the major components of the extracellular matrix, and some members of the ADAMTS family, which mediates mostly cartilage aggrecan loss, remain at this time the major targets for DMOADs.

To date, the most promising strategy is the use of chemical molecules that can block the activity of MMPs. The action of MMPs can also be controlled in a number of ways, such as the inhibition of their synthesis and transformation of the pro-MMPs into active MMPs. A number of MMP inhibitors have already been tested in clinical trials, and data have shown that they may produce significant musculoskeletal side effects. Drug development efforts are now directed at the use of selective inhibitors against specific proteases rather than broad protease inhibition. The main reason is based on the hypothesis that such an approach will allow certain side effects to be avoided. At this time, MMP-13 and ADAMTS-5 are identified as the most attractive targets for the treatment of OA, as recent reports have shown that both these enzymes are the predominant ones involved in the OA process.

**Inhibition of Subchondral Bone Remodeling**

Subchondral bone may be the site of the etiologically most significant OA pathophysiological events. Therefore, therapies that interfere with bone remodeling could possibly block or at least attenuate the progression of cartilage alterations. The rationale in a number of studies in preclinical models of OA is based on data showing that subchondral bone changes are mainly resorptive in nature and anti-resorptive agents could reduce OA progression. Treatment with calcitonin, bisphosphonates, and licofelone inhibited the development of cartilage lesions and subchondral bone resorption. These data strengthen the notion that therapeutic interventions that effectively inhibit bone resorption could potentially be used as DMOADs. Factors, namely receptor activator of NF-kB ligand (RANKL) and osteoprotegerin (OPG), two key elements involved in bone resorption, could also be potential targets for DMOADs. Future clinical trials will hopefully be able to provide answers to the role of subchondral bone remodeling in the pathophysiology of cartilage degradation.

**Cartilage Repair**

A number of strategies aimed at stimulating cartilage anabolism and joint repair have been tested. These include the use of growth factors such as members of the TGF-ß family, IGF-I and FGF, each having been demonstrated to stimulate the formation of hyaline cartilage-like repair tissue. However, although the repair of cartilage lesions may represent an interesting therapeutic DMOAD option, the use of growth factors in the treatment of OA is a challenging avenue of research, as several problems have to be addressed.

**Conclusion**

This review summarizes some of the knowledge we have today on possible therapeutic interventions that can modify the natural course of OA. With major advances in our understanding of the disease process and the recent development of new technologies that can be used to accurately assess and quantify the evolution of structural changes in OA, all of the elements to successfully develop new and effective DMOADs are now in place. It is just a matter of time before a definitive cure for OA is found.

**Disclosure Statements**

Jean-Pierre Pelletier, M.D., and Johanne Martel-Pelletier, Ph.D., declare that they receive consultancy fees and/or honoraria from several pharmaceutical companies and have stock ownership in AthroVision Inc.

**References**


