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Molecular targets in arthritis and recent trends in nanotherapy

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Abstract: Due to its severity and increasing epidemiology, arthritis needs no description. There are various forms of arthritis most of which are disabling, very painful, and common. In spite of breakthroughs in the field of drug discovery, there is no cure for arthritis that can eliminate the disease permanently and ease the pain. The present review focuses on some of the most successful drugs in arthritis therapy and their side effects. Potential new targets in arthritis therapy such as interleukin-1β, interleukin-17A, tumor necrosis factor alpha, osteopontin, and several others have been discussed here, which can lead to refinement of current therapeutic modalities. Mechanisms for different forms of arthritis have been discussed along with the molecules that act as potential biomarkers for arthritis. Due to the difficulty in monitoring the disease progression to detect the advanced manifestations of the diseases, drug-induced cytotoxicity, and problems with drug delivery; nanoparticle therapy has gained the attention of the researchers. The unique properties of nanoparticles make them highly attractive for the design of novel therapeutics or diagnostic agents for arthritis. The review also focuses on the recent trends in nanoformulation development used for arthritis therapy. This review is, therefore, important because it describes the relevance and need for more arthritis research, it brings forth a critical discussion of successful drugs in arthritis and analyses the key molecular targets. The review also identifies several knowledge gaps in the published research so far along with the proposal of new ideas and future directions in arthritis therapy.

Keywords: osteoarthritis, rheumatoid arthritis, interleukin, osteopontin, nanoparticle, bovine lactoferrin

Introduction
Arthritis

Arthritis is an umbrella term for several joint disorders that involves inflammation of one or more joints or the musculoskeletal system. In Australia, disability and chronic pain are majorly caused by arthritis that has affected 3.85 million Australians. With the increase in the aging population, the number of people with arthritis is also growing; hence, the current trends suggest that, by 2050, seven million Australians will suffer from some form of arthritis (http://www.arthritisaustralia.com.au). It was also estimated that 15% (40 million) of Americans had some form of arthritis in 1995 and an estimated 18.2% (59.4 million) will be affected by the year 2020.1 There are over 150 types of rheumatic and musculoskeletal disorders categorized under arthritis; however, the most common form of arthritis is osteoarthritis (OA). In developed countries, OA is among the ten most disabling diseases. Worldwide statistics shows that symptomatic OA will develop in 9.6% of men and 18% of women aged over 60 years (http://www.who.int/). Other arthritis forms that lead to major health burden globally are rheumatoid arthritis (RA), psoriatic arthritis, lupus, and infectious arthritis. Globally, of the 291 conditions
studied, RA was ranked as the 42nd highest contributor to
global disability, just below malaria and just above iodine
deficiency.2

Available treatments for arthritis
There is no standard treatment for arthritis available so far. The
treatment strategy employed includes immunosuppressive
drugs that have several side effects. Tofacitinib, methotrexate (MTX), leflunomide, and hydroxychloroquine have
been commonly used so far for the arthritis treatment. A Janus
Kinase (JAK) inhibitor named tofacitinib (a small molecule)
has been used for the treatment of RA. The mechanism by
which this inhibitor functions is by blocking the JAK signaling
through JAK3 and JAK1 that are heterodimeric receptors of
JAK. Blocking of the JAK receptors (JAK1 and JAK3) by
ofacitinib further leads to blocking of several cytokines
such as interleukins (ILs) 2, 4, 7, 9, and 21, which contribute
significantly in modulating immune response.3 It has been
reported that tofacitinib involves serious infections (cellulitis
[5-mg group] and liver abscess, bronchitis, tuberculous pleu-
eral effusion, and pyelonephritis [10-mg group]).4 Tofacitinib
is administered orally at 50 mg/kg⁵ or using osmotic mini-
pump infusion at doses of 1.5, 5, and 15 mg/kg.⁵

Competitive inhibition of dihydrofolate reductase that
plays an important role in tetrahydrofolate synthesis can be
achieved by MTX.⁷ Other multiple mechanisms are involved
apart from the inhibition of dihydrofolate reductase that
include inhibition of 1) enzymes that play a role in purine
metabolism¹ and 2) binding of IL-1 beta to its cell-surface
receptor.⁸ Some of the commonly associated side effects of
using MTX are ulcerative stomatitis, liver damage (hepa-
totoxicity), low count of white blood cells, which further
lead to nausea, abdominal pain, fever, fatigue, infection,
dizziness, and acute pneumonitis. In a few cases, it rarely
leads to pulmonary fibrosis,¹⁰ MTX can be administered
intraperitoneally at 0.01 mL/kg in 7% sodium bicarbonate,¹¹
intraperitoneal injections (1 mL) (0.05–0.5 mg/kg) in normal
saline (0.9%),¹² intramuscularly at 0.3 mg/kg twice a week,¹³
by oral gavage at 0.2 mg/kg/day,¹⁴ or mixed with powdered
food at 0.2 mg/kg/day.¹⁵ Tofacitinib has been proven to be
functionally, clinically, and radiographically more effective
than MTX in treating patients with RA.¹⁵

Leflunomide (brand names: Arablec, Arava, Lunava,
Repsol) is an immunosuppressive disease-modifying anti-
arthritic drug.¹⁶ Inhibition of mitochondrial enzyme named
dihydroorotate dehydrogenase that is involved in de novo
pyrimidine synthesis is the primary mode by which lefluno-
mide acts as an immunomodulatory drug. This inhibits
the reproduction of any rapidly dividing cells including the
lymphocytes. However, like every other drug some dose-
limiting side effects are associated with the drug, such as lung
disease, liver damage, and finally immunosuppression.¹⁷

Hydroxychloroquine is an antimalarial drug.¹⁸ The
mechanism by which antimalarial drug chloroquine and
hydroxychloroquine act on cells is by increasing the pH
within intracellular vacuoles that alter the degradation of
protein in lysosomes by acidic hydrolases, this does not
allow the assembly of macromolecules in the endosomes.
Another way by which these drugs act is by post-translational
modification of the proteins in Golgi apparatus. Interference
with the “antigen processing” in antigen-presenting cells
and macrophages is the proposed mechanism for attribut-
ing antirheumatic properties to the above-mentioned drugs.
Acidic cytoplasmic compartments are required for the anti-
genic protein to be digested and for the peptides to assemble
with the alpha and beta chains of major histocompatibility
class (MHC) II proteins. For the antigens to be processed
and digested in order for it to assemble with the alpha and
beta chains of the MHC class II proteins, acidic pH in the
cytoplasmic components is essential. Enabling the formation
of the virus peptide–MHC complex will stop the production
of CD4⁺ T cells hence avoiding an immune response against
autoantigenic peptides and inhibiting this complex forma-
tion should be an essential feature of the antimalarial.¹⁹ The
most commonly associated effects of antimalarial drugs are
usually mild nausea and diarrhea with occasional stomach
cramps.

Key molecular targets in arthritis
There are several reports stating various mechanisms for
different forms of arthritis. Some key molecules have been
identified and are being used as the targets by the upcoming
antiarthritis therapies (Table 1).

Cytokines
Cytokines have been indicated to play a critical role in
the pathological process of development of OA. IL-1β is one
such cytokine that is responsible for the cartilage matrix
degradation and destruction of the articular cartilage. IL-1β
inhibits the type II collagen synthesis of hyaline cartilage
that changes and destroys the surrounding environment of
cartilage cells and leads to variations in the structure of car-
tilage protein. Studies have reported that IL-1β content in OA
patient’s knee joint synovial fluid (SF) is higher than healthy
people and IL-1β content is significantly positive correlated
with patient’s knee joint OA score. Therefore, IL-1β content
in knee joint SF can be used not only as a reference index
in the diagnosis of OA, but also as an important therapeutic