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The Development of Novel Therapies for Rheumatoid Arthritis

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Abstract

Background—Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease that affects approximately 0.5 to 1 percent of the adults worldwide and commonly results in joint destruction and significant impairment in the quality of life. RA is considered as an autoimmune disease with unknown etiology. Many pathogenic pathways of RA have been revealed recently, which led to development of various novel therapies.

Objective—The current treatments of RA include 4 categories: non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, non-biologic disease-modifying anti-rheumatic drugs (DMARDs) and biologic DMARDs. In this review, we will discuss some of the most recent development in antirheumatic therapies.

Methods—Using SciFinder Scholar and PubMed as main searching tools, we evaluated various newly developed therapies for RA. Under each drug category, emphases are placed on the mode of action, limitation of the drugs and new drug candidates from the patents search. Those well-established therapies will only be reviewed briefly.

Conclusion—During the past 20 years, most of the development of new therapies is in DMARDs, especially biological DMARDs. With the discovery of new pathways and the application of drug delivery strategies, more growth is anticipated in this research field.

Keywords

rheumatoid arthritis; DMARDs; glucocorticoids; NSAIDs; drug delivery

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects approximately 0.5 to 1 percent of the general population worldwide and commonly results in joint destruction and significant impairment in the quality of life of the patients.[1] This disease is 2 to 3 times more common in women than in men and can start at any age, but most commonly starts in middle adult life (aged 40–60).[2] RA results in more than 9 million physician visits and more than 250,000 hospitalizations per year in the developed world.[3,4]

RA usually involves multiple joints in a symmetrical pattern. The predominant symptoms of RA are pain, stiffness, and swelling of peripheral joints. In the early stages, the most commonly involved joints are those of hands, feet and knees, while in chronic RA, damage can occur in

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almost all peripheral joints.[5] Although RA is most often only considered as a disease of the joints, it can also cause a variety of extra-articular manifestations. A hallmark of RA is synovial inflammation and its severity may vary with disease progression. The long-term prognosis of RA is poor. Studies have shown that the risk of mortality for men with RA is 38% greater (55% for women) than the general population and their life expectancy is reduced by an average of 3 to 18 years.[6] In this review, we will briefly discuss the pathogenesis of RA and then focus on the novel therapeutic developments.

2. Pathogenesis of RA

RA is considered an autoimmune disease with unknown etiology. Although its cause remains obscure, many of pathogenic pathways that are involved in RA development have been revealed over the past twenty years.

For decades, MHC Class II molecules have been shown to play an important role in the pathogenesis of RA. More specifically the HLA-DR β chain has been correlated with not only the development of RA, but also the severity of the disease. Disease-associated HLA-DR alleles are thought to present arthritis related peptides, which lead to the stimulation of autoantigen specific T cells in the joints. Additionally, variations in the protein tyrosine phosphatase non-receptor type 22 (PTPN22) gene has been identified to have a statistically significant association with rheumatoid factor-positive RA patients.[7] The presence of the variations in PTPN22 also influences age of RA onset. Those who carry the gene develop RA two years earlier than those without.

Like many other forms of arthritis, RA is initially characterized by an inflammatory response of the synovial membrane, including hyperplasia, increased vascularity and infiltration of inflammatory cells, primarily antigen-driven CD4+ T cells. These cells, through cell-cell contact and production of different cytokines, such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), then activate monocytes, macrophages and synovial fibroblasts to overproduce the proinflammatory cytokines IL-1, IL-6, and TNF-α, which appear to play a pivotal role in the progression of RA. Consequently, these cytokines are now very popular therapeutic targets for the treatment of RA.[8] In addition to those mentioned above, many other cytokines and chemokines, such as IL-17, IL-18, IL-15 and angiogenic factors, are also present in the inflammatory synovial membrane. These soluble molecules trigger signal transduction pathways, which lead to the activation of transcription factors and induction of variety of genes that are responsible for inflammation and tissue degradation. Among these products are various enzymes, such as the matrix metalloproteinases (MMPs). Whereas MMPs present in the joint are the major mediators involved in cartilage degradation, bone erosion mainly happens via osteoclast secreted acids and cathepsin K. Osteoclasts are hematopoietic origin and are differentiated within the synovial membrane, in which the receptor activator of nuclear factor κ B (RANK) ligand plays a critical role.[9]

3. Treatments for RA

Improved understanding of the pathogenesis of rheumatoid arthritis has led to the development of various RA treatments. The current therapies for RA are divided into four categories: non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, non-biologic disease-modifying anti-rheumatic drugs (DMARDs) and biologic DMARDs. Under each category, emphasis will be placed on the mode of action, limitation of the drugs and new drug candidates. Those well-established therapies will only be reviewed briefly.

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3.1 NSAIDs

Non-steroidal anti-inflammatory Drugs (NSAIDs) are drugs with analgesic, antipyretic and anti-inflammatory effects. Since RA is an inflammatory disease, medications that can suppress inflammation, such as NSAIDs and glucocorticoids, are used as the first-line therapy.

NSAIDs are usually employed as bridge therapy while waiting for the slow-acting disease-modifying anti-rheumatic drugs (DMARDs) to become effective, because that they can very effectively relieve pain and stiffness at RA onset. However, NSAIDs should not be used alone in confirmed RA since they have not been found to slow the clinical or radiographic progression of the disease.[10]

The mechanism of NSAIDs action was first elucidated by John Vane in 1971, who later received the Nobel Prize for his work.[11] The primary molecular target of NSAIDs is cyclooxygenase (COX), which is critical in the metabolism of cell membrane-derived arachidonic acid to form proinflammatory prostaglandins. Two isoforms of COX have been extensively studied in humans: COX-1 and COX-2. COX-1 is expressed constitutively in most tissues and is involved in normal tissue homeostasis such as gastric protection from hydrochloric acid. COX-2, is a predominantly inducible isoenzyme that is expressed constitutively in limited tissues (e.g., kidneys, brain), and can be rapidly upregulated at sites of inflammation and tissue injury.

3.1.1 Side effects—NSAIDs are well tolerated for short periods, but long-term administration may result in persistent adverse events. The most significant adverse event associated with NSAIDs is gastrointestinal (GI) complications, such as gastric ulceration, bleeding, dyspepsia and nausea, which is responsible for more than 100,000 hospitalizations and 16,500 deaths annually in the United States.[12] Another common adverse event of NSAIDs is their potential nephrotoxicity resulting in nephrotic syndrome and interstitial nephritis.

Since 1999, much attention has been directed to COX-2 selective inhibitors (Coxibs). The National Institute for Clinical Excellence (NICE) guidance on COX-2 selective inhibitors for osteoarthritis (OA) and RA outlined that COX-2-selective inhibitors have equivalent efficacy to nonselective NSAIDs, and it has been observed that they could decrease the incidence of gastric and duodenal ulcers by approximately 50 percent as compared with traditional NSAIDs.[13–15] While this strategy is successful to overcome the GI adverse events, some cardiovascular adverse events such as myocardial infarction and cardiac arrest have been observed.[16]

3.1.2 Novel NSAIDs therapy—Currently, the main focus of NSAIDs development is reduction of the side effects. Several efforts have been made in designing new NSAIDs to decrease the adverse drug reactions and to achieve better therapeutic efficacy in RA treatment.

The inhibitory effects of nitric oxide (NO) on NSAIDs-induced leukocyte adherence have been exploited in the development of NO-NSAIDs, also indicated as COX-inhibiting NO-donating drugs. Despite their non-selective profile versus COX isoenzymes, this class of anti-inflammatory agents reduces systemic blood pressure and might have enhanced cardiovascular safety than the coxibs. They may also cause less gastrointestinal damage compared to their parent drugs. Another gaseous mediator, H_2S-releasing NSAIDs derivatives have been recently developed, based on their ability to cause vasodilation and to prevent leukocyte adherence. In preclinical settings, H_2S -releasing NSAIDs produce less gastric damage as compared to the parent drugs. [17]

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Transform Pharmaceuticals, Inc. disclosed the combination use of a COX-2 inhibitor and a diuretic like hydrochlorothiazide. This combination can minimize or eliminate the adverse cardiovascular and/or renal effects that have been associated with one or more COX-2 inhibitors when administered without the incorporation of an appropriate diuretic. [18] The faster clearance of COX-2 inhibitors due to the incorporation of diuretic may contribute to the adverse effects reduction.

Unigen Pharmaceuticals, Inc. disclosed a novel composition of matter comprised of a mixture of free-B-ring flavonoids and flavans isolated from the Scutellaria genus of plants and the Acacia genus of plants, respectively. The composition of the invention is effective in simultaneously inhibiting both the COX-2 and arachidonate 5-lipoxygenase (5-LO) enzymes. [19] It has been suggested that NSAID-induced gastric inflammation is largely due to metabolites of 5-LO, particularly leukotriene B4 (LTB4), which attracts cells to the site of a gastric lesion thus causing further damage.[20,21] As a dual inhibitor of COX-2 and 5-LO, the compounds cited in the invention exhibited a similar effectiveness on pain relief, better effectiveness at decreasing stiffness, and marked improvement of physical function compared to the prescription drug Celebrex™ (Pfizer, Inc.) in clinical studies.[19] The adverse events associated with the cardiovascular system are not clear.

Altana Pharma AG disclosed a pharmaceutical combination comprising the phosphodiesterase 4 inhibitor (PDE4 inhibitor), and a conventional NSAID, 2-[(2, 6-dichlorophenyl) amino] benzeneacetic acid. PDE4 is the major cAMP-metabolizing enzyme found in inflammatory and immune cells. PDE4 inhibitors have proven potential as anti-inflammatory drugs, especially in airway diseases. They suppress the release of inflammatory signals, e.g., cytokines, and inhibit the production of reactive oxygen species. This combined use can minimize gastrointestinal side effects, such as gastric erosions and ulcer, which are frequently associated with the use of conventional NSAIDs.[22]

Clearly, the withdrawal of several blockbuster COX-2 inhibitors from the market has left the once very active field of NSAID development quiet. Very few new compounds have been developed recently. While this drug category will never go away as pain alleviation is a critical part of RA management, people are backing off from the COX-2 paradigm and probing new strategies to overcome the side effects associated with NSAIDs.

3.2 Glucocorticoids

Glucocorticoids (GCs) are a class of steroid hormones characterized by the ability to bind with the cortisol receptors and trigger various biological effects. They have potent anti-inflammatory and immunosuppressive properties, therefore they have been widely used in the treatment of RA. It is estimated that over 50% of patients with rheumatoid arthritis are treated more or less continuously with glucocorticoids.[23] Overall, the market for glucocorticoids is estimated as $10 billion per year.[24]

Glucocorticoids use in RA remains one of the most controversial areas of modern arthritis management. Attitudes towards glucocorticoid therapy in RA range from suspicion to widespread acceptance.[25,26] However, in recent years, there has been a revival of the role of glucocorticoids in the treatment of RA.[27] Studies conducted more recently clearly establish that, with low-dosage long-term treatment, glucocorticoids can substantially reduce the rate of erosion progression in RA, in addition to their recognized anti-inflammatory and immunosuppressive properties with short and medium-term use.[28–30] Given the slow onset of traditional DMARDs, low dose glucocorticoids are often used as a bridge therapy to control symptoms until the DMARDs or biological agents become effective. At present, monotherapy of GCs is generally not recommended.

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The therapeutic, anti-inflammatory, immunosuppressive and adverse effects of the GCs are due to different modes of transcription regulation by the GR ligand complex. One mechanism is transactivation: the ligand-activated GR homodimer binds to GC-responsive elements (GREs) in the promoter region of GC-sensitive genes, inducing gene transcription. The other mechanism is transrepression which is more variable: firstly, the activated GR can bind to negative GREs, leading to an inhibition of gene transcription, possibly due to interference with the binding of essential transcription factors. Secondly, the GR may interact via protein-protein interaction with other transcription factors, e.g., activator protein (AP)-1, nuclear factor-kB (NF-kB), thus inhibiting the induction of gene transcription by these factors.[24,31] The relative effects of transactivation and transrepression mechanisms are not yet fully understood, but in combination they result in the down-regulation of proinflammatory chemokines, adhesion molecules and cytokines such as tumor necrosis factor (TNF), interleukin-1(IL-1), IL-6, intercellular cell adhesion molecules (ICAM-1) and vascular cell adhesion molecule (VCAM-1).[32] They also function as selective inhibitors of cyclooxygenase 2 (COX-2) by increasing the synthesis of lipocortin-1, a 37-kDa protein that has an inhibitory effect on phospholipase A2 (PLA2), therefore down regulates the production of arachidonic acid metabolites including prostaglandins and leukotrienes. GCs can also directly induce apoptosis in T cells.[32]

3.2.1 Side effects—Although the GCs exhibit desirable anti-inflammatory and immunosuppressive effects, adverse effects of glucocorticoids have been extensively reported and are familiar to all clinicians. It can be stated that long-term use of GCs is a high-risk factor, whereas total dose is of secondary importance. The adverse effects occur in different organs and the severity ranges from slightly cosmetic aspects to serious disabling and even life threatening situations.[33] Systemic application of GCs usually causes more severe side effects than topical application.

Side effects caused by GCs involve almost all of the organs in human body. Gluococorticoid-induced osteoporosis is the most devastating complication of long-term GC therapy in RA. Other side effects include adrenal insufficiency, cataract, skin atrophy, peptic ulcers and infection. The underlying molecular mechanisms for GC-mediated side effects are complex, distinct, and frequently only partly understood. A recent review of the literature about the side effects associated with low-dose GCs has shown that the overall fear of GC toxicity in RA, as quoted in textbooks and review articles, is probably overestimated based on extrapolations from observations on patients receiving higher-dose therapy.[34] Safety of low-dose GCs needs to undergo serious and systematic reevaluation with properly designed and dedicated studies of adequate size, duration, and state-of-the-art end points. Guidelines for such studies would enhance comprehensiveness and comparability. GCs will likely retain an enormous therapeutic value in treatment of a large variety of rheumatic conditions, especially since it becomes increasingly clear that these agents have disease-modifying potential in RA.

Although glucocorticoids interact with a single receptor, current understanding of the biology of the GC receptor explains how different cells may respond differently to glucocorticoid exposure. This offers new therapeutic possibilities to modulate the overall organism response by using selective glucocorticoid receptor agonists, or by drug delivery system with tissue specificity.

3.2.2 Novel GCs therapy—Most of the work in novel GC therapy has been to develop selective glucocorticoid receptor agonists (or modulators, SGRM), which are active in transrepression with little or no transactivation. It is based on the knowledge that a number of the side effects of glucocorticoids seems to be predominantly mediated by transactivation effects [35–37] and the consensus that transrepression effects are more responsible for the desired anti-inflammatory effects of GCs.[38–40] Schacke et al.[41] investigated a

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nonsteroidal selective GR-agonist ZK 216348 in murine models of skin inflammation. In comparison with prednisolone, ZK 216348 showed similar anti-inflammatory properties with less increase of blood glucose level and, to a lesser extent, reduced skin thinning. Coghlan et al.[42] described the discovery and characterization of AL-438, a GR ligand that exhibits an altered gene regulation profile, able to repress and activate only a subset of the genes normally regulated by GCs. *In vivo* test shows, AL-438 retains full anti-inflammatory efficacy and potency comparable to steroids but its negative effects on bone metabolism and glucose control are reduced at equivalent anti-inflammatory doses. Koehler et al. disclosed novel compounds which are glucocorticoid receptor ligands having a dissociated profile of action (active in transrepression with little or no transactivation), therefore the compounds can be used in the treatment of RA, but no specific data have been presented. [43]

As an interesting approach, prednisone was formulated as delayed releasing tablets (4 hr delay) for evening administration to RA patients. This strategy was designed to optimize the conventional glucocorticoid therapy to be adapted to the circadian rhythms of endogenous cortisol and the symptoms of RA. This adjustment of dosage form significantly reduced the duration of morning stiffness of the joints RA patients. However, the safety profile did not differ from the regular prednisone.[44]

In summary, glucocorticoids, as an time-proven drug category, are still the most potent and fast acting anti-inflammatory drugs used in the treatment of RA. Importantly, these drugs demonstrate significant disease modifying effects. What really hamper their clinical applications are the well-known side effects. The understanding of the transrepression and transactivation mechanisms leads to plausible development of selective transrepression agonists. Nevertheless, such development is not enough because the agonist selectivity is always relative and the long-term application may still be problematic. The “sharpen the old spear” strategies, such as modification of pharmacokinetic profiles or incorporation of tissue specificity (which we will discuss in section 3.5) to the classical glucocorticoids may represent another very promising direction.

3.3 Non-biologic DMARDs

Non-biologic disease-modifying antirheumatic drugs (DMARDs), also known as low molecular weight DMARDs, and small molecule DMARDs, comprise a variety of chemically diverse drugs (Table 1) that approach the task of impeding both the inflammatory and destructive processes of RA through different strategies, but each has been proven effective in its own way. DMARDs are also known as “slow-acting anti-rheumatic drugs”, which gives us a clue as to their working timeframe.

3.3.1 Classical non-biologic DMARDs—The quickest-acting DMARD is methotrexate, which usually takes four to six weeks before one may begin to feel benefits. By contrast, the rest of the DMARDs can take three to six months to be effective, with the exception of oral gold capsules, which can take from six months to a year. The essence of DMARDS, clearly, isn’t rapidity. Rather, it’s the ability to retard or halt the radiographic progression of the disease. Although this was demonstrated decades ago, historically, concern about the toxicity of DMARDs has delayed their use in treating RA. However, rheumatologists now prescribe DMARDs much earlier than in the past, because the consequences of delaying therapy far outweigh the risks of side effects for the majority of patients. It is widely accepted that the initiation of therapy with DMARDs within 3 months after the diagnosis of RA is crucial, as the delay in the introduction of these medications results in substantially more radiographic damage at the end of five years.[45,46]

Non-biologic DMARDs have been used since the 1920s. Even in the era of biological therapies, one such drug, methotrexate (MTX) is still the mainstay of RA treatment and has been used

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as standard to validate other new DMARDs. Current data support the notion that MTX may reduce mortality (mainly cardiovascular) when compared with other DMARDs.[47] However, all currently used DMARDs have limited efficacy, toxicity problems or both (Table 1).

3.3.2 Novel Non-biologic DMARDs

PI3Ks inhibitors: Phosphoinositide 3-kinases (PI3Ks), most notably PI3Kd and PI3K (belong to class I PI3Ks), have crucial and specific roles at all stages of RA disease progression, including antigen signaling in B and T cells, downstream signaling of Fragment Crystallizable Receptors, cytokine receptors and chemokine receptors on mast cells, macrophages, neutrophils and synoviocytes.[48] Wortmannin and LY294002 are potent PI3K inhibitors and they have been extensively used for more than a decade to analyse PI3K-driven pathways, mostly in *ex vivo* studies.[49] However, these molecules do not show specificity and inhibit other closely related enzymes, so that they are too toxic to be used as therapeutics. Currently, more work on class I PI3-kinase isoform specific inhibitors is ongoing, including PI3Kγ inhibitor disclosed by Bayer Pharmaceuticals Corp.[50,51]

MMPs inhibitors: Matrix metalloproteinases (MMPs) seem to be important in RA, as some of them are present in increased amounts and in active forms in RA synovial tissue.[52] MMPs form a family of enzymes, which share a structurally similar domain, in particular the zinc dependent catalytic domain and the activation peptide (propeptide) thought to be responsible for the latency of the proMMP enzyme species. Human MMPs are often divided into subfamilies, usually termed interstitial collagenases (MMP-1, MMP-8 and MMP-13), gelatinases (MMP-2, MMP-9), stromelysins (MMP-3, MMP-7, MMP-10, MMP-11), membrane type (MT)- MMPs and others.[53] Several MMPs inhibitors are efficacious in experimental models of arthritis and therefore constitute interesting compounds for RA therapy.

Dyax Corp.[54] described MMP14-binding proteins or human antibodies useful for treating RA. MMP-14, also known as MT1-MMP, is a type I transmembrane proteinase which participates in pericellular proteolysis of extracellular matrix (ECM) macromolecules. The enzyme is cellular collagenase essential for skeletal development, cancer invasion, growth, and angiogenesis. Developing new means to inhibit the “functional activity” of MT1-MMP may be a new direction to establish treatments for the diseases that MT1-MMP mediates, such as cancer and rheumatoid arthritis.[55]

Cipemastat is the only selective MMP-1 inhibitor which has been evaluated in Phase III trials in RA, but its lack of clinical efficacy, including failure to improve radiographic scores, which is inconsistent with the promising results in rabbit RA models, led to the discontinuation of this program.[56,57]

TNF-α converting enzyme (TACE; ADAM-17) is a membrane-bound disintegrin metalloproteinase that processes the membrane-associated cytokine proTNF-α to a soluble form. Because of the involvement of TNF-α in RA development, TACE represents a hot target for the design of specific synthetic inhibitors as therapeutic agents. For example, Levin described a mechanism by which acetylenic aryl sulfonate hydroxamic acids can inhibit TACE and MMP [58]

Cathepsin inhibitors: The cathepsins (e.g. cathepsin B, L, K, and S) are cysteine proteases that play major roles in intracellular protein degradation and turnover. Cathepsin S-deficient mice showed marked resistance to the development of collagen-induced arthritis due to its involvement in antigen presentation process [59] Aberrant cathepsin B activity is implicated in such disease states as rheumatoid arthritis and bone and joint disorders. Cathepsin K cleaves key bone matrix proteins, type I and II collagen and is involved in extracellular matrix

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metabolism necessary for normal bone growth and remodeling.[60] Due to the critical pathophysiological roles of cathepsins, cathepsin inhibitors are developed as novel DMARDs.

Merck Frosst Canada Ltd.[61] has disclosed several novel compounds, which are cysteine protease inhibitors, to treat diseases (e.g. osteoporosis and RA) in which inhibition of bone resorption is indicated. Jiaoqiang Cai et al.[62] have shown that 6-phenyl-1H-imidazo [4,5-C] pyridine-4-carbonitrile derivatives are cathepsin K and S inhibitors.

Saltzman, et al.[63] disclosed the use of cathepsin Z inhibitors for the treatment of rheumatoid arthritis and other autoimmune diseases. The increased expression and/or activity of cathepsin Z in dendritic cells, is associated with increased dendritic cell antigen presentation. An increase in dendritic cell antigen presentation results in increased Th1 cell activation and differentiation. In autoimmune diseases such as rheumatoid arthritis and multiple sclerosis, increased Th1 cell activation and differentiation is correlated with increased pathology. Therefore, interfering with the expression or activity of cathepsin Z will ameliorate the pathology of an autoimmune disease such as RA.

Glycosidase inhibitors: Scripps Research Inst.[64] has shown that inhibition of glycosidases in the synovial fluid has great utility as a novel chondroprotective approach in treating diseases associated with cartilage degradation. Commonly, cartilage erosion results from the over-catabolism of glycosaminoglycans (GAGs) of the proteoglycan (PG)-hyaluronate complex, which comprises the bulk of cartilage tissue. This cartilage erosion is catalyzed by glycosidases and hexosaminidases. In RA, for example, the dominant glycosidases are the hexosaminidases, which act either alone or in combination with other glycosidases such as β-D-glucuronidase, have been shown to be directly involved in depleting GAGs from cartilage.[65]

While all the non-biologic DMARDs mentioned above have very specific molecular target, their lack of tissue specificity may post a challenging. It has yet to be seen if they would provide acceptable safety profiles in clinical evaluation. Compared to the biologic DMARDs, the cost of non-biologic DMARDs are relatively low.

3.4 Biologic DMARDs

New biological agents developed in the last decade have proven to be effective for a majority of patients unresponsive to traditional therapies. The pro-inflammatory role of cytokines, the involvement of different cell types and their surface molecules in the pathogenesis of RA, provides the rationale for the development of highly specific therapeutics by targeting these molecules. First, the cytokines of interest may be prevented from binding to its cell-surface receptors by soluble receptors, natural antagonists, or monoclonal antibodies. Second, anti-inflammatory cytokines such as IL-4, IL-10 or IL-13, can inhibit the production or expression of inflammatory cytokines. Third, biological agents targeted against differentiation or functionally associated cell-surface antigens can lead to either elimination of the targeted cells or interference with cell function.

3.4.1 Currently used Biologic DMARDs in RA—Most of the approved biologic DMARDs explore the first strategy mentioned above, they impair the binding of pro-inflammatory cytokines to their receptors. Among them, tumor necrosis factor (TNF) and IL-1 have been the most intensively investigated.

TNF antagonists: TNF-α, is an inflammatory cytokine that is mainly produced by macrophages and monocytes, but also by a broad variety of other cell types including lymphoid cells, mast cells, endothelial cells and fibroblasts. TNF-α is an autocrine stimulator as well as a potent paracrine inducer of other inflammatory cytokines. It can attract neutrophils very potently, and help them to stick to the endothelial cells for migration, thereby playing an

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important role in the pathogenesis of RA.[66] Two receptors, TNF-R1 (TNF receptor type 1) and TNF-R2 (TNF receptor type 2), bind to TNF-α. In cultures of synovial cells from patients with RA, blocking TNF-α with antibodies significantly reduced the production of IL-1, IL-6, IL-8, and granulocyte–monocyte colony-stimulating factor. Hence, the blockade of TNF-α may have a more global effect on inflammation than the blockade of other cytokines present in high concentrations in synovial fluids, such as IL-1.[67] Currently, three TNF inhibitors (infliximab, etanercept and adalimumab) have been approved for treatment of RA.

All three of these TNF-α antagonists have shown significant and clinically relevant improvements in active RA and appear to be very effective treatments for RA. In clinical trials, they showed rapid response, with higher or at least comparable efficacy compared to methotrexate[68,69] and the efficacy of combination therapy is greater than monotherapy with either agent alone.[70] As such, TNF blockade has been the major breakthrough in the therapy of RA during the past ten years. However, their practical use has been limited by cost and side effects. Because the clinical trial designs and patient populations studied differ among the three approved TNF-blocking agents and have not been studied in head to head trials, direct comparisons cannot be made among the products and between the various studies. Nonetheless, certain generalizations can be made. First, certain serious, but uncommon, adverse events have been observed with all three products, including serious bacterial infections, tuberculosis and certain opportunistic infections, demyelinating syndromes, and lupus-like reactions.[71–73] Second, lymphoma has been reported in association with all three TNF antagonists,[74] but whether or not there is a causal relationship is debated. Although some observational studies have addressed the risk of malignancy in persons treated with biologics, the uncertainty exists because epidemiologic studies have generally demonstrated that hematopoietic, lung, and skin cancers are increased in RA,[75,76] In addition, evidence has accumulated that severity of RA disease is associated with the risk of lymphoma.[77] Therefore, the increased incidence of lymphoma among patients treated with TNF antagonists, could be ascribed to either severe rheumatoid arthritis or its treatment. More recently, Wolfe and Michaud[78] raised their opinion that biologic therapy is associated with increased risk for skin cancers, but not for solid tumors or lymphoproliferative malignancies by analyses from a large US observational study. However, they also point out this result may be attributed to the short periods of their patients exposure to biologics (3 years). It is possible that with increasing time, the association between malignancy and biologic therapy would become stronger.

IL-1 inhibitor: Interleukin -1 (IL-1) is well established as another key pro-inflammatory cytokine involved in RA. It is mostly produced by monocytes and macrophages but is also produced by endothelial cells, B cells, and activated T cells. The IL-1 signaling system is more complex than the TNF-α system. IL-1 binds to two types of cell-surface receptors. Only type I receptors have a cytoplasmic tail and are capable of intracellular signaling by allowing the engagement of the IL-1 receptor accessory protein (IL-1 RacP). Type II receptors are decoy receptors: they bind circulating IL-1 but do not deliver any intracellular signals. The type I receptor is found in low numbers on many cells, whereas the type II receptor is expressed primarily on neutrophils, monocytes, and B cells. In addition, a naturally occurring antagonist, IL-1–receptor antagonist, binds the type I receptor with high affinity but does not allow engagement of IL-1 RacP, thus providing another mechanism for the inhibition of IL-1 activity. Macrophages in the synovial tissue of patients with RA appear to be an important source of IL-1.[66]

Anakinra is a recombinant form of human IL-1-receptor antagonist that inhibits the proinflammatory cytokine IL-1. It is identical to the nonglycosylated form of the endogenous protein except for the addition of one N-terminal methionine.[79] It has a short half-life, thereby daily injection is required. The most common adverse event related to anakinra is dose-dependent skin irritation at the injection site and an increased susceptibility to infections. In a

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recent meta-analysis, anakinra has been shown to be relatively ineffective compared to tumor necrosis factor alpha (TNF-α) inhibitors in the treatment of RA[80]. However evidence suggests that it may be very useful in certain conditions such as pediatric arthritis.

T cell and B cell inhibitors: T cells have been the most frequently targeted cells in the history of the biological therapy of RA. Ordinarily, full T cell activation requires 1) binding of the T cell receptor to the antigen-MHC complex on the antigen presenting cell (APC) and 2) a costimulatory signal provided by the binding of the T cell's CD28 protein to the B7 (CD80/CD86) protein on the APC. CTLA4 (cytotoxic T-lymphocyte antigen 4) is a CD28-family receptor expressed on mainly CD4+ T cells. It binds the same ligands as CD28, but with higher affinity than CD28. However, in contrast to CD28 which enhances cell function when bound at the same time as the T cell receptor, CTLA4 inhibits the T cell and prevents it from functioning, which makes it a potential therapy for autoimmune diseases. Abatacept is the first member of a new class of drugs known as costimulation blockers. It is a human recombinant fusion protein of CTLA4 and Ig antibody, that acts by binding to CD80/CD86 on antigen-presenting cells and inhibiting interaction with CD28 on T cells, thus preventing one of the co-stimulatory signals needed for full T-cell activation.[81] In December 2005, abatacept was approved by the US Food and Drug Administration for the treatment of adult patients with moderately to severely active RA who have exhibited an inadequate response to traditional disease-modifying anti-rheumatic drugs or tumor necrosis factor antagonists. The major potential risks and side effects of abatacept therapy include serious infections, allergic reactions, or even malignancies.

As discussed previously, B cells seem to play an important role in the pathogenesis of RA as well. Rituximab is a chimeric anti-CD20 monoclonal antibody and has been used as a single agent for the treatment of patients with relapsed or refractory low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL) for many years. CD20 is a widely expressed on almost all normal and malignant B cells, and it functions as an activator of B cells. The exact mode of action of rituximab is unclear, but it has been found to have a general regulatory effect on the cell cycle, and to increase MHC II and adhesion molecules LFA-1 and LFA-3 (lymphocyte function-associated antigen), elicit shedding of CD23, down regulate the B-cell receptor, and induce apoptosis. In 2006, Rituximab was approved in combination use with methotrexate for treatment of moderately- to severely- active rheumatoid arthritis in adults who have had an inadequate response to one or more TNF antagonist therapies to reduce signs and symptoms of the arthritis. The most common adverse events found in the rituximab treated groups include infusion reactions, infection, hepatitis B reactivation and severe skin reactions.

IL-6 inhibitor: IL-6 is a pleiotropic cytokine with roles in inflammation and hematopoiesis. Tocilizumab (TCZ) is a humanized antibody against the soluble IL-6 receptor (sIL-6R) and membrane-bound IL-6 receptor (mIL-6R), blocking these receptor complexes and preventing IL-6 transmembrane signaling.

Studies suggest that reducing the activity of IL-6, one of several key cytokines involved in the inflammatory process, may reduce inflammation of the joints, prevent long-term damage and relieve certain systemic effects of RA such as anemia, fatigue and osteoporosis. The most common adverse events reported in tocilizumab global clinical studies are upper respiratory tract infections, headache, nasopharyngitis and hypertension. As with other biological disease modifying anti-rheumatic drugs (DMARDs), serious infections have been reported in some patients treated with tocilizumab.[82] Further long-term safety and efficacy studies are needed to confirm the therapeutic benefit of this antibody in inflammatory and autoimmune disorders.

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3.4.2 Novel biologic DMARDs

Novel TNF inhibitors: Efforts are currently under way to develop small molecular weight TNF inhibitors that can be produced at low cost and that may have fewer side effects by acting locally in inflamed tissues. One strategy to achieve this goal is through the use of endogenously produced, small molecular weight substances that are known to inhibit TNF production. One such molecule is carbon monoxide (CO). CO inhibits TNF production in vitro and in vivo and has shown impressive anti-inflammatory effects in animal models.[83] CO releasing molecules (CORMs) that can deliver CO directly to therapeutic targets without the formation of intermediate CO-hemoglobin complexes have also been developed. A wide variety of CORMs have been disclosed for their use in the treatment of inflammatory diseases and diseases associated with acute or chronic inflammatory reactions.[84–89]

A polypeptide[90] comprising the isolated amino acid sequence of a pre-ligand assembly domain (PLAD) has been developed. The PLAD is a portion of the extracellular region of TNF receptors that mediates receptor-chain association essential for signaling. According to the invention, in vitro and in vivo data indicate that TNFR PLAD proteins can potently inhibit TNF-α and consequencely ameliorate experimental inflammatory arthritis.

PLA2 inhibitors: Recently, a peptide[91,92] having dual inhibitory activity against secretory phospholipase A2 (sPLA2) and MMPs has been reported. Phospholipase A2 (PLA2) is a key enzyme in the production of diverse mediators of inflammatory conditions. The vast PLA2 enzyme family includes three cellular isoforms (cPLA2s), involved in signal transduction, and ten secretory isoforms (sPLA2s). The cPLA2s and sPLA2 play key roles in arachidonic acid (AA) release during acute inflammation[93]. Group II secretory phospholipase (sPLA2) is known to be proinflammatory in vivo[94], and is associated with the onset of rheumatoid arthritis (RA).[95] Levels of sPLA2 in synovial fluid also correlate with severity of disease in RA patients.[96] The role of sPLA2 in inflammatory arthritis and cancer thus makes the enzyme a potential target for drug development. In an early phase clinical study, 3 days after a single 6-hour infusion, patients treated with Eli Lilly's sPLA2 inhibitor LY333013 experienced significantly greater reduction in swollen and tender joints than the placebo group. However, in another recent clinical trial, treatment by the same inhibitor for 12 weeks was showed well tolerated but ineffective as an adjunct to DMARD treatment of active RA. [97]

Vascular endothelial growth factor (VEGF) inhibitors: Angiogenesis, the process by which new blood vessels are formed by outgrowth from existing ones, plays an important role in active proliferation of inflammatory synovial tissue, which is a principal pathophysiology in RA. VEGF, the most powerful angiogenic cytokine known, is associated with a variety of physiological and pathological neovascularization events. It induces vascular leakage, which is also an important process in mediating inflammation, with the potency about 50,000 times greater than histamine.[98] Anti-VEGF antibody was proven to ameliorate experimental arthritis.[99]

LG Life Sciences Ltd.[100] disclosed a novel compound for inhibition of VEGF receptor 2 kinase (VEGFR2). Such anti-angiogenesis drugs exhibit the effect of inhibiting the activity of VEGFR2 and simultaneously inhibiting the activity of other angiogenesis receptor tyrosine kinase (RTK) families. This combined inhibiting effect is known as one mechanism of significantly increasing the angiogenesis inhibiting effect. In addition, some quinazoline derivatives have been used as VEGF inhibitors.[101,102]

Blocking chemokines: Chemokines or chemoattractant cytokines are a family of small cytokines, which can greatly enhance the recruitment of T cells and macrophages to the inflammatory site. They are produced by a variety of cell types and are divided into four

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families: CC, CXC, CX3C and C chemokines. Chemokines play important roles in inflammation, angiogenesis and Th1/Th2 development, as such they have attracted significant interest in RA research. *In vitro* studies have suggested that CC chemokine receptor (CCR)1, CCR2, CCR5, CXCR3, CC chemokine ligand (CCL)2/monocyte chemoattractant protein (MCP)-1, CCL5/RANTES and CXCL8/IL-8, are intimately involved in cell migration toward the synovial compartment in RA.

Millenium Pharmaceuticals recently reported the completion of phase I with its candidate, MLN-3897, a CCR1 antagonist. In this study, results show MLN3897 to be well-tolerated and to exhibit dose dependent blockage of the CCR1 receptor. A Phase II trial to evaluate MLN3897 in RA is underway.[103]

CCR5 polymorphism seems to be related to the severity of RA[104] and Schering Corp. [105–107] suggested piperazine derivatives may be useful as selective CCR5 antagonists to treat HIV, as well as RA.

Amgen Inc.[108] and Arena Pharmaceticals Inc.[109] have reported on the development of compounds which are modulators of CXCR3 chemokine receptor activity and are useful in the prevention or treatment of RA. The CXCR3 chemokine receptor is expressed primarily in T lymphocytes and this highly selective expression makes it an ideal target for intervention to interrupt inappropriate T cell trafficking.

Carter, et al.[110,111] described a modulator of MCP-1 for the treatment of RA. The chemokine monocyte chemoattractant-1 (MCP-1) and its receptor CC chemokine receptor 2 (CCR-2) play a pivotal role in attracting leukocytes to sites of inflammation and in subsequently activating these cells. When the chemokine MCP-1 binds to CCR-2, it induces a rapid increase in the intracellular calcium concentration, increased expression of cellular adhesion molecules, cellular degranulation, and the promotion of leukocyte migration. It is known that MCP-1 is upregulated in patients with RA.[112] Moreover, several studies have demonstrated the potential therapeutic value of antagonism of the MCP-1/CCR2 interaction in treating RA. Recently a DNA vaccine encoding MCP-1 was shown to ameliorate chronic polyadjuvant-induced arthritis in rats.[113] Likewise, inflammatory disease symptoms could be controlled via direct administration of antibodies for MCP-1 to rats with collagen-induced arthritis. [114]

So far, the available data in animal models and limited data in human disease suggest that chemokine family members might be attractive targets for RA therapy. Targeting one specific chemokine (receptor) may be sufficient to reduce inflammation, despite the apparent redundancy of the system. Theoretical advantages of the chemokine receptor antagonists include oral delivery, controllable safety issues during infection in light of the short half-life (the drug could be discontinued during infection, allowing inflammatory cells to migrate to the site of infection), and the potential of inhibiting the migration of cells that are able to produce proinflammatory cytokines at the site of inflammation.

CSF inhibitors: A hematopoetic factor called “colony stimulating factor” (CSF) is capable of synergizing the chemoattractant capabilities of chemokines and of inducing the accumulation and/or activation in vitro and in vivo of key components of inflammatory responses. Warner Lambert Co. [115,116] disclosed agents that inhibit the production, release or activity of CSF, which can be used in inflammatory diseases such as RA.

Cell surface antigens: T cells: During the past decade, several attempts have been performed to influence the course of RA by reducing T cell number, or interfering with the function of CD4+ cells. Anti-CD4 monoclonal antibodies (mAbs) have been advocated as potential

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therapy in RA because they induce remissions that persist beyond the period of treatment in animal models of RA and other autoimmune diseases.[117] Two mechanisms may be involved: 1) Functional blockade of CD4 co-receptor function during active disease results in long-term unresponsiveness of autoantigen-specific T cells; 2) Treatment results in a shift from Th1 to Th2 predominance of the immune response. However, severe adverse events such as unacceptable CD4 lymphopenia and rash has limited the development of CD4+ immunotherapy.[118]

Isis Innovation [119] disclosed an antibody having a binding affinity for the CD3 antigen complex, thereby used for treatment of chronic joint inflammation. It is known that anti-CD3 monoclonal antibodies can be used to sensitize T-cells to secondary proliferative stimuli such as IL-1 and IL-2. In addition, certain CD3 monoclonal antibodies are themselves mitogenic for T-cells.

Several investigators have targeted various steps in the T cell migration/extravasation process as an approach to suppressing some autoimmune disorders. Phosphosugars, such as mannose-6-phosphate (M6P), have been shown previously to have anti-inflammatory properties, notably inhibition of experimental autoimmune encephalomyelitis (EAE) and adjuvant-induced arthritis in rats. It has been proposed that M6P exerts its anti-inflammatory effects by displacing lysosomal enzymes, which are involved in T-cell extravasation into inflammatory sites, from the 300 kDa mannose-6-phosphate receptor (MPR-300) selectively expressed on the surface of activated T cells.[120] Based on this, Pharmaxix Pty Ltd. [121] has discovered a series of derivatives of mannose-6-phosphate (M6P) that are useful for treating diseases or disorders that are mediated at least in part by such T lymphocyte migration like RA.

P2X receptors inhibitors: Warner Lambert Co. [122,123] provides a method of treatment of IL-1 mediated diseases including RA by combination of a benzamide inhibitor of the P2X7 receptor and other agents. Bernatchez-Lemaire Irma [124] uses histogranin-like compounds to reduce P2X7 function. The P2X7 purinergic receptor (previously known as P2Z receptor), which is a ligand-gated ion channel, is present on a variety of cell types, largely those known to be involved in inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes. Activation of the P2X7 receptor by extracellular nucleotides, in particular adenosine triphosphate (ATP), leads to the release of IL-lβ, T cell proliferation and apoptosis. In experimental animal models, inhibition of P2X7 receptor resulted in relief of pain and attenuation of inflammatory response.[125,126]

Adhesion molecules: Adhesion molecules play a pivotal role in cell recruitment to inflammatory sites. Interfering with the process of adhesion, can therefore reduce cellular accumulation and modify the process of inflammation.

VLA-4, first identified by Dana Farber Cancer Inst, Inc.[127], is a member of the β1 integrin family of cell surface receptors, each of which comprises two subunits, a α chain and a β chain. Intercellular adhesion mediated by VLA-4 and other cell surface receptors are associated with a number of inflammatory responses. At the site of an injury or other inflammatory stimulus, activated vascular endothelial cells express molecules that are adhesive for leukocytes. Currently, several companies are engaged in developing novel RA therapies by inhibiting leukocyte adhesion through binding VLA-4.[128–131]

Another important adhesion molecule is ICAM-1, which is a type of intercellular adhesion molecule continuously present in low concentrations in the membranes of leukocytes and endothelial cells. Litzenburger Tobias et al.[132] described an invention applying recombinant antigen-binding regions and antibodies and functional fragments containing such antigen-

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binding regions that are specific for ICAM1, these antibodies, accordingly, can be used to treat RA and other various disorders associated with inflammation.

Inhibition of signal transduction cascades: MAPK pathways: Two principal pathways activated by TNF-α and IL-1 are the mitogen-activated protein kinases (MAPK) and nuclear factor-kappa B (NF-κB) pathways and molecules of these signal-transduction cascades have been detected in the RA synovial membrane.[133] Various compounds already used in RA therapy act as NF-κB inhibitors, such as glucocorticoids, cyclosporin A and leflunomide. Recently, MAPK pathways have attracted more attention. As p38 MAPK is predominant both in endothelial cells and in the lining layer of RA synovial membrane, the inhibition of p38 MAPK could be of particular interest. Merck & Co Inc.[134,135] described a novel treatment of RA by using inhibitors of p38 MAPK.

Another important MAPK is c-JUN N-terminal kinase (JNK), which has several isoforms that phosphorylate specific sites on c-jun. JNK particularly contributes to metalloproteinase (MMP) gene expression and joint destruction in inflammatory arthritis. Several patents related to JNK application in RA therapy have been filed, and further investigations are warranted.[136–139]

Inflammation relevant cytokines: Several lines of evidence suggest an important role for IL-17 in the pathogenesis of rheumatoid arthritis (RA). IL-17A has not only proinflammatory effects by upregulateing inflammatory cytokine production and prostaglandin production from synovial fibroblasts, but also can promote degradation of cartilage by enhancing MMP production from synovial fibroblasts and articular chondrocytes. Blockade of IL-17 in vivo suppresses inflammation, joint destruction and disease progression in a number of arthritis models.[140] Cooley Godward Kronish LLP.[141] Disclosed an IL-17 binding agent to treat RA. Another invention by Cooper & Dunham, LLP.[142] is based on the unexpected discovery that co-administration of a tumor necrosis factor (TNF) antagonist and an interleukin-12 (IL-12) antagonist produces a rapid and sustained reduction in the signs and symptoms associated with TNF-mediated diseases. Zymogenetics Inc.[143] showed that the administration of IL-21 results in decreasing autoimmune responses and thereby provides a beneficial treatment for autoimmune diseases. IL-21 play roles in T cell costimulation, B cell activation and regulation of hematopoiesis. It probably has less toxic side effects compared to currently-used therapies.

Others: Osteologix, Inc.[144,145] have discovered that compounds containing ionic non-radioactive stable strontium not only have a significant palliative effect when administered orally, they also evoke an anti-catabolic effect by decreasing the degradation of the cartilage matrix. This may be the most important mechanism by which strontium can exert a chondroprotective or structure modifying effect of therapeutic relevance for the prophylaxis and treatment of diseases such as OA and RA.

Several patents [146–149] have described the use of gallium compounds to treat inflammatory arthritis. Gallium has been known for many years to be useful in the treatment of calcium bone disorders. It can both decrease bone resorption and increase bone tissue calcium content.

Jones Day [150] demonstrated an invention relating to a chronic articular inflammation-modulating composition which uses collagen-polyvinylpyrrolidone. Collagen turnover is modulated using collagen-PVP in RA patients since the biocomplex negatively regulates collagenolytic activity and increases the content of type III collagen and tissue inhibitors of metalloproteinases (TIMP-1, a natural MMP inhibitor) to levels similar to those observed in normal synovia.

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Clearly, during the past few years, the most active RA therapy development area is biological DMARDs, which is mainly due to the much-improved understanding of pathogenesis of the diseases. The unique molecular specificity and proven efficacy made the biological DMARDs attractive drug candidates. The potential size of the market and the added value of biologicals also augment the incentive for their commercial development. On the other hand, their high cost comparing to the classical DMARDs and disturbing side effects would also challenge the clinician with respect to the selection of optimal management strategy for their patients.

3.5 Drug delivery systems for RA therapy

Most of the current therapies for RA do not have joint specificity. Therefore, to reach effective drug concentrations in affected joint tissues, high systemic doses of drug must often be administered, which may lead to significant adverse systemic side effects; reduction in drug doses may attenuate toxicity but may lead to decreased therapeutic efficacy. To overcome this limitation, approaches that specifically target agents to affected joints offer unique promise. Wang, et al. [151,152] designed a novel water-soluble, N-(2-hydroxypropyl) methacrylamide (HPMA) based polymeric delivery system that selectively delivers dexamethasone to multiple joints of inflammation. In vitro drug release and in vivo studies to treat adjuvant-induced arthritis (AIA) rats have provided evidence that the therapeutic efficacy of the conjugate is related to its selective accumulation and pH-sensitive drug release (extracellular and intracellular) in arthritic joints. Minimization of adverse extra-articular side effects is expected in this newly developed drug delivery system. Liposomes have also been used in experimental models to deliver GCs to the site of inflammation.[153–156] The effect of a single intravenous treatment with glucocorticoids (GC) encapsulated in PEG-liposomes on both joint inflammation and cartilage destruction was investigated.[154] Treatment of collagen type II-induced arthritis (CIA) mice with 10 mg/kg liposomal prednisolone phosphate resulted in a strong and lasting resolution of joint inflammation, and the reduction of the cartilage damage was observed, whereas 10 mg/kg free drug only became slightly effective after repeated daily injections. Another observation is localisation of gold labelled liposomes in the inflamed joints was seen in the proximity of blood vessels, in the cellular infiltrate and mainly in the synovial lining. Importantly, unaffected joints did not take up liposomes. More recently, Koning, et al. [153] developed an Arg-Gly-Asp peptide (RGD) mediated liposomal drug delivery system that specifically binds angiogenic vascular endothelial cells (VECs) in vitro and endothelium at sites of inflammation in vivo. Using these liposomes to deliver dexamethasone phosphate (DEXP) to VECs at sites of arthritis involvement proved very efficacious in the adjuvant-induced arthritis rat model, indicating promise for the treatment of RA in humans. The selective targeting by liposomes may lead to high concentrations in inflammatory cells at arthritic joints combined with less exposure of healthy non-target tissues to GC.

Compare to the other novel therapy development, the drug delivery strategies focus on the alteration of the pharmacokinetics and biodistribution of the drugs being delivered. Because the drugs investigated so far are all US FDA approved compounds, the clinical evaluation and commercial development of these delivery systems will be much faster and cheaper than the development of a new drug. We would expect this rather under-investigated field to attract more interests in the near future.

4. Expert opinion

During the past 20 years, the treatment of RA has experienced significant progress. Early intervention with DMARDs has greatly improved RA management. Indeed, as American College of Rheumatology (ACR) suggested, the ultimate goals in managing RA are to prevent or control joint damage, prevent loss of function, and decrease pain. Clearly, most of the development of new therapies is in DMARDs, especially biological DMARDs. With the discovery of new pathways and therapeutic targets, we would only expect more growth in this

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drug category. One problem that we would have with the overwhelming development of biologicals is the potential financial impact, which may limit patients' access to these novel and maybe more effective therapies. Therefore, we believe, low molecular weight DMARDs will still play the major role in RA management for a long time. There is also strong motivation for major pharmaceutical companies to pursue this route due to their so called "block buster" effect. Progress in the development of new NSAIDs seems to be hampered by the recent withdrawal of several COX-2 inhibitors. However, we believe the motivation of development in this drug category is still strong because of the clinical needs of symptom alleviation. Due to the general fear of glucocorticoids' side effect, the new development in this area is also limited to agonists that can differentiate transrepression and transactivation. Drug delivery strategy is a novel approach in the treatment of RA. Instead of developing interventions to new molecular targets, drug delivery scientists seek to incorporate arthrotropism to current RA therapies. This strategy is aimed at reduction of systemic toxicity of certain anti-rheumatic therapies, and at the same time enhances the treatment efficacy in the joint by increasing the local drug concentration. Though they were not developed based on any newly discovered molecular pathway, drug delivery strategies would significantly improve the efficacy and safety profile of current RA therapies. Due to the relatively low cost, commercial interests in this approach may become very strong.

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Table 1

Traditional DMARDs in clinical application.

Medications	First used	Characteristics	Toxicity
Gold salts (Gold sodium thiomalate and gold sodium thioglucose)	1928	Longest onset of action, administered only by oral or by intramuscular injection. Lack of sustained clinical activity, slow onset of action, cost, poor long-term compliance.	High incidence of toxicity requiring drug discontinuation: mucocutaneous reations, proteinuria and cytopenias.
Sulphasalazine	1938	the first DMARD specifically synthesized for the treatment of RA. Low cost.	GI-related complications, neutropenia, cytopenias.
Antimalarials (Chloroquine, hydroxychloroquine)	1940s	Less effective than other DMARDs, but also less toxic, readily absorbed orally, extended serum half-lives due to tissue depot effects.	Rare but potential renal toxicity
Methotrexate	1950s	Gold-standard therapy, sustained long-term action, high tolerability, low cost, antimetabolite and antifolate drug.	Hepatitis and cirrhosis, interstitial pneumonitis, cytopenias.
Azathioprine	1960s	An immunosuppressant used to treat severe rheumatoid arthritis.	Vomiting, diarrhea, muscle aches. Increasing risk of developing certain types of cancer, especially skin cancer and lymphoma.
D-penicillamine	1960s	A metabolite of penicillin. Used to treat active rheumatoid arthritis that has not responded to other measures.	Rashes, loss of appetite, nausea, abdominal pain, and loss of the sense of taste. bone marrow suppression and serious kidney disease
Cyclosporine A	1980s	Calcineurin inhibitor. Third-line drug in RA therapy.	Renal insufficiency, anemia, hypertension
Leflunomide	1988	Inhibits de novo pyrimidine synthesis, similar efficacy with methotrexate and sulphasalazine.	Most important serious adverse reaction is hepatotoxicity
Minocycline	1990s	A member of the broad spectrum tetracycline antibiotics, mildly beneficial.	Autoimmune syndromes, headaches and a graying skin pigmentation.

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Table 2

Presently used biologic DMARDs

Drug	Status	Properties
Infliximab	Approved for RA 1999(US)	Chimeric IgG1 anti-TNF-α antibody
Etanercept	Approved 1998 (US)	Soluble TNF-receptor fusion protein
Adalimumab	Approved 2002 (US)	Human monoclonal antibody to TNF
Anakinra	Approved 2001 (US)	Recombinant IL-1 inhibitor
Abatacept	Approved 2005 (US)	Costimulation blockers
Rituximab	Approved for RA 2006 (US)	Chimeric anti-CD20 monoclonal antibody
Tocilizumab	Filed for approval in Japan	Human antibody against IL-6 receptor