

The Development of Targeted Drug Delivery Systems for Rheumatoid Arthritis Treatment

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1. Introduction

Despite the advent of biologics, rheumatoid arthritis continues to be closely linked with pain, functional impairment, and depression, and a significant number of those with moderate to severe rheumatoid arthritis are too disabled to work several years after onset (Sokka et al., 1999). Furthermore, biologics have increased medical costs to nearly \$20,000/patient/year and side effects have hindered use by those with more advanced symptoms (Lundkvist et al., 2008). “Old” disease modifying anti-rheumatic drugs (DMARDs) are also linked to negative consequences as a result of non-specific organ toxicity. The exact cause of rheumatoid arthritis has not yet been identified and, consequently, treatment methods have not been optimally effective. Drug delivery systems may serve to reduce the necessary dosage and increase therapeutic efficacy of old and new rheumatoid arthritis treatments.

Numerous materials have been proposed as drug delivery systems for cancer, and, in recent years, the use of such materials has been increasingly extended to the treatment of rheumatoid arthritis. Liposomes, nanoparticles, micelles, and macromolecule-drug conjugates can be used to increase a drug’s circulatory stability and thereby raise the probability for passive accumulation within the pannus, where permeability is enhanced. Both the specificity and therapeutic efficacy of these drug delivery systems can be further improved by combination with an active targeting moiety, such as an antibody, peptide, or polysaccharide that is specific for receptors concentrated on the surface of cells located within tissue affected by rheumatoid arthritis. The combination of passive and active targeting strategies can be used to optimize delivery of therapeutic agents to reduce toxicity and unwanted side effects and improve patient outcome. This chapter is intended to provide an overview of emerging techniques aimed at improving the efficacy of DMARDs, whilst simultaneously reducing the adverse consequences associated with non-specific targeting. Due to the nature of the disease, this review will focus only on drug delivery systems intended for systemic, rather than local/intra-articular, administration.

2. History and challenges of rheumatoid arthritis treatment

Historically, rheumatoid arthritis has been treated with a combination of anti-inflammatory drugs and immunosuppressants. Although treatment has evolved from non-steroidal anti-

inflammatory drugs (NSAIDs) to disease modifying anti-rheumatic drugs (DMARDs), including modern biologics, all of the drugs in use have severe, potentially life threatening, consequences due to non-specific targeting, often in combination with impaired immune function.

Rheumatoid arthritis treatment originated with NSAIDs, such as aspirin and other salicylates, which act as anti-inflammatory agents by interfering with the activity of cyclooxygenase (COX) enzymes and, consequently, the production of prostaglandins (PGs), which are key mediators of the inflammatory response. Despite a lack of efficacy relative to conventional DMARDs or biologics, NSAID use in combination therapy has continued (Mottram, 2003). The long term side effects of NSAIDs include gastrointestinal and cardiovascular complications, as well as impaired renal function (Dijkmans et al., 1995).

Similar to NSAIDs, glucocorticoids (GCs), including cortisone, dexamethasone, prednisolone, and prednisone, primarily act through inhibition of PG production and are still used in current rheumatoid arthritis treatment strategies. Additionally, GCs reduce the expression of several proinflammatory proteins, including interleukin-1, -2, and -6, granulocyte macrophage-colony stimulating factor (GM-CSF), and tumor necrosis factor- α (TNF- α) (Moreland & O'Dell, 2002). Although high doses can be immunosuppressive, as well as anti-inflammatory, doses are typically kept low in rheumatoid arthritis treatment to minimize the adverse consequences that include gastrointestinal complications, an increased risk of osteoporosis, visual problems, and negative skin effects (Strand & Simon, 2003).

In the 1920s, gold salts were used to treat rheumatoid arthritis based upon the belief that the disease was triggered by an infection (Mottram, 2003). Although the link to a bacterial origin has been dispelled, gold has been classified as the earliest form of DMARD. The side effects of gold include reduced liver and renal function, as well as pulmonary complications. Consequently, the use of gold as a treatment is now limited to only severe rheumatoid arthritis patients who do not respond to other DMARDs.

Several cytotoxic, anti-cancer agents have been adapted as DMARDs. For example, methotrexate has been in use as an oncology drug since 1950 and as a DMARD since 1970. Although the mechanism of action in rheumatoid arthritis remains largely unclear, methotrexate is speculated to either reduce proliferation of infiltrating inflammatory cells or suppress the release of pro-inflammatory cytokines (Mottram, 2003). Despite periodic liver function tests and biopsies for patients undergoing methotrexate treatment, cirrhosis and fibrosis are known side effects, and fatalities have been reported (Goodman & Polisson, 1994; Wolverson & Remlinger, 2007).

Other common DMARDs include immunosuppressants originally developed to prevent organ transplant rejection, such as cyclosporine, tacrolimus, and sirolimus. The immunosuppressive properties of the latter drugs appear to be primarily due to inhibition of T-cell activation (Mottram, 2003). All of these therapeutics are nephrotoxic; consequently, creatinine levels must be monitored during treatment to assess renal dysfunction and kidney damage (Schiffelers et al., 2006; Zachariae, 1999).

A better understanding of disease progression, particularly as pertains the imbalance in pro- and anti-inflammatory cytokines, has led to the recent development of a number of biologic therapies as DMARDs, for example anti-TNF- α monoclonal antibodies such as infliximab and adalimumab. Although the latter agents are intended to be more specific, systemic inhibition of key inflammatory molecules can also have negative consequences. In particular, patients receiving treatment with biologics have an increased incidence of serious infections. Furthermore, the efficacy in individual patients is often unpredictable (Strand et al., 2007).

The pharmacokinetic profiles of most DMARDs are unfavorable (Tarnier & Muller-Ladner, 2008). For example, the bioavailability, peak serum concentration, and half life of orally administered methotrexate varies considerably between patients. The large variability in pharmacokinetic parameters likely contributes to the toxicity observed in some patients (Weinblatt & Kremer, 1988). Given the high incidence of adverse side effects, in addition to variability in drug effectiveness, the application of drug delivery strategies would be a significant advancement in rheumatoid arthritis treatment.

3. Principles of drug delivery

3.1 Passive targeting

In cancer treatment, drug carrier systems with a large hydrodynamic radius to prevent renal filtration and increase circulation time can passively target diseased tissue as a result of leaky vasculature and inadequate lymphatic drainage, an effect known as "enhanced permeation and retention" (EPR) (Gillies & Frechet, 2005; Lee et al., 2006; Padilla De Jesus et al., 2002). Although inflammatory tissue, as found with rheumatoid arthritis, does not display abnormal lymphatic drainage (Xu et al., 2003), long-circulating delivery systems have been shown to selectively accumulate within the inflamed synovial tissue, i.e. the pannus (Fiehn et al., 2004; Metselaar et al., 2002; Schiffelers et al., 2006; Vanniasinghe et al., 2008; Wunder et al., 2003). The pannus possesses an increased vascular permeability similar to that of solid tumors and, consequently, the vasculature can be exploited for passive targeting in an analogous manner (Walsh, 1999). Fig. 1 illustrates the principles behind passive and active targeting of inflamed joint tissue.

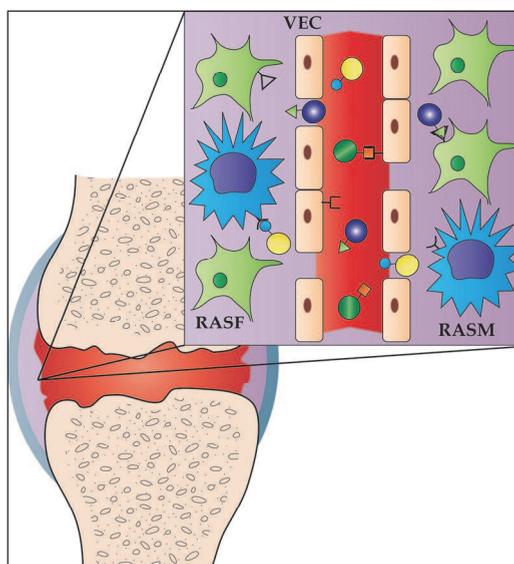


Fig. 1. Drug delivery strategies in the treatment of rheumatoid arthritis. Passive targeting of the pannus can be achieved by creating carriers that can only pass through leaky vasculature, while active targeting can be facilitated by a ligand that is specific for receptors of rheumatoid arthritis synovial fibroblasts (RASFs), rheumatoid arthritis synovial macrophages (RASMs), or activated vascular endothelial cells (VECs).

3.2 Active targeting

In addition to the potential for passive targeting, the two primary cell types found within the pannus tissue, rheumatoid arthritis synovial fibroblasts (RASFs) and rheumatoid arthritis synovial macrophages (RASMs) selectively express surface receptors, such as CD44 (Haynes et al., 1991; Johnson et al., 1993), folate receptor β (Nagayoshi et al., 2005; van der Heijden et al., 2009), and integrin $\alpha_v\beta_3$ (Wilder, 2002) that are candidates for active targeting. Angiogenic vascular endothelial cells (VECs) are also present as a result of neovascularization, and the E-selectin adhesion molecule has been identified as another viable target for drug delivery (Jamar et al., 2002).

3.3 Carrier systems

In general, drug delivery systems can be divided into two categories: polymer-drug conjugates and nanoparticulate carrier systems. "Nanoparticles" in this sense include liposomes and micelles, as well as traditional metallic and polymeric nanoparticles. As drug delivery systems have become increasingly advanced, the distinction between these two categories has become less clear.

3.3.1 Polymer-drug conjugates

In 1975, Ringsdorf proposed a model for polymer-based drug delivery wherein discrete sections of a polymer backbone are used for attachment of therapeutics, solubilizers, and targeting moieties (Fig. 2) (Ringsdorf, 1975). Since this seminal manuscript, numerous macromolecular therapeutics have been synthesized and evaluated. Although initial research focused on the use of N-(2-hydroxypropyl) methacrylamide (HPMA) based upon similarity to Ringsdorf's Model, polymers with a variety of architectures and structural elements are currently being explored, including linear mono- and di-functional polymers, star polymers, and dendrimers (Fig. 3) (Kopecek et al., 2000; Peterson et al., 2003). Dendrimers can alternatively be classified as nanoparticulate carriers when drug molecules are entrapped within the interior rather than covalently linked to the surface functional groups (Gillies & Frechet, 2005; M. Liu & Frechet, 1999). Mono- and di-hydroxyl terminated poly(ethylene glycol) (PEG) have proven to be the most versatile polymers for increasing the stability, solubility, and pharmacokinetic properties of associated therapeutics, with several PEG-drug conjugates on the market for a number of indications (Joralemon et al., 2010). Only recently has this research translated to the development of macromolecular therapeutics for the treatment of rheumatoid arthritis, as discussed further in Section 4. Despite demonstrated success, polymer-drug conjugates suffer from the necessity to chemically modify the drug molecule and the potential to reduce therapeutic activity and efficacy by such modification (Haag & Kratz, 2006; Kim et al., 2009).

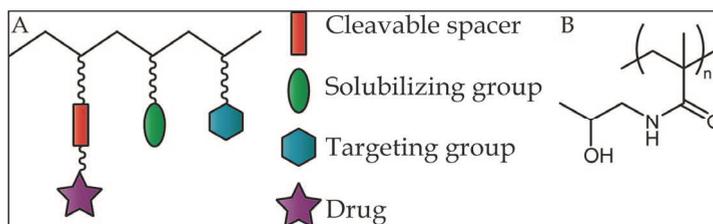


Fig. 2. (A) Ringsdorf's model of polymer-drug conjugates for drug delivery. (B) HPMA was investigated for use due to similarity to Ringsdorf's model.

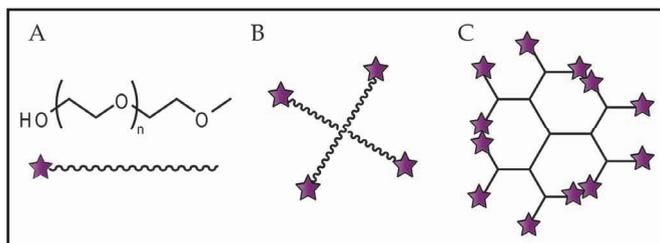


Fig. 3. Various polymer architectures investigated for use in drug delivery via polymer-drug conjugates. (A) Linear polymers, with PEG as an example, (B) star, polymers and (C) dendrimers.

3.3.2 Nanoparticulate carrier systems

Nanoparticulate carrier systems permit entrapment/encapsulation of therapeutics without modification, as is requisite for polymer-drug conjugates. The colloidal particles can range in size from 10 nm to 1 μm ; however, sizes are more typically between 20 and 300 nm, thereby minimizing uptake by macrophages of the reticuloendothelial system, while permitting passive targeting of tissue with leaky vasculature. Liposomes, micelles, metallic nanoparticles, and polymeric nanoparticles constitute the most commonly used nanoparticulate carrier systems for drug delivery (Fig. 4) (Jain, 2008).

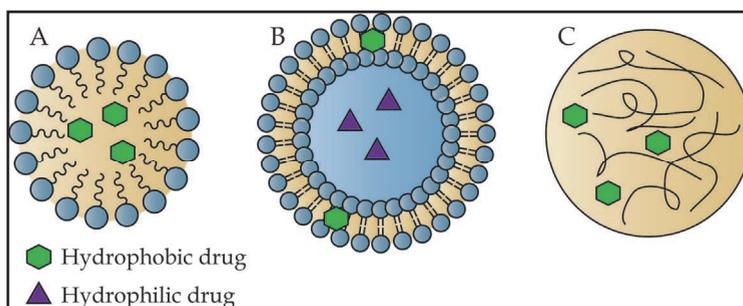


Fig. 4. Various nanoparticulate carrier systems. (A) Micelles, (B) liposomes, and (C) polymeric nanoparticles.

Liposomes are vesicles formed from phospholipid bilayers with aqueous centers. Consequently, liposomes are used to encapsulate both hydrophobic and hydrophilic drugs within the bilayer and the aqueous core, respectively. Liposomal properties are largely controlled through the choice of phospholipids, as well as the addition of sterols, particularly cholesterol, and glycolipids (Jain, 2008). Although conventional liposomes suffer from rapid uptake by the reticuloendothelial system, incorporation of PEG into the bilayer yields so called “stealth” liposomes with enhanced circulation times. Starting with the anticancer compound Doxil (Gabizon, 2001), several PEG-modified liposomes with encapsulated therapeutics have reached commercialization (Joralemon, et al., 2010). As a consequence, liposomal use has been widely studied as a potential carrier system for drug delivery for rheumatoid arthritis (Foong & Green, 1993; Konigsberg et al., 1999; Monkkonen et al., 1993; Monkkonen & Heath, 1993; Monkkonen et al., 1994; Shaw et al., 1979).

Above a certain concentration, referred to as the critical micelle concentration (CMC), molecules that possess both hydrophobic and hydrophilic segments, such as amphiphathic block-co-polymers, will self assemble to form colloidal particles with hydrophobic interiors and hydrophilic exteriors. Micelles are typically smaller than liposomes (20-50 nm) and the hydrophobic cores are used to entrap drugs that possess low aqueous solubility (Haag & Kratz, 2006). The CMC provides an indicator of stability, where systems with low CMCs are not easily disrupted or disintegrated (Oerlemans et al., 2010). Only a handful of investigators have used micelle-based drug delivery systems to improve the efficacy of DMARDs that have historically suffered from unpredictable pharmacokinetics resultant from poor solubility (Bader et al., 2011; Koo et al., 2011; Zhang et al., 2007).

Both metallic and polymeric nanoparticles are used to encapsulate drugs within the solid core. Although nanoparticles are defined as any system with a submicron ($\leq 1 \mu\text{m}$) size (van Vlerken & Amiji, 2006), most typically have sizes below 200 nm (Jain, 2008). Metallic nanoparticles include iron-oxide nanoparticles, silica-gold nanoshells, gold nanoparticles, and Quantum dots (cadmium, selenium, and zinc) (Riehemann et al., 2009; van Vlerken & Amiji, 2006). Although originally developed for cancer treatment, these technologies are currently being translated to rheumatoid arthritis treatment applications (Corthey et al., 2010). The use of metals can yield multifunctional nanoparticles whereby both therapeutic delivery and imaging are facilitated (Riehemann et al., 2009). Polymer-based nanoparticles, are advantageous in that modification permits the ready addition of the following elements: targeting ligands, environment-sensitive drug release, and biologically functional polymers. The carrier systems discussed above can be further modified to optimize disease treatment. For example, co-administration of multiple therapeutics from one convenient platform is feasible. Additional modification with ligands specific for receptors found on diseased cells can facilitate active targeting. Furthermore, surface coating with PEG can be used to tailor circulation time (Riehemann et al., 2009; van Vlerken & Amiji, 2006). As detailed in Section 4, these technologies have only recently been applied in the realm of drug delivery for rheumatoid arthritis treatment.

3.3.3 Therapeutic release from carrier systems

Most drugs are inactive when bound to/encapsulated within the carrier system; therefore, a method that permits drug release at the diseased site is often requisite. Cellular uptake of therapeutic-loaded carrier systems typically proceeds by fluid-phase endocytosis, adsorptive endocytosis, or receptor-mediated endocytosis (Fig. 5). During each of these endocytotic processes, the pH drops from that within the extracellular space ($\text{pH} \approx 7.4$ for healthy tissue and $\text{pH} < 7.4$ for diseased tissue) to pHs of ~ 6.0 and ~ 4.0 in the endosomes and lysosomes, respectively (Haag & Kratz, 2006; Petrak, 2005). Thus, the conjugate and particulate carriers can be formulated such that release is only permitted at a specified pH. Alternatively, drugs may be released after enzymes cause non-specific hydrolysis (Haag & Kratz, 2006; Kim et al., 2009). An ideal carrier system will only respond to environmental features unique to the diseased tissue, such as elevated levels of a specific enzyme. Stimuli-responsive drug delivery systems that are currently in development for the treatment of rheumatoid arthritis will be discussed in Section 5.

4. Current drug delivery systems and strategies for rheumatoid arthritis

A number of carrier systems have been designed to improve rheumatoid arthritis treatment based upon the principles described in Section 3. These carrier systems provide an

opportunity to increase the efficacy of existing rheumatoid arthritis therapeutics while reducing adverse effects. A summary of current drug delivery strategies that encompasses Sections 4 and 5 is given in Table 1.

4.1 Polymer-drug conjugates for rheumatoid arthritis treatment

Several polymer-drug conjugates have been developed to improve the therapeutic efficacy of both conventional DMARDs and biologics. A number of these compounds were only recently applied to rheumatoid arthritis after originally being developed for cancer. For example, methotrexate conjugated to human serum albumin (MTX-HSA) was shown to passively accumulate within the inflamed paws of arthritic mice. Further study revealed a reduction in cellular invasion, a downregulation of proinflammatory cytokine levels, and a decrease in cartilage damage for arthritic mice treated with MTX-HSA relative to untreated, arthritic mice. The conjugates were also useful in preventing the onset of arthritis in mice when administered prior to induction (Fiehn et al., 2004; Wunder et al., 2003). Due to the limitations of exogenous albumin, a methotrexate pro-drug has recently been developed that will react with endogenous albumin upon administration (Fiehn et al., 2008).

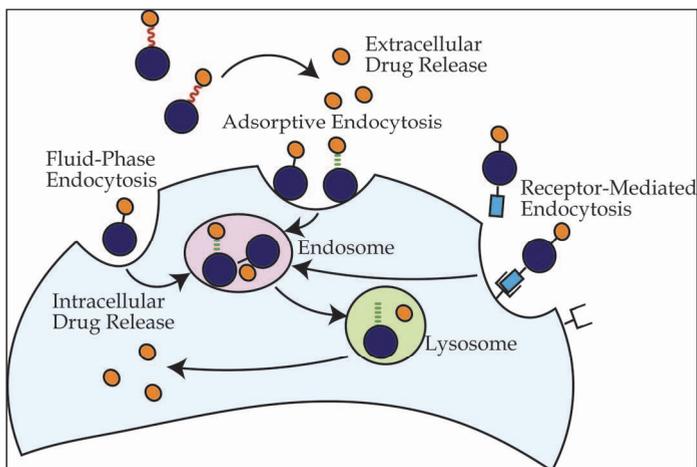


Fig. 5. Cellular uptake of carrier systems occurs by an endocytotic process. Systems can be designed to release their therapeutic payload within the extracellular space, the endosome, or the lysosome.

As mentioned in Section 3, PEG has been used extensively in all areas of drug delivery. PEG-dexamethasone conjugates were recently synthesized that reduced joint inflammation when administered intravenously to arthritis rats (Liu et al., 2010). PEGylation has been applied to biologics, in addition to conventional, small molecule therapeutics. To the authors' knowledge, the only polymer-drug conjugate to reach clinical trials for rheumatoid arthritis treatment thus far is certolizumab pegol (CDP870), a PEG conjugated TNF- α antibody fragment originally developed for treatment of Chron's disease (Barnes & Moots, 2007). Administration to a number of patients who did not respond well to conventional DMARDs, particularly methotrexate, led to a reduction in disease activity and joint damage. Unfortunately, an increase in adverse side effects was also observed (Ruiz Garcia et al.,

Type of Carrier	Material(s)	Targeting Group	Therapeutic	Reference(s)
Polymer-Drug Conjugate	Albumin	—	Methotrexate	(Wunder et al., 2003)
	PEG	—	Cathepsin-K Inhibitor	(Wang et al., 2004)
	HPMA	—	Cathepsin-K Inhibitor	(Wang et al., 2004)
	PEG	—	TNF- α Antibody Fragment	(Barnes & Moots, 2007)
	PEG	—	Dexamethasone	(Liu, et al., 2010)
	HPMA	—	Dexamethasone	(Quan et al., 2010)
	PAMAM Dendrimer	Folate	Methotrexate	(Thomas et al., 2011)
Liposome	Phospholipids Cholesterol	—	Clondronate	(Camilleri et al., 1995; Love et al., 1992)
	Phospholipids (with and without covalently linked methotrexate) Cholesterol	—	Methotrexate	(A. S. Williams, Camilleri, & Williams, 1994)
	Phospholipids Cholesterol PEG	—	Superoxide Dismutase	Corvo et al., 1999)
	Phospholipids Cholesterol PEG	—	Prendisolone	(Metselaar et al., 2002; Metselaar et al., 2003)
	Phospholipids Cholesterol	Sialyl Lewis X		(Hirai et al., 2007)
	Phosphogliv	—	Methotrexate	(Zykova et al., 2007)
	PEG-Phospholipids	Vasoactive Intestinal Peptide	Camptothecin	(Koo et al., 2011)
	Cationic Phospholipids	—	anti-TNF- α /IL- 1 β / IL-6/ IL-18 siRNA	(Khoury et al., 2008; Khoury et al., 2006)

Micelle	PEG-Poly(caprolactone)	—	Cyclosporine A	(Aliabadi et al., 2005)
	Dextran-Polyoxyethylene Cetyl Ether (POE-C ₁₆)	—	Cyclosporine A	(Francis et al., 2005)
	Hydroxypropyl-cellulose-(POE-C ₁₆)	—	Cyclosporine A	(Francis et al., 2005)
	Polysialic Acid-Decylamine	—	Cyclosporine A	(Bader et al., 2011)
Nanoparticle	PLGA	—	Betamethasone	(Higaki et al., 2005)
	PLGA-PEG	—	Betamethasone	(Ishihara et al., 2009)
	PAMAM Dendrimer	Folate	Indomethacin	(Chandrasekar et al., 2007b)
	Polyester	Ligand for E-Selectin	—	(Banquy et al., 2008).
	Cyclodextrin	—	α -Methylprednisolone	(Hwang et al., 2008)
	PLGA-PEG	cLABLE Peptide	—	(Zhang et al., 2008)
	PEG-TRAIL Hyaluronic Acid	Hyaluronic Acid	TRAIL	(Kim et al., 2010),
	Gold Core-Gold(I)-Thiomalate	—	Gold	(Corthey, et al., 2010)
	Chitosan	Folate	IL-1R Agonist	(Fernandes et al., 2008)
Lipid PEG	Folate	NF- κ B Decoy	(Hattori et al., 2006),	

Table 1. Current drug delivery strategies for rheumatoid arthritis

2011), suggesting that PEGylation may not be the ideal method to improve the efficacy of rheumatoid arthritis therapeutics.

Other polymer-drug conjugates have shown some promise *in vitro*, such as PEG and HPMA conjugated cathepsin-K inhibitor (Wang et al., 2004). Furthermore, as will be described in more detail in Section 5, systems such as PEG and HPMA dexamethasone conjugates are now being developed that, not only target the pannus tissue, but also selectively release the therapeutic in the targeted region (Liu, et al., 2010; Quan et al., 2010).

4.2 Liposomal carrier systems for rheumatoid arthritis treatment

Several liposome systems have been tried for improved efficacy of rheumatoid arthritis treatments. This work was pioneered by Williams, et. al., who demonstrated that

technecium labelled liposomes accumulated within the synovial tissue of rheumatoid arthritis patients upon intravenous administration (Williams et al., 1986, 1987). A similar phenomenon was observed for phosphatidylcholine and cholesterol based liposomes given to arthritic rats (Love et al., 1989), and encapsulation of clondronate, an anti-inflammatory therapeutic that reduces bone resorption, resulted in a halt in disease progression and a reversal in inflammation (Camilleri et al., 1995; Love et al., 1992). The efficacy of the liposomal clondronate was attributed to depletion of the synovial macrophages (Love et al., 1992; Richards et al., 1999). Comparable results were obtained with liposomal methotrexate that was prepared by conjugation of the γ -carboxylic acid residue to the phospholipid. The resultant liposomes yielded a significant reduction of established joint inflammation, in combination with a decrease in toxicity, relative to comparable doses of free drug (Williams et al., 1994b). Furthermore, peritoneal macrophages isolated from the liposomal methotrexate treated arthritic rats were shown to express less TNF- α and prostaglandin (PGE₂) (Williams et al., 1994a). Conventional (i.e. not PEGylated) liposomes have also been used by other investigators to improve the efficacy of aurothiomalate (Konigsberg et al., 1999).

Stealth liposomes have been used to improve the therapeutic efficacy of glucocorticoids, the use of which is often hindered by the necessity for frequent intravenous administration and by non-specific organ toxicity. Following on studies that showed an accumulation of PEG liposomes within the inflamed tissue of arthritic rats (Gabizon et al., 1994; Hong & Tseng, 2003), Metselaar et al. (2002; 2003; 2004) investigated the efficacy of prednisolone loaded liposomes. Upon administration to arthritic rats and mice, the prednisolone liposomes reversed the inflammatory response, while free prednisolone had little effect on the course of the disease. The results were attributed purely to the passive targeting capacity of the stealth liposomes (Metselaar et al., 2004; Metselaar et al., 2002; Metselaar et al., 2003). Current research is focused upon extending the use of the stealth liposomes to other glucocorticoids, including dexamethasone and budesonide, and optimizing the therapeutic index (van den Hoven et al., 2011). PEG modified liposomes have also been used to improve the efficacy of superoxide dismutase (SOD), a free radical scavenger which suffers from a short half life. When encapsulated in small, stealth liposomes, the circulation of SOD was significantly extended, and the drug passively accumulated within the joint tissue (Corvo et al., 1999).

4.3 Micelle carrier systems for rheumatoid arthritis treatment

Despite the low aqueous solubility of a number of DMARDs and glucocorticoids, micelles are a relatively unexplored drug delivery system for rheumatoid arthritis treatment. Camptothecin, originally developed as an anti-cancer drug, has recently been proposed as a new method of controlling pannus formation and reducing cartilage degradation. To circumvent problems with solubility and stability, micelles prepared from PEG-phospholipids (Ashok et al., 2004) were used for drug encapsulation. The camptothecin micelles proved to be more effective than free camptothecin at abrogating inflammation when administered to arthritic mice. The efficacy of the micelles was further increased by modification with vasoactive intestinal peptide (VIP) due to the over expression of VIP receptor by activated synovial macrophages (Koo et al., 2011). Similarly, micelles generated from a phospholipid preparation (Phosphogliv) and loaded with methotrexate were better able to reduce inflammation when administered to arthritic rats than the drug alone (Zykova et al., 2007).

Cyclosporine A is indicated for several different conditions; therefore, micelle-based methods for improving the solubility of this DMARD have been more thoroughly researched. Cyclosporine has been successfully encapsulated by block copolymers of PEG and poly(caprolactone) (Aliabadi et al., 2005), PEG phospholipids (Lee et al., 1999), and hydrophobically modified polysaccharides, specifically dextran and hydroxypropylcellulose (Francis et al., 2005). Recently, polysialic acid, a relatively uninvestigated polysaccharide with properties similar to those of PEG in regards to minimizing uptake by the reticuloendothelial system, was used to encapsulate cyclosporine for future use in rheumatoid arthritis treatment (Bader et al., 2011). The utility of the above cyclosporine micelles *in vivo* has not yet been demonstrated.

4.4 Nanoparticle carrier systems for rheumatoid arthritis treatment

Nanoparticle systems for delivery of rheumatoid arthritis therapeutics have primarily been based upon polymers. Numerous researchers have explored the use of poly(D,L-lactic/glycolic acid) (PLGA) nanoparticles based upon their capacity to extend the circulation time and control the release of encapsulated drugs. In the realm of rheumatoid arthritis drug delivery, a glucocorticoid, betamethasone, was incorporated into PLGA nanoparticles with a size of 100-200 nm. Intravenous administration to arthritic rats and mice showed that the PLGA-betamethasone system was more effective at reducing the inflammatory response than the free glucocorticoid (Higaki et al., 2005). Targeting ability and, consequently, efficacy of the betamethasone was further improved by modifying the PLGA nanoparticles with PEG, forming so-called "stealth nanosteroids" (Ishihara et al., 2009).

Other polymeric nanoparticle systems involve covalently linking the drug molecule to one of the components so as to slow down therapeutic release, as occurs for polymer-drug conjugates, while still protecting the drug via encapsulation. For example, α -methylprednisolone was conjugated to cyclodextrin, and the resultant compound self-assembled to yield nanoparticles with a size of approximately 27 nm. When administered intravenously at a frequency of one dose per week to arthritic mice, a significantly greater reduction in synovitis and pannus formation was achieved than that obtained for free methylprednisolone administered daily at an equivalent cumulative dose (Hwang et al., 2008). Another example is the ionic complexation of tumor necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL) conjugated to PEG (PEG-TRAIL), which bears a positive charge, with negatively charged hyaluronic acid (HA) with sizes that range from 100 to 270 nm, dependent upon the relative concentration of the two components. One formulation of the HA-PEG-TRAIL complex was capable of significantly reducing the secretion of proinflammatory mediators relative to PEG-TRAIL alone when administered subcutaneously to arthritic mice (Kim et al., 2010), thereby emphasizing the importance of nanoparticulate carrier systems. The HA may also serve as an active targeting (Section 5).

Despite the demonstrated efficacy of gold as a DMARD (Section 2), and the approval of gold nanoparticles for the treatment of rheumatoid arthritis by the FDA, little research has been conducted specifically directed towards the use of metallic nanoparticles for passive targeting in rheumatoid arthritis. The decline in the use of gold as a rheumatoid arthritis therapeutic was largely based on adverse side effects caused by non-specific toxicity. However, the synthesis of gold core-gold(I)-thiomalate nanoparticles (Au@Au(I)-TM) was recently completed. Au@Au(I)-TM bears surface carboxylate groups which may be further modified for specific drug delivery applications (Cortney et al., 2010); therefore, these nanoparticles may pave the way to a renewed interest in the use of gold in the treatment of rheumatoid arthritis.

5. Future of drug delivery for rheumatoid arthritis

The exploration of drug delivery systems for improved treatment of rheumatoid arthritis is still in the early stages. More advanced concepts that have been applied to other diseases, particularly cancer, are only beginning to be explored by rheumatoid arthritis researchers.

5.1 Active targeting strategies

Current drug delivery systems for rheumatoid arthritis have almost exclusively been developed based upon the principles of passive targeting. Specificity and, consequently, efficacy can be further improved by employing an active targeting moiety. As indicated previously, RASFs and RASMs possess receptors that can potentially be used to increase the ability of the drug carrier systems to discern pannus tissue from healthy tissue. Those receptors that have the highest potential for success are discussed in this section.

Folate receptor β (FR β) has been identified as a viable candidate for active targeting of RASMs. Several transport mechanisms exist whereby folate and folate antagonists, including methotrexate, can enter a cell. Numerous cell types throughout the body constitutively express the reduced folate carrier (RFC), a transmembrane protein. In contrast, membrane associated folate receptors (MFRs) are restricted in expression and facilitate uptake by endocytosis. The beta isoform of MFR (FR β) is expressed selectively by activated macrophages within the pannus tissue (Nagayoshi et al., 2005; van der Heijden et al., 2009). Thus, folate may serve as an effective means of actively targeting the pannus tissue. In support of this, folate-tagged cationic and anionic poly(amidoamine) (PAMAM) dendrimers loaded with indomethacin were more effective at treating arthritic rats than indomethacin-loaded dendrimers that were folate-free (Chandrasekar et al., 2007a; Chandrasekar et al., 2007b; Chauhan et al., 2004). Furthermore, a recent study demonstrated that PAMAM dendrimers covalently linked to both folate and methotrexate could be used to selectively deliver methotrexate to synovial macrophages (Thomas et al., 2011). Although the antifolate MTX does not have a high affinity for any MFRs, several other folate analogs have been identified that possess high affinity for FR β with low affinities for other MFRs and the RFC (van der Heijden et al., 2009). These analogs, therefore, have strong potential to be used as active targeting moieties in the future and may possess inherent anti-rheumatic properties.

RASFs also possess an active targeting receptor in the cell surface adhesion molecule CD44, the hyaluronic acid receptor. Several studies have indicated that CD44 is upregulated in the pannus tissue relative to healthy, normal tissue (Haynes et al., 1991; Johnson et al., 1993). Furthermore, RASFs express numerous CD44 alternatively spliced variants, including long isoforms CD44v3 and CD44v6 that are associated with an enhanced invasive capacity (Croft et al., 1997). CD44 is critical to rheumatoid arthritis pathogenesis, facilitating inflammatory cell migration and signaling activation of lymphocytes (Naor & Nedvetzki, 2003). Despite evidence of upregulation and/or selective expression, the CD44 receptor has not yet been used as an active target for drug delivery in the treatment of rheumatoid arthritis. Some cancer cells also upregulate CD44, and the potential for success using this active targeting strategy has previously been illustrated by anti-cancer drug carrier systems modified with hyaluronic acid oligomers (Ossipov, 2010).

As indicated by the feasibility of passive targeting, neovascularization is a critical component of rheumatoid arthritis pathogenesis (Szekanecz & Koch, 2008). Adhesion molecules, including intercellular cell-adhesion molecule-1 (ICAM-1) and E-selectin, are upregulated within the newly formed vasculature and; therefore, the endothelium serves as

another possibility for active targeting (Banquy et al., 2008; Zhang et al., 2008). Preliminary studies demonstrated that a large number of PLGA-PEG nanoparticles surface modified with a peptide specific for ICAM-1 were endocytosed by vascular endothelial cells as compared to unmodified particles (Zhang et al., 2008). A similar phenomenon was observed for polyester-based polymeric nanoparticles labeled with ligand specific for E-selectin (Banquy et al., 2008). Likewise, liposomes surface modified with the polysaccharide Sialyl Lewis X, which is known to bind selectively to E-selectin, were shown to accumulate within inflamed regions when administered intravenously to arthritic mice (Hirai et al., 2007). The vitronectin receptor, overexpressed by both angiogenic endothelial cells and RASMs (Tandon et al., 2005; Wilder, 2002), is an attractive target based upon the extensive use of Arg-Glyc-Asp (RGD) tripeptide labeled carrier systems for drug delivery to invasive tumor tissue (Hsu et al., 2007). An antibody to $\alpha_v\beta_3$, Vitaxin (ME-522), is currently being clinically developed for rheumatoid arthritis (Wilder, 2002); however, the RGD peptide sequence has not yet been applied towards increasing the targeting ability and efficacy of existing DMARDs.

5.2 Multifunctional carrier systems

A recent push in the realm of drug delivery for cancer treatment has been the development of multifunctional carrier systems whereby a single platform can be used for the release of multiple therapeutics in a controlled fashion or for both therapeutic release and diagnostic imaging (Jabr-Milane et al., 2008; van Vlerken & Amiji, 2006). Some of the success achieved in this “theranostic” approach to cancer treatment has spilled over into the study of improved treatment methods for rheumatoid arthritis. For example, folate-conjugated radiopharmaceuticals designed to target malignant tissue showed significant accumulation in the joints of patients who also had rheumatoid arthritis (Paulos et al., 2004). Radiolabelled biologics have provided an additional example of the potential for theranostics to improve rheumatoid arthritis treatment. ^{99m}Tc -labelled infliximab (^{99m}Tc -infliximab) was used to show a strong correlation between the amount of infliximab taken up by inflamed tissue and a reduction in symptoms and swelling (Malviya et al., 2010).

5.3 Stimuli-responsive carrier systems

As discussed in brief above, in order to be optimally effective, the drug delivery systems must release their payloads at the desired site of action, i.e. the pannus tissue. In the realm of cancer drug delivery, numerous pH- and temperature-responsive carrier systems, in the form of conjugates, dendrimers, liposomes, and micelles, have been developed (Ganta et al., 2008). Although the same potential also exists for rheumatoid arthritis drug delivery, particularly in light of the lower pH of the pannus tissue relative to native tissue, to the authors' knowledge, only two pH-responsive systems, dexamethasone-HPMA conjugates (P-Dex) and dexamethasone-PEG conjugates (PEG-DEX), have been reported. Drug release was shown to increase as the pH decreased. *In vitro* and *in vivo* tests were used to demonstrate that P-Dex and PEG-DEX are more effective than free dexamethasone in regards to reducing the production of proinflammatory mediators, preventing joint damage, and targeting inflamed tissue (Liu et al., 2010; Quan et al., 2010). In addition to temperature and pH, other environmental triggers may be used. For example, elevated elastase levels have been closely linked with inflammation and the increased enzymatic activity may be used for cleavage. The upregulation in enzymes may additionally serve as a means of active targeting (Meers, 2001).

5.4 Gene therapy

Given the nature of rheumatoid arthritis, gene therapy, whereby nucleic acids are introduced to a cell to either “turn off” select genes or upregulate therapeutic genes, is an attractive alternative treatment strategy (Jorgensen & Apparailly, 2010). This approach is limited, however, by the necessity for local administration and low transfection efficiency; therefore, for practical use, drug delivery systems for gene therapy will be required. Small interfering RNA (siRNA), in particular, may be used to knockdown the expression of proinflammatory proteins at the mRNA level. Cationic liposomes, referred to as lipoplexes, have been designed to facilitate systemic delivery of siRNA for rheumatoid arthritis treatment (Khoury et al., 2006, 2008). When administered intravenously to arthritic mice, anti-TNF- α , anti-IL-1 β , anti IL-6, and anti IL-18 siRNA successfully reduced inflammation, bone and cartilage degradation, and secretion of a number of proinflammatory cytokines, including TNF- α and IL-1 β (Khoury et al., 2006, 2008). Similarly, intraperitoneal administration of anti-TNF- α siRNA complexed with chitosan nanoparticles to arthritic mice resulted in a significant reduction in joint swelling, cartilage degradation, and inflammatory cell infiltration (Fernandes et al., 2008). Chitosan nanoparticles were also used to deliver the IL-1 receptor antagonist (IL-1Ra) gene to arthritic rats (Fernandes et al., 2008). Rats treated with the chitosan-gene delivery system showed reduced bone turnover, as well as decreased expression of IL-1 β and PGE2, relative to control rats. The efficacy of the chitosan-IL-1Ra nanoparticles was further improved by modification with folate for active targeting (Fernandes et al., 2008). An innovative strategy towards gene therapy was designed by encapsulating a nuclear factor kappa B (NF- κ B) decoy into stealth lipid-based nanoparticles that were surface modified with folate (Hattori et al., 2006). NF- κ B regulates proinflammatory gene expression and is, therefore, a critical component of rheumatoid arthritis pathogenesis (Brown et al., 2008; Simmonds & Foxwell, 2008). *In vitro*, the nanoparticles were shown to release the NF- κ B into the cytoplasm, as indicated by a reduction in NF- κ B translocation into the nucleus (Hattori et al., 2006), which presumably will result in a decreased expression of proinflammatory cytokines and growth factors.

6. Conclusion

Although the advent of biologics markedly increased the number of available treatment options, numerous rheumatoid arthritis patients still use, either alone or in combination, NSAIDs, GCs, and conventional DMARDs. All of these compounds are associated with severe negative side effects resultant from non-specific organ toxicity. In some cases, the side effects necessitate the cessation of a treatment option that may be effectively altering the course of the disease. The application of drug delivery strategies, as outlined herein, promises to improve patient outcome by reducing the likelihood of an adverse reaction to NSAIDs, GCs, and biologic and conventional DMARDs. These same strategies may be extended in the future to facilitate diagnostic imaging and gene therapy, thereby further increasing the possibility of successfully controlling the progression of the disease in all people that suffer from rheumatoid arthritis.

7. References

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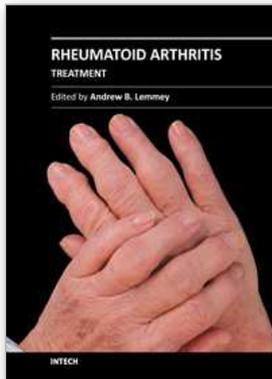
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The purpose of this book is to provide up-to-date, interesting, and thought-provoking perspectives on various aspects of research into current and potential treatments for rheumatoid arthritis (RA). This book features 17 chapters, with contributions from numerous countries (e.g. UK, USA, Canada, Japan, Sweden, Turkey, Bosnia and Herzegovina, Slovakia), including chapters from internationally recognized leaders in rheumatology research. It is anticipated that Rheumatoid Arthritis - Treatment will provide both a useful reference and source of potential areas of investigation for research scientists working in the field of RA and other inflammatory arthropathies.

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