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Macromolecular Nanomedicine of Glucocorticoids for the Treatment of Rheumatoid Arthritis

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Glucocorticoids (GCs) are a class of steroid hormones, characterized by their ability to bind with the cortisol receptors and trigger various biological effects. They have potent anti-inflammatory and immunosuppressive properties, and therefore, following the Nobel Prize-winning discovery in 1948 by Hench and colleagues, glucocorticoids initially were widely used for Rheumatoid Arthritis (RA). However, only within several years, the classical adverse effects of glucocorticoids-including an increased prevalence of adrenal insufficiency, infection, cataracts, and secondary osteoporosis-were frequently noted, particularly at high dose being long-term used, and this markedly limited glucocorticoid use in clinic [1]. Despite the concerns limiting the enthusiasm of GCs use, it is estimated that over 50% of patients with Rheumatoid Arthritis have been treated, more or less, continuously with GCs [2]. Overall, the market for GCs is estimated as $10 billion per year [3].

Today, the use of GCs 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 [4,5]. In recent years, there has been a revival of the role of glucocorticoids in the treatment of RA [6]. Most often, GCs are used in short-term to swiftly control flare, and allow the more slow acting treatments, such as Disease-Modifying Anti-Rheumatic Drugs (DMARDs) to exert their therapeutic effects. Recent studies clearly establish the fact that with low-dosage long-term treatment, glucocorticoids can substantially reduce the rate of bone and cartilage erosion progression in RA, in addition to their well-recognized anti-inflammatory and immunosuppressive properties, with short and medium-term use [7-9].

Adverse effects of glucocorticoids can be mostly attributed to their high cumulative doses. Rapid clearance and a large volume of body distribution account for low concentrations of GCs at the target sites, and necessitate frequent application at high doses. From a pharmacological perspective, incorporation of tissue specificity and alteration of GCs *in vivo* distribution, would serve as a feasible strategy to overcome these limitations, therefore reducing their off-target toxicities.

During past decades, a large number of GC macromolecular nanomedicines have been developed by covalently conjugating GC molecules to biocompatible polymeric carriers, via an ester linker [10-12]. Despite the diversity of polymers (i.e. dextran, chitosan and dendrimers) and the model drug of GCs (i.e. methylprednisolone, prednisolone and budesonide) used, the general design principle of these nanomedicines is very similar. For this type of nanomedicine design, one common concern is the poor *in vivo* stability of ester bond, due to the abundance of esterases in blood circulation. *In vitro* release studies with these nanomedicines displayed rapid hydrolytic kinetics, with nearly 40% of the drug being released within 12-48 h in PBS (pH 7.4) [10-12], Therefore, from this perspective, such designs are not practically suitable for treatment of a chronic inflammatory condition, such as RA, which requires sustained drug activation kinetics.

Successful drug delivery strategies rely to a great extent on the pathophysiological conditions of target tissue. Recognition of the characteristics of the RA joints and synovial pathology suggests that an acid cleavable linker might be an optimal choice for design of nanomedicine. Acidosis of Synovial Fluid (SF) is a characteristic feature of inflamed joints, where the pH value of SF has been shown to be as low as 6.0, and in some cases, even lower than 5.0 [13,14]. By linking the drug and the macromolecular carrier with an acid-cleavable bond (e.g. hydrazone bond, cis-aconityl bond, Schiff base or acetal bond), this unique pathophysiological feature can be exploited as a disease-specific drug activation mechanism, which would further define its inflammatory joint specificity. Moreover, the intracellular lysosomal compartment (pH 5.5-6) might be another activation trigger for nanomedicines with acid-sensitive linkage, since most of the polymeric conjugates are trafficked into a lysosomal compartment, after their endocytosis by activated synoviocytes. In a series of recently published articles, Wang's group successfully exploited this strategy and reported attractive treatment results, by developing a novel N-(2-hydroxypropyl)methacrylamide (HPMA)-based dexamethasone (Dex) nanomedicine [15-18]. The two carbonyl groups of Dex were employed as potential conjugation sites, by linking them to the HPMA copolymer, via a hydrazone bond. An *in vitro* study found that HPMA-Dex nanomedicine was indeed cleavable under acidic conditions (pH=5.0), at a rate of 1% of the total Dex loaded per day during the entire testing period (14 days), while no significant Dex release was found in PBS (pH 6.0 and 7.4) or in rodent plasma [15,17]. Moreover, in an adjuvant-induced arthritis animal model, a single treatment with HPMA-Dex nanomedicine was able to provide complete and sustained resolution of the ankle joint inflammation. The treatment also resulted in structural preservation of the articular bone and cartilage [18]. In addition to the efficacy study, the impact of the structural parameters (e.g. molecular weight, drug loading, etc.) on the nanomedicines' Pharmacokinetics and Biodistribution (PK/BD) profiles has been investigated by Quan et al. [17], using the AA rat model. The increase of either molecular weight (from 14 to 40 kDa) or Dex content (from 0 to 313 μmol/g) facilitated the distribution of HPMA-Dex nanomedicine to the arthritic joints, presumably due to prolonged circulation half-life and enhanced inflammatory cell uptake at the sites of inflammation.

In spite of potential deleterious effects, glucocorticoids continue to be an important and highly prescribed component of the treatment regimen, for patients with Rheumatoid Arthritis. An increasing body

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of literature from well-designed clinical trials supports the efficacy of glucocorticoids, for both short-term symptomatic relief, and as a disease-modifying agent. To better balance the benefits and risk of adverse effects, the introduction of macromolecular nanomedicine for RA represents a promising direction, though still in its infancy, compared to the wide application of macromolecular nanomedicine in cancer treatment. The current macromolecular nanomedicines for RA are primarily designed with an activation mechanism, triggered by enzymes or an acidic environment. More detailed knowledge regarding their exact sites of activation and retention mechanism are still missing. In order to advance the development of this strategy and to accelerate the translation of the nanomedicnes into clinical application, there is a definite need for a thorough and long-term evaluation of the efficacy and toxicities for these nanomedicines in relevant animal models.

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