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Examining Efficacy of Kidney-Targeted Nanoparticle Immunosuppressant Therapy on Lupus Nephritis in a Murine Autoimmune Disease Model

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Abstract

Introduction: Lupus nephritis (LN) is a severe kidney manifestation of systematic lupus erythematosus (SLE) with no known cure. Although typically treated with immunosuppressants, these medications can cause toxic side effects. This study proposes adopting mesoporous silica nanoparticles binding to a kidney-specific ligand, megalin, to locally deliver the immunosuppressive agent with no nephrotoxicity, mycophenolate mofetil. It is hypothesized that this method would inhibit LN progression by locally modulating immune cell activity.

Methods: Silica nanoparticles are linked to the amino groups (-NH2) and polyethyleneimine and conjugated to megalin. These conjugated nanoparticles (NPs) are then loaded with the immunosuppressant mycophenolate mofetil (MMF). The affinity and specificity of these NPs are confirmed using in vitro and ex vivo methods. Murine autoimmune disease mice (MRL-lpr) are used as a model for SLE. The mice received different nanoparticle treatments either conjugated with megalin or not, carrying MMF or not, and not receiving free MMF treatment to investigate the efficacy of megalin-conjugated mesoporous silica nanoparticles (MSN-NPs) at preventing LN. Indicators of health measured included proteinuria and anti-dsDNA concentration, kidney and lymphadenopathy scores and absolute cell counts of leukocytes, T-cells and B-cells from the kidney and other organs as well.

Results: Megalin-conjugated MSN-NPs are anticipated to increase MMF bioavailability within the kidney compared to non-specific MSN-NPs. The mice receiving megalin-conjugated MSN-NPs carrying MMF are expected to decrease proteinuria at the nephrotic range and attenuate local inflammatory immune cell activity. Moreover, it is anticipated that there will be a decrease in lymphatic cell numbers, lymph node size, and repressed inflammation in kidney glomerular and tubulointerstitial regions.

Discussion: Targeted NP immunosuppressant drug delivery is expected to be the most effective at alleviating LN in SLE mice, compared to non-megalin conjugated NP or free drug. Future directions could be investigating toxicity and off-target effects of this drug, other kidney cell markers as targets, and non-human primates as test candidates.

Conclusion: Although megalin-conjugated MSN-NPs carrying MMF has potential for alleviating LN in SLE, a rigorous test of both capacity, safety, and off-targets effects are required to fully appreciate its clinical efficacy.

Keywords: lupus nephritis; autoimmune disease, mesoporous silica nanoparticles, mycophenolate mofetil, kidney, immunosuppressants, nanomedicine, MRL-lpr mice mode

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystemic inflammatory disease that is characterized by the loss of self-tolerance, resulting in one's immune system to inappropriately attack endogenous material. Accordingly, individuals diagnosed with SLE may require lifelong immunosuppressive treatment to control disease symptoms. The overall incidence of SLE is approximately 1-8.7 cases per 100,000 individuals worldwide. Its onset is insidious and multifactorial, although genetic predisposition, female sex, African and Asian ethnicity, microbial infections, and concurrent medical conditions, have been associated with increased risk [1,2]. One of the most common and severe organ manifestations of SLE is lupus nephritis (LN), which is a form of glomerulonephritis. There is no cure or reversal of kidney tissue damage; early diagnosis, such as by the gold standard kidney biopsy, and careful monitoring are the only strategies to prevent further progression. Approximately 5-20% of individuals with LN develop end-stage kidney disease within 10 years of initial diagnosis [2]. In severe cases, kidney transplant may be required, which poses inherent risks of organ rejection. Improving the understanding of LN pathophysiology is important to expand and develop therapeutic initiatives.

Inflammatory Drivers of LN in SLE

LN is a gradual, irreversible process that is catalyzed by immune abnormalities. Anti-DNA autoantibodies, which

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are a hallmark feature of SLE, are produced by activated autoreactive B lymphocytes (B cells). They can form immune complexes that become deposited in kidney tissue, propagating renal inflammation and tissue damage. Dendritic cells and B cells can secrete cytokines such as interferon (IFN)-α, tumor necrosis factor (TNF)-α and interleukin (IL)-6 that may polarize neighboring immune cells to become inflammatory[3]. Meanwhile, T follicular helper (Tfh) cells activate and promote differentiation of germinal centre B cells, and T helper (Th)17 cells can produce inflammatory cytokines, such as IL-17, which is increased in LN and has been associated with chronic inflammation in kidney glomerular and tubular interstitial areas. Other features of LN include an increase in intrarenal complement deposition and activation, inappropriate activation of innate immune cells, and leukocyte infiltration, all of which drive local inflammatory cellular crosstalk [1,3,4].

Opportunities and Challenges for Current Treatments for SLE

SLE patients are typically treated with immunosuppressants (e.g. mycophenolate mofetil, cyclophosphamide) and corticosteroids (e.g. prednisone) [5]. Despite the general effective response, approximately 35% of individuals relapse [6]. Moreover, repetitive, high doses pose risks for long-term organ toxicity. Alternative drugs, such as calcineurin inhibitors (CNIs) may selectively restrict T cell function by inhibiting calcineurin activity. This slows their activation, proliferation and generation of effector and memory T cells [7]. However, the CNIs typically used for SLE treatment, cyclosporin and tacrolimus, have also been associated with acute and chronic nephrotoxicity, irreversible renal and vascular dysfunction, and damage in renal architecture including vessels, tubulointerstitial and glomeruli [8].

Currently, targeted therapeutics and novel biologics are being pursued to treat LN. Belimumab, a recombinant monoclonal antibody was approved by the Food and Drug Administration for treatment of LN in 2020. It works by inhibiting a cytokine that is important for B cell maturation and differentiation, and therefore, the production of autoantibodies. Other biologics currently in clinical trials inhibiting T cells, cytokines (e.g. Type I interferon, IL-6/IL-17), proteosome, and receptor tyrosine kinases, have had inconsistent successes [2]. Therefore, current challenges include improving methods to specifically target the drug to the appropriate cell, increase bioavailability, and lower toxicity.

Nanoparticles: An Emerging Therapeutic Tool for Autoimmune Diseases

Nanoparticles (NPs) are an emerging therapeutic tool to manage specific diseases via precisely targeted drug delivery. They present various advantages over traditional drugs such as improved bioavailability, customizable targeted drug delivery, lower manufacturing cost, and no immunogenicity [9]. In mouse studies of the autoimmune diseases Type I diabetes and multiple sclerosis, NPs induced immunosuppression by promoting T regulatory cell activation and function [10,11]. NPs have also demonstrated some feasibility to treat other chronic inflammatory diseases, such as inflammatory bowel disease, psoriasis, and rheumatoid arthritis [10].

Ganugula et al. investigated the potential of NPs delivering immunosuppressants to treat SLE. In their mouse model of SLE, they utilized P2Ns-GA, a nanoparticle embodiment bonded to gambogic acid, conjugated with cluster of differentiation (CD) 71 transferrin receptor, to deliver the immunosuppressant, cyclosporin A specifically to gut-associated lymphatic tissue. They observed mice transfused with CD71-conjugated nanoparticles had improved SLE symptoms and reduced lymphoproliferation [12]. These promising results guide new approaches to utilize nanoparticle therapy to treat autoimmune diseases.

Colloidal NPs, which incorporate a backbone consisting of an inorganic element or metal core, have recently risen in popularity for use in therapy [13]. Their versatility, modifiability, and capacity to encapsulate larger quantities of material have indicated some success and practicality in cancer models [14]. As such, careful consideration of nanoparticle formulation and design are critical for successful therapeutic application.

The objective of this study is to design safe and long-lasting immunomodulatory nanoparticles that would specifically localize to kidney and diminish LN in SLE.

Methods

Nanoparticle Construction

There are four main steps of nanoparticle-drug carrier synthesis: (1) Synthesis of polymer, (2) conjugation of the kidney-targeted ligand with nanoparticle, (3) selection of the drug, (4) drug encapsulation and release.

Mesoporous nanoparticles (MSNs), inorganic nanoparticles of the size 100 nm are selected as the backbone structure of the drug carrier and decorated grafting silica functional groups to the surface. On the surface of MSN, naturally present silanol groups allow binding with functional groups through silylation using organosilanes. This method can facilitate exterior and interior modifications: in this case, amino functional groups (-NH2) are introduced through APTES binding agent, making the molecule prone to binding to primary amino groups [9].

After the amino functionality are linked, the silica nanoparticles are further functionalized via DVS crosslinker, by reacting the sonicated dispersion of MSN in I-propanol. Following, PEI (polyethyleneimine) solution is added to the modified MSN, such that the branched PEI noncovalently bonded to the particle. By connecting PEI, the particle maintains positively charged amino

groups, that are able to bind to the functional groups of kidney specific receptor, megalin [15].

Mycophenolate mofetil (MMF) is selected as the immunosuppressant drug to be encapsulated due to the lower renal toxicity. MMF has shown great potential by having excellent bioavailability and having low risk nephrotoxicity compared to other immunosuppressant drugs. MMF interferes with T-cells by acting as an inosine monophosphate dehydrogenase inhibitor (IMPDH) to impede T and B cell proliferation [16]. MMF is loaded into the nanoparticle using the adsorption method: the nanoparticle is immersed into a concentrated MMF-solution, letting the drug adsorbed into the porous structure of the particle. MSN is separated from the solution by centrifugation [17].

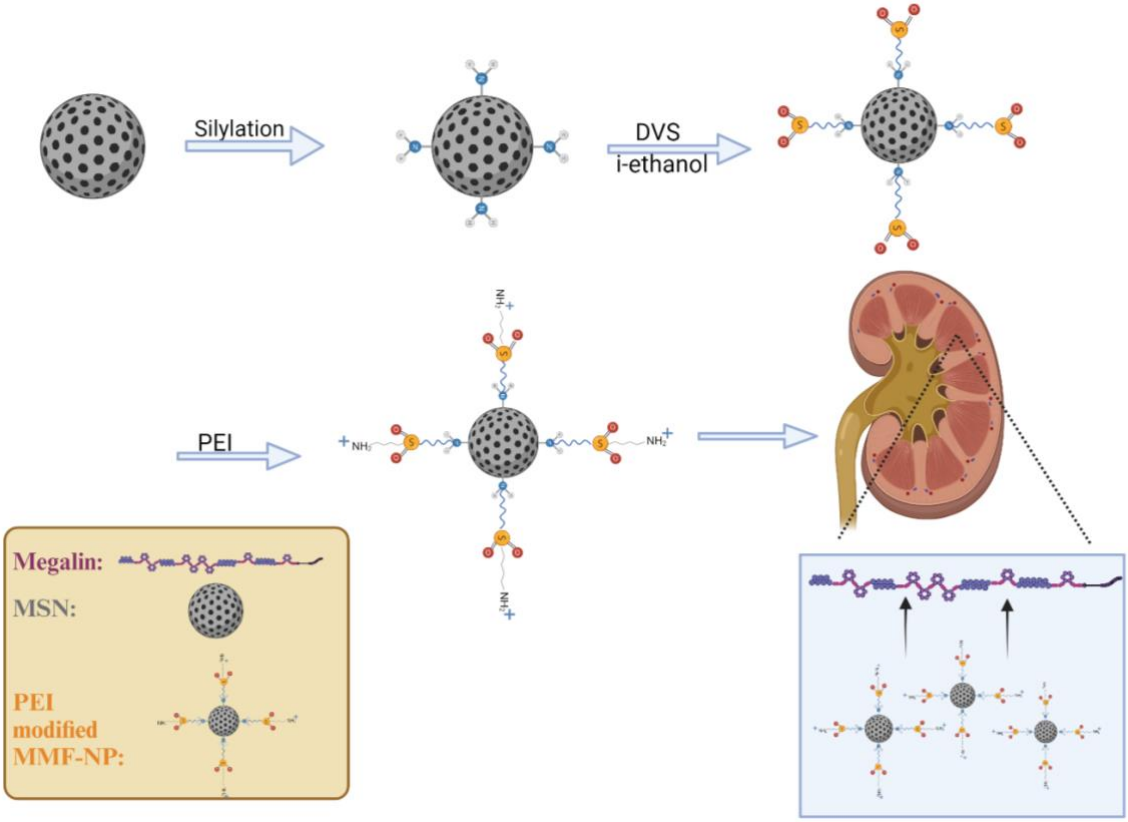

Figure 1. Nanoparticle synthesis: the mesoporous silica nanoparticle obtains amino groups through silylation. For further functionalization, the nanoparticle is added to I-ethanol solution and reacted with PEI. The obtained MMF-NPs can bind to the kidney's megalin [15]. Figure created with Biorender.

Testing Specificity of Nanoparticles

Testing Cell Viability

To measure the metabolic activity, toxicity of the nanoparticles and to provide an indication of their viability, Alamar Blue assay (Thermo Fisher) is utilized on renal cell lines from the kidney tissue. The following cell lines are incubated in Alamar Blue dye solution for overnight: HK-2 kidney epithelial cells, LLC-PK1 proximal tubule epithelial cells and HRGECs renal glomerular endothelial cells. The fluorescence of the incubated cell lines is measured using a microplate reader.

In Vitro Nanoparticle Binding Assay

NPs are first assessed for their affinity to kidney cells using the immortal murine kidney cell line, TKPTS (ATCC=CRL-3361**)**. 2 x 10^5 cells were plated and left to rest overnight in incubator at 37 degrees Celsius. 10, 25, 50, 100μg of nanoparticle conjugate that is ligated with the kidney specific receptor, or non-ligated (negative control) were added to TKPTS, for 60 minutes at room temperature. The samples were washed with 1X phosphate buffer saline (PBS) for non-specific binding, and all samples were spiked with 10^5 cells to delineate the non-binding cell population. Nanoparticles were fluorescently-labelled, and flow cytometry was used to assess the median fluorescence intensity (MFI) at various titrations.

Ex Vivo Kidney Binding Assay

8-week old female MRL/MpJ-Fas^{lpr}/J mice (MRL-*lpr*), which are frequently used as an animal model for SLE, and the healthy control, MRL/MpJ (MRL) are provided by Jackson laboratory and housed in the animal facilities in a

temperature-controlled room and fed a normal diet. From the MFL strain, the kidney, liver, lungs, and intestines are harvested, frozen using liquid nitrogen, and embedded in the OCT compound, and stored at –80 degree Celsius. These tissues could also be sliced at 5 μm and stored in -20 degree Celsius. For checking the specificity of binding to the kidney tissues compared to all the other tissues, the sliced tissues are blocked with nanoparticles that are not possessing the conjugated ligand, and subsequently incubated with labelled nanoparticles. The tissues are washed 2-3 times to remove unbound nanoparticles. The sections are mounted using Dako mounting medium and DAPI staining. The images are scanned without bright field, at 20 X. N.A. (~300 nm) resolution. For co-localization analysis, the collected images are analyzed using the HALO analysis software.

Stability and Localization of MMF-Loaded Kidney Specific Nanoparticles in Vivo.

MRL/MpJ (MRL) female mice are divided into receiving either 5 mg/kg of the kidney targeting MMF-containing NPs, kidney targeting empty NPs, non-kidney specific MMF containing NPs, non-kidney specific, empty NPs and finally, receiving MMF without NPs. The formulations are administered via oral gavage three times a week for 17 weeks. Mice are weighed at the beginning of each week to adjust for dosing. To measure the health of the kidney, urine samples from each mouse are collected using a clean cage with approximately 0.5 kg of hydrophobic sand. The mice are also saphenous bled, and approximately 50 μL of blood is collected at the beginning of each week, including baseline and just prior to sacrifice. The concentrations of the nanoparticles (ng/mg) are obtained from the plasma or the tissues. Following the study endpoint, all mice are sacrificed using cervical dislocation and the tissues are either placed in 10% formalin fixation or flash-frozen in liquid nitrogen.

To track the movement of the labelled nanoparticle within the mouse, MRL/MpJ (MRL) mice are placed in the multispectral optoacoustic imaging (MSOT) machine with a tail-vein catheter to obtain the baseline scans. Afterwards, fluorescently labelled kidney-targeting NPs or non-specific NPs are transfused into the mice. Scans are acquired every 5 minutes at multiple whole body slices for 1 hour following the transfusion. Data is collected and analyzed using the ViewMSOT software.

Efficacy of Kidney-Targeting NPs on LN in SLE Mice

8-week-old female MRL/MpJ-Fas^{lpr}/J mice (MRL-*lpr*) and MRL/MpJ (MRL) are transfused with the NP formulations as described in the previous section. The health of the mice was measured by probability of survival, changes in weight, proteinuria analysis in the urine, the concentration of anti-dsDNA antibodies (mg/mL), kidney pathology score, lymphoadenopathy scoring, skin lesion scoring. Prior to mouse sacrifice, whole blood is collected from using cardiac puncture. The absolute cell counts of white blood cells including CD8+ T-cells, B cells, are measured from whole blood and also in each of the organs that were examined (e.g. kidney, lungs, liver, small intestine) using flow cytometry. The concentrations of drug within each of the tissues examined are compared using an ELISA kit. In parallel, the concentration of anti-dsDNA IgG is obtained from plasma samples diluted 1:800 with 1X PBS, and using the mouse anti-dsDNA IgG antibody assay kit (Chondrex). Cytokine and chemokine concentrations are diluted 1:5 with the manufacturer provided diluent, and measured using the Bio-Plex 200 system (Bio-Rad)[12].

Following mouse sacrifice, formalin-fixed or tissue slides are stained either with H&E or specific immune cell subsets to look at immune cell infiltration. Additionally, the co-localization between the labelled NPs and the immune cells are examined using HALO analysis software. Co-localization is defined as a distance between the NP and the immune cell that is less than 0.5 μm. Internalization of the NP is defined as a complete overlapping of the nanoparticle with the immune cell.

Statistics

Statistical analysis is performed using GraphPad Prism. For all experiments comparing two groups, the unpaired Student's T test is used. For experiments comparing multiple groups, one-way analysis of variance, followed by Tukey's multiple comparisons test, is performed. Statistical differences is considered when $p < 0.05$.

Results

MSN-NPs are predicted to be effective drug carriers in this animal model. MSNs are stable at a wide range of pH and temperatures [9]. Their pore sizes are adjustable to achieve maximal drug delivery, while their surfaces are modifiable to fit various attachment types of different ligands [9].

In an Alamar Blue assay, the fluorescent reading is hypothesized to show high biocompatibility, thus exhibiting results similar or slightly lower compared to untreated cells. However, the PEI coating could potentially contribute to higher cytotoxicity, which suggests further evaluation of size-dependency in relation to cell viability as a potential solution to reduce PEI-induced toxicity [18] [15].

As a marker of MMF-NP effectiveness against LN, mice weight change and survival are assessed. Higher concentrations of MMF-NPs are expected to correlate with weight recovery and increased probability of survival. There are no anticipated changes in appetite and diet preferences, or other behavioural deviations such as decrease in physical activity, social interactions, and sleeping, with NP treatment. Proteinuria samples from each group will be analyzed by Chemstrips, where the severe proteinuria (>100mg/dL) is expected to decrease to <30 mg/dL, the fastest within the group receiving kidney targeting MMF-encapsulated MSN-NPs [19].

After dosing MMF, the immune cell responses and tissue distribution are analyzed. White blood cell counts are expected to return to normal as high ($\approx 40(\times 10^9$ /L)) WBC count is one of the markers in LN [20]. Decrease in CD8+ B-cells are anticipated, as the percentage of activation of these cells are significantly higher in LN patients than in healthy individuals. Mice receiving MMF-NPs are expected to experience attenuated B-cell function and lower autoreactive antibody titres [21].

Overall, reduction in cell activation is anticipated in both local and nonlocal MMF-NPs treatment groups; however, faster improvements are hypothesized for the local MMF-NPs treatment group due to kidney-cell specific binding properties. Specifically, the conjugation of MMF with MSN facilitates completely local delivery, enhancing the absorption of the immunosuppressant, highlighting a clear preference for the MMF-NPs treatment over the free MMF treatment.The nanoparticles bind to megalin in the proximal tubules, enabling the immunosuppressant to be released locally, thereby directly suppressing T-cell activity.

Glomerulonephritis and substantial tubulointerstitial fibrosis are expected to be prevented in MRL-lpr group following treatment with MMF-NPs [12]. A slight overall health improvement is anticipated with non-kidney targeted MMF-NPs, that is not significantly different from unencapsulated MMF administration, while no treatment is expected to have the worst LN outcome.

To guarantee the clearance of the nanoparticle, the nano-bio interactions are investigated. Mesoporous silica nanoparticles ranging from the size of 3.3 nm to 720 nm have been approved for renal clearance, with a preference for sphere-shaped particles. Although nanoparticles of the size 3.3-6 nm are preferred for glomerular basement membrane interactions and have a renal clearance efficiency around 73%-64%, larger molecules can be degraded into smaller portions in the glomerulus, which are hypothesized to result in similarly high percentage of renal clearance [22].

Discussion

The use of nonspecific immunosuppressants in SLE introduces risk for long-term organ toxicity and may be ineffective in a subset of patients. This suggests that novel targeted therapies would be more successful at controlling SLE symptoms, such as LN. In this study, conjugated MSN-NPs are proposed to be an effective drug therapy for delivery of MMF immunosuppressants to kidney to minimize LN in SLE mouse model.

Kidney cell-targeted MSN-NPs are predicted to decrease inflammatory cell recruitment [12] and inflammatory cytokine signalling in the kidney tissues, and simultaneously possess low immunogenicity and toxicity. Moreover, the longer half-life of these MSNs may increase bioavailability and help prevent long-term relapses [23]. While this NP was designed to specifically localize within the kidney, a potential limitation of this study is that it cannot be excluded that there are NPs binding non-locally that may interact with unintended cells or tissues, causing drug release at inappropriate sites. A more thorough analysis of potential off-targets effects is warranted. Another limitation of the model may involve the renal clearance the particle: due to its rather bigger size, renal clearance is not guaranteed, unless the molecule is partitioned into smaller fragments. To achieve a clearance efficiency close to 70%, the application of smaller particles (such as C-dots) is advised.

In this study, MMF was used as an immunosuppressant to inhibit inflammatory cell function. MMF is preferred over other immunosuppressant agents, such as CSA, because of lower nephrotoxicity. However, there are still limitations of its usage, for instance, it cannot be used during pregnancy [24]. Another consequence of MMF usage may be leukopenia, accompanied with suppressed T and B cell function, which may impair ability to resolve infections [25]. Therefore, usage of MMF will require regular medical assessments and potential dose adjustments per individual.

Even though the fluorescence reading is hypothesized to result in high biocompatibility, the usage of PEI-coating still rises some questions regarding cytotoxicity. Future directions could explore utilizing chitosan coating or adjusting MSN-size to balance out the potential toxicity of PEI [18].

While MMF-NP is anticipated to inhibit the progression of LN, it cannot reverse or restore normal kidney tissue architecture following damage that has already occurred. Nonetheless, it is predicted that directly delivering the immunosuppressant to the area of inflammation is overall more beneficial to improve quickness and preciseness of the drug therapy to treat LN specifically compared to unencapsulated MMF. While drug efficacy on health and improvement of LN was primarily assessed in mice, future studies employing larger non-human primates may provide a more informative and comprehensive model to indicate the efficacy in humans. Another focus of future studies could potentially include trials for kidney-specific binding sites other than megalin or various cells – like dendritic cells – directly interacting with T-cells.

Conclusions

This study intended to explore the potential of MSN-NPs immunosuppressant drug delivery to treat LN. By specifically targeting kidney cells, MSN-NPs has the potential precisely deliver immunosuppressant to the inflammatory tissue site, increase local bioavailability, and minimize systematic side effects. Furthermore, the low immunogenicity and toxicity of MSN-NPs, and customization extends its versatility for applications beyond SLE and other autoimmune diseases. Future studies could explore the optimization of MSN-NP pore size to improve drug loading capacity to provide explicit release kinetics control or consider different coating to

enhance biocompatibility. Whether the technology used in this study could also be used for binding sites in other tissues and/or different medication agents deserves further investigation.

List of Abbreviations Used
APTES: (3-aminopropyl) triethoxysilane
CD71: cluster of differentiation 71/ transferrin receptor protein 1
CNI: calcineurin inhibitor
CSA: cyclosporin A
DVS: divinyl sulfone
IgG: immunoglobulin G
IL-17: interleukin-17
IMPDH: inosine monophosphate dehydrogenase
LN: lupus nephritis
MFI: median fluorescence intensity
MMF: mycophenolate mofetil
MMF-NPs: mycophenolate mofetil nanoparticles
MSN: mesoporous silica nanoparticles
MSOT: multispectral optoacoustic imaging
NP: nanoparticle
PBS: phosphate buffer saline
PEI: polyethyleneimine
SLE: dystemic lupus erythematosus

Conflicts of Interest
The author declares that they have no conflict of interests.

Ethics Approval and/or Participant Consent
All experimentation will be conducted in accordance with the Canadian Council for Animal Care.

Authors' Contributions
KM: contributed to study design and planning, drafted the manuscript, and gave final approval of the version to be published.

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