Research Highlights

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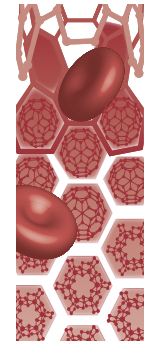
Nanomedicine



Highlights from the latest articles in nanomedicine

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Sticky nanoparticles

Evaluation of: Rose S, Prevoteau A, Elzière P, Hourdet D, Marcellan A, Leibler L. Nanoparticle solutions as adhesives for gels and biological tissues. *Nature* 505(7483), 382–385 (2014).

Polymeric adhesives have been used for gluing two nonpolymeric substances. However, adhering two polymer gels typically requires environmental changes, UV, an electric field or a chemical reaction *in situ*, which may be impractical for particular biotechnology applications. Traditional methods commonly cause self-adhesiveness, which diminishes the materials' maneuverability and its scope of utility. The authors in Rose *et al.* discuss the use of nanoparticles as an adhesive for non-self-adhesive gels at room temperature by simply spreading the solution and pressing the two gels together briefly. As the materials are pulled apart, some polymer strands undergo nanoparticle desorption, while other strands adsorb to the nanoparticles, allowing energy to dissipate during deformation while the gel junction remains intact.

In this study, two gels were formed with similar properties including crosslinking and swelling. One of the gels was made of poly(dimethylacrylamide) and adsorbed to silica nanoparticles, whereas the other gel made from polyacrylamide did not adsorb to these nanoparticles. The nanoparticles enabled the poly(dimethylacrylamide) gels to hold together with strong adhesion, whereas polyacrylamide gels would not adhere. The authors found the strength of adhesion increased as particle size and polymer strand length increased, and as the crosslinking density and material rigidity decreased. In addition, the authors found that the adhesion forces were still strong when the gels were placed in new environments, such as when dehydrated gels became hydrated. Poly(dimethylacrylamide) gels containing up to approximately 98% v/v% water were able to adhere successfully.

The authors demonstrated that the particles were retained on the surface of poly(dimethylacrylamide) gels after multiple washings and soaking in water for several days. In addition, in postjunction failure, the gels have self-repair capabilities following a brief application of force without having to reapply additional nanoparticles. In one example, this nanoparticle adhesive technology was able to bond liver tissue together following nanoparticle application and 30 s of finger pressure. This nanotechnology holds interesting promise for wet adhesion applications in medicine.

Microfluidics to synthesize a nanoparticle library

Evaluation of: Valencia PM, Pridgen EM, Rhee M, Langer R, Farokhzad OC, Karnik R. Microfluidic platform for combinatorial synthesis and optimization of targeted nanoparticles for cancer therapy. *ACS Nano* 7(12), 106710–10680 (2013).

Nanoparticles that enable targeted delivery and sustained release of therapeutic drugs are of great scientific and clinical interest. However, clinical translation of nanoparticles requires a controlled, scalable system that allows for rapid and reproducible synthesis as well as optimization. The authors of Valencia *et al.* developed a microfluidic platform to synthesize a library of poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles that were subsequently optimized with high-throughput screening.

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The microfluidic device has multiple inlets for various precursors, such as PLGA, polyethylene glycol (PEG)-conjugated PLGA of varying molecular weights, PEG-PLGA conjugated to a targeting ligand, and a model drug to be encapsulated by the nanoparticles, docetaxel. These precursors mix and undergo nanoprecipitation inside the microfluidic system to rapidly form a library of nanoparticles each with distinct biophysicochemical properties (size, surface charge, targeting ligand density and drug loading) that are reproducible across batches and homogeneous within a batch. The authors first optimized nontargeted nanoparticles based on minimal uptake by macrophages *in vitro* and found that this correlated to the particles with the longest blood half-life in mice. The precursors to the selected nontargeted nanoparticles were then added with varying amounts of targeting ligand-conjugated PLGA–PEG to synthesize targeted nanoparticles of similar physicochemical properties as nontargeted nanoparticles except for ligand density. These particles were screened for maximal and minimal uptake by prostate cancer cells and macrophages, respectively. The accumulation of the optimized targeted nanoparticle formulation was lower in the spleen and increased 3.5-fold in prostate tumor mass compared with its nontargeted nanoparticle counterpart.

In combination with a previous study that showed *in vivo* optimization and therapeutic effect of a similar library of targeted PLGA nanoparticles synthesized by conventional bulk pipetting [1], this study shows good potential for controlled synthesis and optimization of PLGA nanoparticles towards cancer therapy. The microfluidic platform used in this study may also be useful for the rapid synthesis, optimization and scale-up of other types of polymeric nanoparticles.

A Trojan horse for nanoparticle delivery to tumors

Evaluation of: Cheng Y, Morshed R, Cheng SH *et al.* Nanoparticle-programmed self destructive neural stem cells for glioblastoma targeting and therapy. *Small* 9(24), 4123–4129 (2013).

Nanoparticle delivery of drugs for cancer therapy has the potential to improve treatment efficacy while reducing off-target effects. However, the efficacy of nanoparticle therapies targeting large or dense tissues can be limited by nanoparticle diffusion within the tissue. The authors of Cheng *et al.* sought to overcome this barrier by harnessing the tumor-homing capabilities of neural stem cells (NSCs) and using them as a nanoparticle carrier.

HB1.F3.CD NSCs, which are US FDA approved for local injection in human clinical trials, were loaded with mesoporous silica nanoparticles containing doxorubicin (Dox) linked via acid-labile bonds (MSN-Dox). Through *in vitro* work, the authors were able to show that their MSN-Doxs would release Dox in acidic conditions comparable to endosomal and lysosomal pH. Importantly, the *in vitro* experiments showed HB1.F3.CD NSCs endocytosed MSN-Doxs, maintained their tumor-homing capability and survived for 48 h. This enabled the *in vivo* study in which MSN-Dox-loaded HB1.F3.CD NSCs were injected contralaterally to U87 glioma tumors in mice. Three days later, imaging analysis revealed that 96% of Dox and 96.5% of apoptotic cells were found within the tumor site. Survival studies showed that both intratumorally and contralaterally injected HB1.F3.CD-MSN-Dox cells resulted in significant increases in survival versus MSN-Dox alone.

These results suggest that this system has the potential to be both robust and safe. The self-destruction of the NSCs is inherent in their design, which could prevent potential tumor-initiating side effects. The work presented by Cheng *et al.* demonstrates an exciting strategy for using tumor-targeting cell therapies for improving nanoparticle-based drug delivery.

Albumin nanoparticles for inhibition of acute inflammation

Evaluation of: Wang Z, Li J, Cho J, Malik A. Prevention of vascular inflammation by nanoparticle targeting of adherent neutrophils. *Nat. Nanotechnol.* 9, 204–210 (2014).

Inappropriate triggering of the inflammatory response is implicated in a wide variety of diseases ranging from sepsis to reperfusion injury. In many instances, acute inflammation can lead to serious tissue necrosis or death. Rapid and controlled inhibition of this response is thus desirable for therapeutic applications. In this study, the authors present a simple yet effective nanotechnology platform to prevent neutrophil adherence to vascular endothelium, a key step in the generation of the inflammatory response.

In the design of their vehicle for neutrophil drug delivery, the authors of Wang *et al.* utilized the fact that denatured proteins are quickly opsonized *in vivo* and that adherent neutrophils highly upregulate the Fcγ receptor for antibody constant regions. Through chemical crosslinking of denatured bovine serum albumin, the authors synthesized nanoparticles that could target these adherent neutrophils with high specificity over circulating neutrophils and macrophages. With the use of FcγRIII knockout mice and nanoparticles synthesized with native albumin, the authors were able to demonstrate the targeted uptake of these nanoparticles relied on these two parameters.

To achieve an anti-inflammatory effect, the nanoparticles were loaded with piceatannol, a drug that inhibits a critical kinase required for signaling

of adherence in neutrophils. Due to rapid clearance from circulation, free piceatannol is inefficient at preventing neutrophil attachment. Nanoparticle encapsulation allowed the authors to circumvent this issue and facilitated piceatannol delivery to neutrophils. Utilizing intravital microscopy of TNF-α-treated cremaster muscle, the authors observed *in vivo* detachment of neutrophils from the endothelial wall upon intravenous nanoparticle administration. The authors also demonstrated their particles could prevent neutrophil adherence and sequestration in an acute lung injury model.

By taking advantage of opsonization of denatured protein and FcγR upregulation in adherent neutrophils, this study presents an effective nanoparticle therapy for the inhibition of the inflammatory response. Such a strategy holds promise for the treatment of acute inflammatory disorders.

Reference

1 Hrkach J, Von Hoff D, Mukkaram Ali M *et al.* Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile. *Sci. Transl. Med.* 4, 128ra39 (2012).

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