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Focus on fundamentals: achieving effective nanoparticle targeting

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Abstract

Successful molecular targeting of nanoparticle drug carriers can enhance therapeutic specificity and reduce systemic toxicity. Typically, ligands specific for cognate receptors expressed on the intended target cell type are conjugated to the nanoparticle surface. This approach, often called active targeting, seems to imply that the conjugated ligand imbues the nanoparticle with homing specificity. However, ligand-receptor interactions are mediated by short-range forces and cannot produce magnetic-like attraction over larger distances. Successful targeting actually involves two key characteristics: contact of the nanoparticle with the intended target cell and subsequent ligand-mediated retention at the site. Here we propose a conceptual framework, based on recent literature combined with basic principles of molecular interactions, to guide rational design of nanoparticle targeting strategies.

Keywords

Nanoparticle; vascular targeting; receptor-ligand binding; kinetic competition; ex vivo organ perfusion

Translating the fundamentals of receptor-ligand interactions

Conjugation of cell-specific ligands (including antibodies) to the surface of nanoscale drug carriers (“nanoparticles”) can potentially increase delivery of a therapeutic agent to a desired anatomic site, while decreasing unwanted delivery to other sites. Often described as “active targeting,” this nomenclature can be misinterpreted to imply that ligand-conjugated (see Glossary) drug-carriers acquire the capacity to home to the intended site of therapeutic delivery [1]. However, molecular forces that mediate ligand-receptor binding (e.g. hydrogen bonds and electrostatic interactions) only extend over ~0.3–0.5 nm [2, 3] and cannot provide a long-distance magnetic pull to a site of therapeutic need. Instead, ligand-targeting can

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improve delivery by increasing the likelihood that a nanoparticle is *retained* by a target cell or tissue it happens to *contact*.

Achieving effective nanoparticle targeting is then a question of how to optimize for maximal contact and retention. While empirical approaches are typically used in nanoparticle optimization, the rigorous formalism describing receptor-ligand interactions can potentially provide a more efficient basis for rational-design. However, this formalism generally assumes ideal experimental conditions optimized for specific receptor-ligand binding with negligible non-specific interactions. By contrast, biomedical engineers seeking to exploit receptor-ligand binding for site-specific nanoparticle delivery must contend with conditions that are extremely complex and offer much less control over critical binding parameters (Figure 1). Thus, the central challenge is how to adapt the principles of receptor-ligand binding from the simple *in vitro* environment to the complex conditions encountered *in vivo*.

In this opinion article, we suggest an accessible framework for adapting fundamental principles of molecular binding to produce effective nanoparticle targeting *in vivo*. Because *in vivo* nanoparticle delivery is an inherently kinetic, non-equilibrium process, we suggest that the key to achieving effective site-specific targeting is to focus on factors that influence the rates of nanoparticle accumulation, including rates of accumulation at both desired and undesired sites. Within this framework, we focus on two essential (and sequential) steps for effective targeted nanoparticle retention: *Step 1*– Contact between nanoparticle and the targeted cell or tissue; and *Step 2* – Successful ligand-receptor engagement (Figure 2, Key Figure). This conceptual framework can help assess which cellular targets and therapeutic settings are most likely to benefit from ligand-targeted nanomedicines. We conclude by providing an example of an optimized application: targeting vascular endothelium during *ex vivo* normothermic machine perfusion of isolated human organs being prepared for transplantation.

Winning the kinetic competition

Since most nanoparticles are introduced into the bloodstream, the half-life of nanoparticles in the circulation is a critical determinant of therapeutic efficacy and much effort has been expended to engineer nanoparticles with prolonged half-lives [4–6]. Half-life affects efficacy because targeted nanoparticle delivery *in vivo* is effectively a competition—for a limited supply of agent—between the desired target site versus all off-target sites. Since nanoparticle circulating concentration is continuously falling, this competition is an ever-evolving, non-equilibrium process. Consequently, the steady-state, equilibrium-based binding parameters (e.g. the equilibrium dissociation constant or K_D) typically used to describe receptor-ligand interactions *in vitro* are less applicable *in vivo*. Instead, the efficacy of targeted delivery *in vivo* is dictated by the competitive balance between the rate of accumulation at the target site versus the combined rate of undesired accumulation at competing sites.

This kinetic competition has inspired delivery strategies that avoid “first-pass” elimination of nanoparticles from the circulation by the mononuclear phagocyte system (MPS) [7]. Nanoparticles can be injected into the vasculature just upstream of the target organ,

providing maximal particle exposure prior to subsequent phagocytic elimination. For example, intra-arterial administration of nanoparticles has been used to improve delivery to the brain in a mouse model of cerebrovascular thrombosis [8, 9] and to cardiac vasculature in a healthy pig model [10, 11]. Since the first transit time through the target organ is short, perhaps less than one second, targeted nanoparticles must rapidly bind or extravasate to benefit from this strategy.

Not all tissue sites of therapeutic interest are amenable to immediate upstream administration, meaning phagocyte-mediated elimination of nanoparticles is often an unavoidable challenge. Consequently, targeting can be improved by minimizing the rate of nanoparticle phagocytosis. This can be achieved through the use of inert surface coatings such as poly(ethylene) glycol (PEG) or hyperbranched poly(glycerol) (HPG) that suppress phagocytic clearance [12, 13]. Variation of nanoparticle size, shape, and surface charge can also modulate phagocytosis both *in vitro* and *in vivo* [4]. Biomimicry offers another possible approach. A ‘don’t eat me’ peptide derived from human CD47 has been conjugated to the surface of nanoparticles to reduce phagocytosis *in vivo* in NOD/SCID mice, a strain that recognizes human CD47 [14]. Alternatively, so-called ‘cloaked’ or ‘camouflaged’ nanoparticles are coated with the plasma membrane of platelets or red cells to impart characteristics of these cells. This has been shown to reduce phagocytic elimination in primary cell line human macrophages *in vitro* [15] and following *in vivo* delivery in mouse models [16]. Collectively, these approaches provide evidence of kinetic competition in targeted drug delivery and illustrate how to tip the balance of accumulation in favor of the intended target site.

Making contact: the first step in effective target site retention

Given the short-range nature of molecular interaction forces, nanoparticles must first come in close contact with the target cell before receptor-ligand binding can occur. Several factors that can influence the frequency of contact between nanoparticle and target cell have been identified [17] (Figure 2), but here we focus on the critical issue of target cell accessibility. The most prevalent mode of nanoparticle administration in both experimental models and human clinical trials is intravenous injection (IV) and the most typical targets are solid tumor cells [18, 19] (see Clinician’s Corner, box 1). However, extravascular tumor cells are poorly accessible due to the barrier formed by endothelial cells that line the vasculature and selectively regulate passage between blood and tissue. Consequently, nanoparticle targeting of tumor cells generally fails to significantly alter biodistribution *in vivo* following systemic nanoparticle administration [20, 21]. While tumor vasculature is often “leaky” [22], this can paradoxically limit nanoparticle extravasation by increasing interstitial pressure, thereby reducing outward bulk fluid flow, the means by which nanoparticles cross the vessel wall [23]. Consequently, the fraction of administered dose that escapes the vasculature to accumulate within the tumor is generally only a minor fraction of the injected dose (~1%) [24].

Box 1**Clinician's Corner**

- Particles with submicrometer diameter (“nanoparticles”, typically <200 nm) are being used as drug carriers in clinical trials in attempts to increase local drug concentration while minimizing systemic toxicities.
- When administered systemically (e.g. via the bloodstream), nanoparticle-mediated delivery can be viewed as a competition between delivery to the cells of interest versus undesired phagocytic clearance by the macrophages of the liver and spleen. Some clinical trials have failed because these macrophages are highly efficient at eliminating nanoparticles leading to low levels of delivery to target cells of interest.
- Attaching a ligand to the nanoparticle surface that binds to the cell or tissue of interest, referred to as “targeting,” can improve delivery, but only if: 1) the nanoparticles have access to the desired site (which, if extravascular, is often prevented by the endothelial cell lining of the blood vessels); and 2) if binding of the ligand to its specific cell or tissue-associated receptor functions to efficiently capture and retain the nanoparticle at that site.
- In light of these considerations, the selection of the clinical setting is very important for successful applications of targeted nanoparticle drug delivery.
- As an example, anti-endothelial cell antibodies can be used to successfully target nanoparticle drug carriers to the vascular endothelial cells of an isolated organ that is being machine perfused *ex vivo* prior to transplantation. This setting is in many ways ideal because: 1) endothelial cells, the principal cellular targets of post-operative injuries and graft rejection, are readily accessible to the bloodstream; and 2) the isolated *ex vivo* perfusion circuit circumvents competition from hepatic and splenic macrophages in the graft recipient.

In contrast to the poor accessibility of extravascular cells, vascular endothelium represents a highly accessible cell type to nanoparticles in the bloodstream. Endothelial cells perform a number of key homeostatic functions required for organ health including: 1) regulation of vascular tone; 2) regulation of bidirectional molecule exchange between blood and tissue; 3) active maintenance of blood fluidity by controlling coagulation; and 4) control of inflammation by preventing adhesion and activation of innate and adaptive immune cells [25]. Injurious stimuli can interfere with the normal performance of any of these tasks, causing “endothelial dysfunction” which contributes to the pathophysiology of a wide array of diseases from sepsis to cardiovascular disease to cancer [26]. In addition to homeostatic regulation, endothelial cells can be *activated* to perform specialized functions, such as recruitment of circulating immune cells in infection [25]. Inappropriate endothelial activation can cause inflammatory or autoimmune tissue injury. Alternatively, tumor vessel endothelium can resist activation, impairing anti-tumor immune responses [23]. This combination of direct accessibility and broad pathophysiologic importance in a variety of

disease settings provides significant therapeutic potential for nanoparticle targeting to vascular endothelial cells.

Successful endothelial targeting of drug-loaded nanoparticles has been demonstrated *in vivo* (reviewed in: [11, 17, 27]). Recently, a nanoparticle made of small molecular weight lipids, termed 7C1, was shown to specifically target endothelial cells through an unknown mechanism. These particles effectively delivered silencing nucleic acids to lung endothelium in mouse models of emphysema and Lewis lung carcinoma, [28] and to aortic plaque endothelium in a mouse model of atherosclerosis [29]. Nanoparticle targeting via conjugation of endothelial-specific molecules (e.g. antibodies, natural ligands, peptides etc.) have also been shown to enhance site-specific targeting of endothelium. Anti-CD31 nanoparticles can increase lung targeting *in vivo* by > 10× in a pig model as an example [10, 11]. The success of endothelial targeting underscores the importance of target cell accessibility to ensure nanoparticles frequently collide with the target cell type.

From first contact to stable ligand-nanoparticle capture

Effective retention of a nanoparticle at an accessible site requires engagement between cell-surface-receptor and nanoparticle-surface-ligand (Key Figure 2). The surface density of the target receptor on the cell of interest is critically important to the efficiency of this engagement. *In vivo* phage display libraries have been used to generate peptides specific for receptors highly expressed on endothelium in specific tissues of interest, dubbed ‘vascular zip codes’ [30–32]. Specific peptides conjugated to nanoparticles can target specific vascular beds in a variety of different mouse models of disease including: impaired uteroplacental perfusion in pregnancy [33], Alzheimer’s disease [34], and abdominal aortic aneurysm [35]. Antibodies have also been routinely used to target receptors known to have high levels of expression in specific areas of interest. For example, the endothelial leukocyte adhesion molecule ICAM-1 has much higher expression on activated endothelium at sites of inflammation relative to quiescent endothelium [36, 37]. Targeting ICAM-1 has been used in a mouse model of traumatic brain injury to improve the delivery of the enzyme catalase to reduce reactive oxygen species [38]. Other molecules that are induced in endothelial cell dysfunction also have potential as target receptors. The integrin $\alpha_v\beta_3$, for example, may distinguish angiogenic tumor from normal vasculature potentially providing a mechanism to target therapeutics to these vessels [39].

Conjugate-ligand surface density is also an essential determinant of nanoparticle targeting efficacy [40, 41]. Notably, studies with different particle types, sizes and ligands have demonstrated that excessive levels of ligand density that saturate the full nanoparticle surface appear to actually impair targeting, likely due to steric hindrance [17]. In cell culture, sub-saturating ligand densities were found to be optimal for three different ligands (HER2 affibody, HER2-targeting peptide, and folate) on two sizes of nanoparticles (25 and 50 nm) [41]. These steric effects, which impair the ability of the ligand to properly engage the cognate receptor, underscore the importance of the receptor-ligand binding properties. Relatedly, dual epitope targeting of CD31 can provide ‘collaborative enhancement’ by making epitopes more accessible for effective nanoparticle targeting [42]. Molecular engineering has also been used to improve molecular binding properties through the use of

high affinity single chain targeting antibodies [43]. Collectively, these examples demonstrate how the molecular properties of both the ligand-nanoparticle and the target cell receptor can contribute to more effective targeting.

A final determinant of the stability of nanoparticle capture and subsequent therapeutic efficacy is endocytic fate. Notably, it has been shown in primary cell culture of human umbilical vein endothelial cells that crosslinking of receptors on the cell surface by nanoparticles decorated with a high surface density of ligand can trigger endocytic internalization [44]. This process is dependent upon receptor identity, receptor crosslinking, nanoparticle size, and shape [36, 45]. Moreover, the rate of internalization and the subsequent intracellular fate has also been shown to be sensitive to biological factors (e.g. shear stress, exposure to ischemia [46, 47]). Internalized nanoparticles have the potential benefit of durable retention at the target site, thereby allowing for sustained therapeutic effect by slow release of the encapsulated agent [48].

An optimal application: Delivery during *ex vivo* organ perfusion

The concepts reviewed in the preceding sections suggest an important conclusion: ligand-targeted nanomedicines are not suitable for every disease and therapeutic setting. Instead, just as is true for receptor-ligand binding *in vitro*, conditions must be optimal to produce the desired result. We conclude by highlighting an emerging therapeutic setting that optimizes the potential of targeted nanomedicines, namely endothelial cell targeting during *ex vivo* normothermic machine perfusion (NMP) of isolated organ grafts. This technology aims to better preserve, assess, and revive marginal organs in order to expand the pool of organs available for clinical transplantation [49] (Figure 3). In addition, the *ex vivo* perfusion period creates a unique opportunity for direct delivery of drugs within the perfusate; an approach that can circumvent many of the challenges of systemic drug delivery. In the context of transplantation, therapeutic agents can be delivered directly to the graft endothelium to protect against ischemia reperfusion injury and reduce the intensity of immune-mediated rejection post-transplant.

We have recently demonstrated that nanoparticles administered *ex vivo* can provide prolonged siRNA-mediated knockdown of MHC molecules lasting up to six weeks in the endothelial cells lining a human coronary artery segment transplanted into an immunodeficient mouse [50]. We have also recently shown that conjugation of an anti-CD31 antibody can enhance vascular retention of poly(lactic acid)-poly(ethylene glycol) (PLA-PEG) nanoparticles during *ex vivo* perfusion of human kidneys [51]. In our study, we performed quantitative analysis of vascular-targeted nanoparticle retention in a series of 8 human kidneys. This gave us an opportunity to quantitatively evaluate the efficacy of vascular targeting in an intact human organ with native 3D architecture and cellular complexity.

In addition to the potential of this work in transplantation, our recent study in human kidneys has revealed the value of *ex vivo* perfusion as a quantitative tool to assess nanoparticle targeting efficacy in a translational setting. It is becoming clear that *in vitro* cell cultures are not adequate for predicting the efficacy of targeting *in vivo* [51, 52]. This is probably

because, while easy to work with, cell culture does not replicate the 3D architecture and cellular complexity present *in vivo*. Isolated organs, on the other hand, can provide this complexity and may provide a bridge to identifying the challenges associated with systemic nanoparticle targeting. Furthermore, isolated organ perfusion also provides a simplified setting relative to experiments in live animals with greater control over the parameters relevant to effective targeting (e.g. perfusate composition/viscosity, time dependent nanoparticle concentration) and better opportunity for detailed quantitative assessment. Since these systems can be run side by side in similar experimental platforms, it is also possible that isolated organs could be as an experimental platform to develop a rigorous formalism to predict *in vivo* drug delivery.

Concluding Remarks

Ligand-conjugated nanomedicines are not a panacea for avoiding all of the pitfalls of systemic drug administration, but this approach has the potential to be highly impactful when used in the right setting. Many outstanding questions remain (see Outstanding Questions), however the keys to successful implementation of this technology are becoming clearer and involve careful consideration of the competitive balance of kinetics of accumulation at the target site versus all off-target sites. From this perspective, targeting vascular endothelium during perfusion of isolated organs has significant potential for rapid translational impact. However, even in an idealized setting (such as an isolated organ), realizing benefit from the addition of targeting-ligands still requires careful quantitative attention to the fundamentals of ligand-receptor binding, which though undeniably more complex, are just as important *in vivo* as they are in a test tube.

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Glossary

CD31

cluster of differentiation 31, or platelet-endothelial cell adhesion molecule (PECAM-1), is a cell-cell adhesion protein found at the intercellular junctions of endothelial cells (as well as on the surface of platelets, monocytes, and some lymphocytes). It acts as a mechanosensor of fluid shear stress and is involved in the regulation of leukocyte migration through venular walls.

CD47

cluster of differentiation 47, or integrin associated protein, is a transmembrane, protein ubiquitously expressed on human cells, especially circulating and immune cells, and delivers a “don’t eat me” signal to macrophages.

Equilibrium

the state where the forward reaction rate (ligand + receptor $\rightarrow$ ligand bound to receptor, or $A + B \rightarrow AB$) is equal to the reverse reaction rate (bound ligand and receptor unbind to form

free ligand and receptor). While routinely achievable *in vitro*, the equilibrium state is not generally reached during targeting of nanoparticles to cells of interest.

ICAM-1

intercellular adhesion molecule-1, or cluster of differentiation 54, is a transmembrane cell adhesion protein on endothelial and other cells. Expression levels dramatically increase on activated endothelial cells at sites of inflammation and participates in arrest and transmigration of leukocytes.

Kinetic competition

the competitive environment encountered by ligand-coated nanoparticles that target cells and tissues of interest but also may be captured by specific receptors expressed at other sites, as well as through nonspecific interactions or through phagocytosis by macrophages of the hepatic and splenic sinusoids, all of which reduce the concentration of NP available for binding at the target site as a function of time.

K_D

dissociation equilibrium constant is equal to the ratio of the forward rate of reaction (ligand + receptor $\rightarrow$ bound, or $A + B \rightarrow AB$) to the reverse rate of the reaction (bound $\rightarrow$ free receptor and ligand). The lower the K_D the stronger the reaction, and the more reactants (ligand and receptor) are converted into products (bound), K_D can be used to represent affinity.

Ligand-targeting

an approach that uses conjugation of ligand to the surface of a nanoparticle in order to engage specific receptors expressed on cells and tissues of interest. Ligands used for targeting may take various forms, including peptides, antibodies or antibody fragments.

Mononuclear phagocyte system

this term describes the sinusoidal macrophages of the liver and spleen that serve to remove particulate matter, including nanoparticles, from the bloodstream through phagocytosis. It replaces the earlier term, reticulo-endothelial system, as the sinusoidal endothelial cells of these organs are now known to play no role in such clearance.

Nanoparticle

A submicrometer diameter drug carrier used to deliver therapeutic agents. Nanoparticles may have distinct compositions, such as lipids, cross-linked proteins, or synthetic polymers, that will carry in their capacity to bind and release drugs.

Normothermic machine perfusion

explanted organs are connected to a mechanized circuit that supplies warmed, oxygenated fluids, such as washed and suspended red blood cells, allowing restoration of function in the organ before transplantation

Phage display libraries

bacteriophages are encoded with specific genes of interest, causing the phage to display the associated protein, interaction between the phage and molecules at a target site can help describe the surface of tissues.

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Highlights

- In spite of much effort, ligand-targeted nanoparticles have yet to achieve significant clinical impact.
- The primary approach thus far to optimizing nanoparticle targeting has been largely based on empirical studies. However, fundamental principles of ligand-receptor interactions can be used guide a more rational-design approach.
- The basic principles of binding were developed *in vitro* under simple conditions with complete control over all relevant binding parameters. Adapting these for *in vivo* drug delivery requires understanding the specific challenges present *in vivo*.
- Nanoparticle delivery *in vivo* is highly dynamic and, consequently, targeting should be viewed as a kinetic competition between target site and off-target accumulation.
- Site-specific retention can be maximized by focusing on the two steps that drive local retention: 1) Close contact between nanoparticle and target cell; and 2) Effective ligand-receptor engagement upon contact.

Figure 1. Key differences in receptor-ligand binding *in vitro* versus in *in vivo* nanoparticle targeting

The principles of receptor ligand binding are often determined in simplified *in vitro* experiments, where there is negligible interaction with the inert environment, and the concentrations of ligand and receptor can be controlled to ensure equilibrium conditions are met. By contrast, systemic ligand-mediated targeting is done in a competitive environment, where the concentration of available ligands is diminished over time due to non-specific binding and actions of the mononuclear phagocyte system. In this setting, it is unlikely that delivering ligands in excess of receptors can ever be accomplished regardless of non-specific elimination. Additionally, even though a known amount of ligand-nanoparticle (NP) can be administered, hemodynamic effects on nanoparticle distribution within a vessel and the heterogeneity of the target receptors mean that local concentrations cannot be exactly known. Finally, the accessibility of a target *in vivo* is highly variable depending on the target cell type location. These attributes together contribute to an inherently complex, non-equilibrium environment.

Key Figure 2. Applying the Law of Mass Action to optimize the two steps to *in vivo* ligand-mediated nanoparticle targeting

The first step to maximizing targeted nanoparticle (NP) retention is maximizing the frequency of NP-cell contact. In the Law of Mass action, which can be used to describe the rate of NP-cell binding, this term is represented with concentrations of the target cell (A) and the NP (B). Targeting highly accessible cells (e.g. the endothelium; Left panel) versus cells in the parenchyma, allows NPs to come within close range of the target where molecular interaction forces can act thereby allowing receptor-ligand binding to occur. Reducing NP elimination by the mononuclear phagocytotic system (MPS) slows the reduction of NP concentration over time also allowing for more frequent NP-cell contact (Middle panel). The second step is to design successful ligand engagement of the target cell. Choosing targets and designing NP systems with high density of ligands and receptors can contribute to fast on rates and slow off rates between ligand and receptor, which increases the likelihood that chance contact will result in retention of the NP and reduces the likelihood that the nanoparticle will be released from the cell surface prior to internalization.

Figure 3. Ex vivo organ perfusion as a setting for vascular-targeted nanoparticles

In this procedure, human organs (e.g. kidney, pictured above) are connected to a closed circulation loop, maintained by a mechanical centrifugal pump. Perfusates, such as washed and suspended red blood cells, are kept at or near normal body temperature. Supplying continuous flow supplemented with oxygen supply and necessary nutrients extends the time that an organ can retain healthy function outside of the body while awaiting transplant. The period of *ex vivo* perfusion provides privileged access to the organ, significantly limiting the complications and variables of systemic delivery systems. The isolated nature of the organ also simplifies measurement of nanoparticle delivery characteristics and physiological function to assess any impact of therapeutic delivery.

Table 1

Examples of clinical studies using targeted and non-targeted polymer nanoparticles

Name	Formulation	Targeting molecule	Administration route	Disease indication	Clinical phase	References
Abraxane®	Paclitaxel Albumin	None	Intravenous	Breast cancer, NSCLC, pancreatic cancer	FDA approved	[53]
AZD2811 Nanoparticle	AZD2811 PLA- PEG	None	Intravenous	Acute myeloid leukaemia/High- risk myelodysplastic syndrome	Phase I/II	[54]
BIND-014	Docetaxel PLA- PEG	Prostate-specific membrane antigen ligand	Intravenous	Non-small cell lung cancer, prostate cancer	Phase II	[55]
CALAA-01	siRNA cyclodextrin-PEG	Transferrin	Intravenous	Solid tumors	Phase I	[56]
CRLX101	Camptothecin cyclodextrin-PEG	None	Intravenous	Pancreatic cancer, ovarian cancer, and small cell lung cancer	Phase II	[57]
Genexol- PM	Paclitaxel PLA- PEG	None	Intravenous	Breast, lung, pancreatic cancer	Phase III- IV	[58, 59]
SEL-068	Nicotine- <i>SVPTM</i>	Agonist/T cell helper peptide	Intravenous	Nicotine addiction	Phase I	[60]
SVP- Rapamycin	Rapamycin PLGA+PLA-PEG	None	Intravenous	Gout	Phase II	[61]
Yale BNPs	Avobenzone- Octocrylene PLA- HPG	Bioadhesion to skin	Topical	Prevention of sun damage and skin cancer	Pilot	[62]

NSCLC: Non-small cell lung cancer

PLGA: Poly(lactide-co-glycolide)

PLA-PEG: poly(lactic acid)-poly(ethylene glycol)

PLA-HPG: poly(lactic acid)-hyperbranched polyglycerol