



Perspective

Terminology matters: There is no targeting, but retention

Joshua Reineke

South Dakota State University, Department of Pharmaceutical Sciences, Brookings, SD 57007, United States



1. Introduction

The potential and promise of tumor-targeted nanomedicine has dominated the drug delivery field over the past few decades [1]. Initiated by the seminal concept of Ringsdorf [2] on the polymer-drug conjugates with a ligand interacting with tumor cells, the field has rapidly developed resulting in numerous studies beyond polymer-drug conjugates, extending to liposomes and nanoparticles of varying types decorated with tumor-interacting moieties. This was further potentiated by the observation of the enhanced permeation and retention (EPR) effect by Matsumura and Maeda [3], which described the accumulation of proteins and emulsions into solid tumors through leaky vasculature and reduced drainage from tumors by ineffective lymphatics. More recently, however, there has been a debate around the effectiveness of so-called tumor-targeting nanomedicines [4] and the tumor EPR effect is highly heterogeneous or absent in human tumors [5–7] resulting in poor clinical translation [1]. In fact, nanoparticle targeting does not exist; there is only a highly complex and dynamic distribution through blood circulation. The realization of a clinical benefit is the chief objective [8] and, in my opinion, the “targeting” terminology has confounded progress. As discussed below, recognizing this truth and pushing nanomedicine research beyond the elusive targeting concept provides opportunities to improve the clinical impact of nanomedicines.

2. Promise of nanomedicine

The plight of targeted nanomedicine reminds me of Napoleon's 1812 Russia Campaign, frequently called Napoleon's March and eloquently illustrated by Charles Joseph Minard's map (Fig. 1) [9]. Napoleon is considered one of the greatest military tacticians and he had the largest and most powerful army at the time. However, only 2% of his original troops returned from capturing Moscow and failed in their goal to conquer Russia. It was not a great battle that caused the failed campaign, but a lack of understanding of the many barriers his army faced in the 1800 km round trip march [10]. Napoleon's 2% remaining troops are analogous to about 2% delivery of nanoparticles reaching tumors. One could question the validity of Napoleon as the greatest military tactician and the greatness of his army. Similarly, the promise of nanomedicine is being drawn into question after the many failed clinical studies.

Conversation on nanoparticle-based therapies and diagnostics is often discussed in terms of their promise. The promise of nanoparticle capabilities, behaviors, and other properties have been stated in journal articles dating as far back as the 1970s, and the association of promise with nanoparticles is particularly prevalent in research articles today (Fig. 2). The majority of the research articles of nanoparticles deal with tumor targeting, while there are many other important diseases to address. The association of nano and promise has become poignant due to few nanoparticle-based products currently available for clinical use and a slowed progress in development [1]. Inherent within a promise is the critical aspect of the terminology used.

3. The misnomer of “targeted nanoparticles”

3.1. “Active targeting”

Keeping the importance of terminology within a promise in mind, we need to discuss what is probably the only other term with a greater association to nanoparticles: *targeting*. The two terms have “grown up” together with the idea of targeted medicine evolving from Paul Ehrlich's *magische Kugel* concept of the 1890s and the concept of nanotechnology first mentioned in a short story of the same period by Nikolai Leskov on *The Tale of Cross-eyed Lefty from Tula and the Steel Flea* [11], although the Japanese scientist Norio Taniguchi is credited with the first use of the term nanotechnology [12].

In reference to nanomedicine, ‘active targeting’ is often used to describe a nanoparticle system associated with a so-called “targeting-ligand” that will recognize a specific biochemical entity (e.g., a cell surface receptor, a protein component of the extracellular matrix, a blood constituent, etc.). The goal of this targeted nanomedicine is to have increased accumulation for treatment or detection of a specific target site within the organism and minimize off-target distribution of the nanoparticle. The terminology of ‘targeting’ is misleading in that it indicates a process of active seeking, which is further compounded by the terminology of “active targeting.” “Passive targeting” of the same nanoparticles will have the same distribution at the intended target site as the active targeting. The difference between active and passive targeting, if it exists, can only occur after nanoparticles have a chance to interact with the target cells.

To clarify the concept with my students I often use the analogy of a GPS system commonly used in motor vehicles. The role of the vehicle

E-mail address: Joshua.Reineke@sdstate.edu.

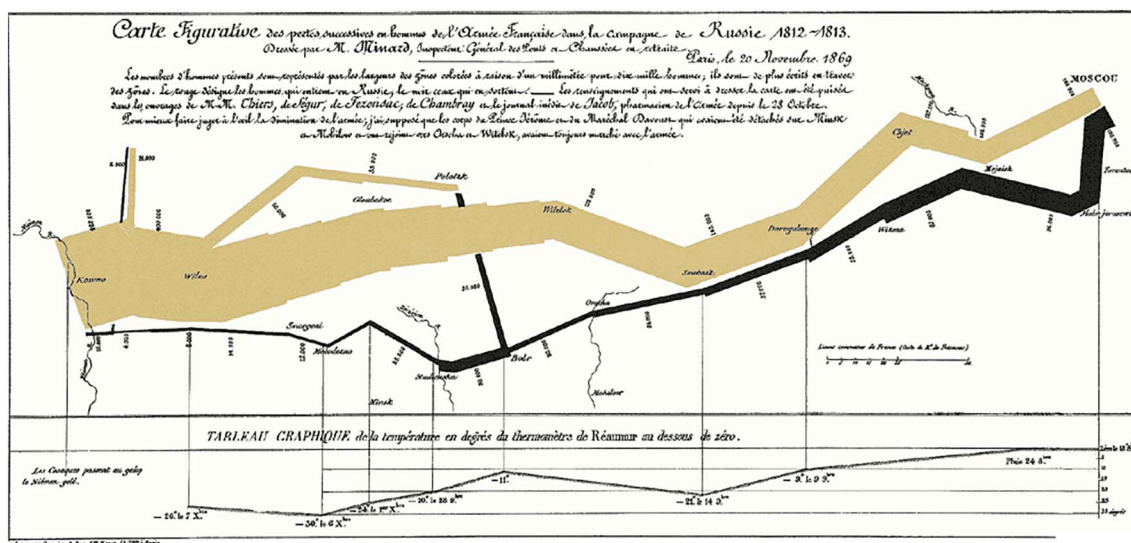


Fig. 1. Charles Joseph Minard's map of Napoleon's 1812 March to Moscow (tan) and return (black). The thickness of the line depicts the number of troops (from reference [9]).

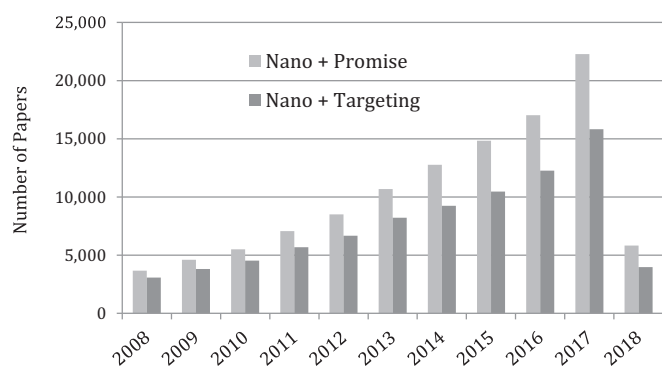


Fig. 2. Number of papers when using the search term “nano” with “promise” or with “targeting”. Search was performed on January 12, 2018 using ScienceDirect.

is the transportation; I am only able to transit where my vehicle is capable of traveling. A large sport utility vehicle may be limited in traveling through narrow city alleyways in much the same way a compact car may be limited over rough terrain. Regardless of what my GPS may tell me, I would not try to drive through the Pacific Ocean on my recent trip from USA to New Zealand, as I know my vehicle cannot overcome that barrier. The role of the GPS is solely to tell me whether I am in the right location (and too often I hear “take a U-turn”). When I am in the correct location it states that I have arrived at my destination and I know to stay there. The GPS does not actively bring me to the location. In much the same manner, a “targeting ligand” does not actively bring a nanoparticle to the target site. It simply retains the particle at the site once it has distributed there. This is only if the nanoparticle has a chance to interact with the receptor on the target cell surface. This is in contrast to the descriptors that are often found within targeted nanomedicine research articles that include: “directed”, “attracted”, “brought to”, “steered”, “converged”... frequently combined with “active.”

Given the misnomer of a “targeting ligand”, I propose the use of an alternative term: “retention ligand”. This more accurately describes the processes involved as delineated with the GPS analogy above. Additionally, ‘targeting’ should be used judiciously to ensure it is not replacing the accurate terms of “distribution and/or accumulation”. As mentioned above, Paul Ehrlich used the term “magic bullet” for the first time, but it does not mean the drug goes only to the target. It means that a substance, which distributes throughout the body, interacts with specific disease-causing agents without harming the body itself. If a

drug is only effective when and where it is necessary, it appears to be targeted, but targeting only to the intended site does not actually exist.

3.2. “Passive targeting”

If we consider that ‘targeting’ is a misnomer because it does not exist, we must also reconsider the term ‘passive targeting’. Although the use of “passive” removes the implication of an active process, it is still a fallacy to call it ‘targeting’ for the same reasons mentioned previously. The processes that are occurring are a distribution based on physicochemical properties of the nanoparticles and their interaction and access through physiological and/or biochemical processes. The terminologies of distribution, biodistribution, and/or accumulation are more accurate descriptors, while keeping in mind that the distribution may be spatially and/or temporally preferential based on the physiology and biochemistry (preferential distribution).

Further, ‘passive targeting’ is largely associated with the EPR effect, while “distribution” has a more broad application. Equating passive targeting or distribution with the EPR effect could carry a negative implication, since the clinical applicability of the EPR effect in cancer has come into question [5]. Preferential distribution of nanomedicines may have great clinical application beyond cancer, including through vascular leakiness in other disease states, as we recently reviewed [13], or through physicochemical nanoparticle properties, physiological properties (disease and healthy state), and/or biochemical processes. Many of these preferential distributions hold a strong clinical potential, as in many cases they may be less heterogeneous within the clinical population relative to the EPR in cancer patients. Are we limiting the application of nanomedicine by focusing almost entirely on the EPR effect? Additional mechanisms of preferential nanomedicine distribution have been largely understudied in a systematic fashion.

3.3. “Evading mononuclear phagocytic system (MPS)”

The best-studied mechanisms of preferential nanomedicine distribution are strategies to achieve prolonged blood circulation as discussed elsewhere [14–16]. This is typically achieved through the strategies of size reduction below 260 nm and increasing the surface hydrophilicity to prevent serum protein adsorption. In both cases, this reduces the capability of macrophages to detect and clear nanoparticles, often known as the mononuclear phagocytic system (MPS) evasion. This terminology has been rightly updated from the previous terminology of reticuloendothelial system (RES) evasion to more accurately describe the mechanism and cells involved in the nanoparticle

clearance from the blood. However, MPS evasion is still fraught with misconception as there is not a complete evasion of the MPS, but rather a slowing of the biological clearing process. The strategies slow the kinetic process, but there is not an absence of the process. Characterization and understanding of these dynamics may enable further advancement in this area. An MPS uptake rate is often described in terms of circulation times; and, if one is comparatively larger than another it is considered stealthy rather than considering a more universally comparable MPS clearance rate (as a note, blood clearance includes tissue distribution and would be a different measure than MPS clearance). Stealth aircraft, as an analogy, are more difficult to detect, but can still be detected [17] – reduced detectability, instead of undetectable. The stealthiness of nanoparticles should not be considered as a binary function, but on a continuum to allow further advancement in this area as it is far from perfected.

3.4. Just semantics?

The proper use of accurate terminology goes beyond semantics. The terminology used has impacts on the understanding of potential when we, as drug delivery scientists, communicate with scientific collaborators outside the nanomedicine field, clinical collaborators, potential corporate and business partners, funding agencies, impacted patients, policy makers, and the general public. Clear understanding of the processes and mechanisms enables a better-defined promise and more accurate assessment of potential. Failed promises negatively impact the field across-the-board even if the failure is simply a misunderstanding of the potential.

4. Opportunities beyond “targeting”

As drug delivery scientists, freeing ourselves from the inaccurate targeting terminology and moving towards accurate descriptors provides additional research opportunities to, hopefully, advance the field for clinical applications. For instance, it contributes impetus towards understanding the dynamic processes involved through kinetic studies of ligand retention, preferential distribution, and MPS clearance, among others. Below are two brief examples of opportunities in particokinetics and personalized nanomedicine as explored in my research.

4.1. Particokinetics

Over the past decade I have describe an area of my research as particokinetics to differentiate it from pharmacokinetics. Put simply, particokinetics is the pharmacokinetics of particulate systems [18,19]. The necessity of a differing terminology is based on the fact that applying traditional pharmacokinetic analysis to particulate systems can be misleading, as it does not capture many kinetic processes critical to the understanding of particle-based system performance. For instance, particokinetics allows for the characterization of retention ligand binding kinetics, preferential distribution kinetics, particle aggregation/de-aggregation kinetics, particle degradation kinetics, and release kinetics of the active pharmaceutical to be integrated into a kinetic model. Major barriers to progress in this area are the lack of analytical techniques to obtain this information from *in vivo* studies, designing mathematical models to integrate the various kinetic profiles, and understanding of the clinical applicability of these studies. We have made initial progress in methodology development of *in vivo* nanoparticle degradation kinetics [20] and differentiation of free drug, protein-bound drug, and particle-bound drug kinetics [21]. We have also adapted physiologically-based pharmacokinetic models to describe nanoparticle distribution as a function of particle properties to enable preferential biodistribution kinetic predictions [22]. Much more work in systematic studies and methodology development is needed, but particokinetics may be an important tool to better understand nanoparticle behavior and tissue-specific retention. As mentioned

previously, if a drug is only effective when and where it is necessary, it appears to be targeted. This effect may be achieved if the treatment site retention kinetics and *in vivo* drug release kinetics are properly aligned.

4.2. Personalized medicine

An important area of possible impact for nanomedicines is in personalized medicine. Although a recent sociological study indicates that the nanomedicine field is limited to personalization through molecular conception and molecular precision [23]. The current approach is largely based on patient stratification identifying patients that could benefit from a given nanomedicine (molecular conception). A variety of patient biometrics and biomarkers may be used in this stratification and a relatively limited number of patients benefit from such nanomedicine interventions. Within a stratified patient group, further research into the molecular precision is explored through “targeted” therapies. If one considers the previous discussion on the systematic understanding of particokinetics, we can image a new approach to personalized medicine from a nanomedicine perspective that goes beyond molecular conception and precision.

A very smart high school student working in my lab, Jay Mehta, and I devised an alternative approach [24] (further developed with undergraduates Ishan Metha and Roxanna Piotrowska) that expands the impact to a larger patient group as illustrated in Fig. 3. Briefly, systematic characterization and understanding of a nanomedicine's *in vivo* behavior (particokinetics) paired with critical biomarkers (determined through particokinetics) enables a two-library approach, wherein a patient stratification allows a nanomedicine to be combined in clinic with a surface modifier to provide the proper retention ligand, preferential distribution, and release kinetics for a positive clinical outcome to multiple stratified patient subgroups. Certainly, there are additional regulatory considerations to this type of personalized medicine, but nanomedicine in its own right has already created numerous regulatory considerations that have since been addressed [25]. Stratification in personalized nanomedicine should not only apply to the patient groups, but to the nanomedicine platform as well to achieve a truly personalized outcome.

5. Denouement

Despite being one of the best military tacticians and having a large and powerful army, Napoleon's 1812 Russian Campaign was a grave failure due to a lack of understanding and simplification of all the barriers his army faced in the march to Moscow. The nanomedicine field is highly developed and has a vast array of sophisticated nanomedicines in its armory. However, if we do not fully understand or oversimplify their behavior in the body and overstate their capability, we will not have the foresight to address many of the barriers in route to a meaningful clinical impact and will continue to have very few nanoparticles successfully make the march to the treatment site.

Accurate terminology is critical in advancing the drug delivery field and in understanding barriers and capabilities. Whether ‘active targeting’ or ‘passive targeting’, the nanoparticles will have the same distribution at the intended target site, while nanoparticles with “targeting ligands” may have a chance to more strongly interact with the target cells. To reiterate, there is no targeting. A danger of using such misnomers is that the researchers who are exposed to this area for the first time will have misconceptions that will probably spill over into their research, making the same mistakes as their predecessors. Additionally, misnomers can result in unintended, and sometimes unrealistic, expectations by individuals outside the drug delivery field. It is time to correct our past mistakes and use the right terminology, such as “retention ligands” to replace ‘targeting ligands’.

Nanoparticle-Based Personalized Medicine

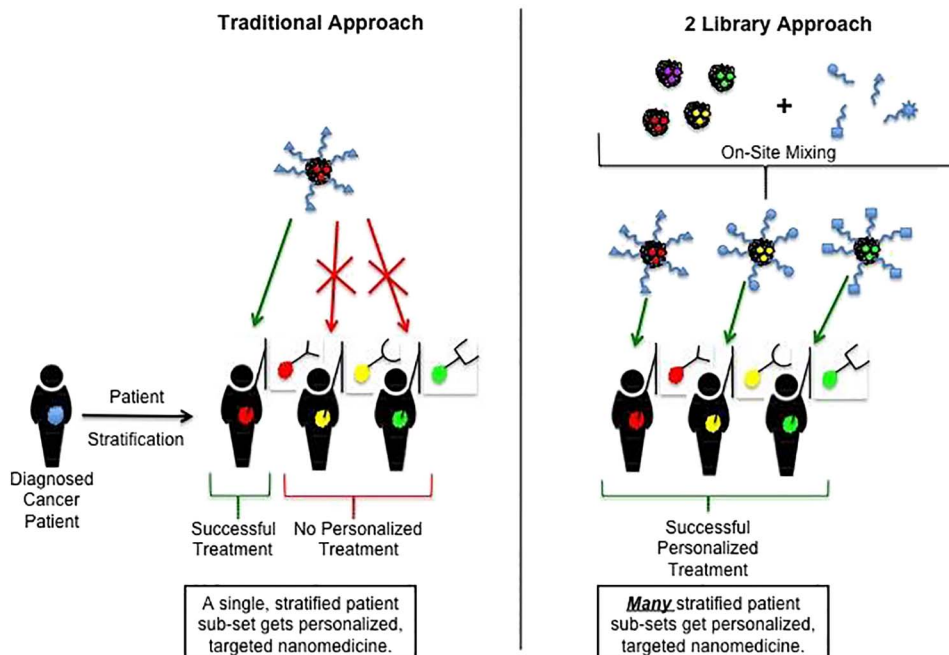


Fig. 3. A proposed personalized nanomedicine approach wherein multiple stratified sub-population groups benefit through on-site surface modification of a nanoparticle platform (two-library approach) versus a traditional personalized medicine approach where only a single stratified sub-population benefits.

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