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Commentary

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Nanomedicine 2.0

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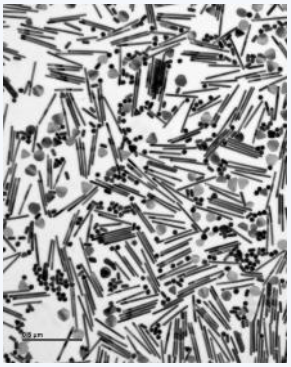
ABSTRACT: Nanotechnology can profoundly change the way we diagnose and treat diseases, but the ability to control how engineered nanoparticles behave within the body remains largely elusive. This Commentary describes the progress and limitations of nanomedicine and the research and experimental philosophies that should be considered in our quest to advance nanotechnology to the clinic.



Nanomedicine development is aimed at improving the diagnosis and treatment of diseases by using the unique properties of engineered nanoparticles to identify disease markers or deliver drugs to target sites.[1−5] There are many benefits to using nanotechnology in medicine. The optical, electrical, and magnetic properties of nanoparticles can be manipulated by changing their size, shape, surface chemistry, and other physicochemical properties. These highly tunable features allow one to create millions of materials with unique properties with an enormous potential to customize the engineering of diagnostic, biomedical, light, and electronic devices. The beneficial physical properties of nanoparticles have been successfully incorporated in *in vitro* diagnostic devices where nanoparticles have been developed for detection of proteins and nucleic acids. A number of nanoparticle-based diagnostic technologies have advanced to patient use or are now being clinically evaluated.[6−8] *In vivo* (in the body), nanoparticles have found limited use in patients. Potentially, nanoparticles can be ideal agents for many *in vivo* medical applications because they have similar sizes to biological molecules and should be able to gain entry into different cellular and tissue compartments. Because we can program their physical properties, this may allow us to precisely manipulate cellular function.

Despite the vision of how nanoparticles can be used in the body, the small number of nanomedicine products in clinical trials for *in vivo* applications and in use for patients suggest the need to re-evaluate the role of nanotechnology in medicine. For example, many researchers have published studies that demonstrate the use of nanoparticles to target and treat tumor cells *in vivo* but there are few in clinical trials or used in patients (Figure 1). Our recent meta-analysis showed that only 0.7% (median) of injected nanoparticles in mouse models are delivered to solid tumors.[9] This study suggests that the low delivery efficiency is one of the key challenges with clinical translation of nanoparticles for cancer applications, as the particles may not be delivered to the targeted site at high enough concentration in human patients to produce an effect. LaBeck et al. showed that drug−liposome formulations do not elicit improved therapeutic efficacy when compared to use of chemotherapeutic agent alone.[10] Many clinically approved drug carrying nanoparticles alter or reduce toxicity when compared to chemotherapeutics rather than enhancing therapeutic efficacy. This result can be expected because changes in the size, surface chemistry, and shape of nanoparticles can alter the biodistribution of the agent, which in turn alters the toxicological profile. These recent meta-analyses have started to question our understanding of the effectiveness of nanotechnology for diagnosing and treating diseases in patients and the mechanism by which nanoparticles are being transported in the body.

While there is an active debate about the fate of the field of nanomedicine,[11−13] my research group and I are extremely optimistic about nanomedicine's future. We have to remember that the field of nanomedicine is at an early stage of development and that the field will go through ups and downs. The up phase occurred at the beginning of the 21st century where the field's focus was to describe and demonstrate the medical utility of nanoparticles, as the imagination of what nanotechnology can do took over. The imagination aspect of the field has established a paradigm of how research should be

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a Classification of clinical trial phases

Phase	Primary goal
0	Pharmacokinetics; particularly oral bioavailability and half-life of the drug
I	Testing of drug on healthy volunteers for dose-ranging
II	Testing of drug on patients to assess efficacy and safety
III	Testing of drug on patients to assess efficacy, effectiveness and safety
IV	Postmarketing surveillance – watching drug use in public

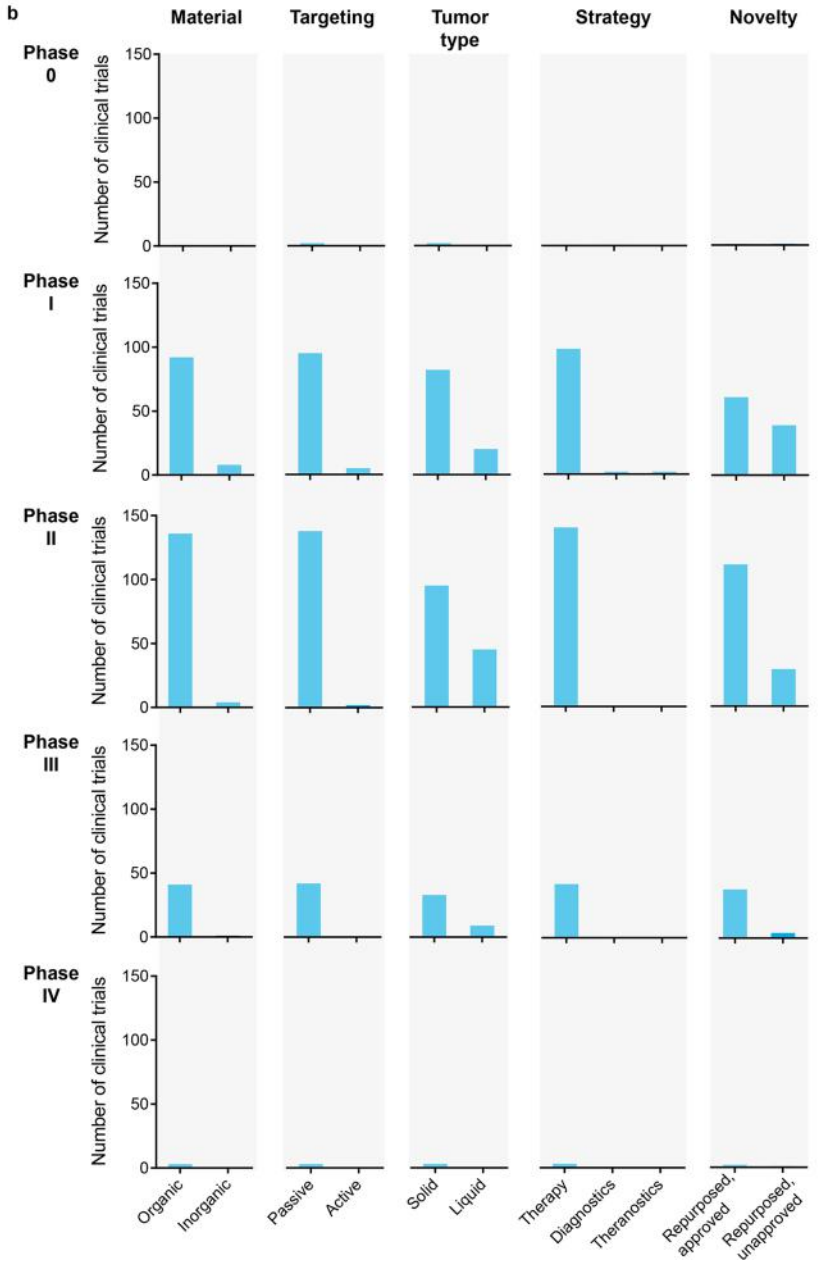

Figure 1. Current state of clinical trials for cancer nanomedicines. (a) Objective of the different clinical trial phases. (b) An analysis of the number of ongoing clinical trials for cancer targeting nanoparticles based on the data in the clinicaltrials.gov database on 2016-Aug-16. The data is organized as material type (organic versus inorganic nanoparticles), targeting (passive versus active targeting), tumor type (solid versus liquid tumors), strategy (use of nanoparticles for therapeutics, diagnostics, or theranostics—combination of therapeutics and diagnostics), and the novelty refers to whether the formulations were repurposed from drugs that were already approved or not. "Repurposed approved" refers to nanoformulations that have already been FDA approved for treatment. The search query "(nanoparticle OR liposome OR micelle) AND cancer" was used. Table and figure caption is courtesy of Dr. Stefan Wilhelm and Nature Publishing Group (with permission). Table adapted from ref 13.

done in nanomedicine, but given the low clinical translation of nanomedicines, it is unclear whether this paradigm is appropriate anymore. The current paradigm leads to the presentation of "exciting" concepts, publications, and stories but this research paradigm is unlikely to lead to a broad range of clinically useful products that yield improvements in patient outcome at this time in history. We are likely entering a somewhat down phase in the field where stakeholders have started to question the field. I would deem this as a healthy phase for nanomedicine innovation as this down phase allows

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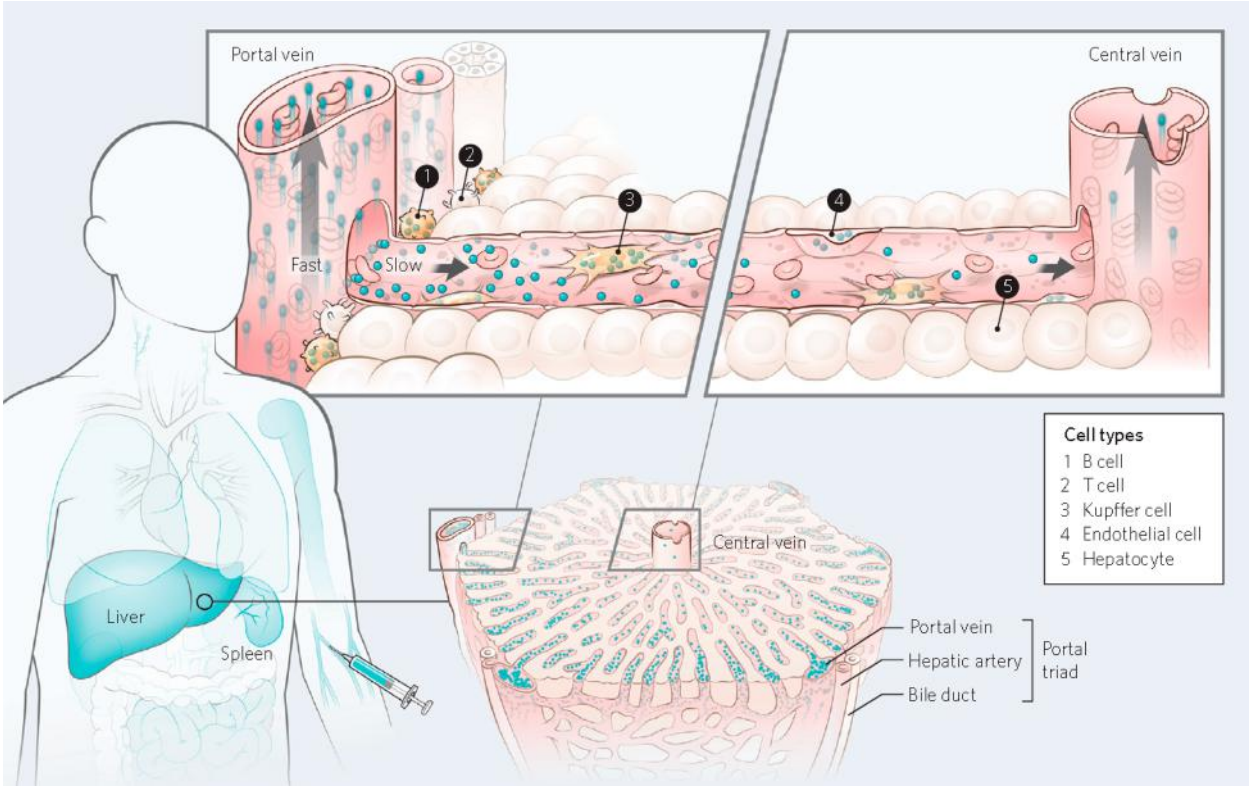

Figure 2. Nanoparticles interact with different organs and cells in the body. This schematic shows the behavior of nanoparticles in the liver. The nanoparticles are moving rapidly through the portal vein, and when they enter the liver sinusoid, the flow rates decrease ~1000 times to increase the probability of nanoparticle interaction with different cell types. The nanoparticles are removed from circulation. If they escape these cells, they flow back into circulation through the central vein. Beyond this organ-level description of nanoparticle behavior in the liver, how serum proteins adsorb to the particle surface, how these proteins mediate cellular uptake, and what happens to nanoparticles in the cells need further investigation. These are some of the many questions that need to be addressed before we can control the pattern of distribution and cellular interaction of nanoparticles in the body. We obtained permission to reproduce the figure from Nature Publishing Group.

the community to re-evaluate and redefine the field. The discussions will eventually lead to a consensus of where nanomedicine research needs to head, and this will lead to the development of a new roadmap to define future activities. When this happens, the field of nanomedicine will be rebooted, that is, Nanomedicine 2.0.

Nanomedicine 1.0 was not without notable milestones. I would deem the major accomplishments of nanomedicine thus far to be (1) establishment and demonstration of end-outcome concepts (e.g., tumor shrinkage, killing bacteria, and brighter imaging signal), (2) development of methods to synthesize and characterize nanoparticles, and (3) development of infrastructures to conduct nanotechnology research. Many researchers, myself included, were trained in this era of nanoexcitement, which is not insignificant in its ability to drive us to make the field as successful as possible. But scientifically, there are major challenges that must be overcome for nanomedicine to thrive including (a) re-evaluating the current perceptions of how nanoparticles behave *in vivo*, (b) providing greater depth for research studies that include a focus on quantification, (c) developing tools and instrumentation that enable the study of nanoparticles in biological systems, and (d) adapting computational and database tools to organize and mine data. These careful, strategic, and decidedly non-glamorous developments will establish a strong foundation that will lead to rapid and systematic translation of nanomedicine for use in clinical settings and generate an enormous benefit to society.

Many nanomedicine concepts are based on "perception" and lack a reproducible solid data support. Perceptions risk becoming confused with reality if highlighted, repeated, or in academic terms, cited frequently enough. Ultimately, however reality defines the true potential applications and parametrizes the field. For example, in 2004, Derfus and co-workers published the first manuscript on the toxicity of CdSe and ZnS-capped CdSe quantum dots in cell-cultured primary hepatocytes.[14] The study showed that the breakdown of CdSe quantum dots and the subsequent release of cadmium ions in the cells are lethal to hepatocytes. However, the cells remained viable in culture when CdSe quantum dots were coated with a thick layer of ZnS because the ZnS minimized the degradation of CdSe. Subsequent studies in mouse models showed that CdSe quantum dot degradation did not induce liver or kidney toxicity because the local dose/exposure was minimized due to washout.[15] The lack of toxicity of these quantum dots was further confirmed in macaque studies.[16] The Derfus study exemplifies the dangers of extrapolating *in vivo* outcomes from *in vitro* findings where interpretation of the study cemented the perception that quantum dots were toxic and should not be used in humans before the *in vivo* studies confirmed the *in vitro* effect. This perception has reduced the enthusiasm for using quantum dots for *in vivo* applications despite many studies demonstrating a lack of quantum dot toxicity *in vivo*. It still remains unclear how dosing and long-term accumulation determines quantum dot toxicity. Another example of a "perception" that has driven the direction of the

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field of nanomedicine is the concept of nanoparticle extravasation into a solid tumor. A classic schematic of tumor extravasation shows nanoparticles diffusing through interendothelial cell gaps in the tumor vessel (i.e., leaky vessels) because nanometer-sized particles are smaller than the size of these gaps (typically <500 nm for most mouse tumor types).[17] However, there is a staggering lack of definitive and direct data to support the existence of actual gaps in the tumor endothelium in different animals models and human patients. It is clear that small molecules and nanoparticles accumulate in solid tumors, and this has been demonstrated as early as the 1900s.[18] Understanding the extravasation mechanism to solid tumor is a critical first step in the intratumoral fate of nanoparticle, but this topic has had limited discussion in the nanomedicine community. The transport of nanoparticles through the gap was accepted as a fact, and because of this, full investigation of nanoparticle transport through tumor vessels was never investigated. When nanoparticles are not effective for treating tumors in patients, researchers have attributed this problem to tumor heterogeneity, variability in mouse models, and differential leakiness in patients versus animals. These factors are likely important contributors, but transport mechanism of nanoparticles through the vessel should have been one of the first considerations (without the ability to enter into the tumor cells' niche, local microenvironment, it may be difficult for many nanoparticles to have desired effects). If the mechanism is a transcytosis mechanism, we may be able to coat the nanoparticle with a molecule that drives entry via this route. Alternatively, if the perception of transport through interendothelial gaps was not pervasive, there may have been greater focus on nanoparticle vascular targeting for imaging and treatment of cancer. A full understanding of the tumor delivery process will allow clinicians and technicians to adjust or modify a nanoparticle design to meet the complex requirement of engineering nanoparticles for solid tumor targeting. Interestingly, the "vascular" biology field has debated molecular extravasation for several decades, either through endothelial cells (transcytosis) or interendothelial cells (gaps).[19,20] This extravasation model exemplifies the dire implications of biasing an entire field of study on an untested and unquestioned and potentially an inaccurate theoretical biological mechanism. A significant amount of time and resource could be wasted in vain since the hypothesis on which the studies were based was flawed.

Once the community is willing to take a critical stand and differentiate perception and hype from reality grounded in controlled reproducible results, our field can identify a series of important questions that must be addressed to advance nanoparticles for *in vivo* applications. When this occurs, there will likely be a focus toward more detailed and mechanistic studies. For example, it is well-known that the liver sequesters nanoparticles, but the specific mechanism by which it does so is unclear. In our recent study, we showed that the liver–nanoparticle interactions are much more complicated than initially thought. We showed that the flow rate of intact hard nanoparticles through the liver sinusoid slows down 1000 times compared to that in periportal veins and central vein to allow for interactions with different cell types of that microenvironment (Figure 2).[21] We were surprised to find that both quantum dots and gold nanoparticles were taken up by endothelial cells, B cells, and Kupffer cells. Our results only provide a first level description of how the liver takes up nanoparticles, and more interestingly, the study raised more important questions about the nanoparticle–liver interaction than it answered. The significance of these studies is that by achieving a deep understanding of how nanoparticles interact with the liver, we will be able to develop solutions to overcome the nondirected sequestration of engineered nanoparticles. Other nanoparticle interactions that need further characterization include those with the blood, spleen, skin, brain, and other organs, as the current understanding is superficial. Elucidating and mapping how each organ interacts with engineered organic and inorganic nanoparticles will be key to developing reasonable strategies to deliver nanoparticles to targeted diseased sites in sufficient concentrations to elicit a therapeutic response or for early diagnosis.

The fundamental studies on the nanoparticle–biological (nano–bio) interaction would be incomplete without a parallel focus on quantification at target biological sites. There is an over-reliance on reporting end outcomes (e.g., survival data or tumor shrinkage) to show the successful utility of a nanotechnology for medical applications. Many of these studies do not conduct full pharmacokinetics and biodistribution analyses of the administered nanoparticles or histopathology analysis, nor do they confirm that nanoparticles actually target cells *in vivo*. Many of these studies justify the end conclusions of *in vivo* studies on the premise that because the injected nanomaterial led to an end outcome, the proposed mechanism must be correct. Fundamentally, the problem with this research approach is that the biology differs between animal models and human patients, so a technology that demonstrates end outcome in one model does not necessarily lead to the same end outcome in another model. Quantification and careful analysis of the engineered nanoparticles in mouse models will allow researchers, technicians, or clinicians to make logical adjustments in an experiment or in clinical use so that the technology has the greatest potential to function as designed. The lack of quantification is pervasive in the field. To illustrate, over 80% of papers published in the last 10 years on targeting nanoparticles to tumors did not report characterization of nanoparticle properties, provide pharmacokinetics parameters, or fully quantify the therapeutic effects but showed images instead. We had to contact over 80% of the authors of those papers to obtain data to determine how well nanoparticles are delivered to solid tumors.[9]

Lastly, there should be a renaissance in the development of new tools and instruments for studying nanoparticle–tissue interaction. Currently, many conclusions of how nanoparticles behave in biological systems are based on techniques that may be flawed or inadequate. Our experience suggests that dynamic light scattering can distort the size of the nanoparticles being observed, fluorescence methods do not provide absolute measurements, tissues containing endogenous metal ions (e.g., iron) can interfere with plasma techniques for quantifying inorganic nanoparticle distribution, and cell culture studies do not recapitulate the function and behavior of nanoparticles *in vivo*. There needs to be a focus on developing techniques to analyze nanoparticles in complex tissues. A good start in that direction would be the development of organoid models that enable one to replicate the three-dimensional complexity of a tissue and its native vasculature. Combining these models with microfluidic systems may allow one to develop a simulated *in vivo* system to study nanoparticle interactions more rapidly than in animals. However, *in vivo* studies still need to be done to validate the findings as biology is complex and difficult to fully mimic *in vitro*. This suggests the need to develop new

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techniques that can analyze nanomaterials in whole organs and animals. Toward this objective, we have recently made tissues optically transparent in whole organs and animals to enable us to visualize the distribution of nanoparticles within whole tissues.[22−24] This technique overcomes the limitations of two-dimensional histopathology analysis, where results may be misinterpreted because the conclusions would be dependent on where the tissues were cut and region of analysis. Furthermore, computational methodologies should also be a major technology focus for nanomedicine. Simulations of nanoparticle interactions with cells and tissues in the body may be important to understanding the nanoparticle−biological interactions and may guide the optimal nanoparticle design for specific clinical applications.[27] Finally, because nanoparticle−biological researchers come from different disciplines, the validity of any of the current techniques are not fully questioned and evaluated. Proper interpretation of the data is dependent on the quality, limitation, and manner in which the technique is used.

I would argue that nanotechnology is the future of medicine, irrespective of the poor current number and outcome of clinical translation. The human body is extremely complex, and that complexity requires new technologies that can move freely in the body and evade biological systems that are aimed at removing, destroying, and eliminating them. Nanoparticles are in the "correct" size range and offer much design flexibilities for building nanosystems to do what you want in the body. But the problem is that we do not really know how to do this. Our perception of nanotechnology design for use in the body is simplistic compared to the complexity of biology. The nano−bio interaction studies, if done properly and systematically, provide rational guidelines (almost like a blueprint) to build medically useful nanosystems. Once the blueprint is in place, new engineering principles will emerge to build increasingly more complex and powerful nanosystems. It is unlikely that a single design or coating will help maneuver a nanoparticle in the body to reach a targeted disease site, so dynamic and molecular assembly of nanoparticle components will likely be a major research focus in the future.[25,26] In my opinion, we currently do not really understand how to control the patterns of nanoparticle behavior *in vivo* and how to design them to navigate the *in vivo* environment to reach the disease site and to function as designed. We need to start to view the organs and cells like "chemical reactors" that change the chemistry of circulating nanomaterials, and these changes determine their fate and function in the body. The Holy Grail of Chemistry should be "determining the chemistry of materials as they circulate in the body and understanding how this chemistry mediates delivery and cellular interaction." Research in Nanomedicine 2.0 should be focused on building a foundation for nanomedicine development that will enable our advancement toward the science-fiction-type applications that may materialize over the next 100−300 years.

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Notes

The author declares no competing financial interest.

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