BIOTECHNOLOGY

Nanomedicine gets personal

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Companion nanoparticle imaging merges with drug delivery technologies toward personalized nanomedicine (Miller et al., this issue).

Personalized medicine is already making an impact on human health. Stunning progress in human genomics now allows clinicians to prescribe drugs for treating breast cancer, leukemia, and cystic fibrosis to subsets of patients based on their genetic profiles. These new agents address an old issue: a well-supported diagnosis cannot guarantee a patient will respond favorably to a standardized treatment. Our now deeper and more nuanced appreciation of human genetic variation—and the expression of that variation in physiological function as well as pathology—is showing us that even well studied diseases can vary in presentation among individuals. This is particularly true of cancers, which reflect both the genetics of the individual and a history of acquired mutations. Cancers often differ depending on their tissue of origin and the stage or grade of disease. But even two cases of one type of cancer, such as non–small cell lung cancer (NSCLC), at the same clinical and pathological stage might differ substantially in cellular composition, organization, and genetic profiles. Thus, it comes as no surprise that individuals with stage IIB NSCLCs do not all respond equally well to standard treatments.

So, how are we to use our increasingly sophisticated understanding of the individuality of disease to treat cancer more effectively? Advances in precision medicine will require continued improvement in our ability to stratify patients within a given diagnostic category, as well as a capacity to tailor therapies specifically to the requirements of a given subset. Focusing on personalizing nanomedicine, instead of pharmacogenomics, Miller et al. report in this issue of *Science Translational Medicine* the use of companion nanoparticle–based imaging to stratify tumors according to a specific physical property of the tumor vasculature (1). By tracking the accumulation of a clinically approved tracer nanoparticle, the authors could identify tumors most likely to accumulate nanoparticles via the enhanced permeability and retention (EPR) effect and, in turn, to respond to nanoparticle-based therapeutic agents.

LEAKY VESSELS PRESENT AN ENHANCED OPPORTUNITY

According to the EPR hypothesis, macromolecules—and, by extension, nanoparticles—will experience enhanced permeation through leaky tumor vasculature thereby allowing them access to the interstitial space of tumors, where they will be retained due to the diminished lymphatic clearance from the tumor interstitium (2). As a result, NPs are predicted to accumulate at higher levels in tumors than in tissues with normal vascular permeability and lymphatic drainage (Fig. 1). Consequently, the EPR effect is widely used as a rationale for using nanomaterials to treat cancer. But the EPR effect has been studied almost exclusively in experimental animals, and the relevance of EPR to human cancers is still unclear. Moreover, even in animal models, different tumors are highly variable in their EPR effect. For example, the EPR effect in brain tumors appears to be weak (3)—perhaps because the permeability of the blood-tumor barrier is almost as low as the blood-brain barrier (4). Low EPR effects in tumors outside the brain have also been reported, and accumulation by EPR in animal tumors accounts for less than 1% of the dose in most cases. Still missing is a way to identify tumors with strong EPR effect, and by extension, a likelihood of responding to EPR-dependent NP therapies.

The report by Miller et al. offers an approach for quantifying the extent of the EPR effect in a particular tumor, offering the potential to identify the extent of the EPR effect in human tumors (1). If it can be translated to humans, clinicians may eventually be able to determine if an individual will respond to NP-based therapies before the therapy is initiated.

READING THE TEA LEAVES FOR EFFECTIVE DISEASE STRATIFICATION

There is obvious value in more precise diagnoses by stratification according to disease expression in individuals, but achieving this goal in practice presents many challenges.
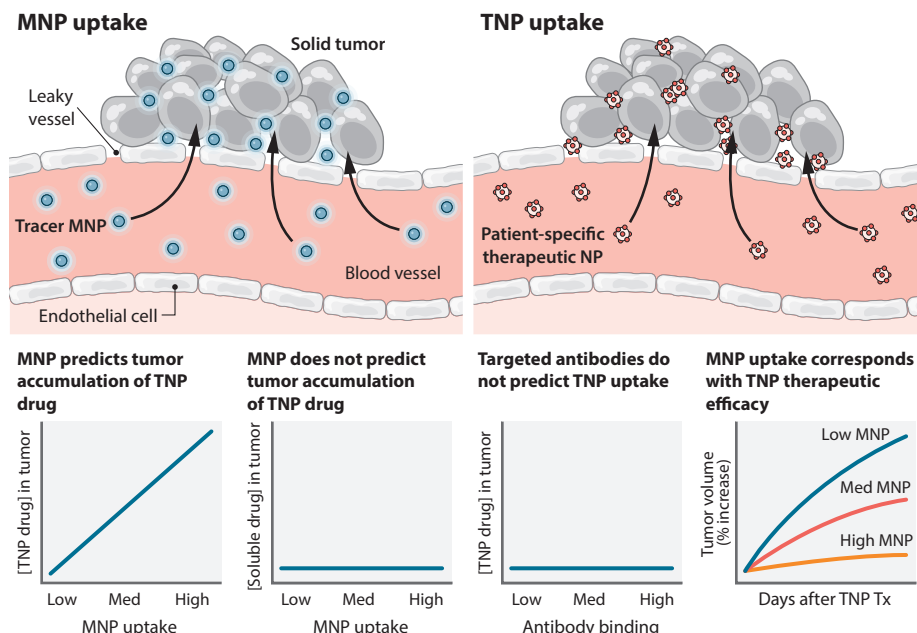

Fig. 1. Tumor-specific profiling of the accumulation of nanomedicines using companion nanoparticles. Companion magnetic nanoparticles (MNP) accumulate within tumors, and can be imaged to predict the accumulation of therapeutic nanoparticles (TNP)—a physical effect that is specific to the nanomedicine drugs. The MNPs did not predict free drug accumulation nor did tumor-specific antibodies predict TNP accumulation (1).

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Genetic information from biopsies is valuable but does not currently provide insight into the physiological state of the tissue (e.g., the extent of vascular leakiness). Additional diagnostic approaches that identify key anatomical or physiological states, but are also non-invasive and safe, are needed. Theranostics (5), non-invasive modalities combining both therapeutic and imaging compounds into multifunctional therapies, have the potential to provide real-time feedback as to whether an agent—or a delivery vehicle with an agent—significantly accumulates at the intended site of action. However, a weakness of theranostics is that it does not allow for pre-selection of patients that will be most responsive to a given treatment.

Miller *et al.* addressed this issue by separating the diagnostic and therapeutic functionalities into two phases, where the diagnostic nanoparticle was first used to select the tumors that would positively respond to a subsequent nanoparticle treatment (Fig. 1) (1). The authors' approach involved first delivering an FDA-approved magnetic nanoparticle (MNP) that could be readily imaged with clinical MRI in order to classify the tumors within groups corresponding to their level of MNP accumulation ("high", "medium", and "low"). This stratification was predictive of the subsequent responses of these tumors to therapeutic nanoparticles (TNP): that is, tumors that accumulated "high" MNP were more likely to accumulate higher levels of the TNP drug cargo, and subsequently led to more substantial reductions in tumor growth. Interestingly, MNP accumulation did not predict the response to free drugs (i.e., drugs not delivered within TNP), nor did the accumulation of tumor localizing antibodies predict accumulation of the TNP. This suggests that it was indeed the EPR of the MNP that predicted accumulation and effectiveness of the TNP (Fig. 1).

The predictive power of the MNP for TNP efficacy is surprising given the significant differences is size and make up of the two classes of NP [MNP – 30 nm carboxymethyl dextran-coated magnetic particle; TNP – 100 nm poly(lactic-*co*-glycolic acid (PLGA)–poly(ethylene glycol) (PEG)]. Moreover, the authors showed that the MNPs and TNPs differentially distributed at the cellular level. MNPs were more significantly taken up by host macrophage relative to TNPs, whereas tumor cells preferentially internalized TNPs over MNPs. However, in order to be predictive of the degree of EPR within a tumor, the MNPs do not need to

have the same cellular fate as the TNP. Rather, the degree of EPR-driven MNP accumulation need only show a strong positive correlation with that of the TNP, regardless of the underlying mechanisms involved. While macrophage-mediated accumulation of MNP in humans may well differ from that observed by Miller *et al.* in mice, such variations can potentially be compensated for by careful application of mathematical modeling to account for human specific (or patient specific) differences in rates of macrophage mediated MNP clearance.

Miller *et al.* used a model to predict the relationship between the accumulation of the tracer MNP and the TNP. The model is particularly important in this case because of the aforementioned differences in size and composition between the two classes of NPs. The development of models based predominantly on the physiology of the tumor, like the one presented here, could lead to even better patient-specific approaches to the delivery of nanomedicines. In this case, the modeling was focused on imaging of a particular tissue function: the accumulation of tracer nanoparticles. In the future, one might imagine that physicians could acquire information from a variety of sources—imaging of anatomy, functional analysis, profiling of cellular and genetic variation in the tissue—which could be sewn together by modeling to provide an exquisite, patient-specific atlas of tumor vulnerability. Our closest contemporary example of this patient-specific modeling approach is the remarkable ability of radiation oncologists and radiation physicists to use mathematical modeling of dose deposition in the design of intensity-modulated radiation therapies that focus the ionizing radiation on the tumors of complex geometry, sparing normal tissues from ill effects (6).

Of course, in ongoing personalized medicine efforts, genomic studies of individuals and their tumors must also rely on modeling to tease out relevant mutations in disease pathophysiology and response to treatment. From all dimensions, personalized medicine will be driven by sound mathematical representations of human biology, physiology, and genetics.

TAILOR-MADE NANOMEDICINE
The ability to distinguish subtle differences in a patient's individual presentation of a given disease will require an expanded palate of therapeutic approaches tuned to the needs of a given patient to improve outcomes. Nanoparticle-based therapies represent an ideal approach for this challenge; they can employ a wide range of materials to encapsulate and deliver a wide range of therapeutics, including chemotherapeutics [such as docetaxel (1, 7) or paclitaxel (1)] and nucleic acids [siRNA and anti-microRNAs (8)]. Many nanoparticle formulations can also be readily made from as small as tens of nanometers up to microns in diameter. Moreover, the surfaces of nanoparticles can be manipulated either to suppress interactions with serum proteins and/or the immune system or alternatively to support the conjugation of targeting ligands to improve cellular uptake in specific cells of interest. This remarkable flexibility of nanoparticle-based agents gives them enormous potential in the coming era of personalized medicine.

Many major challenges must be addressed to realize the full potential of nanotechnology as a primary tool in the personalization of medicine (9, 10). Future nanotherapies will require development of new, versatile nanomaterials safe for use in medicine across a broad range of patient-specific formulations. Current technology can only guide a binary decision: will a specific FDA-approved nanoparticle formulation available (in Miller *et al.*, one drug loaded into a PLGA-PEG nanoparticle of defined size) be helpful for this patient? A more powerful, patient-specific scenario could involve imaging of the EPR effect, combined with genetic and other analyses, to guide a more nuanced decision: What size, composition, and property of nanoparticle should be administered to treat this individual tumor? Two categories of hurdles are before us, if we choose to reach for that state of nanomedicine: first, the technical hurdles of developing safe and effective nanomedicines with tunable properties; and second, the perhaps even more significant challenge of changing our approach to drug production and regulation.

The future of drug development might look radically different from the present. Now, drug formulations are specifically defined, extensively characterized, mass-produced like Ford's Model T, and stocked on a shelf with expiration dates. In a different approach, drug formulations are custom assembled, from elements and modules known to be safe, into nano-structures specifically tuned to the genetics and physiology of the patient. Many of the technical hurdles for this new mode of operation might soon be cleared by advances like that

of Miller *et al*. However, a fundamental change to the way medicines are regulated and commercialized is a much steeper challenge. This challenge must be addressed to realize the enormous potential of personalized nanotherapies.

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