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Revisiting the ‘One Material Fits All’ Rule for Cancer Nanotherapy

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Abstract

The promise of (nano)biomaterials for the treatment of cancer can only be realized following a comprehensive scrutiny of the tumor microenvironment. The generic use of ‘inert’ vehicles that deliver a specific cargo to treat a range of cancer types and disease states obeys the ‘one material fits all’ rule. However, this approach leads to suboptimal and unpredictable clinical outcomes. The key factors constructing the tumor milieu should guide the design of disease-responsive materials. Given the growing availability of nanomaterials for cancer therapy, a material that responds to each patient’s needs and, hence, reacts in a graded manner based on disease cues, would pave the way to precision materials for cancer therapy.

Examining Material Behavior in Light of the Cancer Tissue

Microenvironment

Altered tissue microenvironments are a hallmark of cancer [1], with an immense influence on therapeutic response [2]. Features of the diseased tumor microenvironment that are significantly different from normal tissues include acidosis, hypoxia, overexpressed proteases, oncogenes, and others. These features can serve not only as biomarkers for cancer diagnosis and therapy, but also to regulate the performance of materials in light of the tumor milieu. The success of nanomaterials is highly dependent on the route of administration, toxicity/biocompatibility, circulation time and stability, tissue extravasation, targeting, and cell internalization, as extensively reviewed elsewhere [3,4]. However, new materials have not yet significantly improved the overall survival rates of patients with cancer, although an increasing number of nanomedicines are being commercialized [4].

This lack of significant improvement can be explained by a paradigm that is gaining momentum: the preprogrammed behavior of materials may be altered postimplantation, as the immediate tissue milieu interacts with and modifies the material. Dissecting the features

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of the tumor microenvironment and understanding how they vary from the normal state now defines precision cancer medicine, where (nano)biomaterials are designed to probe and respond to tumor type and state while providing the optimal treatment and, hence, improved clinical outcomes.

A ‘one material fits all’ rule ignores deep variances in target tissues that affect their responses and reactivity. The complex microenvironment *in vivo* at different tissue sites with diverse cell types and under different pathological conditions may alter the properties of a material and, in turn, affect its *in vivo* performance. Physiological and pathophysiological variations between tissue types and states would affect material performance. Hence, merely characterizing the biomaterial is necessary but insufficient to fully comprehend and predict material *in vivo* performance. The resultant material designs must be based on flexibly tunable ‘platforms’ that can be modified to meet even the most-subtle changes in disease type and state [5].

The Impact of the Tumor Microenvironment on the Performance of Materials: Friend or Foe?

Studying how the tissue microenvironment affects material properties has remained an under-explored area. *In vivo* microenvironments are far more complex than those utilized *in vitro*; hence, bench-top findings rarely predict material *in vivo* behavior. Tzur-Balter *et al.* showed that porous silicon particles (PSi), which are increasingly used to deliver chemotherapeutics, undergo enhanced degradation in cancerous environments compared with healthy environments. Upregulation of reactive oxygen species (ROS) by the tumor cells oxidizes the silicon **scaffold** (see Glossary) and catalyzes its degradation [6]. The authors showed that PSi degradation profiles *in vitro* and *in vivo* correlated in the absence of a tumor in a murine model, but only correlated with tumor data when ROS-containing media was used *in vitro*. This work demonstrates that understanding the governing mechanisms associated with specific tumor milieu, and how they might affect the properties of a material, would be predictive of its *in vivo* performance.

The degradation kinetics of gelatin scaffolds was shown in another study to be implant site dependent. Although gelatin scaffolds degrade enzymatically through the action of collagenases, the *in vivo* degradation data did not correlate with different collagenase concentrations *in vitro* but with the same concentration in different volumes. *In vitro* erosion under a 25- μ l diluent correlated with *in vivo* erosion in the subcutaneous space, while a linear relation was obtained for intramuscular and intraperitoneal erosions when a 100- μ l diluent volume was used *in vitro*. The volume of liquid surrounding the gelatin hydrogel affects the swelling ratio, which in turn alters the diffusion kinetics of enzymes into the scaffold and, hence, the degradation kinetics in a tissue-specific manner [7].

In another enlightening study, the assessment of material–tissue interactions with a prototypical adhesive material that interacts with tissue surfaces was exploited to probe and quantify the influence of even subtle modifications in tissue architecture and biology on tissue–biomaterial interactions [8]. Using inflammatory colitis and colon cancer as disease models, the authors were able to find not only a difference in adhesion as determined by the

alteration of tissue surface chemistry compared with normal tissue, but also the existence of a complex interaction that determined the overall biomaterial compatibility. Here, compatibility was contextual, not simply a constitutive property of the material, and was related to the extent and nature of immune cells in the diseased environment present before material implantation. This study delineates how local alterations of the tissue microenvironment can be used to assess disease severity, which in turn guides the choice of optimal material formulation [8].

The current state of the art, where a defined material formulation is designed and optimized in the laboratory irrespective of the final application, is insufficient. It is crucial to carefully study the characteristics of the tissue microenvironment in the settings of the relevant pathology in which materials will be used, and to optimize them under conditions that simulate (pre)clinical conditions to enable predictive behavior to be attained. However, this is not a straightforward task because tissues and cells are transient entities, capable of altering their surroundings by changing protein and enzyme concentrations, pH, redox potential, oxygenation, inflammation, and tumor immunity in response to pathology (Figure 1). These pathophysiological variations profoundly manifest in cancer, where the complex tumor microenvironment imparts multiple cell types, tissue chemistry, and morphology, as well as mechanical stresses that are altered by local pathology with respect to normal tissues [5]. Disease-specific stimuli, such as pH [9], proteases (MMPs) [10], phospholipases (sPLA₂) [11,12], or nucleic acids [13], among others, have been exploited to enable triggered and targeted drug release. However, the impact of these environmental factors on vehicle performance is understudied.

Crafting Clinically Relevant *in vitro* Conditions to Examine Materials Performance

Elucidating a generic protocol for crafting the appropriate preclinical conditions for forecasting material behavior is a challenging endeavor, because the location of implantation and disease type and state will affect materials differently based on their chemical susceptibility and mode of degradation. Thus, generating a set of rigid steps for determining material performance in the settings of disease may render suboptimal results. Instead, the set of considerations that should be assessed *in vitro* to identify the most determinant factors that would then mimic the *in vivo* conditions must be inferred on a case-by-case basis (Figure 2). For instance, the elevated concentration of reactive oxygen species (ROS) in the tumor microenvironment may be the most important factor determining material degradation kinetics when the material is susceptible to oxidative stress degradation, as in the case of silicon. Given that silicon is being used increasingly to deliver chemotherapeutic agents [6,14], cargo release kinetics would deviate from the expected profile if examined in ROS-free media *in vitro*. The effect of pH may be significant for materials that undergo hydrolytic degradation that may be further catalyzed in acidic environments. Such materials may degrade differentially depending on implantation site because the subcutaneous space contains less water than the intraperitoneal space. Natural materials, such as collagen, are expected to degrade differentially in injured or inflamed environments in which MMPs are present and, hence, their effect should be examined *in vitro*. Identifying the determinant

factors affecting material *in vivo* performance would enable *in vitro*–*in vivo* correlations to be attained, and will be particular to each material family and tissue and/or disease microenvironment.

By leveraging disease cues, it is possible to program materials to impart selective treatments while reporting on disease states. We can now exploit the characteristics of the pathological tissue microenvironment to **design** materials that would report on tissue state (**sense**) and provide selective and disease-specific **treatment**. The resulting materials must be based on flexible and tunable ‘platforms’ that can be modified to meet even the most-subtle tissue changes due to disease type and state [5].

Tumor-Specific Material Performance: Design, Sense, and Treat

Biomaterials, in particular materials for diagnostics and therapy, are increasingly used in medicine. These materials serve as structural support, void fillings, and platforms to sense and treat the embedding of cells and drugs. Nevertheless, many materials and devices fail in clinical trials in the face of diverse disease types and disease manifestations, hampering the development of new materials and assessment of the safety, efficacy, and applicability of existing materials.

A range of stimulus-responsive properties, such as mechanically adaptive or pH-, photo-, enzyme-, thermo-, or gene-responsive properties, may be incorporated in the materials to improve their efficacy and selectivity [15–17] (Figure 3). As such, materials are designed to change in response to specific environmental cues. It is essential to understand material contextual behavior and define how, when, and why observations *in vitro* mimic *in vivo* performance. These findings will aid in setting the stage for characterizing material–tissue interactions on a broad scale, optimizing materials design, and developing novel materials for specific tissues, conditions, and applications. An integrative approach that considers dynamic changes in erodible materials and matches their properties with those of specific tissue types and disease states, will allow the development of medical devices with tunable and predictable clinical outcomes.

The ability of materials to communicate with diseased tissues and cells to improve targeting in biological systems, such as inflammatory cell recruitment [18], or to sense microenvironmental signals, such as the expression of a specific mRNA [19] or miRNA [20], has been the source of inspiration for the construction of systems that meet at the interface of biology and nano(bio) technology and that are able to communicate to amplify disease targeting *in vivo*. Bhatia and coworkers reported in 2011 that communicating nanoparticle systems can comprise multiple types of signaling and receiving modules, transmitting information through multiple molecular pathways, and can operate independently to target tumors efficiently and, more importantly, selectively [18]. The authors demonstrated that systems comprising synthetic human proteins and ‘unpretentious’ nanoparticles can be engineered to respond to the tissue microenvironment by transmitting information about selective endogenous biological pathways. In fact, these nanomaterials operated as artificial inputs and outputs of a specific cascade (i.e., coagulation). Like a domino effect, this strategy comprises different apparatuses that communicate with each

other, increasing signal amplification to more efficiently target diseased regions. This system clearly represents a paradigm shift towards the development of diagnostic and therapeutic agents with refined *in vivo* performance.

Later, in 2013, Gao and coworkers designed a smart nanoparticle-based strategy for the imaging of a range of tumors by nonlinear amplification of microenvironmental signals [21]. The authors exploited the acidic angiogenic tumor microenvironment to sense tumor tissues in a variety of mouse cancer models, by using ultra pH-sensitive fluorescent nanoprobe that had tunable, exponential fluorescence activation on encountering subtle physiologically relevant pH changes. These nanoprobe were off while in circulation, and then turned on in response to neovascularization or to low extracellular pH in tumors. The results of this important study enable the identification of tumor tissues based on the nonlinear amplification of tumor microenvironmental signals. These tissues could be independently identified and their origin corroborated by histology or driver mutation.

Alternatively, on-demand processes, such as ‘on/off switch’ platforms [19], allow for custom-made release profiles with outstanding spatial, temporal, and dosage control [22]. The design of stimuli-responsive systems mimicking the response level of living organisms, able to identify the tumor microenvironment and to dynamically distinguish between disease and healthy traits, is of utmost importance. Such systems are capable of producing a certain response based on a specific and desired stimulus: pH [23–25], temperature [26,27], enzymes [28], hydrolytic/proteolytic cleavage [29,30], or genetics [19,20].

The ability to reverse drug resistance in a breast cancer model was achieved using a smart implantable nanogold-containing dextran/dendrimer hydrogel that could sense and silence multi-drug resistance genes before drug release while reporting on these events by fluorescence emission [19,31]. With one single local application using hydrogel scaffolds embedded with a two-pair **Förster fluorescence resonance energy transfer/nanosurface energy transfer (FRET/NSET) gold nanobeacons**, the authors were able to overcome drug resistance by detecting and silencing a multidrug resistance protein (MRP1), before chemotherapeutic drug delivery *in vivo*. Interestingly, these nanobeacons served as an on/off molecular nanoswitches triggered by the increased MRP1 expression within the tumor tissue microenvironment [32]. Once inside and in contact with the mRNA, the DNA hairpin (which forms the nanobeacons) flips out of its zipped configuration and latches on to the target mRNA, blocking its action. Simultaneously, infantry molecules of a chemotherapeutic drug placed in the zipper are released to be free to kill the cancer cell from within [33]. Similar to a gold Trojan nano-horse, this is an excellent example of how one can sense by measuring material response to specific tumor traits, design by exploiting disease traits to impart selectivity, and treat using cancer-specific therapeutic materials.

To achieve the efficiency needed to sense and/or treat cancer, detailed pharmacokinetic (PK) and pharmacodynamic (PD) studies characterizing the fate and effects of administered drugs to establish detailed dosing regimens tailored to the patient’s physiology are urgently needed. Studying real-time material kinetics and dynamics in realistic *in vivo* environments using new imaging techniques would allow for iterative improvements in biomaterial design to achieve ideal material properties [5]. Using appropriately tunable platform materials, this

process can be rapidly implemented to produce high-performing materials during early-stage *in vivo* testing, potentially limiting costly failures later on in the development of a therapy.

Care must be taken to rigorously quantify the chemical, biological, and physical microenvironment at the site of implantation, with emphasis on developing realistic disease models and understanding the changes the disease causes to the tissue. Based on this in-depth characterization, clinical needs should drive the discussion on what material properties are important in light of the observed microenvironment changes. The resultant material designs must be based on flexibly tunable ‘platforms’ that can be modified to meet subtle changes in physiology and disease state. Advances in material design and characterization techniques now allow for more sophisticated tuning of biomaterial properties than previously imagined, and the addition of new and exciting functionalities in targeting, delivery, and sensing [5].

Paradigm Shift in Smart Biomaterial Design: Possible Solutions to Fundamental Problems

Crafting (pre)clinically relevant *in vitro* conditions that would enable forecasting materials behavior *in vivo* is of utmost importance (Figure 4, Key Figure). This approach will help to obtain *in vitro*–*in vivo* correlations and, hence, proper material design. To develop an effective correlation, the physicochemical and dynamic properties of the materials, as well as the physiological tumor milieu, must be taken into consideration. In parallel to studying drug PK and PD, understanding material kinetics (MK) and material dynamics (MD) is key to constructing a functional relation between *in vitro* and *in vivo* domains. These effects were previously defined as material dynamics (how the material affects the diseased tissue) and material kinetics (how the tissue microenvironment affects material properties) [5]. While the first is widely studied routinely, the latter is often neglected despite being key to constructing a functional relation between *in vitro* and *in vivo* domains.

The next rational step would then be to utilize clinical information to inform material design. Disease biomarkers are commonly used to monitor the clinical response to an intervention and are used in early drug development. Disease-specific biomarkers (e.g., gene mutations or polymorphisms, and quantitative gene expression analysis, peptides, proteins, lipids metabolites, and other small molecules) can be identified in a range of biological samples (e.g., plasma, serum, cerebrospinal fluid, bronchoalveolar lavage, or biopsy) and help inform material design. Materials containing disease-specific markers would allow not only for diagnosis, but also for selective and triggered treatment (Figure 4). As each patient expresses different biomarkers, the incorporation of multiple therapeutic cargos into one material that would be released on demand based on specific disease cues would enable multiple patients to be treated with one material, while providing only the necessary therapy.

To bridge the gap between preclinical and clinical studies, the use of patient-derived cells and the establishment of patient-derived xenograft (PDX) models may guide the necessary material modifications required to improve therapeutic outcomes to eradicate tumor cells. Mouse models have become widely available over the past 20 years and permit the engraftment, passage, and study of human tumor cells *in vivo* in a xenograft setting [34]. As

a natural extension of standard tissue culture techniques, the use of freshly resected patient tumors immediately transplanted into murine hosts by developing PDXs is becoming increasingly attractive. In fact, such an approach is crucial to better understand and preserve the genomic integrity and tumor heterogeneity observed in patients. Therefore, PDXtumor models arguably provide the most reproducible approximation of tumors in patients with cancer [34]. Clinical information can aid the selection of mandatory combinatorial treatments that could be used to treat patients with heterogeneous etiologies and manifestations of a disease to yield one material platform that fits all. Hence, for a specific disease, the same treatment platform would manifest itself differentially from one patient to another based on the specific markers and/or triggers it would encounter.

Concluding Remarks

Programming materials to respond to specific cellular and tissue microenvironments representing specific pathological types and states needs to become an everyday practice. The archetype for disease diagnosis and treatment has to change from relatively nonspecific delivery agents to tuned, selective, and cellular- molecular- and mechanism-based devices. This approach is based on embracing multiple material functionalities and involves developing smart and selective materials that respond, interact, and transform in light of the tissue microenvironment. Most of the current approaches lack control over some critical features, such as selectivity and on-demand degradation and release of embedded cargo. The design of personalized materials requires in depth understanding of disease mechanisms and dialing-in means by which treatment would match with particular disease profiles of an individual patient's cellular and molecular signatures. Future efforts should focus on implementing these concepts into the design of personalized smart materials (see Outstanding Questions).

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Glossary

Design:

creation of smart materials that are created in light of the tumor microenvironment, which may incorporate specific biomarkers used later for diagnosis and therapy outcomes.

Förster resonance energy transfer (FRET):

refers to the energy transfer between two chromophores, where a donor chromophore is initially excited and can transfer energy to an acceptor chromophore.

Gold nanobeacons:

comprise a stem-loop DNA single-stranded oligonucleotide that carries a fluorophore and a quencher (gold nanoparticle) at both ends; in the absence of target, the stem-loop structure is closed, forcing the fluorophore and the quencher into close proximity, resulting in fluorescence quenching. Upon hybridization to a complementary target at the palindromic

region, the stem-loop sequence opens, the fluorophore and quencher are spatially separated, and fluorescence is restored.

Material kinetics (MK):

a branch of nanotechnology and materials science dedicated to determining the fate of materials administered externally to a living organism.

Material dynamics (MD):

the study of the biochemical and physiological effects of materials on the body or on microorganisms and the mechanisms of material action and relation between material composition, concentration, and effect.

Nanomaterial surface energy transfer (NSET):

the energy transfer between a molecular dipole and a metallic surface of a nanoparticle. NSET has a higher probability of energy transfer than FRET and is less specific to the chromophore type.

Scaffolds:

materials specially engineered to cause a required cellular interaction to promote the formation of new functional tissues for biological resolutions. They are optimal materials to mimic the native extracellular matrix of the native tissue.

Sense:

smart materials designed to detect a specific trait and/or cue from the tumor microenvironment to produce a diagnosis response.

Treat:

smart materials designed to provide treatment based on the detection of specific trait and/or cue from the tumor microenvironment to produce a therapeutic response.

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Trends

Altered tissue microenvironments are a hallmark of cancer, with immense influence on therapeutic response.

Dissecting the features of the tumor microenvironment and understanding how it varies from the normal state now defines precision cancer medicine. (Nano)Biomaterials can be designed to probe and respond to tumor type and state while providing the optimal treatment and, hence, improved clinical outcomes.

A different aspect of biomaterial design and optimization that has remained unexplored is the study of how the tissue microenvironment affects material properties.

Personalized materials for the delivery of nanoparticles are needed.

Programming materials to respond to specific cellular and tissue microenvironments representing specific pathological types and states needs to become an everyday practice.

Outstanding Questions

Is the ‘one material fits all rule’ still relevant?

How can we formulate disease type- and state-responsive materials?

How can we construct (pre)clinically relevant *in vitro* models in light of the tumor microenvironment to reliably enable the forecasting of the behavior of materials in diverse clinical scenarios?

Figure 1. Established Cancerous Tumors Comprise an Array of Cells and Factors that Contribute to the Tumor Stroma.

The tumor niche is a dynamic system in which several factors, such as acidosis, hypoxia, access to growth factors, apoptosis mechanisms, inflammation, and immune cell interactions, can vary considerably and affect both the tumor and its interaction with materials. Abbreviations: Bcl-2, B cell CLL/lymphoma 2; c-myc, V-Myc avian myelocytomatosis viral oncogene homolog; ECM, extracellular matrix; EGF, epidermal growth factor; EMT, epithelial–mesenchymal transition; Fas, cell surface death receptor; FGF, fibroblast growth factor; MMP, matrix metalloproteinases; p53, tumor suppressor protein; ras, rat sarcoma viral oncogene homolog; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

Figure 2. Case-by-Case Approach for the Identification of Determinant Factors that Control Material Performance *in vivo*.

In vitro–in vivo correlation can be achieved only under (pre)clinically relevant conditions *in vitro*. Abbreviation: MMP, matrix metalloproteinase.

Figure 3. Schematic of the ‘Magic Wheel’ for DESIGN, SENSE and TREAT: Combining a Variety of Triggering Mechanisms and Nanomaterial Formulations to Inquire, Probe, Interact, and Disrupt Diseased Cells and Improve Tumor-Dependent Material Performance.

Exploiting bioengineering tools to systematically probe the role of tumor microenvironment cues (e.g., enzymatic, genetic, molecular, redox, pH, chemical, etc.) in cell and tissue fate and to disturb the tumor by delivering diagnostic (sense) therapeutic (treat) payloads, is of utmost importance and can be used to leverage the full potential of materials.

Key Figure

A Stepwise Integration Approach to Achieve Reliable *in vitro*–*in vivo* Correlations with Concomitant Proper Material Design in light of the Inherent Properties of the Tumor Microenvironment

Figure 4.

Disease type- and state-dependent material platforms will act in a patient-specific manner to obtain optimal clinical outcomes.