Time to empower Cancer Nanotechnology Initiative for Precision Medicine

João Conde¹,²

¹Massachusetts Institute of Technology, Institute for Medical Engineering and Science, Harvard-MIT Division for Health Sciences and Technology, Cambridge, Massachusetts, USA
²School of Engineering and Materials Science, Queen Mary University of London, London, UK

Corresponding author. Email: conde.bio@gmail.com

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Cancer has become the chief proving ground-breaking platforms that can be used for precision medicine. Determining the genetic profile of a tumor, detecting key driver mutations, and trying to disable those drivers with targeted therapies so as to “smash” the brakes on malignant and metastatic cells to control proliferation is the modus operandus of Precision Medicine. Now Cancer Nanotechnology aims to do that for old-line drugs and treatment strategies and bring up reality to the Precision Medicine Initiative. However, how far are we from precision and personalization?

It is forecast that personalization of Precision Nanomedicine may help moving forward the Cancer Nanotechnology initiative, focusing on the combination of stratagems that are able to assemble converging therapy opportunities based on the “intel” from the patient's molecular signature [1]. The outstanding advancement made in Medicine and Biomedical Engineering over the last decade is somewhat due to the fundamental improvements made in Nanotechnology, which includes nanomedicine, nanobiosensing, nanotherapy specifically in the field of precision targeted treatments, high-precise chips, nano-arrays and next-generation biomarkers [2-4].

Innovative soft and hard nanomaterials for tumor targeting [5-7], bone restoration [8, 9] and implantable materials for localized drug delivery [10, 11] have all showed a tremendous enhancement to Precision Medicine. The same goes for other inventions such as nanostructured surfaces for biosensors [12], image-guided implantation of advanced nanomaterials [13, 14], 2D and 3D nanomaterials for biosensors and electronics [15] and smart bioresponsive materials that will definitely move forward Medicine to a new era of personalized healthcare [16].

For the past two decades, advances in genomics, proteomics, metabolomics and systems biology allowed clinicians to forecast personalization of medicine in a data-driven style: drugs and other therapeutic molecules can be designed precisely to

Figure 1. Enabling Personalized Nanomedicine: the Nanotechnology initiative for Precision Medicine.
In fact, Nanotechnology simplifies Personalized Medicine in numerous ways (Figure 1). For example, nanotheranostics (fusion between Therapy & Diagnostics) or nanoimaging assays may assist in the delamination and categorization of patients and in that way, secure personalized therapy procedures in a patient-by-patient basis. Nano-based diagnostic tests also tend to support simplified, more efficient and affordable clinical protocols. Besides, it is now crucial to empower the potential of Nanomedicine to differentially combat cancer using smart and targeted therapy, mediated by highly tumor-specific and cell-specific promoters that mediate highly selective therapy within the tumor microenvironment. The lack of standardized means to treat and profile the tumor microenvironment calls for a paradigm shift in the way we view and treat cancer.

Biomaterials have been increasingly used in the medical field in a wide variety of applications from cell scaffolds to delivery/therapy platforms or biological sensors. Engineered and personalized nanomaterials may be combined either physically or chemically crosslinked with a range of nanomaterials such as carbon-based nanomaterials, polymeric/dendritic nanoparticles or liposomes, inorganic (gold, silver, iron oxide, silica) to achieve the desired property combinations [16-18].

The concept of miniature medical minions isn’t new. Since 1959 that Richard Feynman in a talk at the California Institute of Technology suggested to the possibility of “swallowing the doctor”. From that moment on, researchers realized the potential of materials at nanoscale for disease therapy. Nevertheless, in the last years a massive debate has arisen: is it Cancer Nanotechnology for Precision Medicine hype or hope?

HOW FAR ARE WE FROM PRECISION AND PERSONALIZATION?

According to a Global Market Insights report, the precision medicine market is well established in the developed economies of North America, and Europe (Figure 2a) due to increased awareness regarding respiratory disorders, and rapid technology adoption. However, there is huge potential for market growth during forecast period in the developing and underdeveloped economies of Asia, Africa, and Latin America due to presence of unmet needs, large patient pool, and improving government policies.

Precision Medicine market was over USD 39,726.7 million in 2015 (Figure 2b). Key drivers of the market include increased global incidence of cancer and rise in cancer susceptible aging population will accelerate global precision medicine market growth. Increased global cancer incidence and rise in cancer susceptible aging population will accelerate global precision medicine market growth. High-throughput omics technologies that have been applied in basic biomedical and biological research will fuel bioinformatics segment size. President Barack Obama announced the Precision Medicine Initiative (PMI) in 2015 to revolutionize the concept of medi-
cine and generate scientific evidence required for the development of precision medicine. US FDA would receive USD 10 million as a part of the initiative for building the database to support the research and regulation.

Drug discovery technology was valued at over USD 9 billion in 2015 (Figure 2c), and is estimated to expand at 8.3% CAGR from 2016 to 2023. Biomarker-directed therapies with drugs targeting epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), c-ros oncogene 1 receptor tyrosine kinase (ROS1) have accelerated the development of novel anticancer drugs. The concept of companion diagnostics has also gained significance due to increasing drug failure rates during the recent past. Gene sequencing market size was over USD 8 billion in 2015. Moreover, the recent FDA draft guidelines on next generation sequencing-based tests takes into account individual differences in people’s genes, environments and lifestyles while developing a new kind of healthcare.

Oncology application accounted for over 30% of precision medicine market share in 2015 (Figure 2d) and will grow at 10.9% CAGR estimations from 2016 to 2023. Oncology is leading the way in utilizing the molecular profile of an individual’s cancer genome to optimize disease management. CNS application was valued at over USD 9 billion in 2015 and neurosciences therapeutics has been using the approach for a long time. For instance, the success of Deep Brain Stimulation (DBS) product provides a classic example for application in brain circuitry.

Rising prevalence of chronic disease such as cancer and autoimmune diseases, growing geriatric population, favorable government initiatives, and rapid technological advancements are the major factors driving the global precision medicine market growth in the next 10 years.

The multifaceted tumor microenvironment [19] presents a challenge in developing active anti-cancer therapies that endeavor to harness Nanotechnology [20]. Scientists are recommending fundamental modifications in the field of Cancer Nanotechnology since experiments with animal models and efforts based on current conventions about therapeutic delivery have been unsuccessfully translated into efficacious clinical outcomes [21, 22, 23]. Perhaps the idea of Precision Medicine using Cancer Nanotechnology is nothing more than a vision. In fact, the majority of the research with mice models has hardly translated into fruitful clinical trials. To date and according to a Frost & Sullivan report, there are more than 200 Nanomedicine platforms at several stages of clinical trials, and approximately 150 commercial solutions. This figure will rise considerably in the next 5 years, along with the amount of market participants. Although this can give us the idea that the Industry is bustling with action and enthusiasm, many nano-platforms developed for cancer therapy have not advanced past Phase II of clinical trials and very few were approved and regulated by Food and Drug Administration (FDA). There are hundreds of early clinical trials, but only a handful of late-stage ones have reached completion. The heavy investments required for Research & Development and clinical trials, complexity of manufacturing and regulatory challenges implies substantial loads of funding, at least until the procedures are homogeneous [24, 25].

To overcome this hype, researchers are trying to perfect “targeted delivery” methods using several therapeutic agents, including a variety of nanoscale systems, to selectively abrogate tumors [26-28]. Nevertheless, the current track of research and development has brought only a partial improvement. The bottom line is that up to now there is a scarce number of fruitful nanoformulations approved and used in clinics, so we need to start thinking out of the box.

Numerous approaches have been reported to design nanomaterials sufficiently tiny to pass through pores in blood vessels neighboring tumors but too large to go through the pores of blood vessels in healthy tissue. Nevertheless, at the same time that endothelial cells that build up healthy blood vessels are well structured with tight junctions between them, they are also asymmetrical and distorted, with “wobbly” gaps between the cells, allowing the accumulation of nanomaterials into the fenestrated tumor tissue [6, 29].

However, only a minor percentage of the therapeutic payloads reaches the tumor site, which means that we are treating tumors in a sub-optimal manner. Indeed, a recent meta-analysis has found that only 0.7% (median) of nanoparticles administered systemically actually established their way to the target tumor [30]. This demystifies the idea that nanoparticles go to target tumors merely as a consequence of the blood circulation in a highly efficient way. In fact, only 1-5% (10-50 out of 1,000) of the systemically administered nanoparticles can reach the tumor, which is incredibly low when thinking about efficient index for most of the therapeutic platforms [30, 31]. This suggests that there are severe problems for the translation of cancer targeting nanoparticles applied systemically, because the required amount of nanoparticles that need to be injected would be high both in volume and dose (which may produce stability and toxicity glitches) and would involve the capacity to scale-up nanoparticle manufacture. All of this also implies that the cost of nanoparticles for systemic use in patients may be ridiculously high.

We should recognize that having a specific size, shape, charge or a functional moiety alone is not sufficient to assure a significant therapeutic delivery to target tumors. The tumor microenvironment is too multifaceted to target using this tactic alone [32]. This has to prompt us to think unconventionally or from a new perspective, and see how we can empower developments in Materials Science, and in particular Nanotechnology, to treat the primary tumor in a sustained and efficient manner.

Such a major shift in research emphasis will definitely play a role in developing Personalized/Precision Medicine, “hand-made” to a specific type of cancer and patients. More efficacious treatments involve the use of several types of therapeutic agents (e.g. DNA/RNA, miRNA, siRNA, proteins, and peptides) in combination with numerous drugs to be administered simultaneously or sequentially, or the use of different routes of administration. In fact, most of the Nanotechnology research has relied on the systemic delivery despite the low delivery efficiencies and benefits of the local and sustained delivery platforms. Local therapeutic vehicle opens up new panoramas for real neoadjuvant therapy, with the prospect to reprogram cancer cells to undergo apoptosis and to prevent metastasis along with local drug release or local gene therapy [10, 33-36]. Local application of cargo-containing vehicle at the target site might be the method of choice for multitude of pathologies and different tissues [37, 38] as it allows for the delivery of higher “effective” dose while enhancing therapeutic molecules stability, minimizing side effects and clearance. Moreover, a local therapeutic vehicle opens up new vistas to treat non-re-
sectable tumors, or for washout procedure following tumor resection to prevent recurrence [11], one of the biggest medical problems when treating cancer.

The era of Precision Medicine is just beginning [39], but clinicians have already seen the remarkable improvements in patient care that can be achieved by tailoring drug therapies for the individual profile. Biomaterials scientists must now take on the challenge of translating these insights into the intricate world of material-tissue interactions, where subtle differences in tissue type and disease state may have significant outcomes on material features and clinical efficacy [16]. In this regard exploring the rational design of biomaterials to control a wide range of properties with an eye towards patient-specific tailored materials is of utmost importance [16]. This is an approach we are poised to do. It is not a giant ‘put a man on the moon’ type of mission. It is a very controllable and imperative issue. Nanotechnology offers a “delicate” sensitivity and “robust” precision that is hard to match with any other technology. Within the next decade, Cancer Nanotechnology will definitely change the path of cancer diagnosis and treatment worldwide. But how is its contribution to Precision Medicine?

**HOW TO OVERCOME THE HYPE?**

First of all, we need to look at the numbers. In order to clearly face the facts behind cancer Nanotechnology for Precision Medicine an analysis of the last 16 years was realized (Figure 3), based on the intersection between Pubmed, Web of Science/Knowledge and Google Scholar databases. The search terms “precision OR personalized Medicine” AND “nanoparticles OR nanomedicine OR nanotechnology” were used to identify what was the contribution so far of Nanotechnology to precision medicine in the last 16 years. Looking at the compilation of studies from 2000 to 2016 one can observed that the majority (±92%) of the studies on precision medicine were based on systems that do not take into account any nano-platform or nano-delivery vehicle (Figure 3a). Although there is a growing number of reports on the use of nanomaterials for precision medicine mainly in the last 5 years (Figure 3b), the final frequency (±8%) is poor when comparing Precision Medicine studies with and without the use of Nanotechnology (Figure 3a).

When analyzing the contribution of Precision Medicine and Cancer Nanotechnology in the management of the top deadliest diseases on the planet, we can observe that the great majority (70%) occurs in the treatment of cancer, followed by cardiovascular (specially in coronary artery disease or ischemic heart disease) and respiratory diseases (specially in chronic obstructive pulmonary disease – COPD), both with only 11% each (Figure 3c). Surprisingly, when looking at the frequency of reported studies on Precision Medicine integrated with Nanotechnology by cancer type, leukemia (19%) and glioblastoma (15%) take the “podium”, followed by breast cancer (14%) (Figure 3d).
Besides the need to invest more in using Nanotechnology in Precision Medicine, some key considerations need to be taken into account in the future. First, we used to think that killing the tumor cell would be sufficient to abrogate tumors and cure the cancer, but now we are aware that this is less simple than it seems to be at first sight—all the cancer cells are not the “single players” we have to deal with. There are numerous and diverse cells and blood vessel structure in the tumor microenvironment, which is complex enough to support cancer cells. Most of the times even if drugs are delivered to cells or tissue in the surroundings of the target tumor cells, the treatment may still be hindered by the intricate network of the tumor microenvironment.

Altered tissue microenvironments are a hallmark of cancer [40]. Properties of the diseased tumor microenvironment that are significantly different from normal tissues include acidity, hypoxia, overexpressed proteases, genes and so on [41]. These features can serve not only as biomarkers for cancer diagnosis and therapy but specially to regulate materials performance in light of the tumor milieu [20]. Therefore, dissecting the characteristics of the tumor microenvironment that are of clinical importance in both healthy and disease states can guide the design of disease-responsive materials. A “one material fits all” mindset ignores profound differences in target tissues that affect their responses and reactivity [20, 38]. Thus far little attention has been paid to the role of diseased tissue on material performance, healing capacity and biocompatibility [38]. The complex microenvironment in vivo at different tissue sites with diverse cell types and under altered pathological circumstances may modify material properties and in turn, affect its in vivo performance [20].

Advances in material design can open up a new chapter in personalized cancer medicine, where biomaterials are developed and optimized to precisely match the tumor state, with a concomitant improvement in clinical outcomes. This leads to an interesting question that opens the door to a new field in the biomaterials arena—we are in the era of personalized drugs that target specific cues at a molecular level on a patient-by-patient basis, so why not also personalize biomaterials to match the properties and conditions of each specific tissue type and pathological state to be able to predict performance and improve patient outcome?

Second, some of the described nanomaterials will most likely transform our understanding in how nanomaterials can interact and influence or be influenced by biological mechanisms. This will definitely push forward their integration in future innovative therapy and clinical platforms. However, additional investigation into the ultimate mechanisms of in vivo gene therapy or drug delivery using these nanodevices could expose new platforms of nanoparticle-mediated gene silencing or drug delivery that will have thoughtful consequences for understanding gene regulation or in tackling multidrug resistance, and which could also affect the development of functional genomics and therapeutic applications [42].

Moreover, another important issue that is still unclear is how biocompatible nanocomposites will be following administration either systemic or local, in particular how is the clearance and the recycling of these materials in the long-lasting and sustained release platforms. Future in vivo work will need to cautiously consider the accurate option of chemical modifications to incorporate into the nanomaterials to avoid off-target effects. Some limitations for the correct design and application of nanomaterials, such as pharmacokinetics, biodistribution, and side effects of the nanotherapy; safety profile of nanomaterials before and after conjugation and toxicity, needs to be clarified to validate proficient clinical outcomes. This is especially important for the establishment of a safe regulatory approval for these nanodevices and translation to clinics. It is, therefore, imperative to learn how advances in nanosystem’s capabilities are being used to identify new diagnostic and therapy tools driving the development of personalized medicine in different disease states and pathologies and recognize how to translate Nanotechnology data into an effective and real clinical strategy.

Last but definitely not least, personalized materials for the delivery of therapeutic molecules are needed. The episteme for diseases’ diagnosis and treatment has to be modified from relatively nonspecific delivery agents to tuned, selective and cellular/molecular and mechanism-based devices. However, no studies described so far how to tune materials to react either to cellular microenvironment in specific pathologies, different stages of disease or tune materials to different drug dosages in order not to overload cells with chemical drugs. A range of stimuli responsive properties such as mechanically adaptive, pH and enzymatic responsive or thermo responsive, maybe incorporated in nanomaterials [43]; nevertheless none of these elements tune the material in light of the microenvironment cues nor the disease type and stages.

We have all witnessed a speeding up of our understanding of the molecular and genetic basis of several diseases. Along with this knowledge comes the possibility of re-shaping disease therapeutics together with targeting with more precise therapy. However, for this to succeed the delivery problem associated with the conventional systemic treatments for cancer must be solved. And this problem can only using the smart and efficient nanodelivery vehicles developed by Nanotechnology. For example, in drug discovery, if a drug is not properly delivered or is not selectively delivered, all that is missed is an opportunity for establishing a new active drug treatment. In the same way in clinical medicine making or failing a diagnosis may have shattering costs for patients, the lack of integration between Nanotechnology and Precision medicine for cancer therapy may represent major step-backs in the field. By discussing this astonishing opportunity for Cancer Nanotechnology to realize the full potential of Precision Medicine, I have described possible tasks important to leverage the sustainability of this initiative. Building on this groundwork, the integration of Cancer Nanotechnology on Precision Medicine will provide a fusion between both knowledges in order to redefine disease treatments and provide hope (not hype) for “cohorts” of patients and families to come.

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