An analysis on Cancer Nanotherapy: does Nanotechnology have a delivery problem?

João Conde

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

To date, 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. This prompt researchers to call the status quo treatment regimen into question and ask: Does Cancer Nanotechnology have a delivery problem? Nanotechnology can certainly deliver, but we need more efficient and sustained drug delivery platforms for cancer therapy.

Society is still fighting against a high number of serious and complex illnesses especially with cancer, which has a tremendous deleterious impact not only on the patient himself but also on the whole society as well as on social and health insurance systems [1].

Medical care will for sure be benefiting from the advantages that Nanotechnology can offer, “The manufacturing technology of the 21st century”. The interest in the properties and manipulation of bio- and nanomaterials has increased dramatically in the last years [2]. Nanotechnology is being highly applied in different fields like electronics, optics, communications, chemistry, energy, biology and medicine. Due to the impact of health applications in our society, a big effort is being developed in this area, using nanomaterials for diagnostics [3] as well as gene or drug carriers for tumor targeting [4-7].

Cancer treatments suffer from poor efficacy owing to the lack of efficient delivery systems and to the inherent tumor heterogeneity that requires multi-modal approach to abrogate cancer progression [8,9]. There is broad agreement (though not consensus) that Nanotechnology can definitely address these drawbacks [10]. Nanomaterials and biomaterials, in particular for diagnostics and therapy, are increasingly used in Medicine. These materials serve as structural support, void filling, and as platforms to sense and treat, embedding of cells and drugs [11,12]. Nevertheless, a wake-up call for the status quo regimen in Cancer Nanotechnology delivery is needed as more and more evidence that the efficiency of current nanoparticles to target drugs or other therapeutics to tumors is not as effective as we thought [13,14]. A fresh look at the delivery platforms and routes of administration neglected so far can help us to see that Nanotechnology delivery problem can be overcome by simple changes in the field.

FACING THE TRUTH: LOCAL OVER SYSTEMIC

Nanotechnology has a delivery problem. Achieving “the next big thing” starts with being realistic now. There is more in delivering materials than meets the eye. In fact, the tumor microenvironment is a rough neighborhood for nanomaterials [15]. Tumors create skewed neighborhoods, embedded with their leaky and chaotic blood vessels that are like broken roads or damaged sewers. All the different cells composing the tumor milieu shift to support tumor growth, these unoccupied lots densely overgrown with collagen fibers. And we are trying to get a huge truck-load of medicines into all of this. Is not an easy task and we should not take this for granted, as more and more examples are being reported that Nanotechnology has a delivery problem [13,16,17].

To clearly face the facts behind cancer therapy using nanotechnology an analysis of the last 15 years was realized (Figure 1), based on the intersection between Pubmed, Web of Science/Knowledge and Google Scholar databases. The search terms “nanoparticle OR hydrogel OR gel OR scaffold” AND “human cancer”, “therapy” and “in vivo” were used to identify how nanomaterials were administered (systemically or locally) in the last 15 years, using cancer mice models. Looking at the compilation of studies from 2000 to 2016 one can observed that the majority (±95%) of the materials research for cancer nanotherapy is based on systemic administration rather than local with only 5% from more than 3,000 manuscripts. There is a growing number of reports on the in vivo delivery of nanomaterials mainly in the last 10 years, clearly using a systemic regimen (Figure 1a,b).

The manuscripts were next sorted by the ones presenting quantitative data on “therapy efficacy” and “biodistribution”. The “therapy efficacy” stands for the efficiency in inhibiting tumor growth and the “biodistribution” for the percentage of nanomaterials accumulated in the tumor as well as in the major organs (liver, kidneys, spleen, lungs, heart, intestines and brain). Surprisingly, less than 5% of the manuscripts presented quantitative data on both of these issues, which are crucial to evaluate the therapeutic index and specificity/selectivity of any treatment regimen. This lack of quantitative data represents the first drawback in translating nanomedicines into clinics. We will all have to make an effort on overcoming this in order to advance Nanotechnology into the clinics and into commercialization. The lack of standardization and catego-
The detailed characterization of the therapeutic platforms is of utmost importance and must be fixed in the near future. Interestingly, this analysis also revealed that the therapy efficacy of the local administration of nanomaterials (i.e. nanoparticles embedded on hydrogels, gels or other scaffolds) was significantly higher ($P<0.01$), when comparing to the systemic administration (Figure 1c). This analysis suggests that the average systemic nanotherapies in the last 15 years have a therapeutic index of 53.7±24.6% in terms of reducing the size of the tumor, when compared to the 91.2±7.3% tumor size reduction when the therapeutic cargos are administered locally. 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.

**Figure 1.** Analysis of nanoparticle delivery using systemic or local treatments to tumors from studies published in 2000-2016 and procedure used for the literature survey. (a) Diagram showing the distribution of time points comparing systemic and local therapies for more than 2,500 publications that were identified by the survey. (b) A pie chart comparing the frequencies of local and systemic therapies during the last 15 years is also depicted. Diagrams for (c) therapy efficacy (%) and (d) biodistribution (nanoparticles accumulation at the tumor site and major organs). Statistical analysis was performed using a two-way analysis of variance, ***, $P<0.01$).
On the contrary, with local administration the nanomaterials accumulate almost exclusively at the tumor site (97.2±14.6%), revealing a highly specificity and selectivity towards the application site and targeted tissue.

Moreover, several trends may be observed in the data, when characterizing the nanotherapies applied either systemically or locally (Figure 2). First, nanoparticles applied systemically were extensively used in the treatment of breast, liver and lung cancer (Figure 2a). The same happens with the local therapies with more predominance in breast and liver cancer with fruitful results [20-22]. This highlights the second myth: local therapies can also be applied in more internal organs in an open surgery or in an image-guided ultrasound surgery, as gels are already used in clinics as surgical glues [23] they can also be used as internal drug depots, for example.

Second, nanoparticles administered systemically are predominantly used for drug delivery of chemotherapeutic drugs (42%) and for photo-therapies (21%) like photo-dynamic or photo-thermal treatments (Figure 2b). When looking at the local treatments the trend is similar with more than 60% of the reported studies applied for chemo-therapies. Another important observation is that 10-20% of all cases applied both systemically or locally use combination therapy. The combination therapy certainly plays a crucial role in cancer therapy, as the rationale for combination treatment is to use different therapeutic effectors that work by different mechanisms, in that way reducing the probability that resistant cancer cells will mature and expand. Besides, when different therapeutic payloads with different effects are combined, each one can be administered at its optimal dose, without undesirable side effects.

Analysis of the frequency of studies reporting systemic and local therapies by cell type was next performed (Figure 2c). For both types of therapies, the majority of studies (93% for local and 61% for systemic therapies) was performed only targeting cancer cells, when comparing to the other cell types comprising the tumor microenvironment. Using nanomaterials that target and delivery therapeutic payloads specifically to each type of the cells of the tumor microenvironment (cancer cells, normal cells, immune cells, tumor-associated fibroblasts, endothelial cells and cancer stem cells) to evaluate the therapeutic efficacy in a cell-by-cell basis is of paramount significance. For example, immune cells can both advance as well hinder therapeutic efficacy and this is highly controlled by their activation status within the tumor microenvironment [24]. However, to date little attention was gave to this in Cancer Nanotechnology.

Finally, the lifetime scores in days for systemic and local therapies was performed. These lifetime scores refer to how long the nanoparticles stay in the tumor. Interestingly, the lifetime of the therapeutic cargos is nearly 25 times higher when applied locally (Figure 2d). This clearly shows the superiority of the local platforms over the systemic and conventional ones, as this will dramatically increase the effective dose at the tumor site for longer periods of time.

Figure 2. Characterization of the nanotherapies applied systemically or locally. (a) Frequency (%) of reported studies using systemic and local treatments by cancer type. (b) Data set for systemic and local therapies for each of the therapeutic modalities reported: drug, gene, photo and immuno-therapies, along with combination treatment. (c) Analysis of frequency (%) of studies reporting systemic and local therapies by cell type. (d) Lifetime scores in days for systemic and local therapies. Statistical analysis was performed using a two-way analysis of variance, **, P<0.01).
Nevertheless, and despite these evidences, to date most nanomaterial research has only dealt with targeting tumors giving priority to systemic treatments despite the promise and benefits of local and sustained therapies (Figures 1 and 2) [25]. The reality is that these assumptions concerning excellent tumor size reduction and exclusively accumulation in the tumors using systemic treatments have produced several research articles, but have made no significant advances in translation into patient treatment. These unfortunate failacies must face the inconvenient truth: when looking at the numbers (Figure 1) from the last 15 years 96% of the nanotherapies in cancer used systemic platforms with only 53% therapy efficacy, and only 4% used local despite achieving more than 90% therapeutic efficiency associated with these therapy regimens.

Despite the knowledge that systemic therapies may target any type of cancer, and the same is not possible with local administration a new therapeutic regimen needs to take place and change the way we view and treat cancer. Although local delivery is often used for solid tumors rather than soft tumors, like lung, brain or liver cancer, hydrogel platforms that can gel in situ can be applied directly to organs like liver (by using combined radiofrequency ablation and doxorubicin-eluting polymer implants [26]) or brain (by using the Gliadel Wafers for brain tumors [27]) by direct injection of the gel in an open surgery or the materials can be applied local by inhalation or by intratracheal instillation to treat lung cancer [28,29], for example.

It is also known that if metastasis already exist a systemic approach may be more appropriate to target these secondary tumor sites [5,25]. However, Gilam et al. reported the development of a local hydrogel platform applied in a primary breast tumor, which is able to prevent the establishment of metastasis in the lungs, liver and brain [30], just by targeting and modulating the primary tumor microenvironment. In this study the authors developed a smart delivery vehicle based on hydrogel-embedded gold-nanoparticles providing efficient local and selective sustained release of miR-96 and miR-182, as well as combined therapy of miRNAs with a chemotherapy drug, which dramatically suppressed metastasis in an in vivo orthotopic breast cancer mouse model. This study introduces the therapeutic potential of miRNAs in breast cancer metastasis prevention. This novel combined therapy can definitely improve the clinical outcome by significantly reducing primary tumor mass, as well as reducing – or even preventing – metastasis [30].

Although cancer is viewed and perceived as a ‘systemic’ disease that mandates systemic treatment, this approach is suboptimal in treating the primary tumor. Enabling an efficient systemic delivery is challenging and is nowadays based mainly on empirical research. There is an urgent need to figure it out what really works and what not. On the contrary, the local treatments seem to impart efficacious therapeutic system with a viable and highly potent anticancer therapy, culminating in long-lived tumor eradication. It seems legitimate that researchers need a wake-up call for the status quo regimen in cancer nanotechnology delivery.

**RECONSTRUCTING THE DELIVERY REGIMEN**

Based on the analysis reported herein, systemic therapy is suboptimal in treating the primary tumor. In contrast, local therapeutic vehicle opens up new vistas for effective neoadjuvant therapy, with the opportunity to reprogram cancer cells to undergo apoptosis and to prevent metastasis along with local drug release [20,31-33]. Local administration allows delivering much higher ‘effective’ dose while enhancing therapeutic molecules’ stability, minimizing side effects and clearance. Of equal importance is the ability to overcome accumulation of therapeutic molecules in the liver and kidneys following systemic administration, which makes targeting to other organs difficult.

The conventional treatments for cancer are the systemic administration of chemotherapeutic drugs, which are rapidly cleared from the blood stream and accumulate non-specifically in kidney, spleen, liver and lymph nodes. Although some nanoproducts using systemic administration are getting into clinical trials, such as the protein nanoparticles encapsulating paclitaxel (Abraxane®) for the treatment of breast cancer (ClinicalTrials.gov: NCT00274456), the final results are far from being effective, rounding only 20-30% of subjects showing complete or partial response to therapy. Also importantly, 40-70% of the subjects participating these clinical trials are at risk of adverse/serious side events, as gastrointestinal as well as metabolism and nutrition disorders, vomiting, nausea or even hypertension and cerebrovascular ischemia.

Moreover, there is a lack of nanomaterials standardization in pre-clinical studies. This lack of uniformity in preclinical trials prevents systematic comparison and hence limits advances in the field [34].

Local application of cargo-containing vehicle at the target site might be the method of choice for multitude of pathologies and different tissues [35,36] as it allows for the delivery of higher ‘effective’ dose while enhancing therapeutic molecules stability, minimizing side effects and clearance. In fact, a local therapeutic vehicle opens up new vistas for effective neoadjuvant therapy, treat non-resectable tumors, or for wash-out procedure following tumor resection to prevent recurrence [37].

Just to name a few. In the last years, several local platforms have been developed as highly effective cancer therapy depots. For example, Langer and co-workers have developed a self-healing gel that can be injected into the body and act as a long-term drug depot. In this study, the authors showed that the gels survived a sub-cutaneous injection in mice and successfully released one hydrophobic and one hydrophilic drugs, over several days [32]. This is just an example of how local platforms offer an important advantage over injecting a liquid solution of drug-delivery nanoparticles. While a solution will instantly disperse throughout the body when injected intravenously or leak out of the tumor tissue even if injected intra-tumorally, the gel stays in place after application, allowing the drug to be targeted to a specific tissue. Furthermore, the properties of each gel component can be tuned so the drugs they carry are released at different rates, allowing them to be tailored for different uses [32].

In another striking example, Conde et al. developed hydrogels optimized as prophylactic patches able to perform gene, chemo and phototherapy in a triple-combination approach to achieve complete tumor resection (more than 90% tumor size reduction) when applied to non-resected tumors and to the absence of tumor recurrence when applied following tumor resection [37]. This study also shows the superiority of the
hydrogel over the systemic and intra-tumor injections, providing convincing evidence that the local administration using a hydrogel is instrumental to the achievement of superior therapeutic performance [37].

Another enlightened study reported by Qian and co-workers develops a biodegradable thermo-responsive hybrid hydrogel to prevent the post-operative recurrence of breast cancer. In a metastatic breast cancer model the authors were able to reduce post-operative recurrence in approximately 85% [38].

Taken together these studies provide strong evidence that local platforms are excellent candidates for a successful delivery strategy and represent a rational treatment approach following a comprehensive scrutiny of the tumor microenvironment and host response to different therapeutic modalities.

We have all witnessed a speeding up of our understanding of the molecular and genetic basis of cancer. Along with this knowledge comes the possibility of re-shaping cancer 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 be solved using smart and efficient nanodelivery vehicles and for finding new criteria for survival, tumor size and nanomaterials biodistribution that can match both pre-clinical and clinical trials. From fixing the lack of uniformity in pre-clinical studies to empower existing and extensively used systemic therapies with innovative and highly efficient local platforms. In fact, the local administration may be used to empower systemic delivery and have systemic effects or a local activation [39].

This knowledge is the stepping-stone for the development of smart material platforms that can sense the tumor environment, enhance tissue repair and report on tumor state along with cancer cells suppression (Figure 3) [12]. The ultimate goal must be to create systems like the idea of a local patch, that provides sustained and highly efficient delivery of the therapeutic cargos and which may potentiate the development of individualized therapy based on the patient’s biological information within the biomolecular cancer profiling. It is now imperative to develop a new and more effective treatment strategy following a comprehensive scrutiny and understanding of the tumor microenvironment and host response to different therapeutic modalities based locally tunable therapeutic cargos [15]. This approach will certainly be attractive for drug discovery since this type of analysis captures mechanisms operating in the tumor in its entirety, whilst pinpointing therapeutic targets, which can be selectively modulated to modify response and in response to therapy. With these promising future directions, biomaterials-based local therapy in vivo screening and profiling establishes a new platform for selective and efficient cancer therapy and the discovery of new therapeutic targets.

If we think wisely...the general approach to cancer treatment today is the use of systemic, or whole-body, therapies such as chemotherapy drugs. Nevertheless, the absence of specificity of anticancer drugs means they produce undesired side effects when systemically administered. Furthermore, only a minor dose of the drug reaches the tumor site itself, meaning the primary tumor is not treated as effectively as it should be. This means that we are treating both the source of the cancer – the tumor – and the metastases resulting from that source, in a suboptimal manner.

That must prompted us to think a little bit “out of the box”, to look at how we can leverage advancements in materials...
science, and in particular nanotechnology, to treat the primary tumor in a local and sustained manner. From correcting for the lack of uniformity in pre-clinical studies to empowering existing and extensively used systemic therapies with innovative and highly efficient local platforms, one can leverage existing and future studies to impart better technologies with predictive therapeutic performance. These advances will enable a new generation of drug delivery systems, for example a local patch, which would provide with a sustained and highly efficient delivery of the therapeutic cargos imparting both local and systemic effects that afford individualized therapy based on the patient’s biological signature.

There simply needs to be an understanding that overcoming the enormous difficulties involved in nanodelivery requires more than just rhetoric and nice-looking pictures. Now is the time to change the therapy regimen based on the undoubtedly data we reported in the last 15 years.

Notes

The author declare no competing financial interest.

References

[29] J. Conde; C. Bao; Y. Hernández; C. Bao; D. Cui; P. K. Janssen;


Open Access
This article is licensed under a Creative Commons Attribution 4.0 International License.
© The Author(s) 2018