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Challenges in molecular diagnostic research in cancer nanotechnology

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ABSTRACT

Development of robust cancer prevention strategies have the capacity to reduce the need for therapeutic products, relieve patient's suffering and alleviate the crushing financial burden for both patients and their families. Therefore, the obvious choice that would benefit the largest number of people is to realign the importance and prioritization of diagnostics alongside therapeutics. However, entrepreneurs and policy-makers are more inclined to invest in manufacturers of therapeutics, which produce much higher revenues compared to diagnostics companies. The central aim of this opinion article is i) to identify the reasons for this chasm gap between therapeutic and diagnostic approaches in cancer research; and ii) to draw the attention of researchers, entrepreneurs, and policy-makers to the importance and potential promises of diagnostic approaches in lowering the social burden and cost of cancer.

Introduction

The research in the area of early diagnostics and disease detection is "underdeveloped" compared to the therapeutics, which poses a serious concern in the age of precision health when the overwhelming efforts of forward-looking scientists are directed towards shifting the medicine from being "reactive" (*i.e.* responding to a disease) to "pro-active" (*i.e.* focusing on prediction, prevention and early detection). Here we attempt to analyze this discrepancy in detail and define the underlying reasons that create the gap between diagnostic and therapeutic approaches.

Nanotechnology-based diagnosis and treatment of cancer play key roles in overcoming the limitations of conventional methods by providing more accuracy and precision (*e.g.*, by targeting at cellular scale and sustained delivery of desired biomolecules [1]). One would, therefore, expect that a nano-based diagnostic and treatment approach should be a priority instead of conventional intervention. In reality, however, the focus of clinical, academic and industrial research is on advancing conventional therapeutics, while nano-based diagnostics and treatment continue to be less appreciated. It appears that research in the field of nano-biomedical cancer diagnostic and treatment is underfunded, as reflected by the lower number of scientific publications in this field compared to conventional cancer therapeutics. A recent cursory literature search in PubMed using "cancer diagnostic" as a keyword revealed 978 references, while the search for "cancer therapeutics" produced 6694 references.

Diagnostic *vs.* Therapeutic nanotechnology: A scientific point of view

The reports published by the World Health Organization (WHO) [2] and by the European Federation of Pharmaceutical Industries and Associations [3] identify cancer as one of the most common diseases, with an annual increase of over 14 million new cases leading to 8.8 million deaths per year worldwide. Fortunately, in many cases, the causes of cancer (at least from genomic point of view) have been identified and new strategies for treatment have been developed. The field of cancer therapeutics produced over 323,000 articles published over the last ten years with an average annual growth rate (AAGR) of 3.9% (Fig. 1a). Despite these advancements, no other disease is expected to grow faster than cancer. The rates of incidence and mortality is expected to exceed 70% by 2040 [4]. This shocking prediction is based on the series of concomitant factors such population aging, environmental conditions, gender, lifestyle, diet, the intestinal microflora and molecular heterogeneity. The only alternative solution to reverse the current trend is to promote

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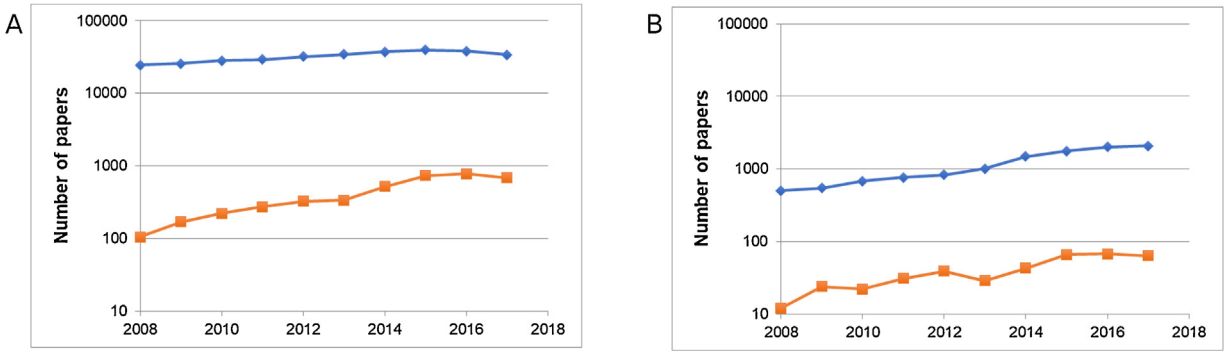

Fig. 1. (A) MEDLINE PubMed was queried with "cancer therapeutics" (light blue diamonds). From 2008 to date, a steady growth has occurred, at an average annual growth rate (AAGR) of 3.9%. Over the same time period, MEDLINE PubMed was queried with a combination of "cancer therapeutics" and "nanotechnology" with the operator AND (orange squares). While the number of publications was much lower than that returned just querying with "cancer therapeutics", it grew at an impressive AAGR of 55.3%. (B) The graph illustrates the number of entries in PubMed using "cancer diagnosis" as a search keyword (light blue diamonds, 31% AAGR) and "cancer diagnosis" in combination with "nanotechnology" with the operator AND (orange squares, 43% AAGR).

and encourage development of novel tools for early recognition of cancer-specific molecular abnormalities before tumor formation.

Recent applications of nano-biotechnology for early diagnostic and treatment of cancer provide a promising alternative to conventional therapeutics and treatments [5,6]. In fact, nanotechnology may offer innovative means to target chemotherapies selectively to cancer cells [7], enable surgical resection of tumors quicker and more precisely and enhance the effectiveness of radiation-based therapies [8]. Over the past decade, large government funds for nanotechnology research have created some of the most sophisticated nanoscience laboratories in the world, and most of them have been engaged in developing innovative medicines to combat cancer. Turning nanotechnology research into innovative solutions has led to an increasing number of cancer-related publications (4152 published documents with AAGR of 55.3%).

Despite the recognition of the fact that early detection leads to improved outcome, better survival and lower cost, early cancer diagnostics have been largely overlooked in the healthcare system [9]. Traditionally, there have been many barriers in developing effective and reliable diagnostic assays. First, many tests do not give "yes" or "no" answers. Second, low-profit margins do not allow big companies to cover development costs. As such, the research field of cancer diagnostics has produced roughly 12,000 publications between 2008–2018 (Fig. 1b) which is more than an order of magnitude lower than those published in the field of cancer therapeutics (Fig. 1a). Similarly, the number of publications describing the use of nanotechnology in cancer diagnostics (400; with a significant AAGR of 43%) has been much lower than those published on cancer therapeutics.

Diagnostic *vs.* therapeutic nanotechnology: funding and industrial success

The market of cancer pharmaceuticals is tightly dominated by the big companies. Priorities of these companies are given to amassing products and innovation through internal R&D, licensing, or acquisition [10]. This model consumes large economical resources but leads to frequent failures, and in most cases, efforts do not materialize in drug approval. For example, in 2017 the whole oncology pipeline had over 600 molecules in late development stage, but only 22 drugs were approved by the Center for Drug Evaluation and Research (CDER) of the FDA in 2016. This is a major slowdown compared to the 45 new drugs in 2015 and 41 in 2014. Approved drugs also cost much more today than in the past decades. The budget for developing a successful drug can exceed $2.6 billion compared to $179 million in the seventies. Most drug candidates do not reach the market, and even already approved drugs are sometimes subject to failure. A 2009–2013 review by the European Medicines Agency showed that among 48 drugs approved for 68 indications, 39–57% did not show an improvement in survival or quality of life over placebo [11].

In contrast to pharmaceutical industry, the diagnostics industry has a much lower risk/lower reward profile. Companies profiled in this market include Thermo Fisher Scientific Inc., Alere Inc., Biomerieux, Danaher Corporation, F. Hoffmann-La Roche AG, Becton Dickinson, Bio-Rad Laboratories, Bayer AG, Sysmex Corporation, and Johnson & Johnson. Today's diagnostic tests are accurate and less time consuming. In fact, some of them can be comfortably used at home without professional supervision (pregnancy test, blood glucose test and others).

Unfortunately, in the last decades similar advances have not been made in the area of cancer diagnosis except for some progress in early detection of specific malignancies. To date, most studies have sought to identify tumor-specific antigens such as prostate specific antigen (PSA) as a marker for early diagnosis of prostate cancer. Identification of specific cancer biomarkers in blood plasma is a promising approach for early cancer detection. However, due to their low specificity and sensitivity, traditional tumor biomarkers alone or in combination with cancer detection models obtained by machine learning are still not available in clinic for cancer detection in general population [12]. This is the case, for example, for pancreatic ductal adenocarcinoma (PDAC), a tumor with high mortality [13]. Screening methods for early detection of PDAC and similar aggressive malignancies would enable identification of asymptomatic candidates, who could be promptly reported for diagnosis and treatment [14]. Screening may pave a way to radically limit the epidemiological impact of cancer by preventing or slowing down its progress through available interventions. Recently, the National Cancer Institute (NCI) has recognized that nano-based technologies may offer exciting opportunities, potentially becoming a "game changer" in advancing cancer diagnosis. This is the case, for instance, for nanoparticle (NP)-based imaging that will likely provide superior diagnostic and prognostic information that is otherwise difficult to obtain, potentially advancing personalized clinical care.

Diagnostic *vs.* Therapeutic technology in the emerging field of precision health

It is well known that response to external stimuli differs among individuals and that patients with the same condition show different sensitivity and therapeutic response to the same drug. The term "precision medicine" has now been used with increasing frequency to indicate a new approach to medicine in which patient's individual

variability plays a major role [15]. Many biological factors [16] such as cell type, cell size, cell sex and the varying complexity of tumor microenvironment play a key role in determining the heterogeneity of a given cancer leading to patients' diversity in response to drugs. Among these factors, continuously changing tumor microenvironment with its spatial and temporal heterogeneities can seriously impact the outcome of cancer treatment [17].

While efforts have been made at advancing new cancer therapeutics on the market, much less focus has been directed to precision monitoring and diagnostics, *i.e.* to the tools that are necessary to predict, prevent or identify the disease early. As has been emphasized by Dr. Sanjeev Sam Gambhir (Stanford University), the focus of health care has to shift from "precision medicine" to "precision health", which would provide customized monitoring to healthy individuals, identify those at risk early and timely detect any signs of malignancy [18]. The availability of these tools would reduce the overall treatment costs and dramatically improve the outcome. However, today's diagnostic tools are not at the forefront of modern oncology even though precision molecular diagnostics called companion diagnostics are among mandatory prerequisites for the beneficial use of the targeted drugs [19]. For example, without precise laboratory diagnosis of the V600E mutation in melanoma or HER2 amplification in breast cancer, there would be no benefit for the patients to be treated with the drugs against these markers in addition to unjustifiable financial burden to the healthcare systems.

It is obvious that precision diagnostics should be considered as the necessary premise for the development of precision therapies. A 2009 report by The Lewin Group, one of the largest health care policy research groups, estimates that laboratory diagnostics account for less than 5% of hospital costs and about 1.6% of all Medicare costs while laboratory test results have as much as 60–70% impact on the health care decision-making [20].

Overall, to successfully treat cancer patients, scientists need to develop precision diagnostics that would be accurate and reliable. With regular access to screening programs and early diagnosis, patients would have immediate access to treatments that may lead to better outcomes. Within this framework, the emerging field of the nanobiointeractions may pave the way to success of precision diagnostics.

NanobioInterfaces:a challenge to therapeutic and diagnostic nanotechnology

For more than two decades, grafting polymers such as polyethylene glycol (PEG) [21,22] to nanocarriers' surface has been considered as a new drug delivery option for cancer patients and represented one of the greatest opportunities for the cancer market (*e.g.* stealth liposomal drugs [23]). Researchers and pharmaceutical companies have recognized that modification of the PEG-molecule terminus with targeting ligands could produce ideal nanodevices for targeted delivery of nanomedicines [24,25]. Some targeted products developed by pharmaceutical companies have shown promise but have not exceeded the level of development and are not commercially available [26]. This failure and the loss of financial support for development of innovative nano-biomedical based drug delivery systems and devices, prevented researchers to overcome their limited understanding of the biological behavior of nanomaterials exposed to physiological environments. Recently, the scientific community has started to unravel several "hidden factors" existing at the interface between nanomaterials and biological systems [16,27]. We now know that as soon as functionalized NPs are exposed to a biological environment such as body fluid, their surface is immediately covered by biomolecules present in the media resulting in formation of biomolecular corona (BC) that evolves mainly quantitatively over time with small qualitative variations [28,29] and is influenced by physico-chemical properties of the NPs [30], the source of biomolecules (*e.g.* plasma *vs.* serum [31]; human plasma *vs.* mouse plasma [32]), media concentration [30,33] as well as temperature [34], flow dynamics [35] and exposure time [36]. A turning point was achieved when researchers discovered that grafting PEG and other polymers to the surface of NPs does not completely preclude adsorption of plasma proteins [37] making the surface of nanomaterials inaccessible to the interaction with the medium exposed. The interaction of the NPs with cellular and extracellular components take place through the protein present in BC formed on the surface of the NPs [36]. Moreover, a recent study [38] demonstrated that PEG can also affect the composition of the corona preventing non-specific cellular uptake. As a result, it is clear that most targeted nanomaterials can lose their targeting capabilities in a physiological environment and acquire potentially unpredictable functionalities [15]. There are several proposed approaches (*e.g.*, using zwitterionic coatings [39,40]) that can reduce the masking effects of protein corona [27]. Thus, designing innovative functionalized NPs could potentially be an efficient method for developing targeted corona-covered nanomaterials with reduced adverse effects produced by the random nonspecific corona. Formation of protein corona can also affect immune system response which may influence the safety and efficacy of the diagnostic/therapeutic nanoparticles [41–43].

The overlooked aspects of nanomedicine demand the review of many previous discoveries and experiments performed *in vivo*. On the other hand, because corona formation is inevitable and may vary in different people, it could be explored for development of safe and efficient nanotechnologies. Indeed, the possibility of controlling the composition of corona could enable new exciting opportunities in 'camouflaging' a nanomaterial, *e.g.* mitigating toxicity and directing biodistribution. Hajipour et al. [44,45] have demonstrated that patients with various diseases, including cancers exhibit personalized coronas that evolve over time with disease progression. For example, corona could trigger variable cellular processes relevant to efficacy of drug treatment such as controlled release, production of reactive oxygen species, lipid peroxidation and apoptosis.

Combination of these findings have formed a new paradigm postulating that the interaction between the nanomaterial and biological fluid could create a nanobiointerface leading to a formation of a specific biomolecular corona, which could be responsible for different personalized responses to drug treatments and, in turn, for many failures of clinical trials. Now, researchers need to develop a more in-depth understanding of the interaction between NP surface and macromolecules, in particular proteins within the corona. However, considering that personalized corona will impact targeting capability of the drug, the outcomes will differ from patient to patient. Therefore, to exploit the corona for targeted drug delivery it is essential to design customized NPs for cancer patients with similar proteomes which may cause difficulties in commercialization of these materials [46].

On the other hand, NPs containing a specific corona could be designed to develop safe, user-friendly and cheap methods for cancer diagnostics. Upon exposure to patient serum, NPs could function as a ñano-concentratorf̈or specific proteins with affinity to a specific surface of NPs. Alteration in the BC composition has already been exploited for developing of a liposome-blood test for early detection of PDAC [47], which was able to discriminate between healthy individuals and pancreatic cancer patients with a total correctness rate of 88% [47]. Recent research suggested that BC composition is also influenced by tumor size and presence of distant metastases in PDAC [48], though it needs to be confirmed on larger cohorts. In another study, characterization of the protein corona formed around lipid NPs upon exposure to plasma proteins

allowed for identifying patients with meningeal tumors thus opening a new door for early diagnosis of central nervous system (CNS) cancer [49]. Extensive investigations are necessary to validate clinical applications of BC-based blood tests, and to rigorously evaluate the factors that may influence their specificity and sensitivity.

Lastly, we expect that by comparing corona profiles of cancer patients and healthy individuals, new insights on the biology and stage of many types of cancer may be generated. This is a key issue that is attracting increasing interest and deserves further investigation in the future.

Conclusions and recommendations

Over the last decade, nanotechnology has provided researchers with the unprecedented opportunity to manipulate nanomaterials to generate entirely novel therapeutic and diagnostic agents for cancer patients. However, as in any other field of science, advancements in cancer research are strongly related to availability of funding. Today, financial support coming from the government is often inadequate and an increasing flow of money is coming from big private firms that dominate the market. But, business models of big pharmaceutical companies aim at accumulating drugs in the pipeline rather than developing companion diagnostic tools. However, such tools could be vital for development of highly effective therapeutics for cancer patients.

A turning point in the development of new technologies for cancer diagnosis will come from the exploitation of the biomolecular corona that surrounds nanomaterials *in vivo*. BC-enabled blood tests can provide early detection of cancer with high sensitivity and specificity, allowing scientists to detect minor changes in plasma proteins even at a very early stage of disease. Development of these technologies is still in its infancy, but investigation of BC can add new knowledge to the quest in earlier disease detection.

Finally, we personally believe that the field is in desperate need of researchers, venture capitalists, entrepreneurs, and media advocates who are either extraordinarily empathetic, or whose lives have been directly affected by these devastating diseases [50]. We imagine a large, well-organized movement, motivated not by wealth or fame, but by a wholehearted commitment to changing the course of the healthcare through improving early diagnosis and treatment of disease and relieving the suffering of both patients and their families. Absent such a movement, we should expect to see the continued failure of early disease detection combined with substantial increase in the prevalence and incidence of diseases, as they evolve and acquire resistance to current therapeutic approaches. History teaches that even a few people like Leroy Edgar Burney (who was the first to publicly identify tobacco as a cause of lung cancer) and Rachel Carson (who combated pesticides as a cause of bird population decimation), can change the course of the world for the better. We call upon funding agencies, researchers, entrepreneurs, and media to help re-balance the energy/funding disparity between diagnostic and therapeutic efforts. We believe this will set the stage for a dramatic cost reduction in the medical field, ultimately protecting patients from catastrophic diseases and their families from both emotional and financial duress.

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