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Pharmaceutical Cancer Nanotechnology: Shortening Hurtles to Clinical Translation

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Short Commentary

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Nanoparticles offer a distinct array of properties that may potentially improve cancer therapy. Nanoparticles possess an extraordinarily large surface-area-to-volume ratio for drug loading, increased blood circulation half-life, and inherent contrast enhancing properties for imaging purposes. Therefore, nanoparticle research has been exponentially accelerated for the past 15 years, and translational research greatly aided by the NCI Alliance for Nanotechnology in Cancer and Nanotechnology Characterization lab. However, only the simplest formulations of nanoparticles are currently approved for clinical use (Abraxane, Doxil, Myocet, daunoxome, Oncaspar, DepoCyt, MARQIBO), which aid in passive tumor targeting through their enhanced permeability and retention effect. While this is still quite an achievement, promises such as targeted, multifunctional therapies have yet to be realized. What are the difficulties in translating these potentially curative nanoparticles into clinical use?

We are reaching a plateau in nano-biomedical research where only the most unique or effective therapies will likely receive funding and thus further development. For example, BIND Therapeutics' Accurins technology provides a promising platform for improving site-specific delivery of chemotherapies [1]. This "shake-and-bake" approach where a variety of drugs could be encapsulated in their polymeric targeted delivery vehicle is a great example of a successful nanomedicine, but has yet to prove effective in human Phase III trials. Highly complex nanomedicines could prove useful once obstacles such as reproducibility and scale up are solved. For example, multistage vector therapeutics offer the ability to sequentially overcome the multitude of biological barriers in tumor targeted drug delivery [2].

In conducting this translational research, we must remember that the first batch of patients that receive our cutting edge technology in clinical trials will be late stage, poor prognosis, previously treated subjects. This signifies an enormous hurdle in that the nanomedicine must be incredibly biocompatible to prevent overwhelming an already highly stressed system, and able to overcome molecular resistance mechanisms that have already evolved. The nanomedicines to be accepted therapies will be those that can be incorporated in and directly improve outcomes compared to current standard-of-care therapies. For example, glioblastoma (GBM), an aggressive form of brain cancer, is one of the most deadly cancers with a 14-16 month median survival [3]. Standard of care includes surgery followed by radiation and adjuvant chemotherapy. However, the invasive nature of GBM precludes complete resection and its rapid genetic mutation produces resistance to combined radiation and chemotherapy.

It is well established that the degree of resection of many brain tumors while lessening the surgical morbidity has a direct correlation with patient outcome [4,5]. Therefore, providing surgeons the tools to remove a greater proportion of tumor tissue without further damaging normal brain could help improve patient outcomes and thus progression free survival. Fluorophore-conjugated NPs and inherently fluorescent NPs such as silica coated or quantum dots have been studied to provide intra-operative visualization of tumor cells. The drawback to this strategy is that even if single cells invading normal brain can be visualized, it will be impossible to remove them without damaging the surrounding brain. This has given rise to the idea of a "roach motel" where

invading brain cancer cells are attracted back to the resection cavity, or out of the brain, for safer and more effective radical resection [6].

Only approximately half of GBM patients respond to the standard chemotherapy. Temozolomide (TMZ), a DNA alkylating agent, has provided the greatest survival benefit in the past 30 years, increasing median survival by approximately 4 months [7]. Temozolomide methylates DNA and because the position opposite of the O6-methylated guanine cannot find an adequate binding partner, long-lived nicks are induced in the DNA which ends up killing the cell. The resistant patient population was found to have, in part, increased activity of the DNA repair protein, MGMT, which removes methyl groups from guanine [8,9]. The MGMT inhibitor O6-benzylguanine failed clinical trials because of its poor biodistribution leading to myelotoxicity when combined with TMZ [10]. Improving site-specific delivery to the tumor by loading into NPs should greatly increase the number of patients that will respond to the chemotherapy [11]. Additionally, knockdown of MGMT through siRNA delivery should also have a significant impact on improving progression free survival, although siRNA delivery into the brain has proven to be a significant obstacle.

Lastly, radiotherapy has seen significant improvements through the development of the gamma knife and proton therapy, which both offer highly focus, stereotactic delivery of radiation. Nevertheless, brain cancer cells, especially those that have already received a cycle of radiotherapy, often become highly resistant. Radiotherapy kills cells through the formation of free radicals that induce DNA double strand breaks (DSBs). However, radiotherapy is very inefficient in generating these DSBs, as only 2 DSBs are formed per 106 base pairs per Gy gamma rays. Over 60% of the damage caused by the radiation is easily repaired by the base excision repair (BER) pathway (approximately 60 abasic lesions are formed per 106 base pairs per Gy gamma rays) [12]. If unrepaired, these abasic sites will evolve into cytotoxic DSBs. Therefore, inhibiting this BER pathway could lead to a 30-fold increase in effectiveness of radiotherapy. Ape1 is the sole repair activity enzyme involved in the removal of abasic sites in human cells and thus represents an ideal target for BER pathway inhibition. NP-mediated knockdown of Ape1 activity does significantly sensitize brain cancer cells to low doses of radiotherapy, and should greatly improve the effects of focused radiation when administered to brain tumor patients [13].

These examples, based on pioneering nanoparticle-based therapies, represent some of the strategies that will hopefully offer a better solution for patients. By improving upon current standard protocols that have to date offered less than satisfactory outcomes, patients in clinical trials should be allowed to receive IRB approved new nanoparticle treatments with the potential promise of improved quality of life and increased survival. It is disappointing that only a few nanoparticle solutions have so far yielded improved progression free survival in clinical trials despite the significant amount of time and money invested into NP development. As we reach this seemingly insurmountable plateau in nanomedicine research, we now need to redouble our efforts through translational studies with novel nanoparticle probes. This will require innovative solutions of new NP-based therapies that have been borne from intense “bench to bedside” collaboration with physicians to provide the best chance for the patients most in need of these therapies.

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