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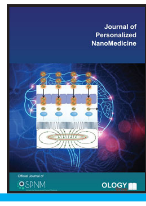

Expert Opinion

Cancer Nanomedicine: Present Clinical Scenario

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Cancer nanotechnology is a rapidly upcoming field that promise rationale approaches to counteract recurrence of the highly proliferative disorder. Among many organic and inorganic nanomaterials such as dendrimers, silica, carbon nanotube and graphene to name a few, biodegradable liposomes and polymeric nanoparticles have been explored as effective drug delivery vehicles due to their passive tumor-targeting ability, to improve hydrophobic drug therapeutic efficacy and reduce general side effects of chemotherapy. Liposomes are considered effective drug delivery systems evidenced by the success of few liposomal formulations such as Doxorubicin (Doxil®), Daunorubicin (DaunoXome®), Cytarabine (DepoCy®) and Vincristine (ONCO-TCS®). Many more liposomal formulations are presently in various stages of clinical trials [(1)]. Polymers, owing to their versatile chemistry, serve as the backbone for nanoformulations and facilitate in engineering a variety of hybrid nanomedicines. Recent development in this regard is a nanoparticle drug conjugate (NDC), CRLX-101®, consisting of an anti-cancer payload that is chemically conjugated to a polymer backbone with a linker. This is currently in Phase II clinical trial against Non-small cell lung cancer (NCT01380769), rectal cancer (NCT00333502) and renal cell carcinoma (NCT02010567). A variable of this polymeric nanomedicine platform, CRLX-301® has recently entered Phase-I/IIa dose escalation study against advanced solid tumors (NCT02380677).

An effective nanomedicine possess tumor-targeting ligands such as folic acid and anti-EGFR-2 (erbB2/Her2) antibody, not only to enhance their ability to be localized to the solid tumor mass, but also allows for targeting the nanoparticles to early stage tumors and metastatic cancer cells. Folic acid, being a well-known cancer targeting ligand, belongs to a new class of targeting moieties called small molecule ligands. These are low molecular weight organic molecules with average molecular weight of 0.5 Kda. They are extremely stable, relatively easy to handle and have low production cost [1-3]. These molecules can be coupled on any target using facile conjugating methods with uniform surface ligand densities on a desired nanoparticle. They have fewer immunogenic effects *in-vivo* and are reproducible, scalable, and economical to manufacture. Folic acid was one of the first small molecules to be used for molecular targeting as it has high affinity for folate receptors overexpressed in many types of tumor cells [4-6]. While folate receptor targeting is in various stages of clinical trials (Phase-I to Phase III) for delivery of therapeutic agents such as desacetyl vinblastine hydrazide (NCT01170650), mitomycin-C (NCT01577654), tubulysin (NCT01999738) and epothilone (NCT0055017), they are yet to be tested in humans for nanotechnology based interventions [7]. Alternatively, carbohydrate molecules such as glucose (Glufosfamide; NCT00441467), galactose, mannose are also explored as low molecular weight targeting agents. Small molecules from a series of urea-based Prostate Specific Antigen (PSA) inhibitors to target PSA receptors on prostate cancer cells with specific affinity as that of antibodies and aptamers have been reported [(8-10]. A small molecule classified under this series, the pseudomimetic dipeptide 2-([(5-amino-1-carboxypentyl) carbamoyl] amino) pentanedioic acid [8], has been used as a targeting ligand in the development of BIND-014®, the first receptor targeted polymeric nanomedicine developed by Prof Robert Langer's group [11]. As BIND-014® has already reached phase-II clinical trials for solid tumors such as prostate (NCT01812746) and small cell lung cancers (NCT01792479), these new class of targeting ligands can safely be used in humans. Along these lines, delivery of the nanotherapeutics can be enhanced by the functionality of nanoparticles with targeting moieties directed against any number of tumor-specific markers.

Apart from improvements in conventional chemotherapy, radical approaches have gained momentum in treatment of rapidly proliferating cancers such as glioblastoma multiforme. Magnetic nanoparticles including but not limited to iron oxide, are intensively studied in generating remotely triggered hyperthermia apart from being widely explored as magnetic resonance contrast agents. Recently, a german nanomedicine company, MagForceTM tested its product NanoTherm® containing iron oxide for its efficacy and risk factors towards intratumoral hyperthermia in conjugation with reduced radiation dose in a group of 66 patients with first hand and recurrent glioblastoma (German Clinical trial registration: DRKS00005476). The outcome was promising with no serious complications and since has been tested in other cancers of prostate, eosophagous and pancreas. Another module that has evolved tremendously within a decade is gold nanostructure mediated photothermal therapy. Different shapes and morphology such as rods, shells, cages, stars have been studied to take this potential nanomedical technology forward to clinics against many types of malignancies. Nanogold has the ability to absorb wavelengths in spectral region of visible to near infra-red (NIR) due to its suface plasmon resonance phenomenon. Absorption in the NIR region (650-900nm) has its advantage in biological applications as tissue and blood components are transparent to this window and allow photons to penetrate better than visible light. NIR absorbing colloidal gold nanostructures can absorb these photons and radiate intense heat, which can kill cancer cells instantaneously. This method has gained prime importance in recent years with the development of nanoshells on polymeric nanoparticles and carbon nanotubes to carry a chemotherapeutic payload and to enhance plasmonic properties respectively. Gold nanoshell over silica nanoparticles termed Aurolase®, developed by Nanospectra Biosciences Inc. (The company is based at Houston, Texas and was founded on intellectual property from Rice University and collaborative research with scientists at MD Anderson cancer centre) has completed Phase I pilot study against refractory and/or recurrent tumors of the head and neck (NCT00848042) and another study is on-going against primary and/or metastatic lung cancers for intratumoral laser ablation. This photothermal therapeutic intervention is explored as standalone treatment or in conjugation with radiation therapy. Radiation is one of the prime source of treatment for early stage cancers due to its non-invasiveness and has been found to be synergistic with chemotherapy. As oxygen is the prime source of reactive molecular species in cancer cells, hypoxic tumor microenvironment can render the malignant tissue less responsive to radiation therapy. Nanotechnology offers radiosenstization platform to improve the effect of this conventional module. While nanoparticles constituting gold are being studied for generation of hydroxyl and oxygen free radicals when bombarded with X-ray, newer nanomaterials have already reached clinical trials. NanobiotixTM has developed hafnium oxide based product NBTXR3® that showed promise in Phase-I and entered Phase-I/II (NCT02379845) in 2015 towards dose escalation and safety of the recommended dose for treatment of metastatic hepatocellular carcinoma.

Nanotechnology has the potential to offer radical solutions to alleviate the burden of critical malignant conditions to improve patients' quality of life. While there are a range of nanomaterials that has shown promise in preclinical studies, fewer have reached market or clinical trial due to limited resources & funding to scale up, improve their quality via Good Manufacturing Practice (GMP) assessments and go through the stringent procedure for approval as investigational new drug (IND) to be enrolled for Phase I pilot studies. Also a fair number of entrepreneurs need to start new ventures related to nanomedical technology across the globe so that intellectual properties stranded in various countries due to short comings in financial and human resource can see the day of light to serve the purpose they are invented/discovered for, i.e., to combat and succeed against one of the serious threat to human race, Cancer!

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