Size matters: nanoparticles in cancer therapy

Bhavya Khullar and Sarah Iqbal

The CEO of the corporate giant Apple, Steve Jobs, passed away at the early age of 56 due to a rare form of pancreatic cancer. He was a billionaire who could afford the best of treatment and care. Yet he lost his life to cancer[1]. This is not because there are not enough effective drugs to treat cancer or cancer cells are drug-resistant. It is because the methods of drug delivery are ineffective. Cancer treatment requires a different approach.

Even though 50 new anticancer drugs have been approved by the FDA in the past decade, cancer continues to claim lives. According to the most recent WHO report, cancer is among the leading causes of mortality in the world and is projected to affect 22 million people by 2032 (ref. 2). The picture is clear – we are struggling with cancer therapy.

The drugs employed in therapy, and even those that are on trial, can kill cancer cells in petri plates. However, the drugs seem less effective when administered to patients. The human body is designed to neutralize foreign and toxic substances which enter our body. So most drugs are transformed to less reactive forms and get rapidly cleared from the system. Moreover, many drugs can not penetrate the tumour and this undermines their effectiveness.

More importantly, anticancer drugs are non-specific. They cannot differentiate between normal and malignant cells and often end up damaging healthy tissues. This causes hair loss, organ dysfunction, and weakness, leading to low-quality life. These pitfalls can be avoided with the use of nanotechnology.

Nanotechnology allows scientists to engineer drug particles of the order of a few nanometres – smaller than a hair's width. It serves two purposes: increased penetration in tumours and delayed clearance of the drug from the system. Incidentally, nanoparticles can selectively deliver drugs by utilizing the inherent property of cancer cells – their enhanced permeability and retention. Cancer cells have leaky vasculature and enhanced retention. This allows nanoparticles to enter and accumulate within tumours with relative ease, when compared to normal cells. However, nanoparticles get diluted as the mode of delivery is through the bloodstream. To improve the concentration of the nanoparticles at the site of the cancer, scientists are looking at diverse ways to ensure that therapeutic nanoparticles specifically target malignant lesions.

Using a combination of new design and novel therapeutics, researchers are making significant progress. Last month, Indian scientists working on different aspects of nano-sized drug delivery systems made notable advances.

Scientists at the CSIR-National Chemical Laboratory, Pune, in collaboration with universities in Lucknow and Aligarh, synthesized terbium oxide (Tb_2O_3) nanoparticles by putting a naturally occurring fungus into action[3]. Commercially available Tb_4O_7 is reduced to Tb_2O_3 by incubating it with a suspension of *Fusarium oxysporum* in controlled conditions of pH and temperature. The aqueous crystals of Tb_2O_3, isolated from the fungal suspension, were stable and did not form aggregates or clumps. Hence, they could be isolated as crystals with long-term stability.

The non-toxicity and efficacy of these nanoparticles were validated in both human carcinoma cell lines and primary rat osteoblasts. The results indicate that they could bring some relief to patients of Osteosarcoma, the most common primary malignant bone tumour. Osteosarcoma causes significant morbidity and mortality in children and adolescents.

The study opens research avenues to test if we can make other inorganic nanoparticles in similar biogenic ways, while retaining their efficacy and inherent properties.

Synthesis of nanoparticles is not new. In fact, the first deliberately created nanoparticles were inorganic and came into existence in 1857 when Michael Faraday prepared gold colloidal particles. The oldest nanoparticles used for drug delivery came more than a hundred years later: simple lipid bilayer envelopes which could carry a drug in their lumen. When administered near the cancerous tissue they could kill tumour cells. Because liposomes have poor solubility, they were not effective in achieving desired drug concentrations at the site[4]. To combat this shortcoming, scientists have started using a plethora of techniques to entrap drug preparations.

The solubility of drug preparations can be improved by using biodegradable polymers for entrapment. This enhances both the solubility and the circulation time of drug nanoparticles. One such polymer is chitosan. Last month, a team of scientists from the Jadavpur University, West Bengal, in collaboration with the Vidyasagar University, West Bengal, and the GLA University, Uttar Pradesh, reported use of chitosan loaded nanoparticles for targeted drug delivery[5]. In their study, Karmakar and his team investigated the efficiency of a metal-organo-complex as cancer therapeutic.

Several metal nanoparticles have displayed enhanced toxicity in cancer cells but copper nanoparticles have not been explored adequately. Copper is known to upset the redox machinery within cells causing damage to DNA which increases its odds at killing cancer cells. Interestingly, the complex chosen by the scientists also bears structural resemblance to curcumin. The scientists encapsulated the copper complex within a chitosan-polystyrene matrix and utilized surface chemistry for adding specificity tags on the drug carriers. Cancer cells express a larger number of folate receptors. Some of them also express the human epidermal growth factor receptor or Her-2 receptors. In order to increase the specificity of drug carriers, the researchers linked either folic acid or a Her-2 specific peptide on the surface of these carriers. The preparation was then administered to breast cancer cells in vitro and to mice bearing breast cancer tumours. In both cases, the therapy was found to be very efficient in killing tumour cells. In mice, therapy could halve the tumour volume and increase mouse survival time. The advantage of this method is that it couples a novel design with a novel therapeutic for maximizing therapeutic benefits.

Scientists at the ISF College of Pharmacy, Punjab, used a similar approach to develop another drug delivery system for cancer. Narendra Kumar Jain and his

group constructed quantum dots of the order of 30 nm that are capable of entrapping drugs with 99% efficiency[6]. The design involves a zinc-manganese metal core that helps to tether the drug. A chitosan layer prevents rapid clearance of the drug from the core. The scientists coupled doxorubicin, an anticancer drug, to quantum dots. This conjugate was assessed for anticancer efficiency and distribution within the body.

Incidentally, Doxil, a liposome based nanoparticle containing doxorubicin, was the first nanoparticle therapeutic to be approved by the FDA in 1995. It was used to treat some types of cancers, including metastatic ovarian cancer and AIDS-related Kaposi's sarcoma. But due to its high toxicity and rapid degradation rates, its use as a chemotherapeutic has been limited. To overcome this problem, the scientists in Punjab coupled the drug bearing nanodots with folate. This makes the model more specific for tumour cells, which contain a larger number of folate receptors.

Due to their small size, the quantum dots were found to be internalized rapidly within the breast cancer cells in petri plates and cause cell death. Animal studies show similar results. In the beginning, there was a rapid clearance of the nanodots from the body which subsided after two hours. Quantum dots can be used to image the cells where they accumulate. These vehicles were quickly taken up by the liver followed by kidney, lungs and spleen from where the drug showed slow release.

There is another definite advantage to these nanodots: they display an enhanced drug unloading capacity in an acidic environment. Since tumours usually have an acidic pH, these drug-bearing nanodots promise a more robust tumour-specific action. These can thus be developed to serve as an important member of the anticancer drug armamentarium in the years to come. The design of the drug carrier is an important aspect of drug delivery. An ideal carrier should be inert and possess multiple sites for drug binding.

In a recent publication, N. K. Jain who is affiliated with the ISF College of Pharmacy, Punjab and the Rajiv Gandhi Technical University, Madhya Pradesh, elucidated a special class of drug delivery molecules – dendrimers[7]. Dendrimers are hollow spheres of long chain polymers bearing different functional groups on the surface. Their architecture allows drugs to either be entrapped within the empty space or be chemically linked to the surface. This prevents drug degradation and clearance.

Despite their complex structure, dendrimers are just about a few 100 nanometres in size, making them permeable to cells. Presently, some researchers are trying to make full use of the dendrimer's architecture to code recognition of tumour cells. Others are also looking at ways to engineer chemical switches that would help the dendrimers unload drugs at specific destinations. The fact that they are biodegradable makes them a promising candidate for drug delivery.

Cancer is different from many other diseases. Not only does it deteriorate the body, it also levies a hefty cost on relationships, emotional well-being, time and money. Lab visits, tests, procedures, radiation, chemotherapy, surgery, hospitalization and even palliative care are a burden to the pocket. Unfortunately, even after all that investment, the results are dismal.

According to a recent report in WHO, cancer causes the death of about 7% Indians each year. To a large extent, this results from poor therapeutic options. The fact that we have multiple options to treat cancer in petri plates has put a lot of onus on nanotechnology to define the success of therapeutic regimes.

1. Harmon, K., The puzzle of pancreatic cancer: how Steve jobs did not beat the odds – but Nobel Winner Ralph Steinman did, 2011; https://www.scientificamerican.com/article/pancreatic-cancer-type-jobs/ (retrieved on 3 November 2016).
2. World Health Organisation, Cancer, 2015; http://www.who.int/mediacentre/factsheets/fs297/en/ (retrieved on 3 November 2016).
3. Eram, S. *et al.*, *Spectrochim. Acta Part A*, 2016, **168**, 123–131.
4. Nguyen, K. T., *J. Nanomedic Nanotechnol.*, 2011, **2**(5), 1000103e.
5. Pramanik, A. *et al.*, *Mater. Sci. Eng. C*, 2016; **68**, 327–337
6. Bajwa, N. *et al.*, *Artif. Cells Nanomed Biotechnol*., 2016, **44**(7), 1774–1782.
7. Singh, J. *et al.*, *Artif. Cells Nanomed Biotechnol*., 2016, **44**(7), 1626–1634.

Bhavya Khullar is in the Pediatric Biology Center, Translational Health Science and Technology Institute, NCR Biotech Cluster, Faridabad 121 001, India; Sarah Iqbal is in the Department of Biochemistry, Faculty of Life Sciences, Aligarh Muslim University, Aligarh 202 002, India.
scienceandmediaworkshops@gmail.com