Title:	Development of Nanotherapeutic platforms for the treatment and management of solid cancer
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Abstract: The present thesis is focussed on the development of novel therapeutic nanoplatforms to treat highly malignant solid tumours and unhealed wounds which used to develop post-surgical resection of the tumours. The nanoplatforms were developed to address multiple challenges in cancer therapeutics like low bioavailability of the highly efficient and poorly water-soluble drugs, high dose requirement of chemotherapeutic drugs and associated systemic toxicities along with providing solutions to the unhealed chronic wounds, failed to heal post resection of tumors. Protein-based nanocarrier systems were developed using albumin proteins viz; Bovine serum albumin, Human serum albumin and lactalbumin to load poorly water-soluble drugs curcumin, fenretinide (4-HPR) and Genistein respectively. In addition to the protein nanoparticles, a novel nanocrystal-based platform of Paclitaxel is prepared with nearly 100 per cent drug loading efficiency. The prepared formulation is termed as paclitaxel nanocrystalline assemblies (PNAS) which are true to type, highly fluorescent and Cremophor EL free formulation of Paclitaxel. Hydrogel based injectable nanoplatform was developed using natural polysaccharide □-Carrageenan and a pigmented protein C-phycocyanin to accelerate wound healing and provide real-time monitoring of the wound recovery through in vivo fluorescence imaging. The therapeutic potential of nanoformulations was evaluated in the in-vitro and in-vivo models of various malignant solid tumours including, Glioblastoma multiforme, paediatric Neuroblastoma, Oral squamous cell carcinoma and Hepatocellular carcinoma. The wound healing potential of the injectable hydrogel was evaluated in the in-vivo wound healing mice models. All the platforms were designed to address the challenge faced by the clinicians during the treatment of the disease. Nanocurcumin platform, in combination with the blue light phototherapy, is designed to restrict the growth of glioma stem cells (GSCs), the main culprit in the tumour recurrence. The GSCs proliferate during the time lag between tumour resection and the onset of chemotherapy and radiotherapy. Therefore, the current platform is best suited to target this phase of the treatment and prevent cancer recurrence. The nanocurcumin platform has shown immense potential in restricting the growth of GSCs in a combination of the blue light phototherapy at a very minimal dose which is non-toxic to the healthy cells. Following bovine serum albumin-based nanocurcumin platforms, another platform using Lactalbumin and Genistein (GLNPs) was designed to address the oral squamous cell carcinoma (OSCC) and its epigenetic regulation. Lactalbumin (whey protein) and Genistein (a flavonoid present in the soybean) are highly consumed by the people in their daily nutritional requirement. The idea was conceived to target OSCC through nutraceutical molecules. The developed nanoformulation was highly biocompatible and potent in restricting the growth of OSCC along with reversing the histone modifications caused by PRC-1 and PRC-2 complex proteins. GLNPs work through the reestablishment of the epigenetic modification (downregulating the expression of epigenetic gene silencer H3K27me3, UbH2AK119 along with EZH2 and Bmi-1) and the onset of critical apoptotic machinery (increased Bax: Bcl-2, caspase-3 activation) to halt the progress of OSCC. Following the successful results of BSA and lactalbumin based nanoformulations in Glioblastoma multiforme and OSCC, another essential albumin protein, Human serum albumin (HSA) was used to develop 4HPR loaded HSA nanoparticles (4HPRNPs) to target neuroblastoma. All these albumin protein nanoparticles have immense potential to be used to treat any form of solid cancer including Brain tumor, breast cancer, liver cancer, pancreatic cancer etc. The synthesized HSA nanoparticles were modified using acetylsalicylic acid to incorporate acetyl moieties on the surface. Thus, 4HPRNPs and acetyl modified particles (4HPRANPs) were targeted to the highly malignant paediatric neuroblastoma. The concept of acetyl modification was put forward to address the acetyl and methyl modifications of histones. These modifications work as the epigenetic regulators which are possibly responsible for the metastasis in neuroblastoma. The developed 4HPRANPs nanoformulation successfully restricted the growth and lymph node metastasis in the in-vivo xenograft model of neuroblastoma in nude mice. The acetyl modification found to be a contributing factor in downregulating the epigenetic gene repressor H3K27me3, along with significantly improving the acetylation at histone 3. After the successful results of protein-based nanoparticles, a nanocarrier free formulation of Paclitaxel was developed. This nanocarrier free formulation of Paclitaxel (PNAS) was designed for the TACE application in the HCC. It provides the advantage of increased payload and higher retention of a chemotherapeutic drug inside the tumour site for a prolonged period. The molecule showed unique morphology with sustained drug release behaviour along with multichannel fluorescence properties. The therapeutic efficacy of the molecules is successfully verified at a clinically significant dose of Paclitaxel through a significant reduction in the volume of the 3D spheroid model of hepatocellular carcinoma (HCC). In addition to the chemotherapy-based treatment, the surgical removal of tumours leaves behind the unhealed wound. These unhealed wounds always remain a healthcare challenge in the cancer patients. The further onset of chemotherapy and radiotherapy post-resection makes these wounds chronic and nearly impossible to heal. This wound healing complication was addressed by an injectable hydrogel system based on ionic crosslinking of □-carrageenan monomers along with C-phycocyanin. The synthesized hydrogel was nanoporous with hydrophilic surface and good mechanical stiffness. Hydrogel material provided haemostasis, reduced inflammation, along with the proliferation of dermal fibroblasts in in vitro and in vivo conditions. The hydrogel successfully demonstrated the potential for accelerating tissue repair and real-time monitoring of the wounds in the mice model system. All the developed nanotherapeutic platforms have shown tremendous potential in addressing the different challenges in cancer therapeutics and post-treatment management of solid cancers.

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