TARGETED HYBRID NANOPARTICLES FOR DRUG DELIVERY TO BRAIN

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The central nervous system (CNS) poses a unique challenge for drug delivery. The existence of blood–brain barrier (BBB) hampers the effective treatment of CNS diseases. Almost all macromolecular drugs and more than 98% of small molecule drugs including neurological drugs, anti-cancer agents, antibiotics, etc. cannot pass the BBB. The BBB is a brain-specific, selective barrier that regulates the transport of substances between the circulation and the brain. The barrier properties of healthy BBB are mainly due to the presence of tight junctions between the endothelial cells, which are steadily maintained by astrocytes and pericytes. Further anatomical features, such as abundant presence of multidrug resistance proteins, e.g., P-glycoprotein (P-gp) and multidrug resistance proteins (MDRPs), can prevent drug accumulation inside the brain; as a result, the administered drugs remain unsuccessful or cannot achieve the wanted physiological effect. Thus, BBB being the bottleneck in the medication of CNS diseases is primary focus in the development of novel CNS drug delivery techniques. Nanotechnology offers the possibility to deliver small molecules/drugs against CNS disorders across BBB.

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Kamalinder leads the Nanomedicine and Innovative technologies research group at UCLan within the faculty of Clinical and Biomedical Sciences at University of Central Lancashire. With more than 30 years experience in academia, her research interests are in the field of advanced drug delivery and drug targeting with focus on formulation design and development, and evaluation of different biocompatible nanoparticle-based platform technologies including protein, lipid and hybrid nanoparticles and exploiting them to deliver drugs across various biological barriers.

The incidence of neurodegenerative diseases and aggressive brain cancers is continually growing. Glioblastoma multiforme (GBM) is one of the most aggressive and deadliest CNS tumours and is classified as grade IV malignant tumour. Standard treatment for GBM consists of surgical resection, radiotherapy and temozolomide as adjuvant and concomitant chemotherapy. The only approved chemotherapeutic agents for GBM treatment are temozolomide (oral and I.V), carmustine (I.V and implants), lomustine (oral). Even after massive progress in the therapeutic field, the survival rate is notably low (15-18 months) making GBM treatment a big challenge. Though GBM patients show variable/partial and heterogeneous BBB disruption but have regions with intact BBB, which is sufficient to limit drug access to tumour cells. Additionally, BBB disruption does not necessarily imply loss of other biological mechanisms such as efflux transport system which hamper drug delivery across BBB.

We have developed safe and biocompatible hybrid nanoparticle-based platform technology for delivering CNS negative drugs across the BBB using commercially available and scalable processes. These nanoparticles have been suitably appended with VEGF targeted ligand for targeting to GBM. The presentation will discuss the Quality by design development of these novel biomimetic protein-lipid hybrid nanoparticles. A critical and important requirement for nanoparticulate brain delivery systems is that they are rapidly biodegradable, i.e. over a time frame of a few days. Hybrid nanoparticles being fabricated from endogenous materials are free from challenges of toxicity and immunogenicity which polymer based nanodrugs face due to their accumulation in brain. Nanoparticle formulation has been optimized for product and process parameters using rotatable central composite design to assure that the critical quality parameters, particle size, polydispersity index, entrapment efficiency and total drug are within the specified limits and meet the quality target product profile.

Hybrid nanoparticles showed more than seven times higher permeability than the free cytotoxic drug when tested using a 3D *in-vitro* BBB model with no active efflux of nanoparticles. The nanoparticles showed preferential targeting followed by concentration and time dependent uptake by U87MG GBM cells with improved efficacy. These nanoparticles hold promise in future GBM treatment and the platform technology opens translational avenues for the challenging task of drug delivery in CNS therapeutics ■