Nanogels for anticancer drug delivery

The applications of Nanogels in the field of medicine are currently under rapid growth of interest with more focus given on improving current therapies and diagnostic modalities. Nanogels composed of ionic or non-ionic network of amphiphilic polymer chains, when dispersed in aqueous media swell to considerable volume. Biological agents and drugs can be loaded into the nanogel by physical and chemical interactions between the agent and the functional group in the polymer matrix, resulting in unique class of polymeric nanocarrier with high dispersion stability. The most attractive features of the nanogels include high biocompatibility, versatility in design, and controlled release of payload with wide range of drug loading and release, the specificity and ability to physically protect biological molecules from degradation invivo and have been preclinically investigated for different anticancer drugs.

In a study on targeted nanogels done by Baklaushev et al, the therapeutic efficacy of cisplatin loaded nanogels was checked on glioma cells 101/8. Nanogels synthesised using PMAA polymer cross-linked with $CaCl_2$. Nanogels upon EDC activation cross-linked to monoclonal antibodies Cx43 and BSAT1 specific for targeting gliomal cells along with flexible PEG linker resulting in a size of 123 ± 5 nm, with a zeta potential of -15±5 mV. Targeted nanogels significantly reduced the intrastriatal glioma compared to the control group receiving 5% dextrose up to the 30th day of the study. But no significance was observed for animals treated with targeted nanogels and free cisplatin. Heparin-polyethyleneimine (HPEI)nanogels loaded with cisplatin along with shRNA were synthesised by Lili Liu et al for targeting CLDN3 gene up regulated in ovarian cancer. These nanogels showed

superior biodegradability, excellent blood compatibility and low-toxicity. Western blot analysis and CLDN3 immunostaining were done to check the knockdown efficiency. Nude mice bearing intraperitoneal ovarian carcinomas were treated with drug loaded nanogels and the results showed that pshCLDN3/HPEI effectively suppressed the expression of CLDN3 in ovarian cancer along with synergistic antitumor activity when compared to cisplatin alone, along with low systemic toxicity. Nukolova NV et al loaded cisplatin into PEG-b-PMAA nanogels conjugated with (D-Lys6)-LHRH. With a loading efficiency of 35%, the nanogel showed receptor based cytotoxicity cells positive for LHRH showed greater uptake and cytotoxicity compared to LHRH negative ovarian cancer cells. Invivo antitumor activity was more for LHRH-nanogels with less toxicity compared to equimolar dose of free cisplatin and untargeted nanogels. A pH and thermal responsive nanogelwas developed for cisplatin delivery by conjugating the MAA, NIPAm, mPEGMA with MBA as the cross-linker. The pH response is achieved with breaking the bond between COOH and cisplatin in presence of the chlorine ion present in the human body. The acidic response is modified by incorporating thermal responsive NIPAm, this will slow down the cisplatin release from the nanogel structure. Cellular uptake was mainly localized in cytoplasm. Invivo antitumor activity using breast cancer mice modals showed better activity with longer circulation time. In the study by Jin et al, controlled delivery of cisplatin to ovarian cancer cells SKOV-3 were achieved using a biodegradable nanogel made by cocondensation polymerization of piperazine with 2, 2-bis(acryloxymethyl)propionic acid, PEG 2, 2-bis(acryloxymethyl)propionate macromonomer (mPEG). Carboxylic acid-functionalized poly(beta -aminoester)graft-poly(ethylene glycol) nanogels

were size of around 200nm, negatively charged with water soluble nature. The cytotoxicity of nanogels on SKOV-3 cells were significantly lower than the free cisplatin whereas the invivo activity towards SKOV3 tumor xenografted immunecompromised mice was same. According to Jin et al, this decrease in cytotoxicity of cisplatin loaded nanogel on SKOV-3 cells due to the drug release kinetics which showed an initial burst release, making the response of cisplatin similar to that of free cisplatin. Also negatively charged nanogel will limit the cellular internalization delaying the cisplatin response. Only with biodistribution studies the similarity in the activity of free cisplatin and nanogel loaded cisplatin be proved. Maeda et al synthesised water soluble β-1, 3-glucan schizophyllan (SPG) nanogel which can be recognized by an immunocyte receptor called dectin-1. When naphthalene introduced into the side chain of SPG (nSPG), it formed nanogel by physical cross-link and gained capability to ingest hydrophobic compounds such as doxorubicin.

The in vitro assay revealed that this nanogel can be used as specific delivery of anti-cancer drugs to immunocytes. A dual-responsive prodrug nanogel system that shows very low unspecific drug leaching, but efficient intracellular release of the payload triggered by the intracellular conditions. This dual-responsive prodrug nanogel was prepared by an inverse nanoprecipitation method, which is mild and surfactant free, and based on a thiol-disulfide exchange reaction and thiol-Michael addition reaction. Highly biocompatible hyperbranched polyglycerol (hPG) was cross-linked with disulfide bonds, to obtain biodegradable nanogels, which could be degraded under intracellular reductive conditions. Doxorubicin (DOX) was conjugated to the biodegradable nanogel matrix via an acid-labile hydrazone linker. Two

different prodrug nanogels were prepared with a size of approximately 150nm, which is big enough to take the advantage of the enhanced permeation and retention (EPR) effect in tumor tissue. Cell culture analysis by microscopy and flow cytometry revealed that the prodrug nanogels were efficiently internalized by tumor cells. Distinct release profiles of DOX were achieved by adjusting the nanogel architecture, and online detection of cytotoxicity showed that, unlike free DOX, the dual-responsive prodrug nanogels exhibited a delay in the onset of toxicity, indicating the different uptake mechanism and the need for prodrug activation to induce cell death. To achieve effective intracellular anticancer drug delivery, the polymeric vesicles supplemented with the pH-responsive outlayered gels as a delivery system of doxorubicin (DOX) were developed from self-assembly of the lipid/polypeptide adduct, distearin grafted poly(γ-glutamic acid) (poly(γ-GA)), followed by sequential deposition of chitosan and poly(γ-GA-co-γ-glutamyl oxysuccinimide)-g-monomethoxy poly(ethylene glycol) in combination with in situ covalent cross-linking on assembly surfaces. The resultant gel-caged polymeric vesicles (GCPVs) showed superior performance in regulating drug release in response to the external pH change. Under typical physiological conditions (pH 7. 4 and 37 °C) at which the γ-GA/DOX ionic pairings remained mostly undisturbed, the dense outlayered gels of GCPVs significantly reduced the premature leakage of the uncomplexed payload. With the environmental pH being reduced from pH 7. 4 to 4. 7, the drug liberation was appreciably promoted by the massive disruption of the ionic γ-GA/DOX complexes along with the significant swelling of nanogel layers upon the increased protonation of chitosan chain segments. After being internalized by HeLa cells via endocytosis, GCPVs exhibited cytotoxic effect

comparable to free DOX achieved by rapidly releasing the payload in intracellular acidic endosomes and lysosomes. This strongly implies the great promise of such unique GCPVs as an intracellular drug delivery carrier for potential anticancer treatment. The triple layered nanogel developed by Xiong MH et al, can deliver the drug doxorubicin specifically in the bacteria accumulated tumor environment. The bacteria SBY1 can selectively infect and proliferate in tumors owing to the unique environment within solid tumors, including hypoxia, aberrant neovasculature, and local immune suppression is more in tumor compared to the normal tissue; upon nanogel administration these bacteria will trigger the selective degradation of the PCL fence of TLND resulting in DOX release and thus killing tumor cells. Chitin PLA composite nanogel were loaded with Doxorubicin (Dox) for the treatment of liver cancer. Nanogels were of size of around 270±20 nm with higher swelling and degradation in acidic pH. Drug entrapment efficiency and in vitro drug release studies were carried out and showed a higher drug release at acidic pH compared to neutral pH. The cytotoxicity of the composite nanogels was analysed toward HepG2 (human liver cancer) cell lines.