Preface

Lung cancer (LC) is a fatal disease with significantly higher death rates with a median survival time of less than one year. The main limitation and harmful effects of traditional anticancer medications result from their ability to accumulate widely in healthy tissues with reduced levels being present in cancerous tissues. Currently, the majority of drug delivery techniques administer the active drug by utilising a phenomenon known as enhanced permeability and retention (EPR), although various active targeting moieties have been used in order to target particular cancerous tissues. Still, these attempts resulted in minimal therapeutic outcomes, suggesting that there is crucial need for developing a novel formulation or therapeutic method for more effective lung cancer treatment. Particularly, gemcitabine (GMC) produces its cytotoxic activity upon internalization into the cell cytoplasm and there it is subject to phosphorylation (active form) to interfere with DNA synthesis and trigger the death of cells. However, the major barrier associated with the anticancer efficacy of GMC arises from the efficient delivery of the drug into cancerous cells. In the current research project, our objective was to develop a novel therapeutic delivery approach with the potential to enhance the therapeutic effectiveness of anticancer drug.

In this context, the nanocarrier based targeted therapeutic approach has the potential for effective delivery of drugs in cancerous regions. Targeted delivery of these therapeutic agents precisely to the definite cancerous positions is a challenge to cancer therapy. One of the promising techniques for effective and highly specific delivery of drugs into cells require the use of a variety of targeting moieties or ligands that attach directly to the surface of cells. So, along with monotarget functionalized NPs, dual targeted nano-therapeutic carriers were developed for delivering chemotherapeutic drug selectively and specifically to lung cancer cells.

This strategy has been widely used in cancers where specific receptors are over-expressed. Lung cancer cells most frequently overexpress the multiple receptors on their surface, including epidermal growth factor receptors (EGFR), glycan receptors and others. Targeting ligands grafted onto biopolymeric carriers such as chitosan have been used to improve the specificity for multiple

nanocarriers loaded with therapeutic drugs for cancerous cells (target cells) while protecting normal cells (off-target cells). Towards this perspective, Neu5Ac and Cxmab were coupled with the GMC-loaded CSN-NPs that attached to glycan and EGFR receptors overexpressed in lung cancerous A-549 cells and B[a]P induced lung cancer in Swiss albino mice.

The objectives of this investigation were to optimize, develop and evaluate the physiochemical properties of mono targeted (glycan receptor) and dual targeted (EGFR and glycan receptor) functionalized GMC-CSN-NPs. The chimeric monoclonal antibody (mAb) Cxmab and Neu5Ac conjugated polymeric nanoparticulate formulations containing GMC were prepared by ionic gelation method and optimized by design of experiments (DoE) using Box Behnken Design (BBD). The prepared nanoformulations were characterized for various physicochemical parameters including entrapment efficiency, hydrodynamic particle size diameter, surface charge, morphology assessment, XRD, DSC, FTIR, XPS analysis and release profile at cancerous site with pH 5.5 and physiological pH 7.4. *In vitro* cellular uptake, cytotoxicity studies, wound healing assay, apoptosis assay by Annexin-V/PI staining was assessed on A-549 lung cancer cells. Further *in vivo* histopathology, bio distribution profile, bio-imaging for glycan receptor targeted and *in vivo* anticancer efficacy for both glycan and EGFR-glycan receptor targeted GMC loaded chitosan nanoparticles was evaluated and reported. The studies showed selective and specific delivery of GMC at cancerous site, indicating towards its therapeutic potential for lung cancer therapeutics.