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Gemcitabine encapsulated albumin nanoparticles against human pancreatic cancer cells

Venkata K. Pulipati[1] and **Dai Lu**[2]
[1]Irma Lerma Rangel, USA
[2]Texas A&M University, USA

Pancreatic cancer is a malignant tumor with poor prognosis. Overall survival rate of patients with pancreatic cancer is less than 6%. Gemcitabine (GEMZAR®), 2'-deoxy-2',2'-difluorocytidine, is a broad spectrum oncolytic compound with antitumor activity in many solid tumors. It has been approved by the FDA as the first-line treatment for patients with locally advanced (stage II or stage III) or metastatic (stage IV) adenocarcinoma of the pancreas. For treatment of pancreatic cancer, gemzar is typically administered by intravenous infusion at a dose of 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks. The tumor response rates of gemicitabine are approximately 10%. Depending on age and gender, gemcitabine half-life for short infusions (<70 min) ranged from 42 to 94 minutes, and the half-life for long infusions (70 to 285 min) varied from 245 to 638 minutes. Gemcitabine is mainly cleaned through urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2´-deoxy-2´,2´-difluorouridine (dFdU), accounted for 99% of the excreted dose. These indicated some metabolic liability of gemcitabine. Additionally, a number of cancers including pancreatic cancer show initial sensitivity to gemcitabine therapy followed by the rapid development of resistance. The drug resistances maybe partially arise from the loss of transporters responsible for the cellular uptake of gemcitabine. Kinetic studies have shown that gemcitabine intracellular uptake is preferentially mediated by hENT1 and, to a lesser extent, by hCNT1 and hCNT3. To increase its therapeutic levels, gemcitabine is generally administered at high doses (1000 mg/m^2) that often cause side effects (neutropenia etc). To improve its metabolic stability and cytotoxic activity, we developed albumin nanoparticles encapsulated with gemcitabine to enhance the therapeutic effects of gemcitabine.

Albumin nanoparticles can target tumor cells through passive and active tumor targeting processes. The passive process is mediated by EPR (enhanced permeability and retention) effect whereas the active targeting process of albumin is most likely mediated through glycoprotein-60 (gp-60) mediated transcytosis. Therefore, the uptake of gemcitabine encapsulated albumin nanoparticles can be facilitated by gp-60 mediated transcytosis, and accumulated in tumor by interacting with SPARC (secreted protein, acidic and rich in cysteine) and released its carried drugs in cancer cells. The drug-loaded albumin nanoparticles were fabricated through an innovative desolvation process that does not involve any cross linking agents or process. The nanoparticles were evaluated against human pancreatic cancer cells BXPC-3 and MiaPaCa cells, as well as gemcitabine-resistant MiaPaCa cells. The nanomedicinal particles are stable for months.