INCAPSULATED NO-GEMCITABINE: GASEOUS SOLUTION FOR MDR PANCREATIC CANCER

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Since the late 1990's, gemcitabine (GEM) has been available as the standard of care regimen for advanced pancreatic ductal adenocarcinoma (PDAC). However, the resistance to chemotherapy treatment is the main issue against a successful anti-cancer therapy.[1] Nitric oxide (NO) is a small free radical molecule involved in many physiologic and pathologic pathways in human cells. It plays also a key role in tumor biology and at micromolar concentrations it displays antitumor effects.[2,3] In our previous study we have successfully used a multitarget approach, combining antitumor drug doxorubicin with NO donor moieties, overcoming MDR in the colon and breast cancer cells.[4,5]
In this study, we synthesized a small library of seven NO-releasing gemcitabine conjugates (NO-GEMs) in order to improve the effectiveness of GEM in PDAC cell lines (**Figure 1**). Among the new NO-GEM multitarget compound GCB2 was identified as the most effective compound in inhibiting cancer cell growth. To improve its uptake and minimize side effects we encapsulated it in liposomes (LIPO-GCB2), increasing its antiproliferative and apoptotic effect, especially in GEM-resistant Panc1 cells, as compared to standard GEM. We observed that GCB2 and LIPO-GCB2 were able to nitrate tyrosine residues of the multidrug resistant protein MRP5, which is involved in the extrusion of GEM, favoring the intracellular accumulation of GEM and triggering apoptotic cell death in GEM-resistant PDAC cells. Our results support the development of a new antitumor strategy against GEM-resistant PDAC cells based on the usage of NO-releasing GEM encapsulated in liposomes.

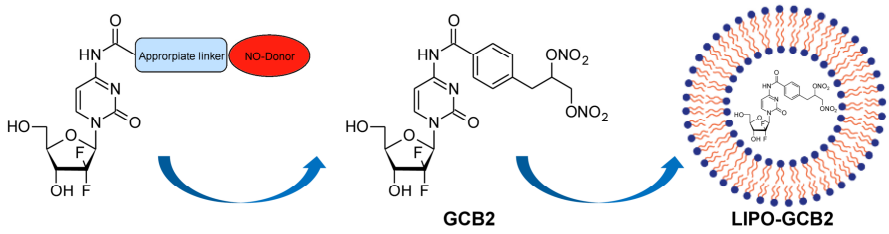

Figure 1. NO-GEM, GCB2 and LIPO-GCB2.

References

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