Nanotherapy targeting RHAMM^{B}-positive pancreatic neuroendocrine tumors

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Pancreatic neuroendocrine tumors (PNETs) represent one-third of gastroenteropancreatic neuroendocrine tumors and are the second malignancy of the pancreas. The 5-year survival rate of metastatic PNETs is only about 15%. Sadly, most patients will die of metastatic disease. Novel therapies are urgently needed. We have recently demonstrated that receptor for hyaluronic acid-mediated motility isoform B (RHAMM^{B}) is upregulated in PNETs and promotes metastasis of PNETs. We have also reported that Bcl-xL accelerates the formation of PNETs with invasive properties. We designed a RHAMM-targeted Combination Therapy (RCT) as a novel therapeutic for PNETs. Using a unique fabrication technology, a stepwise layer-by-layer (LbL) process, several active ingredients, including siRNA against pro-invasive/pro-survival Bcl-xL, mitochondria-fusing peptides, and RHAMM targeting ligand, were assembled into a nanoparticle for effective co-delivery and integrated efficacy.

We found that RCT was efficiently internalized by RHAMM^{B}-positive PNET cells, but not by RHAMM^{B}-negative control tumor cells. The encapsulated Bcl-xL siRNA and the mitochondria-fusing peptide were released inside RHAMM^{B}-positive PNET cells to induce apoptosis by silencing Bcl-xL and disrupting mitochondrial membrane. A synergistic cell killing effect was achieved in cell culture study (> 83% cell death). In a preclinical mouse model, the systemically-injected RCT significantly reduced tumor burden (> 65% reduction) and sustained the blood glucose levels of mice bearing RHAMM^{B}-positive insulinomas.

In summary, RCT loaded with Bcl-xL siRNA and the mitochondria-fusing peptide could be a promising drug to treat RHAMM^{B}-positive PNETs. Because RHAMM^{B} is upregulated in many different cancer types and RHAMM protein expression is restricted in normal adult tissues, we anticipate a board application of RCT which carries multiple functional therapeutics for treating cancers that overexpress RHAMM^{B}.