Development of a Cathepsin B-Responsive Hydrogel for the Targeted Delivery of Cancer Immunotherapy

Kaleekal, Noah (School: Irvington High School)

Adoptive Cell Therapy (ACT) is a promising form of Immunotherapy, wherein T-Lymphocytes are propagated in the laboratory and re-infused into patients. However, a major limitation to ACT is Cytokine Release Syndrome, a life-threatening autoimmune disorder. Proposed strategies include the targeted delivery and controlled release of ACT to tumors. Hydrogels are biomaterials with suitable conditions for cell viability. Cathepsin B is a protease overexpressed on cancer cells, and is selectively capable of cleaving the dipeptide Valine-Citrulline (VCit). To overcome the current limitations of ACT, I developed a hydrogel incorporating the VCit peptide, to selectively degrade from a Cathepsin B stimulus, for targeted delivery and controlled release of ACT. VCit was synthesized using Fmoc-SPPS, purified using Prep-HPLC, and confirmed by Mass Spectroscopy. The peptide was conjugated to the polymer Polyethylene Glycol Diacrylate via Michael-type addition, which was confirmed by NMR. Following gelation under UVA light, the hydrogel was incubated in a Cathepsin B solution to assess degradation over 24 hours. After 0.5 hours, the hydrogel displayed, on average, a 41.4% reduction in weight, significantly higher than controls, and minimal weight was lost in the remaining period. These results indicate the hydrogel's rapid and controlled degradation in correlation with Cathepsin B levels. Furthermore, the hydrogel was able to release a 5-fold greater number of T-cells in Cathepsin B solutions than water. These results suggest clinical utility of this hydrogel for controlled and direct delivery of ACT to overcome existing side effects. Future research will further quantify and optimize the hydrogel performance through in-vivo studies.