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Peptide-targeted immunotherapeutic nanoparticles for intravesical treatment of bladder cancer

Bladder carcinoma is the most expensive tumor type to treat on a cost per patient basis from diagnosis to death[1]. Intravesical Bacillus Calmette Guerin (BCG) instillation is the only approved immunotherapy for treatment of superficial bladder carcinoma. Unfortunately, frequent relapses, high local morbidity and the risk of systemic mycobacterial infection are significant limitations of this therapeutic approach[2]. BCG utilizes an adhesin protein known as fibronectin attachment protein that contains a critical peptide sequence for binding to bladder tumor cells. Previously, we have shown that multivalent peptide targeted liposomes promote fibronectin-integrin microaggregation and internalization via a caveolae dependent mechanism with a strict ≤70 nm size cutoff[3]. Microfluidics offers the potential of formulating scale size controlled nanoparticles in a reproducible manner. Using a chemtrix flow reactor system, we have developed pH sensitive CpG lipid nanoparticles[4] and organic solvent purified elastin like peptide complexes[5] for targeted delivery of these oligonucleotides to activate cells expressing toll like receptor 9 (TLR)9 to mount an innate immune response characterized by the production of Th1 and proinflammatory cytokines[6]. Since (TLR)9 receptors are located within intracellular acidic compartments, such as endosomes and lysosomes, these vehicles have been designed to release their CpG cargo after internalization. Data showing that these peptide targeted nanoparticles specifically bind to and are internalized by bladder tumor cells will be presented. Confocal studies have also been performed to track the cellular fate of these targeted carrier systems. Our findings show that only the pH-sensitive formulations are capable of releasing their payload after 12 h and stimulating a cytokine response. Collectively, our findings suggest that these peptide targeted immunostimulatory complexes may be at low-risk, highly efficient alternative to BCG immunotherapy.

Recent Publications

1. VerHeul R, Sweet C and Thompson D H (2018) Rapid and simple purification of elastin-like polypeptides directly from whole cells and cell lysates by organic solvent extraction. Biomaterials Science 6:863-876.
2. Decaestecker K and Oosterlinck W (2015) Managing the adverse events of intravesical bacillus Calmette–Guérin therapy. Research and Reports in Urology 7:157-63.
3. Coon B G, Crist S, González-Bonet A M, Kim H K, Sowa J, Thompson D H, Ratliff T L and Aguilar R C (2012) Fibronectin attachment protein (FAP) from Bacillus Calmette-Guerin as a targeting agent for bladder tumor cells. International Journal of Cancer 131: 591-600.
4. Bode C, Zhao G, Steinhagen F, Kinjo T and Klinman D M (2011) CpG DNA as a vaccine adjuvant. Expert Rev. Vaccines 10:499-511.
5. Mariotto A B, Yabroff K R, Shao Y, Feuer E J and Brown M L (2011) Projections of the Cost of Cancer Care in the United States: 2010–2020. J. Nat'l. Cancer Inst. 103(2):117-128.

Biography

David H Thompson received Bachelor Degree in Chemistry and Biology from the University of Missouri and a PhD Degree in Organic Chemistry from Colorado State University. After Postdoctoral studies at the Oregon Health and Sciences University, he joined the department of Chemical & Biological Sciences at the same institution as an Assistant Professor during 1987-1994 before moving to Purdue University where, he is currently a Professor of Chemistry and Head of the Medicinal Chemistry Group, Purdue Center for Cancer Research. He has published over 145 papers, many focused on the area of bioresponsive material development for drug delivery.

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