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Structural approaches for targeted therapy

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Tumor associated carbohydrate antigens (TACAs) are a class of glycans with important structural and signaling functions playing a major role in cell proliferation, differentiation and apoptosis relevant to oncology. Tumor cells expressing TACAs influence prognosis and survival of cancer patients. We have used structure-based approaches to study antigen-antibody interactions in the tumor micro-environment and designed a peptidyl ligand that mimics the molecular topology of TACAs even though they are chemically dissimilar but functionally equivalent molecular structures. The work on antibody-TACA interactions suggests that in designing antibodies, careful consideration should be made in using mutations that enhance the rigidity of an antibody. Our work also suggests that electrostatics play a major role in the recognition of the model antigen examined. Discrimination against wanted targets through repulsive electrostatic interactions might be more fruitful than a strong optimization of target binding. Increased specificity toward one target leads to decreased affinity toward others. Models for TACA targeting reagents are typified by TACA reactive monoclonal antibodies, lectins and perhaps oncolytic viruses that target sialylated receptors. Peptides reactive with TACA may, in particular, be interesting carbohydrate binding agents, forming the basis of novel drugs that combine the advantages of antibodies and small molecules. We have developed a peptidyl ligand that binds to the TF or T antigen (Galβ1- 3GalNAc). The designed peptidyl ligand was observed functionally to mediate cell signaling of TF expressing cell lines, suggesting that TF antigens might be functionally interesting.

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Analysis of the controlled drug release (CDR) from biopolymer nanoparticles during the initial burst using a novel modeling method

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In the initial stage of the controlled release of a drug from a nanoparticle into a medium a phenomenon referred to as burst can occur. During burst a large amount of drug is released over a small period of time. Apart from the loss in the overall CDR time of actuation, high initial drug release rates can result into toxic drug levels, which would not be attained otherwise. The initial burst has been studied in the past but with little success in elucidating the mechanisms that control the phenomenon. In this contribution, a mathematical model is established to investigate how experimental conditions and nanoparticle formulations impact on the initial burst release. Experimental conditions, nanoparticle formulations and drug release profiles were extracted from publications for drug-PLGA or PLGA/PEG carriers and a database was created. Subsequently, statistical methods were utilized to analyze the data and a model was developed that can predict the burst release based on experimental conditions and nanoparticle formulations. Good agreement between model predictions and experimental burst data was obtained. Further analysis revealed that a clear augmentation in the intensity of the burst is obtained when PEG is bound to PLGA. It also seems that an increase in the burst release occurs for greater carrier particles, i.e., going from 5E1 nanometers towards microparticles. The increased understanding of the burst release can in future be used to manipulate the system more rationally e.g., to reduce the intensity of the burst release.

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