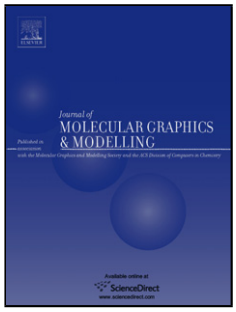

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PII: S1093-3263(16)30185-1
DOI: http://dx.doi.org/doi:10.1016/j.jmgm.2016.10.018
Reference: JMG 6778

To appear in: *Journal of Molecular Graphics and Modelling*

Received date: 9-9-2016
Revised date: 22-10-2016
Accepted date: 29-10-2016

Please cite this article as: Alice R. Walker, Robin Bonomi, Vadim Popov, Juri G. Gelovani, G. Andrés Cisneros, Investigating carbohydrate based ligands for galectin-3 with docking andmolecular dynamics studies, *<![CDATA[Journal of Molecular Graphics and Modelling]]>* (2016), http://dx.doi.org/10.1016/j.jmgm.2016.10.018

Investigating carbohydrate based ligands for galectin-3 with docking and molecular dynamics studies

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Abstract

Galectin–3 (Gal–3) is a carbohydrate binding protein that is overexpressed in several types of cancers, including pancreatic cancer, which makes it a good target for both imaging and therapeutic drug design. A ligand library specialized for ^{18}F positron emission tomography (PET) has been investigated with molecular dynamics (MD) and free energy methods to determine the relative binding energies of various potential ligands. Our results suggest that traditional docking methods can give good results when complemented by molecular dynamics and free energy methods for these types of ligands. Available experimental binding affinities for a small number of the tested compounds show very good agreement with the calculated energies and provide the rational approach for design of Gal-3 ligands with even higher affinity.

Keywords: galectin-3, molecular dynamics, docking, carbohydrate based ligands

1. Introduction

Pancreatic cancer has an extremely high mortality rate compared to other types of cancer[1]. This high mortality is due to the difficulty of diagnosis and treatment. Although pancreatic cancer only accounts for 3% of new cancer cases diagnosed in the US, it is responsible for 7% of cancer related deaths due to its high mortality rate, making it the 12th most common cancer type to be diagnosed but the 4th most common cause of death due to cancer [1]. The primary treatment for pancreatic cancer is curative resection, or complete removal of the tumor [2]. However, this requires early diagnosis as well as accurate determination of the tumor location in the pancreas[1]. Improvements for diagnosing pancreatic cancer are, therefore, a crucial component of the treatment process and a subject of intense study.

Positron emission tomography (PET) is a sensitive and effective technique for detecting tumors in the body [3, 4]. PET requires a radioactive isotope that undergoes positron emission decay, e.g. ^{18}F. PET requires an imaging agent with a high binding affinity and specificity to the cells of interest, so that the radiotracer accumulation in the affected tissue is faster than the isotopic decay[5]. The current tracer of choice, fluorodeoxyglucose (FDG), takes advantage of the increased metabolic uptake of glucose in cancer cells. However, FDG is not always effective at detecting smaller, less glycolytic tumors (i.e., early stage pancreatic carcinomas), and often results in false positives due to other physical anomalies that can result in increased glucose uptake, such as inflammation [6, 7]. Therefore, there is great interest in finding targets that are specific for pancreatic cancer and in the development of possible ligands that overcome the aforementioned shortcomings.

There are many attractive targets for imaging agents for cancer, one of which is Galectin–3 (Gal–3). This protein is one of the most studied galectins, and contains a globular carbohydrate recognition domain (CRD) comprised of five– and six–stranded beta sheets [8]. This CRD contains a conserved sequence of residues (Asp-Trp-Gly-Arg) which selectively bind beta–galactosides. Gal–3 also has a particularly high affinity for disaccharides containing one or more galactose subunits. Gal–3 is highly overexpressed in many malignant tumors, especially in pancreatic, breast, prostate, and thyroid carcinomas, and has been implicated in a wide variety of cancer function, including growth, apoptosis, and metastasis [9, 10, 11, 12].