Application of parallel blind docking with BINDSURF for the study of platinum derived compounds as anticancer drugs

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Abstract. The clinical use of platinum(II)-based drugs incurs serious side effects due to the non-specific reactions with both malignant and normal cells. To circumvent such major drawback, novel metallodrugs might be combined with suitable carrier molecules, as antibodies, to ensure selective attacks on tumors while sparing healthy tissues. In this contribution, we investigate the stability of a novel Pt(II) drug embedded in Herceptin, an antibody able to reconise the breast cancer cells, by using a parallel blind docking approach called BINDSURF. Our calculations reveal the main ligand-protein interactions in the binding pocket. The reported data can be therefore used to further rationalise the synthesis of improved drugs beyond classical cisplatin derivatives.

Keywords: Drug Discovery, GPUs, HPC

1 Introduction

The unexpected discovery of the platinum salts bioactivity by Rosenberg ca. sixty years ago [1] opened the door to a new a cancer treatment: the chemother-

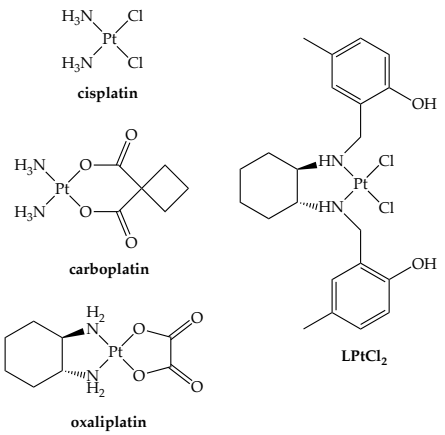

Fig. 1. Chemical structures of platinum(II)-based anticancer compounds

apy with transition metals [2]. In spite of the huge effort devoted to the synthesis of novel platinum(II) derivatives, only few anticancer drugs are routinely used in hospitals since the publication of the Rosenberg's seminal work: the original cisplatin approved in 1978 for treatment of ovarian and testicular cancer, the second-generation carboplatin approved in 1989 for treatment of ovarian cancer, and a third-generation drug oxaliplatin approved in 2002 for treatment of metastatic colorectal cancer (see Figure 1) [3, 4]. Indeed, these three compounds are the most widely used drugs in the treatment of cancer [5].

The bioactivity of cisplatin-based drugs mainly involves two sequential steps. At an early stage, the hydrolysis of cisplatin leads to a diaqua-complex, where the leaving(s) group(s) is replaced by water molecules since both Pt–Cl and Pt–O bonds are weaker than their Pt–N counterparts in square-planar Pt compounds [6]. The activated drug might subsequently interact with a wide spectrum of molecules such as proteins and peptides [7], though it is generally accepted that binding to DNA is the ultimate step in the anticancer activity [8, 9]. More specifically cisplatin derivates react with two adjacent guanine-cytosine bases pairs (GC) at N7 places leading to an intrastrand Pt-DNA cross-links adduct [10–12]. The caused disruption on both hydrogen bonding and stacking pattern of the the base pairs finally induces the cancer cell apoptosis [13]. Unfortunately, none of the approved platinum-based drugs are able to distinguish between healthy and malignant cells. Such lack of tumour selectivity results in the localisation of the damage in non-target tissues, which is the origin of the critical side effects associated to chemotherapy, including its high neurotoxicity as well as the acquired tumour resistance [14]. Consequently, one of the greatest challenges for chemotherapy is to selectively drive the drug towards cancerous cells [15].

To minimise chemotherapy risk, novel cancer therapies can clearly take advantage of the so-called carrier molecules, that is, a host molecule able to protect

the drug from side reactions while releasing it on the tumour area [16]. Among all possible carrier molecules, the use of antibodies is a very promising alternative as they can be biologically programmed to recognise cancer cells [17, 18]. This is the case of Herceptin (trastuzumab), a humanised monoclonal antibody able to selectively bind to the Her2/neu over-expressed protein of breast cancer cells [19]. In that framework, Sun and co-workers have recently demonstrated that cisplatin could be covalently coupled to Herceptin by using dumbbell-like Au-Fe_3O_4 nanoparticles [20]. Following this conjugation strategy, the platinum drug was covalently bound to a bifunctional ligand that fix both cisplatin and herceptin. According to their experimental evidences, the Herceptin enhances the cytotoxicity of Pt in cancerous cells [20]. There is, however, a more straightforward approach proposed by Gao, Zingaro *et al.*, who synthesised the novel platinum(II) compound $LPtCl_2$ (see Fig. 1) [21]. As one can see, $LPtCl_2$ drug is based on the oxaliplatin structure, and both share the central (R,R)-diaminocyclohexane moiety. In contrast, $LPtCl_2$ has two 2-hydroxy-5methyl groups that lead to a large affinity for Herceptin in its activated form $[LPt(H_2O)_2]$. This chemical feature allows to use a direct labelling procedure instead of a more complex stepwise synthesis. As Gao, Zingaro and co-workers concluded, this novel drug is bound to the Herceptin by metal complex coordination rather than by a covalent bond. Unfortunately, despite the potential application of the antibodies as carrier molecules, biological data of such action are still scarce due to the complexity of the system.

The present work fulfills this gap in the literature. More specifically, we use a parallel blind docking approach called BINDSURF [22] for quantifying the chemical interactions that govern the $LPt(H_2O)_2$–Herceptin binding. Our theoretical predictions can help in the development of novel therapies based on the immunoconjugation of metallodrugs.

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