

that opposes microtubule assembly.

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Snapshot of Translesion Synthesis of a Cisplatin 1,3-GTG Intrastrand Cross-link. Sabine Schneider^a, Thomas Reißner^a, Thomas Carell^a. ^a*Department of Pharmacy and Chemistry, Ludwig Maximilians University, Munich, Germany.*
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First discovered in the 60s, cisplatin (*cis*-diaminedichloridoplatinum(II)) is still one of the most widely used anticancer chemotherapeutic agents. Its cytotoxic properties rely on its ability to form stable and persisting DNA adducts, resulting in cell cycle arrest and apoptosis (reviewed in [1]). The major formed DNA adduct of cisplatin is the 1,2-intrastrand cross-link of adjacent purines. In addition 1,3-intrastrand cross-links of nonadjacent guanines as well as interstrand cross-links were also found [2, 3]. Its second generation analogue carboplatin (*cis*-diamine-[1,1-cyclobutanedicarboxylato]platinum(II)) is less toxic and has fewer side-effects than cisplatin, and was introduced into the clinics in the mid 1980s. Interestingly, carboplatin and cisplatin only differ in their leaving groups and form comparable DNA adducts, but show a different distribution of these adducts, with the 1,3-intrastrand cross-links of nonadjacent guanines, Pt-GTG, as the major adduct of carboplatin [4].

Nevertheless, tumours can commonly be intrinsically resistant or acquire resistance during the course of therapy against these drugs. The major cellular mechanism contributing to clinical cisplatin resistance include: decreased cellular uptake and increased efflux of the drug, increased cytoplasmic detoxification, inhibition of apoptosis, repair and increased bypass of the DNA adducts (reviewed in [1]). The mechanism of DNA lesion tolerance, known as translesion synthesis (TLS) is a universal, often error-prone response to arrested replication forks. TLS involves a multitude of specialized DNA polymerases, often belonging to the Y-family of polymerases, characterized by their ability to replicate across damaged sites and their low fidelity when replicating undamaged DNA. This can either be error-prone, resulting in mutations or accurate in respect to the damaged site (reviewed in [5]).

DNA polymerase η is a key player in TLS and responsible for the suppression of UV induced mutations [6]. Its abundance also has been correlated to the susceptibility of tumor cells to treatment with cisplatin [7-9].

Here we investigated the ability of Pol η to replicate template DNA containing a platinum 1,3-dGTG intrastrand cross-link, the major DNA adduct of the anticancer drug carboplatin. In contrast to the 1,2-dGG cisplatin adduct

[10], Pol η is not able to bypass this lesion. The X-ray crystal structure of Pol η in complex with template DNA containing the 1,3-dGTG adduct reveals the molecular basis of this lesion to prevent TLS by Pol η .

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Improvement of Drug Virtual Screen by GA/GP: Docking Studies on Tubulin Inhibitors as Anticancer Agents. Po-Tsang Huang^a, Chi-Hwa Wang^a, Shiao-Chun Wang^a, Chin-Tzong Pang^a, Kuo-Long Lou^a. ^a*Institutes of Biochemistry and Molecular Biology, College of Medicine, National Taiwan University, Taiwan.*

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Conventional procedures for drug design have been very expensive and time-consuming. Due to the enormous progress in information technology during recent years, it is expected to shorten the required research time spent in the early stage of development through computer calculation. CADD (Computer Aided Drug Design) is one of the most powerful concepts applied to satisfy such demand. Upon docking simulations, it is allowed to find out the binding sites and orientations between target proteins and drug molecules in several days. This is not only to save the time and the cost used in drug development, but also for us able to understand the structural implications used for further design. However, it is still currently difficult to formalize efficient software to carry out the docking simulations as a standard procedure leading to definite results with high accuracy. Therefore, we are in attempt to propose a new category of programming, for which the standard effectiveness for docking procedure can be anticipated in the near future. To initiate such computer simulations, many factors have to be taken into consideration. The first is to decide which algorithms should be applied to perform the job. GA (Genetic Algorithms) and GP (Genetic Programming) seem to be excellent candidates to solve this problem. The next concern is the determination of scoring function, which is appropriate for either GA or GP to generate their scores. As being the best commercially available scoring function with high accuracy and flexibility, X-score is used to satisfy this purpose. Our study has been thus concentrated in the search of binding site(s) between protein and the drug molecule through docking simulations by applying the aforementioned special algorithms and