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Water soluble platinum (II) complexes: Glut mediated cytotoxic properties and selective tumor targeting

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A series of sugar-conjugated malonato-platinum(II) complexes were designed and synthesized to evaluate the influence of different substitutions and different carbon chain lengths of the leaving group on water solubility and cytotoxicity against 6 human carcinoma celllines. The complex Glu-F-Pt exhibited a higher water solubility by almost 150 times and processed up to 10-fold more active in cytotoxicity against HT-29 cell lines in comparison to the most commonly used platinum anticancer drug oxaliplatin. The therapeutic index (LD50/IC50) was measured on BALB/c nude mice and the result showed that Glu-F-Pt expanded anticancer therapeutic window, indicating the potency in enhancing drug safety. In addition, the maximum tolerated dose finding experiments of Glu-F-Pt was performed on DBA/2 mice in order to evaluate their toxicity profiles. The mean lifespan of Glu-F-Pt was compared with that of oxaliplatin under an equitoxic dose regimen and the result was of % ILS >191.4 for Glu-Pt, and 148.0 for oxaliplatin, respectively. Cytotoxicity assay of Glu-F-Pt with and without phlorizin, an established inhibitor of mammalian glucose transporter, was performed to verify our hypothesis that the anti-tumor activity of sugar conjugated platinum complex is due to the active uptake by glucose transporters (GLUTs). This result suggested that the uptake of the 2C-Glu was regulated via the glucose transporters, whereas the cell-killing potency of oxaliplatin was not affected under the same circumstances, which confirmed our speculation that the sugar conjugated platinum (II) complex is transported by cancer cell through glucose transporter and achieves selective tumor targeting. Based on these arguments, the fluoro substituted sugar conjugate further support pre-clinical development for it to become a new class of Pt (II) antitumor agent for targeted therapy drugs.

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Disclosure of negative trial results: A call for action

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In the past few years the scientific community has discussed on how to tackle research misconduct. However, little progress has been made in another important and relevant issue that can lead to incorrect assessments to be on the clinical efficacy of treatments, the reporting of negative clinical trials. The file-drawer effect influences publication of research results more than rejection by journals. The file drawer effect is the non-reporting of results, often negative or neutral, from clinical trials in a specific area of research. There is evidence to support that editors tend to reject research where the results are not statistically significant. Moreover, it has been suggested that clinical trials with significant positive results had a higher probability of being included in meta-analyses than studies showing negative results. The trend to publication bias, the so called positive-outcome bias, is very common because reviewers and editors are less likely to publish negative results and findings that are not statistically significant. Withholding results are an example of misconduct research which can result in the use of drug therapies that are harmful, ineffective, unethical, and expensive; since clinical research that doesn't confirm the expected benefits of those treatments and their related clinical trial data remain unpublished. The key to avoiding underreporting and hyper-claiming research should be to motivate investigators to submit all good quality studies for publication and, to contribute to the education of journal editors, reviewers, and investigators alike that null or negative findings are as important as positive ones. To date, one of the most significant concerns of clinical trial databases, such as trail registries, consists in the difficulty of reporting research findings held by the sponsor. Therefore, the data are often not available for public access. Unfortunately, only two registries currently existing (Clinicaltrials.gov and the EU Clinical Trials Register) work to ensure clinical trial documentation. In order to avoid withholding results, there is an urgent need to improve the policies of scientific Journals for publication and access to clinical trial data.

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