Glyco-Conjugation Strategy for Targeted Delivery of Platinum Anticancer Drugs

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The three FDA approved platinum anticancer drugs, cisplatin, carboplatin and oxaliplatin, are widely used in the clinic to treat various forms of cancer including testicular, ovarian, cervical, head and neck, non-small-cell lung, and colorectal cancer.[1] Despite their phenomenal clinical success, however, the severe undesired side effects such as nephrotoxicity, myelosuppression, peripheral neuropathy, ototoxicity, and nausea are main drawbacks of platinum-based chemotherapy.[1] The side effectes could be mitigated byintroducing tumor-targeting properties into platinum anticancer compounds, thereby reducing the nonspecific platinum accumulation in the healthy tissues. Glucose transporter GLUT1 is known to widely overexpress in many human cancers and its expression levels in tumor biopsy samples correlate well with poor prognosis.[1] We designed various D-glucose-platinum(II) conjugates (Glc-Pts) for targeted delivery of platinum anticancer drugs to cancer cells.[2] To investigate the effect of D-glucose substitution position on the biological activity of Glc-Pts, we synthesized all possible positional isomers (C1α, C1β, C2, C3, C4, and C6) of a Glc-Pt.[3] The biological activities of the compounds were evaluated both *in vitro* and *in vivo*. We discovered that varying the position of substitution of D-glucose alters not only the cellular uptake and cytotoxicity profile but also the GLUT1 specificity of resulting glycoconjugates. Results from this study revealed that the C2-substituted Glc-Pt **2** has the highest GLUT1-specific internalization, which also reflects the best cancer-targeting ability. In a syngeneic breast cancer mouse model overexpressing GLUT1, **2** showed excellent antitumor efficacy and selective uptake in tumors with no observable toxicity. [3] The design, synthesis, anticancer activity and in-depth characterization of the cellular uptake mechanism of Glc-Pts will be presented in the research seminar. Additionally, in the second half of the seminar, I will briefly discuss my future research plans.

References.

1. L. Kelland, Nat. Rev. Cancer, 2007, 7, 573; L. Szablewski, Biophys. Acta. 2013, 1835, 164.
2. M. Patra, T. C. Johnstone, K. Suntharalingam, S. J. Lippard, Angew. Chem. Int. Ed. 2016, 55, 2550.
3. M. Patra, S. G. Awuah, S. J. Lippard, J. Am. Chem. Soc., 2016, 138, 12541.