ANTI-CANCER METAL MEDICINES WITH N-HETEROCYCLIC CARBENE LIGANDS

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ABSTRACT

The clinical success of cisplatin has led to tremendous advances in new metal coordination compounds for anti-cancer applications. The distinct planar coordination geometry and coordination unsaturation of d^8 and d^{10} metal ions render their metal complexes to be unique scaffolds for the design of new diagnosis and therapy for treatment of cancers. Ligands with C donor atom(s) such as N-heterocyclic carbene (NHC) are used to construct cationic gold(III), Au(I), Pd(II), Pt(II) and Ir(III) complexes with good stability and cell permeability under physiological conditions. N-heterocyclic carbene ligands are able to stabilize metal ions against demetallation and render the metal complexes to be strongly emissive in solutions through suppression of excited state structural distortion. The rich luminescent properties of metal-N-heterocyclic carbene complexes are convenient spectroscopic handles for tracking of the complexes inside the cells and can be used for the detection of biomolecules of relevance to cancers. Some of these complexes exhibit potent cytotoxicity toward cancer cells and *in vivo* anti-tumor activities in multiple mice models of cancer including the cis-platin resistant ones. We have applied a panel of techniques including click chemistry and photo-affinity probes, cellular thermal-shift proteomics, and transcriptomic profiling to identify the direct molecular targets of anti-cancer metal complexes. The anti-cancer pincer type d^8 metal complexes have been found to engage multiple anti-cancer targets, which is beneficial for the design of new chemotherapy for drug resistant cancers. We have also developed chemical formulation strategies to the research on highly cytotoxic anti-cancer metal complexes with an objective to lower the toxic side effects.

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