

THE CELLULAR UPTAKE OF LUMINESCENT RUTHENIUM COMPLEXES

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ABSTRACT

Transition metal complexes have enormous potential as diagnostic and therapeutic agents, but their internalization and distribution in living cells are only poorly understood. Here, we perform one of the few systematic explorations of the uptake efficiency and mechanism of a class of metal complexes: luminescent dipyrrophenazine (dppz) complexes of ruthenium(II). Substitution of the ancillary ligands permits variation in the overall complex charge, size, and hydrophobicity. We find that internalization of these complexes occurs mostly through passive diffusion, driven by the membrane potential, and that hydrophobicity, rather than size, is the most important determinant of compound accumulation. Across different cell types with all compounds, mostly uneven cytoplasmic staining is observed with near exclusion from the nucleus. Conjugation to cell-penetrating peptides, such as D-octaarginine, increases uptake efficiency, but leads to trapping in endosomes below a threshold concentration. Above this threshold concentration, substantial staining of the nucleus as well as the cytosol is observed. An appended fluorescein tag lowers the threshold concentration, indicating the importance of payload to the internalization and distribution of cell-penetrating peptides. Shorter peptides, including the nuclear targeting signal RrRK (where r = D-arginine), are also studied, though none have as high a degree of uptake nor as low a threshold concentration as the octaarginine conjugate. These studies provide a basis for the future design and optimization of metal complexes for biological application.

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