HETEROBIMETALLIC RUTHENIUM-FERROCENE COMPLEXES AS ANTICANCER AGENTS

Enas Aljohani,[b] Benjamin J. Hofmann,[a] Tameryn Stringer,[b,c] Rianne M. Lord[a]

[a] University of Warwick, Coventry, United Kingdom
[b] University of East Anglia, Norwich, United Kingdom
[c] University of Waikato, Hamilton, New Zealand

Ruthenium-based metallodrugs have emerged as promising alternatives to platinum chemotherapeutics, owing to their ability to access multiple oxidation states under physiological and hypoxic conditions and their comparatively lower cytotoxicity toward healthy cells. While organometallic Ru(II) "piano stool" compounds have been widely explored due to their straightforward synthesis and readily tuneable ligand environments,[1] coordination Ru(II) compounds remain comparatively underdeveloped, largely due to more demanding synthetic routes and challenges associated with isomerisation that complicate their preparation and characterisation.[2]

Ligand selection plays a central role in governing the stability and cytotoxicity of metallodrugs, with β-diketonate ligands widely used to modulate physicochemical and biological properties.[3] We have shown that incorporation of ferrocenyl moieties into β-diketonate ligand frameworks significantly enhances cytotoxicity, yielding coordination complexes with nanomolar potency,[4] and organometallic analogues which further promote the generation of intracellular reactive oxygen species and enhance the cellular uptake of both ruthenium and iron, thereby contributing to increased cell death.[5] Building on these findings, we have expanded the libraries to include PTA (1,3,5-triaza-7-phosphaadamantane) ligands in organometallic complexes (**Figure 1a**) and phenanthroline ligands in coordination complexes (**Figure 1b**) to further enhance biological activity. This work compares organometallic and coordination Ru(II) systems and identifies key structural and functional features to inform the rational design of next-generation ruthenium-based therapeutics

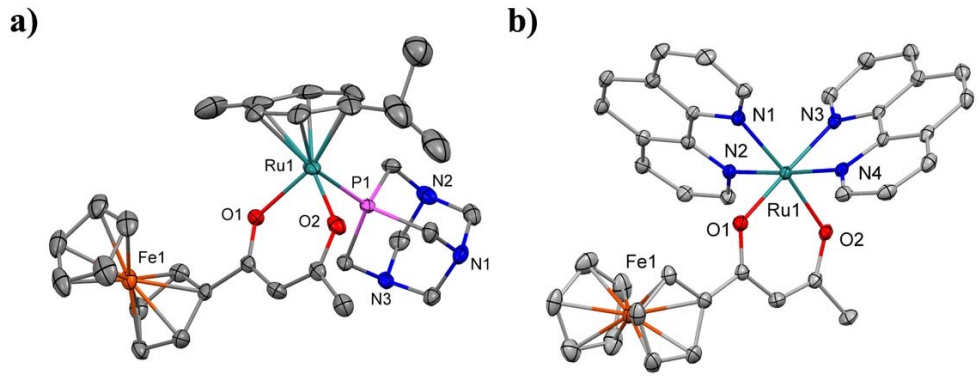

Figure 1 Molecular structures of **a)** an organometallic Ru-Fc PTA compound and **b)** a coordination Ru-Fc phenanthroline compound.

[1] L. Zeng et al. *Chem. Soc. Rev.* 2017, **46,** 5771–5804

[2] A. Levina et al. *Coord. Chem. Rev.* 2009, 253, 1589–1616.

[3] R. M. Lord et al. *J. Med. Chem.* 2015, **58**(12), 4940–4953

[4] M. Allison et al. *Chem. Eur. J.* 2021, **27**(11), 3737-3744

[5] M. Allison et al. *Organometallics* 2023, **42**(15), 1869–1881