

Next Generation Anticancer Agents: A Polypharmacological Approach

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According to the Indian Council of Medical Research (ICMR), cancer cases in India are estimated to increase by 25% by 2025. Platinum drugs cisplatin, carboplatin and oxaliplatin are the frontline treatment options for a variety of localized as well as metastatic cancers. However, their efficacy is often comprised due to inherent and acquired resistance in cancers. To circumvent this issue, we recently designed dual-targeting platinum-ferrocene (Pt-Fc) bimetallic hybrids with potent anticancer activity. These Pt-Fc hybrids exerted antitumor activity through multi-pronged mechanism of action and shows an excellent anticancer efficacy in A2780 mice xenograft model.¹ In the present study we sought to improve the *in vivo* antitumor efficacy through tuning the reactivity of this promising class of Pt-Fc hybrid anticancer agents. we have demonstrated that reactivity is a key determinant of *in vitro* cytotoxicity, plasma stability, *in vivo* tumour accumulation and anticancer efficacy platinum complexes comprising of β -diketonate leaving group. Finally, we identified a novel antitumor agent, that exerted higher tumour inhibitory potential and better safety profile as compared to the newest generation of platinum drug oxaliplatin (manuscript submitted). Both the Pt-Fc derivative has much lower platinum cross-resistance compared to cisplatin, but was unable to circumvent the resistance completely.¹ Encouraged by the lack of cross-platinum resistance of ruthenium (Ru) compounds, we synthesized a Ru-Fc derivative (**1**) and evaluated its anticancer potential *in vitro* and *In vivo*. To the best of our knowledge, this is the first report on evaluation of toxicity and antiangiogenic activity of a Ru-Fc bimetallic conjugate.²

Reference:

1. Gadre, S.; **Manikandan M**, Patra, M* et.al. A rationally designed bimetallic platinum (II)-ferrocene antitumor agent induces non-apoptotic cell death and exerts *in vivo* efficacy. *Chem.A Eur. J.* **2022**, 28, No. e202201259
2. **Manikandan M**, Malay Patra* et.al. Potent Ruthenium–Ferrocene Bimetallic Antitumor Antiangiogenic Agent That Circumvents Platinum Resistance: From Synthesis and Mechanistic Studies to *In Vivo* Evaluation in Zebrafish. *J. Med. Chem.* **2022**, 65, 16353–16371.