INTEGRATING COORDINATION CHEMISTRY AND BIOMOLECULAR BINDING INSIGHTS FOR NEXT-GENERATION METALLODRUGS AGAINST CANCER AND AMR

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Cancer and antimicrobial resistance (AMR) represent two of the most formidable biomedical challenges of our time, demanding therapeutic strategies that transcend the limitations of conventional small-molecule drugs. Transition metal complexes, distinguished by their diverse coordination geometries, redox activity, and biomolecular recognition capabilities, offer a powerful platform for next-generation therapeutics. Central to this paradigm is the modulation of biomolecular interactions, particularly with DNA and human serum albumin (HSA), the most abundant transport protein in human blood plasma, which is emerging as a defining principle in the design of novel metallodrugs.

In our research group, we pursue the rational design of metallodrugs that exploit DNA and HSA interactions as central determinants of therapeutic performance. Recent preliminary work has demonstrated how distinct ligand scaffolds and metal centers can be tailored to achieve complementary outcomes: pyrrole imine complexes of Au(III), Pd(II), and Zn(II) showed intercalative DNA binding with selective cytotoxicity against colon carcinoma cells[1]; salicylaldehyde-derived Co(II) Schiff base complexes enhanced DNA intercalation against breast adenocarcinoma cells while minimizing HSA binding, thereby increasing free drug availability[2]; and Ru(II) pyrazolyl pyridine half-sandwich complexes exhibited selective antibacterial activity against multidrug-resistant *Acinetobacter baumannii* through combined intercalation and groove binding[3]. These experimental findings were further corroborated by computational studies, which provided mechanistic insight into binding modes and energetics.

Collectively, our studies establish a framework that unites mechanistic precision with translational potential. By situating DNA-HSA interactions at the core of metallodrug design, this approach not only advances the rational development of next-generation metallodrugs but also positions coordination chemistry as a transformative driver in tackling the global health crises of cancer and antimicrobial resistance.

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[1] Z. Mnqokoyi, S. Sookai and M. Nowakowska, RSC Advances, 2026, Manuscript submitted.

[2] S. Sookai, I Waziri, AJ Muller and M. Nowakowska, New J. Chem., 2026, 50, 471.

[3] M.C. Joseph, S. Sookai, R. Mphephu, M. Nowakowska, and A.J. Swarts, ChemBioChem., 2026 Manuscript submitted.