

## **Tackling Neurological Off-target Side Effects of Platinum Chemotherapeutics using Redox Modulation**

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### Summary:

Platinum-based chemotherapeutics, such as oxaliplatin, remain essential in first-line cancer treatment but are associated with severe off-target neurotoxicity, notably chemotherapy-induced peripheral neuropathy (CIPN). Oxaliplatin-induced peripheral neuropathy (OIPN) affects up to 85% of patients receiving oxaliplatin in the treatment for colorectal cancer, and significantly compromises quality of life, often leading to dose reduction or treatment discontinuation. Despite its prevalence, no effective preventive therapy exists, and current interventions are limited to symptomatic management. Addressing this critical unmet need, the project, involving a multidisciplinary French- Singaporean collaboration, proposes to mitigate platinum-induced neurotoxicity while preserving anticancer efficacy. Our preliminary data demonstrate promising outcomes: Pt(IV) conjugates incorporating Mn-based superoxide dismutase mimics significantly reduced neuropathy in mice and zebrafish while enhancing tumor suppression. On this basis, the PhD project aims at: (i) synthesis of Pt(IV) prodrugs with intracellular activation and synergistic functionalities for redox modulation and targeted delivery; (ii) evaluation in cellular models, both cancerous and neuronal to uncover differences in mode of action; (iii) screening in our recently developed zebrafish neuropathy model to accelerate the identification of new Pt(IV) complexes towards further animal studies and preclinical translation.