Logic-gate Light-Activated Drug-Delivery Systems for the Treatment of Aggressive Cancers

Abstract

Cancer continues to be a leading cause of mortality, claiming a staggering 10 million lives in 2020 alone. Many aggressive cancer types are still treated with heavy doses of highly cytotoxic metal-based chemotherapy (e.g., cisplatin) as first and only line of therapy. This causes extremely detrimental side-effects in patients, limits the duration of treatment courses and consequently leads to high relapse rates and abysmal prognosis (e.g., <10% 5-year survival rate for pancreatic adenocarcinoma). Therefore, despite remarkable progress in new-generation treatments, the need to improve treatment efficacy and mitigate side effects remains critically unmet. In this context, the development of "magic bullet" treatments in the form of cancer-targeting drug-delivery systems (DDSs) activatable on demand represents a beacon of hope for enhancing clinical outcomes.

The ICB group specialises in the development of metal complexes and their application in targeted anticancer therapy. Among the potential alternatives to platinum therapy, ruthenium complexes have emerged as promising drug candidates, with multiple Ru(II) compounds recently entering clinical trials.[1] To exploit their raw potential whilst addressing their pharmacokinetic limitations (e.g., off-target effects), the team develops cutting-edge DDSs allowing their controlled release in tumour tissues[2] upon exposure to internal (e.g., overexpressed cancer enzymes[3]) or external activating triggers (e.g., light irradiation[4]). The team's experience has for example allowed the development of new "photocage" compounds able to functionally encapsulate drugs in an inactive form, and release them with high spatial and temporal control under light irradiation.[5-7] However, both internal and external stimuli taken individually present drawbacks associated with widespread distribution, non-specificity, leakage or side-effects.

This PhD project aims to pioneer a highly targeted treatment approach for aggressive cancers by synergising the advantages of internal and external stimuli in a "logic-gate" manner. The initial strategy will implement an innovative "catch-and-release" approach in which only the combination of an overexpressed cancer protease and of light irradiation can lead to target-specific drug release.

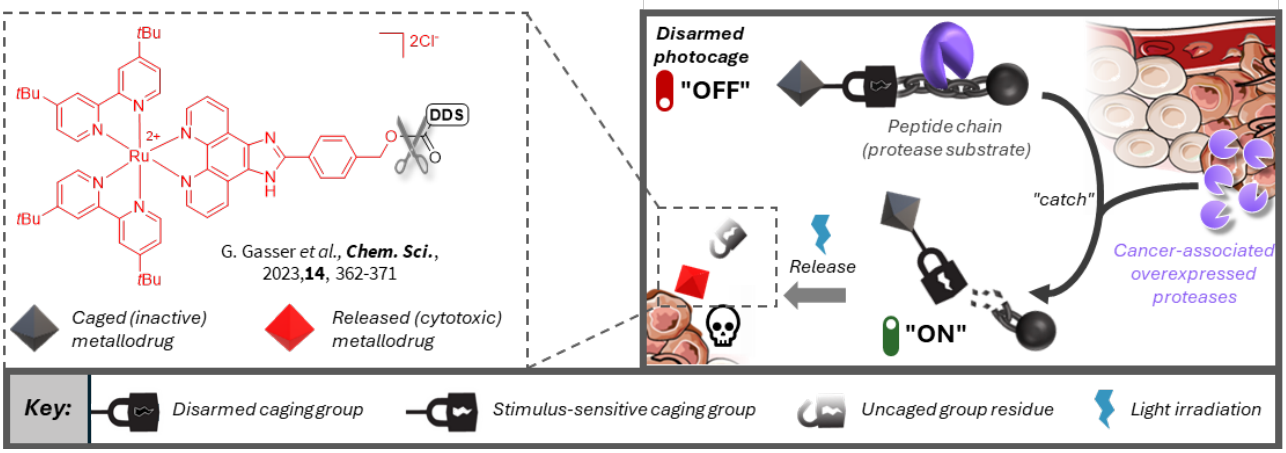

Figure 1. Overview of the "logic-gate" drug delivery systems, combining internal and external stimuli, developed in the project to release Ru(II) metallodrugs in cancer cells.

The methodology will involves preparing conditionally photo-activatable prodrugs utilizing photo-cleavable protecting groups (PPGs).[8] The innovative aspect of this approach involves deliberately suppressing the photocage's photochemical properties by incorporating a protease-cleavable "capping moiety" onto a critical position of the photocage. Upon encountering target proteases within tumour tissues, the peptide substrate will be cleaved, restoring the photocage's photochemical properties. This will enable the subsequent release of the metallodrug through non-focused light irradiation, allowing for targeted activation and virtually eliminating the risk of toxicity to healthy tissues.

Throughout this project, the PhD candidate will design and synthesise novel caged analogues of Ruthenium-based metallodrugs that have shown promising anticancer activity. The candidate will use organic, inorganic and peptide synthesis techniques, as well as formulation strategies, and evaluate the properties of the new DDSs using optical spectroscopy and enzymatic assays. Computer-aided compound design may also be implemented in collaboration with groups of theoretical chemistry, particularly to optimise the photo-physical properties of the photocages and design highly specific protease substrates. Finally, the logic-gate uncaging strategy will be tested *in-vitro* and *in-vivo* using tumour models of aggressive cancers with unmet clinical needs.

References

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