Optimizing the phototherapy effects of metallodrug photosensitizers for cancer treatment

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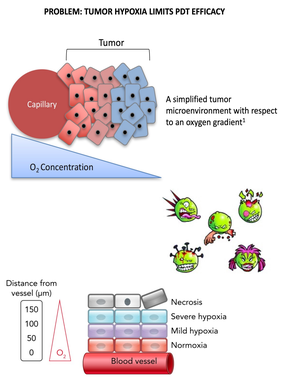
Background

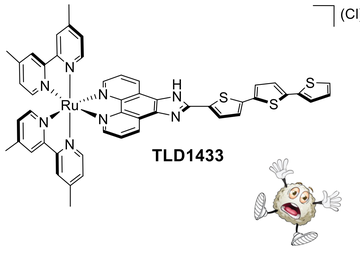
Cancer is a leading cause of death globally. Surgery, chemotherapy, radiation have proven effective for a number of cancer types, but many cancers are resistant so complementary approaches are urgently needed. Photodynamic therapy (PDT) as one such approach, where light is used to activate a photosensitizer (PS) in the presence of oxygen to form cytotoxic singlet oxygen and other reactive oxygen species (ROS) that destroy tumors and can induce an antitumor immune response. It has the advantage of being highly selective with minimal side effects because toxicity is generated only where the PS, light, and oxygen overlap in space and time.

However, PDT is less effective in hypoxia due to its oxygen dependence. Also, the PDT treatment itself can render cells and tissue hypoxic due to oxygen consumption and reduced blood flow at the tumor. Tumor hypoxia presents a challenge not only for PDT but for cancer therapy in general. Hypoxia can disrupt drug uptake and function, and induce other cellular adaptations that render treatment ineffective.



Objectives

Our group has developed light-responsive transition metal complexes that exploit oxygen-independent phototoxic pathways for treating some of the most aggressive and drug-resistant tumors. One of our PSs, TLD1433, is currently in Phase 2 clinical trials (NCT03945162) for treating bladder cancer with PDT.



By gaining a better understanding of TLD1433, this project will optimize the phototherapy effects of subsequent generation PSs, with a focus on addressing the issue of hypoxia.

The oligothiophene containing transition metal complexes appears to be capable of photoredox catalysis involving long-lived triplet states, which will be prioritized here. The strategy will focus on the light parameters, and the immunological response.

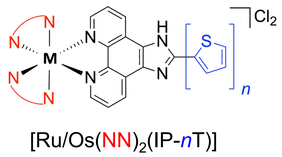
Structures

red = co-Ligands

NN
- a = bpy
- b = phen
- c = 4,4'-dmb
- ae = 4,4'dtfmb
- w = 4,7-dmphen

blue = PDT ligands

n = 4



[Ru/Os(NN)$_2$(IP-*n*T)]

Photocytotoxicity & light parameters

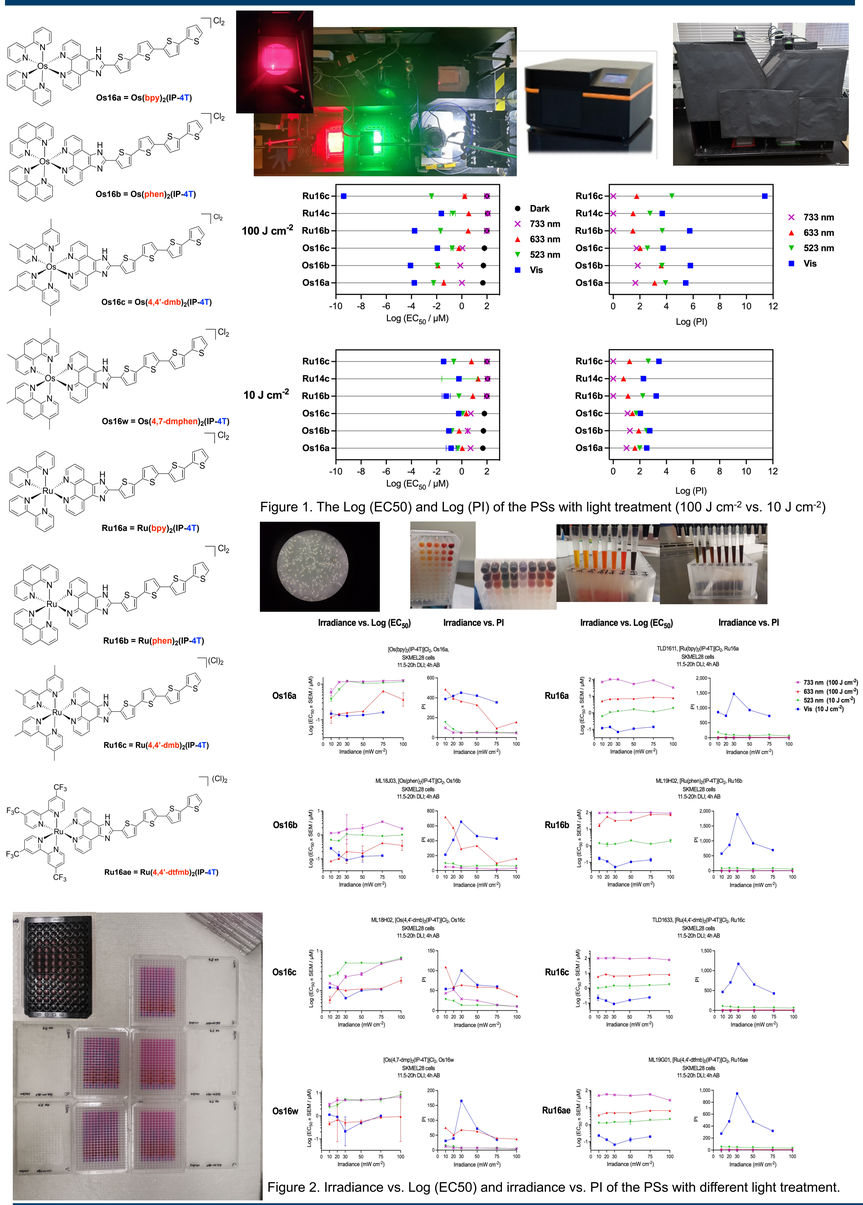
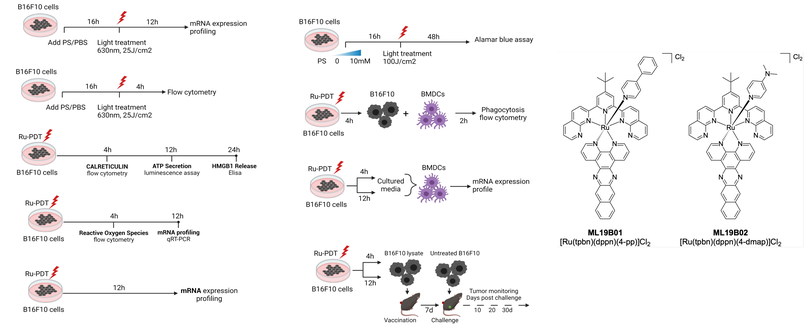


Figure 1. The Log (EC50) and Log (PI) of the PSs with light treatment (100 J cm^{-2} vs. 10 J cm^{-2})

Figure 2. Irradiance vs. Log (EC50) and irradiance vs. PI of the PSs with different light treatment.

Immunogenic cell death (ICD)



The PSs ML19B01 and ML19B02 generated the immunomodulatory effects in various immunological pathways including proinflammatory and type 1 interferon pathways (Figure 3). The CALR surface translocation, ATP secretion, and HMGB1 release of the 2 PSs suggested distinct ICD hallmark-inducing capacity (Figure 4)

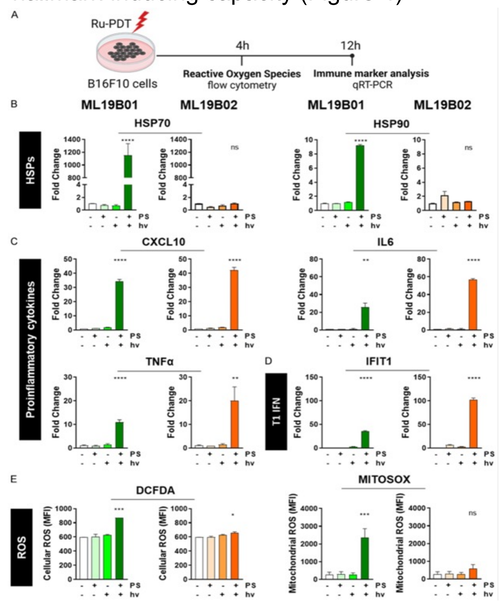


Figure 3. qRT-PCR analysis for genes associated with immune markers and ROS analysis of PDT treated B16F10 cells with ML19B01 and ML19B02.

Compared to unvaccinated control mice, mice that were vaccinated with the PSs-PDT improved tumor-free survival and tumor growth delay, suggesting that the vaccination with B16F10 that were treated with the 2 PSs induced similar protection against tumor challenge.

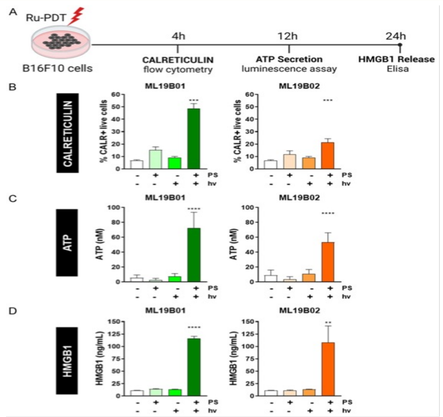


Figure 4. Analysis of surface calreticulin (CALR) expression, ATP secretion, and HMGB1 release upon PDT treatment.

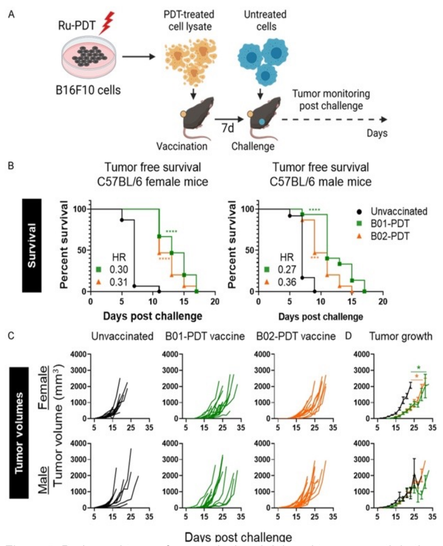


Figure 5. Prolonged tumor-free survival and delayed tumor growth in the B16F10 mouse melanoma by immunization with the PSs-PDT treated cancer cells.

Conclusions

The light regimens with various parameters including wavelength, fluence, irradiance, DLI and delivery scheme play an important role in optimizing PDT effect. The gold standard ICD confirmation in vivo (vaccination) showed anti-tumor effects with the PSs tested. We will further probe the relationships between the PSs and light parameters that yield optimal in vitro production of immunogenic cell death (ICD) hallmarks and determine whether they eradicate tumors and result in antitumor immune responses in vivo.

Acknowledgements

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