Approaches for optimization of the phototherapy efficiency with metallodrug photosensitizers in cancer treatment

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Photodynamic Therapy (PDT)

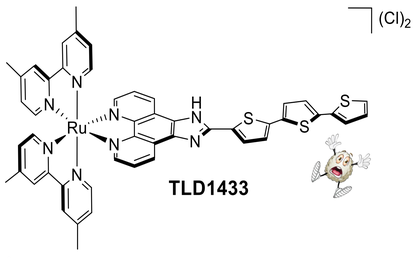
Cancer remains a global health crisis. **Tumor hypoxia** presents a major challenge in cancer therapy. Hypoxia can disrupt drug uptake and function, and induce other cellular adaptations that render treatment ineffective. Many cancers are resistant so complementary approaches are urgently needed.

In **photodynamic therapy** (PDT), where light is applied to activate photosensitizers (PSs) in the presence of oxygen, singlet oxygen and other reactive oxygen species (ROS) can be generated via a cascade of photochemical events to damage or kill tumor cells with minimal dark toxicity, which can induce an antitumor immune response. It has become one of the most promising treatments for cancers with increasing successful clinical trials.

However, PDT is particularly susceptible to hypoxia since the antitumor effects rely primarily on the sensitization of singlet oxygen and other ROS. Also, the PDT treatment itself can render cells and tissue hypoxic due to oxygen consumption and reduced blood flow at the tumor.

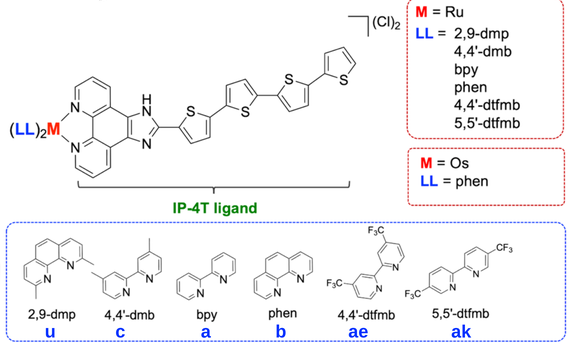
Highly Active Metallodrug PSs

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.

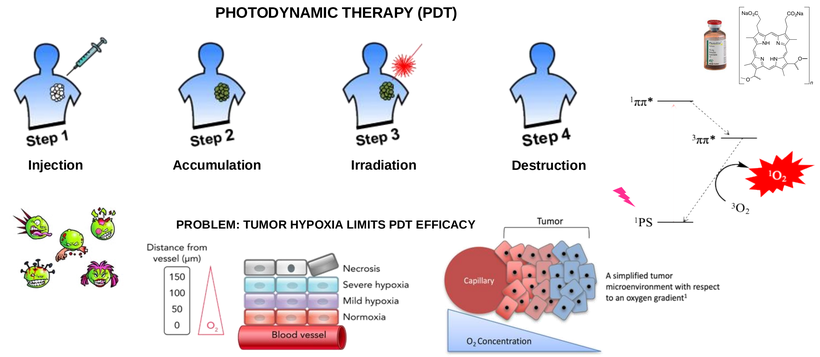
Hypoxia-active



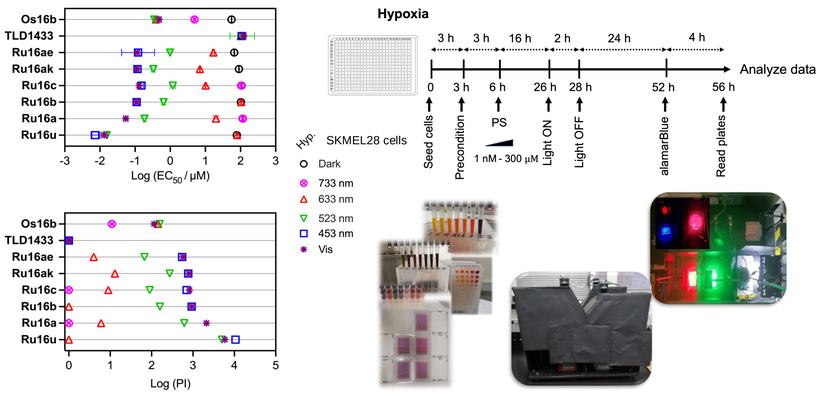
Objectives

The oligothiophene (especially **4T**) containing transition metal complexes appears to be capable of **photoredox** catalysis involving **long-lived triplet states** to generate cytotoxic reactive molecular species (RMS) through **O_2-independent** pathways.

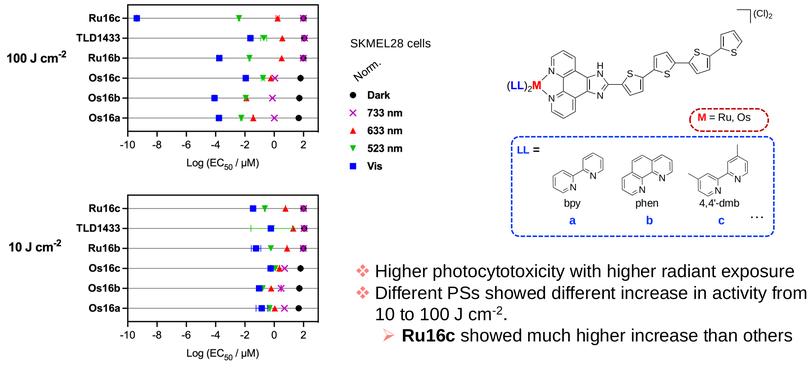
By gaining a better understanding of TLD1433, this poster will mainly focus on the **light regimens** of the highly active PSs including such hypoxia-active ones for **optimal PDT effects**.



Hypoxia Photocytotoxicity

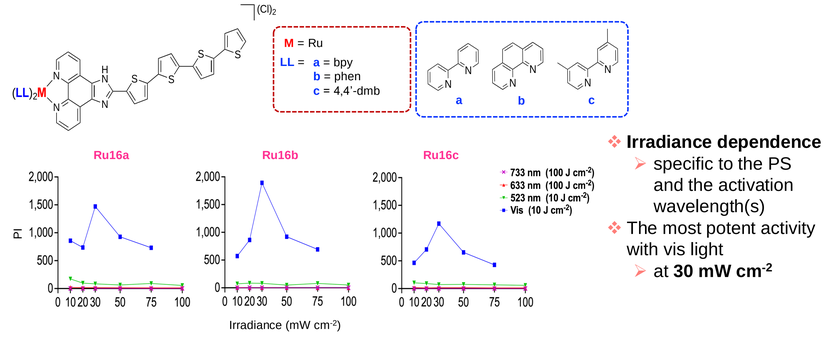


Photocytotoxicity & Radiant Exposure



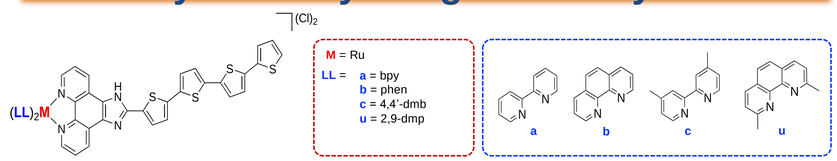
- Higher photocytotoxicity with higher radiant exposure
- Different PSs showed different increase in activity from 10 to 100 J cm^{-2}.
  - **Ru16c** showed much higher increase than others

Photocytotoxicity & Light Irradiance



- **Irradiance dependence**
  - specific to the PS and the activation wavelength(s)
- The most potent activity with vis light
  - at **30 mW cm^{-2}**

Photocytotoxicity & Light Delivery Scheme



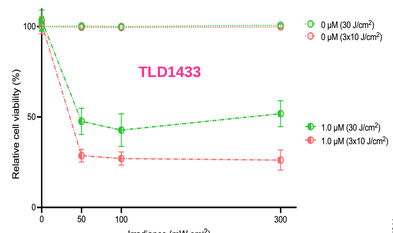
- SKMEL28 under normoxia
- Concentrations chosen for cell viability (~ 50%)
- **Light parameters**
  - ✓ **Wavelength**: **Green** (525 nm) and **Blue** (445 nm) lasers
  - ✓ **Irradiance range**: 50, 100, 300 mW cm^{-2}
  - ✓ **Radiant exposure**: 30 J cm^{-2}
  - ✓ **Light delivery schemes**
    - **Continuous**: 30 J cm^{-2} x 1 run
    - **Fractionated**: 10 J cm^{-2} x 3 runs (1.5h off-light in btw)

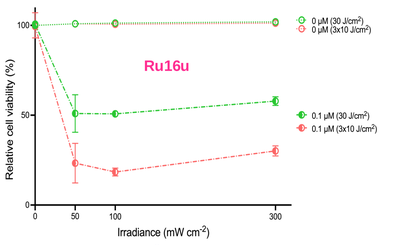
Aim for ~ 50% or larger cell kill

Why?

- Dependence (irradiance-, delivery scheme-) may get attenuated at very low and very high cell kill.

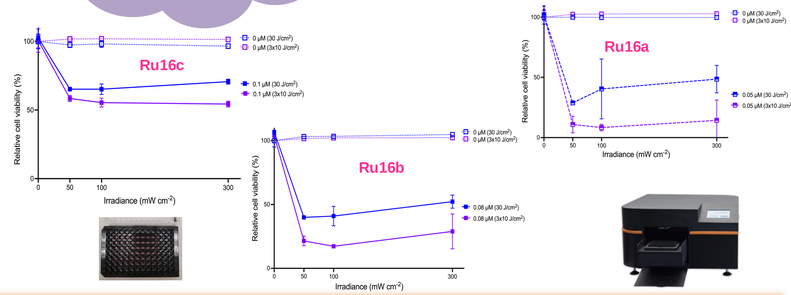
- **Fractionated light delivery has shown higher photocytotoxicity than continuous light delivery in all tested PSs.**
- **PDT effects may get optimized when using fractionated light delivery at 300 mW cm^{-2}.**
- **The correlation btw irradiance and photocytotoxicity can be more complicated than the lines shown here.**
  - **The trend shown by each line needs more data points to be more accurate**
  - **Lower irradiance (<50 mW cm^{-2}) could show lower cell viability**





Fractionated Light Delivery

- **Less irradiance-dependence in photocytotoxicity?**
  - **50 to 300 mW cm^{-2} = 6X less light exposure time ☺**



Conclusions & Future Studies

The light regimens with various parameters including wavelength, radiant exposure, irradiance, DLI and delivery scheme play an important role in optimizing PDT effect. We will further probe the relationships between the PSs and light parameters for optimal PDT effects on in vitro production of immunogenic cell death (ICD) hallmarks and in vivo antitumor immune responses.

Acknowledgements

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