

Development of New Cyclometalated Iridium(III) Complexes for Induction of Programmed Cell Death, Detection of Dead Cells, and Mechanistic Study

Shin Aoki^{1,2,3,*} Kenta Yokoi¹, Chandrasekar Balachandran¹, Kohei Yamaguchi¹

¹Faculty of Pharmaceutical Sciences, Tokyo University of Science, Noda, 278-8510, Japan

²Research Institute for Science and technology, Tokyo University of Science, Noda, 278-8510, Japan

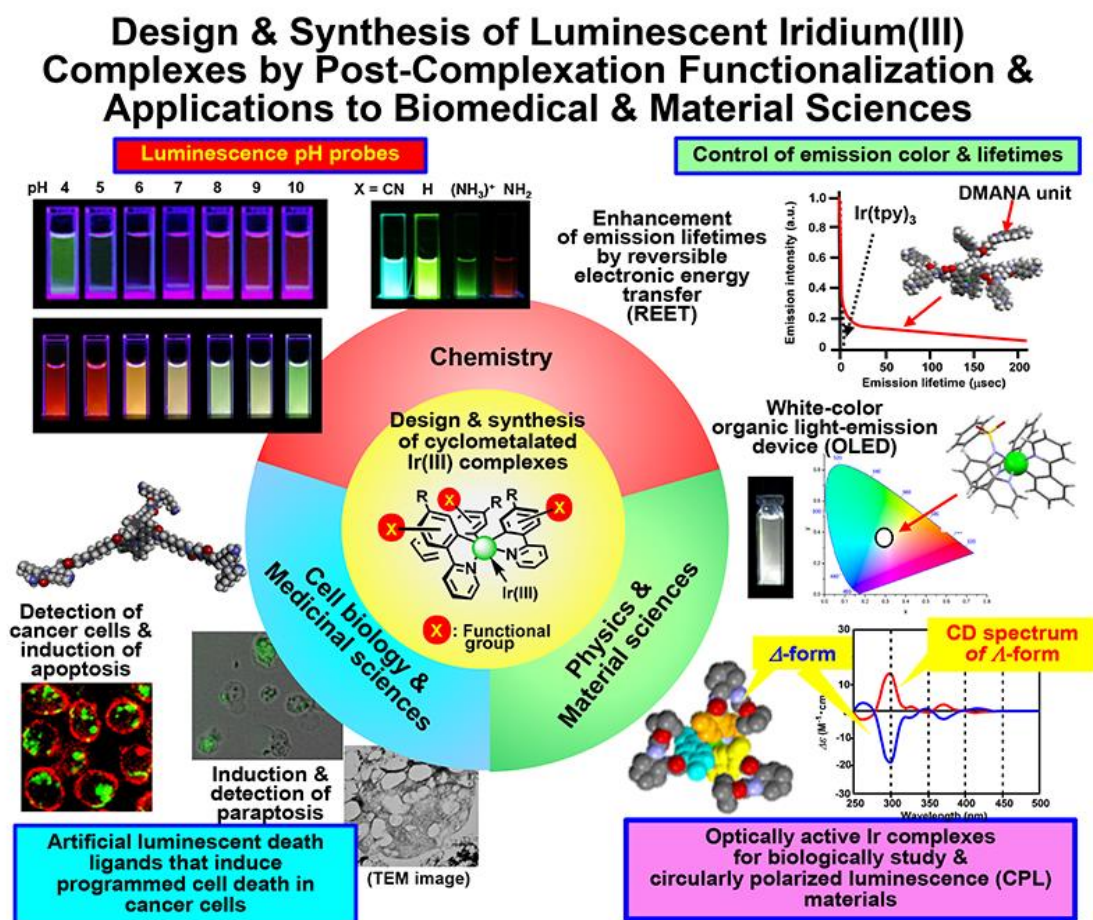
³Research Institute for Biomedical Sciences, Tokyo University of Science, Noda, 278-8510, Japan

*Corresponding author: E-mail: shinaoki@rs.tus.ac.jp

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Graphical Abstract



Abstract

Cyclometalated iridium(III) (Ir(III)) complexes such as *fac*-Ir(tolpy)₃ (tolpy = 2-(4'-tolyl)pyridine) are extremely stable in water and organic solvents and are used as organic light emission diodes (OLEDs) and cell imaging materials, due to their high stability and excellent emission properties such as large Stokes' shifts, high phosphorescent quantum yields, and relatively longer lifetimes (μs order) than that of many fluorescent molecules (ns order). These attractive photochemical and structural properties make cyclometalated Ir complexes important candidates for the use in biological applications such as chemosensors, photocatalysts in organic synthetic chemistry, living cell staining, *in vivo* tumor imaging, and anti-cancer agents. Because it is generally difficult to synthesize various metal complexes that contain labile and/or unstable functional groups under harsh reaction conditions (such as high temperature), we have developed the synthetic methods for various hybrid compounds of cyclometalated iridium(III) complexes by "post-complexation functionalization (PCF)" including regioselective substitution reactions of basic Ir complexes [1]. It is assumed that these functionalization reactions would be powerful methods for the synthesis of a variety of Ir complexes possessing labile functional groups such as peptides, chromophores as well as other moieties that would otherwise be difficult to produce for the applications to biomedical and material science. In this paper, we would like to present the results of the following three projects.

- 1) Design and synthesis of cyclometalated Ir(III) complexes that exhibit blue, green, and red color luminescence emission and respond to pH in solutions [1].
- 2) Design and synthesis of luminescent Ir(III) complex-peptide hybrids (IPH) that detects cancer cells and induce their programmed cell death, apoptosis and necrosis, and paraptosis, in cancer cells [2].
- 3) Design and synthesis of Ir(III) complex-peptide hybrids (IPH) function as inducers of paraptosis in cancer cells and detectors of dead cancer cells [3-5].

Mechanistic studies of cell death induced by IPHs having peptide units that had been known to bind to death receptors expressed on cell membrane of cancer cells suggest that apoptosis and necrosis-like cell death are differentiated by the position of the hydrophilic linkers between Ir complex core and the peptide units. On the other hand, IPHs that have basic (cationic) peptide units have been found to induce paraptosis, which has recently been reported as one of PCD mechanisms, not apoptosis nor necrosis. Interestingly, it was found that our IPHs induce the direct Ca^{2+} transfer from the endoplasmic reticulum (ER) to mitochondria, the loss of mitochondria membrane potential, membrane fusion between the ER and mitochondria, and the vacuolization of intracellular organelles in cancer cells [3-5]. Paraptosis induced by IPHs has been proposed as paraptosis-II, which is different from previously known paraptosis (paraptosis-I) induced by celastrol and other natural products, in which the Ca^{2+} overload in mitochondria is negligibly induced [5]. These findings suggest that IPHs could be a promising tool for controlling apoptosis and necrosis by activation of the extra- and intracellular cell death pathways and to develop new anticancer drugs that detect cancer cells and induce their cell death.

Keywords: Cyclometalated iridium complexes; post-complexation functionalization; hybrid molecules; luminescence property; anticancer activity.

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References

1. S. Aoki, Y. Matsuo, S. Ogura, H. *et al.*, *Inorg. Chem.*, **2011**, *50*, 806. .
2. A.-A. Masum, K. Yokoi, Y. Hisamatsu, K. Naito, B. Shashni, S. Aoki, *Bioorg. Med. Chem.*, **2018**, *26*, 4804.
3. K. Yokoi, C. Balachandran, M. Umezawa, K. Tsuchiya, A. Mitrić, S. Aoki, *ACS Omega*, **2020**, *5*, 6983.
4. C. Balachandran, K. Yokoi, K. Naito, *et al.* *Molecules* **2021**, *26*, 7028 (32 pages)
5. K. Yokoi, K. Yamaguchi, M. Umezawa, K. Tsuchiya, S. Aoki, *Biochemistry*, **2022**, accepted.

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