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Clinical Image
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Design and Synthesis of Luminescent Ir Complex-Peptide Hybrids for Theranostics of Cancer

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It is obvious that theranostic (diagnosis and treatment) of cancer is one of most urgent and important challenges in cancer therapy. Cyclometalated iridium (Ir (III)) complexes such as *fac*-Ir $(tpy)_3$ **1** (tpy = 2-(4-tolyl)pyridine) (Figure 1) draw an increasing attention as one of the potential imaging tools to study extra-and intracellular events, because of their significant stability and excellent photo physical properties such as high-luminescence quantum yields, the long luminescence lifetimes (~μs order), and significant Stokes shift under physiological conditions. We previously reported some examples of Ir complexes that can be functionalized as red and white color emitters, pH sensors, photosensitizers and cell death inducer of cancer cells [1-5]. Recently, we proposed artificial luminescent Ir complexe-peptide hybrids (IPHs)**2** having cationic peptides that bind to anionic biomolecules on the cell membrane or cyclic peptide units that bind to death receptors (DRs) overexpressed on cancer cells, as inducers and detectors of cell death of cancer cells, typically, a human T-lymphoma Jurkat cells.

It was found IPHscontaining cationic peptides such as KKGG (K:lysine and G: glycine) and KKKGG sequences and alkyl chain linkers of adequate length (C6 and C8) exhibit considerable cytotoxicity against Jurkat cells (EC_{50} values are 7.3~16 μM) and that dead cells are well stained with these Ir complexes [6]. It was also revealed that IPHs having KDKKGG, KKDKGG, and KKKDGG peptides containing and aspartic acid (D) showed only negligible cytotoxic activities, although they also possess a +9 charge. Further mechanistic studies suggest that these IPHs interact with biomolecules on the cell surface and/or membrane receptors to trigger the Ca^{2+} dependent pathway and intracellular Ca^{2+} response, resulting in necrosis-like cell death accompanied by membrane disruption [7,8]. The results of photo affinity labeling experiments using IPHs containing photo reactive 3-trifluoromethyl-3-phenyldiazirine (TFPD) groups suggest that the Ca^{2+} complex of calmodulin (CaM), which is a well-known Ca^{2+}-binding protein, is one of target proteins of the KKGG-IPHs [7,8]. On the other hand, IPHs having cyclic peptide bind to DRs on the cell membrane of Jurkat cells and undergo internalization into the cytoplasm, resulting in the induction of slow cell death [9]. These results suggest that IPHs are potential agents for the theranostic of cancer and related diseases and even for mechanistic study of cell death processes.

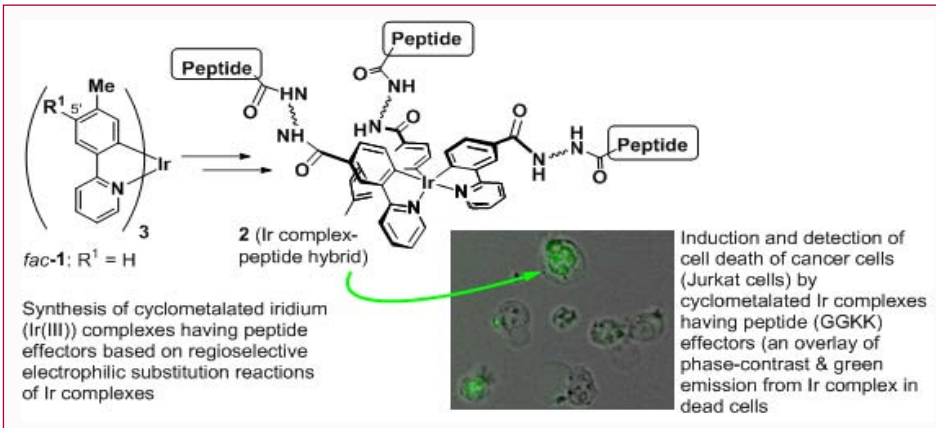

Figure 1: Synthesis of cyxlometalated iridium (Ir (111)) complexes habing peptide effectors based on regioselecitive electrophilic substitution reactions of Ir complexes.

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