

Rational Development of Various Small Molecule-based Fluorescence Probes and Their Application to Optical Tumor Imaging

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Fluorescence imaging is one of the most powerful techniques currently available for continuous observation of dynamic intracellular processes in living cells. Suitable fluorescence probes are naturally of critical importance for fluorescence imaging, but only a very limited range of biomolecules can currently be visualized because of the lack of flexible design strategies for fluorescence probes. Recently, we demonstrated that the fluorescence properties of most visible light-excitabile fluorophores could be controlled and anticipated precisely by using the concept of intramolecular photoinduced electron transfer (PeT). Based on these photo-physical findings, we succeeded to construct several totally rational design strategies for novel fluorescence probes, and to develop a wide variety of novel fluorescence probes.

One of our representative probes is those for beta-galactosidase based on the TokyoGreen scaffold. Very recently, we could establish a novel and highly activatable strategy for sensitive and selective optical imaging of imbedded tumor in the peritoneum by utilizing these beta-galactosidase probes. We took a two step procedure in that a lectin is used to localize beta-galactosidase to cancer cells as an activating enzyme, and subsequent administration of a highly-sensitive fluorescence probe for the enzyme have afforded remarkable fluorescence activation selectively in tumor mass. Since the probes themselves are almost non-fluorescent, background fluorescence from normal sites were fairly low, and since tumor-targeted enzyme can catalyze numerous substrate turnovers, a great number of fluorescent molecules could be produced. The consequent close-up investigation using fluorescence microscopy revealed that cancer microfoci as small as 200 micrometer could be successfully visualized. Therefore, rapid and sensitive detection of tumor *in vivo* with high tumor-to-background ratio could be accomplished with our novel fluorescence probes.