Fluorescent Nucleosides and Nucleotides

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Nucleic acids experience diverse cellular perturbations. These may include hybridization and dissociation, strand cleavage and ligation, conformational changes, base flipping, excision and modification, as well as perturbations induced upon ligand binding and aggregation into membrane-less cellular compartments. As such, nucleic acids attract increasing attention as drug targets (e.g., bacterial rRNA or riboswitches as targets for antibiotics) and as potential drugs (e.g., anti-sense, siRNA or gRNA for disease-specific gene silencing/editing). Additionally, nucleosides and nucleotides are involved in signaling, metabolic and regulatory processes and are viable drug targets. Our research program aims to develop fluorescent nucleoside analogues that facilitate the monitoring of nucleoside-, nucleotide- and nucleic acid-based transformations at nucleoside/tide-"resolution" in real-time.

The main criteria directing the design of emissive nucleosides are to maintain the highest possible structural similarity to the natural nucleobases, to shift the emission to long wavelengths, to retain adequate emission quantum efficiency and, importantly, to display sensitivity to the microenvironment. We define nucleosides that fulfill such critical constraints as being ***isomorphic***. To serve as effective probes, one (or all) of the analog's photophysical parameters must respond to microenvironmental changes. We described such attributes as ***responsiveness***. We have advanced several families of emissive nucleosides, each with distinct levels of isomorphicity and responsiveness (Figure 1).

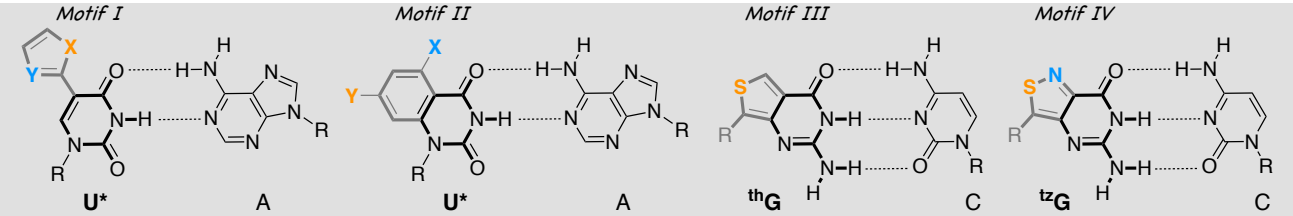

Figure 1. Four motifs of emissive nucleosides developed in the Tor lab

The lecture will articulate the fundamental challenges and will present the design, synthesis and photophysical features of emissive nucleosides. Selected examples for their utilization in "real-time" fluorescence-based discovery and biophysical assays will be given.

Selected References

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