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Pyrrole-Imidazole Polyamides as artificial genetic switches

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We have been undertaking original research on the molecular recognition of DNA by antitumor antibiotics, and the analysis of atom-specific chemical reaction on DNA. By reconstituting such knowledge, various functionalized sequence-specific DNA binding pyrrole-imidazole polyamides (PIPs) were synthesized as an artificial genetic switch, which can switch on and switch off the gene expression on demand. We recently developed alkylating PIP that could switches off cancer related KRAS gene and RUNX 1-3 controling genes. To switch on the gene expression we need to consider Epigenetics. We developed a SAHA-PIP containing sequence-specific pyrrole-imidazole polyamides (PIPs) and HDAC inhibiting SAHA. Evaluation of the effect of SAHA-PIPs on genome-wide gene expression in human dermal fibroblasts (HDFs) divulged that each SAHA-PIP could differentially activate the therapeutically important genes. Conjugation of DNA binding domain of 'I' with HAT activating CTB remarkably activated identical cluster of genes as SAHA-PIP 'I' to substantiate the role of PIP in sequence-specific gene regulation. Recently we introduced Bromodomain inhibitor to PIP to activate gene expression in sequence-specific manner. To extend recognition sequence, we introduce host-guest system to facilitate cooperative binding to target sequence. In this talk recent progress of regulation of the gene expression using designed PIPs will be discussed.