JUMPING THROUGH PROTONATION STATES: ENGINEERING pH-GATED TRANSITIONS FOR SELECTIVE AND EFFICIENT DOUBLE STRAND DNA PHOTOCLEAVAGE. **Saumya Roy**, Wang-Yong Yang**,** Diego A. R. Zorio, Boondaniwon Phrathep, Zach Rengert, Diego Zorio, Igor V. Alabugin* *Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306-4390, USA*.

The more acidic extracellular environment of solid tumors, relative to that of the normal cells, can be explored in the design of tumor-specific DNA cleaving agents. But control of reactivity and selectivity becomes especially challenging when chemical processes have to work in the complexity of biological environments. We designed, synthesized and characterized “switchable” molecular systems for pH-gated double strand DNA-cleavage which combine an efficient DNA-photocleaving agent and a pH-regulated part derived from a dipeptide. Variations in the relative number of the α-amino vs ε-amino groups of dipeptide allowed better control over the reactivity and selectivity of the ds DNA cleavage. The efficiency of ds-cleavage is increased dramatically at the slightly acidic pH where it exceeds the ds:ss ratio for the most efficient of non-enzymatic ds DNA cleavers, the natural enediyne calicheamicin.