Synthetic manipulation of biological macromolecules

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The macromolecules of life, particularly proteins and oligonucleotides, drive biological function and are increasingly the agents of therapeutic intervention in medicine. Despite their central importance, organic chemists often consider them to be the targets of synthetic small molecules rather than the synthetic targets themselves. We have developed a set of highly chemoselective ligation methods that facilitate the chemical manufacture of proteins and nucleic acids. These methods allow us to better understand their biological functions with the hope of harnessing their potent activities to improve human health. The development of the Native Chemical Ligation / Desulfurization approach for protein synthesis will be discussed and how it can be applied to the synthesis of complex macromolecular targets including peptide therapeutics and proteins that are the mirror image of the molecules produced in biological systems. Reversible Absorption to a Solid Support (RASS) approach will be presented with applications to protein and nucleic acid targets including DNA encoded libraries for drug discovery and a platform for the discovery of potent new RNA therapeutics. Together, these methods provide a robust toolkit for macromolecule synthesis that has been broadly utilized to advance peptide and oligonucleotide science.