α-Diaminobutyric Acid-Linked Hairpin Polyamide-Alkylator Conjugates

Thesis by

Sherry M. Tsai

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…for my parents…

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Abstract

The ability to control gene expression through the use of DNA sequence-specific, cell-permeable molecules holds therapeutic promise. Pyrrole-imidazole polyamides are a class of synthetic ligands that can be programmed to bind a broad repertoire of DNA sequences with affinities and specificities comparable to natural DNA-binding proteins. These ligands are generally linked via a turn moiety, resulting in a 'hairpin' structure. Conjugation of polyamides to the non-specific DNA alkylator chlorambucil produces molecules capable of the sequence-specific alkylation of DNA that can arrest gene transcription. We have identified α-diaminobutyric acid (α-DABA) as a new turn moiety that can give polyamide-chlorambucil conjugates distinctive biological properties in cellular and small animal models; this may be due to their increased DNA alkylation specificities relative to the standard γ-DABA-linked conjugates. A general characterization of α-DABA-linked polyamides and their conjugates is reported.

Also described is the development of a modular synthesis of chondroitin sulfate (CS) glycosaminoglycans — a class of linear, sulfated oligosaccharides that play critical roles in neuronal development, cell division, and spinal cord injury. CS structure *in vivo* is complex and heterogeneous, hampering efforts to understand its precise biological roles. Access to CS molecules of precisely defined structures is critical to understanding their structure-function relationships. The reported synthetic route is capable of accessing CS structures of defined lengths and sulfation motifs, providing a new approach to understanding these important molecules.

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