A New Class of Metal-Chelating Nucleic Acids

Megan Lockard, Mildred Rodriguez, and Jonathan J. Wilker

Department of Chemistry, Purdue University

Antisense oligonucleotides are emerging as an intriguing class of rationally designed therapeutics. Binding of nucleic acid-based drugs to the mRNA of a disease-causing gene can halt expression of a deleterious protein. Given the high fidelity of base-base interactions, these nucleic acid drugs have great potential for having a high degree of target specificity.[1,2] However, several obstacles must be overcome for antisense oligonucleotides to function as effective therapeutic agents: stability to degrading enzymes, capacity to effectively bind m-RNA, and ability to enter the cell.[3] To address these challenges, synthetic efforts have often focused on the development of oligonucleotides with modifications to the phosphate backbone, the site of degradation by nucleases.[4] The major categories of these molecules include phosphorothioate oligodeoxynucleotides, methylphosphonate oligodeoxynucleotides, and peptide nucleic acids. [1,5] We are developing a new class of metal-chelating nucleic acids in which phosphodiester linkages or an entire nucleoside have been replaced by metal-ligand complexes. A diverse group of ligands have been selected to afford many metal-ligand combinations. Appropriately protected ligands are synthesized and incorporated in short oligonucleotide strands via standard automated synthesis. Complementary strands are combined with the antisense oligonucleotides. Stability of these duplexes is then assessed in the presence and absence of metal ions.

---

[1] Kurreck, J. *Eur. J. Biochem.* **2003**, *270*, 1628-1644.
[2] De Mesmaeker, A., Häner, R., Martin, P., and Moser, H.E. *Acc. Chem. Res.* **1995**, *28*, 366-374.
[3] Alama, A. *Pharmacol. Res.* **1997**, *36*, 171-178.
[4] Braasch, D.A. and Corey, D. R. *Biochemistry.* **2002**, *41*, 4503-4510.
[5] Milligan, J.F., Matteucci, M.D., and Martin, J.C. *J. Med. Chem.* **1993**, *36*, 1923-1937.