CHAPTER 8: CONCLUSIONS

This thesis is a story about metalloinsertion that began before anyone knew that metalloinsertion exists. Without question, the turning point in our laboratory's study of mismatch-specific metal complexes was the elucidation of the structure of $Rh(bpy)_2(chrysi)^{3+}$ bound to a C•A mismatch. The structure was a revelation, teaching us that these complexes bind their target sites not by traditional metallointercalation but by a new binding mode: metalloinsertion. The bulky metal complex binds the DNA from the minor groove, extrudes the mispaired bases, and replaces the ejected bases in the helical π-stack with its own sterically expansive ligand.

The crystal structure answered one of our most enduring and fundamental questions: how do mismatch-specific metal complexes bind their target sites in DNA? Not surprisingly, the answer to this question illuminated explanations for other puzzling issues, including the enantioselectivity of mismatch recognition and the correlation between binding affinity and mismatch destabilization. Yet as so often happens in science, and discovery in general, the answer to one question sprouted many more inquiries. Many of these focused on the generality of the new binding mode. What sort of sterically expansive ligands can metalloinsertors use to bind mismatches? Does metalloinsertion occur at other thermodynamically destabilized DNA defects? How general is the detailed structure of this new binding mode? How can we apply this new understanding of metalloinsertion to the design of useful bifunctional conjugates?

One by one, these are the questions we have tried to answer in this thesis. First, our studies of $Ru(bpy)_2(eilatin)^{2+}$ clearly illustrate that while ligand width is essential to mismatch-specific metalloinsertion, an excess of steric bulk can lead to a loss of site

selectivity. Next, investigations with other thermodynamically destabilized DNA defects reveal that site-specific metalloinsertion is not exclusive to mismatches, extending almost certainly to abasic sites and most probably to single base bulges. Third, two new crystal structures strongly reinforce the generality of metalloinsertion at mismatched sites and support the binding mode as a new paradigm for interactions between metal complexes and DNA. And finally, the development of new bifunctional conjugates, ranging from mismatch-specific fluorophores to mismatch-targeted radiotherapeutics, reflects our aim to apply our understanding of the detailed structure of metalloinsertion to the design and synthesis of clinically useful agents.

In the end, however, it is our sincere hope that the impact of this work will lie not only in the answers it provides but also in the questions it provokes. It is perhaps then appropriate that we conclude with the words of John Muir: "But in every walk with Nature, one receives far more than he seeks."

Muir, J. *Steep Trails*. Houghton Mifflin Company: New York, 1918.