9.11: Design of New Inorganic Anticancer Drugs

1. Objectives

Although chemotherapy has made significant contributions to cancer treatment, the effect of cisplatin on testicular cancer being a showcase example, early detection and surgical removal of all neoplastic tissue still remain the preferred means of combating most forms of the disease. What steps need to be taken to devise better chemotherapeutic agents? One answer is to understand the biochemical mechanisms that underlie the transformation of normal into neoplastic cells and to attack the disease on the basis of that knowledge. The value of this approach is indisputable, but it need not be the only one. We have seen that *cis*-$[Pt(NH_3)_2Cl_2]$, a simple third-row transition-metal complex containing no carbon atoms, can contribute significantly to cancer chemotherapy. This example alone should lead us to search for improved inorganic drugs based on the evolving knowledge of the mechanism of action of *cis*-DDP. What then should our objectives be? Three answers are immediately apparent. First, we need to find compounds that are active against resistant cells. Such compounds are termed "second-generation" platinum drugs, and are the focus of much activity in the pharmaceutical industry. Their development will be facilitated by understanding the fundamental biochemistry of cisplatin drug resistance, designing complexes to circumvent the cellular resistance mechanisms. Second, there needs to be an improved spectrum of activity, to be provided by the so-called "third-generation" compounds. The major cancers of the colon, breast, and lung are not effectively diminished by cisplatin chemotherapy. Finally, cisplatin toxicity is often dose-limiting, and there is a need for agents with a greater chemotherapeutic index-to-toxicity ratio. Some of these objectives may ultimately be met by modifying the mode of delivery of cisplatin, for example, by encapsulating the drug in a tumor-seeking liposome or attaching it to a tissue-specific monoclonal antibody. A major step in alternative delivery has recently been taken with the development of a class of oral platinum complexes that have just entered clinical trials.[54] These complexes are platinum(IV) cycloalkylamine species of the kind *cis*, *trans*, *cis*-$[Pt(NH_3)(C_6H_5NH_2)(O_2CCH_3)_2Cl_2]$. The prospects are reasonably good that new platinum and other metal anticancer drugs can be designed in a bioinorganic chemical approach to the problem.

2. Strategies for Drug Development

a. Can We Build on Our Knowledge About Cisplatin?

If we consider what is known about the molecular mechanism of cisplatin, what properties are desirable in the design of new metal complexes for testing? The molecules should be reasonably stable kinetrically and soluble in biological fluids, cross the cell membrane, bind covalently to DNA, and inhibit gene function. As described previously in this section of the chapter, powerful methods are now available to screen compounds for these properties in a relatively short time. But there are additional factors required for metallodrug anticancer activity, above and beyond these criteria; *trans*-DDP, after all, has all five of the above properties and is not active. Probably one should add to the list the requirement that the complex have two substitutionally labile *cis* sites for intrastrand crosslinking of adjacent DNA nucleotides; such a criterion would, of course, rule out molecules like *trans*-DDP. Recall, however, that *cis*-$[Pt(NH_3)_2(4\text{-X-py})Cl]^+$ complexes (X = Br, Me) are active. These cations have the five properties listed above, but, as far as is currently known, bind only monofunctionally to DNA. The pyridine ring moiety of a covalently attached platinum atom could possibly intercalate into a neighboring interbase pair site on the DNA, making a pseudointrastrand crosslinked adduct structurally similar to the *cis*-DDP-d(pGpG) structure. Further information is required about these active, monofunctional cations before any firm conclusions can be drawn. Nevertheless, it is useful to remember that if the requirement of two substitutionally labile *cis* ligands had been rigorously followed, this new class of monofunctional platinum complexes would not have been discovered.

Another rationale for designing new platinum or other metal antitumor drugs could emerge with a better understanding of the SSRPs in the mechanism of action of cisplatin. For example, if they serve to protect cisplatin lesions on DNA from repair, one would want to design complexes that form adducts that bind even more strongly to the purified protein. The strength of this binding interaction, having been a serendipitous discovery, surely cannot have been maximized. A tighter SSRP-platinated DNA complex would require the use of less platinum, and thus afford lower toxicities.

b. Is Platinum Uniquely Suited?

Given the above criteria, platinum is the only metal to be chosen for further drug development? The answer to this question is "probably not" but a few points need to be kept in mind. Given the assumption that the geometry of the *cis*-$[Pt(NH_3)_2\{d(GpG)\}]$ intrastrand crosslink was important for the antitumor activity of cisplatin, computer graphics methods were employed to probe the stereochemical consequences of modifying this structure.[155] Addition of axial chloride or water ligands in fifth and sixth

coordination positions to form pseudo-octahedral adducts, for example, introduces several steric clashes with the guanosine O6 atoms. An octahedral complex, for example *cis*,*cis*,*cis*-$[Pt(NH_3)_2Cl_2(OH)_2]$, bifunctionally coordinated to DNA either would not form an intrastrand d(GpG) crosslink or would form an adduct structurally different from that made by *cis*-DDP. This octahedral complex Pt(IV), known as "tetraplatin" in the pharmaceutical industry, is active, but is believed to be reduced *in vivo* to platinum(II) before coordinating to DNA.[156,157] These considerations might imply that the best strategy for inorganic drug development would be to employ square-planar d^8 complexes. Clearly there are as yet no definitive answers. Nevertheless, the criteria derived from the mechanism of action studies of cisplatin represent an excellent starting point for designing new antitumor metallodrugs.

c. How Important are Amine Ligands?

Here again, the answer is not unequivocal, but amines (including NH_3) are probably ideally suited ligands for covalent DNA-binding metal complexes. Even completely inert complexes such as $[Co(NH_3)_6]^{3+}$ show sequence and DNA polymorph binding preferences,[158] suggesting that the N-H bonds orient toward the phosphate and heterocyclic nitrogen atoms in the major groove, forming hydrogen-bonding interactions. This chemistry is analogous to the binding and recognition of organic amines and polyamines, such as spermine and spermidine, by nucleic acids. Apart from amines, hydrophobic groove-binding and/or intercalating ligands such as o-phenanthroline and its derivatives should be considered. Molecules such as $[Rh(DIP)_3]^{3+}$, where DIP = 4,7-diphenyl-1,10penanthroline, bind to DNA and have proved to be useful structural probes (Chapter 8). Recent work has shown that $[Rh(DIP)_2Cl_2]^+$ binds preferentially to d(GpG) sequences, like cisplatin, although its antitumor properties have not yet been investigated.[159]

3. Second and Third-generation Platinum Anticancer Drugs

Improvements over cisplatin have been made, most notably the molecule carboplatin (Figure 9.4), which is less nephrotoxic and has been reported to be effective in some patients where cisplatin chemotherapy has failed. These properties come solely from the dicarboxylate leaving group, which is kinetically more inert to substitution. Studies with monoclonal antibodies have shown the DNA adducts of carboplatin to be identical with those formed by *cis*-DDP.[117]Other platinum compounds that have undergone clinical trials are close analogues of *cis*-$[PtA_2X_2]$, or tetraplatin, *cis*,*cis*,*cis*-$[PtA_2X_2Y_2]$, that obey the classic structure-activity relationships. The activity of cationic triamines, *cis*-$[Pt(NH_3)_2LCI]CI$, where L is pyridine, a substituted pyridine, pyrimidine, or purine, against S180 ascites and L1210 tumors in mice opens a new vista of possible structures to be tried. The intercalator-linked complex AO-Pt (Figure 9.26) has also been found to show activity in the S180 ascites system, suggesting a further class of complexes that could be studied. The oral compounds, *cis*,*trans*,*cis*-$[Pt(NH_3)(C_6H_5NH_2)(O_2CCH_3)_2Cl_2]$, survive the digestive tract, are taken across the gastrointestinal mucosa, and metabolize to *cis*-$[Pt(NH_3)(C_6H_5NH_2)Cl_2]$, a cisplatin analogue.[54] As such they are effective pro-drugs that could become the major platinum agent in clinical use. Until these recent advances, there was a general impression that, by chance, the best compound discovered was the first one, cisplatin. There is now sufficient reason to expect that innovative experimentation will lead to improved drugs, bearing in mind the comment made earlier (Section IV.G.) that sustained individual effort for up to a decade can be required to move a compound from the laboratory bench into the clinic.

4. Nonplatinum Antitumor Metal Complexes

a. Soft Metals

As mentioned in Section IV.E., some compounds of Pd(II), Au(I), Rh(II), and Ru(II or III) have been screened for antitumor activity, but much more work needs to be done in this arena. The higher metal-ligand exchange rates of Pd(II), ~10^5 faster than those of Pt(Il), make these complexes potentially more toxic, as some preliminary animal studies have shown. By use of chelating or organometallic complexes, however, this problem might be avoided. The properties of Ru, Rh, and to a lesser extent Au amine and polypyridine complexes would seem to make them attractive candidates, and indeed there appears to be renewed interest in these molecules.[160] Inorganic chemists interested in pursuing drug development with these metals need to forge alliances with biological colleagues equipped to do the necessary animal screening and to develop in-house expertise for cell culture and related biochemical work. The techniques are not all that difficult and it is actually fun to undertake studies of the biological consequences of metallodrug chemistry.

b. Metallocenes and Metallocene Dihalides[36-37]

Although complexes such as $[(C_5H_5)_2TiCl_2]$ are superficially analogous to *cis*-DDP, in being potentially bifunctional DNA crosslinking agents, their hydrolytic reactions are sufficiently different to cast doubt on the value of this comparison. The fact that

antitumor activity has been found for this very different class of inorganic compound, however, suggests that perhaps bioinorganic chemists have explored only a very small sample of possible metallodrugs.

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