**Studies in Molecular Structure Help to Develop New Cancer Drugs**

As researchers continue to investigate the unusual multiplication and proliferation of cells that produce cancer, they find that because certain transition metals inhibit cell growth, they may provide agents for cancer therapy. With the discovery of the antitumor inorganic metallodrug, cisplatin [*cis* diaminedichloroplatinum(II)], and related complexes such as carboplatin and oxaliplatin, by Michigan State University Professor Barnett Rosenberg, researchers found that cisplatin was an effective cytostatic[1] drug. However, due to its high level of toxicity, cisplatin produced unfortunate side-effects that include nausea and vomiting, kidney toxicity and, to lesser extents, hearing loss and peripheral neuropathy (a reduction in sensation along with numbness in affected areas). In addition, the drug was not able to prevent rectum and colon malignancies; some cancers resisted the drug altogether. However, discovery of the drug led researchers to believe that effective cytostatic therapies could result from transition-metal-based compounds, much like cisplatin. Studies done on transition metals show that their cytostatic properties could possibly be used for cancer therapy.

Through studies based upon the effectiveness of cisplatin, and from subsequent development of ruthenium complexes used to combat tumor activity, researchers have discovered the importance of chemical kinetics and molecular structure when developing new cytostatic treatments(8). Research to develop more effective drugs has been challenging and slow. Increasing demand for efficient treatments



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has caused researchers to study the molecular structures of specific metalorganic compounds and to relate their molecular structures to their ability to fight cancer cells. DNA binding, stacking, and hydrogen bonding specific to certain transition metals, has proved effective against some tumor cells. However, to synthesize effective drugs, the metal complexes had to meet specific criteria. These include: good water solubility, effective blood and membrane transport, effective DNA binding that allows slow reaction with proteins, and successful contact with specified tumor cells in tumors that have resisted cisplatin(8). Upon comparing the combativeness of metal complexes with these requirements, researchers found that Ruthenium proved to be an effective candidate.

Studies on the ability of ruthenium complexes to mimic iron in binding to DNA, exchange ligands, and assume different oxidation states, have also been significant in attacking cancer cells. The ligand-exchange kinetics, more specifically the rate of Ruthenium complexes to lose or gain molecules called ligands and to bind to other molecules depend on the structure of the complex. Figure 1 shows one type of ligand-exchange. If the drug is unable to bind to DNA for the necessary amount of time, then researchers are unable to monitor its activity against the tumor. The drug may be actively interacting with the tumor, but its ability (or lack of ability) to remain situated on the tumor, has led to further research on the effectiveness of various transition metals. As reported by Reedijk, knowing the kinetics of interaction of transition metal complexes, specifically those of Ruthenium, may lead to improved treatment against cancer cells(8). Ligand-exchange kinetics is also related to the specific shape of the molecule. If the shape leads to slower interaction due to steric hindrance[5] between axial components of the complex with DNA molecules in the tumor, then the drug is less effective. Research is in progress to develop drugs that lead to stronger and faster axial component interaction (8).



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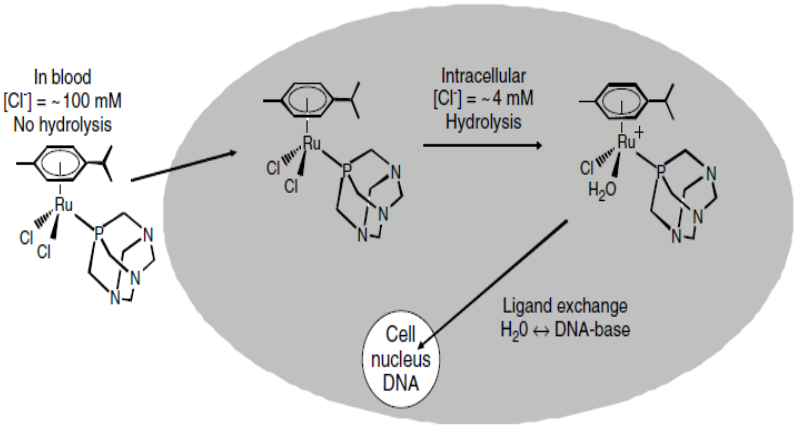


Figure 1. Exchange of chloride ligands with water between Ruthenium compounds. *Allardyce, Claire S., and Paul J. Dyson. "Medicinal Properties of Organometallic Compounds." Topics Organometallic Chemistry 17 (2006): 177-210. CAPLUS. Web. 3 Feb. 2010. <https://scifinder.cas.org/scifinder/view/link_v1/reference.jsf?l=BmxxGlm8wGo-uftQoXTgX2b0B9NCUduqqv8kaqYmsuftnjRrob6k_Q>.*

New drug-monitoring techniques are important for recording the activity and effectiveness of newly designed drugs. Highly efficient fluorescent labeling and improved microscopy will lead to better monitoring of novel treatments; data concerning monitoring can be used to improve research in the interaction of various ruthenium complexes with biologically significant molecules. Mass Spectroscopy and Nuclear Magnetic Resonance techniques can help detect the specific interactions of the transition-metal-based drugs within the DNA sequence and provide evidence concerning their effectiveness (8). Researchers at the Universities of Edinburgh, Warwick and Leeds used Nuclear Magnetic Resonance spectra of the Ruthenium



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complexes to monitor significant cell death of Ovarian and Cancer cells (8). X-ray crystallography, used by these researchers, displayed the cytotoxic nature of bonds formed with ruthenium (II) complexes. There have also been reports of *trans* and *cis* reactions of platinum compounds with nucleic acids in DNA as a labeling technique to monitor the activity of transition metal complexes. The platinum is selectively attached to a nucleotide and marked by a fluorescent label which can be detected within the body. Figure 2 shows one possible structure of this label with a platinum compound. These studies are likely to lead to better development of effective anticancer agents (8).

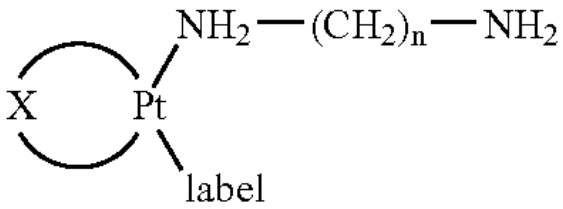


Figure 2. One type of kinetically controlled labeling technique using a Platinum Compound.
*Houthoff, H.J, Reedjik, J, Jelsma, T, Heetebrij, R. J, Volkers, H. H. Methods for labeling nucleotides, labeled nucleotides and useful intermediates. Application Information WO97?NL559 19971008.*

Ruthenium, in group 8 of the periodic table, is cytostatically active. As reported by Sava and Bergamo, due to Ruthenium's octahedral structure and its ability to combine with certain ligands, it binds to cancerous tumors more than to other biological tissues. This attraction to specific malignancies not only supports Ruthenium's role as an effective cytostatic agent, but it can also serve as a mechanism to aid in the imaging of tumors (6). Studies done by Clark and



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Sava show that Ruthenium's ability to bind to other biological molecules (eg. transferrin molecules in the plasma[2] and on the surface of tumor cells) enables its entry into the cancerous sites (6). Figures 3 and 4 show the structures of *cis* and *trans*-($Ru(II)(DMSO)_4Cl_2$) and an example of a heterocyclic ruthenium complex can be seen in Figure 5. Ruthenium has many advantages relative to cisplatin due to its low toxicity, its ability to bind to molecules located on the tumor site, and its overall cytostatic tendencies. The chemical properties of Ruthenium such as its octahedral shape, its function as a ligand binding molecule, its various oxidation states, and its ability to be monitored, make Ruthenium a strong candidate for cancer research.

Ruthenium is also an effective alternate to the cisplatin complex because it has a direct ability to bind to the DNA molecule. Ruthenium binds to the purine groups[6] within the DNA molecule; this binding later inhibits DNA synthesis in the cell. Figure 6 shows the location where the Ruthenium compound binds to the N-7 atom on the purine group. This is a key function that [1]characterizes Ruthenium's inhibition of cancer-cell proliferation (6). It is the structures of the various Ruthenium complexes that enable them to bind to specific purine groups in DNA. A study by Keppler found that certain *trans* and *cis* forms of Ruthenium complexes had effective results in combating carciosarcoma, colon tumors, and melanomas (6). Upon taking a closer look at the *cis* and *trans* dimethyl sulphoxides of Ruthenium (II) in Figures 3 and 4, the significance of the structure of the molecule is clearly evident. Mestroni showed that the *trans* form of the



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compound is a far more effective candidate in antimestasis[3] than the *cis* isomer. In the *cis*-[Ru(II)(DMSO)4Cl2] compound, three of the four DMSO molecules are connected to the Sulfur atoms, whereas the fourth DMSO is attached to the oxygen. However, in *trans*-[Ru(II)(DMSO)4Cl2], every DMSO atom is connected to the Sulfur molecule. This is significant because the *trans* form loses more DMSO molecules than the *cis* form when in contact with water; after disassociating into chloride anions and forming cations, the *trans* molecule contains three reactive groups compared to only two from *cis*. Because of this difference in reactive groups, and because of significant steric hindrance, *cis* is an inert molecule that does not function as effectively as the *trans* molecule (3). Mestroni also found that as an effective binding compound, the reaction rate of the *trans* isomer is much larger than that of the *cis* isomer, but both produce changes in DNA conformation (3). The different structures also account for the ability of the *trans* isomer to inhibit RNA synthesis while the *cis* is unable to do so. Studies done by Novakova have shown that the isomer's effectiveness is related to its mode of binding, similar to that of cisplatin (3).

Another structural form of Ruthenium (III), Ruthenium-N-heterocyclic, has also proven to be an anticancer agent. Figure 5 shows the structure of a heterocyclic Ruthenium compound. Studies by Keppler found that Ruthenium-N-heterocyclic has been used against colorectal tumors and has proven effective because it has minimal side-effects (3). This complex was especially active because it could induce apoptosis[4] of cells due to its ability to interact with



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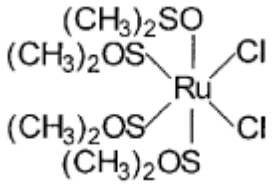
transferrin receptor molecules located on the surface of a cell. Ruthenium-N-heterocyclic binds to the transferrin transporter, which then takes it to the tumor site, and is then transported into the cell, and converted to Ruthenium (II). This process is biologically lethal to diseased cells that have the Ruthenium (III) form within the cell. The cytotoxic nature of Ruthenium (II) in the cell activates inhibition of the cancer cell and is due to different ligands binding to Ruthenium (II) in comparison to Ruthenium (III) (2). However, due to the structure of the complex, attacking the diseased cell does not need to take place in the interior of the cell, but can also take place on the outer surface, by surrounding and confining the cancer cell(2).

Latest reports have affirmed Ruthenium's ability to kill cancer cells. In an article published in the *ScienceDaily* on October 19, 2009, "Unusual Metals Could Forge New Cancer Drug", it was reported that research by Dr. Patrick McGowan, at the University of Leeds, showed that Ruthenium and Osmium were both elements that showed inhibitive ability against Ovarian cancer. Cells that resist cisplatin, were susceptible to the Ruthenium and Osmium complexes. With these current studies showing promising developments of alternative transition metals against cancer cells, it may be possible to end the proliferation of cancer cells.

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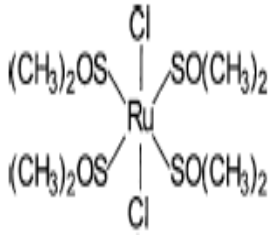


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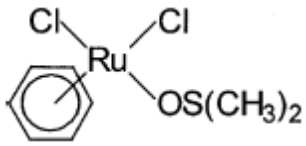
Figures 3 and 4. Figure 3 show cis--[Ru(II)(DMSO)4Cl2] while Figure 4 shows *trans*-[Ru(II)(DMSO)4Cl2]. *Cis- and trans-[Ru(II)(DMSO)4Cl2] Viktor Brabec , Olga Novakova. (2006). DNA binding mode of ruthenium complexes and relationship to tumor cell toxicity. Drug Resistance Updates 9 (2006) 111–122. 113. Retrieved 27 Janruary, 2009, from Science Direct.*




**5**

Figure 5. An example of a heterocyclic Ruthenium compound. *Heterocyclic complexes. Viktor Brabec , Olga Novakova. (2006). DNA binding mode of ruthenium complexes and relationship to tumor cell toxicity. Drug Resistance Updates 9 (2006) 111–122. 113. Retrieved 27 Janruary, 2009, from Science Direct.*

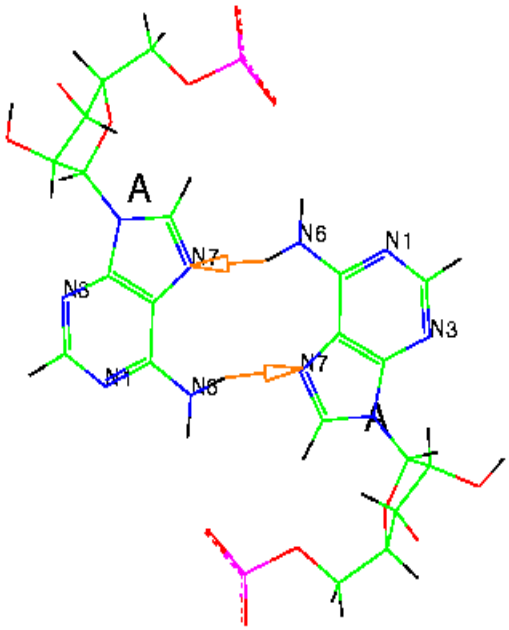



Figure 6. The N-7 atom on the purine group is one location of Ruthenium compound binding. *"The Base Pair Directory." Image Library of Biological Macromolecules. JENA. Web. 2 Apr. 2010. <http://www.imb-jena.de/ImgLibDoc/bp/aa.html>.*



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