APPENDIX A

Declaration of Stephen G. Chaney, PhD

I, Stephen Chaney, PhD, hereby declare as follows:

1) Background and Qualifications

I obtained my B.S. degree in Chemistry from Duke University, my PhD degree in Biochemistry from UCLA and completed my postdoctoral training in the Department of Microbiology at Washington University in St. Louis. I have been at the University of North Carolina for 34 years where I am currently Medical Alumni Distinguished Teaching Professor of Biochemistry and Biophysics. For the past 25 years, my research has focused on platinum anticancer agents. I have extensively studied cisplatin (*cis*-diamminedichloroplatinum(II)), Pt(dach)Cl_2 (*cis*-1,2-diaminocyclohexanedichloroplatinum(II)), malonatoplatinum (*cis*-1,2-diaminocyclohexanemalonatoplatinum(II)), ormaplatin (tetraplatin, (*trans-RR*)1,2-diaminocyclohexanetetrachloroplatinum(IV)), oxaliplatin ((*trans-RR*)1,2-diaminocyclohexaneoxalatoplatinum(II)) and their biotransformation products. I developed a new HPLC methodology to separate the chemical biotransformation products of Pt(dach)Cl_2, malonatoplatin, tetraplatin and oxaliplatin[1,2] and have studied the biotransformations of those compounds *in vitro*[2-8], in cell culture[9-12], in rats[13-15] and in conjunction with human clinical trials[16-18]. I have studied the effect of the carrier ligand (*cis*-diammine and dach (1,2-diaminocyclohexane)), leaving ligands (chloride, malonate, oxalate, water and methionine) and oxidation state (platinum (IV) or platinum (II)) on the cellular uptake[4,10,11,19,20], cytotoxicity in cell culture[10,11,19,20], pharmacokinetics[15,16,18], toxicity in dorsal root ganglia explant cutures[6] and toxicity in animals[21]. I have also characterized the effect of the DNA adducts formed by cisplatin and oxaliplatin on the molecular processes related to the efficacy, toxicity and mutagenicity of those adducts[22-40]. I have over 100 refereed (peer-reviewed) papers and review articles, and I have been invited to speak at the last four International Symposia on Platinum Compounds in Cancer Chemotherapy. A copy of my Curriculum Vitae is attached as Exhibit A.

2) The Action Mechanism of Platinum Anticancer Agents

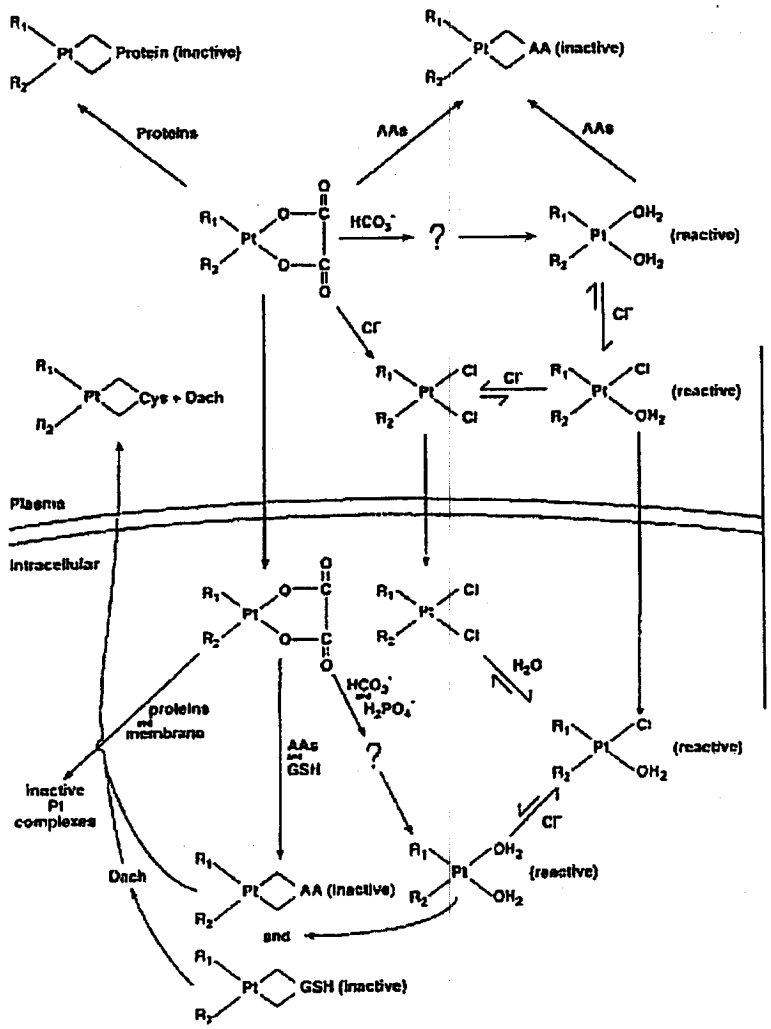
Platinum complexes are thought to enter the cell by passive diffusion[41], although recent research has suggested that certain transporters[42,43] and/or endocytosis[44,45] may play a role as well. Once inside the cell, almost all platinum anticancer agents are thought to be activated to extremely reactive aquated platinum(II) complexes, which react with cellular membranes, protein, RNA and DNA[46]. In dividing cells, platinum-DNA adducts are thought to be the cytotoxic lesion [46]. However, in non-dividing cells toxicity may be caused by damage to the cell membranes, inactivation of critical enzymes or inhibition of transcription[47]. In addition, the presence of platinum adducts on the DNA has been postulated to trigger apoptosis directly[48] or "hijack" essential transcription factors[49,50].

3) Biotransformations of Platinum Compounds with Carboxylic Acid Leaving Ligands

Effective platinum anticancer agents are generally relatively stable in the bloodstream and are activated to aquated platinum(II) complexes once they are taken up by the cell. In the case of platinum(II) complexes with chloro leaving ligands such as cisplatin or $Pt(dach)Cl_2$, this intracellular activation was well understood when I began my study of platinum anticancer agents. The extracellular chloride concentration is around 0.1 M, while the intracellular chloride concentration is around 3 mM. At 3 mM chloride concentration, the $t_{1/2}$ for dissociation of the chloro ligand from cisplatin is ~2 hours[51,52]. Thus, the aquation rate of cisplatin at physiological intracellular chloride concentrations was clearly sufficient to account for the biological activity of cisplatin. However, the intracellular activation mechanism of platinum(II) complexes with dicarboxylic acid leaving ligands was much less clear because the $t_{1/2}$ for dissociation of those leaving ligands in water is on the order of 90-240 hours[53]. In order to develop models for activation of platinum(II) complexes with dicarboxylic acid leaving ligand, we incubated malonatoplatin and oxaliplatin with biologically relevant nucleophiles at physiological concentrations and characterized the reaction products by HPLC[1-3,9]. Those studies showed that both bicarbonate and phosphate at physiological concentrations were relatively effective at displacing malonate and oxalate ligands[1-3]. Because both the Pt(dach)(phosphato) and Pt(dach)(bicarbonato) complexes readily dissociated to form aquated Pt(dach) complexes, we postulated that these reactions likely represented activation pathways[1-3]. Furthermore, the rate of these reactions was sufficient to explain the intracellular activation of malonatoplatin and oxaliplatin under physiological conditions.

Glutathione, amino acids, citrate, lactate and creatine at physiological concentrations were also capable of displacing the malate and oxalate ligands, with glutathione and the sulfur-containing amino acids being the most reactive[1-3]. However, the Pt(dach)(amino acid) complexes were all quite stable. For example, all of the Pt(dach)(amino acid) complexes tested were relatively unreactive towards DNA[1-3]. The Pt(dach)(methionine) complex was purified and characterized in detail. It was shown to consist primarily of the Pt(dach)(mono-methionine) complex by LC/MS[2,3]. It was not taken up by mouse L1210 cells[3] and was taken up at a reduced rate by human HT 29 colon carcinoma cells[11], presumably because it was positively charged. It also did not have appreciable cytotoxicity towards cultured HT-29 cells[11] or neurotoxicity to rat dorsal root ganglia in explant culture[6]. On the basis of these data, we postulated that the displacement of the malonate and oxalate ligands from malonatoplatin and oxaliplatin, respectively, by glutathione and amino acids most likely represented inactivation pathways[2,3,9].

We did not characterize the Pt(dach)(citrato) and Pt(dach)(lactato) complexes, because the Pt(dach)(citrate) and Pt(dach)(isocitrato) complexes had already been shown to be biologically active[54-56]. Thus, we concluded that these reactions represented potential activation pathways. We summarized these biotransformation studies in the model[2,5,9,57] shown below:



4) <u>Buffered Solutions of Oxaliplatin</u>

I have been asked to consider whether or not byproducts of the reaction of $Pt(dach)(H_2O)_2^+$ or oxaliplatin with carboxylic acid buffers could be cytotoxic or have undesirable toxicity. Our data clearly show that buffered solutions containing the conjugate base of either inorganic acids (phosphoric acid, carbonic acid) or organic acids (carboxylic acids and amino acids) can displace the oxalate ligand from oxaliplatin, giving rise to new complexes. Our data further show that formation of some of these complexes represents a likely activation pathway. Data from other labs show that many, but not all, of the Pt(dach)(carboxylato) complexes that can be formed in this manner have biological activity. For example, Pt(dach) complexes containing citrate, isocitrate, ascorbate, tartrate and 4-carboxyphalate as the leaving ligand all displayed comparable cytotoxicity to malonatoplatin and oxaliplatin in the mouse L1210 tumor model, while Pt(dach) complexes containing pyruvate or aspartate as the leaving ligand did not display

any biological activity[54-56,58-60]. Moreover, the type and severity of toxicity caused by these complexes may well be different from oxaliplatin. For example, in phase I/II clinical trials the Pt(dach)(4-carboxyphalato) and Pt(dach)(isocitrato) complexes both showed greater myelosuppression and less neurotoxicity than oxaliplatin[61,62].

When evaluating the potential efficacy and toxicity of a compound such as tartratoplatin (*trans-RR*)diaminocyclohexanetartratoplatinum(II), which is likely to form when oxaliplatin is stored in a buffered solution containing tartrate, it is important to understand that the efficacy and toxicity of such contaminants cannot easily be predicted on the basis of its similarity to oxaliplatin. While some properties of platinum complexes (*e.g.* cellular uptake, cross-resistance and mutagenicity) can be explained on the basis of their hydrophobicity, aqueous stability and carrier ligand (*e.g. cis*-diammine vs. 1,2-diaminocyclohexane), other important characteristics are very difficult to predict on the basis of structural similarities. Efficacy, tumor range, and the extent and type of toxicity are determined by a combination of pharmacokinetics, pharmacodynamics, biotransformations and other factors that are not clearly understood. In the case of the Pt(dach) platinum complexes, it is quite clear that their characteristics are not solely dependent on the diaminocyclohexane carrier ligand. For example, of the Pt(dach) complexes evaluated to date, only oxaliplatin has been shown to display clear efficacy in the treatment of metastatic colon cancer[63,64] and only oxaliplatin and ormaplatin have been reported to display neurotoxicity as the dose-limiting toxicity[61-63,65].

5) Conclusions

Buffered solutions containing oxaliplatin and the conjugate base of either inorganic acids or carboxylic acids are likely to undergo chemical exchange reactions in which the conjugate base displaces the oxalate ligand, leading to the formation of new Pt(dach) complexes. Many of these new Pt(dach) complexes are likely to have biological activity and toxicity. This is particularly true for tartratoplatin, which has already been shown to be biologically active[55]. Moreover, the tumor specificity and the toxicity of tartratoplatin and similar platinum complexes formed in this manner are not predictable and cannot be assumed to be the same as oxaliplatin. Thus, if a company were to propose formulating oxaliplatin in a buffer system contain tartrate or the conjugate base of any other acid, it should be incumbent on that company to demonstrate that no significant formation of new Pt(dach) complexes occurs under their anticipated storage conditions. If significant amounts of new Pt(dach) complexes did form upon storage, pre-clinical and clinical tests should be performed to determine that these byproducts do not have any unexpected toxicity and retain the same tumor specificity as oxaliplatin.

Dated: September 7, 2006

Stephen D. Chaney

Stephen Chaney

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