Supplemental Declaration of Stephen G. Chaney, Ph.D.

I, Stephen Chaney, Ph.D., hereby make the following declaration in support of that Supplemental Position Paper submitted by sanofi-aventis S.A.:

I. 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-diaminedichloroplatinum(II)), Pt(dach)Cl₂ (cis-1,2-diaminocyclohexanedichloroplatinum(II)), malonatoplatinum (cis-1,2-diaminocyclohexanemalonatoplatinum(II)), ormaplatin (tetraplatin, (trans-RR)1,2-diaminocyclohexanetetrachloroplatinum(IV)), oxaliplatin ((trans-RR)1,2-diaminocyclohexanexoxalatoplatinum(II)) and their biotransformation products. I developed a new HPLC methodology to separate the chemical biotransformation products of Pt(dach)Cl₂, malonatoplatinum, tetraplatin and oxaliplatin¹,² and have studied the biotransformations of those compounds in vitro,²⁻⁸ in cell culture,⁹⁻¹² in rats¹³⁻¹⁵ 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 cultures⁶ 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. I am the same Stephen Chaney who authored a declaration in support of the original Position Paper submitted by sanofi-aventis.

II. Solutions of Oxaliplatin With Added Sugar

I have been asked to consider whether or not oxaliplatin might form byproducts if stored in sugar solutions for extended periods of time and whether any of the byproducts that do form could be cytotoxic or have undesirable toxicity. I have reviewed the Report from Sanofi-Synthelabo Recherche (August 2004) of a study wherein lactose, maltose, glucose and sucrose were added to solutions of oxaliplatin in water. That Report shows that the addition of sugars to oxaliplatin increases the formation of certain complexes during storage as compared to a solution of oxaliplatin in water (without added sugars) under the same storage conditions. In particular, the complexes that formed in increased amounts were Pt(IV)(DACH)(OH)₂(oxalato), a dimer formed from Pt(II)(DACH)(H₂O)₂, and a number of unidentified complexes derived from both Pt(IV)(DACH)(oxalato)(X₂) (where X₂ = unidentified ligands) and Pt(II)(DACH)(H₂O)₂.
The Pt(IV)(DACH) and Pt(II)(DACH) complexes that are increased by the addition of sugars to oxaliplatin are likely to be active in humans. Although the structures of some of the particular complexes resulting from the reactions of sugars with oxaliplatin and its related chemical compounds (Pt(IV)(DACH)(OH)2(oxalato) and Pt(II)(DACH)(H2O)2) are currently unknown, it is well established that Pt(II)(DACH)(H2O)2 and Pt(IV)(DACH) derivatives are active and potentially toxic.6,11,21,58,59,62 Moreover, the type and severity of toxicity caused by these complexes may well be different from oxaliplatin. For example, we have shown that Pt(II)(DACH)(H2O)(Cl) and Pt(II)(DACH)(H2O)2 are more cytotoxic than oxaliplatin in HT-29 cells11 and are more neurotoxic than oxaliplatin in a rat dorsal root ganglia neurite outgrowth assay6. With respect to the Pt(IV)(DACH) compounds Yamashita et al.58 and Siddik et al.59 have shown that while Pt(IV)(DACH)(OH)2(oxalato) is less cytotoxic than oxaliplatin in L1210 cells, other closely related Pt(IV)(DACH)(oxalato)(X)2 compounds have equal or greater cytotoxicity than oxaliplatin in L1210 cells. The neurotoxicity of these Pt(IV)(DACH) compounds relative to oxaliplatin has not been determined, but we have shown that ormaplatin (tetraplatin, (trans-RR)1,2-diaminocyclohexanetetrachloroplatinum(IV)) is more neurotoxic than oxaliplatin both in dorsal root ganglia explant cultures6 and in a Wistar rat model in vivo.21 Ormaplatin has also been shown to be more neurotoxic than oxaliplatin in human clinical trials.62

When evaluating the suitability of a formulation of oxaliplatin in a solution containing a sugar it is important to evaluate the stability of oxaliplatin over the expected shelf life of that formulation and to identify any new Pt(DACH) complexes that form. Furthermore, when evaluating the potential efficacy and toxicity of the Pt(DACH) complexes that do form, such as those identified in the sanofi-aventis Report, it is important to understand that the efficacy and toxicity of such contaminants cannot easily be predicted on the basis of their similarity to oxaliplatin or other prior tested compounds. 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 cancer60,61 and only oxaliplatin and ormaplatin have been reported to display neurotoxicity as the dose-limiting toxicity60-62.

III. Conclusions

Solutions containing oxaliplatin and a sugar can undergo chemical reactions leading to increases in the formation of certain Pt(DACH) complexes, which may have unexpected toxicity and may not retain the same tumor specificity as oxaliplatin.
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References


