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SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF SANTA CRUZ

ELYZABETH SILVAH, individually, and as Guardian Ad Litem for JAIAH SILVAH, Plaintiffs, vs. NANETTE MICKIEWICZ, M.D. an individual; HOWARD SALEM MAGARIAN, M.D., an individual; PLANNED PARENTHOOD, a business entity; GLAXOSMITHKLINE, a corporation and DOES 1 through 50, inclusive, Defendants.	Case No. CV 145704 Judge Arthur Danner, III Complaint Filed February 14, 2003 **DECLARATION OF KEVIN J. SCANLON, Ph.D.** TRIAL DATE: 5/23/05

I, Kevin J. Scanlon, Ph.D., declare:

1. I make this declaration with personal knowledge of the following facts, and, if called, could and would competently testify thereto to a reasonable degree of medical

and scientific certainty.

2. I am a molecular Biochemical Pharmacologist and Gene Therapist. I received a Bachelor of Arts degree in Biology/Chemistry from Sacred Heart University in Fairfield, Connecticut, and a Ph.D. in Biochemistry and Molecular Biology from the University of London, England. I also did post-doctoral research in Biochemical Pharmacology at Yale University School of Medicine. From 1985 through 1996, I was the head of the Biochemical Pharmacology Section at the City of Hope National Medical Center in Duarte, California. From 1996 through 2000, I was Vice President and Director of Cancer Research worldwide at Berlex Biosciences, a Division of Schering AG in Berlin, Germany. Until 2004, I was responsible for the creation and teaching of Pharmaceutical Development graduate courses at the Keck Graduate Institute in Claremont, California. I am a member of the Scientific Advisory Board of the National Institute of Cellular Biotechnology headquartered in Dublin, Ireland (2000-present). I am the Co-Editor of Cancer Gene Therapy (1993-present). I serve on the editorial boards of a number of cancer-related publications including Antisense and Nucleic Acid Drug Development, In Vivo, Journal of Chemotherapy, Molecular Biotechnology, Molecular Pharmacology and Current Opinion in Molecular Therapeutics. I was the President of the International Society of Cancer Gene Therapy from 2001-2003 and have been a council member since 1996.

3. This declaration is based on my scientific training and experience, including my original research relating to AZT, upon my knowledge and review of the published medical literature as it pertains to cancer chemotherapy, the use of chemicals known as nucleoside analogues, and the biochemical properties and uses of AZT, alone and in conjunction with so-called cytotoxic cancer chemotherapeutic agents.

4. I am readily familiar with the chemical, biochemical and pharmacological properties of 3'-azido-2', 3'-dideoxythymidine (also known as "AZT"or Retrovir), and I

have personally investigated AZT both in vitro (in my laboratory) and in a clinical setting. I am the lead author of several scientific studies concerning AZT published in the medical literature, including Scanlon K.J., et al., "*Overexpression of DNA Replication and Repair Enzymes in Cisplatin-Resistent Human Colon Carcinoma HCT8 Cells and Circumvention by Azidothymidine,*" Cancer Communications, 1:269-275 (1989) and Scanlon K.J., et al., "*Potentiation of Azidothymidine Cytotoxicity in Cisplatin-Resistent Human Ovarian Carcinoma Cells,*" Cancer Communications, 2:339-343 (1990). I am also a co-author of the clinical study relating to the combined use of AZT and cisplatin referred to by plaintiffs in this case as the "Morgan Paper" (Morgan, et al., "Phase I Study of Cisdiamminedichloroplatinum in Combination with "*Azidothymidine in the Treatment of Patients with Advanced Malignancies,*" Cancer Chemotherapy Pharmacology, 51:459-464 (2003).

5. I have reviewed declarations of David Rasnick, Ph.D., and Philip Incao, M.D. submitted to the court in this litigation. In my opinion, the conclusions asserted by Rasnick and Incao as to the investigation and use of AZT in the area of cancer treatment are at best misleading, and, in many instances, are substantively inaccurate.

6. In order to understand how AZT works, and why it is not cytotoxic to "host" (human) cells, and therefore an ineffective cancer agent, one must understand the cellular components known as nucleosides and nucleotides and their role in DNA synthesis. Cells can grow only by using nucleic acids to make DNA. Nucleic acids are either purines (**A**denine or **G**uanine) or pyrimidines (**T**hymidine or **C**ytosine). These nucleic acids need to be activated into nucleosides by the addition of a sugar (deoxyribose) and activated into nucleotides by being phosphorylated (addition of three phosphate groups) into their active form for DNA synthesis. The cell requires four nucleotide tri-phosphate pools of activated (A, G, C and T) bases for DNA synthesis. DNA is made in the cells by a DNA synthesis (DNA polymerases) and repair enzyme complexes that can reproduce an exact copy of DNA. The DNA is a double stranded molecule that is held together by base pairs (hydrogen bonding) of either A: T or G: C. The sequences of these bases code for the

diversity and complexity of life on this Earth.

7. If a mistake in a nucleic acid base sequence occurs there is a potential for DNA mutation. If this mutation is in a critical area of the gene, it can be lethal or lead to evolutionary divergence. Fortunately, the human DNA synthesis complex also contains repair enzymes that "proof read" the newly synthesized strands of DNA for any mistakes (i.e. incorrect bases in the sequences of DNA). This is unlike most viral DNA synthesis and repair complexes, which do not have selective proof reading enzymes. HIV, an RNA retrovirus, lacks repair capacity in the Reverse Transcriptase enzyme, and thus is susceptible to mistakes in replication that are not identified and repaired causing mutations that can, for example, lead to the development of several different subtypes of HIV.

8. "Nucleoside analogues", such as AZT, are simply synthetic (in the case of a drug) or natural chemicals that resemble nucleosides in their structure and/or function (sometime called "fraudulent" nucleosides) some of which may, under certain conditions, incorporate into DNA synthesis.

9. Historically, nucleoside analogues have been synthesized and screened for biochemical activity since the 1940's. These analogues (~10,000) were screened against cancer cells *in vitro* (~100), from mice to human, without effectiveness as cancer therapeutic agents. This lack of anti-cancer activity has been documented at the National Cancer Institute and dozens of cancer centers and cancer research institutes worldwide, over the past 50 years. These analogues are ineffective as cancer drugs because as single agents these they are pharmacologically inactive and have a limited capacity to be activated. Human cancer cells have difficulty transporting and activating nucleoside and nucleotide analogues. Accordingly, the value of nucleoside analogues in cancer therapy has been limited to their use in *combination* with other agents that allow analogues to become activated. For example, some purine nucleoside analogues have been successfully used in the treatment of cancer from the early 1950's, but only when used in combination with other drugs that facilitate analogue activity in human cancer cells. Thus, the fluoropyrimidine analogues, such as 5-Fluorouracil analogues, have been effective in colon

carcinoma with combination chemotherapy. The cytidine analogues such as Ara-C, 5-Azacytidine and Gemcitabine have been useful in the treatment of leukemias and solid tumors in drug combinations.

10. As single agents, however, the nucleoside analogues developed to date have only been shown effective in clinical use as anti-viral or anti-retroviral medications, partly because the analogues used for such purposes selectively target viral DNA synthesis, with little if any effect on the host (human) cells, providing a very favorable Therapeutic Index (i.e., dose needed to be effective without causing unacceptable side effects). For example, Acyclovir (Zovirax) is a very safe and effective herpes treatment. It is an acyclic guanine nucleoside that lacks the3'hydroxylon the side chain. Acyclovir inhibits viral DNA synthesis through its being selectively activated by the viral Herpes Simplex Virus (HSV) thymidine kinase. The affinity of Acyclovir the HSV kinase is ~200 fold greater than for the host DNA synthesis complex. This increases the pool size of activated drug over the endogenous triphosphate (dGTP) pools.

8. AZT is a pyramidine nucleoside analogue of thymidine. AZT has a very specific biochemical activity, which makes it quite effective as an anti-retroviral (e.g., anti-HIV) compound, but essentially useless as an anticancer drug. Retroviral replication requires the enzyme, Reverse Transcriptase (RT), to transcribe the RNA molecule into a single strand DNA to form a DNA /RNA hybrid. The specificity of the RT to incorporate DNA bases on to the RNA transcript is not enzymaticaly specific, which explains why AZT can be easily be incorporated into the viral DNA strand. RT does not have proofreading capabilities (the ability to recognize the incorporation of the "false" nucleoside and eliminate it), which allows AZT to remain in incorporated and to then "chain terminate" HIV replication. Conversely, human host DNA and the human replication complex (DNA polymerases and DNA repair enzymes) are very selective and have a strong proof reading capacity to repair incorrect bases. As a result, it is extremely difficult for AZT to incorporate into human DNA without the DNA being repaired, especially when the drug is used at concentrations associated with HIV treatment. Both

pharmacology and medical textbooks classify AZT as an antiviral agent for the reasons described above.

9. It is true that AZT was originally synthesized in the early 1960's, along with numerous other nucleoside analogues, with the objective of investigating the possibility that the chemical could have some application to cancer. However, the compound was not "developed" as a cancer chemotherapy drug as that term is normally used in pharmaceutical research. Thousands of chemicals are synthesized in laboratories each year. A subset of newly synthesized chemicals with theoretical drug applications is then tested in vitro (in the laboratory) to determine whether they have desirable biochemical activities. Potential cancer agents are analyzed in this manner through cytotoxicity "screens," in which the effects of a chemical on cancer cells grown in a Petri dish are analyzed. A further subset of screened chemicals that demonstrate desirable characteristics (and thus theoretical application to one or more human diseases) may then proceed to investigation *in vivo (*animal studies*)*. Such animal studies would include, for example, experiments designed to look at toxicology and potential dose ranges. An even smaller number of experimental agents then advance to the human clinical trials stage in which the most crucial phase of drug development occurs, and in which a drug must be shown to be both reasonably safe and efficacious. Many compounds that show promise in preclinical experiments have failed in clinical trials. The FDA ultimately and solely approves this therapeutics for use in the general population.

10. In the case of AZT, prior to its development and approval as an antiretroviral medication, the compound was not pursued as a potential cancer therapy. This was not because of its "toxicity," but because of its lack of activity against cancer cells during the course of *in vitro* experiments (cancer screens). To put it in lay terms, AZT was rejected as potential "cytotoxic" cancer chemotherapy for the very reason that it was demonstrably not cytotoxic at any concentration termed and showed a limited effect on cancer cells; maximum tolerated dose (MTD). For this reason, AZT was never "developed" as a cancer chemotherapy drug, and it is not, nor has it ever been, indicated or

used in humans for that purpose. Indeed, it would be unethical to treat cancer patients with AZT monotherapy in clinical trials since the drug would likely be no more effective than the placebo control.

11. Subsequent to the approval of AZT as a drug to treat AIDS patients, there was renewed interest in the investigation of AZT in the treatment of some cancers, but only as an adjunct to certain "traditional" cytotoxic chemotherapeutic agents. For example, in our clinical study (mischaracterized by Drs. Rasnick and Incao as a study of the use of AZT as "cancer chemotherapy") we *combined* AZT with cisplatin, a well-known cancer chemotherapy drug, in order to reverse cellular resistance to cisplatin therapy. In our studies, AZT alone in cisplatin sensitive human tumor cells or cisplatin resistant cells was *ineffective* as a single cancer chemotherapy agent because AZT has limited ability to permeate cancer cells, was poorly activated, and any activated AZT would be diluted in the large endogenous thymidine triphosphate pool. However, we found that a sub-optimal dose of cisplatin to the cisplatin resistant cancer cells activated DNA replication complex enzymes and altered the pools of the DNA bases, including thymidine. The drug treated resistant tumor cells were "tricked" into using AZT as a natural base because these cells were desperate to use any nucleoside or analogue. In other words, cisplatin artificially tricked the cells into activating AZT (recognizing it as thymidine), which was present in excess in the cells. In addition, AZT, unlike other pyrimidine analogues, was effective, in combination with cisplatin, because it *selectively* chain terminated DNA synthesis and repair in the cisplatin resistant cancer cells. This was a very novel and unique exploitation of an antiviral agent, AZT, for treating cancer. However, it is important to understand that the activation of AZT and its resulting ability to overcome normal human DNA proof reading and repair mechanisms in our study was a function of the combination of the drug with cisplatin. AZT is not a stand-alone cancer chemotherapy agent, as demonstrated in my previous publications, and this study never said nor implied that it is, nor am I aware of any human study in which AZT has been used as a single agent for non-viral based cancer chemotherapy.

12. In my opinion, it is medically and scientifically inaccurate to describe AZT as a "cancer chemotherapy" agent, much less a "toxic cancer chemotherapy agent". AZT is demonstrably ineffective as a single agent cancer therapy for the reasons described above, and has never been approved for such use. The experimental use of AZT in patients with non-viral or HIV-associated malignancies has been limited to studies, like ours, which created biochemical conditions through combination therapies that artificially facilitated the incorporation of AZT into cancer cell DNA. Those conditions are not analogous to the use of AZT in the setting of HIV where the drug is biochemically precluded from achieving effective DNA incorporation.

I declare under penalty of perjury pursuant to the laws of the State of California that the foregoing is true and correct, and that this Declaration was executed on April 4, 2005, at Los Angeles, California.

Kevin J. Scanlon, Ph.D.