UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

UNITED STATES OF AMERICA EX REL. DR. HELENE Z. HILL,	:	CASE NO. 03-4837 (DMC)
PLAINTIFF,	:	
v.	:	
UNIVERSITY OF MEDICINE & DENTISTRY OF NEW JERSEY, DR. ROGER W. HOWELL and DR. ANUPAM BISHAYEE,	:	
DEFENDANTS.	:	

PLAINTIFF'S REPLY BRIEF IN SUPPORT OF
MOTION FOR SUMMARY JUDGMENT

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POINT I

DEFENDANTS' LACK OF COMPLIANCE WITH LOCAL RULE 56.1(a) RENDERS PLAINTIFF'S STATEMENT OF MATERIAL FACTS UNDISPUTED FOR PURPOSES OF THESE MOTIONS

Defendants' opposition to Plaintiff's Motion for Summary Judgment failed to comply with Local Rule 56.1 (a). Defendants failed to file with the Clerk a responsive statement to Plaintiff's Statement of Undisputed Material Facts in a timely manner. Consequently, Plaintiff's Statement of Undisputed Material Facts is to deemed to be undisputed for purposes of this summary judgment motion.[1]

POINT II

PLAINTIFF'S EXPERTS ARE QUALIFIED AND HAVE RENDERED ADMISSIBLE EXPERT EVIDENCE UNDER FED. R. EVID. 702

The Defendants opposition at last confronts the issue of expert testimony that its moving papers chose to ignore. It is clear, however, that the matters under consideration are sufficiently specialized that consideration of such testimony is warranted in order to reach a valid conclusion as to Plaintiff's claims. Skalski v Elliot Equipment Co., 2010 WL 891582 (D.N.J. 2010).

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[1]The filing of the statement is required at the time **opposition** papers are **due** to be filed **with the Clerk**. Local Rule 56.1 (a); Fed R. Civ. P. 5 (d) (2) and (3). The deadline date for the parties' opposition papers to be filed was midnight, June 21, 2010. Defendants 5:33 p.m. filing on that date (ECF Document No. 50) did not include a responsive statement. It was filed at 9:53 a.m. on June 22, 2010 (ECF Document No. 51). The statement is untimely filed and its acceptance works a prejudice to Plaintiff, because Defendants now seek to dispute facts which the rule deems to be undisputed.

A. STANDARDS UNDER FED. R. EVID. 702

Federal Rule of Evidence 702 governs the admissibility of expert testimony. Qualification as an expert is viewed liberally and may be based on "a broad range of knowledge, skills and training". In re TMI Litig., 193 F.3d 613, 664 (3rd Cir. 1999); In re Fosamax Products Liability Litigation; 645 F. Supp. 2d 164, 172 (S.D.N.Y. 2009). A witnesses' qualifications is determined by comparing the area in which the witness has superior knowledge, skill, experience, or education with the subject matter of the witness's testimony. Id.

Rule 702's three reliability elements were added in 2000 to codify the holdings of Daubert v Merrill Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993) and its progeny, Kumho Tire Co., 526 U.S. 137 (1999) and General Elec. Co. v Joiner, 522 U.S. 136 (1997). In Daubert, supra at 597, the Court interpreted Rule 702 to require district courts to act as gatekeepers by ensuring that expert scientific testimony "both rests on a reliable foundation and is relevant to the task at hand". This requires a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue". Id. at 592-593.

To be scientifically valid, the subject of expert testimony, the subject of expert testimony need not be "known to a certainty" because, "arguably, there are no certainties in science." Daubert, 590 U.S. at 590. Rather, the testimony must rest

on "good grounds, based on what is known." Id. Daubert set forth a non-exclusive list of factors that a district court might consider in gauging the reliability of scientific testimony. These factors are: (1) whether the theory has been tested; (2) whether the theory has been subject to peer review and publication; (3) the known or potential rate of error and whether standards and controls exist and have been maintained with respect to the technique; and (4) the general acceptance of the methodology in the scientific community.

Whether some or all of the factors apply in a particular case depends on the facts, the expert's particular expertise, and the subject of his testimony. Kumho Tire, 526 U.S. at 138. District courts are afforded broad discretion both in determining the relevant factors to be employed in assessing reliability and in determining whether that testimony is in fact reliable. In re Fosamax, supra at 173.

The requirement that expert testimony "assist the trier of fact" is said to go primarily to relevance. Daubert, 590 U.S. at 591. Daubert describes 'relevance' as a question of "fit"; that is, whether expert testimony proffered in the case is sufficiently tied to the facts of the case that it will aid the jury in resolving a factual dispute".

A district court, in fulfillment of its gate-keeping function to determine reliability, undertakes an examination of the facts on which the expert relies, the method by which the expert draws an opinion from those facts, and how the expert

applies the facts and methods to the case at hand. Amorgianos v National R.R. Passenger Corp., 303 F.3d 256, 267 (2nd Cir. 2002). Notwithstanding that examination, and in accordance with the liberal admissibility standards of the Federal Rules of Evidence, only serious flaws in reasoning or methodology will warrant exclusion. Id. It has been held that as long as an expert's scientific testimony rests upon 'good grounds, based on what is known, it should be tested by the adversary process – competing expert testimony and active cross-examination – rather than excluded from juror/court's scrutiny for fear that they/it will not grasp its complexities or satisfactorily weight its inadequacies. Daubert, 590 U.S. at 596. Thus, if an expert's testimony lies within "the range where experts might reasonably differ", the trier of fact should decide among the conflicting views of different experts. In re Fosamax, supra at 173.

The ultimate object of the court's gate-keeping role under Rule 702 is make certain that an expert, whether basing testimony on professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field. Id. at 174.

B. DR. ROBBIN'S REPORT

Dr. Robbins is an esteemed and qualified radiation biologist whose report in this case concluded that fraud was committed. (See Certification of Michael E.

Robbins and Hill S.J.Exhibit 108.) Robbins concluded the Bishayee data were impossible to generate, and thus fraudulent, because:

(1) Tritiated thymidine (^{3}H-TdR) blocks the movement of cells through the various phases of the cell cycle. Thus cells that are not in the S phase of the cell cycle during the overnight incubation with ^{3}H-TdR cannot enter the S phase, will not incorporate^{3}H-TdR into their DNA, and will not be killed by the subsequent radioactive decay of the $^3H^2$ (Hill S.J. Exhibit 108 at 3);

(2) No deoxycytidine (dCyd) was present in the medium at the time the cells were exposed to ^{3}H-TdR. Thus its absence in the medium failed to prevent the ^{3}H-TdR from blocking cell movement through the cell cycle (Hill S.J. Exhibit 108 at 4); and,

(3) No attempt was made to synchronize the cells into the same phase of the cell cycle prior to treatment of with ^{3}H-TdR (Hill S.J. Exhibit 108 at 4).

Reason No. 1

Based on his review of the Bishayee experiments before him, Robbins opined that Tritiated thymidine (^{3}H-TdR) blocked the movement of cells through the various phases of the cell cycle. Thus cells that were not in the S phase of the cell cycle during the overnight incubation with ^{3}H-TdR could not enter the S phase, did

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[2]While taking issue with Reason No. 1 of the Robbins report, Feinendegen concedes that, if Robbins is correct on Reason No. 1, he would agree with Robbins on Reasons 2 and 3 (Hill S.J Exhibit 117: Feinendegen Deposition at173/10-22; 88/17-90/17).

not incorporate^{3}H-TdR into their DNA, and were not killed by the subsequent radioactive decay of the ^{3}H. Data reporting the contrary were thus fraudulent.

Feinendegen opines that tritiated thymidine does not always serve to block the cell cycle; and, that the blocking depends on the amount of thymidine molecules that have entered the cellular nucleotide pool (the "thymidine pool")[3] (Certification of Leonard, Exhibit D, Report at 2-3). [4] Feinendegen never specifically identified the size of the pool for V79, referring instead to what he called "indirect evidence" of what the pool size is (Hill S.J. Exhibit 117: Feinendegen Deposition 40/13-44/6). In contrast, Robbins noted that Feinendegen's sophistry is the scientific equivalent to not specifying the pool size. He noted that there is nothing in the scientific literature that specifies what the pool size in V79 cells is, as opposed to a range (Hill S.J. Exhibit 118: Robbins Deposition 70/2-70/23).

Feinendegen further sought to distinguish between high and low specific activity ^{3}H-TdR; stating that high specific activity ^{3}H-TdR permits sufficient numbers of tritium atoms to be incorporated into the DNA without perturbing the

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[3]Thymidine is a building block of DNA and the thymidine pool contains the precursors for DNA (Hill S.J. Exhibit 117: Feinendegen Deposition at 33).

[4]An understanding of the "pool" is gleaned by considering the analogy of an Olympic size swimming pool to a child's wading pool. If one throws a bucket of dye into the pool it has no noticeable effect on the color of the water. If one throws that same bucket of dye into a children's wading pool, it does affect the color. The size of the pool thus needs to be known to determine the effect that the dye thrown in has on the color of the water (Hill S.J. Exhibit 117: Feinendegen Deposition 34/6-25).

cell cycle. He concluded that Bishayee used high specific activity ^{3}H-TdR that permitted 100% labeling of the cells to occur without perturbing the cell cycle. On page 8 of his report (Leonard Certification, Exhibit D), he calculates that concentration of thymidine to have been 0.12 micromole. In such concentration, Feinendegen indicates there was no reason for deoxycytidine (Robbins Reason 2) or cell synchronization (Robbins Reason 3) to be utilized or performed. (Exhibit D: Feinendegen Report at 4) (Hill S.J. Exhibit 117: Feinendegen Deposition 63/20-64/6 and 88/17-90/17) because the cell cycle was not perturbed.

Robbins easily refuted Feinendegen's hypothesis that the amount of tritiated thymidine that was added in the **Bishayee experiments** was too small to affect the thymidine pool and therefore not interfere with the cell cycle (Hill S.J. Exhibit 118: Robbins Deposition 70/2-72/16)[5]. He noted scientific literature which convincingly demonstrates that the effects of adding ^{3}H-TdR in concentrations even on the order of one hundred fold **lower** than the concentrations used by Bishayee perturbs the cell cycle. (Hill S.J. Exhibit 119: J. E. Cleaver, Thymidine Metabolism and Cell Kinetics, North-Holland Publishing Company - Amsterdam, John Wiley & Sons, Inc - New York, 1967, pp 85-90). This concentration of tritiated thymidine is

[5]Robbins commented on the thymidine pool at the invitation of Defendants at his deposition (Hill S.J. Exhibit 118: Robbins Deposition at 57/9-61/17). The scheduling order made no provision for his reply to Dr. Feinendegen's report. It is noted that his report had cited to the literature which dealt with the issue of the thymidine pool and on which he had relied in rendering his opinion. (Hill S.J. Exhibit 118: Robbins Deposition 70/2-23)

smaller than what Feinendegen believed was too low to block the cell cycle in Bishayee's experiments; and, would, in fact, perturb the cell cycle. Another journal paper, Cleaver J.E., Holford, R.M., Investigations into the Incorporation of [3H]thymidine into DNA in L-strain cells and the Formation of a Pool of Phosphorylated Derivatives During Pulse Labelling. Biochim Biophys Acta 103, 654-671, 1965 (Hill S.J. Exhibit 120), demonstrates that a $1/1000^{th}$ fold (10^{-9} M) thymidine affected the pool.[6] This concentration is also **lower** than that used by Bishayee and thus renders Feinendegen's hypothesis impotent.

Robbins further refutes Feinendegen on the issue of high specific activity, pointing out and relying on two additional articles in the scientific literature: (1) Hu, V.W., Black, G.E., Torres-Duarte, A., Abramson, F.P. 3H-thymidine is a defective tool with which to measure rates of DNA synthesis. FASEB J 16, 1456-1457, 2002 (Hill S.J. Exhibit 121); and, (2) Keprtova J and Minarova, E. The effect of 3H-thymidine on the proliferation of in vitro cultured mammalian cells. Gen Physiol Biophys 4, 81-92, 1985 (Hill S.J. Exhibit 122). Feinendegen admitted his familiarity with the Hu paper and the fact it shows there to be biphasic, rather than exponential killing of cells using high specific activity tritiated thymidine (Hill S.J.

[6]Feinendegen admitted he has cited this paper in his book, but deliberately omitted any reference to it his report (Hill S.J. Exhibit 117: Feinendegen Deposition 44/12-47/12).

Exhibit 121) (Hill S.J. Exhibit 117: Feinendegen Deposition 103/`2-104/24)[7]. Feinendegen acknowledged the high specific activity to be about the same specific activity as that used by Bishayee. (Id.). Indeed, the concentration was .13 micromole. (See Hill S.J. 121 at the section entitled "Materials and Methods: Cell-labeling Protocols) as compared to .12. micromole for Bishayee.

The Keprtova paper also showed biphasic, rather than exponential, killing of V79 cells when no deoxycytidine was added to the medium, using high specific activity ^{3}H-TdR that was only one-third (1/3rd) the amount that Bishayee had utilized (Hill S.J. Exhibit 122) (Hill S.J. Exhibit 117: Feinendegen Deposition 94/6-17; 99/3-103/11).

Feinendegen's citation to K. Fujikawa-Yamamato and S. Odashima, "Synergistic effects of hydroxyurea and thymidine on the growth inhibition of V79 cells" Cell Structure and Function 14, 399-405 (1989) to claim that the minimum concentration of thymidine in the culture medium required for blocking V79 cells in various phases of the cell cycle is about 500 times higher than the concentration used by Bishayee (Leonard Certification: Exhibit D at 8-9) fails to refute the literature relied on by Robbins because that experiment dealt only with thymidine and not tritiated thymidine (Hill S.J. Exhibit 117: Feinendegen Deposition 47/16-

[7]A biphasic decline in survival is one where there is a decline followed by a plateau of survival. When there is an exponential decline, there is no plateau. (Hill S.J. Exhibit 123: Howell Deposition 60/ 4-10).

48/21). Moreover, Robbins noted that the experiments cited in Feinendegen's report were based on entirely different experimental designs – to show blockage of the cell cycle by thymidine. In contrast the Bishayee experiments used tritiated thymidine not to look at the cell cycle effect, but to see what consequences radiating cells had on cell survival. (Hill S.J. Exhibit 118: Robbins Deposition 61/18-62/25; 78/4-79/5). Feinendegen was thus comparing apples to oranges in his report. This is not surprising given how little information Feinendegen reviewed in order to prepare his report. He admits that in preparing his report, he never read any of the experiment protocols (Hill S.J. Exhibit 117: Feinendegen Deposition 75/14-76/14)[8]. In contrast, Robbins did review all of the protocols (Hill S.J. Exhibit 118: Robbins Deposition 17/7-15).

Based on the above, Robbins analysis of both the Bishayee data and the scientific literature overwhelmingly demonstrated that ^{3}H-TdR did block the movement of cells through the various phases of the cell cycle; and, that the exponential kill rates reported by Bishayee were fraudulent. His opinion thus supports a grant of summary judgment to Plaintiff.

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[8]Feinendegen acknowledged he has never been retained as an expert in the United States and has been retired for over 16 years (Hill S.J. Exhibit 117: Feinendegen Deposition 8/22-9/19).

Reason No. 2

Because Feinendegen hitched his star only to Reason No. 1, he refused to acknowledge the relevancy of the literature that supports Robbins conclusion that deoxycytidine needed to be added to the medium used in the Bishayee experiments in order to prevent the cell cycle block effect of ^{3}H-TdR (Hill S.J. Exhibit 108: Robbins report at 2 and 4). See: (1) Bedford et al, "Cell Killing by Gamma Rays and Beta Particles from Tritiated Water and Incorporated Tritiated Thymidine", Rad Research 63: 531 (1975) (exponential killing of V79 cells by tritiated thymidine in a medium containing deoxycytidine) (Hill S.J. Exhibit 124); (2) Marin & Bender, "A Comparison of Mammalian Cell-Killing by Incorporated ^{3}H-thymidine and ^{3}H-uridine", Int J Rad Biol 7: 235 (1963) (exponential killing of Chinese hamster cells by tritiated thymidine in a medium containing deoxycytidine); (3) Chan et al., "The Radiotoxicity of Iodine-125 in Mammalian Cells", Rad Research 67: 332 (1976) (exponential killing of V79 cells in a medium containing deoxycytidine)(Hill S.J. Exhibit 126); (4) Burki and Okada, "Killing of Cultured Mammalian Cells by Radioactive Decay of Tritiated Thymidine at -196°C", Rad Research 41: 409 (1970)(to overcome biphasic survival curves, deoxycytidine was added to the tritiated thymidine)(Hill S.J. Exhibit 127) (Hill S.J. Exhibit 117: Feinendegen Deposition 81/18- 88/16).

Feinendegen further refused to acknowledge the relevance of papers showing that survival was biphasic, rather than exponential, when deoxycytidine was absent from the medium. See: (1) Drew and Painter, "Action of Tritiated Thymidine on the Clonal Growth of Mammalian Cells", Rad Research 11: 535 (1959) (biphasic killing of cells with no added deoxycytidine)(Hill S.J. Exhibit 128); (2) Drew and Painter, "Further Studies on the Clonal Growth of HeLa S3 Cells Treated with Tritiated Thymidine", Rad Research 16: 303 (1962)(biphasic killing of cells with no deoxycytidine added) (Hill S.J. Exhibit 129); (3) Keprtova & Minarova, " The Effect of 3H-Thymidine on the Proliferation of In Vitro Cultured Mammalian Cells", Gen Physiol Biophys 4: 81 (1985) (biphasic killing of cells with no deoxycytidine)(Hill S.J. Exhibit 122); (4) Hu et al.,'^{3}H-thymidine is a defective tool with which to measure rates of DNA synthesis'. FASEB J publ on-line 7/1/2002 (biphasic killing of cells using high specific activity tritiated thymidine and no added deoxycytidine) (Hill S.J. Exhibit 121); (5) Persaud, et al., "Assessment of Low Linear Energy Transfer of Radiation Induced Bystander Mutagenesis in a Three Dimensional Culture Model" Cancer Research 65:9876 (2005)(biphasic killing of cells with no added deoxycytidine) (Hill S.J. Exhibit 130) (Hill S.J. Exhibit 117: Feinendegen Deposition 91/3-107).

Bishayee could not even indicate whether the protocols for his experiments called for the use of deoxycytidine in the medium. Bishayee had no recollection of

ever using deoxycytidine, nor did he even know what deoxycytidine is (Hill S.J. Exhibit 131: Bishayee Deposition 7/19-72/13). By that admission, it is reasonable to conclude deoxycytidine was never added to the medium. Feinendegen concludes that deoxycytidine was not added to the medium (Leonard Certification Exhibit D, Feinendegen Report at 3).

Reason No. 3

Robbins report notes that if all the cells were in the same phase of the cell cycle then there was a possibility that they would have been in the S phase of the cell cycle at the time the ^{3}H-TdR was added. No attempt was made by Bishayee to synchronize the cells into the same phase of the cell cycle. (Hill S.J. Exhibit 108: Robbins Report at 2 and 4).

Bishayee indicated he did not even know what cell synchronization is, let alone having an ability to recall ever making an attempt to doing so. (Hill S.J. Exhibit 131: Bishayee Deposition 72/14-73/24). By that admission, it is reasonable to conclude he never did it. Indeed, Feinendegen concludes that Bishayee correctly chose not to synchronize, but omits to state the facts on which he found that to be conscious choice (Leonard Certification Exhibit D: Feinendegen Report at 4).

Feinendegen noted and concedes that if Robbins is correct on Reason No. 1, he would agree with Robbins on Reason 3 (Hill S.J. Exhibit 117: Feinendegen Deposition 173/10-22; 88/17-90/17).

C. Dr. Pitt's Report

Dr. Pitt's knowledge, skill, experience, training and education qualify him to serve as an expert statistician in this case (Hill S.J. Exhibit 104) (Hill S.J. Exhibit 132: Pitt Deposition 10/4-30/22). Such skill, experience, training and education allowed for him to employ the "Mossiman" technique which ORI itself publicizes as a valid statistical technique for determining fraudulent data (Hill S.J. Exhibit 115). Utilizing the control data which was obtained from Howell/UMDNJ after the start of this case (See Plaintiff's S.J. Opposition Brief Point II), Pitt determined the probability that non-fabricated data could result in the frequencies reported by Bishayee is considerably less than one chance in one hundred billion! (Hill S.J. Exhibit 104 at 1-8) (Hill S.J. Exhibit 132: Pitt Deposition 40/2-70/15. Defendants admit they have not offered any statistical expert(s) to refute the methodology Pitt employed, the significance of what was found by Pitt, or the soundness of his opinions and conclusions.

Dr. Pitt thereafter extended the analysis. He analyzed the colony data that was recorded in groups of three by Bishayee to determine the frequency with which one of the three measurements in each group is close to the average of the three measurements. He further determined the frequency with which the two least significant or right most digits in Bishayee's digits were equal. (Hill S.J. Exhibit 104 at 1-2, 8-13). His analysis demonstrated that Bishayee repeatedly and deliberately

invented one value in each triad to force his data to conform to the experimental results he wished to report (Hill S.J. Exhibit 132: Pitt Deposition 70/16-86/2). He further determined that the relative frequency with which the two least significant digits in Bishayee's measurements are equal had a probability of occurring in less than one chance in 10 million (Hill S.J. 132: 86/15-94/9). Dr. Pitt expressed full confidence that the techniques and methodology that he developed are ones for which he is confident in the validity thereof, based on a reasonable degree of mathematical and statistical probability; and, generally acceptable in the mathematics and statistics community (Hill S.J. Exhibit 132: Pitt Deposition 112/24-113/21). Defendants again admit they have failed to offer any statistical expert(s) to refute the methodology he employed, the significance of what was found by Pitt, or the soundness of his opinions and conclusions.

Conclusion

For all of the foregoing reasons, it is respectfully requested that Plaintiff's Motion for Summary Judgment be granted; that Defendants' Motion for Summary Judgment be denied; and, that Defendants' Counterclaim be dismissed with Prejudice.

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