random sampling because it might thwart the goal to terminate African–American employees.

Finally, the evidence Williams points to in support of his *prima facie* case also supports a finding of pretext. For example, the evidence that Wells Fargo treated three similarly situated non-African–American employees more favorably than Williams and the other terminated African–American employees creates a question of fact on the issue of pretext.

Conclusion

Williams has adduced enough evidence to make out a *prima facie* case of racial discrimination. There is sufficient evidence from which a reasonable juror could infer that the reasons given by Wells Fargo for firing him were pretextual and non-African–American employees were treated more favorably. Therefore, the motion for summary judgment will be denied.

ORDER

AND NOW, this 3rd day of July, 2008, upon consideration of Defendant, Wells Fargo's, Motion for Summary Judgment (Document No. 24) and the plaintiff's response, it is **ORDERED** that the motion is **DENIED.**

Andrea PERRY, et al.

v.

NOVARTIS PHARMACEUTICALS CORP.

Civil Action No. 05–5350.

United States District Court, E.D. Pennsylvania.

July 9, 2008.

Background: Parents of patient who had developed lymphoblastic lymphoma following use of Elidel, a prescription drug for the treatment of atopic dermatitis, brought suit against drug manufacturer alleging, inter alia, negligent failure to warn. Manufacturer moved to exclude testimony of parents' experts and for summary judgment.

Holdings: The District Court, Dalzell, J., held that:

(1) expert opinion of toxicology professor, that pimecrolimus could cause non-Hodgkin lymphoma (NHL) in humans, was reliable;

(2) expert opinion of hematology and oncology specialist, that pimecrolimus cream causes lymphoma in humans, was not reliable;

(3) expert opinion of toxicology professor, and of hematology and oncology specialist, that exposure to Elidel was substantial cause of child's cancer, was not reliable; and

(4) expert opinion of toxicology professor, and of hematology and oncology specialist, that exposure to Elidel was substantial cause of child's cancer, failed to meet fit requirement.

Motions granted.

1. Federal Civil Procedure ⚿927.5

Although replies and sur-replies were generally disfavored, District Court would consider such briefs upon motion to exclude testimony in toxic tort action against drug manufacturer, because of importance of issue at hand and in view of Court's proceeding without hearing.

2. Federal Civil Procedure ⚿927.5

The question whether a hearing to take testimony from experts themselves is

necessary on a motion to dismiss expert testimony rests in the sound discretion of the District Court.

3. Evidence ⚿508, 535, 555.2

In evaluating opinion testimony on a motion to exclude expert testimony, the District Court acts as a gatekeeper, preventing opinion testimony that does not meet the requirements of qualification, reliability, and fit from reaching the jury. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

4. Evidence ⚿555.2

Because the District Court addresses a motion to exclude expert testimony in its role as gatekeeper rather than as finder of fact, its focus must be solely on principles and methodology, not on the conclusions that they generate. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

5. Evidence ⚿555.2

For scientific testimony to be sufficiently reliable, it must be derived by the scientific method and must be supported by appropriate validation. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

6. Evidence ⚿555.2

The scientific method, from which scientific testimony must be derived to be sufficiently reliable, requires the generation of testable hypotheses that are then subjected to the real world crucible of experimentation, falsification/validation, and replication. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

7. Evidence ⚿555.2

So long as an expert has good grounds for opinion testimony, the scientific evidence is deemed sufficiently reliable, but the need for good grounds means that any step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible; this is true whether the step completely changes a reliable methodology or merely misapplies that methodology. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

8. Evidence ⚿555.2

Although the Rules of Evidence embody a strong preference for admitting any evidence that may assist the trier of fact, the trial judge must have considerable leeway in deciding in a particular case how to go about determining whether particular expert testimony is reliable. Fed. Rules Evid.Rule 702, 28 U.S.C.A.

9. Evidence ⚿508

The District Court must consider whether expert testimony proffered in a case is sufficiently tied to the facts of the case that it will aid the jury in resolving a factual dispute. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

10. Evidence ⚿508

The expert opinion rule's "helpfulness" standard, also known as "fit," requires a valid scientific connection to the pertinent inquiry as a precondition to admissibility; this requirement is, in the end, the ultimate touchstone of admissibility. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

See publication Words and Phrases for other judicial constructions and definitions.

11. Negligence ⚿404

In toxic tort cases, general causation is a necessary element of specific causation.

12. Evidence ⚿528(1)

Expert's general causation conclusions are relevant and admissible in a toxic tort action when they form a link in a causal chain that helps a jury reach a conclusion on the ultimate causation question.

13. Evidence ⚿528(1), 555.5

Just as there is no fit, thus precluding the admission of expert testimony in a

toxic tort case, where there is too great an analytical gap between the data and the opinion offered, there is also no fit when there is too great an analytical gap between an expert's general causation conclusion and the specific causation question the jury must ultimately answer. Fed. Rules Evid.Rule 702, 28 U.S.C.A.

14. Evidence ⚿555.5

An expert's journey from general causation to specific causation in a toxic tort case need not be just a two-step process; so long as, taken together, the experts are able to draw a chain of scientifically-reliable causal links that meets plaintiffs' requirements under the substantive tort law, the evidence is admissible and it will be left to the jury to establish the relative credibility of the parties' competing experts. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

15. Evidence ⚿555.5

Where expert reports leave wide, unexplained gaps in the causal chain in a toxic tort case, the evidence is not helpful to the trier of fact and must be excluded. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

16. Evidence ⚿557

While an expert's conclusions reached on the basis of other studies could be sufficiently reliable in a toxic tort case where no epidemiological studies have been conducted, no reliable scientific approach can simply ignore the epidemiology that exists. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

17. Evidence ⚿555.10, 557

Expert opinion of toxicology professor, that pimecrolimus could cause non-Hodgkin lymphoma (NHL) in humans, was reliable, as required for admission of such testimony in toxic tort action against manufacturer of prescription drug Elidel, given animal studies showing that, at high enough doses, pimecrolimus could cause both systemic immunosuppression and related lymphoproliferative disorders, and pimecrolimus's relationship to cyclosporine and tacrolimus. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

18. Evidence ⚿555.2, 555.4(2)

The non-existence of good data does not allow expert witnesses to speculate or base their conclusions on inadequate supporting science. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

19. Evidence ⚿555.10, 557

In toxic tort cases where no adequate study shows the link between a substance and a disease, expert testimony will generally be inadmissible, even if there are hints in the data that some link might exist. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

20. Evidence ⚿555.10, 557

Expert opinion of hematology and oncology specialist, that pimecrolimus cream causes lymphoma in humans, was not reliable, and thus was inadmissible in toxic tort action against manufacturer of prescription drug Elidel, given lack of experimental data supporting link between elevated levels of pimecrolimus in lymphoid tissue and development of lymphoma. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

21. Evidence ⚿555.10

To result in an admissible conclusion in a toxic tort case, a differential diagnosis should reliably rule out reasonable alternative causes of the alleged harm or idiopathic causes; admissible expert testimony need not rule out all alternative causes, but where a defendant points to a plausible alternative cause and the doctor offers no explanation for why he or she has concluded that it was not the sole cause, that doctor's methodology is unreliable. Fed. Rules Evid.Rule 702, 28 U.S.C.A.

22. Evidence ⚿555.10

Expert opinion of toxicology professor, and of hematology and oncology specialist, that exposure to prescription drug Elidel was substantial cause of child's cancer, was not reliable, and thus was inadmissible in toxic tort action, where differential diagnosis procedure they employed failed to adequately account for the possibility that child's T-cell lymphoblastic lymphoma (T–LBL) was idiopathic. Fed. Rules Evid.Rule 702, 28 U.S.C.A.

23. Evidence ⚿528(1)

In a toxic tort case, the question of fit deals both with the relevance of an experts' conclusion to the scientific questions at issue and with any analytical gaps in the experts' conclusions that may render them misleading when applied to the evidence in the case. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

24. Evidence ⚿528(1), 555.10, 557

Expert opinion of toxicology professor, and of hematology and oncology specialist, that exposure to prescription drug Elidel was substantial cause of child's cancer, failed to meet fit requirement for admissibility in toxic tort case, in that they failed to address disparity in dosages child received and dosages in animal studies on which they relied. Fed.Rules Evid.Rule 702, 28 U.S.C.A.

Brian P. McCafferty, Kenney Lennon & Egan PC, Plymouth Meeting, PA, Christopher M. Van De Kieft, Moshe H. Horn, Jonathan Shub, Seeger Weiss LLP, New York, NY, Larry M. Roth, The Law Offices of Larry M. Roth PA, Orlando, FL, Francine A. Hochberg, Jonathan Shub, Seeger Weiss LLP, Philadelphia, PA, for Andrea Perry, et al.

Joe G. Hollingsworth, Katharine R. Latimer, Bonnie J. Semilof, Peter J. Skalaban, Jr., James D. Hicks, Spriggs & Hollingsworth, Washington, DC, Madeline M. Sherry, Gibbons, Del Deo, Dolan, Griffinger & Vecchione, P.C., Philadelphia, PA, for Novartis Pharmaceuticals Corporation.

Shanin Specter, Kline & Specter, P.C., Philadelphia, PA, for The Pennsylvania Lawyers Association.

Sharon Swingle, U.S. Department of Justice, Civil Division, Washington, DC, for The Food and Drug Administration.

MEMORANDUM

DALZELL, District Judge.

[1, 2] This case arises from Andreas Perry's diagnosis of lymphoblastic lymphoma in October of 2003. Andreas's parents, plaintiffs in this action, allege that his use of Elidel, a prescription drug manufactured by defendant Novartis Pharmaceuticals Corporation, caused his lymphoma. The parties have completed discovery limited to the issue of causation and Novartis has filed a motion to exclude the testimony of plaintiffs' experts, Dr. Martyn T. Smith and Dr. E. Anders Kolb. As we have the parties' briefs [1] and copious supporting

1. On June 3, 2008, Novartis filed a motion for leave to file a reply brief, attaching the proposed brief. On June 17, plaintiffs filed an opposition to the motion that was, in essence, a sur-reply brief. Although replies and sur-replies are generally disfavored, because of the importance of the issue at hand and since both parties have had an additional chance to be heard, and in view of our proceeding without a hearing, we will consider both additional briefs in our analysis.

documentation,[2] we now address the motion.

I. Factual Background

A. Andreas Perry's Medical History[3]

Andreas Perry was born on April 19, 2001 after a full-term pregnancy with no significant complications. As an infant, he developed mild eczema—also known as atopic dermatitis—over twenty to thirty percent of his body, specifically on parts of his legs, arms, and torso. For the first two years of his life, this was treated only with non-prescription emollients. On April 30, 2003, after a flare-up that the emollients could not relieve, Perry's pediatrician, Dr. Lisa Parviskhan, gave Andrea Perry samples of Elidel to use on her son.[4] The Perrys used about one two-gram sample tube of Elidel a day over twenty percent of Andreas's body for about two weeks.[5] At the end of June, 2003, the Perrys again treated Andreas with Elidel from sample tubes, again for about two weeks. At the end of August, 2003, they applied Elidel to Andreas for one week. In all, the Perrys estimate that Andreas received between sixty and sixty-four grams of Elidel cream over a period of about four months ending in late August of 2003.[6]

On October 13, 2003, Andreas Perry visited Dr. Parviskhan with a two-week history of fever, cough, and weight loss.[7] After a chest x-ray revealed a mass in his chest, Andreas was referred first to Chester County Hospital and then to Children's Hospital of Philadelphia ("CHOP"). On October 15, after a biopsy of the mass, the doctors at CHOP diagnosed a T-cell lymphoblastic lymphoma ("T–LBL"). They

2. On May 27, 2008, after consultation between Chambers staff and counsel for the parties, it was agreed that, because of the comprehensive paper record that the parties have prepared, a hearing to take testimony from the experts themselves was not necessary. The question of whether to hold such a hearing "rests in the sound discretion of the district court." *Padillas v. Stork–Gamco, Inc.*, 186 F.3d 412, 418 (3d Cir.1999).

3. To the extent there are disputed facts regarding Perry's medical history, we view them here in the light most favorable to plaintiffs.

4. It does not appear from the record that Dr. Parviskhan examined Andreas on this occasion. Andrea Perry worked in Dr. Parviskhan's office and it appears that Dr. Parviskhan provided the samples solely on the basis of Andrea Perry's report of Andreas's condition.

5. Because the discussion ahead will deal with matters of dosage, we must calculate his approximate dosage for reference. The dose Andreas Perry received was 20 mg per day applied to the skin. *See* Pl.Ex. 13 at 4 (stating that each gram of Elidel cream contains 10 mg of pimecrolimus). Although the record does not reveal Andreas Perry's weight at the time he first received Elidel, the fiftieth percentile for weight among 24–month–old boys is between 12.5 and 12.75 kg and the fifth percentile is between 10.5 and 10.75 kg. *See* Centers for Disease Control, Boys Length–for–Age and Weight–for–Age Percentiles, at http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/Set1/boys_length_weight.html (last visited June 5, 2008). There is no suggestion in the medical records that Andreas Perry was abnormally small. Thus, we may assume for purposes of this motion that at the time of his treatment Andreas weighed at least 10.5 kg. Dosage is typically measured in milligrams per kilogram of body weight per day or mg/kg/day. Thus, Andreas Perry's dosage during the time of his treatment was something less than 2 mg/kg/day applied to the skin.

6. Since the treatment was intermittent, Andreas Perry actually received significantly less than 2 mg/kg/day over the full four-month period.

7. Again, Dr. Parviskhan appears to have given Andrea Perry samples on October 5, 2003, this time of Zithromax, without an examination of her son.

immediately began an aggressive and apparently successful chemotherapy protocol lasting for 113 weeks. Andreas Perry has now been cancer-free for more than two years.

B. Non–Hodgkin Lymphoma

T–LBL is a form of non-Hodgkin lymphoma ("NHL"), a class of cancers that affect the lymphatic system. The lymphatic system is made up of a several types of cells, collectively referred to as lymphocytes. Of these, two figure prominently in the analysis that follows—B-cells and T-cells. B-cells are mainly produced in the bone marrow and reside in the lymph nodes. Report of Dr. E. Anders Kolb ("Kolb Rpt.") at 3. They are primarily responsible for antibody production. *Id.* T-cells are mainly produced in the thymus and also reside in lymph nodes. *Id.* T-cells are "helper and suppressor cells that regulate immune reactions." *Id.* In particular, T-cells are responsible for destroying abnormal cells including those that are infected with a virus or are cancerous. Report of Dr. Emanuel Rubin ("Rubin Rpt.") at 3–4. As a result, people with immune deficiency—regardless of whether that state is congenital, disease-related, or drug-induced—"are at higher risk of developing cancers, both of solid organs and lymphomas." *Id.* at 5.

C. Pharmaceutical Immunosuppression

Pimecrolimus, the active ingredient in Elidel, is one of a class of drugs known as calcineurin inhibitors. Calcineurin inhibitors are known to inhibit immune system function. Two other calcineurin inhibitors, tacrolimus and cyclosporine, are used as immunosuppressive therapy to prevent rejection after organ transplants. In this context, both tacrolimus and cyclosporine have been associated with increased incidence of post-transplant lymphoproliferative disorder ("PTLD"). PTLD is similar in presentation to NHL and is generally secondary to systemic immunosuppression following a solid organ transplant. About 90% of PTLD cases represent B-cell lymphomas. Report of Dr. Mitchell S. Cairo ("Cairo Rpt.") at 7; *see also* Kolb Dep. 170:17–22 ("[S]omewhere between eight to 14 percent [of post-transplant lymphomas] are of T-cell in origin."). The World Health Association's International Agency for Research on Cancer ("IARC") has concluded that cyclosporine is carcinogenic in humans based on a combination of animal studies and epidemiological evaluations. *See* Pl.Ex. 15.

D. The Experts

Martyn T. Smith, Ph.D, is a professor of toxicology at the School of Public Health, University of California, Berkeley. He has been on the faculty of the University of California since 1982. He holds a Bachelor of Science in Biology from Queen Elizabeth College, University of London, and a Ph.D. in Biochemistry from the Medical College of St. Bartholomew's Hospital, London. He is a Fellow of the American Association for the Advancement of Science and a full member of the Society of Toxicology. His career has been focused on the study of the toxic effects of chemicals and drugs on the human body and his current research addresses the causes of leukemia and lymphoma.

E. Anders Kolb, M.D., is a board-certified specialist in pediatric hematology and oncology and the Director of the Blood and Bone Marrow Transplantation Center at the Alfred I. duPont Hospital for Children in Wilmington, DE. He holds a B.A. from the University of Pennsylvania and an M.D. from Jefferson Medical College. He is a member of the American Association for Cancer Research, the American Soci-

ety of Hematology, the American Society for Blood and Bone Marrow Transplants, and the Society for Pediatric Research.

Seymour Grufferman, M.D., Dr.P.H, is a Research Professor in the Epidemiology Division of the Department of Internal Medicine at the University of New Mexico. Previously, he was the Chairman of the Department of Clinical Epidemiology and Preventive Medicine at the University of Pittsburgh School of Medicine. He holds a B.S. from City College of New York, an M.D. from the State University of New York, and an M.P.H., M.S., and Dr.P.H. from the Harvard University School of Public Health. He served as the Chief of Pediatrics and Military Public Health at the U.S. Air Force hospital in Tachikawa, Japan and on the faculty at the Duke University Medical Center. He has published multiple peer-reviewed papers on the epidemiology of NHL and other hematopoietic malignancies.

Mitchell S. Cairo, M.D., is a Professor of Pediatrics, Medicine, and Pathology at Columbia University. He is the Chief of the Division of Blood and Marrow Transplantation at the Morgan Stanley Children's Hospital in New York City. He has published more than 200 peer-reviewed papers in the area of pediatric hematology-oncology and stem cell transplantation. He was the Chair of the first and second International Symposia on Childhood, Adolescent and Young Adult Non–Hodgkin Lymphoma. He is the lead author of the chapter on NHL in children in the 7th edition of the textbook *Cancer Medicine.*

John M. Cullen, V.M.D., Ph.D., is on the faculty at North Carolina State University where he is the Course Director for General Pathology. He received undergraduate and veterinary degrees from the University of Pennsylvania and completed a Ph.D. in Comparative Pathology at the University of California, Davis. He has been a board-certified member of the American College of Veterinary Pathology for more than twenty-five years.

Gerald B. Kasting, Ph.D., is a Professor of Pharmaceutics and Cosmetic Science at the James L. Winkle College of Pharmacy at the University of Cincinnati. He received his B.A. from Vanderbilt University and his Ph.D. in Physical Chemistry from the Massachusetts Institute of Technology. His research centers on the transport of drugs and other chemicals into and through the human skin. He was co-chair of the Gordon Research Conference on Barrier Function of Mammalian Skin.

Emanuel Rubin, M.D., is the Gonzalo E. Aponte Distinguished Professor of Pathology at Jefferson Medical College in Philadelphia. He received his B.S. from Villanova University and his M.D. from Harvard Medical School. He has been a board-certified member of the American Board of Pathology for more than forty-five years. He has won many awards, including the F.K. Mostofi Distinguished Service Award from the U.S.-Canadian Academy of Pathology and a Lifetime Achievement Award from the American Society of Investigative Pathology. His textbook, *Pathology,* is now in its fifth edition and is one of the most widely used English-language pathology texts in the world.

II. Legal Standard

The Federal Rules of Evidence tell us that, where "scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue," an expert who is qualified "by knowledge, skill, experience, training, or education" may offer testimony in the form of an opinion. Fed.R.Evid. 702. Such evidence is admissible only where "(1) the testimony is based upon sufficient facts or data, (2) the testimony is

the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case." *Id.*

[3] The current version of Rule 702 incorporates the Supreme Court's holding in *Daubert v. Merrell Dow Pharm., Inc.,* 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993) in the form of what our Court of Appeals has called "a trilogy of restrictions on expert testimony: qualification, reliability and fit." *Schneider v. Fried,* 320 F.3d 396, 404 (3d Cir.2003). In evaluating opinion testimony on a motion such as this one, "the district court acts as a gatekeeper, preventing opinion testimony that does not meet the requirements of qualification, reliability and fit from reaching the jury." *Id.*

[4–6] Because we address this motion in our role as gatekeeper rather than as finder of fact, our "focus ... must be solely on principles and methodology, not on the conclusions that they generate." *Daubert,* 509 U.S. at 595, 113 S.Ct. 2786. Nevertheless, in order to admit the evidence, we must be satisfied that the proffered testimony represents what Rule 702 refers to as "scientific ... knowledge." As *Daubert* explains: "The adjective 'scientific' implies a grounding in the methods and procedures of science. Similarly, the word 'knowledge' connotes more than subjective belief or unsupported speculation." 509 U.S. at 590, 113 S.Ct. 2786. In other words, in order for scientific testimony to be sufficiently reliable, it "must be derived by the scientific method" and "must be supported by appropriate validation." *Id.* The scientific method requires "the generation of testable hypotheses that are then subjected to the real world crucible of experimentation, falsification/validation, and replication." *Caraker v. Sandoz Pharma. Corp.,* 188 F.Supp.2d 1026, 1030 (S.D.Ill.2001).

[7, 8] "The reliability requirement ... should not be applied too strictly." *Holbrook v. Lykes Bros. S.S. Co.,* 80 F.3d 777, 784 (3d Cir.1996). So long as "the expert has 'good grounds' for the testimony, the scientific evidence is deemed sufficiently reliable." *Id.* The need for good grounds, however, "means that *any* step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible. This is true whether the step completely changes a reliable methodology or merely misapplies that methodology." *In re Paoli R.R. Yard PCB Litig.,* 35 F.3d 717, 745 (3d Cir.1994) (emphasis in original). Although "[t]he Rules of Evidence embody a strong preference for admitting any evidence that may assist the trier of fact," *Pineda v. Ford Motor Co.,* 520 F.3d 237, 243 (3d Cir.2008), "the trial judge must have considerable leeway in deciding in a particular case how to go about determining whether particular expert testimony is reliable." *Kumho Tire Co. v. Carmichael,* 526 U.S. 137, 152, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999).

[9, 10] We must also consider "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." *Daubert,* 509 U.S. at 591, 113 S.Ct. 2786 (quoting *United States v. Downing,* 753 F.2d 1224, 1242 (3d Cir. 1985)). "Rule 702's 'helpfulness' standard requires a valid scientific connection to the pertinent inquiry as a precondition to admissibility." *Id.* at 591–92, 113 S.Ct. 2786. This helpfulness requirement—which our Court of Appeals calls "fit"—is, in the end, "the ultimate touchstone of admissibility." *Holbrook,* 80 F.3d at 784.

III. The Expert Reports

Each of plaintiffs' experts reaches conclusions as to two issues. With regard to

general causation, each concludes that Elidel is capable of causing harm of the sort that Andreas Perry suffered. With regard to specific causation, each concludes that Andreas Perry's Elidel use was actually a contributing factor to his development of T–LBL. Because their conclusions and the precise methods by which they arrived at those conclusions are central to this motion, we will review each in detail.

A. Dr. Martyn T. Smith

1. General Causation

In his report, Dr. Smith concludes that "pimecrolimus is a cause of non-Hodgkin lymphoma in humans." Report of Dr. Martyn T. Smith ("Smith Rpt.") ¶ 12. Dr. Smith bases that conclusion on his observations that: (1) pimecrolimus produced lymphomas in mice and monkeys and non-lymphoma tumors in rats; (2) cyclosporine and tacrolimus are well-described carcinogens in humans when used systemically to prevent transplant rejection; multiple case reports link dermal use of pimecrolimus to lymphoma; and (4) there exist biologically plausible mechanisms by which pimecrolimus could cause lymphoma. *Id.*

Dr. Smith notes several animal studies in his report. In a two-year rat dermal carcinogenicity study,[8] Novartis scientists discovered follicular cell adenoma of the thyroid in male rats at all three dose levels: 2 mg/kg/day, 6 mg/kg/day, and 10 mg/kg/day. Smith Rpt. ¶ 27. In the dermal mouse studies that were conducted, lymphoproliferative changes, atrophy of the thymus, and changes in the lymph nodes were noted in mice receiving high doses of ethanolic solution. *Id.* ¶ 28 (citing pages ENDA 0005542–80). In oral gavage[9] studies in mice, malignant lymphomas, thymic atrophy, and hyperplasia of the lymph nodes were noted at a dose of 45 mg/kg/day. *Id.* at 29. In oral gavage studies in rats, statistically significant increases in benign thymomas were observed at dosages of 5/mg/kg/day in one study and 10/mg/kg/day in another. *Id.*

Novartis also conducted studies in monkeys. In particular, Dr. Smith cites a 39–week oral toxicology study that was cut short when monkeys at the higher two dose levels (45 mg/kg/day and 120 mg/kg/day) suffered severe reactions, including death, all of which were associated with immunosuppressive related lymphoproliferative disorder. *Id.* ¶ 31. One of the monkeys in the low-dose group, 15 mg/kg/day, also had immunosuppressive-related lymphoproliferative disorder and thus the study failed to identify a no observed adverse effect level (NOAEL), which was one of its original goals. *Id.*

Dr. Smith next notes the lack of strong, reliable evidence for or against carcinogenicity based on human studies because of the nonexistence of data that is sufficiently statistically powerful. *Id.* ¶¶ 37–39. He notes, however, that tacrolimus and cyclosporine, two compounds with similar biological operation—and, in the case of tacrolimus, similar chemical structure—have been shown to significantly increase lymphoma risk when used in post-transplant immunosuppressive therapy. He then goes on to examine case reports from MedWatch,[10] which include thirty-four re-

8. Dr. Smith's report does not specifically identify this report and it does not appear to have been included as an exhibit. Dr. Cullen identifies it as T–132 at pages ENDA 0035921–26.

9. "Oral gavage is accomplished by preparing a solution or suspension of the test article and injecting it through a tube that passes through the mouth, down the esophagus and directly into the stomach." Report of Dr. John M. Cullen ("Cullen Rpt.") at 9.

10. MedWatch is the Food and Drug Administration's program for "reporting serious reactions, product quality problems, therapeutic

ports of malignancy, including nineteen cases of lymphoma among patients taking Elidel. *Id.* ¶ 41. Dr. Smith notes that several of these reports show incidence of lymphoma "without obvious alternative causes." *Id.* ¶ 42.

Dr. Smith's report goes on to examine possible mechanisms by which pimecrolimus exposure might induce lymphoma in humans. He begins by noting that immune deficiency, whether congenital, iatrogenic, or acquired, is a strong risk factor for NHL. *Id.* ¶ 43. Pimecrolimus is a calcineurin inhibitor and is known to suppress immune function. IARC has identified cyclosporine, another calcineurin inhibitor, as a known, or Group 1, human carcinogen. Pl.Ex. 15. Dr. Smith hypothesizes that, were IARC to evaluate the data that he examined,[11] it would conclude that pimecrolimus is a Group 2A carcinogen: a substance that "is probably carcinogenic to humans." Smith Rpt. ¶ 70.

Dr. Smith notes that other calcineurin inhibitors inhibit programmed cell death or apoptosis both in cell culture and in human transplant patients. *Id.* ¶ 55. Although this reaction has not been closely studied in pimecrolimus, this is another mechanism by which Elidel might cause cancer. A December, 2006 gene expression profiling study found that some genes in the p53 apoptosis pathway were partially inhibited in female monkeys orally dosed with pimecrolimus. *Id.* ¶ 56. That study found that, after oral administration of 45 mg/kg of pimecrolimus, the expression of certain B-cell markers was reduced—a sign of reduced numbers of B-cells—which could, in turn, be the result of damaged T-cells in the thymus. *Id.* ¶ 59. Finally, Dr. Smith hypothesizes that calcineurin inhibitors may reduce the ability of DNA in the cell to repair itself. *Id.* ¶ 64. As a result, because it is also a calcineurin inhibitor, "one would expect that pimecrolimus will likewise inhibit DNA repair." *Id.* Dr. Smith cites no study that has examined the effect of pimecrolimus itself on DNA repair.

Dr. Smith further concludes that, although dermal studies of pimecrolimus generally show very low levels of the drug in the blood, those levels are not "a useful measure of tissue exposure." *Id.* ¶ 91. In particular, Dr. Smith notes several studies that found significantly higher levels of pimecrolimus in the lymph nodes, thymus, and bone marrow than in the blood. *Id.* ¶¶ 75–88.

Based on all of these factors, Dr. Smith concludes that "pimecrolimus is a cause of non-Hodgkin lymphoma in humans." *Id.* ¶ 68.

2. Specific Causation

After reviewing Andreas Perry's medical history, Dr. Smith begins his analysis by noting that "the type of lymphoblastic lymphoma in Andreas is extremely rare and, in the presence of a known risk factor for NHL such as immunosuppressive therapy, unlikely to be simply due to chance." *Id.* ¶ 100. Dr. Smith notes that Andreas Perry's cancer was centered in the thymus, which is known to be a target of pimecrolimus. *Id.* ¶ 101. Dr. Smith characterizes Andreas Perry's exposure as "substantial and prolonged" and finds that such application could result in "significant concen-

inequivalence/failure, and product use errors with human medical products, such as drugs and medical devices.'' MedWatch—Reporting by Consumers *at* http://www.fda.gov/medwatch/report/consumer/consumer.htm (last visited June 5, 2008).

11. This is not possible because many of the studies Dr. Smith examined are not published and remain proprietary to Novartis and its related entities.

trations in bone marrow, the thymus, and lymph nodes." *Id.* ¶ 102. Given the "temporal relationship" between Andreas Perry's exposure and his cancer, the link to a known target organ, the "absence of other risk factors," the rarity of T–LBL in young children, the known toxicity of related drugs, and the existence of plausible mechanisms of action, Dr. Smith concludes that his exposure to pimecrolimus was "a substantial factor in [Andreas Perry's] presentation with lymphoblastic lymphoma." *Id.* ¶ 105.

B. Dr. E. Anders Kolb

1. General Causation

Dr. Kolb begins his analysis by noting that cyclosporine and tacrolimus "are known causes of lymphoproliferative disease and lymphoma." Kolb Rpt. at 5. Based on his review of the animal studies, Dr. Kolb finds that "pimecrolimus is carcinogenic in several species of animals" and notes that, in animal studies, it has been associated with "pleomorphic lymphoma, leukemia, lymphoproliferative disease, follicular cell adenoma of the thyroid, thymic atrophy, and benign thymoma." *Id.* Dr. Kolb notes that changes in lymphoid tissues were also seen with dermal application. He describes a study [12] in which high dose dermal pimecrolimus given to mice resulted in a decrease in circulating lymphatic cells. Other mouse dermal studies found transient thymic medullary hyperplasia and levels of pimecrolimus in the lymph nodes up to 6.5 times that in the blood.

Dr. Kolb also examined the pharmacokinetic (PK) studies [13] Novartis conducted as part of its clinical testing. Following topical administration, the tested cohort of children under 2.5 years of age experienced a decrease in the mean absolute lymphocyte count, suggesting that pimecrolimus has an effect on lymphoid tissue in young children. *Id.* at 6. These studies were not large enough to develop statistically significant measures of the effect. *Id.* They also did not explore the possibility of concentration of pimecrolimus in human lymphatic tissue. *Id.*

A number of animal studies, however, have suggested concentration in the lymphatic system. Studies in mice found concentrations in lymphatic tissue ranging from 34 to 122 times that in blood at 24 hours after dermal administration. Similar results were found with minipigs. *Id.* In a topical application study with cynomolgus monkeys, the study's scientists observed very wide variations in the level of pimecrolimus in lymph nodes, but some had concentrations in draining lymph nodes as high as 622 times that in blood. *Id.* Dr. Kolb concludes that these data showed that "carcinogenic levels of the drug may be achieved in lymphoid tissues even with dermal administration." *Id.* at 7.

Like Dr. Smith, Dr. Kolb examined possible biological mechanisms by which pimecrolimus could cause lymphoma and lymphoproliferative disorder. Like Dr. Smith, he concluded that this could occur because of immunosuppressive effect or by inhibiting apoptosis. *Id.*

12. Dr. Kolb's report does not cite to or specifically identify any of the studies he addresses. While we trust that these studies actually exist, the lack of citations made our process of coordinating his findings with those of the six other experts in this case significantly more difficult.

13. Pharmacokinetic studies describe the processes by which a drug is absorbed, diffused throughout the body, metabolized, and excreted.

Dr. Kolb observes that the human clinical trial with pimecrolimus revealed no increase in lymphoma risk. *Id.* He notes, however, that because lymphoma is very rare in the general population, he would not expect to see an increase in the relatively small population that the studies encompassed. *Id.* at 7–8. He also examined the MedWatch case reports and notes that, while they were too few in number to predict a relative risk, the malignancies reported were disproportionately T-cell lymphomas. *Id.* at 8.

Dr. Kolb concludes that based on the "repeated findings of carcinogenicity in multiple animal species (including in primates closely related to man), the similar effects of closely-related compounds, the biologically plausible mechanisms of carcinogenesis, the high concentrations of pimecrolimus in susceptible lymphoid tissue seen with dermal application, and lymphoma reports in humans ... pimecrolimus generally—and pimecrolimus cream specifically—is capable of causing lymphoma in humans." *Id.*

2. Specific Causation

Dr. Kolb begins his specific causation analysis by noting that there is no evidence of congenital or acquired immune deficiency, family history of lymphoma, viral infection, or environmental exposure in Andreas Perry's medical history that would suggest any of those as risk factors for development of NHL. Because exposure to a calcineurin inhibitor, namely pimecrolimus, was the only known NHL risk factor Dr. Kolb could identify, he concluded that "the use of pimecrolimus cream to treat Andreas Perry's eczema was a substantial factor in his development of lymphoblastic lymphoma." *Id.* at 11.

IV. Analysis

Although Novartis has also challenged Dr. Smith's qualifications to render an opinion on specific causation, we first focus our attention on the substance of plaintiffs' proffered expert testimony. In particular, we address whether the methodology by which the experts have reached their conclusions is reliable and whether those conclusions will assist the trier of fact in resolving an issue of fact in this case.

[11] Courts in toxic tort cases often separate the causation inquiry into general causation—whether the substance is capable of causing the observed harm in general—and specific causation—whether the substance actually caused the harm a particular individual suffered. Plaintiffs' experts here have done the same, each drawing conclusions about both the capacity of pimecrolimus to cause NHL in humans and its particular effect in Andreas Perry's case. We note, however, that while this division between general and specific causation is frequently a helpful model, the core issue that the jury will have to address in this case is whether Andreas Perry's exposure to Elidel was a substantial cause of his T–LBL.[14] In the end, the question of fit comes down to whether an expert's conclusions can assist the jury in deciding that difficult question.

[12, 13] General causation conclusions are relevant when they form a link in a causal chain that helps a jury reach a conclusion on the ultimate causation question. As other courts have recognized, while "the incidence of adverse effects in the general population[,] when exposed, cannot indicate the actual cause of a given individual's disease or condition," the admission of general causation evidence is an

14. To the extent that courts have required a separate finding of general causation, we interpret that as a necessary element of any finding of specific causation.

attempt to "balance the need to compensate those who have been injured by the wrongful actions of another with the concept deeply imbedded in our jurisprudence that a defendant cannot be found liable for an injury unless the preponderance of the evidence supports cause in fact." *Merrell Dow Pharms. Inc. v. Havner,* 953 S.W.2d 706, 718 (Tex.1997). Conclusions about general causation, however, exist on a continuum. It should be obvious, for example, that an expert's conclusion that "Elidel cream, used as directed, causes T-cell lymphoblastic lymphoma in humans" is more useful to a jury, and therefore more relevant, than a conclusion that "calcineurin inhibitors cause cancer in mammals." Just as "there is no fit where there is 'simply too great an analytical gap between the data and the opinion offered,' " *Soldo v. Sandoz Pharms. Corp.,* 244 F.Supp.2d 434, 527 (W.D.Pa.2003) (quoting *General Electric Co. v. Joiner,* 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997)), there is also no fit when there is too great an analytical gap between an expert's general causation conclusion and the specific causation question the jury must ultimately answer.

[14, 15] It is also true that the expert's journey from general causation to specific causation need not be just a two-step process. So long as, taken together, the experts are able to draw a chain of scientifically-reliable causal links that meets plaintiffs' requirements under the substantive tort law, the evidence is admissible and it will be left to the jury to establish the relative credibility of the parties' competing experts. Where, however, the expert reports leave wide, unexplained gaps in the causal chain, the evidence is not helpful to the trier of fact and must be excluded.

As a matter of process, then, our analysis should begin by examining each of the experts' conclusions to determine if the method the expert has used to reach that conclusion is reliable. We must then examine those conclusions that are sufficiently reliable to be admissible and determine if, taken collectively, they form a sufficient causal chain to aid the trier of fact in reaching the ultimate conclusion on causation: whether Andreas Perry's exposure to Elidel was a substantial factor in his contraction of T–LBL.

A. Dr. Smith's General Causation Conclusions

Dr. Smith concluded that "pimecrolimus is a cause of non-Hodgkin lymphoma in humans." Smith Rpt. ¶ 12. In reaching that conclusion he relied on animal studies, lymphoma data associated with the related drugs cyclosporine and tacrolimus, unpublished case reports of lymphoma in humans, and the availability of biologically plausible mechanisms for causation. *Id.* Although there existed at least one published epidemiologic study on the link between pimecrolimus and lymphoma at the time of his report,[15] Dr. Smith did not consider any epidemiology studies in reaching his conclusion. *See* Smith Dep. at 101:3–9; Smith Rpt., ex. B (listing the sources Dr. Smith consulted). It is unclear whether Dr. Smith knew of the existence of the Arellano study, although he does aver that he conducted searches of the "peer-reviewed scientific and medical literature" that should have revealed it. Smith Rpt., ex. B at 10. Dr. Smith did, however, address the epidemiological studies in his supplemental report.

15. The Arellano study, which is defendant's exhibit 30, was published in the Journal of Investigative Dermatology in November of 2006. Dr. Smith's initial report is dated January 8, 2008.

[16] Although "it has not been declared in [the Third Circuit] that epidemiological studies are an indispensable element in the presentation of a prima facie drug product liability case," *Lanzilotti v. Merrell Dow Pharms. Inc.,* 1986 WL 7832 at *2 (E.D.Pa. July 10 1986), "[e]pidemiology is 'the primary generally accepted methodology for demonstrating a causal relation between a chemical compound and a set of symptoms or a disease,' " *Soldo,* 244 F.Supp.2d at 532 (quoting *Conde v. Velsicol Chem. Corp.,* 804 F.Supp. 972, 1025–26 (S.D.Ohio 1992)). Thus, while an expert's conclusions reached on the basis of other studies could be sufficiently reliable where no epidemiological studies have been conducted, no reliable scientific approach can simply ignore the epidemiology that exists. Although Dr. Smith raises some questions about the effectiveness of the study protocol, *see* Smith Supp. Rpt. ¶¶ 16–21, the Arellano study is the only published epidemiological study that addresses the issue in this case and any admissible analysis must give that study serious consideration. It is, therefore, most disquieting that Dr. Smith fails to even mention that study in his initial report.[16] Nevertheless, he addresses that study and others in his supplemental report.

Dr. Smith points out various flaws in the design of the Arellano study. For our purposes, the most important of these is that the study is significantly underpowered to reach the conclusion that there is no link between pimecrolimus and NHL. Thus, Dr. Smith observes, although the Arellano study found no evidence of a link, it did not include a sufficient number of patients to conclude that no such link exists. *Id.* ¶ 21. In his supplemental report, Dr. Smith also examines a subsequent study that Novartis engaged a firm known as i3 Drug Safety to conduct. *Id.* ¶ 22.[17] The i3 study dealt with a much larger cohort of pimecrolimus patients in order to increase its statistical power. *Id.* In analyzing the i3 study, Dr. Smith notes that it found a statistically significant 2.89–fold increase in lymphoma among pimecrolimus-treated patients as compared to the general population. *Id.* ¶ 23. This finding, however, does not support Dr. Smith's conclusion that pimecrolimus is a cause specifically of NHL because it deals with lymphoma in general. The i3 study did *not* find a statistically significant[18] increase among pimecrolimus users in NHL cases as compared to the general population. *See* Pl.Ex. 30 at ELED–01697516, tbl. 9a. In addition, when compared with untreated dermatitis patients, pimecrolimus users saw no statistically significant increase in risk of either lymphoma generally or NHL. *See id.* at ELED–01697515, tbl. 8a. As the study's authors discuss, this may be a sign that patients who are prescribed topical dermatitis agents may already be at increased risk for lymphoma due to unobserved factors. *Id.* at ELED–01697502.

Given that Dr. Smith's general causation conclusion was that a link exists between pimecrolimus and NHL, and not lymphoma in general, his decision to focus on the

16. Without addressing any particular study or offering any support for his conclusion, Dr. Smith simply concludes that "there are no adequately designed or suitably powered clinical trials or epidemiology studies of the risk of Non–Hodgkin Lymphoma (NHL) following pimercrolimus [*sic*] treatment." Smith Rpt. ¶ 37.

17. The final report from the i3 study is in the record as plaintiffs' exhibit 30.

18. In this study, a relative risk findi statistically significant at p=0.05 when the 95% interval does not include 1. Although the study relative risk of NHL among pimecrolimus patients confidence interval runs from 0.95 to 5.54.

generalized lymphoma data rather than the NHL-specific data is highly questionable. Indeed, Dr. Smith admitted that he has never combined diagnoses of NHL, Hodgkin lymphoma, and cutaneous lymphoma for statistical purposes in any study he has conducted. Smith Supp. Dep. 57:7–11. Yet it is that combined number on which he chooses to focus his analysis in this case. It therefore appears that Dr. Smith's analysis of the i3 report focused not on the findings that were most relevant to the hypothesis he sought to test but on the findings that were most helpful to his paying client. While this approach is, sadly, not uncommon, it is incompatible with the reliable application of the scientific method.

Dr. Smith's decision to ignore the epidemiological data in his original analysis, and his focus in his analysis of the i3 study on a result of questionable relevance to his conclusion, cast doubt on the objectivity of his analysis. It is clear, however, that what epidemiological data exist lead to no strong conclusions for or against a link between pimecrolimus and NHL. We must, therefore, as Dr. Smith does, focus on the results from animal studies if we are to determine whether any scientifically provable link between pimecrolimus and NHL in humans exists.

Dr. Smith's conclusion with regard to general causation is only that pimecrolimus exposure can cause NHL in humans. He is not specific about dosage or method of administration. Thus, although defendant raises many concerns about the relevance of animal studies that use oral gavage or ethanol solutions to increase bioavailability, those are not germane to the reliability of the methods Dr. Smith used to arrive at his general conclusion.[19] Rather, the question before us is whether Dr. Smith's conclusion that at some level of exposure pimecrolimus can cause NHL in humans is reliable. Dr. Smith identifies three studies in which animals given pimecrolimus developed lymphoma—two in mice and one in monkeys. Smith Rpt. ¶¶ 28, 29, 31. In none of these studies does Dr. Smith specifically identify the lymphoma as NHL.[20] Dr. Smith also identifies four additional studies in which non-lymphoma tumors were found. *Id.* ¶¶ 27, 29, 30.

While those seven studies, taken in the context of the hundreds of studies that Novartis performed, might not be sufficient to support a finding of carcinogenicity, Dr. Smith also examined pimecrolimus's similarity to other drugs about which more is known. Like tacrolimus and cyclosporine, pimecrolimus is a calcineurin inhibitor. All three drugs bind to immunophilins and block T-cell activation. *Id.* ¶ 23. In organ transplant patients, cyclosporine and tacrolimus are commonly administered in large doses orally or intravenously in order to provide systemic immunosuppression. Cairo Rpt. at 3. Such immunosuppression is known to increase the risk of lymphoma. Rubin Rpt. at 5. Indeed, IARC has identified cyclosporine as a known human carcinogen on the basis of both animal and human data. Smith Rpt. ¶ 22.

[17] The animal studies Dr. Smith relied on show that, at high enough doses, pimecrolimus can cause both systemic im-

19. To be sure, when we look at "fit" and the existence of analytical gaps, we are concerned with Dr. Smith's ability to provide a scientifically reliable bridge between the doses in laboratory animals and the dose Andreas Perry actually received.

20. Indeed, it is not even clear from Dr. Smith's report that the distinction between NHL and other lymphomas is meaningful in non-human mammals.

munosuppression and related lymphoproliferative disorders. Thus, taken in the context of its relationship to cyclosporine and tacrolimus, Dr. Smith's conclusion that under some circumstances pimecrolimus can cause NHL in humans is based on a reliable scientific approach. This does not mean, of course, that the Perrys have conclusively shown that pimecrolimus is a cause of NHL in humans. At this stage, we need only conclude that there are good grounds for Dr. Smith's conclusion. "The judge might think that there are good grounds for an expert's conclusion even if the judge thinks that there are better grounds for some alternative conclusion, and even if the judge thinks that a scientist's methodology has some flaws such that if they had been corrected, the scientist would have reached a different result." *Paoli*, 35 F.3d at 744. Because there are good grounds for Dr. Smith to conclude that pimecrolimus can cause NHL in humans, we find that determination reliable.

B. Dr. Kolb's General Causation Conclusion

Dr. Kolb's general causation conclusion is similar to Dr. Smith's, but differs in two key respects. Dr. Kolb concludes that "pimecrolimus generally—and pimecrolimus cream specifically—is capable of causing lymphoma in humans." Kolb Rpt. at 8. Thus, Dr. Kolb's conclusion is not limited to NHL but concerns lymphoma generally and, more importantly for our purposes, specifies that pimecrolimus cream—that is, dermal application of pimecrolimus—is capable of causing lymphoma.

Like Dr. Smith, Dr. Kolb chose not to review the epidemiological studies that existed at the time of his report and he addresses them only cursorily in his supplemental report, a decision that again gives us pause as we consider the reliability of Dr. Kolb's method. Nevertheless, because it is the area where his report and methodology differ most significantly from that of Dr. Smith, and because it is a key basis for his findings, we will concentrate on Dr. Kolb's analysis of dermal application of pimecrolimus. As Dr. Kolb himself notes, exposure to dermally-applied pimecrolimus will vary greatly among individuals depending on where on the body it is applied, the condition of the underlying skin, and various other factors. Kolb Supp. Rpt. at 2. It is therefore surprising that Dr. Kolb places significant weight on a PK study of only four patients between 0.67 and 2.5 years of age. Kolb Rpt. at 6. In that study, the mean absolute lymphocyte counts of each of the patients declined over the course of the study, although in no case did it fall outside the normal range or to what Dr. Cairo refers to as a "clinically relevant low level." [21] Cairo Rpt. at 16. As Dr. Kolb notes, this study was far to small to have any statistical power, the study's authors did not discuss this effect in their analysis, and no follow-up studies were suggested, either by Novartis or by the FDA.[22] Kolb Rpt. at 6.

Dr. Kolb goes on to examine the possible concentration of pimecrolimus in various tissues of the body. This effect has never been studied in human patients. *Id.* Therefore, Dr. Kolb concludes, "the exposure of children to pimecrolimus cream must be deduced from animal studies where concentrations of pimecrolimus in tissue were measured." *Id.*

[18, 19] Before we examine those studies, however, we must make clear that the

21. Because plaintiffs do not appear to have provided a copy of this study, we cannot review the results for ourselves.

22. This study appears to have been one of a set submitted to the FDA as part of the New Drug Application for Elidel.

non-existence of good data does not allow expert witnesses to speculate or base their conclusions on inadequate supporting science. In cases where no adequate study shows the link between a substance and a disease, expert testimony will generally be inadmissible, even if there are hints in the data that some link might exist. This may mean that early victims of toxic torts are left without redress because they are unable to prove their cases with the scientific data that exists. While this is a regrettable result in those individual cases, it is an unavoidable reality of the structure of our legal system and is necessary to protect the interests of defendants who might otherwise be subject to crippling verdicts on the basis of slender scientific evidence. As the Seventh Circuit has noted, "[t]he courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it." *Rosen v. Ciba–Geigy Corp.*, 78 F.3d 316, 319 (7th Cir.1996). Thus, even though Dr. Kolb may have carefully examined all the data that exists with regard to accumulation of pimecrolimus in lymphatic tissue, his conclusion is admissible only if those data are objectively sufficient to support it. In particular, suggestions in the expert reports that Novartis should have conducted additional studies or designed their studies differently are irrelevant here. Plaintiffs' experts may only base their conclusions on existing data. It will not do for either plaintiffs' experts or counsel to raise vague inferences that Novartis's failure to conduct certain studies is somehow evidence of malfeasance or guilt.

Dr. Kolb examined studies in mice, minipigs, and monkeys that showed accumulations of pimecrolimus in lymphoid tissues that were significantly higher than those in the blood.[23] Kolb Rpt. at 6–7. From this, Dr. Kolb concludes that "carcinogenic levels of the drug may be achieved in lymphoid tissues even with dermal administration." *Id.* at 7. Dr. Kolb, however, offers no basis for concluding that accumulation of pimecrolimus in lymphoid tissue is likely to increase the risk of lymphoma. Indeed, at his deposition Dr. Kolb testified that he was aware of no evidence of lymphoma being associated with the accumulation of *any compound* in the thymus, lymph nodes, or spleen. Kolb Dep. at 97:5–98:5. *See also* Smith Dep. at 128:10–13 (testifying that he was unaware of any studies that "have demonstrated specific clinical consequences of any chemical accumulating in lymph nodes").

Without some reliable scientific link between accumulation of pimecrolimus in lymphatic tissue and development of lymphoma, we cannot accept Dr. Kolb's conclusion that dermal application of pimecrolimus can lead to cancer in humans. The generally accepted scientific measure of systemic exposure to a drug is referred to as the area under the curve ("AUC") and represents the area under a curve that graphs blood concentration against time. Report of Dr. Gerald B. Kasting ("Kasting Rpt.") at 14. By this measure, exposure in humans who receive pimecrolimus cream is extremely low. *See, e.g.*, Pl.Ex. 32 at ELED–317919–25. This is to be expected based on pimecrolimus's high lipophilicity and high molecular weight. *See* Kasting Rpt. at 17, 30. Although Dr. Kolb is concerned that AUC may not accurately measure bioavailability of pimecrolimus, without *some* science linking accumulation of carcinogens in the lymphatic system and subsequent development of cancer, there is

23. In many cases, the blood levels of animals and humans given pimecrolimus cream were too low to measure.

no scientific basis for using another method here.

The evidence that pimecrolimus collects at elevated levels in lymphoid tissue may well warrant further study. Based on the data that exist today, however, any link that plaintiffs' experts draw between dermal application of pimecrolimus and increased risk of lymphoma is mere guesswork—educated guesswork, but guesswork nonetheless. While such speculation is appropriate in the laboratory where a hypothesis can be tested by experiment, it has no place in the courtroom where no such testing is possible.

[20] Because there are no experimental data that support a link between elevated levels of pimecrolimus in lymphoid tissue and development of lymphoma, we find that Dr. Kolb's conclusion that pimecrolimus cream causes lymphoma in humans is unreliable and therefore inadmissible.

C. Specific Causation Conclusions

Plaintiffs' two experts reach essentially the same conclusion with regard to specific causation by using the same methodology, and so we will treat those conclusions together. Each expert examines the risk factors for NHL—including, based on his general causation conclusion, pimecrolimus exposure—and each engages in a differential diagnosis. In each case, after finding that no other risk factor for NHL is present,[24] the expert concludes that because pimecrolimus exposure is the only risk factor present and because the disease is rare, Andreas Perry's treatment with Elidel is a substantial factor in his presentation with T–LBL. Smith Rpt. ¶¶ 100–105; Kolb Rpt. at 11.

[21] In order to result in an admissible conclusion, a differential diagnosis should "reliably rule out reasonable alternative causes of [the alleged harm] or idiopathic causes." *Soldo,* 244 F.Supp.2d at 567. Admissible expert testimony need not rule out *all* alternative causes, but "where a defendant points to a plausible alternative cause and the doctor offers *no* explanation for why he or she has concluded that it was not the sole cause, that doctor's methodology is unreliable." *Heller,* 167 F.3d at 156 (quoting *Paoli,* 35 F.3d at 759 n. 27).

Here, the differential diagnoses Drs. Smith and Kolb engage in fail to exclude—much less address in their reports—the likelihood that Andreas Perry's lymphoma had no known cause. As Dr. Kolb admitted, most NHL cases and, more specifically, most T–LBL cases, are idiopathic, having no known cause. Kolb Dep. 129:20–130:20. Faced with similar situations, our sister courts have excluded experts' differential diagnoses where they failed to adequately account for the likelihood that the disease was caused by an unknown factor. *Doe v. Ortho–Clinical Diagnostics, Inc.,* 440 F.Supp.2d 465, 478 (M.D.N.C.2006), for example, excluded the testimony of plaintiffs' expert because "he did not properly perform the differential diagnosis given his failure to consider within his analysis the high probability that an unknown genetic cause cannot be ruled out as the specific cause of Minor Child Doe's autism." Similarly, in *Whiting v. Boston Edison Co.,* 891 F.Supp. 12 (D.Mass.1995), the court excluded expert testimony that radiation was the cause of plaintiff's acute lymphocytic leukemia. The court reasoned that "[d]ifferential diagnosis, as the technique is used in the medical profession, consists of the comparison of a pa-

24. The other risk factors relevant to childhood T–LBL are congenital or acquired immune deficiency, family history, viral infection, and environmental factors. *See* Kolb Rpt. at 11.

tient's symptoms to symptoms associated with a known set of diseases. The idea is to find the disease that matches the symptoms. If 90 percent of the causes of a disease are unknown, it is impossible to eliminate an unknown disease as the efficient cause of a patient's illness." *Id.* at 21 n. 41.

When questioned at his deposition about how he had excluded "no known cause" in Andreas Perry's illness, Dr. Kolb merely reiterated the factors he identified in his report that, in his opinion, point to pimecrolimus as a cause of lymphoma. Kolb Dep. at 130:25–132:20. Similarly, the only reason Dr. Smith gave for distinguishing Andreas's lymphoma from one of unknown cause was the existence of a known risk factor, namely exposure to pimecrolimus. Smith Dep. at 220:25–221:6. Standing alone, the presence of a known risk factor is not a sufficient basis for ruling out idiopathic origin in a particular case, particularly where most cases of the disease have no known cause.

This is not to say that where most diagnoses of a disease are idiopathic it is impossible to prove specific causation. But in those cases, analysis beyond a differential diagnosis will likely be required. Here, for example, because lymphoma caused by immunosuppressant drugs is well-understood, Drs. Smith and Kolb could have compared the presentation of Andreas Perry's symptoms with those common in post-transplant lymphoma cases. Doing so, however, would not have served plaintiffs' purposes. Andreas Perry's presentation is very different from the typical case of PTLD—those lymphomas that occur after a solid organ transplant ("SOT"), most likely from systemic use of immunosuppressive agents. Cairo Rpt. at 6. For example, "[o]ver 90% of PTLDs following SOT secondary to systemic immune suppression including the use of cyclosporine A and tacrolimus have a histology consistent with B-cell origin or B-cell non Hodgkin lymphoma." *Id.* Andreas Perry's lymphoma, however, was of T-cell origin. Further, in those cases that are of T-cell origin, "PTLD occurs late with a median time of 4.2 years after SOT." *Id.* Of the five cases of T-lymphoblastic PTLD that Dr. Cairo reviewed, none had a presentation sooner than 1.7 years after the start of immunosuppression therapy. *Id.* at 7. Andreas Perry's lymphoma was detected less than seven months after his first exposure to Elidel.

In 2005, the Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology published a joint report. *See* Luz Fonancier, et al., *Report of the Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology,* 115 J. Allergy & Clin. Immunol. 1249 (2005). That report listed five features that "characterize lymphomas occurring in the setting of immunomodulatory or immunosuppressive therapy." *Id.* at 1250. Those were "(1) frequent occurrence in unusual sites, including soft tissue, joint spaces, and lungs; (2) polymorphous and pleomorphic large cell or Hodgkin's-like morphology; (3) presence of the Epstein–Barr genome in lymphoma cells; (4) B-cell lymphomas developing weeks, months, or, less commonly, up to several years after receipt of immunomodulatory therapy; and (5) lymphomas spontaneously regressing after withdrawal of immunomodulatory therapy without the need for chemotherapy or radiation therapy in a significant percentage of cases (30% to 50%)." *Id.* None of those features have been associated with Andreas Perry's cancer. Indeed, at the time of Andreas Perry's presentation, he had re-

ceived no Elidel for more than six weeks, but his cancer was still growing so aggressively that it began to constrict his airway and cause difficulty breathing. Plaintiffs' experts offer no reason to expect that NHL caused by pimecrolimus exposure would likely present differently than PTLD caused by other calcineurin inhibitors. Indeed, their heavy reliance on the similarities between pimecrolimus, cyclosporine, and tacrolimus would lead us to expect a presentation very similar to that common with cyclosporine and tacrolimus.

Neither is there any evidence in Andreas Perry's medical records that at any time during his use of Elidel he experienced any systemic immunosuppression. Indeed, Dr. Kolb testified that he found "no clinical evidence of immunosuppression." Kolb Dep. at 35:5–6. In patients who are systemically immunosuppressed, for example, the development of opportunistic infections is common. Cairo Rpt. at 3. There is no suggestion of opportunistic infection in Andreas Perry's medical records. Kolb Dep. at 34:3–8. There is also no suggestion that any of Andreas's treating physicians at CHOP were concerned that his cancer was related to immunosuppression. *Id.* at 32:15–19. Nor is there any suggestion in the records that the doctors at CHOP tested for involvement of the Epstein–Barr Virus, a common factor in immunosuppression-related lymphomas. *Id.* at 32:21–25. The doctors who directly treated Andreas Perry apparently saw no reason to explore either disease-related or environmental immunosuppression as a potential cause of his cancer.[25] Nevertheless, plaintiffs' experts assert that they can reliably conclude based only on the written record that the cancer was caused by a particular immunosuppressant agent, namely Elidel.

Because the methods by which plaintiffs' experts suggest that Elidel could have caused Andreas Perry's cancer are related to systemic immunosuppression,[26] the absence of any evidence of systemic immunosuppression should be a significant factor in establishing any causal link. But plaintiffs' experts ignore this factor entirely and conclude, based solely on the presence of a risk factor, that Elidel was a cause of Andreas Perry's T–LBL.

[22] Because the differential diagnosis procedure that plaintiffs' experts employed fails to adequately account for the possibility that Andreas Perry's T–LBL was idiopathic, we find on this record that their conclusions that exposure to Elidel was a substantial cause of his cancer are unreliable and therefore inadmissible.[27]

25. Indeed, their decision to immediately begin an aggressive and lengthy course of chemotherapy is strong evidence that they did not believe that the boy's cancer was immunosuppression-related since many such cancers go into remission spontaneously once the immunosuppressant agent is removed.

26. Dr. Smith suggests three possible biological mechanisms by which this could occur. The first is systemic immunosuppression directly. Smith Rpt. ¶¶ 46–51. The second is resistance to apoptosis. *Id.* ¶¶ 52–61. His support for this mechanism is based on a study of systemically immunosuppressed patients, *id.* ¶ 55, and a study involving oral doses of pimecrolimus in monkeys at levels known to cause systemic immunosuppression, *id.* ¶¶ 56, 59. Dr. Smith suggests a third method, inhibition of DNA repair, but bases that on a conclusion that calcineurin inhibitors "block UV-induced nuclear localization of a protein called NFAT," for which he provides no support either in the literature or his experience. *Id.* ¶ 64.

27. Novartis also challenges Dr. Smith's qualifications to reach a conclusion on specific causation because he is not a Medical Doctor and does not treat patients. Because we find that the conclusion is unreliable, we need not address the issue of Dr. Smith's qualifications.

D. Fit

[23] In order to be admissible, expert conclusions must also be helpful to the finder of fact, a quality our Court of Appeals has described as "fit." *Holbrook*, 80 F.3d at 784. The question of fit deals both with the relevance of the conclusion to the scientific questions at issue and with any analytical gaps in the experts' conclusions that may render them misleading when applied to the evidence in the case.

Here, the primary problem with fit is just such an analytical gap. Drs. Smith and Kolb fail to address the disparity in the dosages Andreas Perry received and the dosages in the animal studies on which they rely. As we discussed above, Andreas Perry's exposure was no more than 2 mg of pimecrolimus per kilogram of body weight per day during the times he received the drug. In all the animal studies on which plaintiffs' experts rely, only a single study found any carcinogenisis at such a low dose: a two-year dermal study in rats in which follicular cell adenoma of the thyroid was found at doses of 2 mg/kg/day.[28] Smith Rpt. ¶ 27. As Dr. Cullen points out, "follicular cell adenomas ... are recognized by the general toxicology community and in the scientific literature as rat species or rat strain-related tumor types with little if any relationship to human disease." Cullen Rpt. at 19.

Even were we to credit Dr. Kolb's conclusion that AUC fails to adequately address bioavailability of pimecrolimus after dermal application, plaintiffs' experts would still have to show that the quantity of pimecrolimus applied to Andreas Perry's skin was sufficient to cause NHL. The animal studies do not support this conclusion. Drs. Smith and Kolb make no attempt to demonstrate sufficient dosage, but instead simply ignore the question of dosage entirely making only vague and unquantifiable statements like "Andreas Perry was exposed to a substantial amount of pimecrolimus cream for a prolonged period of time." Smith Rpt. ¶ 99. The failure to address the issue of dosage in a scientific manner is just one more reason to conclude that plaintiffs' experts did not reach their conclusions on the basis of the scientific method.

Plaintiffs' experts' general causation conclusions are primarily based on the animal studies and so their failure to satisfactorily address this analytical gap related to dosage levels undermines the usefulness of those conclusions to a jury. Further, the significant analytical gap dealing with dosage means that, even were we to find the specific causation conclusions reliable, we would still exclude them on fit grounds. Plaintiffs' experts have failed to form a scientifically-grounded chain of inference between their general causation finding and their specific causation finding.

Further, as we discussed above, fit should be addressed in the context of those conclusions that are sufficiently reliable in their methodology to be admissible. As we concluded above, the only conclusion that meets this reliability standard is Dr. Smith's conclusion that pimecrolimus can be a cause of NHL in humans. It should be obvious that this limited conclusion, standing alone, cannot help a lay finder of fact render a decision on the causation issues in this case. We note, for example, that both wood dust and alcoholic beverages are on the IARC list of known human

28. Dr. Smith describes the concentration of the cream in that study as one-fifth that marketed as Elidel. Smith Rpt. ¶ 27. The concentration of the cream itself is, of course, completely irrelevant without also making reference to the quantity of the cream applied. We do not look favorably on this attempt to obfuscate the dosage levels studied.

carcinogens.[29] That fact, standing alone, would not allow a lay jury to render an opinion that any plaintiff's cancer was caused by exposure to one of those two common substances.

[24] We find that the reports of plaintiffs' experts in this case do not meet the fit requirements of *Daubert* and *Paoli* and are therefore inadmissible.

E. Summary Judgment

The parties agree that plaintiffs require expert evidence to prove their case. Because Novartis has challenged the admissibility of that expert evidence, they have also moved for summary judgment on the grounds that if that evidence is excluded plaintiffs cannot prove their case and summary judgment is appropriate. Plaintiffs acknowledge that the only evidence that is sufficient to create a genuine question of material fact with regard to causation is their expert testimony. Pl. S.J. Resp. at 3. Because we have judged that evidence inadmissible under the *Daubert* standard, we must also grant defendant's motion for summary judgment.

ORDER

AND NOW, this 9th day of July, 2008, upon consideration of defendant's motion to exclude plaintiffs' experts (docket entry # 139) and motion for summary judgment (docket entry # 138), plaintiffs' responses (docket entries 142 & 143), defendant's motion for leave to file a reply brief (docket entry # 145) and plaintiffs' response (docket entry # 149), and for the reasons articulated in the accompanying Memorandum of Law, it is hereby ORDERED that:

1. Defendant's motion for leave to file a reply brief is GRANTED;

2. Defendant's motion to exclude plaintiffs' experts is GRANTED;

3. Defendants' motion for summary judgment is GRANTED; and

4. The Clerk of Court shall CLOSE this matter statistically.

JUDGMENT

AND NOW, this 9th day of July, 2008, the Court having this day granted defendant's motion for summary judgment, JUDGMENT IS ENTERED in favor of defendant Novartis Pharmaceuticals Corporation and against plaintiffs Andrea Perry and George Perry.

GENERAL STAR INDEMNITY COMPANY, Plaintiff,

v.

VIRGIN ISLANDS PORT AUTHORITY, Defendant.

Civil No. 2001–188.

District Court, Virgin Islands, D. St. Croix.

May 29, 2008.

Background: Insurer sued insured, a port authority, seeking, inter alia, a declaration stating that the insured had to reimburse the insurer for all costs and attorneys' fees expended defending the insured in underlying litigation arising from an airport extension construction project. Insurer moved for summary judgment.

29. This list is available at http://monographs.iarc.fr/ENG/Classification/crthgr01list.php.