In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 19-193V
Filed: December 19, 2025

TRUDY SCHNEIDERMANN, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	Special Master Horner

Mark Theodore Sadaka, Law Offices of Sadaka Associates, LLC, Englewood, NJ, for petitioner.
Parisa Tabassian, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

On February 1, 2019, petitioner, Trudy Schneidermann, filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10, *et seq.* (2012) ("Vaccine Act"),[2] alleging that tetanus diphtheria and acellular pertussis ("Tdap") vaccine received on February 5, 2016, caused her to suffer a shoulder injury related to vaccine administration ("SIRVA") as well as peripheral neuropathy, paresthesia, and fibromyalgia. (ECF No. 1.) On October 7, 2024, petitioner moved for a ruling on the written record. (ECF No. 83.) In her motion, petitioner clarifies her condition as "Fibromyalgia or a Fibromyalgia-like condition," which she further asserts explains her neurologic symptoms. (*Id*.) She abandoned any assertion of a SIRVA. (*Id*.) For the reasons set forth below, I conclude that petitioner is *not* entitled to an award of compensation.

[1] Because this document contains a reasoned explanation for the action taken in this case, it must be made publicly accessible and will be posted on the United States Court of Federal Claims' website, and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the document will be available to anyone with access to the internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will redact such material from public access.

[2] Within this ruling, all citations to § 300aa will be the relevant sections of the Vaccine Act at 42 U.S.C. § 300aa-10-34.

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a *causal link* between the vaccination and the injury. In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination, and the petitioner is automatically entitled to compensation, unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A); § 300aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B).

Alternatively, if no injury falling within the Table can be shown, a petitioner could still demonstrate entitlement to an award by instead showing that the vaccine recipient's injury or death was caused-in-fact by the vaccination in question. § 300aa-13(a)(1)(A); § 300aa-11(c)(1)(C)(ii). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321-22 (Fed. Cir. 2010) (quoting *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006). To successfully demonstrate causation-in-fact, petitioner bears a burden to show: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005).

In this case, petitioner has alleged that the Tdap vaccine caused her to suffer fibromyalgia (or a similar condition). Fibromyalgia is not listed on the Vaccine Injury Table. Accordingly, petitioner must satisfy the above-described *Althen* test for establishing causation-in-fact.

Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. § 300aa-13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly*, 592 F.3d at 1322 n.2 (alternation in original); *see also Snowbank Enters., Inc. v. United States*, 6 Cl. Ct. 476, 486 (1984) (explaining that mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical

certainty is not required. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). In finding causation, a program fact-finder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1279-80. However, a petitioner may not receive a Vaccine Program award based solely on her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1).

Cases in the Vaccine Program are assigned to special masters who are responsible for "conducting all proceedings, including taking such evidence as may be appropriate, making the requisite findings of fact and conclusions of law, preparing a decision, and determining the amount of compensation, if any, to be awarded." Vaccine Rule 3(b)(1). Special masters must ensure each party has had a "full and fair opportunity" to develop the record. Vaccine Rule 3(b)(2). However, special masters are empowered to determine the format for taking evidence based on the circumstances of each case. Vaccine Rule 8(a); Vaccine Rule 8(d). Special masters are not bound by common law or statutory rules of evidence but must consider all relevant and reliable evidence in keeping with fundamental fairness to both parties. Vaccine Rule 8(b)(1). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." § 300aa-13(b)(1)(A). The special master is required to draw plausible inferences and articulate a rational basis for the decision. *Winkler v. Sec'y of Health & Human Servs.*, 88 F.4th 958, 963 (Fed. Cir. 2023) (citing *Hines ex rel. Sevier v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1528 (Fed. Cir. 1991)).

II. Procedural History

Petitioner initially filed medical records marked as Exhibits 1-11 and then filed her Statement of Completion in March of 2019. (ECF Nos. 8-10.) However, additional records marked as Exhibits 12-13 were later filed between March and September of 2020. (ECF Nos. 19, 28.) After petitioner filed a second Statement of Completion in October of 2020 (ECF No. 29), respondent filed his Rule 4 Report in December of 2020 (ECF No. 31). Although respondent acknowledged that petitioner suffered some form of neuropathy, he contended that her diagnosis remained unclear and that she had not demonstrated that she suffered any of the conditions alleged in her petition. (*Id*. at 14-15.) He further contended that petitioner's presentation was inconsistent with a Table SIRVA and that the medical record evidence does not support vaccine causation-in-fact for any of petitioner's alleged injuries or any neurologic injuries. (*Id*. at 17-18.)

Thereafter, it took petitioner two years, until December of 2022, to secure an expert report supporting her claim. (ECF No. 53; Ex. 18.) In the interim, petitioner filed

additional medical records marked as Exhibits 14-16. (ECF Nos. 41, 47.) Petitioner's expert, immunologist David Axelrod, M.D., narrowed petitioner's claim, opining that petitioner suffered vaccine-caused fibromyalgia. (Ex. 18.) In response, respondent filed a report by rheumatologist Maxime Kinet, M.D., Ph.D. (ECF No. 55; Ex. A.) Dr. Kinet agreed that petitioner suffered fibromyalgia but opined that it was unrelated to her vaccination. (*Id*.) The parties then filed further responsive expert reports between June of 2023 and April of 2024. (ECF Nos. 59, 62, 70, 74; Exs. 19, 32; C, D.) While an entitlement hearing was scheduled (ECF No. 68), it was later cancelled at petitioner's request (ECF No. 79).

Petitioner filed a motion for a ruling on the written record on October 7, 2024. (ECF No. 83.) Respondent filed his response on November 25, 2024, and petitioner filed her reply on January 6, 2025. (ECF Nos. 84, 86.) Thus, this case is now ripe for resolution. I have determined that the parties have had a full and fair opportunity to present their cases and that it is appropriate to resolve entitlement on the existing record. *See* Vaccine Rule 8(d); Vaccine Rule 3(b)(2); *see also Kreizenbeck v. Sec'y of Health & Human Servs*., 945 F.3d 1362, 1366 (Fed. Cir. 2020) (noting that "special masters must determine that the record is comprehensive and fully developed before ruling on the record").

III. Factual History

Petitioner had a long medical history relative to her injury claim, during which time her diagnosis was often unclear. However, because her ultimate diagnosis of fibromyalgia is not disputed, there is no need to explain that history in detail.

Petitioner received the Tdap vaccination at issue on February 5, 2016. (Ex. 3, p. 104; Ex. 4, p. 98.) She received the vaccination in connection with a medical encounter for rashes that appeared to be eczema. (Ex. 4, pp. 96-98.) She had a history of prior musculoskeletal complaints, including chronic lower back pain for which she was taking Mobic. (*Id.* at 11-18.)

Seven days after vaccination, on February 12, 2016, petitioner presented to her primary care provider with a complaint of swelling in the right arm in which she had received the vaccination. (Ex. 4, p. 113.) She also complained of chest pain, throat tightness, shortness of breath, stiffness and numbness in her arm, and tingling in both legs. (*Id.*) Petitioner reported that these symptoms arose the day after her vaccination. (*Id.*) She also reported a rash on her face that developed three days after the vaccination. (*Id*.) The symptoms were improving by the time of her medical encounter; however, petitioner was still experiencing diffuse myalgia and paresthesia. (*Id*.) Her physician was unclear whether she was suffering a viral syndrome or an allergy or hypersensitivity reaction to the vaccine. (*Id*. at 114.)

On February 18, 2016, petitioner presented in follow up with complaints of upper back pain, bilateral foot and knee pain, chest discomfort, swelling in her feet and forearms, and not feeling well. (Ex. 4, p. 124.) However, her physician doubted her

reliability as a historian. (*Id*.) It was also noted that petitioner was stressed by the death of her stepmother,[3] who passed away about two days after the vaccination at issue. (*Id*. at 124, 248; Ex. 13, pp. 22, 29.) She was diagnosed with myalgia and the physician also questioned whether she had a component of depression. (Ex. 4, p. 125.)

Thereafter, petitioner continued to return for care of a variety of symptoms. (*See, e.g.*, Ex. 4, pp. 157-58, 178-80, 193-95, 226-28, 352-56; Ex. 2, pp. 40-46, 50-62; Ex. 6, pp. 6-13; Ex. 9, pp. 13-20; Ex. 12, pp. 868-70, 935-40, 1015-19, Ex. 13, pp. 13-34.) Though she repeatedly described her vaccination as a turning point in her health, objective testing was generally unrevealing and her physicians felt her condition may be anxiety related, questioning her history as "quite convoluted." (*See, e.g.*, Ex. 4, p. 178; Ex. 2, p. 46; Ex. 13, p. 18.) Pertinent to the expert opinions presented in this case, petitioner's initial post-vaccination bloodwork of February 18, 2016, which included screening for the inflammatory marker erythrocyte sedimentation rate ("ESR"), was normal. (Ex. 4, p. 132.) However, on March 25, 2016, approximately 49 days post-vaccination, petitioner was tested for C-Reactive Protein ("CRP"), a different inflammatory marker, and it was mildly elevated at 11 mg/L versus a reference range of 0.0-9.9 mg/L. (Ex. 2, p. 64.) At that time, ESR remained normal. (*Id*. at 65.) Eventually, petitioner was diagnosed as having fibromyalgia (Ex. 4, pp. 352, 354, 382; Ex. 6, pp. 12-13) and both parties' experts concur with that diagnosis (Ex. 18, pp. 17-21; Ex. A, p. 5).

IV. Expert Opinions

a. Initial Reports

i. David Axelrod, M.D., for petitioner (Exhibit 18)[4]

According to Dr. Axelrod, fibromyalgia is a "central sensitization," meaning that it is a dysfunction of nociceptive[5] inputs at a central level. (Ex. 18, pp. 21, 23 (citing

[3] Although this record indicates that petitioner's stepmother had passed away, other records include notations indicating that petitioner's mother had died around two days post-vaccination (*see* Ex. 4, pp. 113, 248; Ex. 13, pp. 22, 29).

[4] Dr. Axelrod received his medical degree the University of Michigan Medical School in 1974. (Ex. 17, p. 1.) Thereafter, he completed a residency in internal medicine at University of Toronto School of Medicine and William Beaumont Hospital-Royal Oak. (*Id.*) Dr. Axelrod went on to complete a fellowship in in allergy, immunology, and rheumatology at McGill University and was a medical staff fellow in the laboratory of clinical immunology at the National Institutes of Health. (*Id.*) He is board certified in internal medicine, adult rheumatology, allergy, and immunology. (Ex. 18, p. 1.) Throughout the course of his career, Dr. Axelrod held various academic and clinical appointments at different institutions. (Ex. 17, p. 2.) He has co-authored twelve peer-reviewed publications. (Ex. 17, p. 3.)

[5] Nociception refers to the ability feel pain, caused by the stimulation of a nociceptor, which is a receptor for pain caused by an injury to body tissue(s). The injury triggering the pain may be from physical stimuli, including mechanical, thermal, or electrical stimuli, or due to chemical stimuli, including the presence of a toxin or excess levels of a nontoxic substance. Most nociceptors are located in the skin or the walls of viscera. *Nociception*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=34162 (last visited Dec. 15, 2025); *Nociceptor*,

Marina de Tommaso et al., *The Puzzle of Fibromyalgia Between Central Sensitization Syndrome and Small Fiber Neuropathy: A Narrative Review on Neurophysiological and Morphological Evidence*, 43 NEUROLOGICAL SCIS. 1667 (2022) (Ex. 62)).) That is, nociceptive processing evokes a painful state by increasing neuronal sensitization. (*Id*. at 21 (citing Gilson Gonçalves dos Santos et al., *Neuraxial Cytokines in Pain States*, FRONTIERS IMMUNOLOGY, Jan. 28, 2020, at 1 (Ex. 69)).) Dr. Axelrod opines that, following her February 5, 2016 Tdap vaccination, petitioner "developed the expected cytokine response to vaccination." (*Id*. at 30.) However, this expected cytokine response nonetheless increased the permeability of her blood brain barrier, permitting both the innate and adaptive immune responses to the vaccine to enter her central nervous system. (*Id*.) He suggests that petitioner then suffered two processes. (*Id.*) The cytokines activated astroglia, which in turn produce more cytokines, leading to perpetuation of chronic pain through central sensitization. (*Id.*) Additionally, molecular mimicry resulted in autoreactive lymphocytes that further augmented and perpetuated her central sensitization. (*Id.*) All of this resulted in fibromyalgia. (*Id*.)

Dr. Axelrod indicates that this process is mediated by a number of different cytokines (IL-1β, TGF-β, IL-17, IL-6, TNF-α, TGF-β1, IFN-1α, IFN-γ, IL-8); however, he highlights IL-1β as being responsible for the activation of astroglia. (Ex. 18, pp. 21-22. (citing Wei Guo et al., *Glial-Cytokine-Neuronal Interactions Underlying the Mechanisms of Persistent Pain*, 27 J. NEUROSCIENCE 6006 (2007) (Ex. 76)).) Dr. Axelrod cites a paper by Rochfort et al. for the proposition that IL-6 and TNF-α, which are released following vaccination, can lead to movement of cytokines into the central nervous system. (*Id*. at 22 (citing Keith D. Rochfort et al., *Downregulation of Blood-Brain Barrier Phenotype by Proinflammatory Cytokines Involves NADPH Oxidase-Dependent ROS Generation: Consequences for Interendothelial Adherens and Tight Junctions*, 9 PLOS ONE e101815 (2014) (Ex. 75) (*see also* Ex. C, Tab 2)).) He further cites Kashiwagi et al. as demonstrating that vaccines increase several cytokines, but particularly IL-1β, IL-6, G-CSF, and TNF-α, between 6-24 hours post-vaccination. (*Id*. (citing Yasuyo Kashiwagi et al., *Production of Inflammatory Cytokines in Response to Diphtheria-Pertussis-Tetanus (DPT),* Haemophilus Influenzae *Type B (Hib), and 7-Valent Pneumococcal (PCV7) Vaccines*, 10 HUM. VACCINES & IMMUNOTHERAPEUTICS 677 (2014) (Ex. 70) (*see* also Ex. C, Tab 1)).)

Additionally, Dr. Axelrod cites Goebel et al., a mouse model study, for the proposition that some symptoms of fibromyalgia may be related to autoreactive IgG.[6] (Ex. 18, p. 23 (citing Andreas Goebel et al., *Passive Transfer of Fibromyalgia Symptoms from Patients to Mice*, 131 J. CLINICAL INVESTIGATION e144201 (2021) (Ex. 78) (*see also* Ex. A, Tab 40)).) Mice administered IgG from fibromyalgia patients showed hypersensitivity to mechanical pressure as measured from Aδ and C-type nerve

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DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=34163 (last visited Dec. 15, 2025).

[6] Immunoglobulin G, or IgG, is one class of glycoproteins that function as antibodies. *Immunoglobulin*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=24894 (last visited Dec. 16, 2025).

fibers. (*Id*. (discussing Goebel et al., *supra*, at Ex. 78).) Administration of fibromyalgia IgG reduced intraepidermal nerve fiber density within 14 days of administration. (*Id*. at 24 (discussing Goebel et al., *supra*, at Ex. 78).) IgG was consistently found in the dorsal root ganglia, but not in the brain or spinal cord tissue. (*Id*. at 23 (discussing Goebel et al., *supra*, at Ex. 78).) Notably, however, this proposed mechanism did not induce cytokine production or systemic inflammation. (*Id.* (discussing Goebel et al., *supra*, at Ex. 78).)

Dr. Axelrod proposes that components of the Tdap vaccine have similar amino acid sequences with human N-methyl-D-aspartate ("NMDA") receptors and that Kawasaki et al. demonstrated that IL-1β and TNF-α increases spontaneous postsynaptic currents, which enhances glutamate releases, mediated in pertinent part by NMDA receptors. (*Id*. at 24-25 (citing Yasuhiko Kawasaki et al., *Cytokine Mechanisms of Central Sensitization: Distinct Overlapping Role of Interleukin-1β, Interleukin-6, and Tumor Necrosis Factor-α in Regulating Synaptic and Neuronal Activity in the Superficial Spinal Cord*, 28 J. NEUROSCIENCE 5189 (2008) (Ex. 79)).) This immune response would act as an agonist,[7] further inducing the persistence of IL-1β. (*Id.* at 25.)

According to Dr. Axelrod, petitioner's initial symptoms of pain and swelling at the injection site on the evening of her vaccination are consistent with the kinetics of a post-vaccination cytokine response. (Ex. 18, pp. 26, 29 (citing Prescribing Information, Adacel (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Absorbed): Suspension for Intramuscular Injection [hereinafter Adacel Package Insert] (Ex. 63); Kashiwagi, *supra*, at Ex. 70).) A primary immune response may peak by 14 days after exposure, with a secondary immune response having a greater and faster response, which would be expected to occur between about 10-25 days. (*Id.* at 27-28 (citing ABUL K. ABBAS ET AL., *Properties and Overview of Immune Responses*, *in* CELLULAR & MOLECULAR IMMUNOLOGY 1 (9th ed. 2018) (Ex. 80); Thomas J. Lawley et al., *A Prospective Clinical and Immunologic Analysis of Patients with Serum Sickness*, 311 NEJM 1407 (1984) (Ex. 81); John J. Miller et al., *The Speed of the Secondary Immune Response to Tetanus Toxoid with a Review of War Reports and Observations on Simultaneous Injection of Toxoid and Antitoxin*, 3 PEDIATRICS 64 (1949) (Ex. 82)).) Dr. Axelrod suggests that this is consistent with the package insert for the Tdap vaccine, which indicates that neuropathic events occurred within 28 days of vaccination. (*Id*. at 26, 29 (citing Adacel Package Insert, *supra*, at Ex. 63).) He stresses that no other cause for petitioner's fibromyalgia was identified by her treating physicians. (*Id*. at 26.)

[7] Agonists are molecules that act to promote signaling through a particular pathway. (Ex. C, p. 6 n.b.) Small molecules or larger biomolecules, such as monoclonal antibodies, can act as agonists. (*Id.*) Agonists can be naturally occurring or synthetic molecules. (*Id.*)

ii. Maxime Kinet, M.D., Ph.D., for respondent (Exhibit A)[8]

Dr. Kinet likewise opines that petitioner suffered fibromyalgia and similarly describes the condition as involving a hypersensitization of neural circuits. (Ex. A, p. 5 (citing Daniel J. Clauw, *Fibromyalgia and Related Conditions*, 90 MAYO CLINIC PROCS. 680 (2015) (Ex. A, Tab 4); Kathleen A. Sluka & Daniel J. Clauw, *Neurobiology of Fibromyalgia and Chronic Widespread Pain*, 338 NEUROSCIENCE 114 (2016) (Ex. A, Tab 8); Charles J. Vierck Jr., *Mechanisms Underlying Development of Spatially Distributed Chronic Pain (Fibromyalgia)*, 124 PAIN 242 (2006) (Ex. A, Tab 9)).) However, he contends that "Dr. Axelrod is very selective in his citing of the literature on possible immunologic components to fibromyalgia," noting that several large meta-analyses have failed to find consistent immune abnormalities underlying the condition. (*Id.* (citing Nurcan Üçeyler et al., *Systematic Review with Meta-Analysis: Cytokines in Fibromyalgia Syndrome*, BMC MUSCULOSKELETAL DISORDERS, Oct. 28, 2011, at 1 (Ex. A, Tab 10); Luke Furtado O'Mahony et al., *Is Fibromyalgia Associated with a Unique Cytokine Profile? A Systematic Review and Meta-Analysis*, 60 RHEUMATOLOGY 2602 (2021) (Ex. A, Tab 11); Judy H. Cho & Marc Feldman, *Heterogeneity of Autoimmune Diseases: Pathophysiologic Insights from Genetics and Implications for New Therapies*, 21 NATURE MED. 730 (2015) (Ex. A, Tab 12)).) Moreover, genetic research has implicated genes relating to neurotransmission in the development of fibromyalgia but not found significant evidence that the immune system plays a role in the pathogenesis of the condition. (*Id*. (citing Rosalba Siracusa et al., *Fibromyalgia: Pathogenesis, Mechanisms, Diagnosis and Treatment Options Update*, INT'L J. MOLECULAR SCIS. 3891 (2021) (Ex. A, Tab 3); Young Ho Lee et al., *Candidate Gene Studies of Fibromyalgia: A Systematic Review and Meta-Analysis*, 32 RHEUMATOLOGY INT'L 417 (2012) (Ex. A, Tab 13); Dan Buskila & Piercarlo Sarzi-Puttini, *Biology and Therapy of Fibromyalgia: Genetic Aspects of Fibromyalgia Syndrome*, ARTHRITIS RSCH. & THERAPY, July 28, 2006, at 1 (Ex. A, Tab 14); Lesley M. Arnold et al., *The Fibromyalgia Family Study*, 65 ARTHRITIS & RHEUMATISM 1122 (2013) (Ex. A, Tab 15)).)

Dr. Kinet opines that Dr. Axelrod's cytokine theory is neither plausible nor supported by the cited literature. (Ex. A, pp. 5-6.) Citing several epidemiologic studies, he notes that fibromyalgia has not emerged as a safety concern relative to vaccination despite being a common condition. (*Id.* at 6 (citing Peter Van den Steen et al., *Immunogenicity and Safety of Reduced-Antigen Tetanus, Diphtheria and Acellular Pertussis Vaccination in Adults Treated for Obstructive Airway Disease*, HUM. VACCINES & IMMUNOTHERAPEUTICS, Feb. 6, 2023, at 1 (Ex. A, Tab 16); Shelly A. McNeil et al., *Comparison of the Safety and Immunogenicity of Concomitant and Sequential Administration of an Adult Formulation Tetanus and Diphtheria Toxoids Adsorbed Combined with Acellular Pertussis (Tdap) Vaccine and Trivalent Inactivated Influenza*

[8] Dr. Kinet received his medical degree from Weill Cornell Medical College in 2017, and his Ph.D. in developmental biology from the Rockefeller University in 2016. (Ex. A, p. 1; Ex. B, p. 1.) Thereafter, he completed a residency in internal medicine and fellowship in rheumatology at the University of California San Francisco. (Ex. B, p. 1.) Dr. Kinet is board-certified in internal medicine and rheumatology, and he maintains his license to practice medicine in California. (*Id.*) Currently, Dr. Kinet serves as an Assistant Professor of Medicine in the Division of Rheumatology at the University of California San Francisco. (*Id.*; Ex. A, p. 1.) He has published five peer-reviewed journal articles. (Ex. B, pp. 2-3.)

Vaccine in Adults, 25 VACCINE 3464 (2007); Jiawei Xu et al., *The Effectiveness and Safety of Pertussis Booster Vaccination for Adolescents and Adults: A Systematic Review and Meta-Analysis*, MED., 2019, at 1 (Ex. A, Tab 18)).) Moreover, because cytokines are invariant immune mediators, if Dr. Axelrod's theory were correct, then "any individual who sustains any kind of transient local inflammatory insult runs a measurably high risk not only of fibromyalgia but of all sorts of immune-mediated and infectious central nervous system afflictions." (*Id*. at 6.) He stresses, however, that "[t]his is patently not the case." (*Id*.) In petitioner's case, there was no post-vaccination fever to suggest high level of cytokine activity affecting the central nervous system, erythrocyte sedimentation rate (ESR), a marker of inflammation, was normal, and there was no evidence of inflammation in petitioner's white blood cell count and/or platelet count. (*Id*. (citing Ex. 4, p. 132).) Thus, "there is no biochemical evidence of sustained, systemic, vaccine-induced inflammation." (*Id.*)

Regarding the proposed cross-reaction between the vaccine and NMDA receptors, Dr. Kinet observes that Dr. Axelrod's opinion lacks any detail regarding the mechanism of cross reaction, noting, for example, that he did not specify whether he asserts a cellular or humoral process. (Ex. A, p. 6.) Even if those details were provided, Dr. Kinet opines that homology alone would not support the invocation of molecular mimicry. (*Id*. at 6-7.) But in any event, no evidence supports NMDA receptors as an autoimmune target leading to fibromyalgia. (*Id*. at 7.) Rather, anti-NMDA receptor antibodies are known to cause limbic encephalitis, which is a potentially lethal condition that presents with complex and severe neuropsychiatric features. (*Id*. (citing Josep Dalmau et al., *Anti-NMDA-Receptor Encephalitis: Case Series and Analysis of the Effects of Antibodies*, 7 LANCET NEUROLOGY 1091 (2008) (Ex. A, Tab 32); Josep Dalmau et al., *Paraneoplastic Anti*-N-*methyl-D-Aspartate Receptor Encephalitis Associated with Ovarian Teratoma*, 61 ANNALS NEUROLOGY 25 (2007) (EX. A, Tab 33); Maarten J. Titulaer et al., *Treatment and Prognostic Factors for Long-Term Outcome in Patients with Anti-NMDA Receptor Encephalitis: An Observational Cohort Study*, 12 LANCET NEUROLOGY 157 (2013) (Ex. A, Tab 34)).) This was not petitioner's presentation. (*Id*.) Moreover, studies have shown that anti-NMDR antibodies cause decreased receptor localization at the cell surface, decreased neuronal excitation, and decreased neuronal plasticity. (*Id*. (citing Laurent Ladépêche et al., *NMDA Receptor Autoantibodies in Autoimmune Encephalitis Cause a Subunit-Specific Nanoscale Redistribution of NMDA Receptors*, 23 CELL REPS. 3759 (2018) (Ex. A, Tab 36); Ethan G. Hughes et al., *Cellular and Synaptic Mechanisms of Anti-NMDA Receptor Encephalitis*, 30 J. NEUROSCIENCE 5866 (2010) (Ex. A, Tab 37); Qing Zhang et al., *Suppression of Synaptic Plasticity by Cerebrospinal Fluid from Anti-NMDA Receptor Encephalitis Patients*, 45 NEUROBIOLOGY DISEASES 610 (2012) (Ex. A, Tab 38); Charles A. Dean et al., *Regulation of NMDA Receptor Signaling at Single Synapses by Human Anti-NMDA Receptor Antibodies*, FRONTIERS MOLECULAR NEUROSCIENCE, July 28, 2022, at 1 (Ex. A, Tab 39)).) According to Dr. Kinet, this directly contradicts Dr. Axelrod's suggestion that these antibodies would have an agonistic effect. (*Id*. (referencing Ex. 18, pp. 24-25).)

Additionally, the Goebel et al. study relied on by Dr. Axelrod specifically found that the IgG examined in the study was excluded from the brain and spinal cord, presumably as a result of the blood brain barrier, and found binding of the IgG only in the dorsal root ganglion, which is outside the blood brain barrier. (Ex. A, p. 7 (discussing Goebel et al., *supra*, at Ex. A, Tab 40).) Thus, the Goebel et al. study does not support Dr. Axelrod's theory of central nervous system cross-reactivity. (*Id*.) The mechanism of intraepidermal fiber loss and conduction abnormalities actually shown by the Goebel et al. study were not invoked by Dr. Axelrod and are not relevant to petitioner's own clinical presentation. (*Id*.) Dr. Kinet also observes that the Goebel study has significant limitations. (*Id.* at 7-8.) While "thought-provoking," it is inadequate to reach any conclusions about what happens in actual patients, especially not conclusions that would propose to overturn conventional thinking. (*Id*. (discussing Goebel et al., *supra*, at Ex. A, Tab 40).)

Dr. Kinet also notes that other risk factors for fibromyalgia could have contributed to petitioner's condition. (Ex. A, p. 8.) Accepted risk factors include psychosocial trauma and cancer. (*Id.* (citing Siracusa et al., *supra*, at Ex. A, Tab 3; Clauw, *supra*, at Ex. A, Tab 4; Vierck, *supra*, at Ex. A, Tab 9; Yarden Yavne et al., *A Systematic Review of Precipitating Physical and Psychological Traumatic Events in the Development of Fibromyalgia*, 48 SEMINARS ARTHRITIS & RHEUMATOLOGY 121 (2018) (Ex. A, Tab 42); Brian Walitt et al., *The Presence and Characteristics of Fibromyalgia in the 2012 National Health Interview Survey*, 10 PLOS ONE e0138024 (2015) (Ex. A, Tab 7); Nuray Akkaya et al., *Frequency of Fibromyalgia Syndrome in Breast Cancer Patients*, 18 J. CLINICAL ONCOLOGY 285 (2013) (Ex. A, Tab 43)).) Petitioner's mother had passed away close in time to the vaccination in question and she suffered thyroid cancer. (*Id*.) Additionally, it has been suggested that other peripheral nociceptive inputs are necessary to initiate and maintain fibromyalgia. (*Id*. (citing Clauw, *supra*, at Ex. A, Tab 4; Vierck, *supra*, at Ex. A, Tab 9).) Thus, it is relevant that petitioner had a known history of lumbar radiculopathy, scoliosis, adhesive capsulitis, and osteoarthritis. (*Id*.)

b. First Supplemental Reports

i. Dr. Axelrod (Exhibit 19)

Regarding epidemiologic association between Tdap vaccines and fibromyalgia, Dr. Axelrod questions the ability of the studies cited by Dr. Kinet to detect rare events. (Ex. 19, pp. 5-6.) He stresses that "the absence of evidence is not the same as evidence of absence of a relationship." (*Id*. at 6.) He opines that it is never reasonable to claim that a study has proven a negative or for case-control or cohort studies to purport to deny a causal relationship. (*Id*. (citing Phil Alderson, *Absence of Evidence is not Evidence of Absence: We Need to Report Uncertain Results and Do it Clearly*, 328 BMJ 476 (2004) (Ex. 25)).) He notes that the 2012 report by the Institute of Medicine ("IOM"), as cited by Dr. Kinet, neither accepted *nor rejected* a causal relationship between the Tdap vaccine and fibromyalgia. (*Id.* at 10 (citing INSTITUTE OF MED., ADVERSE EFFECTS OF VACCINES: EVIDENCE AND CAUSALITY (Kathleen Stratton eds., 2012) (Ex. 30, p. 610)).)

Discussing Dr. Kinet's citation of meta-analyses of fibromyalgia literature, Dr. Axelrod indicates that Üçeyler et al. did find that the better-quality studies they had reviewed found higher serum levels of IL-6 as compared to controls. (Ex. 19, p. 1 (discussing Üçeyler et al., *supra*, at Ex. A, Tab 10).) Other studies examined also showed other cytokine elevations, including IL-1RA, IL-8, IL-1β, and TNF. (*Id*. (citing Üçeyler et al., *supra*, at Ex. A, Tab 10, pp. 7, 9).) Ultimately, the Üçeyler et al. authors concluded that a cytokine-mediated hypothesis for fibromyalgia is "plausible." (*Id*. (quoting Üçeyler et al., *supra*, at Ex. A, Tab 10, p. 12).) According to Dr. Axelrod, the meta-analysis by O'Mahony et al. similarly evidences elevations of TNF-α, IL-8, IL-10, and IL-6 among fibromyalgia patients. (*Id*. at 2 (discussing O'Mahony et al., *supra*, at Ex. A, Tab 11).) Dr. Axelrod opines that "[t]hese studies suggest that cytokines might participate in the pathophysiology of fibromyalgia." (*Id*.) Thus, Dr. Axelrod again cites Gonçalves dos Santos et al. as support for the proposition that cytokines can induce nociceptive processing." (*Id*. (citing Gonçalves dos Santos et al., *supra*, at Ex. 69).) He asserts that petitioner's initial pain and swelling at the vaccine injection site demonstrates a cytokine response. (*Id*.) Whereas Dr. Kinet opined that a fever should be expected in such a response, Dr. Axelrod indicates that Kashiwagi et al. demonstrates that not all post-vaccination cytokine responses include a fever. (*Id*. at 6-7 (citing Kashiwagi et al., *supra*, at Ex. 70).) Dr. Axelrod suggests that not all autoimmune conditions have elevated ESR or CRP, but notes that petitioner had elevated CRP on March 25, 2016. (*Id*. at 7 (citing Ex. 2, p. 64).)

Based on his citation to the Goebel et al. study, Dr. Axelrod confirms that he asserts that fibromyalgia involved a humoral response. (Ex. 19, p. 8 (citing Goebel et al., *supra*, at 78).) He contends that the paper by Siracusa et al., cited by Dr. Kinet as supporting a genetic rather than immunologic cause for fibromyalgia, actually supports an autoimmune basis for the condition when read in conjunction with the Kawasaki et al. and Goebel et al. papers cited in his first report. (*Id*. at 4.) Specifically, the Siracusa et al. authors note that neurotransmission dysfunction in fibromyalgia includes alterations in glutamate. (*Id*. (citing Siracusa et al., *supra*, at Ex. A, Tab 3, p. 2).) He asserts this is consistent with the observation in Kawasaki et al. that central sensitization is due to increased excitatory synaptic transmission, as mediated by NMDA receptors. (*Id*. (citing Kawaski et al., *supra*, at Ex. 79).) Further, Siracusa et al. stated that antagonists to NMDA receptors improved fibromyalgia in some groups, which supports the notion that IgG acts as an agonist at the NMDA receptor which might reproduce fibromyalgia, as otherwise shown in the Goebel et al. study. (*Id*. (citing Siracusa et al., *supra*, at Ex. A, Tab 3, p. 4; Goebel et al., *supra*, at Ex. 78).) He asserts that the Siracusa et al. authors are explicit in agreeing that fibromyalgia may result from activation of both the innate and adaptive immune responses affecting both the peripheral tissues and central nervous system. (*Id*. (citing Siracusa et al., *supra*, at Ex. A, Tab 3, p. 7).) Dr. Axelrod suggests that the findings of the Goebel et al. study show that IgG to the NMDA receptor need not necessarily result in encephalitis. (*Id*. at 10 (discussing Goebel et al., *supra*, at Ex. 78).) He contends that the Goebel study did not include findings referable

to the central nervous system because the experiment did not induce a cytokine response that would have opened up the blood brain barrier.[9] (*Id*. at 9-10.)

Dr. Axelrod agrees that psychosocial trauma and malignancy can incite fibromyalgia. (Ex. 19, p. 11.) However, while he notes that petitioner's screening indicated moderate depression and anxiety, he stresses that she did not have clinical signs of depression or sadness. (*Id.*) Dr. Axelrod suggests that petitioner's other pain complaints (lumbar radiculopathy, adhesive capsulitis, carpal tunnel syndrome, rib fractures, and osteoarthritis) all occurred after her fibromyalgia diagnosis. (*Id*.)

ii. Dr. Kinet (Exhibit C)

Dr. Kinet stresses that Dr. Axelrod has not substantiated that a cytokine response to vaccination would increase permeability of the blood brain barrier. (Ex. C, pp. 1-3.) While he agrees that the analysis by Üçeyler et al. indicates a possible (but yet to be reproduced) elevation of IL-6 among fibromyalgia patients, he disagrees with Dr. Axelrod's assertion that any of the other referenced cytokines were demonstrated to have been different from controls. (*Id*. at 1-2 (discussing Üçeyler et al., *supra*, at Ex. A, Tab 10).) Further, Kashiwagi et al., as cited by Dr. Axelrod with respect to post-vaccination cytokine response, is not informative for several reasons. (*Id.* at 2-3.) First, because the study involved children, it examined the DTaP vaccine rather than the Tdap vaccine at issue in this case. (*Id.* at 2.) DTaP would produce higher levels of cytokines due to higher doses of diphtheria and pertussis. (*Id*.) Second, the study's results for *in vivo* cytokine measurement did not find a statistically significant difference between non-febrile vaccines receiving a single vaccine dose, like petitioner, and controls. (*Id*. at 2-3.) Moreover, this data is a composite of children receiving several different types of vaccine. (*Id*. at 3.) And, third, nothing in the study supports Dr. Axelrod's assertion that it demonstrates that cytokine elevations were "maintained." (*Id*.)

Dr. Axelrod's reliance on Rochfort et al., an *in vitro* study with no *in vivo* component, to demonstrate that vaccine-induced cytokines (namely IL-6 and TNF-α) can increase permeability of the blood brain barrier is also misplaced. (Ex. C, pp. 3-4 (discussing Rochfort et al., *supra*, at Ex. C, Tab 2).) First, absent any *in vivo* component, it is inaccurate to assert that the study even attempted to show, let alone actually showed, that the results led to immune cells moving into the central nervous system. (*Id*.) Second, the doses of IL-6 and TNF-α administered in the study were "vastly higher" than would be seen in humans undergoing vaccination. (*Id.* at 4.) For example, the lowest concentration of either cytokine used in the Rochfort et al. experiments was 1 ng/mL – that is, *nanogram* per milliliter. (*Id.* (citing Rochfort et al., *supra*, at Ex. C, Tab 2, pp. 4, 6 figs.1, 3).) By contrast, the average serum concentrations of IL-6 and TNF-α observed in Kashiwagi was 10-30 pg/mL, which is

[9] Dr. Axelrod agrees that the finding by Goebel et al. of reduced intraepidermal nerve fiber density is not relevant to petitioner as she did not have evidence of such a finding. (Ex. 19, p. 10.) However, he opined that small fiber neuropathy cannot be entirely excluded despite her normal skin biopsy. (*Id.*; *see also* Ex. 32, pp. 12-13.)

picograms per milliliter, and the highest level observed was under 200 pg/mL. (*Id*. (citing Kashiwagi et al., *supra*, at Ex. C, Tab 1, p. 6 fig.3).) Thus, Rochfort et al. used a non-physiologic level of cytokines 5-10,000-fold higher than would be seen post-vaccination. (*Id*. at 4.) (A nanogram is 1,000-times the size of a picogram.) Moreover, to the extent patients with fibromyalgia have been observed to have elevated IL-6 and TNF-α, these results have likewise been in the 1-20 pg/mL range. (*Id.* (citing Üçeyler et al., *supra*, at Ex. A, Tab 10).) Thus, even setting vaccination aside, it is also the case that the Rochfort et al. findings are based on cytokine levels 500-100,000 fold what is seen in fibromyalgia. (*Id*. (discussing Rochfort et al., *supra*, at Ex. C, Tab 2).)

Thus, it is "extremely improbable" that petitioner experienced cytokine levels comparable to those observed in Rochfort et al. (Ex. C, pp. 4-5.) Dr. Axelrod's reliance on elevated CRP occurring 49 days post-vaccination on March 25, 2016, is undermined by the fact that petitioner had normal ESR on February 18, 2016, very soon after the vaccination. (*Id*. at 4 (citing Ex. 4, p. 132).) Moreover, the March 25, 2016 elevation was only mild. (*Id*.)

Regarding the autoimmune component of Dr. Axelrod's theory, Dr. Kinet also asserts that Dr. Axelrod has not done enough to demonstrate homology between vaccine components, noting that Dr. Axelrod has shown only short amino acid sequences and has not provided any alignments, noting that "[a]mino acid similarity does not equate to amino acid identity." (Ex. C, p. 5.) While Dr. Axelrod is correct that the Goebel et al. study did not result in the development of an encephalitis, that study did not actually examine the role of anti-NMDA receptor antibodies and was only a mouse model study. (*Id*. at 6 (discussing Goebel et al., *supra*, at Ex. A, Tab 40).) "Dr. Axelrod fails to address how this study supports a role for antibodies in causing central sensitization, as the authors localize antibodies only to the peripheral nervous system, not the central nervous system." (*Id*.) Indeed, Dr. Kinet stresses that Dr. Axelrod himself described the Goebel et al. study as demonstrating that IgG does not need to cross the blood brain barrier to cause fibromyalgia (*Id.* (discussing Ex. 19, p. 10)), whereas his stated theory of causation posits precisely that – that cytokines permit the adaptive immune response from vaccination to enter the central nervous system (*Id.* (discussing Ex. 18, p. 30)). Furthermore, Dr. Kinet suggests that agonistic anti-NMDA antibodies, as relied upon by Dr. Axelrod, have never been shown to exist in humans. (*Id.*) He asserts that the development of agonistic antibodies is "quite challenging" and that the process is poorly understood. (*Id* (citing Patrick A. Mayes et al., *The Promise and Challenges of Immune Agonist Antibody Development in Cancer*, 17 NATURE REVS. DRUG DISCOVERY 509 (2018) (Ex C, Tab 10); Jane Sanders et al., *TSH Receptor Monoclonal Antibodies with Agonist, Antagonist, and Inverse Agonist Activities*, 485 METHODS ENZYMOLOGY 393 (2010) (Ex. C, Tab 11)).) Thus, he charges that Dr. Axelrod is positing the existence of anti-NMDA receptor antibodies with agonistic function "without any sort of proof-of-concept for how these might even come about or function." (*Id*.) He reiterates that his prior report included citations demonstrating that within humans, anti-NMDA receptor antibodies create changes in neuronal activity opposite of what Dr. Axelrod proposes. (*Id*. at 7.)

c. Second Supplemental Reports

i. Dr. Axelrod (Exhibit 32)

Dr. Axelrod further emphasizes that the package insert for the Tdap vaccine indicates that systemic side effects such as body aches or muscle weakness, tiredness, sore or swollen joints, or rash, have been observed within 14 days of vaccination. (Ex. 32, p. 1 (citing Adacel Package Insert, *supra*, at Ex. 63).) He posits that such reactions are indicative of a cytokine response to vaccination and further that petitioner's initial post-vaccination presentation on February 12, 2016 is consistent with such a response. (*Id*.) He contends that ESR is slow to respond to acute phase reactions and is often a false negative early in an inflammatory process. (*Id*. at 5 (citing Michael Harrison, *Erythrocyte Sedimentation Rate and C-Reactive Protein*, 38 AUSTL. PRESCRIBER 93 (2015) (Ex. 44)).)

Dr. Axelrod disagrees with Dr. Kinet's assertion that the DTaP vaccine would necessarily produce more cytokines than the Tdap vaccine, noting a study by van der Lee et al. that found greater cytokine levels, specifically IFN-γ, IL-13, and IL-17, post Tdap vaccination than were observed by Kashiwagi et al. (Ex. 32, p. 2 (citing Saskia van der Lee et al., *Robust Humoral and Cellular Immune Responses to Pertussis in Adults After a First Acellular Booster Vaccination*, FRONTIERS IMMUNOLOGY, Apr. 4, 2018, at 1 (Ex. 41)).) Similarly, a study by Rice et al. detected IL-6 and TNF-α levels higher than those measured by Kashiwagi et al.[10] (*Id*. at 3 (citing Thomas F. Rice et al., *Modification of Innate Immune Responses to* Bordetella pertussis *in Babies from Pertussis Vaccinated Pregnancies*, EBIOMEDICINE, 2021, at 1 (Ex. 42).) Citing Gonçalves dos Santos et al., Dr. Axelrod contends that IFN-γ, IL-17, IL-6, and TNF-α can all be associated with pain. (*Id*. at 2-3 (citing Gonçalves dos Santos et al., *supra*, at Ex. 69).)

Dr. Axelrod acknowledges that the lowest cytokine dose observed by Rochfort et al. to have significant effect on interendothelial junction protein was 1 ng/mL. (Ex. 32, p. 3 (discussing Rochfort et al., *supra*, at Ex. 75).) However, he notes that the Rice et al. paper, for example, found increased IL-6 of 866 pg/mL with a confidence interval ranging up to 1,930 pg/mL, which would be above the 1 ng/mL used in the Rochfort et al. study. (*Id*.) He stresses that these were *in vitro* studies and, therefore, "[w]e do not know the levels that reach the blood brain barrier." (*Id*.) Dr. Axelrod acknowledges that the Rochfort et al. study does not prove that cytokines downregulate the blood brain barrier in humans but suggests that it still provides evidence to explain how immune mediators and cells move through the blood brain barrier. (*Id*. at 4.) He further asserts that a study by Banks et al. specifically showed that IL-6 can cross the blood brain barrier. (*Id.* at 5 (citing William A. Banks et al., *Penetration of Interleukin-6 Across the*

[10] Dr. Axelrod also sought to refute Dr. Kinet's assertion that the Kashiwagi et al. paper does not provide statistical evidence of elevated IL-6, stressing that the confidence interval for IL-6 in subjects with fever did not overlap with the confidence interval for the control group, meaning the finding was statistically significant. (Ex. 32, p. 4.) Importantly, however, Dr. Kinet's observation was specific to the non-febrile group. (Ex. C, pp. 2-3.)

Murine Blood-Brain Barrier, 179 NEUROSCIENCE LETTERS 53 (1994) (Ex. 43) (*see also* ECF No. 74-4).)[11]

Dr. Axelrod suggests that amino acid sequences as short as 3-5 amino acids in length can support molecular mimicry and further asserts that his prior report did include the alignments. (Ex. 32, pp. 5-6.) Moreover, according to Dr. Axelrod, a study by Park et al., which examined lupus patients with and without fibromyalgia, did, contrary to Dr. Kinet's assertion, find that NMDA receptor antibodies are associated with fibromyalgia. (*Id*. at 6 (citing D.J. Park et al., *Anti-N-Methyl-D-Aspartate Receptor Antibodies Are Associated with Fibromyalgia in Patients with Systemic Lupus Erythematosus: A Case-Controlled Study*, 35 CLINICAL & EXPERIMENTAL RHEUMATOLOGY 54 (2017) (Ex. 50)).) Although he acknowledges that the Goebel et al. study did not look at the specificity of the human IgG they administered, it still demonstrates that fibromyalgia is autoimmune in at least some subjects and that activation of NMDA receptors is at least a component of the condition. (*Id.* (discussing Goebel et al., *supra*, at Ex. 78).) Moreover, although Dr. Kinet raised the fact that the disease elicited in the Goebel et al. study was short-lived, the transient IgG half-life of IgG within the mouse model is not indicative of what would happen in humans. (*Id*. at 7.) In human autoimmune disease, "the immune cells that produce the immune response remain and may continue to produce antibodies that interact with target antigens in the dorsal root ganglion that result in Fibromyalgia, with chronic pain." (*Id*.) Specifically, "[a]n agonist antibody directed to the NMDA receptor would be expected to cause the chronic pain associated with Fibromyalgia." (*Id*.) However, Dr. Axelrod stresses that, given the agonist role, the anti-NMDA receptor antibodies would not likely be destructive. (*Id*.)

Citing evidence pertaining to Graves' disease, Dr. Axelrod asserts that agonist antibodies have been shown to exist in humans. (Ex. 32, p. 10 (citing Terry J. Smith & Laszlo Hegedüs, *Graves' Disease*, 375 NEJM 1552 (2016) (Ex. 57); Krzysztof Michalek et al., *TSH Receptor Autantibodies*, 9 AUTOIMMUNE REVS. 113 (2009) (Ex. 58)).) Regarding NMDA receptor antibodies, Dr. Axelrod stresses that the study by Park et al. showed an association with fibromyalgia. (*Id.* (citing Park et al., *supra*, at Ex. 50).) He explains that

> [t]he authors note that the NMDA receptor system is involved in chronic pain disorders, including Fibromyalgia. The authors note that selective antagonists have anti-nociceptive activity. Therefore, an agonist effect would be expected to cause pain. Unfortunately, the authors do not address the issue of agonist activity at the NMDA receptor.

(*Id.* (discussing Park et al., *supra*, at Ex. 50).) However, he also cites Wollmuth et al. for the proposition that NMDA receptor autoantibodies are polyspecific, potentially resulting in "no effect, decreased effect (antagonist) or increased effect (agonist)." (*Id*. (citing

[11] Petitioner filed a copy of the study by Banks et al. that only includes the abstract. (Ex. 43.) Thereafter, respondent filed a complete copy of the article marked as "Respondent's Revised Exhibit 34." (ECF No. 74-4.) In this decision, the study by Banks et al. will be cited to as Exhibit 43, though the complete copy is available instead at ECF No. 74-4.

Lonnie P. Wollmuth et al., *The Diverse and Complex Modes of Action of Anti-NMDA Receptor Autoantibodies*, NEUROPHARMACOLOGY, Aug. 15, 2021, at 1 (Ex. 59)).) Nonetheless, he acknowledges that Wollmuth et al. does not address fibromyalgia. (*Id*.) Dr. Axelrod cites a number of papers from which he questions both the idea that NMDA receptors cause rather than mediate encephalitis and the notion that they act exclusively as antagonists rather than agonists. (*Id*. at 11-12 (citing Justus B. H. Wilke et al., *Autoantibodies Against NMDA Receptor 1 Modify Rather than Cause Encephalitis*, 26 MOLECULAR PSYCHIATRY 7746 (2021) (Ex. 60); Dalmau et al., *supra*, at Ex. A, Tab 32); Josep Dalmau et al., *supra*, at Ex. A, Tab 33; Titulaer et al., *supra,* at Ex. A, Tab 34; Francesc Graus et al., *A Clinical Approach to Diagnosis of Autoimmune Encephalitis*, 15 LANCET NEUROLOGY 391 (2016) (Ex. A, Tab 35); Emilia H. Moscato et al., *Acute Mechanisms Underlying Antibody Effects in Anti-N-Methyl-D-Aspartate Receptor Encephalitis*, 76 ANNALS NEUROLOGY 108 (2014) (Ex. 61); Ladépêche et al., *supra*, at Ex. A, Tab 36; Dean et al., *supra*, at Ex. A, Tab 39)

Dr. Axelrod acknowledges that the Goebel et al. study did not find IgG in the spinal cord, did not examine the brain, and did not investigate the effects of cytokines. (Ex. 32, pp. 7-8.) However, he cites Martinez-Lavin, as suggesting that "'[t]he focus is being shifted from considering fibromyalgia a centralized pain syndrome to recognizing the role of autonomic and peripheral nociceptive nervous systems in the generation of widespread pain, fatigue, and insomnia.' The author states that the dorsal root ganglia have features allowing them to convert varied afferent stressful impulses into neuropathic pain." (*Id*. at 8 (citing Manuel Martínez-Lavin, *Dorsal Root Ganglia: Fibromyalgia Pain Factory?*, 40 CLINICAL RHEUMATOLOGY 783 (2021) (Ex. 52)).) Further to this, Dr. Axelrod introduces the idea that he can alternatively demonstrate molecular mimicry between components of the Tdap vaccine and voltage-activated sodium channels, which he posits play a role in the pathophysiology of neuropathic pain at the dorsal root ganglia. (*Id*. at 8.)

Further still, Dr. Axelrod also notes that a study by Ryabkova et al. found that fibromyalgia patients have autoantibodies to GABA receptors. (Ex. 32, p. 9 (citing Varvara A. Ryabkova et al., *Autoantibody Correlation Signatures in Fibromyalgia and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Association with Symptom Severity*, BIOMEDICINES, Jan. 18, 2023, at 1 (Ex. 53)).) He explains that GABA inhibits pain or sensory processing. (*Id.*) Therefore, blocking the effect of GABA would favor increased perception of pain. (*Id*. (citing Daniel J. Clauw, *Fibromyalgia and Related Syndromes*, *in* RHEUMATOLOGY 736 (Marc C. Hochberg et al. eds., 7th ed. 2019) (Ex. 54) (*see also* Ex. 73)).) A study by Wang et al. demonstrated GABA receptor expression in the dorsal root ganglia, which Dr. Axelrod notes to correlate to the findings of the Goebel et al. study. (*Id*. (citing Caixue Wang et al., *Neuropathic Injury-Induced Plasticity of GABAergic System in Peripheral Sensory Ganglia*, FRONTIERS PHARMACOLOGY, July 27, 2021, at 1 (Ex. 55)).) However, he also suggests that GABA receptors have been found in various parts of the brain. (*Id.* (citing Mary J. Allen et al., *Gaba Receptor*, STATPEARLS [INTERNET] (last updated Feb. 13, 2023) (Ex. 56)).) As with the NMDA receptors and the voltage-activated sodium channels, Dr. Axelrod asserts

that he has located common amino acid sequences with the components of the Tdap vaccine. (*Id*. at 9-10.)

ii. Dr. Kinet (Exhibit D)

Dr. Kinet suggests that Dr. Axelrod misrepresents the findings of the van der Lee et al. and Rice et al. studies. (Ex. D, pp. 1-2 (discussing van der Lee et al., *supra*, at Ex. 41; Rice et al., *supra*, at Ex. 42).) Whereas Dr. Axelrod implies that these studies are informative of what occurs in the body post-vaccination, the studies actually involved *in vitro* stimulation of sampled cells. (*Id.*) This concentrates large numbers of cells into a small culture volume, which results in cytokine levels that "will necessarily be vastly higher than those encountered in circulating human blood." (*Id.* at 2.) Thus, Dr. Kinet suggests that it is not ultimately informative that these *in vitro* results are higher than the *in vivo* results demonstrated by the Kashiwagi et al. study. (*Id*.) Moreover, it is "biologically meaningless" that any of the results from the Rice et al. study reached an elevation consistent with the threshold for downregulating the blood brain barrier as determined by the Rochfort et al. study, because the Rice et al. study did not examine circulating cytokine concentrations. (*Id*. at 2 (referencing Rice et al., *supra*, at Ex. 42).) Although Dr. Kinet agrees that Banks et al. showed that some IL-6 can cross the blood brain barrier, he stressed that the amount of IL-6 to enter the central nervous system was limited and quickly dissipated within minutes, undercutting the notion that a small, transient post-vaccination IL-6 elevation would operate to induce wholesale blood brain barrier dysfunction and providing no evidence that it would allow for entry of other pathological molecules through the blood brain barrier. (*Id*. at 3 (discussing Banks et al., *supra*, at Ex. 43).) Moreover, Dr. Axelrod's theory specifically relied on IL-1β as activating astroglia to result in NMDA receptor-mediated chronic pain (*Id.* at 4 (citing Ex. 18, p. 22)); however, Kashiwagi et al. showed that following vaccination, no detectable IL-1β was observed in the sera of either febrile or non-febrile subjects. (*Id*. at 4 (citing Kashiwagi et al., *supra*, at Ex. 70, p. 4).) Nor, for that matter, does the Guo et al. study cited by Dr. Axelrod actually support that IL-1β activates astroglia. (*Id*. at 4-5 (citing Guo et al., *supra*, at Ex. 76).)

After reviewing Dr. Axelrod's proposed sequence alignments for potential homology between the Tdap vaccine and NMDA receptor subunits, Dr. Kinet indicates that they at most show matching sequences that are three amino acids long, which he opines is inadequate to credibly suggest the potential for cross-reactivity. (Ex. D, p. 5.) Moreover, even if Dr. Axelrod had demonstrated homology, there is still a lack of evidence to support the proposed homology as having any pathologic significance. (*Id*. at 6.) Dr. Kinet disagrees that Park et al., as cited by Dr. Axelrod to implicate NMDR receptor antibodies in fibromyalgia, can be applied in this case. (*Id*. at 7.) The Park et al. study examined these antibodies in the context of lupus, which is known in some cases to have central nervous system manifestations. (*Id.* (discussing Park et al., *supra*, at Ex. 50).) Because the Park et al. study subjects with NMDR receptor antibodies likely have neuropsychiatric lupus, it is not informative of any role for these antibodies in the development of fibromyalgia. (*Id.*). Instead, the authors explain that they have shown these antibodies to be "an independent predictor of concomitant

[fibromyalgia] and [neuropsychiatric lupus]." (*Id*. at 7 (quoting (Park et al., *supra*, at Ex. 50, p. 1).) Indeed, as part of this finding, the study showed that anti-NMDA receptor antibody titers did not differ significantly between subjects with fibromyalgia only and controls. (*Id*.) Although Dr. Axelrod cited Wollmuth et al. for the proposition that anti-NDMDA receptor antibodies can act as agonists, this study does not address fibromyalgia and, in any event, these agonistic antibodies still resulted in neuronal cell death, which is inconsistent with petitioner's normal MRI. (*Id*. (citing Takahisa Gono et al., *NR2-Reactive Antibody Decreases Cell Viability Through Augmentation of* Ca^{2+} *Influx in Systemic Lupus Erythematosus*,63 ARTHRITIS & RHEUMATISM 3952 (2011) (Ex. D, Tab 9); Thomas W. Faust et al., *Neurotoxic Lupus Autoantibodies Alter Brain Function Through Two Distinct Mechanisms*, 107 PROCS. NAT'L ACAD. SCIS. USA 18569 (2010) (Ex. D, Tab 10); Lorraine A. DeGiorgio et al., *A Subset of Lupus Anti-DNA Antibodies Cross-Reacts with the NR2 Glutamate Receptor in Systemic Lupus Erythematosus*, 7 NATURE MED. 1189 (2001) (Ex. D, Tab 11)).)

To the extent Dr. Axelrod newly suggests that the vaccine resulted instead in immune activity at the dorsal root ganglion, Dr. Axelrod relies on potential cross reaction between vaccine components and voltage-gated sodium channels; however, Dr. Kinet opines that these proposed homologies suffer the same shortcomings as those Dr. Axelrod proposed relative to the NMDA receptors. (Ex. D, p. 8.) Moreover, Dr. Axelrod has not explained how the putative antibodies would create chronic pain, citing no evidence of such antibodies being present in humans or resulting in agonist activity. (*Id.*) Even acknowledging that fibromyalgia could involve inflammation at the dorsal root ganglion, petitioner's spinal MRI did not demonstrate any inflammation. (*Id*. (citing Ex. 9, p. 89; Ex. 13, pp. 96-97).)

With regard to Dr. Axelrod's further invocation of anti-GABA receptor antibodies, Dr. Kinet suggests that the Ryabkova et al. study actually suggests that these antibodies are potentially implicated in chronic fatigue syndrome but not fibromyalgia. (Ex. D, p. 8 (discussing Ryabkova et al., *supra*, at Ex. 53).) Specifically, the study found that anti-GABA receptor antibodies were found in equal proportions among chronic fatigue syndrome subjects with and without fibromyalgia. (*Id*.) Moreover, there was no correlation with symptom presentation. (*Id.*) But in any event, the homology Dr. Axelrod proposes with regard to GABA receptors is no more robust than his other proposed homologies relative to either NMDA receptors or voltage-gated sodium channels. (*Id*.) And, as with NMDA receptors, GABA receptors are otherwise associated with central nervous system inflammatory disease, which petitioner does not have, rather than fibromyalgia. (*Id.*) Specifically, GABA receptor antibodies are associated with limbic encephalitis and neuropsychiatric lupus. (*Id.* at 8-9 (citing Romana Höftberger et al., *Encephalitis and* $GABA_B$ *Receptor Antibodies: Novel Findings in a New Case Series of 20 Patients*, 81 NEUROLOGY 1500 (2013) (Ex. D, Tab 14); Haruka Tsuchiya et al., *Identification of Novel Autoantibodies to* $GABA_B$ *Receptors in Patients with Neuropsychiatric Systemic Lupus Erythematosus*, 53 RHEUMATOLOGY 1219 (2014) (Ex. D, Tab 15); Fei Zhu et al., *Clinical Characteristics of Antia-GABA-B Receptor Encephalitis*, FRONTIERS NEUROLOGY, May 21, 2020, at 1 (Ex. D, Tab 16);

Qiang Li et al., *Clinical Characteristics and Prognosis of Anti- $GABA_B$ R Encephalitis: A Single-Center Experience*, MED., 2023, at 1 (Ex. D, Tab 17)).)

V. Party Contentions

In her motion for a ruling on the written record, petitioner stresses that the experts agree that she suffered fibromyalgia. (ECF No. 83, p. 7.) She further contends that the experts agree that fibromyalgia is cytokine-mediated, and that molecular mimicry is a viable theory for the development of autoimmunity. (*Id.*) Thus, petitioner urges acceptance of Dr. Axelrod's theory pursuant to *Althen* prong one, explaining Dr. Axelrod as opining that fibromyalgia is an autoimmune condition wherein the innate response to Tdap vaccination elevated pro-inflammatory cytokines (IL-6, TNF-α, and lL-1β) to a degree that opened the blood brain barrier, permitting both the innate and adaptive immune responses to enter the central nervous system, resulting in central sensitization and chronic pain driven by autoantibodies. (*Id*. at 8.) Regarding *Althen* prong two, petitioner relies on the following as "key" points: a temporal association between vaccination and onset of symptoms; the established role of cytokines in pain syndromes; "the possibility of immune system dysregulation leading to her fibromyalgia-like condition"; and the fact that Dr. Axelrod's theory is supported by scientific literature associating fibromyalgia with abnormal immune response, cytokine elevations, and autoantibodies. (*Id*. at 9-10). Petitioner argues that her history demonstrates appropriate timing under *Althen* prong three, because the cytokine response to vaccination typically peaks between 24-48 hours post-vaccination. (*Id*. at 11.)

However, respondent disputes that petitioner has shown that the Tdap vaccine can open up the blood brain barrier or that this is a relevant mechanism for fibromyalgia. (ECF No. 84, pp. 15-20.) Respondent also disputes that petitioner has not reliably demonstrated that the molecular mimics posited by Dr. Axelrod explain fibromyalgia. (*Id*. at 20-26.) Respondent submits there is a lack of clinical data to support petitioner's showing under *Althen* prong two and, further, that his expert has reasonably raised other known inciting factors for fibromyalgia as being implicated in this case, including psychosocial trauma and cancer. (*Id.* at 27-30.) In particular, respondent stresses the absence of any markers of inflammation as part of petitioner's initial post-vaccination presentation (no fever, no elevation of ESR). (*Id*. at 28.) Respondent argues that petitioner's failure to satisfy *Althen* prong one necessarily means she cannot satisfy *Althen* prong three. (*Id.* at 31-32.)

In reply, petitioner contends that Dr. Axelrod's theory is based on well-established principles of immunology and suggests with respect to molecular mimicry that respondent has overlooked the fact that Dr. Axelrod has provided specific homologies, which she contends is beyond what is necessary to meet her burden of proof. (ECF No. 86, p. 2.) And, although respondent raised the presence of other risk factors for fibromyalgia, these alternative explanations fail to account for the acute onset of petitioner's symptoms. (*Id*. at 2-3.) In particular, petitioner had no prior history of fibromyalgia. (*Id*. at 3.) Petitioner argues that the timing of onset "precisely" aligns with the expected timeframe for a cytokine response and that this is "compelling evidence."

(*Id*.) Finally, petitioner asserts that respondent's reliance on cancer or psychological stress as alternative causes of petitioner's fibromyalgia is speculative and insufficient to meet respondent's own shifted burden of proof. (*Id.* at 4.)

VI. Discussion

a. Petitioner has not met her burden of proof under *Althen* prong one

Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received can cause the type of injury alleged. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006) (quoting *Pafford v. Sec'y of Health & Human Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *aff'd*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352 (Fed. Cir. 2006)). Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994). Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *See Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378 (Fed. Cir. 2009) (citing *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325-26 (Fed. Cir. 2006)). However, "[a] petitioner must provide a 'reputable medical or scientific explanation' for [their] theory." *Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019) (quoting *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1322 (Fed. Cir. 2010)). "While it does not require medical or scientific certainty, it must still be 'sound and reliable.'" *Id.* (quoting *Knudsen*, 35 F.3d at 548-49).

As described extensively above, Dr. Axelrod's theory is premised as a threshold matter on the notion that a post-vaccinal fibromyalgia can be explained by the fact that the cytokine response to vaccination is significant enough to open up the blood brain barrier, ultimately resulting in sensitization within the central nervous system. However, this assertion is not reliably supported.[12]

[12] In his final report, Dr. Axelrod alternatively suggested that a post-vaccinal immune response could affect the dorsal root ganglia, which would not implicate the blood brain barrier. (Ex. 32, p. 8.) This was seemingly to account for the fact that one of his primary references, Goebel et al., did not demonstrate the immune response that he posited within the central nervous system. (*Id*.) However, in his second report, Dr. Axelrod had previously discounted the significance of the Goebel findings relative to the peripheral nervous system of reduced intraepidermal nerve fiber density. (Ex. 19, p. 10 (discussing Goebel et al., *supra*, at Ex. 78).) And, in any event, this belated addition to Dr. Axelrod's opinion does not erase his clear reliance on an immune response crossing the blood-brain barrier, which he sought to defend extensively in his first two reports. Indeed, even after the filing of Dr. Axelrod's third and final report, petitioner's motion for a ruling on the written record still centers her discussion of *Althen* prong one around Dr. Axelrod's assertion that cytokines increase the permeability of the blood brain barrier. (ECF No. 83, pp. 8-9.) Nor, for that matter, are the findings of the Goebel et al. study sufficient to support a stand-alone theory of causation. Indeed, if they were, then it would be very strange that Dr. Axelrod assembled an entirely different theory despite having cited the Goebel et al. study in his first report. Petitioner has not argued that she has met her burden of proof based on such an alternative theory. (ECF Nos. 83, 86.)

Even where there is some reason to suspect a condition may be cytokine-mediated, this does not automatically lead to the conclusion that vaccines can cause the injury merely because vaccines produce some cytokine elevations. *See, e.g.*, *Kaltenmark v. Sec'y of Health & Human Servs*., No. 17-1362V, 2023 WL 8870299, at *29-35 (Fed. Cl. Spec. Mstr. Nov. 27, 2023); *Dean ex rel. I.D. v. Sec'y of Health & Human Servs.,* No. 13-808V, 2017 WL 2926605, at *16-18 (Fed. Cl. Spec. Mstr. June 9, 2017) (explaining in the context of alleged encephalopathy that, even though "[m]any of the general principles (as evidenced by Petitioner's expert reports plus the filed medical or scientific literature) that underlie this theory are not disputed," "[t]he most immediately apparent weakness in this case's causation theory is the heavy lifting it assigns to the post-vaccination cytokine production process as the cause of almost all of the pathologic effects of the vaccines at issue"); *Bohn ex rel. G.B. v. Sec'y of Health & Human Servs.*, No. 16-0265V, 2021 WL 4302367, at *16-21 (Fed. Cl. Spec. Mstr. Aug. 23, 2021) (explaining that petitioner's experts sought "to marry via their *ipse dixit* literature showing elevated proinflammatory post-vaccination cytokines on the one hand with literature showing SCLS and cytokine storm as being injurious cytokine-mediated conditions on the other," but that "the literature filed in this case demonstrates only that cytokine levels observed post-vaccination are dramatically lower than the levels of cytokines measured in those experiencing injurious systemic cytokine reactions"). Acknowledging that a vaccine will induce some inflammatory immune response, mere invocation of a vaccine's intended immune response is not in and of itself sufficient to carry petitioner's burden under *Althen* prong one. *See Elvira ex rel. D.E. v. Sec'y of Health & Human Servs.*, No. 17-531V, 2024 WL 4966035, at *20 (Fed. Cl. Spec. Mstr. Nov. 6, 2024); *Vanore v. Sec'y of Health & Human Servs.*, No. 21-0870V, 2024 WL 3200287, at *18 (Fed. Cl. Spec. Mstr. May 31, 2024); *Kalajdzic ex rel. A.K. v. Sec'y of Health & Human Servs.*, No. 17-792V, 2022 WL 2678877, at *23 (Fed. Cl. Spec. Mstr. June 17, 2022), *mot. for rev. denied*, No. 17-792V, 2024 WL 4524777 (Fed. Cl. Oct. 18, 2024), *aff'd*, No. 2023-1321, 2024 WL 3064398 (Fed. Cir. June 20, 2024); *Cordova v. Sec'y of Health & Human Servs*., No. 17-1282V, 2021 WL 3285367, at *17 (Fed. Cl. Spec. Mstr. June 23, 2021). There must be some additional evidence linking the vaccine's immune response to the pathology of petitioner's actual condition. For example, the Chief Special Master has observed:

> I have on many occasions considered theories asserting a vaccine-caused, cytokine-driven process led to injury, but have repeatedly deemed such theories wanting, absent evidence connecting the process (no matter how scientifically plausible it might be) with additional proof sufficient to render it "more likely than not" that the immune processes outlined could be rendered pathogenic by introduction of a vaccine. Otherwise, such a theory only attempts to transmute the expected reaction to a vaccine into pathology.

M.R. v. Sec'y of Health & Human Servs., No. 16-1024V, 2023 WL 4936727, at *27 (Fed. Cl. Spec. Mstr. June 30, 2023) (citing *Dean*, 2017 WL 2926605, at *17).

Here, even if one granted petitioner the assumption that the study by Rochfort et al. is informative of how the blood brain barrier functions, the record evidence does not

support the conclusion that a Tdap vaccine can generate a cytokine response comparable to what was demonstrated by Rochfort et al. In particular, the study by Kashiwagi et al., as cited by Dr. Axelrod, demonstrates that in a real-world context, vaccines promote cytokine levels that are orders of magnitude less than what might be expected to meaningfully affect the blood brain barrier. (*Compare* Rochfort et al., *supra*, at Ex. 75, pp. 4, 6 figs. 1, 3 (indicating that 1 ng/mL was the lowest concentration of IL-6 and TNF-α used in the study), *with* Kashiwagi et al., *supra*, at Ex. 70, p. 6 fig.3 (indicating that the highest concentration of IL-6 and TNF-α detected in both febrile and non-febrile individuals within 24 hours after vaccination was under 200 pg/mL); *see also* Ex. C, p. 4.) Indeed, the importance of the distinction between studies involving picograms of cytokines (such as Kashiwagi et al.) versus nanograms of cytokines (such as Rochfort et al.) has also been observed in prior cases. *See, e.g.*, *Kaltenmark*, 2023 WL 8870299, at *32-33; *Brunson ex rel. T.A. v. Sec'y of Health & Human Servs.*, No. 17-530V, 2020 WL 5755502, at *13 n.12 (Fed. Cl. Spec. Mstr. Sept. 3, 2020); *Nunez v. Sec'y of Health & Human Servs.*, No. 14-863V, 2019 WL 2462667, at *31 (Fed. Cl. Spec. Mstr. Mar. 29, 2019), *mot. for rev. denied*, 144 Fed. Cl. 540 (2019), *aff'd*, 825 F. App'x 816 (Fed. Cir. 2020); *Copenhaver v. Sec'y of Health & Human Servs.*, No. 13-1002V, 2016 WL 3456436, at *13 n.22 (Fed. Cl. Spec. Mstr. May 31, 2016), *mot. for rev. denied*, 129 Fed. Cl. 176 (2016). Moreover, many prior decisions have also explained that the Kashiwagi et al. study does not suggest that vaccines produce any pathologic cytokine response. *E.g.*, *Bohannon v. Sec'y of Health & Human Servs.*, No. 23-235V, 2025 WL 413454, at *22 (Fed. Cl. Spec. Mstr. Jan. 2, 2025); *Hayward v. Sec'y of Health & Human Servs*., No. 15-005V, 2018 WL 2772495, at *17-18 (Fed. Cl. Spec Mtr. May 4, 2018); *Dean*, 2017 WL 2926605, at *16-17; *Copenhaver*, 2016 WL 3456436, at *9-14 (Fed. Cl. Spec. Mstr. May 31, 2016) (infant's death not caused by cytokine upregulation due to vaccination); *Cozart v. Sec'y of Health & Human Servs.*, No. 00-590V, 2015 WL 6746499, at *6-7 (Fed. Cl. Spec. Mstr. Oct. 15, 2015), *mot. for rev. denied*, 126 Fed. Cl. 488 (2016).

Seeking to overcome this issue, Dr. Axelrod additionally cites studies by Rice et al. and van der Lee et al., which he indicates show higher cytokine levels than did Kashiwagi et al. (Ex. 32, pp. 2-3 (discussing Rice et al., *supra*, at Ex. 42; van der Lee et al., *supra*, at Ex. 41).) Importantly, however, the actual findings of these two studies still fall short of the 1 ng/mL threshold evidenced by the Rochfort et al. study. (van der Lee et al., *supra*, at Ex. 41, p. 9 fig.9; Rice et al., *supra*, at Ex. 42, pp. 4-5 fig.1 (finding concentrations of 866 pg/mL of IL-6 and 191 pg/mL of TNF-α 24 hours post-vaccination with no significant increase in IL-1β).) In fact, Dr. Axelrod does not rely on the study results, but rather on the confidence intervals for the findings at issue, suggesting that the upper end of the confidence interval indicates that cytokines could potentially reach the requisite level despite the study's actual findings. (Ex. 32, p. 3.) This is speculative and unreliable. The confidence interval is an expression of uncertainty, not a finding, and it is generally the breadth of the confidence interval that is considered informative. *E.g.*, *Mead v. Sec'y of Health & Human Servs.*, No. 03-215V, 2010 WL 892248, at *42 (Fed. Cl. Spec. Mstr. Mar. 12, 2010) (describing confidence intervals as "the range of uncertainty"). Considering the confidence interval as a whole, it is also quite possible that the actual cytokine levels were *lower* than what the study reported. (*See* van der

Lee et al., *supra*, at Ex. 41, p. 9 fig.9; Rice et al., *supra*, at Ex. 42, pp. 4-5 fig.1.) In any event, Dr. Kinet further observes that, as *in vitro* studies, neither the Rice et al. study nor van der Lee et al. study contradict the Kashiwagi et al. study findings, which showed cytokine levels in circulation. (Ex. D, pp. 1-3.) And, although Dr. Axelrod separately cited a study by Banks et al. to otherwise show that IL-6 can cross the blood brain barrier (Ex. 32, p. 5 (citing Banks et al., *supra*, at Ex. 43)), this is of limited value given that Dr. Axelrod's theory relies on IL-1β in particular (Ex. 18, pp. 21-22, 24-25). As Dr. Kinet observed, the Banks et al. study does not demonstrate that anything other than IL-6 traffics across the blood brain barrier and Kashiwagi et al. demonstrated no post-vaccination increase in IL-1β. (Ex. D, pp. 3-4; Kashiwagi et al., *supra*, at Ex. 70, p. 4 (stating that "[n]o detectable IL-1β was observed in sera in both febrile and non-febrile groups).) Thus, petitioner is not persuasive with regard to this threshold premise introduced by Dr. Axelrod.

Assuming *arguendo* that petitioner had succeeded in suggesting that the Tdap vaccine could open up the blood brain barrier, Dr. Axelrod additionally asserts that components of the Tdap vaccine represented molecular mimics of either NMDA receptors or GABA receptors leading to cross-reaction within the central nervous system, ultimately manifesting chronic pain and fibromyalgia – *i.e.* he asserts that fibromyalgia can be explained by the concept of molecular mimicry. Importantly, however, molecular mimicry is a potential mechanism specific to autoimmune conditions. Yet, petitioner has not preponderantly demonstrated that fibromyalgia is an autoimmune condition. While literature in this case does propose various immune mechanisms for fibromyalgia, Dr. Kinet stresses that no consistent immune abnormalities have been documented. (Ex. A, p. 5.) For example, a meta-analysis by Üçeyler et al. from 2011 explained that "[t]he pathophysiology of [fibromyalgia] is incompletely understood and although the syndrome can be characterized by an identifiable group of signs and symptoms, there is no recognized etiologic agent and no consistent anatomical alteration that would qualify [fibromyalgia] as a disease." (Üçeyler et al., *supra*, at Ex. A, Tab 10, p. 1.) As of 2021, Siracusa et al., which Dr. Axelrod argued to support his theory (Ex. 19, p. 4), likewise explained that "[t]he pathophysiological factors of [fibromyalgia] are not yet well known and continue to be the focus of much research." (Siracusa et al., *supra*, at Ex. A, Tab 3, p. 2.)

Moreover, even assuming *arguendo* that the concept of molecular mimicry was applicable, there are several additional problems with Dr. Axelrod's theory. Indeed, Dr. Kinet addressed the shortcomings of Dr. Axelrod's molecular mimicry theories at length throughout his reports. Here, discussion is limited to the two most basic flaws, either of which alone could be considered fatal.

First, Dr. Axelrod has purported to demonstrate homology by finding very short amino acid sequences. However, he has not demonstrated that the degree of homology he has detected could be pathologic. In prior cases where molecular mimicry has been persuasively advanced, other experts have identified the minimum degree of homology that would support the disease-causing potential of the proposed homology. *E.g.*, *Riese v. Sec'y of Health & Human Servs.*, No. 19-477V, 2025 WL 3463267, at *13,

*21 (Fed. Cl. Spec. Mstr. Nov. 3, 2025); *Mullins v. Sec'y of Health & Human Servs.*, No. 19-320V, 2024 WL 4045424, at *16-18, *44-45 (Fed. Cl. Spec. Mstr. Aug. 8, 2024). Here, however, Dr. Axelrod has not done so, even after specific challenge from Dr. Kinet. (Ex. C, p. 5; Ex. D, p. 5.) Moreover, the degree of homology Dr. Axelrod asserts (as little as three amino acids) is shorter than what has generally been discussed by other experts in prior cases. *E.g.*, *Bartoszek v. Sec'y of Health & Human Servs.*, No. 17-1254V, 2024 WL 4263604, at *11 n.9 (Fed. Cl. Spec. Mstr. Aug. 27, 2024) (Dr. Steinman opining that a molecular mimic must share at least five out of twelve amino acids); *Girardi v. Sec'y of Health & Human Servs.*, No. 17-181V, 2024 WL 4565887, at *8 (Fed. Cl. Spec. Mstr. Sept. 27, 2024) (same); *Mullins*, 2024 WL 4045424, at *16-17 (Dr. Steinman opining that a homology of just five identical amino acids is sufficient for molecular mimicry). *But see Coons v. Sec'y of Health & Human Servs.*, No. 20-1067V, 2024 WL 1741619, at *9 (Fed. Cl. Spec. Mstr. Mar. 29, 2024). Indeed, the fact that Dr. Axelrod variously purported to find the Tdap vaccine homologous to three unrelated targets – NMDA receptors, GABA receptors, and voltage-activated sodium channels – undercuts the notion that what he found were meaningful mimics. As prior decisions have observed, "the finding of sequence homology does not necessarily mean the similarity has significance to the immune system." *Tullio v. Sec'y of Health & Human Servs.*, No. 15-51V, 2019 WL 7580149, at *15 (Fed. Cl. Spec. Mstr. Dec. 19, 2019), *aff'd*, 149 Fed. Cl. 448 (2020); *see also Caredio ex rel. D.C. v. Sec'y of Health & Human Servs.*, No. 17-0079V, 2021 WL 4100294, at *31 (Fed. Cl. Spec. Mstr. July 30, 2021) ("[D]emonstration of homology alone is not enough to establish a preponderant causation theory." (emphasis omitted) (citing *Schultz v. Sec'y of Health & Human Servs.*, No. 16-539V, 2020 WL 1039161, at *22 n.24 (Fed. Cl. Spec. Mstr. Jan. 24, 2020))), *mot. for rev. denied*, No. 17-79V, 2021 WL 6058835 (Fed. Cl. Dec. 3, 2021).

Second, even though Dr. Axelrod has provided an explanation as to how NMDA receptors and/or GABA receptors might be linked to symptoms consistent with fibromyalgia (*e.g.*, Ex. 19, p. 4 (discussing Siracusa et al., *supra*, at Ex. A, Tab 3, p. 4); Ex. 32, p. 9 (discussing Ryabkova et al., *supra*, at Ex. 53)), he has not shown that antibodies against either of these receptors have been implicated in the pathogenesis of fibromyalgia. The closest Dr. Axelrod comes to substantiating a role for NMDA receptors in fibromyalgia patients is his citation to the Park et al. study. (Ex. 32, p. 10 (discussing Park et al., *supra*, at Ex. 50).) However, Dr. Kinet is persuasive in observing that the Park et al. study more readily implicates anti-NMDA receptor antibodies in neuropsychiatric lupus than fibromyalgia. (Ex. D, p. 7 (discussing Park et al., *supra*, at Ex. 50).) Dr. Axelrod cited Ryabkova et al. as demonstrating the presence of GABA receptor antibodies in patient with fibromyalgia (Ex. 32, p. 9), but Dr. Kinet observed that the Ryabkova et al. study more readily implicated these antibodies in chronic fatigue syndrome rather than fibromyalgia (Ex. D, p. 8 (Ryabkova et al., *supra*, at Ex. 53)). Although Dr. Axelrod relied at least in part on the Goebel et al. study, Dr. Kinet is persuasive in explaining that this study alone is not enough to establish the pathogenesis of fibromyalgia in human subjects or to overturn conventional thinking on the nature of the condition. (Ex. A, pp. 7-8.) Moreover, Dr. Axelrod's theory does not entirely align with the Goebel et al. paper in that he favors a role for autoimmunity occurring in the central nervous system (Ex. 18, p. 30), and the Goebel study did not

include any findings referable to the brain or spinal cord (Goebel et al., *supra*, at Ex. 78, p. 5; *see also* Ex. C, p. 6; Ex. 32, pp. 7-8) Moreover, Dr. Kinet is persuasive in contending that antibodies against NMDA receptors and GABA receptors are implicated in limbic encephalitis and neuropsychiatric lupus. (Ex. A, p. 7; Ex. D, pp. 7-9.) Dr. Axelrod contended that NMDA receptors are implicated in a number of different contexts (*e.g.*, Ex. 18, pp. 22, 24; Ex. 19, pp. 3-4; Ex. 32, pp. 6-7) and, in particular, notes that the Goebel et al. study suggests that immune attack on NMDA receptors need not necessarily result in encephalitis (Ex. 19, p. 10). Importantly, however, Dr. Axelrod ultimately conceded that the Goebel et al. study did not include any findings relative to the central nervous system (Ex. 32, pp. 7-8) whereas his theory posits an autoimmune attack against receptors in the brain (Ex. 18, p. 30). Dr. Axelrod has not explained how it would be reasonable to invoke an autoimmune attack against NMDA receptors in the brain without that attack resulting in the type of encephalitic or neuropsychiatric features otherwise associated with anti-NMDA receptor antibodies.

Molecular mimicry "is a generally accepted scientific principle, [but] mere invocation of the scientific term does not carry a petitioner's burden in a Program case." *Deshler v. Sec'y of Health & Human Servs*., No. 16-1070V, 2020 WL 4593162, at *20 (Fed. Cl. Spec. Mstr. July 1, 2020) (citing *Forrest v. Sec'y of Health & Human Servs.*, No. 14-1046V, 2019 WL 925495, at *3 (Fed. Cl. Spec. Mstr. Jan. 28, 2019)). Prior cases have explained that when assessing theories based on molecular mimicry in light of petitioner's preponderant burden of proof, "[t]he line must be drawn somewhere between speculation and certainty." *Brayboy v. Sec'y of Health & Human Servs.*, No. 15-183V, 2021 WL 4453146, at *19 (Fed. Cl. Spec. Mstr. Aug. 30, 2021). Here, considering the record as a whole and accounting for the fact that petitioner is not obligated to demonstrate scientific certainty, Dr. Axelrod has not succeeded in crossing the line from speculation. Nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)); *see also Isaac v. Sec'y of Health & Human Servs*., No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012) ("The weight to be given to an expert's opinion is based in part on the size of the gap between the science and the opinion proffered."), *mot. for rev. denied*, 108 Fed. Cl. 743, ***aff'd***, 540 F. App'x 999 (Fed. Cir. 2013).

Finally, in contrast to what Dr. Axelrod theorizes on petitioner's behalf, Dr. Kinet explains that vaccination is not otherwise thought to be a risk factor for fibromyalgia, citing several studies showing fibromyalgia has not been identified as a safety concern relative to the Tdap vaccine. (Ex. A, p. 5 (citing Van den Steen et al., *supra*, at Ex. A, Tab 16; McNeil et al., *supra*, at Ex. A, Tab 17; Xu et al., *supra*, at Ex. A, Tab 18).) Dr. Axelrod is correct to note that it is difficult to impossible for epidemiology to prove a negative. (Ex. 19, pp. 5-6.) And, indeed, petitioners in general are not obligated to come forward with epidemiologic proof. *Capizzano,* 440 F.3d at 1325-26. However, special masters are permitted to weigh the epidemiologic studies that are submitted. *D'Tiole v. Sec'y of Health & Human Servs.*, 726 F. App'x 809, 811 (Fed. Cir. 2018)

(explaining that "[n]othing in *Althen* or *Capizzano* requires the Special Master to ignore probative epidemiological evidence that undermines petitioner's theory"). In this case, Dr. Kinet is persuasive in suggesting that fibromyalgia is a common enough condition, and the studies of record are large enough, that they should be viewed as having some tendency to make petitioner's theory less likely to be correct. (Ex. A, pp. 5-6.) Although Dr. Axelrod cautioned that "absence of evidence is not the same as evidence of absence of a relationship" (Ex. 19, p. 6), he did not offer any specific criticisms of the relative value or reliability of the studies introduced by Dr. Kinet.

In that regard, although prior decisions are not binding, *Boatmon*, 941 F.3d at 1358, it is also worth noting that prior petitioners in this program have tried, but failed, to implicate various vaccinations, including the Tdap vaccination, as a cause of fibromyalgia. *Williams v. Sec'y of Health & Human Servs*., No. 19-1269V, 2024 WL 5040482 (Fed. Cl. Spec. Mstr. Nov. 13, 2024) (flu vaccine); *Ruzicka v. Sec'y of Health & Human Servs.*, No. 17-109V, 2023 WL 8352496 (Fed. Cl. Spec. Mstr. Nov. 13, 2023) (Tdap vaccine); *Cowart v. Sec'y of Health & Human Servs*., No. 16-513V, 2021 WL 253977 (Fed. Cl. Spec. Mstr. Jan. 5, 2021) (meningococcal conjugate vaccine); *Balasco v. Sec'y of Health & Human Servs*., No. 17-215V, 2020 WL 1240917 (Fed. Cl. Spec Mstr. Feb. 14, 2020) (HPV vaccine); *Fankhauser v. Sec'y of Health & Human Servs*., No. 09-590V, 2014 WL 7015509 (Fed. Cl. Spec. Mstr. Nov. 24, 2014) (HPV vaccine); *Doe/70 v. Sec'y of Health & Human Servs*., No. V, 2011 WL 539133, (Fed. Cl. Spec. Mstr. Feb. 9, 2011) (hepatitis B vaccine); *Doe/71 v. Sec'y of Health & Human Servs*., No. V, 2010 WL 2545721 (Fed. Cl. Spec. Mstr. May 26, 2010) (hepatitis B vaccine), *mot. for rev. denied*, 95 Fed. Cl. 598 (2010); *Lee v. Sec'y of Health & Human Servs*., No. 03-2479V, 2005 WL 1125672 (Fed. Cl. Spec. Mstr. Apr. 8, 2005) (hepatitis B vaccine).

In light of the above, and considering the record as a whole, petitioner has not demonstrated a sound and reliable theory of causation implicating the Tdap vaccine as a potential cause of fibromyalgia. Therefore, she has not met her preponderant burden of proof under *Althen* prong one.

b. *Althen* prong one is dispositive

Because I have concluded that petitioner has not demonstrated that the Tdap vaccine likely can cause fibromyalgia, it is not necessary to address in detail whether the vaccine did so in this particular case. Given the outcome regarding *Althen* prong one, by definition it likely did not. Thus, I do not separately reach *Althen* prongs two and three in this decision. *Trollinger v. Sec'y of Health & Human Servs.*, 167 Fed. Cl. 127, 142 (2023) (affirming a dismissal based on a dispositive finding that petitioner had not satisfied *Althen* prong one). However, I note briefly that the evidence regarding *Althen* prongs two and three is not so robust as to otherwise influence the analysis under *Althen* prong one. *Capizzano*, 440 F.3d at 1326 (explaining that evidence used to satisfy one *Althen* prong can overlap to help satisfy another); *Patton v. Sec'y of Health & Human Servs*., 157 Fed. Cl. 159, 169 (2021) (finding that the diagnoses of the treating physicians that the petitioner suffered vaccine-caused brachial neuritis

supported the reliability of petitioner's expert's theory of causation). *But see Tripp v. Sec'y of Health & Human Servs.*, 178 Fed. Cl. 688, 699 (2025) (rejecting as "circular" the petitioner's argument that because treating physicians had diagnosed petitioner with cerebellitis post-vaccination, the flu vaccine therefore can cause cerebellitis).

In particular, although petitioner repeatedly raised to her treating physicians her belief that her vaccination was a turning point in her health (*e.g.*, Ex. 4, pp. 193, 249; Ex. 9, p. 6), none of the treating physicians opined that petitioner's condition was vaccine-caused. Indeed, in her motion for a ruling on the record, petitioner argues that her showing under *Althen* prong two is primarily supported by temporal association coupled with Dr. Axelrod's showing as to general causation. (ECF No. 83, pp. 9-10; ECF No. 86, pp. 2-3.) However, the Federal Circuit has explained that "[a]lthough probative, neither a mere showing of a proximate temporal relationship between vaccination and injury, nor a simplistic elimination of other potential causes of the injury suffices, without more, to meet the burden of showing actual causation." *Althen*, 418 F.3d at 1278 (citing *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1149 (Fed. Cir. 1992)). Moreover, Dr. Axelrod's opinion as to general causation was less persuasive than that of Dr. Kinet for all the reasons discussed above.

Although petitioner's initial post-vaccination presentation was striking and her treating physician contemplated whether she was experiencing an allergic or hypersensitivity reaction to the vaccination (*e.g.*, Ex. 4, pp. 113-14, 123), Dr. Axelrod explained that the package insert for the Tdap vaccine confirms that systemic side effects such as body aches or muscle weakness, tiredness, sore or swollen joints, or rash, have been observed within 14 days of vaccination. (Ex. 32, p. 1 (citing Adacel Package Insert, *supra*, at Ex. 63).) Thus, even if petitioner satisfied *Althen* prong three relative to the expected timing for a cytokine reaction, these transient side effects are not equivalent to fibromyalgia. Nor does the data within the package insert suggest that the Tdap vaccine can cause fibromyalgia. In any event, satisfying *Althen* prong three alone does not entitle petitioner to compensation. *E.g.*, *Hibbard v. Sec'y of Health & Human Servs.*, 698 F.3d 1355, 1364-65 (Fed. Cir. 2012) (holding the special master did not err in resolving the case pursuant to *Althen* prong two when respondent conceded that petitioner met *Althen* prong three).

VII. Conclusion

There is no question that petitioner has suffered. She has my sympathy, and I do not question her sincerity in bringing this claim. However, for all the reasons discussed above, I find that petitioner has not met her burden of proof in this case. Therefore, pursuant to § 300aa-12(d)(3)(A) and Vaccine Rule 10, this decision concludes that petitioner is not entitled to an award of compensation. Absent a timely motion for review, the Clerk is directed to enter judgment dismissing this case for insufficient proof in accordance with Vaccine Rule 11(a).

IT IS SO ORDERED.

s/Daniel T. Horner
Daniel T. Horner
Special Master