In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 10-659V
Filed: December 8, 2015

* *	**PUBLISHED**
MARIA PEREZ, *	
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Petitioner, *	Special Master Lisa Hamilton-Fieldman
*	
v. *	
*	Vaccine Act Entitlement; Causation-in-fact;
SECRETARY OF HEALTH AND *	Guillain-Barré syndrome ("GBS"); Toll-like
HUMAN SERVICES, *	Receptors; Tetanus Vaccine.
*	
Respondent. *	
* *	

Diana Stadelnikas-Sedar, Maglio, Christopher & Toale, Sarasota, FL, for Petitioner;
Althea Walker Davis, U.S. Department of Justice, Washington, DC, for Respondent.

DECISION DENYING ENTITLEMENT[1]

I. INTRODUCTION

On September 30, 2010, Maria Perez ("Petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program ("the Program"),[2] alleging that she suffered Guillain-Barré syndrome ("GBS") as a result of the administration of a tetanus vaccination that she received on February 2, 2009. Petition ("Pet.") at 1-2.

[1] Because this Published Decision contains a reasoned explanation for the undersigned's action in this case, she intends to post this document on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, § 205, 116 Stat. 2899, 2913 (Dec. 17, 2002). As provided by Vaccine Rule 18(b), each party has 14 days within which to request redaction "of any information furnished by that party (1) that is trade secret or commercial or financial information and is privileged or confidential, or (2) that are medical files and similar files the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). In the absence of such motion, the entire decision will be available to the public. *Id.*

[2] The Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 *et seq.* (hereinafter "Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

Respondent recommended against compensation, arguing that Petitioner had failed to make a prima *facie case* that her February 2009 tetanus vaccination caused-in-fact her GBS. *See* Respondent's Rule 4 Report ("Resp't's Report"), filed July 18, 2011, at 17-18. Further, Respondent alleged that "[t]he evidence in this case suggests possible alternative causes for [P]etitioner's condition, including her viral illness in late March, 2009, and cellulitis." *Id.* at 18. Petitioner submitted an expert report authored by Dr. Lawrence Steinman, M.D., on February 1, 2013. Petitioner's Exhibit ("Pet'r's Ex.") 13. An expert report authored by Dr. Thomas Leist was filed by Respondent on June 3, 2013. Respondent's Exhibit ("Resp't's Ex.") A. An entitlement hearing was held in Washington D.C., on January 29, 2014, during which the parties' experts testified. The parties requested and were granted the opportunity to file post-hearing briefs, which were filed on April 16, 2014.

For the reasons set forth below, the undersigned concludes that Petitioner has failed to establish a medical theory causally connecting her tetanus vaccination to her GBS, and that Petitioner's case has not met the requisite legal standard under *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005). Accordingly, Petitioner is not entitled to a Program award.

II. FACTUAL BACKGROUND

a. Petitioner's Medical History

Maria Perez was born on December 11, 1938. *See* Pet'r's Ex. 1 at 1. Petitioner's past medical history is significant for a number of conditions, including diabetes mellitus, gastroesophageal reflux disease ("GERD"), severe arthritis including degenerative joint disease of the left shoulder, hypertension, and gallbladder disease. Pet'r's Ex. 7 at 48.

On December 10, 2008, Petitioner saw Dr. Jeffrey Loman, her primary care physician, for severe pain in her chest wall. Pet'r's Ex. 1 at 310. Later that same day, Petitioner sought treatment in the emergency room of the Baptist Hospital of Miami for left shoulder pain "radiating into chest and left scapular assoicated [sic] with swelling and vomiting" which "started about 7 days ago and is still present and worsening." Pet'r's Ex. 7 at 395. She denied any feelings of weakness, tingling, or numbness. *Id*. at 403. She was treated with IV medications for pain, including Percocet and dilaudid, *id.* at 404, and vancomycin, an antibiotic, *id.* at 405, after which her pain level dropped from 9/10, *id.* at 404, to 0/10. *Id*. at 405. A contrast MRI was recommended, which Petitioner declined, and she left the hospital on December 11, 2008, against medical advice. *Id*. at 406. Dr. Loman saw her again on December

11, 2008, after her ER visit, for "chest wall hematoma vs. abscess." Pet'r's Ex. 1 at 309. He counseled Petitioner about the "risk for infectious disease sepsis." *Id.*[3]

On December 12, 2008, Baptist Hospital of Miami advised Dr. Loman that blood cultures drawn during Petitioner's emergency room visit had tested positive for staphylococcus aureus ("staph"). Pet'r's Ex. 1 at 309; Pet'r's Ex. 7 at 402. Petitioner returned to Baptist Hospital on December 12, 2008, where she was admitted and evaluated by Lorraine Dowdy, D.O., an infectious disease specialist. Pet'r's Ex. 7 at 48. Dr. Dowdy diagnosed Petitioner with cellulitis[4] and an abscess of the super scapular area, septicemia,[5] leukocytosis,[6] an elevated sedimentation rate, and diabetes mellitus. *Id*. at 49-50.

During her admission at Baptist Hospital for the abscess and related issues, Petitioner underwent a neurological examination that demonstrated intact light touch sensations, normal reflexes, and a normal gait. Pet'r's Ex. 7 at 152-53. On December 19, 2008, James Benenati, M.D., and Dean Chauvin, M.D., performed an aspiration of Petitioner's upper left back near the shoulder girdle. *Id.* at 51-52. The extracted fluid cultures were positive for staph infection. *Id*. at 75. Petitioner also received an influenza ("flu") vaccination on December 20, 2008, and was discharged with diagnoses of a left scapular abscess, staph bacteremia, right scapular swelling with redness, and leukocytosis. Pet'r's Ex. 7 at 20, 38-39. She still had active cellulitis on January 15, 2009, despite treatment. Pet'r's Ex. 1 at 75, 305, 306.

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[3] "Sepsis is the body's overwhelming and life-threatening response to infection which can lead to tissue damage, organ failure, and death." Centers for Disease Control and Prevention website, http:/www.cdc.gov/sepsis/ (last visited December 2, 2015).

[4] Cellulitis is "an acute, diffuse, spreading, edematous, suppurative inflammation of the deep subcutaneous tissues and sometimes muscle, sometimes with abscess formation. It is usually caused by infection of a wound, burn, or other cutaneous lesion by bacteria, especially group A streptococci and *Staphylococcus aureus*, but it may also occur in immunocompromised hosts or following erysipelas (q.v.)." *Dorland's Illustrated Medical Dictionary* ("*Dorland's*"), 325 (32nd ed. 2012).

[5] Septicemia is "systemic disease associated with the presence and persistence of pathogenic microorganisms or their toxins in the blood. Called also *blood poisoning* and *sepsis*." *Dorland's*, 1693.

[6] Leukocytosis is "a transient increase in the number of leukocytes in the blood; seen normally with strenuous exercise and pathologically accompanying hemorrhage, fever, infection, or inflammation." *Dorland's*, 1028.

On February 2, 2009, Petitioner went to her primary care physician for treatment of a bird bite on her right hand, and she received the tetanus toxoid vaccination at issue in this case. [7] Pet'r's Ex. 1 at 74, 304. The visit notes indicated that Petitioner "refuse[d] to stay to finish visit and left." *Id*. at 304. The diagnosis from this visit was cellulitis on her right hand. *Id*.

On March 25, 2009, Petitioner went to the emergency room at Kendall Regional Medical Center for vomiting and a potential viral infection. Pet'r's Ex. 2 at 111; Tr. 40. Petitioner complained that she had been vomiting for three days and that her whole body hurt. Pet'r's Ex. 8 at 1. "Associated signs and symptoms" included nausea, three episodes of diarrhea in the past twenty-four hours, and generalized body aches. *Id.* at 3. Movement was an aggravating factor. *Id.* Petitioner rated her pain as 10 out of 10. *Id.* at 1. Petitioner's blood tests revealed an elevated white cell count. *Id.* at 22. She reported resolution of her pain and was discharged on March 26, 2009. *Id.* at 6.

On April 1, 2009, Petitioner presented to the Emergency Room of Doctor's Hospital, complaining of tingling in the arms and legs, dizziness, bilateral upper and lower extremity numbness, and weakness in her extremities. Pet'r's Ex. 6 at 44. A brain CT without contrast performed on April 2, 2009 showed "almost complete opacification in the left spheroid sinus consistent with sinusitis." *Id.* at 52. She was diagnosed with ataxia and labyrinthitis,[8] and further testing was recommended. *Id.* at 45, 47. However, Petitioner left the hospital against medical advice on April 2, 2009, and the physicians were left with an incomplete workup. *Id.* at 45-46.

Petitioner's weakness worsened: she developed difficulty swallowing, double vision, and shortness of breath. Pet'r's Ex. 12 at 82. She was admitted to the critical care unit of Kendall Regional Medical Center ("Kendall") on April 3, 2009, after presenting with severe muscle weakness, including "profound respiratory muscle weakness" which required intubation and mechanical ventilator support. Pet'r's' Ex. 2 at 62. She also required catheterization for plasmapheresis and IV access, *id.* at 76, and the placement of a nasal feeding tube. *Id.* at 66. She was evaluated by a neurologist, Dr. Sanjiv Sahoo, M.D., the following day. *Id.* at 85. Dr. Sahoo noted "flu-like symptoms" "a week ago." *Id.* Petitioner reported eyelid drooping for the prior three to four days; mild, intermittent double vision; problems swallowing and slurring her speech; and bilateral, progressive lower and upper extremity weakness without sensory loss. *Id.*

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[7] No vaccination record that provided the type of tetanus vaccine administered (i.e., Tdap, Td, etc.), its manufacturer, or lot number, was ever located. The fact that the vaccine was given, however, is not disputed.

[8] Labyrinthitis is "inflammation of the internal ear; it may be accompanied by hearing loss or vertigo." *Dorland's*, 995.

She could not walk, was unable to lift her arms and legs off the bed, and had mild right-sided facial weakness and drooling. *Id.*

Petitioner's treaters at Kendall initially diagnosed her critical condition as myasthenia gravis.[9] Pet'r's Ex. 2 at 76-78; *see also* Tr. 14-15. She received treatment with multiple courses of intravenous immunoglobulin ("IVIG") and plasmapheresis. Pet'r's Ex. 2 at 52, 69-70. A tracheostomy was performed on April 24, 2009, because Petitioner could not be weaned from the respirator. *Id.* at 56.

Petitioner was transferred to South Miami Hospital on April 27, 2009. Pet'r's Ex. 12 at 70. Treating physicians at South Miami found her clinical course to be more compatible with a diagnosis of GBS than myasthenia gravis, *see id.* at 114-131, although myasthenia gravis and GBS can coexist. Pet'r's Ex. 13 at 17; *see also* Tr. 50. There is no factual dispute between the parties that Petitioner has been diagnosed with Guillain-Barrè syndrome ("GBS"). Neurologist Dr. Victor H. Barredo noted on May 13, 2009 that "[s]on tells me this [neurological injury] was preceded by gastrointestinal illness not atypical for Guillain Bare [sic] Syndrome," Pet'r's Ex. 12 at 377, but "[n]ot sure if Campylobacter titers would be diagnostic at this time." *Id.* at 378. He also noted "axonal loss," "elevated CSF protein that was compatible with Guillain Bare [sic] syndrome," and a "[c]ourse complicated by MRSA[10] and GI bleed last week." *Id.* at 377-78.

After months of plasmapheresis and treatments for multiple complications, Petitioner was eventually discharged from South Miami Hospital on August 20, 2009. Pet'r's Ex. 12 at 70-74. She spent a month at West Gables Rehabilitation Hospital until her discharge on October 9, 2009. Pet'r's Ex. 3 at 31-33. She was again hospitalized at Jackson Memorial Hospital from February 18, 2010, to March 24, 2010, for inpatient rehabilitation. Pet'r's Ex. 4 at 2-9. Her chief complaint was listed as "[g]lobal weakness s/p GBS," *id.* at 3; her history of note says "Pt stated that it all started after a bout of 'gastritis.'" *Id.*

[9] Myasthenia gravis is "an autoimmune disease of neuromuscular function due to the presence of antibodies to acetylcholine receptors at the neuromuscular junction; characteristics include muscle fatigue and exhaustion that fluctuates in severity, without sensory disturbance or atrophy." *Dorland's* at 1214.

[10] MRSA is "methicillin-resistant *Staphylococcus aureus*." *Dorland's* at 1184.

III. PETITIONER'S INJURY: GUILLAIN-BARRÉ SYNDROME ("GBS")

GBS is an inflammatory disease in which the body's immune system attacks part of the peripheral nervous system.[11] Pet'r's Ex. 13 at 8 (quoting the National Institute of Neurological Disorders and Stroke website ("NINDS"), http://www.ninds.nih.gov/disorders/gbs/gbs.htm (last visited Dec. 2, 2015)). "Guillain-Barré syndrome (GBS) is the leading cause of acute flaccid paralysis in developed countries and is characterized by various degrees of weakness, sensory abnormalities and autonomic dysfunction." Pet'r's Ex. 22[12] at 2. The disorder includes varying degrees of weakness or tingling sensations in the legs, and can spread to the arms and upper body. Pet'r's Ex. 13 at 8, citing NINDS. The patient is often put on a ventilator to assist with breathing. *Id.*, citing NINDS.

Typically, GBS occurs a few days or weeks after the patient has had symptoms of a respiratory or gastrointestinal infection. *Id*., citing NINDS; *see also* Resp't's Ex. E at 2.[13] Both experts agree and abundant medical literature provides that two-thirds of GBS patients have a history of a preceding infection. *Id*.; Tr. 43, 114. The most common infections are gastrointestinal illnesses or upper respiratory infections. Tr. 43. *Campylobacter jejuni* ("Campylobacter" or "C jejuni"), a common gastrointestinal virus, is one of the most common pathogens having a strong association with the subsequent development of GBS. Tr. 44; *Haber* at 5. "Molecular mimicry and a cross-reactive immune response play a crucial part in its pathogenesis, at least in those cases with a preceding *Campylobacter jejuni* infection and with antibodies to gangliosides." *van Doorn* at 939. Molecular mimicry is a possible avenue for vaccine-induced GBS as well. *See generally Haber* (discussing the existence of causal relationships between certain vaccines and GBS); *van Doorn* at 2-3. "[T]he concept of molecular mimicry states that when the immune system is attacking a component of a virus or bacteria that is shared with the nervous system, [the] cross-reaction to the common structure results in damage to the nervous system." Tr. 11. This includes a break in tolerance to myelin antigens. Tr. 48. Maria Perez suffered from an axonal form of GBS, which means that it predominantly involves the axons underlying the myelin more than the myelin itself. Tr. 36-37. In this form, the nerves as well as the myelin are damaged. *Id.*

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[11] When the body attacks itself in this way, it is called an autoimmune disease. Pet'r's Ex. 13 at 8.

[12] Haber, P., et al., *Vaccines and Guillain-Barré Syndrome*, Drug Safety, 2009; 32(4): 309-23 [hereinafter *Haber*].

[13] van Doorn, P.A., et al., *Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome,* Lancet Neurol., 2008; 7: 939-50 [hereinafter *van Doorn*].

Nothing in the evidence presented by either party concerning GBS or the process of molecular mimicry indicates either that GBS develops but then remains latent until it is triggered by another exogenous event, or that the process of molecular mimicry needs a trigger other than the initial vaccine or infection to induce the symptoms of GBS.

IV. QUALIFICATIONS OF THE EXPERTS

A. Petitioner's Expert: Dr. Lawrence Steinman

At the time of hearing, Petitioner's expert in this case, Dr. Steinman, was a board certified neurologist and a professor of neurology at Stanford University. Pet'r's Ex. 13 at 3; Tr. 6. He saw adult as well as pediatric neurology patients. Pet'r's Ex. 13 at 3. He has served on advisory panels, received multiple awards for his work, and held numerous vaccine-related patents. *Id*. He had previously testified as an expert in the Vaccine Program. *Id.*

In coming to his conclusions, Dr. Steinman reviewed Petitioner's medical records, and relied on published work relating to autoimmune disease, T-cells and autoantibodies recognizing myelin basic proteins in multiple sclerosis patients, *see, e.g.*, Pet'r's Ex. 17, and on scientific literature that explains molecular mimicry, vaccines, and GBS, *see, e.g., Haber*. Pet'r's Ex. 13 at 4.

B. Respondent's Expert: Dr. Thomas Leist

At the time of hearing, Dr. Leist was an attending physician and associate professor of neurology at Thomas Jefferson University. Resp't's Ex. D at 1; Tr. 92. In addition to his medical degree, he has a Ph.D. in biochemistry with a focus on immunology. Tr. 93. He was the director of the neuroimmunology fellowship program and the Multiple Sclerosis Center at Thomas Jefferson University. *Id*. at 92. He is a board certified adult neurologist. *Id.* at 93. The majority of his time was spent seeing patients, and the balance of his time he spent conducting research and teaching students. *Id.* at 94-95.

In reaching his conclusions, Dr. Leist relied on Petitioner's clinical course, medical records, and medical literature. Resp't's Ex. A; Tr. 102. The medical literature submitted consists of articles discussing the research done to determine whether the tetanus vaccine can cause GBS as well as the causal relationship between gastroenteritis and GBS. *See* Resp't's Exs. B, C, E – H.

V. APPLICABLE LEGAL STANDARD

To receive compensation under the Program, Petitioner must prove either 1) that she suffered a "Table Injury" — i.e., an injury falling within the Vaccine Injury Table[14] — corresponding to one of her vaccinations, or 2) that Petitioner suffered an injury that was actually caused by a vaccine. *See* 42 U.S.C.A. § 300aa-13(a)(1)(A); *see also* § 300aa-11(c)(1). Petitioner has not claimed a Table Injury, and an examination of the record has not revealed any possible Table Injury.

Absent a Table Injury, Petitioner must show that the vaccine was "not only a 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)). To do so, Petitioner must satisfy all prongs of the test established by the Federal Circuit in *Althen*. 418 F.3d 1274, 1279 (Fed. Cir. 2005). The *Althen* test requires petitioners to set forth: "(1) a medical theory causally connecting the vaccination and the injury ("*Althen* Prong One"); (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury ("*Althen* Prong Two"); and (3) a showing of a proximate temporal relationship between vaccination and injury ("*Althen* Prong Three")." *Id.* To establish entitlement to compensation under the Program, Petitioner is required to establish each of the three prongs of *Althen* by a preponderance of the evidence. *Id.*

The preponderance of the evidence standard has been interpreted to mean that the Petitioner must show that the fact is more likely than not. *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1322 n. 2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). "[T]he purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280.

In determining whether Petitioner is entitled to compensation, the special master must consider all relevant, reliable material contained in the record. 42 U.S.C.A. § 300aa-13(b)(1). That material can include circumstantial evidence. *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325 (Fed. Cir. 2006). Although a Vaccine Act claimant is not required to present proof of causation to the level of scientific certainty, as the finder of fact, a special master is "entitled—indeed, expected—to make determinations as to the reliability of the

[14] The Vaccine Injury Table "lists the vaccines covered under the Act; describes each vaccine's compensable, adverse side effects; and indicates how soon after vaccination those side effects should first manifest themselves. Claimants who show that a listed injury first manifested itself at the appropriate time are prima facie entitled to compensation." *Bruesewitz v. Wyeth LLC*, 562 U.S. 223, 228 (2011) (citing 42 U.S.C.A. § 300aa-14(a)).

evidence presented…and, if appropriate, as to the credibility of the persons presenting that evidence." *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1326 (Fed. Cir. 2010). In *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, the Supreme Court set forth a number of factors courts should consider in evaluating the reliability of expert testimony. *Daubert*, 509 U.S. 579, 592 (1993). According to *Terran v. Sec'y of Health & Human Servs.*, it is appropriate for special masters to utilize *Daubert*'s factors as a framework for evaluating the reliability of causation-in-fact theories presented in Program cases. *Terran*, 195 F.3d 1302, 1316 (Fed. Cir. 1999); *see also Coombs v. Sec'y of Health & Human Servs.*, No. 08-818V, 2014 WL 1677584, at *3 (Fed. Cl. Spec. Mstr. Apr. 8, 2014). *Terran* clarified that a special master is not required to apply all of the *Daubert* factors, but is encouraged to use the *Daubert* framework as a tool for inquiring into the reliability of the evidence. 195 F.3d at 1316.

Accordingly, the Vaccine Program regularly uses the following *Daubert* factors in evaluating experts' opinions:

> (1) whether a theory or technique can be and has been tested;
> (2) whether the theory or technique has been subjected to peer review and publication;
> (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and
> (4) whether the theory or technique enjoys general acceptance within a relevant scientific community.

Daubert, 509 U.S. at 592–95; *see, e.g., Terran*, 195 F.3d at 1316; *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 744 (2009).

Where opinion evidence is only connected to data upon which it purports to rely by the *ipse dixit* of the expert, that evidence may be accorded less weight. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) (explaining that "[n]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert."). A special master may also deem an opinion or theory unreliable where there is simply too great an analytical gap between the data and the opinion proffered. *Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (quoting *Joiner*, 522 U.S. at 146); *see also Caves v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 119, 136 (2011), *aff'd sub nom. Caves v. Sec'y of Health & Human Servs.*, 463 F. App'x 932 (Fed. Cir. 2012).

If Petitioner satisfies all three prongs of *Althen* by a preponderance of the evidence, she establishes a *prima facie* case. *Walther v. Sec'y of Health & Human Servs.*, 485 F.3d 1146, 1149-51 (Fed. Cir. 2007). After Petitioner has established a *prima facie* case, the burden shifts to

Respondent to demonstrate, also by a preponderance of the evidence, that the injury was actually caused by factors unrelated to the administration of the vaccine. *Walther*, 485 F.3d at 1151; 42 U.S.C.A. § 300aa–13(a)(1)(B). Accordingly, "[i]f the evidence is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 550 (Fed. Cir. 1994).

VI. EXPERT TESTIMONY

A. Petitioner's Medical Theories

The theory of causation presented in Dr. Steinman's expert report relies heavily on the biological process of molecular mimicry, and specifically on the mimicry between the protein sequences in the flu vaccine and myelin self molecules, as one explanation of the pathogenesis of GBS. Pet'r's Ex. 13 at 9-14. Petitioner argues that

> [i]n essence, instructing that by the process of molecular mimicry, the immune system "mistakes" myelin in the peripheral nervous system for parts of the antigen it has been "taught" to recognize by the **flu vaccine**, and attacks or cross reacts with the myelin proteins causing demyelination, presenting as Guillain Barre [sic] syndrome. *By this process*, a **tetanus vaccine** can cause Guillain Barre [sic] syndrome thereby satisfying *Althen's* first prong.

Petitioner's Pre-Hearing Submissions, filed December 9, 2013, at 7 (emphasis added). However, at hearing Petitioner clarified, through Dr. Steinman, that she was not claiming that the flu vaccine she received December 20, 2008 was the cause of her GBS, nor was she claiming a homology between the tetanus vaccine and myelin that could cause GBS through the process of molecular mimicry. Tr. 17-21, 46, 65.[15] Rather, Dr. Steinman argued, a tetanus vaccine can "rev up" an individual's innate immune system, causing the expression of toll-like receptors ("TLRs"), that may play a role in the pathogenesis of GBS. Tr. 21-23, 49-58; Pet'r's Ex. 25.[16] After this "rev'g up," Dr. Steinman asserted, the immune system "smolders" for a period of days or even weeks, before the GBS caused by the "rev'g up" manifests. Tr. 23, 68-70, 76, 78.

[15] Homologies exist between a component of a vaccine and myelin basic proteins in the body when the vaccine component has an amino acid sequence in it that is structurally similar to that of the myelin protein. Tr. 13; Pet'r's Ex. 13 at 10. This occurs at both the T-cell level and the antibody level. Tr. 13. Only when these homologies exist can the process of molecular mimicry take place.

[16] Wang, Y., et al., *Expression of Toll-Like Receptors 2, 4, and 9 in Patients with Guillain-Barré Syndrome*, Neuroimmunomodulation 2012; 19: 60-68 [hereinafter "*Wang*"].

Alternatively, Dr. Steinman opined that the tetanus vaccination does not cause GBS directly. Rather, Dr. Steinman contended, after the adaptive immune system has been activated by an infection or a vaccine and myelin has been identified as the antigen through the process of molecular mimicry, the tetanus vaccine acts as a trigger to activate the innate immune system's TLRs, leading to GBS. *See* Tr. 46. In other words, an initial infection or the flu vaccine is required to cause the molecular mimicry which results in the destruction of myelin, i.e., GBS; but the tetanus vaccine acts as a trigger for the GBS to become symptomatic. Tr. 76. According to this theory, the innate immune response prompted by the tetanus vaccine is critical for augmentation of the adaptive immune response to myelin caused by infection or unrelated vaccine. Pet'r's Ex. 13 at 14. It is not clear whether Dr. Steinman is arguing that the adaptive immune response (i.e., molecular mimicry) and the innate immune response (i.e., the vaccine "trigger") are codependent and must both be present for an individual to develop GBS. If so, he does not explain what part of the molecular mimicry process cannot occur without the trigger. If not, he does not explain how the tetanus vaccine alone can cause GBS, although he testified at one point that it can. Tr. 21 ("I do want to say explicitly that she would have had this [GBS] just with the tetanus shot.").

Thus, Dr. Steinman contended that in Petitioner's case her adaptive immune system recognized a protein sequence in her myelin as a protein sequence in an antigen unrelated to the tetanus vaccine, causing the antibodies and T-cells to attack her myelin as the antigen; that attack on myelin causes the symptoms of GBS. Tr. 64. Dr. Steinman stated that the unrelated antigen in Petitioner's case could have been the influenza shot, an undiagnosed Campylobacter virus (a type of gastroenteritis), or even the staphylococcus infection. Tr. 66, 70-71; *see also* Pet'r's Ex. 13 at 11-12. There is evidence that the staph infection was not resolved at the time Petitioner received the tetanus vaccine. Tr. 73-74. He then strongly contended that the surfacing of the GBS required a trigger to "rev up" the innate immune system, and therefore, the GBS sat latently[17] until such a trigger, namely, the tetanus vaccine was introduced. *See* Tr. 22, 50, 67, 76. The process of "rev'g up" the innate immune system allegedly "pushed [Petitioner] over the

[17] At one point Dr. Steinman did assert that it was not the GBS he was talking about "smoldering," but "the immune system." Tr. 82. "Day one of GBS," Dr. Steinman stated, "is the day that clinical diagnosis is made." *Id*. The resulting theoretical confusion is the same, however. Whether it is "GBS," or the adaptive immune process of molecular mimicry, or the demyelination that occurs once the molecular mimicry process has identified the myelin protein as the antigen, or the "rev'g up" of the innate immune system resulting in the expression of TLRs, some part of that process has to stall, plateau, be interrupted somehow, awaiting the trigger, for Dr. Steinman's theory to work. This was clearly Dr. Leist's understanding as well: he testified that he has "a problem with the proposition of this interrupted, novel . . .mechanism by which something happens, the cells lie there, then something else happens, and now they decide to go up in a certain way." Tr. 174.

threshold" and caused the onset of GBS symptoms. Tr. 67.

Finally, once the innate immune response was triggered on February 2, 2009, it took eight weeks for Petitioner to present with an onset of GBS symptoms. Tr. 76. Dr. Steinman contends that the innate immune response somehow persisted due to "smoldering latencies." Tr. 67-70, 76, 78.

B. **Respondent's Medical Theory**

Dr. Leist opined that Petitioner's GBS was caused by a gastrointestinal illness, not the tetanus vaccine. Resp't's Ex. A at 6. Petitioner presented to the hospital with symptoms of a gastrointestinal illness on March 25, 2009, including three days of vomiting, generalized body aches, nausea, diarrhea, and an elevated white cell count. Pet'r's Ex. 8 at 1, 3; Tr. 97-98. Petitioner was diagnosed with an unknown gastrointestinal virus. *See* Tr. 97-98; *see also* Resp't's Ex. A at 6. Petitioner then presented to the ER of Doctors Hospital on April 1, 2009 with a complaint of dizziness and dysesthesia in arms and legs, Pet'r's Ex. 6 at 44-47, and a few days later was re-admitted for respiratory distress, bilateral ptosis, dysarthria, and flaccid quadriparesis. Pet'r's Ex. 2 at 85. This admission resulted in her GBS diagnosis. Pet'r's Ex. 1 at 67..

Dr. Leist explained that this clinical course is "consistent with para-infectious Guillain-Barre [sic] syndrome with axonal features occurring within less than two weeks of a likely infectious illness with gastrointestinal symptoms." Resp't's Ex. A at 6. It is widely accepted that two-thirds of individuals with Guillain-Barré syndrome have a history of a recent infection, such as a gastrointestinal illness. Resp't's Ex. A at 6; Tr. 43, 56, 161. Dr. Leist conceded that whether Petitioner had C jejuni or another type of gastrointestinal illness is unknown. Tr. 102.

Regarding Petitioner's theory of the case, Dr. Leist opined that toll-like receptors can become elevated as a result of numerous conditions, such as infections, chronic diabetes, and hyperlipidemia, all of which Petitioner had. Tr. 108.[18] He dismissed Dr. Steinman's argument concerning toll-like receptors being an indication of tetanus-induced GBS as "speculative" and "significantly hypothesis-driven." Tr. 109. Dr. Leist also pointed out that Dr. Steinman did not provide a reliable explanation as to why the myelin reactive cells were dormant after the process of molecular mimicry had begun, no matter the source of the process's inception. Tr. 174. Lastly, Dr. Leist opined that Ms. Perez had early features of axonal loss with the Guillain-Barré

[18] Dr. Steinman also acknowledges that other causes can produce elevated TLRs. Tr. 22. He also acknowledges that Petitioner had many of these potential causes of TLR elevation. Tr. 60-61.

syndrome, and it is not clear how tetanus toxoid containing vaccines would cause an axonal form of Guillain-Barré syndrome. Resp't's Ex. A at 7.

Respondent contended that Petitioner did not meet her burden of proof because she failed to establish a causal association between the tetanus vaccine and the GBS. *See* Respondent's Post-Hearing Brief ("Resp't's Post-Hearing Br.") at 26-27. Respondent further contended that while Respondent did not have the burden to prove an alternative cause of Petitioner's GBS, Respondent nonetheless put forth preponderant evidence of causation due to the viral illness in the weeks preceding the onset of her GBS. *Id*.

VII. ANALYSIS

A. *Althen* Prong One: Medical Theory

To satisfy the first prong of *Althen*, Petitioner must provide "a medical theory causally connecting the vaccination and the injury." *Althen*, 418 F.3d at 1278 (quoting *Grant v. Sec'y of Health & Human Servs.*, 956 F. 2d 1144, 1148 (Fed. Cir.1992)). Petitioner's theory must show that it is more likely than not that the vaccine she received "can" cause the type of injury Petitioner alleges the vaccine caused. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006).

The medical theory set forth by the Petitioner must be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 548-49. However, the theory cannot be baseless or completely speculative; it must be informed by "sound and reliable medical or scientific explanation." *Id.* at 548*; see also Veryzer v. Sec'y of Health & Human Servs.*, 98 Fed. Cl. 214, 223 (2011) (noting that under 42 U.S.C.A. § 300aa-13(b)(1) and Vaccine Rule 8(b)(1), special masters must consider only evidence that is both "relevant" and "reliable"). When a petitioner proffers a medical opinion to support her theory, the basis for the opinion and the reliability of that basis must be considered in determining how much weight to afford the offered opinion. *See Broekelschen v. Sec'y of Health & Human Servs.*, 618 F. 3d 1339, 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); *Perreira v. Sec'y of Health & Human Servs.*, 33 F.3d 1375, 1377 n. 6 (Fed. Cir. 1994) ("An expert opinion is no better than the soundness of the reasons supporting it") (citing *Fehrs v. United States*, 620 F.2d 255, 265 (Ct. Cl. 1980)).

As previously discussed, at times in her expert report, at hearing, and in pleadings, Petitioner argued that her GBS was caused directly by the tetanus vaccine. *See,e.g.,* Tr. 21-23. However, Petitioner primarily argued an alternative theory of causation. *See* Pet'r's Ex. 13 at 17; Tr. 84-85. In Petitioner's alternative theory of the case, she concedes that the tetanus vaccination

did not directly cause her GBS, but rather that the vaccination acted as a trigger, without which the GBS would not have manifested. *See* Tr. 64-65, 67. Dr. Steinman contends that one of the infections from which Petitoner suffered, or the flu vaccine she received, elicited an adaptive immune response that resulted in the molecular mimicry process and an attack on the myelin sheaths, but that that process did not manifest as symptomatic GBS until it was triggered by the tetanus vaccine. Tr. 85.

The theory of molecular mimicry described by Dr. Steinman is straightforward. In Dr. Steinman's expert report, for example, it is described thus: "Foreign antigens that are structurally similar to self-peptides react to lymphocytes. B cell binding will lead to excretion of immunoglobulins, complement activation, and presentation to T cells via MHC, which leads to T cell activation." Pet'r's Ex. 13 at 5 (citing the Johns Hopkins Arthritis Center website, http://www.hopkinsarthritis.org/physician-corner/rheumatology-rounds/round-21-an-old-paradigm-revisited-the-case-of-a-29-year-old-woman-with-painful-blue-digits/ (last visited December 3, 2015)). There is no evidence anywhere in the record to suggest that this process stops or plateaus or is latent at any point, or that it requires a trigger to become symptomatic. Yet his theory regarding the causal connection between the tetanus vaccine and GBS is that once the process of molecular mimicry has begun, it gets interrupted somehow, and requires an appropriate push or trigger to bring about the clinical symptoms of GBS. Petitioner is thereby implying that the disease process that is ultimately diagnosed as GBS was somehow latently or asymptomatically dormant in the body, but she provides absolutely no evidence of scientific or medical literature that supports a theory of interrupted or latent GBS. An explanation for this requisite latency is not only lacking in scientific literature, it is also nonexistent in Dr. Steinman's report and testimony. It is an analytical gap in Dr. Steinman's methodology that was not filled by any of the evidence submitted in the case. As Dr. Leist put it,

> I have a real problem with the proposition of this interrupted, novel – and I really use this word novel in the truest sense of the word -- mechanism by which something happens, the cells lie there, then something else happens, and now they decide to go up in a certain way. I mean, this above and beyond what I would consider an established, reviewed, and accepted theory.

Tr. 174. The undersigned has that problem with Petitioner's theory, too.

Dr. Steinman's theory is that the tetanus vaccination "rev's up" the innate immune system, generating toll-like receptors that trigger the already existing adaptive immune system's process of molecular mimicry, resulting in GBS. This portion of his "rev'g up" theory rests on the expression of toll-like receptors. *See* Tr. 61. Both parties' experts agree that there is a possible association between elevated TLRs and GBS, generally. Tr. 22, 108-09. However, while Dr. Steinman relies heavily upon this association, the article upon which this argument

rests states only that "[e]xpression of TLR2, 4 and 9 as well as their related signaling molecules were higher in GBS patients compared to healthy controls . . . . The TLR signaling pathway may be involved in the pathogenesis of GBS." *Wang* at 3. Nothing in the article suggests a resolution of the previously discussed questions about the alleged "smoldering" of the innate immune system; if anything, it contributes to the picture of GBS as developing relatively linearly, as both an innate and an adaptive immune process, without the need for a secondary trigger such as that suggested by Dr. Steinman. Finally, even if TLRs do somehow play a triggering role in the pathogenesis of GBS, there is nothing in this article that suggests that the source of the elevated TLRs is a pathogen other than the infection or immunization that causes the adaptive immune reaction, the molecular mimicry, in the first place, nor did Dr. Steinman explain why the TLRs from the tetanus vaccine would be any more causative than other sources of TLRs, including the infections, and other vaccines. Tr. 22, 62, 174.

Assuming that the analytical gaps previously discussed are somehow bridged, a third, temporal gap in Petitioner's theory still exists: that the innate immune response somehow persists and "smolders" for an eight-week time period without triggering the adaptive immune system's molecular mimicry process, or that the adaptive immune system's process, once triggered, "smolders," instead of causing symptoms of GBS within a few days or at most a few weeks, as the scientific literature would suggest. Tr. 67-70, 76, 78, 81; Pet'r's Ex. 13 at 5; *van Doorn* at 2. Petitioner provides absolutely no sound reason for why this "smoldering" would occur. Tr. 67-70, 76, 78, 81. When asked, Dr. Steinman simply stated that "I don't know why things smolder. They do." Tr. 76. While Dr. Steinman clearly believes this is true, the *ipse dixit* of an expert, without more, does not constitute reliable evidence upon which the undersigned can rely in determining entitlement. *Joiner*, 522 U.S. 136, 146 (1997) ("[n]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert.")

For all of the foregoing reasons, the undersigned finds that Petitioner has failed to present preponderant evidence that the tetanus vaccine can cause GBS, as required by the first prong of *Althen.*

B. *Althen* Prong Two: Logical Sequence of Cause and Effect and *Althen* Prong Three: Temporal Association

While the first prong of Althen focuses on general causation, that is, whether the administered vaccine can cause the particular injury from which the vaccinee suffers, the second prong focuses on specific causation, that is, whether the administered vaccine actually caused the injury. *See Pafford*, 451 F.3d at 1355-56; *see also Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1326 (Fed. Cir. 2006). To satisfy the second prong of *Althen,* Petitioner must establish "a logical sequence of cause and effect showing that the vaccination was the

reason for the injury." *Althen*, 418 F.3d at 1278. Petitioner may satisfy her burden by presenting circumstantial evidence and reliable medical opinions; she is not required to offer "epidemiologic studies, rechallenge, presence of pathological markers or genetic disposition, or general acceptance in the scientific and medical communities" to establish a logical sequence of cause and effect. *Capizzano*, 440 F.3d at 1322.

To satisfy the third prong of *Althen*, petitioners must produce preponderant evidence of "a proximate temporal relationship between vaccination and injury." *Althen*, 418 F.3d at 1278. This prong helps to establish the connection between the causal theory of Prong One and the more fact-based cause and effect arguments of Prong Two by demonstrating "that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008).

While Petitioner's failure to satisfy the first prong of *Althen* renders an analysis of the remaining *Althen* prongs unnecessary, in an abundance of caution, the undersigned will nevertheless proceed with a brief analysis of those prongs. In this context, it is appropriate to consider Respondent's medical theory of the case, in addition to other expert testimony and evidence, in order to assess the persuasiveness of Petitioner's proof on the issues of causation-in-fact and appropriate temporal association. Respondent may offer evidence, or point to existing evidence in the record, that contradicts or weakens a petitioner's evidence, and in so doing demonstrate that the petitioner cannot meet her overall burden. *Stone v. Sec'y of Health & Human Servs.,* 676 F.3d 1373, 1379 (Fed. Cir. 2012) ("[o]ur decisions support the commonsense proposition that evidence of other possible sources of injury can be relevant not only to the 'factors unrelated' defense, but also to whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question"); *La Londe v. Sec'y of Health & Human Servs.,* 110 Fed. Cl. 184, 198 (2013) ("[r]egardless of whether the burden ever shifts to the respondent, the special master may consider the evidence presented by the respondent in determining whether the petitioner has established a prima facie case), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). The special master "must consider all relevant and reliable evidence governed by principles of fundamental fairness to both parties," and may consider evidence of an alternate cause to evaluate if Petitioner has established a prima facie case of causation with preponderant evidence. Vaccine Rule 8(b)(1); *see also Cedillo*, 617 F.3d at 1339; *Doe v. Sec'y of Health & Human Servs.*, 601 F.3d 1349, 1356-58 (Fed. Cir. 2010).

Accordingly, Respondent put forward a theory to aid the court in assessing whether Petitioner established a *prima facie* case by preponderant evidence. Respondent's medical theory is that the gastrointestinal illness with which Petitioner was diagnosed a few days prior to the onset of her GBS symptoms was the cause of Petitioner's GBS. *See* Resp't's Post-Hearing Br. at 27.

The onset of Petitioner's GBS symptoms was April 1, 2009, about eight weeks after Petitioner received the tetanus vaccination. Pet'r's Ex. 6 at 44, 47. However, a few days prior to that onset, on March 25, 2009, Petitioner went to the emergency room complaining of vomiting for three days, diarrhea and that her whole body hurt. Pet'r's Ex. 8 at 1. She was diagnosed with an unknown gastrointestinal virus. Pet'r's Ex. 2 at 111.

Although the *type*[19] of gastroenteritis Petitioner had is uncertain, there is no dispute that Petitioner did in fact have gastroenteritis, including an elevated white cell count, approximately seven days prior to GBS onset. *See* Tr. 154; Pet'r's Ex. 2 at 82. In addition, Petitioner had the axonal form of GBS, which Petitioner's expert Dr. Steinman stated is often caused by Campylobacter. Tr. 54. Respondent further contended that the most logical evidence of causation is the illness immediately preceding the onset of Petitioner's neurological symptoms. Resp't's Post-Hearing Br. at 16-17. In other words, Respondent contended that whether Petitioner had Campylobacter or some other gastrointestinal illness, the diagnosis of a gastrointestinal illness, the presence of an elevated white cell count, and the appropriate time frame are collectively preponderant evidence of Respondent's theory;. At a minimum, Respondent argued, that evidence casts doubt on Petitioner's theories sufficient to prevent a finding that she has proven her case by preponderant evidence. *See* Resp't's Ex. A at 6; Tr. 102.

The undersigned agrees with Respondent. As to Petitioner's first theory, that the tetanus vaccine alone caused her GBS, even if the undersigned were to accept Petitioner's theory that elevated TLRs alone could cause GBS (which the undersigned does not), the undersigned does not find persuasive that it was the vaccine that caused that "rev'g up" of the immune system, rather than either the unresolved staph infection in Petitioner's shoulder or the cellulitis in her right hand. If the tetanus vaccine could cause the necessary "rev'g up," the undersigned is not persuaded that Petitioner's "rev'd up" immune system would then stop "rev'g up", and simply "smolder" for eight weeks until it caused symptomatic GBS. And finally, the undersigned is not persuaded that Petitioner's "smoldering" immune system would somehow leapfrog over the gastrointestinal virus, only to manifest as GBS one week later.

Similarly, as to Petitioner's alternate, "trigger" theory: if either the staph infection in Petitioner's shoulder, the flu vaccine, or the cellulitis in Petitioner's right hand had initiated the process of molecular mimicry that can cause GBS, the undersigned is not persuaded that that process needs a trigger, vaccine or otherwise, to manifest as GBS. If the vaccine did trigger the GBS, the undersigned is not persuaded that the already activated molecular mimicry process

[19] Dr. Leist contends that the "absence of a proof [of the presence of Campylobacter] is not proof of absence." Tr. 155. Dr. Steinman's sole reason for rejecting gastroenteritis as a cause of Petitioner's GBS is simply that the presence of Campylobacter, specifically, was not known. Tr. 22, 40.

smoldered for another eight weeks before manifesting in GBS symptoms. And again, as Respondent argued, even if all of the other steps were medically plausible and legally persuasive, the undersigned is not persuaded that the molecular mimicry process, with the vaccine push behind it, would have leapfrogged a virus virulent enough to bring Petitioner to the emergency room, and waited yet another week before manifesting itself as GBS.

In sum, Petitioner has failed to satisfy prong two of *Althen*: she has not put forward preponderant evidence that the tetanus vaccine did, in fact, cause her GBS. Likewise, as to prong three of *Althen*, Petitioner has not provided preponderant evidence that eight weeks between the tetanus vaccine and the GBS is a reasonable time period, especially in light of the intervening gastrointestinal illness. Petitioner has failed to meet her burden under prongs two and three of *Althen*.

VIII. CONCLUSION

The undersigned is sympathetic to the fact that Petitioner suffers from GBS. However, under the law, the undersigned can authorize compensation only if a medical condition or injury either falls within one of the "Table Injury" categories, or is shown by medical records or a competent medical opinion to be vaccine-caused. No such proof exists in the record.

Therefore, the undersigned has no choice but to hereby **DENY** this claim. The Clerk shall enter judgment in accord with this decision.

IT IS SO ORDERED.

/s/ Lisa D. Hamilton-Fieldman
Lisa D. Hamilton-Fieldman
Special Master